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Women in pediatric critical care: 2021

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Women in pediatric critical care: 2021

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ORIGINAL RESEARCH
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The Relationships Amongst Pediatric Nurses' Work Environments, Work Attitudes, and Experiences of Burnout

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Background: Pediatric nurses care for some of the most vulnerable patients in our healthcare system. Research on health care provider organizational behavior shows that the quality of care nurses provide is directly related to their well-being, influenced by Burnout and job stress, in the workplace. However, most of the research conducted on nursing populations neglects to separately study nurses who care for children. In a resource limited system where health care provider well-being is recognized as a priority, it is important for administrators to understand the environmental and attitudinal work factors most influential to pediatric nurse work outcomes in order to target optimization strategies. The aim of the study was to identify which *modifiable* work environment factors, e.g., [Incivility, Perceived Organizational Support, Quality of Work-life] make the *greatest* contribution to the work outcome of Burnout (i.e., Personal Accomplishment, Emotional Exhaustion, Depersonalization) in pediatric nurses.

Methods: A cross-sectional survey design was used at a large quaternary care pediatric hospital in Toronto, Canada. We administered a survey to a convenience sample of all registered nurses with >3 months experience in the Pediatric, Cardiac, and Neonatal Intensive Care Units from January 2021–March 2021. Path analysis was used to test our proposed model which was specified *a priori* based on a review of the literature.

Results: 143 nurses completed the survey. Path analysis of the tested model resulted in good fit. Quality of Work-life had the largest direct effect on Work Engagement ($\beta = 0.582$, S.E. $= 0.111$, $p < 0.001$). Work Engagement had the largest direct effect on Personal Accomplishment ($\beta = 0.68$, S.E. $= 0.53$, $p < 0.001$). Quality of Work-life had the largest indirect effect on Personal Accomplishment ($\beta = 0.4$, S.E. $= 0.65$, $p < 0.001$), Emotional Exhaustion ($\beta = -0.33$, S.E. $= 0.87$, $p < 0.001$), and Depersonalization ($\beta = -0.17$, S.E. $= 0.41$, $p = 0.006$), respectively. Work Engagement had the largest total effect on Personal Accomplishment ($\beta = 0.68$, S.E. $= 0.64$, $p < 0.001$) and the third largest total effect on Emotional Exhaustion ($\beta = -0.57$, S.E. $= 0.83$, $p < 0.001$). Quality of Work-life had the second largest total effect on Work Engagement ($\beta = 0.58$, S.E. $= 0.11$, $p < 0.001$) indicating that Quality of Work-life is mediated through Work Engagement for its effect on Burnout.

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Conclusions: Our results indicate work environment and work attitude factors that can provide organizational leadership with a targeted focus to reduce pediatric critical care nurse Burnout, and thus improve provider well-being, in a resource limited system.

Keywords: nurses, pediatrics, burnout—professional, organizational behavior (OB), critical care

BACKGROUND

Pediatric nurses care for some of the most vulnerable patients in our healthcare system. These nurses skillfully manage the highly specialized care of children and the complex family dynamics that are inherent to the work (1). Pediatric nurse well-being in the workplace has been shown to be directly and positively related to nurses' attitudes about engaging with patients and families (2), and the quality of care provided (3–6). Pediatric nurses are a separate population from nurses who care for adults because of the specialized nature of providing care to children. Children are typically seen as a vulnerable population, and along with this, there is a high potential for empathetic engagement and inherent complexities in the relationships with families (7, 8). More specifically, pediatric/neonatal critical care nurses care for the most severely ill and injured children at the highest risk of death (9). As the stakes for this patient population are arguably the highest in the hospital, stressors of the work environment are enhanced; the care needs are highly complex and the stress to the families adds additional challenges (10, 11). Pediatric/neonatal critical care nurses are a subspecialty within a specialty. A supply-demand issue ensues as these nurses cannot be easily replaced or supplemented. Thus they are continually asked to do more (care for more patients, run more technology) with less (less time, resources, support) (1). Much of the organizational behavior research conducted to date on nursing populations has focused on general adult care nurses and excluded studying nurses who care for children (12, 13), particularly in pediatric critical care settings.

Work outcomes refer to occupational performance factors that are influenced by work attitudes and the work environment (14). The current study focuses on the work outcome of Burnout as it is one of the most established organizational behavior concepts, with over 40 years of literature available on the topic across numerous industries (15). Maslach and Jackson (1981) define Burnout by three components; Emotional Exhaustion, Depersonalization, and lack of Personal Accomplishment (16). Emotional Exhaustion refers to nurses feeling emotionally drained from their work; Depersonalization is the development of cynicism, particularly toward patients; and lack of Personal Accomplishment refers to nurses' feelings of dissatisfaction with the care they are providing (16). Nurse Burnout impacts at the level of the provider, the patient, and the organization (17). Burnout is positively associated with nurses' intent to leave their jobs (18), decreased quality of life (19), and negatively associated with the safety of the work environment (3, 4).

Nurses working in critical care commonly experience Burnout, with rates as high as 73% for Emotional Exhaustion, 60% for a lack of Personal Accomplishment, and 48% noting Depersonalization (20). Most of the currently available literature on pediatric nurse work outcomes, such as Burnout, focus on factors like race, marital status, or the experience of death in the workplace (21–23) or on high cost/low yield factors like nurses' personality traits (22). The former set of factors are non-modifiable and cannot be feasibly changed (e.g., race), while high cost/low yield factors are technically modifiable but it would not be fiscally or temporally responsible to try and impact (e.g., personality traits) (24). So while it is beneficial to be aware of the impact of these factors, they are not ideal targets for efficient modification by health care organizations. In a health care climate where resources are limited, it is important for administrators to know which environmental and attitudinal work factors make the greatest contribution to pediatric nurse work outcomes to target their optimization strategies in the most cost-effective way.

Our study began with a review of the literature on what is known about pediatric nurse Burnout (17). From there, an additional search of the literature was undertaken to investigate factors that impact Burnout in the broader health care population. Using this data and the framework of the Theory of Reasoned Action we proposed a conceptual model. **Figure 1** illustrates the proposed conceptual model where the pediatric nursing work environment influences work outcomes through work attitudes, thus influencing work outcomes directly.

Factors Related to Burnout

Work Environment

Incivility in the Workplace

Workplace Incivility is defined as; "low intensity behaviors that are rude, lack consideration of others, in violation of workplace norms for respect, where the intent to harm is ambiguous" (25). These behaviors serve as a pre-cursor for an exchange, or spiral, of coercive behavior.

Quality of Work Life

Sirgy et al. define quality of work life (QWL) as; "employee satisfaction with a variety of needs through resources, activities, and outcomes stemming from participation in the workplace. Thus, satisfaction from workplace experiences contributes to job satisfaction and satisfaction in other life domains. Satisfaction in the major life domains (e.g., work life, family life, home life, leisure life) contributes directly to satisfaction with overall life" (26).

Abbreviations: PICU, Pediatric Intensive Care Unit; CCCU, Cardiac Critical Care Unit; NICU, Neonatal Intensive Care Unit; MBI, Maslach Burnout Inventory; POS, Perceived Organizational Support; QWL, Quality of Work-life; WE, Work Engagement; EE, Emotional Exhaustion; DP, Depersonalization; PA, Personal Accomplishment.

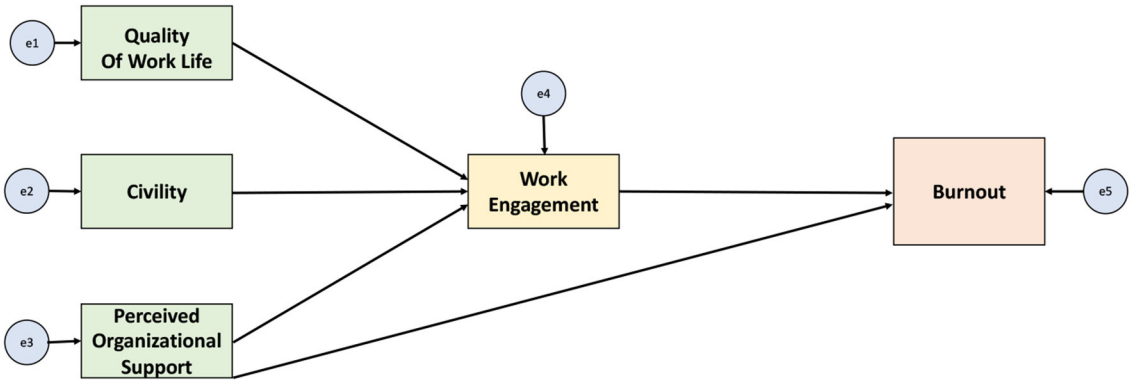

FIGURE 1 | The relationship between factors of the work environment, work attitudes, and the work outcomes of Burnout.

Perceived Organizational Support

Perceived organizational support (POS) is defined by the extent to which the employee perceives "the organization values their contributions and cares about their well-being" (27). POS is inversely related to nurse Burnout (27–29); POS is positively related to Work Engagement in nurses (30); and POS is inversely related to nurses' intent to leave (31–33).

Work Attitudes

Work Engagement

Schaufeli, Bakker, & Salanova (2006) define Work Engagement as; "a positive, fulfilling work-related state of mind that is characterized by vigor, dedication, and absorption. To be able to increase nurses' engagement with their patients and families we must think about possible interventions in the same light. Highly engaged nurses are essential for ethical, safe, and comprehensive care (34). Work Engagement may be challenging to directly modify, but work outcomes can be influenced *through* more easily modifiable factors of the work environment (14). Similar to work environment factors, pediatric nurses have not been separately studied in the nursing Work Engagement literature.

Study Objectives

1) To test a model of modifiable work environment features and attitudes in relation to the work-related outcome of Burnout in a sample of pediatric critical care nurses.

2) To rank the modifiable work environment factors based on their relationship with Burnout among pediatric critical care nurses.

METHODS

This study used a cross-sectional survey design to test a model of the relationships between organizational and attitudinal factors and Burnout in a convenience sample of nurses at a large quaternary care pediatric hospital in Toronto, Canada. The study was approved by the Research Ethics Board (#1000072502) at the Hospital for Sick Children.

Study Setting

The study took place in a 300-bed tertiary care hospital with a 41-bed critical care unit and a 38-bed neonatal intensive care unit in Toronto, Canada. A total of 443 Registered Nurses (RNs) work in the Cardiac Critical Care Unit (CCCU), Pediatric Critical Care Unit (PICU) and the Neonatal Intensive Care Unit (NICU) combined.

Sample and Recruitment

Inclusion criteria required that nurses had worked in the PICU, CCCU, or NICU for >3 months. Nurses undergoing orientation were excluded. All nurses in this organization are Registered Nurses (RNs). Nurses on leave (medical, parental, or otherwise) were excluded from participation as they were not actively working on the unit and not contactable via the hospital email server. All nurses working on these units were contacted via email for participation in the study. QR codes linking to the survey were also advertised on posters throughout the units. Surveys were completed and submitted automatically and anonymously online through *REDCap Software* (35). Data collection was conducted from January 6, 2021 to March 22, 2021. Of note, this data collection period was during the Coronavirus disease 2019 (COVID-19) pandemic. For context, participants were asked if they have cared for a COVID-19 positive patient or patient under investigation for COVID-19. Participant consent was implied by survey submission. Participants were offered a $5 coffee card as a thank you for their participation.

Data Collection Tools

The survey was made up of established instruments, previously used with nurses, that had good psychometric properties. Demographic information was also collected, along with a final open-ended question for nurses to include any other thoughts on the topic.

Maslach Burnout Inventory

Burnout was measured using the Maslach Burnout Inventory for Human Services Survey for Medical Personnel [MBI-HSS(MP)] with subscales for Depersonalization, Emotional Exhaustion, and Personal Accomplishment. Each subscale's items are scored on

TABLE 1 | Data collection tools and psychometric properties.

Factor	Tool	Number of questions	Scale	Cronbach's alpha	Scoring	Our cronbach's Alpha
Civility	The workplace incivilityscale	7	Likert (0–6)	0.93	Total mean across items	0.8854
Perceived organizational support	Survey of perceived organizational support—shorted version	8	Likert (1–7)	0.86–0.88	Total means across items	0.8110
Quality of work life	Quality of work life measure	17	Likert (1–7)	0.85	Total means across items	0.8622
Work engagement	Utrecht work engagement scale-9	9	Likert (0–6)	0.89–0.97	Total Mean across items	0.8516
Burnout	Maslach burnout inventory –HSS	22	Likert (0–7)	0.89	Three subscale scores (EE, DP, PA)	0.8661

a Likert scale from 0 to 6, indicating the frequency that the item applies in the providers experience ranging from with 0 indicating "never" to 6 indicating a frequency of "everyday" (36).

Work Attitudes

Utrecht Work Engagement Scale

Work Engagement was measured by the Utrecht Work Engagement Scale shortened 9-item version (UWES-9). [All items are measured on a 7-point Likert scale (0 = never–6 = always) and Work Engagement scoring categories include "very high", "high", "average", "low" and "very low" (37)].

Work Environment Features

Workplace Incivility Scale

The Workplace Incivility Scale (WIS), created by Cortina et al. was selected because it is a 7-item tool and measures a single construct of Workplace Incivility with an Cronbach's alpha = 0.89 and demonstrated validity (38). The tool is scored on a 7-point Likert scale where respondents self-report how often they experience instances of Workplace Incivility on a scale from 0 = never to 6 = daily (38).

The Survey of Perceived Organizational Support

The Survey of Perceived Organizational Support shortened 8-item tool uses a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree) (39).

Quality of Work Life Measure

The Quality of Work Life Measure, developed by Sirgy et al. in 2001, combines both needs satisfaction and spillover theories within the 7-factor, 16 item tool with response options on a 7-point Likert scale (1 = very untrue to 7 = very true) (26).

Where multiple options or versions of tools were available, we selected the shortest version if there were similar psychometric properties to reduce the overall survey length. (Cronbach's alpha was calculated for each data collection tool; all had acceptable reliability with a Cronbach's alpha >0.7 Data collection tools and their psychometric properties for this sample are in **Table 1**).

Analysis

Sample demographics and scale scores were summarized using descriptive statistics including means, standard deviations (SD), counts, and proportions as appropriate for the type of data and scoring guidelines for the scales. In addition, a correlation matrix was estimated to determine the relationship between each of the variables used in the path model.

Analysis Objective 1

Path analysis was used to test the model (**Figure 1**) of the relationships amongst *modifiable* work environment features, work attitudes and Burnout among pediatric critical care nurses. Path analysis is a component of Structural Equation Modeling (SEM); a simple case that does not include latent variables. Path analysis is most appropriate for our study as our model does not contain latent variables, therefore no measurement model is needed. **Three** subscales of Burnout were included in the model: Emotional Exhaustion, Depersonalization, Personal Accomplishment. Quality of Work-life, Perceived Organizational Support and Civility were the exogeneous variables, and Work Engagement was modeled to mediate the relationship between the exogenous variables and the outcome. In addition, a path for the direct effect of Perceived Organizational Support on Burnout was tested (**Figure 1**). STATA (Version 15) was used to conduct the path analysis and effect sizes were calculated (40). Indirect effects were calculated using bootstrapping. Acceptable model fit was indicated by a non-significant χ^2 value, a comparative fit index (CDI) >0.90, a Tucker-Lewis index (TLI) 0.0.90, a root mean square standard error of approximation (RMSEA) <0.05 (41). Missing values were addressed using full information maximum likelihood estimation (FIML).

Objective 2

Modifiable work environment factors were ranked (by their correlation coefficient) based on their contribution to explaining Burnout among pediatric critical care nurses (42).

Sample Size

Minimum sample size for our study was calculated using the N:q rule, there were $q = 7$ parameters that require estimates. The ratio of 10:1 was used, indicating a minimum sample size

of $n = 70$ (41). In order to improve the trustworthiness of the results, we chose to use a ratio of 15:1, for a minimum sample size of $n = 105$ in order to adequately power the analysis.

RESULTS

Response Rate

The survey link was distributed to 443 nurses in the PICU/NICU/CCCU. The distribution of respondents was 44.8% from PICU, 37.1% from NICU, and 17.5% from CCCU. Of the 158 surveys opened, 15 had no data thus were excluded, and 143 were fully or partially completed for a response rate of 32.3%. Surveys that had any complete instruments were used in the calculation of mean scores. Only surveys that had all instruments completed were used for the path model ($n = 117$). Surveys with missing data were analyzed for any commonalities. Distributions for years of experience, FTE, and highest degree achieved were all similar distribution to the fully completed survey sample. NICU incomplete surveys were slightly higher amongst the incomplete surveys, perhaps indicating a higher level of interruptions during completion. At baseline, NICU nurses carry a higher patient load (more 2:1 assignments) than the other two units.

Demographic Characteristics

The majority of respondents worked full time (>0.8 Full-time equivalent) and completed a bachelor's degree as their highest degree held. Our sample was fairly evenly distributed by nurses of different years of experience. The majority of our sample had also taken care of a COVID-19 positive patient (**Table 2**).

A summary of each of the mean scores for each of the tools used in the path analysis can be found in **Table 3**. The mean Emotional Exhaustion score was 24.6 with 40% scoring high level of Emotional Exhaustion. The mean Depersonalization score was 9.1 with 44.6% scoring a high level of Depersonalization. The mean Personal Accomplishment score is 32.8 with 47.7% scoring a high level of Personal Accomplishment (**Table 4**). The correlations between Work Engagement, Quality of Work-life, Workplace Incivility, Emotional Exhaustion, Depersonalization, and Personal Accomplishment were all significant (**Table 5**).

Objective 1: Results of Path Analysis

Path analysis of the tested model resulted in good fit, as demonstrated by a non-significant ($\chi^2(6) = 10.6$, $p = 0.1015$), Root mean squared error of approximation (RMSEA) = 0.08, Comparative Fit Index (CFI) = 0.90, Tucker Lewis Index (TLI) 0.93, and CD = 0.33. Our model accounts for 27% of the variance in Work Engagement scores, 44% of the variance in Emotional Exhaustion scores, 16% of the variance in Depersonalization scores, and 46% of the variance in Personal Accomplishment scores. The coefficient of determination for the entire model is low (CD = 0.33) which is common for social science based research (43). **Figure 2** presents the significant standardized coefficients from the path analysis.

TABLE 2 | Respondent characteristics ($n = 143$).

Respondent characteristics	*N* (%)
Unit	
PICU	64 (44.8%)
CCCU	53 (37.1%)
NICU	25 (17.5%)
Prefer not to respond	1 (0.7%)
Years of work experience	
0–5 years	45 (31.5%)
6–10 years	42 (29.4%)
>10 years	56 (39.2%)
Full time equivalents	
<0.5	3 (2.0%)
0.5–0.8	26 (18.2%)
>0.8	56 (39.2%)
Prefer not to respond	4 (2.8%)
Highest academic degree achieved	
Diploma	6 (4.2%)
Bachelor's Degree	120 (84%)
Master's Degree	17 (11.9%)
Cared for a COVID-19 patient under investigation or positive patient?	
Yes	124 (86.7%)
No	19 (13.3%)

Pediatric Intensive Care Unit (PICU), Cardiac Critical Care Unit (CCCU), Neonatal Intensive Care Unit (NICU).

TABLE 3 | Summary data of Work Environment and Work Engagement scores.

Variable	Obs.	Mean (SD)	Min.	Max.
Quality of work-life	130	4.83 (0.81)	2.44	6.44
Perceived organizational support	127	3.12 (0.82)	1	4.50
Work engagement	124	3.92 (0.82)	1.89	5.67
Workplace incivility	124	2.34 (0.80)	1	4.86

Work Outcomes

Emotional Exhaustion is strongly inversely associated with Work Engagement ($\beta = -0.570$, $p < 0.001$) and moderately inversely associated with Perceived Organizational Support ($\beta = -0.226$, $p = 0.003$). Depersonalization is moderately inversely associated with Work Engagement ($\beta = -0.290$, $p < 0.001$) and Perceived Organizational Support ($\beta = -0.200$, $p = 0.028$) Personal Accomplishment is strongly associated with Work Engagement (0.680, $p < 0.001$) and not statistically significantly associated with Perceived Organizational Support ($\beta = -0.034$, $p = 0.668$). The subcomponents of Burnout are weakly associated with each other (**Figure 2**).

Work Environment

Workplace Incivility is not associated with Work Engagement ($\beta = 0.090$, $p = 0.333$). Quality of Work-life is strongly positively associated with Work Engagement ($\beta = 0.580$, $p < 0.001$) Perceived Organizational Support is not associated with Work Engagement ($\beta = -0.053$, $p = 0.593$) (**Figure 2**).

TABLE 4 | Burnout subscale scores by category.

Emotional exhaustion (0–54)	*n* = 130	Depersonalization (0–30)	*n* = 130	Personal accomplishment (0–48)	*n* = 130
High (≥27)	52 (40%)	High (≥10)	58(44.6%)	High (0–33)	62 (47.7%)
Moderate (19–26)	49 (37.7%)	Moderate (6–9)	38 (29.2%)	Moderate (34–39)	50 (38.5%)
Low (0–18)	29 (22.3%)	Low (0–5)	34 (26.2%)	Low (≥40)	18 (14%)

TABLE 5 | Number of respondents, Pearson correlations, scale means and standard deviations *(n = 117)*.

Study variables	Mean (SD)	1	2	3	4	5	6	7
1. Quality of Work Life	4.7 (0.80)	1.0						
2. Perceived organizational support	3.2 (0.78)	0.57**	1.0					
3. Workplace incivility	2.32 (0.80)	−0.49**	0.3**	1.0				
4. Work engagement	3.92 (0.83)	0.53**	0.28**	−0.21*	1.0			
5. Burnout: emotional exhaustion	24.6 (9.49)	−0.52**	−0.37**	0.32**	−0.63**	1.0		
6. Burnout: depersonalization	9.10 (5.35)	−0.31**	−0.28**	0.19*	−0.33**	0.5**	1.0	
7. Burnout: personal accomplishment	33.03 (5.59)	0.49**	0.19*	−0.19*	0.65**	−0.38**	−0.27**	1.0

*$p < 0.5$, **$p < 0.01$.

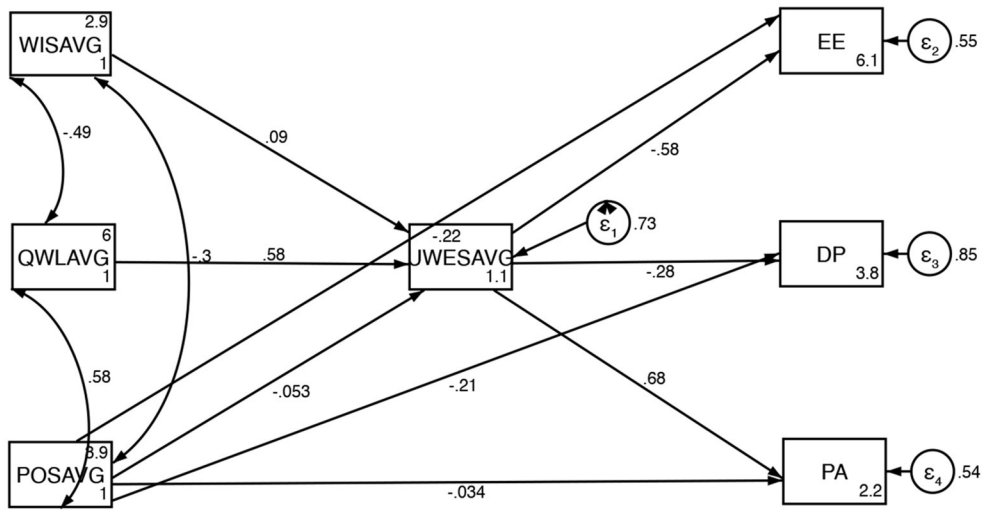

FIGURE 2 | Conceptualized framework with standard coefficients from path analysis. WISAVG, Workplace IncivilityScore Average; QWLAVG, Quality of Work-life Average; POSAVG, Perceived Organizational Support Average; UWESAVG, Utrecht Workplace Engagement Survey Average; EE, Emotional Exhaustion; DP, Depersonalization; PA, Personal Accomplishment.

Direct Effects of Variables on Burnout

Quality of Work-life had a statistically significant direct positive association with Work Engagement. Both Work Engagement and Perceived Organizational support had significant direct effect on Emotional Exhaustion and Depersonalization. Work Engagement had a significant direct effect on Personal Accomplishment (**Table 6**).

Mediating Role of Work Engagement

Quality of Work-life impacted each of the relationships between the organizational factors and all three subcomponents

TABLE 6 | Direct effects with standardized coefficients.

	Coefficient	Standard Error (S.E.)	*z*	*P* > |*z*|	Standardized coefficient (*β*)	Rank
Work engagement						
Workplace incivility	0.095	0.098	0.97	0.333	0.09	
Quality of work-life	0.608	0.111	5.48	0.000	**0.582***	**2**
Perceived organizational support	−0.055	0.103	−0.53	0.593	−0.053	
Emotional exhaustion						
Work engagement	−6.411	0.832	−7.71	0.000	**−0.571***	**3**
Workplace incivility	No path					
Quality of work-life	No path					
Perceived organizational support	−2.624	0.872	−3.01	0.003	**−0.226***	**5**
Depersonalization						
Work engagement	−1.845	0.576	−3.21	0.001	**−0.292***	**4**
Workplace incivility	No path					
Quality of work-life	No path					
Perceived organizational support	−1.329	0.603	−2.20	0.028	**−0.204***	
Personal accomplishment						
Work engagement	5.065	0.525	9.66	0.000	**0.683***	**1**
Workplace incivility	No path					
Quality of work-life	No path					
Perceived organizational support	−0.261	0.608	−0.43	0.668	−0.034	

Numbers that are bold also indicate top ranked numbers (just to make them stand out).

of Burnout through the mediation of Work Engagement. Quality of Work-life has a statistically significant indirect effect on Emotional Exhaustion through Work Engagement of $\beta = -0.332$, $z = -4.47$, $p < 0.001$. Quality of Work-life has a statistically significant indirect effect on Depersonalization through Work Engagement of $\beta = -0.170$, $z = -2.77$, $p = 0.006$. Quality of Work-life has a statistically significant indirect effect on Personal Accomplishment through Work Engagement of $\beta = 0.397$, $z = 4.73$ $p < 0.001$. Workplace Incivility and Perceived Organizational Support did not have any statistically significant indirect effect on the subcomponents of Burnout mediated by Work Engagement (**Table 7**).

Objective 2: Ranking of Variables

Based on the net value of the standardized coefficients representing the total effects, the strength of the relationships amongst the variables included in the path analysis rank in the following order from strongest to weakest: (1) Work Engagement and Personal Accomplishment, (2) Quality of Work-life and Work Engagement, (3) Work Engagement and Emotional Exhaustion, (4) Quality of Work-life and Personal Accomplishment, (5) Quality of Work-life and Emotional Exhaustion, and (6) Perceived Organizational Support and Emotional Exhaustion (**Table 8**).

DISCUSSION

We tested a model of the relationships amongst modifiable environmental and attitudinal factors and Burnout, and ranked the strength of the relationship in order to guide managers and leaders on how to better support nursing staff. Our model had good fit, supporting the hypothesized relationships between the work environment, work attitudes and work outcomes assessed.

Direct Effects of Work Environment on Burnout

We observed a significant positive relationship between Quality of Work-life and Work Engagement, a relationship that has been supported in previous work on registered nurses (44). By addressing elements of work-life such as physical needs (e.g., compensation, time off, health benefits) and esteem and actualization needs (e.g., relationships, skill development, and the realization of one's potential) organizations can directly impact Work Engagement. Not only does this improve the well-being of clinicians, but their enhanced well-being has also been shown to improve patient care as well as increase hospital revenues (45). This is also in congruence with the Job-Demands Resources model (JD-R) that states greater job demands (stress) and lack of resources (defined as factors similar to those of Quality of Work-life) results in greater Burnout and the inverse results in greater Work Engagement (46).

Additionally, we found that Work Engagement has significant negative/inverse relationships with all of the sub-components of Burnout; a result that is also consistent with the results presented by Hetzel-Riggin et al. in 2020 when evaluating nurses and nursing students (47). By improving Work Engagement, organizations can significantly influence the experience of Emotional Exhaustion,

TABLE 7 | Indirect effects with standardized coefficients.

	Coefficient	Standard Error (S.E.)	*z*	*P* > |*z*|	Standardized coefficient (*β*)	Rank
Work engagement						
Workplace incivility	No path					
Quality of work-life	No path					
Perceived organizational support	No path					
Emotional exhaustion						
Work engagement	No path					
Workplace incivility	−0.610	0.635	−0.96	0.336	−0.051	
Quality of work-life	−3.901	0.873	−4.47	0.000	**−0.333***	**2**
Perceived organizational support	0.353	0.663	0.53	0.594	0.030	
Depersonalization						
Work engagement	No path					
Workplace incivility	−0.176	0.189	−0.93	0.354	−0.026	
Quality of work-life	−1.122	0.406	−2.77	0.006	**−0.170***	**3**
Perceived organizational support	0.102	0.193	0.53	0.599	0.016	
personal accomplishment						
Work engagement	No path					
Workplace incivility	0.482	0.500	0.96	0.335	0.061	
Quality of work-life	3.082	0.651	4.73	0.000	**0.397***	**1**
Perceived organizational support	−0.279	0.524	−0.53	0.595	−0.036	

Numbers that are bold also indicate top ranked numbers (just to make them stand out).

TABLE 8 | Total effects with standardized coefficients.

	Coefficient	Standard error (S.E.)	*z*	*P* > |*z*|	Standardized coefficient (*β*)	Rank
Work engagement						
Workplace incivility	0.095	0.098	0.97	0.333	0.090	
Quality of work-life	0.608	0.111	5.48	0.000	**0.582***	**2**
Perceived organizational support	−0.0550	0.103	−0.53	0.593	−0.053	
Emotional exhaustion						
Work engagement	−6.411	0.832	−7.71	0.000	**−0.571***	**3**
Workplace incivility	−0.6102	0.635	−0.96	0.336	−0.051	
Quality of work-life	−3.901	0.872	−4.47	0.000	**−0.332***	**5**
Perceived organizational support	−2.271	1.101	−2.06	0.039	**−0.196***	**6**
Depersonalization						
Work engagement	−1.845	0.576	−3.21	0.001	−0.292	
Workplace incivility	−0.176	0.189	−0.93	0.354	−0.026	
Quality of work-life	−1.122	0.406	−2.77	0.006	−0.170	
Perceived organizational support	−1.227	0.644	−1.91	0.057	−0.188	
Personal accomplishment						
Work engagement	5.065	0.525	9.66	0.000	**0.683***	**1**
Workplace incivility	0.482	0.500	0.96	0.335	0.061	
Quality of work-life	3.082	0.651	4.73	0.000	**0.397***	**4**
Perceived organizational support	−0.540	0.855	−0.63	0.528	−0.070	

**denotes statistical significance at p < 0.001. Numbers that are bold also indicate top ranked numbers (just to make them stand out).*

Depersonalization, and Personal Accomplishment in their staff. However, directly modifying work attitudes, and more specifically Work Engagement, is challenging (14). The mediating role of Work Engagement between the work environment and Burnout that is identified in this study and explained below.

Mediating Role of Work Engagement

We identified Work Engagement as a significant mediator of the effect of Quality of Work-life on the subcomponents of Burnout. These results illuminate an important point: intervening on the work environment, without considering the mediating effects of Work Engagement, may have a limited effect on Burnout.

Berta et al.'s study on Health Support Workers supports our model by where features of the work environment are related to Burnout through work attitudes, such as Work Engagement (14). Addressing Quality of Work-life occurs at the interface of the work environment and individuals' role identities. Some strategies to address Quality of Work-life include decentralized organizational structures, improved team work, key stakeholder involvement in decision-making, performance feedback and role clarity, incentive plans, and promotion opportunities from within (48, 49). By improving work-life, there is also an opportunity to improve employees' overall life, through the concept of spillover (49). Sirgy et al. explain that spillover occurs when our reactions to work-life spill over into our non-work life, and note that the reverse can also occur (48). These could provide strategies for organizational leaders to influence pediatric nurse Burnout through Work Engagement with the modulation of the work environment.

Influencing Pediatric Critical Care Nurse Burnout

All three subcomponents of Burnout were influenced by Work Engagement. This means that hospital leadership can address Burnout *through* the influence of Quality of Work-life on Work Engagement.

Importantly, these results provide an evidence-based, directed strategy for administrators to target in a resource-limited system. The more engaged the nurse is with their work, the greater their sense of more Personal Accomplishment, and the less Emotional Exhaustion and feeling of Depersonalization (cynicism) they experience. This is supported by previous literature on the impact of Work Engagement on Burnout (14, 50). Work Engagement can mediate the relationship between the demands of the job and nurse Burnout (47, 51, 52). Nurse Work Engagement also impacts the patients' experience of care (53). Increased nurse Work Engagement has been shown to have positive effects on both personal and organizational outcomes. To be able to increase nurses' engagement with their patients and families we must think about possible interventions in the same light. Highly engaged nurses are essential for ethical, safe, and comprehensive care (34, 50). As Work Engagement is a work attitude that is difficult to directly influence, addressing areas of the work environment are instrumental in improving Work Engagement and, subsequently, Burnout. Quality of Work-life is not only directly correlated with Work Engagement, it is influenced by an employee's satisfaction with how their needs are being met through the resources, outcomes and activities that are derived from their participation in work, indicating that improving these factors of the work environment will also have a positive impact on nurse Burnout (26).

This study illustrates the importance of the impact of the work environment on Work Engagement and, subsequently, Burnout. We are hopeful that this data, and studies like it, will reinforce the thinking that workplace interventions can contribute in a meaningful way to reducing nurse Burnout. Many current workplace well-being recommendations focus only on self-care for pediatric nurse Burnout—our findings highlight that this recommendation is incomplete, and there are ways leadership can adapt the work environment to also optimize well-being (54). More needs to be done at an organizational level to intervene on the factors that significantly impact pediatric nurse Burnout in the workplace, as demonstrated in this study.

Limitations

This is a single center study in a Western setting, thus local context and experience limits generalizability (55). This is a cross-sectional study with a modest response rate which limits causal and temporal inference. Nurses historically have fairly poor survey response rates (<60%) (56). The results are sufficient to provide targeted recommendations for interventions at this study site (57), and, by providing a detailed description of the study context, the findings aim to be reproducible and adaptable to other health care settings and populations such as other pediatric critical care units and even pediatric nurses as a whole. The data reflects nurses who chose to participate in the study and may be influenced by selection bias. Effort was made to recruit a sample that is representative of the critical care nursing population at SickKids through distribution to all eligible participants, however despite our best efforts, the sample is not identical to the actual sample distribution. There is also vulnerability to possible bias in the responses due to perceived social desirability, despite anonymity. Participants self-selected to participate in the study; this could have introduced bias in that those with the most extreme feelings may be over-represented.

Path analysis is an explanatory technique and thus is guided by known or hypothesized relationships from the literature. It is important to note that the primary limitation of path analysis is that it does not infer causality or directionality (58).

We acknowledge the impact of the COVID-19 global pandemic and, specifically, its impact on front line essential workers such as pediatric critical care nurses. Nurses, now more than ever, are experiencing the impacts of their work on their well-being; these results will be timely and readily implementable. Further research to confirm and explore these results with pediatric critical care nurses is needed to fully illuminate the conclusions and to design practical interventions to address Burnout. Phase 2 of this study will aim to address this component.

Theoretical Contributions

At this time, and to our knowledge, there are no previous studies that have considered all of the concepts explored here simultaneously, nor could we find previous studies that have ranked the correlation of work attitudes and work environment factors' contributions to pediatric nurse Burnout. Therefore, the findings of this study advance the understanding of the impacts of the work environment and work attitudes on the work outcome of Burnout in pediatric critical care nurses.

CONCLUSION

We found that, in this single center study of pediatric critical care nurses, Burnout levels were high. Pediatric critical care nurse Burnout was most impacted by Work Engagement and quality of work life. Work Engagement is a significant mediator between

the work environment and the subcomponents of Burnout. Future interventions for pediatric nurse Burnout by modifying work environment, particularly through the modulation of Work Engagement, have the potential to positively impact the well-being of nurses, and ultimately the care they provide to our most vulnerable patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Research Ethics Board at the Hospital for Sick Children in Toronto, Canada (REB #1000072502). It is also approved by the University of Toronto. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LB was involved in the study design, data collection, data analysis, data interpretation, and drafting and finalizing the manuscript. WB and KC were involved in data interpretation, and substantively revised the manuscript for important intellectual content. KW was involved in the study design, data interpretation, and substantively revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agree both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

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Cost Efficacy of Rapid Whole Genome Sequencing in the Pediatric Intensive Care Unit

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The diagnostic and clinical utility of rapid whole genome sequencing (rWGS) for critically ill children in the intensive care unit (ICU) has been substantiated by multiple studies, but comprehensive cost-effectiveness evaluation of rWGS in the ICU outside of the neonatal age group is lacking. In this study, we examined cost data retrospectively for a cohort of 38 children in a regional pediatric ICU (PICU) who received rWGS. We identified seven of 17 patients who received molecular diagnoses by rWGS and had resultant changes in clinical management with sufficient clarity to permit cost and quality adjusted life years (QALY) modeling. Cost of PICU care was estimated to be reduced by $184,846 and a total of 12.1 QALYs were gained among these seven patients. The total cost of rWGS for patients and families for the entire cohort (38 probands) was $239,400. Thus, the net cost of rWGS was $54,554, representing $4,509 per QALY gained. This quantitative, retrospective examination of healthcare utilization associated with rWGS-informed medicine interventions in the PICU revealed approximately one-third of a QALY gained per patient tested at a cost per QALY that was approximately one-tenth of that typically sought for cost-effective new medical interventions. This evidence suggests that performance of rWGS as a first-tier test in selected PICU children with diseases of unknown etiology is associated with acceptable cost-per-QALY gained.

Keywords: genomic sequencing, rapid whole genome sequencing, pediatric intensive care, critical care, cost analysis, health economics, quality adjusted life year (QALY)

INTRODUCTION

Rapid whole genomic sequencing (rWGS) is transforming the diagnosis of single locus genetic disease among inpatient children. Recent technological advances enable return of results in less than one day, which enables timely provision of optimal care broadly for critically ill patients, effecting immediate changes in the trajectory of their clinical management (1–5). Mounting evidence supports the diagnostic and clinical utility of rWGS and was further substantiated by a

recent meta-analysis (6). Though earlier studies were focused primarily on infants in the neonatal intensive care unit (NICU), recent studies examining children outside of the neonatal period in the pediatric intensive care unit (PICU) have yielded similar diagnostic and clinical utility rates (5, 7, 8). Our group recently published a retrospective cohort study of 38 critically ill children in the PICU and found that rWGS resulted in a molecular diagnosis in 17 of 38 children (45%) (5). Seventy-six percent of diagnoses affected clinical management of the patient (5).

Despite increasingly clear-cut clinical evidence supporting use of rWGS, several barriers have precluded its widespread implementation. One of the most significant is the ongoing need for prior authorization for reimbursement. To achieve rWGS coverage policy determinations, payors frequently raise concern related to the associated cost. To buttress the proposition that timely diagnosis may decrease overall costs by optimizing clinical management, several studies have recently demonstrated cost-effectiveness for early utilization of rWGS or rapid whole exome sequencing (rWES) compared to traditional diagnostic investigations (9–12). In 2018, Stark et al. estimated the cost savings in a group of 21 critically ill children who received a diagnosis by rWES to be AU$543,178 (US$424,101), due to avoidance of planned tests and procedures and reduced length of stay (13). Schofield et al. expanded the cost analysis of a cohort of 80 infants in Australia to include increased projected quality life-years (QALYs) attributable to early molecular diagnosis as well as the economic effects of cascade testing in first-degree relatives (14). Each of these models resulted in incremental cost savings, lending further credence to the assertion that early deployment of rWGS in suspected single locus genetic disorders is increasingly cost-effective (14). Though compelling, the aforementioned precision medicine health economics analyses were performed outside of the United States, specifically in single-payer systems such as Australia (15) which limits its applicability to the complex and fractured United States health care system (12, 14–17).

Recent analyses of critically ill infants diagnosed by rWGS have found associated reductions in hospital length of stay and significant net cost savings (4, 9, 17). However, in nearly all cases, the infants studied were from the NICU (4, 9, 17). Though these studies demonstrated the cost-effectiveness of genomic sequencing for acutely ill infants, a fiscal examination exclusive to the PICU (where the average age is much older) has not been done.

Additionally, only a modest number of groups have endeavored to include QALYs as the outcome measure in their economic analyses, as recommended by major health technology assessment agencies when performing a cost-utility analysis (4, 14, 18, 19). The QALY is the preferred metric because it combines two different benefits attributed to a particular intervention- longevity and quality of life- into a single number that can be compared between alternative interventions (20). The monetary value of a QALY (cost per QALY) is a marker of value used to establish the comparative value of different healthcare interventions. A QALY is used to optimally direct resources (21–23). Historically, in the US the QALY benchmark for a clinical intervention that is worth the investment has been $50,000, though it has not been adjusted for inflation and suggestions have been made recently that this number should be increased (22, 24). Thus, inclusion of QALYs is imperative to any cost-utility analysis because health outcomes and improvement of said outcomes is arguably the driving goal behind the allocation of limited healthcare resources.

In a world of finite health care resources, studies are urgently needed to determine whether rWGS in the PICU setting is an efficient use of limited health care resources, and thereby advise policy development and resource allocation. We endeavored to measure the financial and clinical impact of rWGS on acutely ill children using established measures of comparative effectiveness.

RESULTS

Study Population

This was an economic analysis of a previously published cohort of critically ill children who received rWGS. The patients' clinical characteristics have been previously described (5). Briefly, this cohort included 38 children ranging in age from 4 months to 17 years (mean 5.73 years) (5). Of the 38 study participants, 17 received a molecular diagnosis (45%) and 13 of the 17 (76%) had an associated change in clinical management (5). Aside from the increased costs of diagnostic testing, two patients (6180 and 6207) were identified to have an increased cost of care attributable to rWGS testing (related to additional intravenous immunoglobulin administration and earlier initiation of Factor XIII replacement). Detailed cost and QALY modeling were performed for eight of the 13 patients who had a change in clinical management (**Table 1**). Quantitative modeling was not possible in the other five patients with changes in management following rWGS-based diagnoses (**Supplementary Table 1**). None of these five cases were thought to likely have a net increase in the estimated cost of care. They included patients 6031, 6118, and 7002 in whom there was a lack of substantial literature to precisely predict the morbidity risk avoided by the intervention, and patients 6183 and 7039 for whom there was insufficient documentation to substantiate specific clinical management changes that ensued following palliative care consultation.

Cases Modeled (Reached Delphi Consensus)

A Delphi consensus was reached in 7 of 8 subjects receiving a molecular diagnosis resulting in a previously reported clinical management change (**Table 1**). Detailed counterfactual trajectories and the questions posed (as presented to the Delphi panelists) are available in **Supplementary Material**. The seven counterfactuals to reach consensus are briefly described herein. For the eighth patient, 6052, who was diagnosed with a homozygous recessive variant in *TANGO2* (OMIM#616878; Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration) the Delphi panel failed to reach consensus on whether a molecular diagnosis likely reduced the length of hospital stay for a metabolic crisis.

TABLE 1 | Precision medicine interventions in eight of 13 patients who received molecular diagnoses and had resultant changes in clinical care.

Patient	Gene	Diagnosis name	Intervention modeled	Delphi panel consensus (Y/N)	Cost savings/ costs incurred	QALY savings
6007	*PCDH19*	Early infantile epileptic encephalopathy	Pulse steroids instead of ICU transfer for midazolam infusion	Y	$9,795	-
6052	*TANGO2*	Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN)	Carries letter describing diagnosis/treatment recommendations. Subsequent acute encephalopathic episode improved secondary to recommendations	N	n/a	n/a
6147	*TRNT1*	Sideroblastic anemia with B cell immunodeficiency, periodic fevers, and developmental delay (SIFD)	Change in family's goals of care avoided one hospitalization, skin biopsy, and EGD/intestinal biopsies	Y	$74,556	-
6153	*AIRE*	Autoimmune polyendocrinopathy syndrome, type I	Vaccination for encapsulated organisms decreased risk of mortality	Y	-	0.12
6159	*COL4A4*	Thin basement membrane nephropathy/ Alport syndrome	Avoided a renal biopsy	Y	$8,108	-
6180	*BTK*	Agammaglobulinemia, X-linked	Received 6 additional doses of IVIG	Y	-$9,856 (incurred cost)	-
6193	*NALCN*	Congenital contractures of the limbs and face, hypotonia, developmental delay (CLIFAHDD)	Transitioned to home care with non-invasive positive pressure ventilation on hospice instead of remaining in hospital	Y	$134,538	-
6207	*F13A1*	Factor XIIIA deficiency	Decreased risk of repeat CNS bleed and associated mortality and neurologic complication by initiating prophylactic Factor XIII replacement	Y	-$32,295 (incurred cost)	11.98
Total:					$184,846	12.1

ICU, intensive care unit; EGD, esophagogastroduodenoscopy; IVIG, intravenous immunoglobulin; CNS, central nervous system.

Cases With Cost Savings and/or QALY Savings

For Patient 6007, rWGS identified a deletion in *PCHD19* (OMIM#300088; Developmental and epileptic encephalopathy 9) resulting in pulse dose methylprednisolone for refractory seizures and avoidance of PICU care for a midazolam infusion (**Table 1**). For Patient 6147, diagnosis of homozygous variants in *TRNT1* (OMIM#616084; Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay) led to palliative care consultation and a change in 'code status' to 'Allow Natural Death'. The family chose to decline diagnostic procedures and an admission for treatment of sepsis, in line with their shifted goals of care. Patient 6153 was diagnosed with compound heterozygous variants in *AIRE* (OMIM#240300; Autoimmune polyendocrinopathy syndrome, type I) and was subsequently advised to receive 23-valent pneumococcal and meningococcal vaccination due to risk of development of functional asplenism, decreasing her long-term risk of morbidity and mortality due to infection with these encapsulated organisms. A renal biopsy had been recommended for patient 6159 during her ICU admission as part of her diagnostic workup for acute renal failure, but once rWGS revealed a likely pathogenic variant in *COL4A4*, associated with Alport syndrome/thin basement membrane nephropathy (OMIM#141200; thin-basement-membrane nephropathy), the nephrologist canceled plans for the biopsy. Though *COL4A4* is listed on commercial gene panels for nephrotic syndrome, the turnaround time is 4 weeks and results would not have returned prior to the planned biopsy. Patient 6193 was admitted for respiratory failure and rWGS revealed a *de novo*, likely pathogenic variant in *NALCN* (OMIM#616266; Congenital contractures of the limbs and face, hypotonia, and developmental delay), which resulted in a palliative care consult and facilitated the transition to home non-invasive positive pressure ventilation (NPPV), as opposed to ongoing hospitalization while awaiting symptom resolution.

Cases With Incurred Costs

For Patient 6180, admitted to the PICU for pseudomonal septic shock, the rWGS diagnosis of a *de novo*, pathogenic variant in *BTK* (OMIM#300755; Agammaglobulinemia, X-linked 1) led to administration of additional doses of intravenous immunoglobulin (IVIG) (**Table 1**). Costs associated with the extra IVIG administration were considered as costs incurred as a result of the genomic diagnosis. Cost savings of preventing further disease morbidity from delayed diagnosis of primary immunodeficiency and unmitigated sepsis were not calculated. Patient 6207 was an 8-month-old who presented with right arm paralysis and was found to have a large intraparenchymal hematoma. rWGS identified homozygous variants in *F13A1* (OMIM#613225; Factor XIIIA deficiency), and he was immediately started on prophylaxis with recombinant coagulation FXIII A-subunit, decreasing his risk for another central nervous system (CNS) bleed and the associated potential

neurologic complications and mortality. Costs associated with the earlier administration for Factor XIII were considered as costs incurred as a result of the genomic diagnosis.

Impact of rWGS-Associated Precision Medicine on Healthcare Utilization

The total cost for clinical investigations, interventions, procedures, medications, and inpatient room stays, as well as QALYs, when applicable, are presented in **Table 1** for the seven patients and Delphi questions that reached consensus. Estimated cumulative savings due to rWGS were $184,846. Over 70% of estimated savings derived from reduced or avoided hospital length of stay. The remainder was due to avoided professional fees and major procedures (**Table 1**). The estimated charge for each avoided or incurred intervention can be found in **Supplementary Table 2**.

QALY Modeling

QALY modeling was performed and QALY gain was identified for the two patients with Delphi consensus. The total estimated benefit from rWGS in these two children was 12.1 QALYs saved (patients 6153 and 6207). The greatest benefit was in patient 6207, who was diagnosed with severe Factor XIII deficiency (11.98 QALYs saved). Without treatment, his risk of dying if he were to have a second central nervous system (CNS) bleed would be 12%, with the mean age of death being 1.5 ± 2 years (26–29). QALYs saved by avoiding this risk of death amounted to 9.08 (**Supplementary Table 3**). Additionally, of patients who survive a subsequent CNS bleed, 72.6% have neurologic complications (28). Prophylaxis with Factor XIII replacement resulted in a gain of 2.9 QALYs due to avoided neurologic disability (**Supplementary Table 3**).

Cost of rWGS

An estimated cost of $7,400 was applied per trio rWGS performed. This is an average of total costs from previous cases sequenced at Rady Children's Institute for Genomic Medicine (RCIGM) and includes the cost sequencing and interpretation. Total cost of rWGS for the entire cohort of 38 probands and their families was $239,400 (**Supplementary Table 4**).

Cost Effectiveness Analysis

Total cost savings for the seven patients that reached Delphi consensus and were modeled was $184,846. This included $156,575 in hospital cost savings (length of stay, avoided procedures) and $28,271 in avoided professional fees. To arrive at that total, we also subtracted incurred costs, specifically the cost of the additional administered doses of IVIG and associated physician fees for patient 6180 and the cost of earlier administration of Factor XIII replacement and associated professional fees for patient 6207 as a result of the molecular diagnoses. We compared the total costs of sequencing the cohort of 38 patients and their families with the costs saved in the seven cases modeled. Total cost of sequencing the patients and families was $239,400. Total cost savings were therefore negative $54,554, indicating a modest net financial loss (**Figure 1**). A total of 12.1 QALYs were gained in two of the seven patients modeled

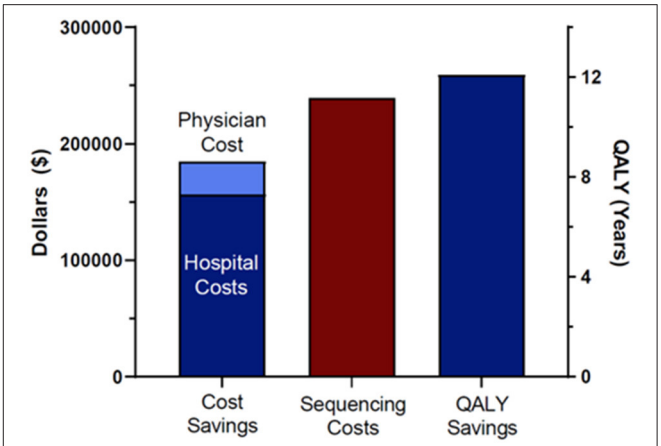

FIGURE 1 | Cost savings, sequencing costs, and QALY saving. Sequencing costs included all 38 patients in the original cohort and their family members.

(**Figure 1**). Most of these gains were due to the difference in quality of life attributed to a decreased risk of mortality and neurologic complication for patient 6207. The difference in total costs (cost savings minus costs of sequencing) for the 38 probands and families, as stated above, was $54,554 (net negative). Thus, we spent $54,554 to save 12.1 QALYs, a cost of $4,509 per QALY. Interventions with an ICER below $50,000 are considered high value (22–24, 30, 31).

DISCUSSION

Genetic disorders are a leading cause of mortality in the NICU and PICU, and affected children are disproportionally admitted to intensive care units (32–37). Rapid whole genomic sequencing for diagnosis of monogenic disorders is becoming increasingly applicable to critical care, as evidence continues to demonstrate that timely deployment of precision medicine leads to optimal clinical care (1, 2, 38–41). As with any new technologic advancement, the benefits of rWGS must be systematically evaluated while considering costs, societal acceptability, and willingness of funders to reimburse. In the United States especially, where healthcare costs are higher per capita than in any other nation (42), information regarding cost-effectiveness may be especially important for health system financiers and policymakers. Despite increasing evidence that sequencing improves clinical outcomes and more recent data demonstrating that it also reduces costs of care, routine application of rWGS in the ICU has remained a challenge, perhaps largely in part due to exceedingly rare reimbursement for testing by payers (1, 38, 43–47). Much of the cost-effectiveness data initially emerged from countries with universal health care and its application to a fragmented United States healthcare system could be complex (12, 16, 17, 48, 49). Farnaes et al. analyzed a cohort of six NICU patients in the United States diagnosed by rWGS and showed a reduction in hospital length of stay by 124 days resulting in a combined inpatient cost savings of $803,200 (approximately $19,000 per infant) (4). Subsequently, in 2018, the California

state legislature commissioned and funded Project Baby Bear to determine if the economic and clinical benefits of rWGS could be reproduced at five different sites across the state. In this quality improvement project, Dimmock et al. completed an examination of 184 prospectively-evaluated critically ill children under 1 year of age who received rWGS across five ICUs in California (9). A diagnostic rate of 40% in this cohort, coupled with a 32% change in clinical management for diagnosed patients, produced a net cost savings of between $500,000 and $1.2 million ($12,041 to $15,786 per infant sequenced, in USD) (9). While results for both of these investigations demonstrated that rWGS can be implemented cost-effectively for critically ill infants in the United States, the children in these two cohorts were less than one year old, leaving open the question of whether these findings translate to children in the PICU up to 18 years of age. In this study, we present the first cost utility analysis of rWGS in the PICU in the United States to our knowledge.

We were able to quantify the impact in healthcare utilization for seven of 13 (54%) previously published PICU cases in which a molecular diagnosis was made by rWGS and a resultant change in management occurred. rWGS was estimated to lead to a reduction in the cost of care for these seven patients by $184,846 after subtracting incurred clinical costs. These estimates are conservative and reflect the judgment of independent Delphi panels. Most of the cost savings was due to reductions in the length of hospital stay. Conclusive diagnoses enabled clinicians to prognosticate illness trajectory more confidently; in some cases (patients 6147 and 6193), this information empowered parents to shift their goals for clinical care to comfort rather than curative or prolonged care. After accounting for the cost of sequencing all 38 patients in the PICU cohort, as well as their families ($239,400), there was a net financial loss of $54,554. However, the consensus of the Delphi panels was that rWGS diagnoses also resulted in a gain of 12.1 QALYs, averaging a cost of $4,509 per QALY. Even the most conservative analysts regard an intervention with cost-per-QALY under $20,000 to be justifiable, while the most commonly used willingness-to-pay thresholds by funders are higher, ranging from $50,000-100,000 per QALY or higher (22–24, 30, 31). Therefore, despite a small net financial loss, when taking the QALY gains into account the analysis of this PICU cohort provides robust cost-effective evidence in favor of rWGS in PICUs.

There are several limitations in this study. Although also appearing to reduce rather than increase total costs, the impact of precision medicine could not be quantified in six of the 13 diagnosed patients with changes in management attributable to first line rWGS (five patients in whom changes could not be financially modeled (**Supplementary Table 1**) and one patient, 6052, in whom Delphi did not reach consensus). The number of patients modeled limits our generalizability. We also did not systematically obtain the costs of tests or other investigations that were avoided due to performing rWGS. In a related study, costs of avoided testing averaged $162-$378 per patient (9). Additionally, this is a small study with a heterogeneous population, limiting generalizability and introducing potential bias. Due to the rarity of these diseases and the novelty of some of the molecular diagnoses identified, we were unable to use historical matched controls and instead relied upon counterfactual trajectories that were confirmed (or refuted) by an independent Delphi panel. This approach (counterfactual trajectory with expert panel consensus) was chosen because we knew from experience that the children receiving rWGS diagnoses would have rare genetic diseases, making identification of matched historical controls unlikely (50, 51). Furthermore, insufficient information exists in the literature regarding natural history or routine clinical practice for many of these uncommon disorders (4, 38, 41). Some assumptions, supported by the available literature, were made about long-term patient outcomes. We also included incurred costs as a result of rWGS diagnosis (patients 6180 and 6207). These patients were diagnosed between 2016 and 2018 and we reported the costs at that time and have not adjusted for inflation. Our conservative approach may significantly underestimate the actual benefits accrued. The IRB for the original cohort study (5) did not allow for reporting of variants of uncertain significance (VUS), which possibly could have led to incurred costs if VUS results compelled clinicians to order additional testing. Generalization of this data to the broader United States context assumes that the costs for a given medication or procedure at Rady Children's Hospital are representative of other facilities. Clinical management may also vary based on institution, as will decisions to proceed with palliative care. The analysis assumed that average charges over the last three inpatient days of a patient's hospitalization were a fair substitute for the charges of an avoided inpatient day. Finally, this study is unlikely to be applicable outside of the US healthcare system, as costs of ICU treatment may vary widely between different countries.

The patients in our original cohort received rWGS early and quickly while in the PICU. Other studies have shown that early diagnosis results in a higher clinical benefit and cost savings (4, 9, 14, 52). It is likely that our cost utility analysis benefited from timely ascertainment of the underlying molecular diagnosis. Recently, faster turnaround times (TAT) (1, 2, 9) afford clinicians opportunities to avoid further investigations and affect management leading to cost savings and gained QALYs. If rWGS had been used later in the clinical course, these impactful windows for high-yield intervention may be missed. The current TAT in 2021 compared to this historical cohort also limits generalizability here (1, 2, 9). In sensitivity analyses of the Project Baby Bear study, Dimmock et al. found proportionately lower cost savings for TATs of 7 or 14 days compared to TATs of 3 days. The TAT for the seven patients who reached consensus and were analyzed in our cohort was 17.6 days (mean was 13.6 for the entire cohort of 38) (5). Thus, it is possible that if we had had more rapid TATs during the original study (2016-2018), potentially the cost savings could have been more substantial in this cohort. Making a genetic diagnosis has the potential to be beneficial at any point in life, but evidence suggests that identifying children early and quickly, prior to significant damage and definitive medical decision points, results in the greatest utility (9, 38).

Though this study focused particularly on cost analysis of rWGS in critically ill children, the economic factor is only one component of many that need to be considered when evaluating potential implementation of rWGS in the PICU.

Future studies should also continue to explore the societal impact of implementing rWGS, including from the perspectives of families whose children have received rWGS. Surveys of these families in one rWGS NICU study found that that although only 23% of infants received an rWGS diagnosis, 97% of parents reported that genomic testing was at least somewhat useful (53). It would be important to determine whether or not PICU families feel similarly. Furthermore, the PICU tends to be more clinically heterogeneous than the NICU, owing in part to the wider age range, thus it may be beneficial to parse out which subsets of PICU patients (perhaps by clinical presentation, body system affected, age, etc.) are most likely to receive rWGS diagnoses that lead to changes in management and even changes in clinical outcome.

This study supports the use of rWGS for critically ill children with suspected single locus genetic conditions from an economic (including cost-per-QALY) perspective. Future studies should evaluate the comparative effectiveness of children with lower acuity and/or more broad use of rWGS as recent studies in infants have demonstrated cost effectiveness when routinely sequencing all children admitted to NICU without clear etiology (9). With such testing now approved by some commercial insurers (44) and anticipated state sponsored programs (54, 55), studies should be performed to better understand the barriers to broader implementation.

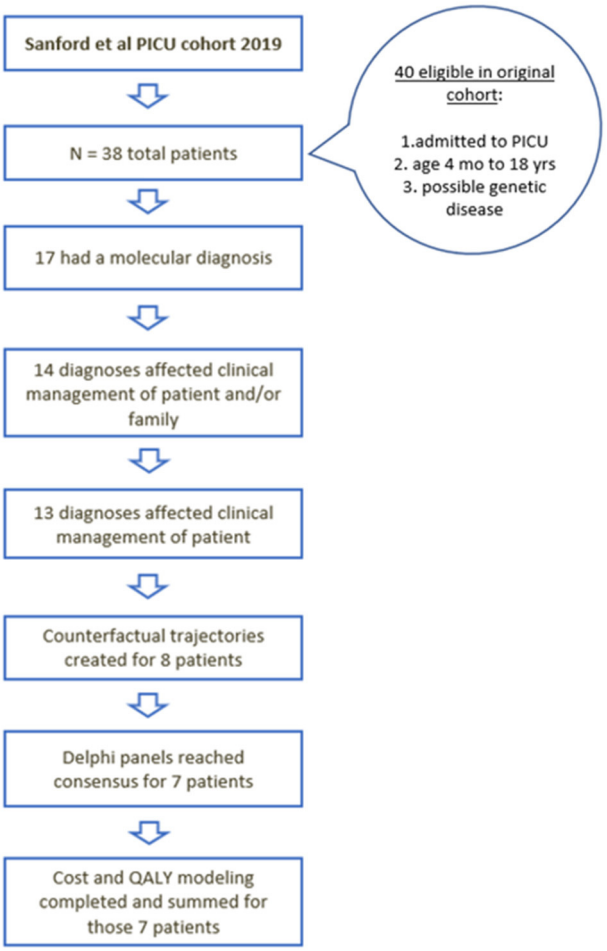

FIGURE 2 | Flow diagram of the children who were initially included, received diagnosis, had changes in management, and underwent cost utility analysis.

MATERIALS AND METHODS

Study Design

This study was approved by the institutional review board (IRB) at the University of California, San Diego. Retrospective comparison of healthcare utilization following molecular diagnosis by rapid genome sequencing was evaluated for a previously described cohort of inpatients in the PICU at Rady Children's Hospital in San Diego, California. Written informed consent was obtained from at least one parent or guardian. Details of the original investigation design, workflow, and inclusion/exclusion criteria have been previously published (5). The present analysis was performed utilizing this same cohort of patients to determine the financial impact of rWGS in critically ill children.

Selection of Affected Children

Characteristics of the initial cohort of 38 children in the PICU who received rWGS have been described elsewhere (5). Seventeen of the 38 children received a molecular diagnosis by rWGS and 13 had a change in their clinical management as a result of the genomic diagnosis (**Figure 2**) (5). Of those 13, detailed QALY and ongoing cost of care modeling was modeled for eight patients (**Table 1**). The economic effect of precision medicine was unable to be quantitatively determined in the remaining five children (**Supplementary Table 1**).

Sequencing and Bioinformatics

Analysis DNA was isolated, and 2x100 or 2x150 nucleotide rWGS was performed to ∼45-fold coverage as previously described (4). Sequence alignment to the reference human genome and nucleotide variant calling was by DRAGEN (Illumina Inc, San Diego, CA) (4). An automated copy number variation pipeline was implemented in July 2017, which identified CNVs with a combination of the tools Manta and CNVnator (56, 57). Prior to July 2017, any CNV diagnoses were made via manual inspection of raw genomic data. Variants were annotated, analyzed, and interpreted with Opal Clinical (Fabric Genomics, Oakland, CA). All causative SNVs were confirmed by Sanger sequencing and CNVs were confirmed by MLPA and qPCR or aCGH. No variants failed confirmation.

Phenotyping Information, Variant Filtering, and Variant Interpretation

Clinical features were manually extracted from electronic medical records (EMR) and translated into Human Phenotype Ontology (HPO) terms. The HPO terms were used in analysis in two ways: (1) To generate a patient-specific gene list (58–60) to provide an initial filtered list of variants; and (2) To prioritize variants by phenotypic overlap and potential variant consequence using VAAST and Phevor in the Opal

Clinical platform (61). Nucleotide variants were filtered by predicted consequence, an allele frequency <0.5% in the ExAC and gnomAD databases, and inheritance pattern if parental data was available. Variants in genes previously implicated in human disease were required for clinical reporting. CNVs were filtered by events overlapping the OMIM Morbid gene list (∼4,000 genes) and an internal frequency of <2%. Variants selected for full manual curation underwent gene curation to determine the strength of the known gene-disease relationship and the overlap with the patient's disease, and all variants were interpreted in accordance with the American College of Medical Genetics/Association of Molecular Pathology (ACMG/AMP) recommendations (62, 63). Per IRB protocol and initial guidance from the FDA, only pathogenic and likely pathogenic variants were allowed to be reported. Variants of uncertain significance could not be reported. We did not specifically evaluate for any of the 59 genes identified by the ACMG/AMP as reportable incidental findings (64). During the consent process, families were offered the choice to opt out of receiving medically actionable incidental findings that were inadvertently discovered.

Delphi Panel

We utilized a modified Delphi method (25) to establish consensus for counterfactual trajectories including the anticipated standard of care in the absence of rWGS. The Delphi panel consisted of ten pediatric critical care board certified physicians at ten independent institutions. It is difficult to identify matched controls for patients suffer from rare genetic diseases and more often than not there is not enough disorder-specific information in published literature to dictate concrete clinical management practices for many of these rare diseases (4, 9, 38, 43). Consequently, we used a counterfactual trajectory with a modified Delphi panel to establish consensus for the counterfactual trajectories as previously described (4, 5). An external panel of ten attending pediatric intensivists board-certified in pediatric critical care from ten unique institutions was assembled. Panelists were not currently funded by RCIGM and did not have financial ties to RCIGM. Panelists did receive an honorarium of $200 for survey completion. For the final patient, 6207, because the patient had a rare ($n = 133$ in the literature) and specific hematologic genetic disorder that had the potential to significantly impact his quality of life and life expectancy, we considered that it was more appropriate for pediatric hematologists to evaluate the counterfactual trajectory. Thus, a panel of five pediatric hematologists from three different institutions was gathered.

The panel developed consensus on counterfactual trajectories using the Delphi Method, a structured, systematic method that uses consensus expert opinion to make an educated decision (4, 5, 25). Within the counterfactuals, when the molecular diagnosis was considered in the differential diagnosis, we utilized available literature on time to diagnosis and turnaround times for clinically available testing to form a reasonable assessment for when correct testing (gene panel, single gene sequencing, etc.) would have been obtained if rWGS had not been available. For ultra-rare or atypical presentations of syndromes this was difficult to assess. Consensus methods such as the Delphi are increasingly used in medicine to develop guidelines for controversial subjects and to make consensus-based determinations when insufficient information is available (51). Expert panelists review the available knowledge and are surveyed for their responses to specific questions. For this study, the questions posed to the Delphi panel were developed by the authors with guidance from medical geneticists and health economics experts. The replies are scored to determine the variation in response; if consensus is not reached, the questions are returned to the panelists for a second round, with the mean of responses from the previous round visible to the panelists, but the panelists remain anonymous to one another and the study team. The process is halted after a predefined stop criterion is reached; in this case, the criterion was the completion of two rounds. The questions that did not reach consensus after two rounds were excluded from the analysis.

The Likert scale was used as the survey instrument. The Likert items available to select from where: strongly disagree, disagree, neutral (neither agree nor disagree), agree, strongly agree, or unable to comment. Panelists had the option to indicate that they did not have sufficient expertise to answer a question (unable to comment), and their score was then excluded for that question. The answers were given numerical scores: strongly disagree was scored as 1, disagree as 2, neutral as 3, agree as 4, and strongly agree as 5. The mean consensus score for each question was then calculated. Questions with a mean consensus score of >/= 4 (agree/strongly agree) or </=2 (disagree/strongly disagree) were considered to reach consensus. Questions that did not meet consensus during the first round were marked with the group's score and were returned to the panelists for a second round, so that each panelist was aware of the group mean when they responded to the questions in the second round. If the panelists failed to reach consensus on a question in the second round, those items were discarded. Likert scale scoring by individual panelists can be found in **Supplementary Table 5**. Only the replies that met consensus were included in cost modeling.

Cost Modeling

Healthcare utilization was modeled in eight of 13 patients in whom rWGS resulted in a change in clinical management that could be quantified by comparing actual healthcare utilization with that of a counterfactual diagnostic trajectory as has been previously described (4, 9). A modified Delphi method was used to establish consensus for counterfactual trajectories as described above (4, 5, 25). Data obtained included both cost savings and costs incurred due to molecular diagnosis. To determine the costs for these specific patients, billing personnel from Rady Children's Hospital extracted all associated clinical investigations, interventions, procedures, medications, and inpatient room costs from the medical records. Counterfactual resource utilization was estimated based on values available in the literature and institutional costs. Professional costs were estimated by multiplying the accrued hospital costs by a published ratio for professional services (65). Modeling and methods for estimating associated costs are further detailed in the **Supplementary Materials**.

QALY Modeling and Cost Utility Analysis

Quality of life (QOL) was modeled using QALYs. The formula used was QALY = QOL * number of years. QOL adjustments used for each case are shown in **Supplementary Table 3**. Estimates of QOL adjustments for mild, moderate, and severe neurological devastation and death, as well as life expectancy for each of these cases, were obtained from literature review (22, 26–29, 66–69). Life expectancy was modified based on gender. Cost per QALY is the preferred assessment tool used by payers to optimize resource allocation, with each QALY gained valued in the United States at ∼$50,000–$100,000 (21–24). Cost effectiveness of rapid GS was measured with the incremental cost effectiveness ratio (ICER). The ICER is the cost per incremental gain in quality adjusted life years.

Estimating Cost Savings From Reduced Length of Stay and Avoided Procedures

For patients with identified increases in length of stay or procedures we intended to capture the actual costs of these days or procedures. For patients with an anticipated change in the length of stay as determined by Delphi consensus, the average cost of the patients last 3 days of hospitalization without procedures were utilized to estimate the daily cost of hospitalization. For avoided procedural costs, one to three comparable cases were identified and included anesthesia, operating room, and supply charges.

DATA AVAILABILITY STATEMENT

The raw economic data supporting the conclusions of this article will be made available by the authors, without undue reservation. While no DNA sequence was generated as a part of this published work, all novel DNA sequence variants have been uploaded to ClinVar under our institutional identifier, Organization ID: 506081. For further details see **Supplementary Table 6**. All data associated with this study are present in the paper, **Supplementary Materials**, or are available at the Longitudinal Pediatric Data Resource under a data use agreement and subject to the limitations of the informed consent documents for each subject (Accession Number nbs000003.v1.p, https://nbstrn.org/tools/lpdr). Requests to access the datasets should be directed to the corresponding author (Erica Sanford Kobayashi).

ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) at the University of California, San Diego. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ES, NC, and DD: conceptualization. BW, BE, KP, EA, BB, CG, NR, JG, AD, EI, and CT: data curation. BW and WB: formal analysis and resources. SK: funding acquisition. LF, DD, SC, and BW: methodology. SK and CH: supervision. ES, DD, and NC: visualization. ES: writing—original draft. ES, NC, CH, SK, DD, BW, CT, AD, and SR: writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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BRIEF RESEARCH REPORT
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Human Trafficking ICD-10 Code Utilization in Pediatric Tertiary Care Centers Within the United States

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Background: Human trafficking is a global public health issue that affects pediatric patients widely. The International Labor Organization estimates children comprise approximately 25% of the identified trafficked persons globally, with domestic estimates including over 2000 children a year. Trafficked children experience a broad range of health consequences leading to interface with healthcare systems during their exploitation. In June 2018, *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) released diagnostic codes for human trafficking.

Objective: To use a large, multicenter database of US pediatric hospitalizations to describe the utilization of the ICD-10-CM codes related to child trafficking, as well as the demographic and clinical characteristics of these children.

Methods: This study was descriptive in nature. Encounters using data from the Pediatric Health Information System database (PHIS) with ICD-10-CM codes indicating trafficking from June 1, 2018 to March 1st, 2020 were included in the study cohort, with data collection continuing for 30 days after first hospital encounter, until March 31st, 2020. Patients 19 years old and younger were included. Condition-specific prevalence as well as demographic and clinical characteristics for patient encounters were analyzed. Study subjects were followed for 30 days after first hospital encounter to describe healthcare utilization patterns.

Results: During the study period, 0.005% ($n = 293$) of patient encounters in the PHIS database were identified as trafficked children. The children of our cohort were mostly female (90%), non-Hispanic Black (38%), and had public insurance (59%). Nearly two-thirds of patients ($n = 190$) had a documented mental health disorder at the initial encounter, with 32.1% classified as the principal diagnosis. Our cohort had a 30-day hospital inpatient, overnight observation, or emergency department readmission rate of 16% ($n = 48$).

Discussion: Our study demonstrates a low utilization of human trafficking ICD-10-CM codes in academic children's health centers, with code usage predominantly assigned to Non-Hispanic Black teenage girls. As comparison, in 2019 the National Human Trafficking Hotline identified 2,582 trafficked US children in a single year. These results

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suggest widespread under-recognition of child trafficking in health care settings, including the intensive care unit, in addition to racial and socioeconomic disparities amongst trafficked children.

Keywords: public health, pediatrics, child abuse, *International Classification of Diseases*, human trafficking

INTRODUCTION

Human trafficking—the use of force, fraud, or coercion to perform sex or labor acts—is a devastating public health problem leading to the exploitation of children (1). The International Labor Organization estimates that children comprise approximately 25% of the identified trafficked persons globally (1–3). The prevalence and incidence of human trafficking in the United States (U.S.) is unknown, and recent estimates are based on data largely from the National Human Trafficking Hotline and the Counter Trafficking Data Collaborative (4, 5). Trafficked individuals experience a broad range of health consequences—including physical trauma, malnutrition, communicable disease, and mental health disorders—and most trafficked individuals have interfaced with the healthcare system during their exploitation (1, 6–8). Therefore, health care providers play a vital role in identifying and aiding trafficked children (1, 7–10).

In June 2018, the U.S. Centers for Disease Control and Prevention adopted diagnostic codes classifying human trafficking in the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) (11, 12). The United States is the only country thus far to adopt diagnosis codes for human trafficking. From the creation of these codes, valuable data can now be collected to determine prevalence, define characteristics, and create strategies to aid children afflicted by human trafficking (10, 13). The objective of this study was to use a large, multicenter database of U.S. pediatric hospitalizations to describe the utilization of the newly adopted ICD-10-CM codes related to child human trafficking, and the demographic and clinical characteristics of these children. We hypothesized that use of these new ICD-10 codes would be low, reflecting both an under-recognition of the magnitude of this public health problem and limited awareness of the availability of coding among healthcare providers.

MATERIALS AND METHODS

Study Design and Data Source

This was a descriptive study of the Pediatric Health Information System (PHIS), an administrative discharge database inclusive of data from 49 academic children's hospitals accounting for nearly 15% of all pediatric hospitalizations in the US (14). PHIS contains patient-level data including demographics, admission and discharge dates, and clinical and resource utilization data at the emergency department (ED), inpatient, and observation level. The database is de-identified, and encrypted patient identifiers allow for tracking of study subjects across multiple hospitalizations. Database quality is assured jointly by Children's Hospital Association (Lenexa, KS), participating hospitals, and Truven Health Analytics (Ann Arbor, MI). The study was reviewed by the University Hospitals Institutional Review Board and exempt from ethical oversight (STUDY20201822), as this was an analysis of a de-identified administrative dataset. We used STROBE cross-sectional reporting guidelines (15).

Abbreviations: US, United States; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification;* PHIS, Pediatric Health Information System; ED, emergency department; APR-DRG, All Patient Refined Diagnosis Related Group; IQR, interquartile range; Q, Quarter.

Study Population

Children <19 years of age discharged from a PHIS hospital with ICD-10-CM codes indicating trafficking (Y076, Z62813, T7452, T7652, Z0481, Z9142, T7451, T7651, T7662, T74.62, Z04.82) from June 1, 2018 to March 1st, 2020 were included in the study cohort as index hospitalizations, with data collection continuing for 30 days after index hospitalization, until March 31st, 2020. Index hospitalization was defined as the first hospital encounter within the PHIS system during the study period. All children with an inpatient, observation, or ED level encounter at index hospitalization were included.

Study Procedures

This was a descriptive study. We collected patient demographics, neighborhood characteristics, and clinical characteristics at index hospitalization. Demographic data included age, sex, race and ethnicity, and insurance type. Race was defined as Non-Hispanic White, Non-Hispanic Black, Hispanic or Latino, or "other," which included Asian, Pacific Islander, Native American, and other/unknown. Insurance was categorized as private, public, or uninsured/other. Neighborhood characteristics, based on patient ZIP code, included estimated median household income and urban (dichotomized as yes or no) location. Collected clinical characteristics included presence of an infection diagnosis or mental health disorder diagnosis (both are based on a PHIS "flag"), All Patient Refined Diagnosis Related Group (APR-DRG) severity index—categorized as mild, moderate, severe, or extreme, need for admission to the pediatric intensive care unit, hospital length of stay, and hospital discharge disposition. Study subjects were followed for 30 days after index admission to describe healthcare utilization patterns, including healthcare encounter location and principle diagnoses at the repeat hospital encounter.

Statistical Analyses

Demographics, neighborhood characteristics, and clinical characteristics of the study subjects were described using medians with interquartile range [IQR] for continuous variables and frequency with percentages for categorical variables, as appropriate. Differences based on location of index hospital

TABLE 1 | Frequency of human trafficking ICD-10 codes utilized by healthcare providers during study period.

International Classification of Diseases (ICD)−10 codes		*N* (%) (*n* = 293)
Y076	Multiple perpetrators of maltreatment and neglect	99 (33.8)
Z62813	Personal history of forced labor or sexual exploitation in childhood	62 (21.2)
T7452	Child sexual exploitation, confirmed	60 (20.5)
T7652	Child sexual exploitation, suspected	50 (17.1)
Z0481	Encounter for examination and observation of victim following forced sexual exploitation	15 (5.1)
Z9142	Personal history of forced labor or sexual exploitation	4 (1.4)
T7451	Adult forced sexual exploitation—confirmed	1 (0.3)
T7651	Adult forced sexual exploitation—suspected	1 (0.3)
T7662	Child forced labor exploitation, suspected	1 (0.3)
T7462	Child forced labor exploitation, confirmed	0 (0)
Z0482	Encounter for examination and observation of victim following forced labor exploitation	0 (0)

encounter were described using the Wilcoxon rank-sum test or chi-square test/Fisher exact test. A *p*-value of less than 0.05 was considered as statistically significant. All analyses were conducted in SAS software, version 9.4 and R software, version 3.5.3.

RESULTS

During the 22-month study period, there were 6,366,691 total patients encounters in the PHIS database, of which 0.005% ($n = 293$) included an ICD-10-CM code for human trafficking. Of these 293 included encounters, 57% ($n = 167$) occurred in the ED. Frequency and descriptors of the ICD-10 codes during the study period are included in **Table 1**. The most common code utilized in the ED was Y07.6, "multiple perpetrators of maltreatment and neglect" (33.8%), while the most common code utilized among hospital encounters was Z62.813, "personal history of forced labor or sexual exploitation in childhood" (21.2%; **Table 1**). Ninety percent ($n = 264$) of included children were female (90.1%), with a median age of 15 years [IQR 13–16]. The majority ($n = 112$) identified as Non-Hispanic Black, with Non-Hispanic White identification as the second most common ($n = 83$). Nearly two-thirds of patients ($n = 190$) had a documented mental health disorder at the initial encounter, with 32.1% classified as the principal diagnosis. There were differences in insurance status, illness severity, illness characteristics, and discharge disposition between ED and hospital encounters (**Table 2**). Most providers utilizing human trafficking ICD-10-CM codes were emergency medicine physicians (42.7%), pediatricians (24.2%), and psychiatrists (7.8%; **Table 3**).

Nineteen percent ($n = 55$) of children had a healthcare visit at a PHIS hospital within 30 days of the initial encounter, with a 30-day hospital inpatient/observation or ED readmission rate of 16% ($n = 48$; **Table 2**). One-third of principal diagnoses at the 30-day re-encounter were categorized as child maltreatment including ICD-10 codes for sexual abuse, physical abuse and trafficking/exploitation (32.7%), followed by codes for mental health disorders (30.9%), and physical trauma (14.5%; **Table 4**).

DISCUSSION

Using a large multicenter dataset, we described the prevalence, demographics, and clinical characteristics of trafficked children seeking healthcare at 49 US academic children's hospitals based on the utilization of newly adopted ICD-10-CM codes. ICD-10-CM codes were used as a surrogate in this study to designate awareness of human trafficking amongst pediatric patients. We had several important findings. First, we demonstrated a low use of trafficking ICD-10-CM codes among children receiving care in the ED or admitted to the hospital. Second, mental health disorders were common in this cohort, and third, most identified trafficked children were Non-Hispanic Black adolescent girls from urban neighborhoods primarily coded for sex trafficking. Our findings suggest there is an urgent need to educate healthcare providers on the importance of screening and identifying trafficked children.

During the 22-month study period, only 0.005% of patient encounters in the PHIS database were identified as trafficked children. In 2019, the National Human Trafficking Hotline identified 2,582 trafficked U.S. children (4). The true prevalence of trafficking among U.S. children is unknown. Multiple organizations, including the U.S. Department of State, acknowledge current estimates of human trafficking are inaccurate because it is an elusive crime and identifying victims is challenging (16–18). Similar to previous studies showing underuse of ICD codes among physically abused children, the utilization of ICD-10-CM trafficking codes in our study likely underrepresents the actual number of trafficked children in the PHIS database (19). Healthcare providers are more likely to be aware that trafficking exists, but not equipped to recognize signs of trafficking (20, 21). Additionally, provider perception of trafficked individuals could bias who is being screened for trafficking (21). Our study found higher use of ICD-10-CM codes among pediatric ED and psychiatry subspecialty providers. This likely reflects an increased awareness related to the known association between trafficking and acute exacerbations of underlying psychiatric conditions requiring immediate medical attention (6, 7, 22). Nevertheless, trafficked individuals may present to any clinical setting (23). A recent case series of trafficked pediatric patients admitted to the intensive care unit concluded the severity of their illness was potentially exacerbated due to poor access to medical care (23). Provider bias and the elusive nature of human trafficking emphasize that a high index of suspicion should be maintained for identification of trafficking, indicating the need for universal education and training (7, 9).

TABLE 2 | Descriptive statistics of pediatric trafficking encounters based on encounter location, 2018 Q3 to 2019 Q3.

	Overall encounters (*n* = 293)	ED encounters (*n* = 167)	Hospital encounters (*n* = 126)	*p*-value
ICD-10 code[a], *n (%)*				<0.001
Y07.6	99 (33.8)	78 (46.7)	21 (16.7)	
Z62.813	62 (21.2)	13 (7.8)	49 (38.9)	
T74.52	60 (20.5)	39 (23.4)	21 (16.7)	
T76.52	50 (17.1)	21 (12.6)	29 (23.0)	
Z04.81	15 (5.1)	14 (8.4)	1 (0.8)	
Others	7 (2.4)	2 (1.2)	5 (4.0)	
Age, years	15 [13–16]	15 [13–16]	15 [14–16]	0.126
Female, *n* (%)	264 (90.1)	146 (87.4)	118 (70.7)	0.117
Race/Ethnicity[b], *n* (%)				0.993
Non-hispanic black	112 (38.2)	65 (38.9)	47 (37.3)	
Non-hispanic white	83 (28.3)	47 (28.1)	36 (28.6)	
Hispanic or latino	67 (22.9)	38 (22.8)	29 (23.0)	
Other	20 (6.8)	11 (6.6)	9 (7.1)	
Estimated household income[c], *$US*	37,720 [29,030–48,556]	36,189 [29,293–48,699]	41,590 [30,127–49,437]	0.115
Urban (%)[d], *n* (%)	258 (88.1)	148 (88.6)	110 (87.3)	0.942
Insurance, *n* (%)				0.002
Public	173 (59.0)	86 (51.5)	87 (69.0)	
Private	63 (21.5)	39 (23.4)	24 (19.0)	
Uninsured	25 (8.5)	22 (13.2)	3 (2.4)	
Others	32 (10.9)	20 (12.0)	12 (9.5)	
Illness severity, *n* (%)				<0.001
Minor	113 (38.6)	95 (56.9)	10 (7.9)	
Moderate	116 (44.1)	56 (33.5)	46 (36.5)	
Major	56 (19.1)	14 (8.4)	30 (23.8)	
Extreme	7 (2.4)	1 (0.6)	2 (1.6)	
Infection diagnosis, *n (%)*	63 (21.5)	16 (9.6)	47 (37.3)	<0.001
Mental health disorder diagnosis, *n* (%)	190 (64.8)	76 (45.5)	114 (90.5)	<0.001
Discharge disposition[e], *n* (%)				<0.001
Routine	218 (74.4)	148 (88.6)	70 (55.6)	
Inpatient psychiatric unit	35 (11.9)	10 (6.0)	25 (19.8)	
Another health care facility	30 (10.2)	5 (3.0)	25 (19.8)	
Law enforcement	4 (1.4)	3 (1.8)	1 (0.8)	
Died	1 (0.3)	0 (0.0)	1 (0.8)	
30-day repeat patient encounter, *n* (%)	55 (18.7)	18 (10.7)	30 (23.8)	0.077

Q, quarter; ED, emergency department; ICD-10, International Classification of Diseases, Tenth Revision; US, United States; data presented as n (%) or median [interquartile range], as appropriate.[#a]ICD-10 codes include: Y07.6, multiple perpetrators of maltreatment or neglect; Z62.813, personal history of forced labor of sexual exploitation in childhood; T74.52, child sexual exploitation—confirmed; T76.52, child sexual exploitation—suspected; Z04.81, encounter for examination and observation of victim following forced sexual exploitation; "other" includes T74.51, adult forced sexual exploitation—confirmed (n = 1); T76.51, adult forced sexual exploitation—suspected (n = 1); T76.62, child forced labor exploitation, suspected (n = 1); Z91.42, personal history of forced labor or sexual exploitation (n = 4); [b]8 encounters with missing race data; [c]11 encounters with missing income data; [d]11 encounters with missing urban data; [e]5 patients with unknown disposition data.

Confidentiality concerns for trafficked children likely contributes to low documentation and low diagnosis code utilization. ICD-10-CM diagnoses codes may be viewable on printed discharge materials, electronic patient portals, insurance summaries, and in the electronic health record (10, 11). Safety concerns that may discourage the use of these codes include the risk of health information being viewed by the patient's trafficker, potential legal implications such as in immigration proceedings, and a risk of discrimination toward trafficked persons (10, 11). Because of the importance of reliable documentation, hospitals caring for at-risk children should preemptively develop confidential systems to safely identify these patients (11).

Trafficked children may also be reluctant to seek healthcare. In a systematic review, three major sub-groups of themes were identified and noted to be significant barriers to healthcare utilization for trafficked children (24). Some of the barriers included trafficker control, physical confinement, lack of trust in

TABLE 3 | Physician subspecialty and utilization of ICD-10 codes.

	***N* (%) (*n* =293)**
Pediatric sub-specialties	
Emergency medicine	125 (42.7)
General pediatrics	71 (24.2)
Psychiatry	23 (7.8)
Hospital medicine	13 (4.4)
Adolescent medicine	5 (1.7)
Surgery–pediatric/general	3 (1.0)
Critical care medicine	2 (0.7)
Endocrinology	2 (0.7)
Infectious disease	2 (0.7)
Sports medicine	2 (0.7)
Child Abuse	1 (0.3)
Other sub-specialties	
Obstetrics-gynecology	3 (1.0)
Not otherwise specified	33 (11.9)
Anesthesiology	3 (1.0)

TABLE 4 | Principal ICD-10 diagnoses for healthcare visits within 30 days of initial encounter[a].

Principal ICD-10 diagnosis codes	**Frequency (%) (*N* = 55)**
Child abuse or trafficking (exploitation)	18 (32.7)
→ T74.22—child sexual abuse confirmed initial	
→ T76.52—child sexual exploitation suspected initial	
→ T74.52—child sexual exploitation confirmed initial	
→ Z04.81—encounter for exam & observation of victim with forced sex exploitation	
→ T74.12—child physical abuse confirmed initial	
→ T76.12—child physical abuse suspected initial	
→ T76.22—child sexual abuse suspected initial	
→ T76.52—child sexual exploitation suspected sequela	
Mental health disorders	17 (30.9)
→ R45.851—suicidal ideations	
→ T43.222—poisoning by anti-depressant, intentional self-harm initial	
→ T43.632—poison methylphenidate intentional self-harm initial	
→ T46.5X2—poison by anti-hypertension drugs for self-harm initial	
→ T50.902—poison drug, substance not specified self-harm initial	
→ F31.2—bipolar disorder current episode manic severe with psych features	
→ F32.89—depressive episodes	
→ F33.2—major depressive disorder recurrent severe without psychotic features	
→ F43.10—post-traumatic stress disorder	
→ F32.9—major depressive disorder single episode	
Physical trauma (excluding abuse)	8 (14.5)
→ S09.90X—injury head, not specified	
→ S02.2XX—fracture nasal bones initial closed fracture	
→ S02.602—open fracture of left mandible	
→ S06.2X9—diffuse traumatic brain injury with loss of consciousness	
→ S06.5X9—traumatic subdural hemorrhage with loss of consciousness	
→ S09.93X—injury face, not specified	
→ R41.89—symptoms and signs involving cognitive function and awareness	
Reproductive health	3 (5.5)
→ A56.8—sexually transmitted chlamydial infect sites	
→ N89.8 - non-inflammatory disorders vagina	
→ O42.913—preterm premature rupture of membranes onset labor	
Miscellaneous	9 (16.4)
→ B33.8—viral diseases	
→ E10.10—type 1 diabetes mellitus with ketoacidosis, but without coma	
→ E11.65—type 2 diabetes mellitus with hyperglycemia	
→ G40.909—not specified epilepsy without status epilepticus	
→ J81.1—chronic pulmonary edema	
→ K80.20—calculus gallbladder without cholecystitis or obstruction	
→ L02.414—cutaneous abscess left upper limb	
→ R04.0—epistaxis	
→ T18.9XX—foreign body alimentary tract, not specified	

ICD-10, International Classification of Diseases, Tenth Revision; data presented as n (%) as appropriate. [a]Seven of the 55 readmission encounters were clinic visits, 30 were inpatient or observation encounters, and 18 were emergency department encounters.

healthcare providers, concerns about confidentiality, decreased knowledge of the healthcare system, and emotional reluctance (24). Cost and long appointment wait times were also cited (24). Another systematic review also reported legal repercussions, perception of biased care, trafficker control, or lack of interest in engagement with healthcare for various reasons facilitated as barriers to seeking healthcare (25). These barriers indicate that a decrease in ICD-10 codes utilization could also be due to decreased presentation of trafficked children to healthcare systems. The provision of trauma informed, patient centered care could reduce many of these survivor barriers to seeking healthcare (24, 26).

Psychiatric illness was common in our cohort of children. Nearly two-thirds received a mental health disorder diagnosis at the initial hospital visit, and nearly one-third of the principal diagnoses were mental health-related among those children seen within 30 days of the index hospitalization. Our data is consistent with prior literature demonstrating a high prevalence of psychiatric disease among trafficked youth both domestically and internationally (6, 8, 22, 27, 28). Two U.S. based studies found high rates of mental health disorders, including posttraumatic stress disorder, depression, and substance abuse amongst trafficked youth (8, 28). Internationally, a study of 207 trafficked women and adolescent girls in Europe reported 56% of the participants had symptoms consistent with posttraumatic stress disorder and depression (6, 27). Similar results were seen in Southeast Asia's Mekong region, with high rates of depression and suicide amongst trafficked teenage girls (27). Increase in the provision of mental health support and trauma informed care can reduce the impact of psychiatric illness in this vulnerable population.

Trafficked children are at high risk of re-exploitation, especially by family members (5). Most patients in our study were discharged home leading to potential re-exploitation. Of the study participants, 19% sought medical care within 30 days of the initial encounter with abuse-related, trafficking-related,

and mental health-related principal diagnoses being the most common. The readmission diagnoses emphasize the cycle of re-exploitation, indicating that further work is necessary to reduce re-traumatization and develop safe discharge plans for these children.

Most children in our cohort were Non-Hispanic Black teenage girls living in urban, low-income neighborhoods. While human trafficking affects children across race and socioeconomic lines, existing literature and data reports have suggested that human trafficking disproportionately affects racial and ethnic minorities, consistent with our results (28–31). A single center retrospective study at a pediatric hospital of 63 patients reported that 98% of their participants identified as female and 54% identified as Non-Hispanic Black (30). Another multi-center study of 84 all female patients reported 56% as Non-Hispanic Black (28). However, there are few studies from larger national cohorts that comprehensively examine the racial and ethnic profile of trafficked youth, and the disparities associated (31). While, our study draws from a national sample, it is still most likely an underestimation of child human trafficking for the aforementioned reasons, demonstrating a research gap in the field requiring further exploration of sociodemographic characteristics of trafficked youth.

Identified codes in our study were utilized almost exclusively for sexual exploitation, suggesting limited awareness of labor trafficking. In one year, the National Human Trafficking Hotline identified over 1,300 cases of labor trafficking, including 115 cases of child labor, a number that is again likely a vast underestimation of the problem, but still higher than the one labor exploitation code utilized in this study cohort (4, 32).

This study has limitations. First, this study included children's hospitals that participate in PHIS, a database limited to tertiary and quaternary care pediatric hospitals, affecting the generalizability of our results; ICD-10-CM code utilization for trafficked children evaluated at smaller, rural, or non-academic centers is not described by this study. Second, the human trafficking ICD-10-CM codes have only recently become available, and there may be a natural increase in code usage as awareness of their availability increases amongst providers. Lastly, the codes could be underutilized due to the provider hesitancies described above, including concerns for patient safety.

CONCLUSION

This large multicenter descriptive study demonstrated a low utilization of human trafficking ICD-10-CM codes by health care providers in academic children's health centers, and the trafficking codes that were used were predominantly assigned to Non-Hispanic Black teenage girls. While prospective studies are necessary to validate our findings, these results suggest there is widespread under-recognition of child trafficking in health care settings, in addition to racial and socioeconomic disparities amongst trafficked children. Until awareness improves children will go unaided, further exacerbating an already devastating public health problem. Health care institutions should act immediately to systematize provider education, patient screening and identification, and implement safe, accessible, trauma-informed interventions for trafficked children.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AG and PP conceptualized the manuscript, conducted a literature search, and drafted the initial manuscript. SM conducted statistical analysis on the data. KS conceptualized the manuscript, provided guidance on data analysis, and reviewed and revised the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Exploring Pediatric Nurses' Perspectives on Their Work Environment, Work Attitudes, and Experience of Burnout: What Really Matters?

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Background: Pediatric nurses care for some of the most vulnerable patients in our healthcare system and are vulnerable to the impact of the stress of their work on their well-being. Burnout is a potential response to chronic interpersonal stressors and a negative work outcome linked to personal and professional consequences. A thorough understanding of the experience and factors associated with burnout in this population is an important part of developing interventions to mitigate or prevent this workplace outcome. Therefore, our study objectives were to: (1) explain and expand our understanding of pediatric critical care nurses experience of burnout in relation to their work environment and work engagement; (2) provide recommendations for nursing administrators to improve nurses' work environment, work attitudes, and work outcomes.

Methods: A convenience sample of pediatric critical care nurses from a large pediatric quaternary care hospital in Ontario, Canada were invited to participate in this second phase of a sequential explanatory mixed-methods study. Semi-structured interviews were conducted, with and main themes and subthemes distilled through the method of interpretive description.

Results: A total of 18 PICU/CCCU/NICU nurses participated. Derived themes included the experience and identification of burnout, including its prevalence and elusiveness. Their experiences of quality of work-life included themes such as compensation, emotional support at work, respect, their professional identity, and spill over into home life. They discussed components of work engagement, including the work itself, investment into their growth and development, and the meaning of their work. The self-care subthemes included the importance of preparation and recovery, and the use of physical and mental separation as a preservation strategy. The participants' recommendations for strategies to mitigate burnout were also summarized.

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Conclusion: Burnout is a complex and regularly occurring experience for pediatric critical care nurses. Although the experience may be difficult to self-identify, the impacts on the individuals are profound. Further research and organizational support are needed to test practical and evidence-based interventions to improve the well-being of this population.

Keywords: burnout, quality of work-life, work engagement, nurses, pediatric, qualitative

INTRODUCTION

Even prior to the SARS-CoV-2 (COVID-19) pandemic, frontline critical care workers were known to be on the brink of a well-being crisis (1–3). There are multiple sources of distress in critical care, including clinical situations involving end-of-life or prolongation of life, contextual factors related to the work environment, team communication and relationships, and more recently, resource related dilemmas (4). In 2014, many organizations added a fourth objective to the Institute for Health Care Improvement's Triple Aim of Health Care focused on health care provider well-being, in acknowledgment of the impact provider well-being has on patient satisfaction, clinical outcomes, and health care costs (5). In 2016, the Critical Care Societies Collaborative (CCSC) based in the United States, published "A Call for Action" on burnout in critical care health care professionals urging key stakeholders to address critical care health care provider burnout to improve both patient and provider well-being (6). Locally, Critical Care Services Ontario (CCSO) has recently begun publishing province-wide surveys of critical care practitioner burnout to monitor the well-being of Ontario's critical care staff (7).

Burnout is a psychological syndrome emerging as a prolonged response to chronic interpersonal stressors on the job (8). Burnout has shown to have physical, psychological and occupational consequences across working populations (9). Maslach states that there are three key dimensions of burnout: emotional exhaustion, depersonalization, and lack of accomplishment (8). When applied to health care settings, emotional exhaustion refers to when the health care provider feels emotionally drained from their work. Depersonalization is the development of cynicism, particularly toward patients. Lack of personal accomplishment is when the health care provider feels a sense of ineffectiveness and dissatisfaction with the care they are providing (10). Burnout impacts at the level of the provider, the patient, and the organization (11).

While all health care providers are at high risk of burnout, pediatric nurses care for some of the most vulnerable patients in our healthcare system and are particularly vulnerable to the impact of the stress of their work on their well-being. These nurses skillfully manage the highly specialized care of children and the complex family dynamics that are inherent to the work (11). A recent scoping review demonstrated that burnout was prevalent in pediatric nurses and was related to aspects of the work environment, work attitudes, and work outcomes (11).

Abbreviations: PICU, Pediatric Intensive Care Unit; CCCU, Cardiac Critical Care Unit; NICU, Neonatal Intensive Care Unit.

Within the population of pediatric nurses, pediatric/neonatal critical care nurses are a subspecialty within a specialty. These highly specialized nurses cannot be easily replaced or supplemented and they care for the most severely ill and injured children at the highest risk of death (12, 13). In 2021, we used the Theory of Reasoned Action to guide an examination of modifiable work environment factors that had the greatest association with the work outcome of burnout in a sample of pediatric/neonatal critical care nurses. Simplified, the Theory of Reasoned Action states that our beliefs about our work environment, influence our work attitudes and are directly related to our behavioral intentions and, in turn, our behaviors at work (work outcomes) (14–16). We conducted a survey to examine factors of the work environment (e.g., quality of work-life, perceived organizational support, and workplace incivility) and work attitudes (e.g., work engagement) of pediatric critical care nurses and their relationship to burnout. Quality of work-life and work engagement were identified as the most important factors (17). However, in the interests of mitigating or preventing burnout, a thorough understanding of the experience of workplace burnout and related factors from the perspective of nurses is required. Therefore, building on our survey findings we aimed to: (1) explain and expand our understanding of pediatric critical care nurses experience of burnout in relation to their work environment and work engagement and (2) provide recommendations for nursing administrators to improve nurses' work environment, work attitudes, and work outcomes.

MATERIALS AND METHODS

Study Design

This study is the second phase of a two-phased mixed methods evaluation of pediatric nurses working in critical care using a convenience sample of nurses at a large quaternary care pediatric hospital in Toronto, Canada. The explanatory sequential mixed methods design began with a quantitative cross-sectional survey which was developed based on the Theory of Reasoned Action (17). Study findings were used to build the semi-structured interview guide for the current study.

Guided by the methodology of constructivist grounded theory, and using the analytic method of interpretive description, the current study utilized semi-structured qualitative interviews to contextualize, illuminate, and explore the experience of burnout and related factors at work in the sample of pediatric critical care nurses (18).

Study Location and Context

The hospital is a 300-bed tertiary care hospital with a 41-bed critical care unit and 36-bed Neonatal Intensive Care Unit (NICU). The critical care unit is divided into multi-organ medical-surgical, and cardiac services. Four-hundred and forty-three RNs work in the combined Cardiac Critical Care Unit (CCCU), Pediatric Intensive Care Unit (PICU), and NICU. These units are largely homogeneous in the nurses' skill set and acuity of their work here, and across similar facilities, which increases transferability of the results (19). Interviews were conducted in the Summer of 2021 during the COVID-19 pandemic. Of note, in an unprecedented move, the PICU admitted adult COVID-19 patients in the months leading up to the interviews which was a unique experience for the pediatric nurses working this time. The adult patients had been discharged 3 weeks prior to initiation of data collection.

Eligibility and Recruitment

Registered Nurses who had worked in the PICU, CCCU, or NICU for more than 3 months and completed a survey in the quantitative phase of the study were eligible to take part in the study. Nurses who participated in the quantitative phase of the study were asked to indicate if they were interested in participating in the this qualitative phase of the study. Interested participants were contacted via email and semi-structured interviews were booked on a first-come-first-served bases.

Semi-Structured Interview Guide Creation

The semi-structured interview guide was developed using the process of integration and building as described by Creswell and Creswell (19) based on the relationships uncovered in quantitative phase of the study (17). In accordance with the Theory of Reasoned Action, factors of the work environment influenced work attitudes, and work attitudes influenced work outcomes. Results of the quantitative phase indicated that quality of work-life and work engagement had the greatest impact on burnout (17). Therefore, interview guide questions were designed to more deeply explore these topics with the nurses. The interview questions were reviewed with three critical care nurses for refinement and to ensure question clarity (18). Demographic data of the participants were collected at the start of the interview. The semi-structured interview guide can be found in **Supplementary Appendix A**.

Data Collection

One-on-one interviews were conducted over Zoom. Video conference allowed for flexible timing of interviews and compliance with COVID-19 social distancing rules. Interviews ranged from 25 to 60 min in length. Two trained research team members who worked in the critical care areas conducted interviews [one Clinical Nurse Specialist (LB) and one Social Worker (SS)]. However, the person who conducted a particular interview was chosen to avoid interviewing any participants who directly reported to them to promote participant comfort, participant psychological safety, and limit investigator bias. Consent was obtained from each participant prior to the commencement of the interviews. All interviews were audio recorded and subsequently transcribed. Transcriptions were reviewed by a study team member for accuracy.

Data Analysis

Data collection and analysis were iterative allowing for clarification of concepts in subsequent interviews and increased credibility and confirmability of the results. Using the principles of interpretive description, the initial analysis of the transcripts was used to break the data down into broad themes and sub-themes in the early stages while avoiding restricting findings to the self-evident (20). Care was taken to not lose the contextual whole of the data through this process, in line with the principles of interpretive description (20, 21). Following the process described by Thorne (21), coding proceeded through intellectual inquiry (as opposed to line-by-line coding) to ensure context was respected, with the intention of constructing truths. In order to fulfill Objective 2, recommendations brought forward by the participants for nursing administrators to improve nurses' work environment, work attitudes, and work outcomes were summarized and collated. As per the process described by Bowen et al. (18), a second team member (KW) reviewed the coding, and conflicts were discussed with a third team member (KC or WB) (18, 22). Interviews continued on a rolling basis until new themes were no longer surfacing.

RESULTS

Demographic Information

A total of 18 nurses participated in the semi-structured interviews. All participants contacted for an interview consented and participated in the process. Participants came from each of the three units, four from PICU, five from CCCU, and nine from NICU. Participants of different years of experience were all represented with 8 with 0–5 years, 5 with 6–10 years, and 5 with >10 years of experience. All participants had achieved a bachelor's degree or higher, and almost all had cared for a COVID-19 positive patient/patient under investigation. No participants worked casually, and almost all worked full-time (>0.8 FTE).

Themes

We identified four key themes from participants' exploration of their experiences with workplace burnout: the experience and identification of burnout, quality of work-life, work engagement and self-care. Nurses spoke about the prevalence of burnout and the challenge of identifying it within oneself. The theme of quality of work-life captures the collegial and compensatory factors that influence the nurses' experience. The theme of work engagement includes factors of the physical work, as well as the opportunities and meaning it creates. The theme of self-care addresses the personal strategies implemented to try and mitigate their experience of burnout. Of note, self-care was not specifically explored through questions in the interview guide but came up as an important factor related to burnout across

most of the interviews. Each theme and its associate subthemes are described below. All sub-themes were novel and derived exclusively from the data.

The Experience and Identification of Burnout

Within the theme of the experience and identification of burnout, two subthemes were identified: prevalence and elusiveness.

Prevalence

All participants made it evident that burnout was prevalent, and that they had experienced it at some point in their career. One participant described their experience as the following; *"…it was a lot of dread coming into work and, even once I'm there, just not wanting to be there. I think once I got home, it was just not wanting do anything and just recover…"* ***(Participant 7, NICU)***.

Elusiveness

Many participants discussed how burnout is highly elusive and difficult to self-identify. Participants stated; "… *you don't know you're burnt out until you're like, 'I don't understand why I'm completely overwhelmed and I can't do my job,' and then (you realize), oh I'm burnt out, I didn't know that"* ***(Participant 8, NICU)***. Another participant reported; *"…you have to recognize it yourself and usually people can't"* ***(Participant 6, NICU)***. Another spoke about not truly understanding what burnout was until they experienced it themselves, *"I didn't think I would burn out. I kind of didn't think that burnout was a real thing necessarily. I thought people just got tired and needed vacations or needed a job change, which I now see are all evidence of burnout. There it is, that's what they've been talking about*" ***(Participant 13, PICU)***.

Quality of Work-Life

Within the theme of quality of work-life five subthemes were identified: benefits and compensation; context-based emotional support; respect as a professional; identity; and quality of work-life spillover.

Benefits and Compensation

Benefits and compensation were frequently referenced by participants. The ability to self-schedule was by far the most positive benefit highlighted. Participants had mixed opinions on the quality and quantity of the health benefits provided. In terms of compensation, many participants cited that at a unit/organizational level, they do not get properly compensated for the length of time that they work (staying late, missing breaks), as well as feeling they should be compensated differently than ward nurses due to the nature and complexity of critical care work. *"…. working in a PICU or a NICU or the CCCU…I feel that the work is so much more stressful on a different level, not to say that people that work on the floor don't have stress, but these nurses are being trained and qualified to work in an ICU. I feel that we should be compensated a little bit more…"* ***(Participant 11, NICU)***. Others brought up the broader issue of the insufficient compensation for nurses at the government level; *"… it does seem like a slap in the face from the government…we can't get the same increases we see from police….We're also doing a very demanding job, and it would be nice if we could also see the same kind of increase that other professions get; I think that could be better"* ***(Participant 15, CCCU)***.

Context-Based Emotional Support

Participants resoundingly echoed the importance of the team to mitigate burnout. When asked what kept her coming back to work every day, one participant said, *"The people. It's no questions asked, we have the best team. I think just the supportive nature of the relationships largely, just like-minded people that even in the worst of times understand what you do and can find lightheartedness in the worst moments. Just good people who share the passion"* ***(Participant 12, CCCU)***. When it comes to dealing with the specific challenges of the work many participants brought up the idea of context-based emotional support that they can only get from others who have had similar experiences. "… *(it) fills your cup with that space to vent in a way, where people understand what you're talking about you know you can't go and talk to your non-nursing friends about things, you can't go to therapy and talk about things they don't get it, they can talk about concepts, but they don't really understand what it's like to be in that room with that dynamic all day. Sharing experiences and just really validating each other – it took away the sense of aloneness it fills your cup, so you can come back and do it again…you know that person in that room totally gets what you're going through with one look"* ***(Participant 13, PICU)***.

Respect as a Professional

Although some participants felt there was adequate acknowledgment from their peers, management, and the organization, many referenced challenges with feeling respected as a professional. Participants reported feeling disrespected by patient families, being treated like they were regarded as more of a resource than a person/professional at the level of the organization as well as not feeling valued by society in general for the work they do. "… *you see people retire and (the organization) was their life and they literally just leave and it's like its nothing, another gear in the machine,…people who were these huge parts of the unit were gone and you just move on. That's what made me realize it's just a job*" ***(Participant 4, NICU)***.

Identity

Many participants spoke about their identity within the context of critical care nursing. They felt as though critical care nurses are unique as their role and experience differ so greatly from other areas in the hospital. As such, they require different levels of support, and they should not be expected to follow the same policies or guidelines that are applied broadly across the hospital. There was consensus that critical care work should be recognized for its uniqueness by both the organization and the public at large, *"I mean, I think we're all biased and think that our units are the best, but I think we do exceptional work, and I think no one wants to talk about us. I think we do amazing things, but no one wants to talk about us because we're not oncology we're not the sellable unit, nobody wants to hear about the kid that's in ICU it's a parent's worst nightmare, we're not commercial material"* ***(Participant 13, PICU)***.

Many brought up how the practice of floating (a resource management strategy where nurses have to work outside their area of expertise) undermines their highly specialized skillset; *"…when we're floating a lot, I know that, for me I've never*

worked on the Ward. I was born and raised an ICU nurse, so for me going in and floating the wards. . .I knew I was going to do it every other shift. I think (that) also contributes to burnout" ***(Participant 9, PICU)***.

Some spoke about the discordance between their experience as a nurse and the "brand" of the organization, or the "nurses are heroes" trope being touted in the media, especially during the COVID-19 pandemic. "*I'm not going to lie though, a 1% raise is a bit of a slap in the face this year. . . I mean 'you're all heroes,' but here's 10 cents, you know?"* ***(Participant 4, NICU)***.

"The superhero stuff, none of us buy into it, it's for the public" ***(Participant 13, PICU***).

Quality of Work-Life Spillover

The link between well-being at work and well-being at home was identified, *"I think, because if you aren't enjoying the work you do, then that's going to filter in when you're not at work as well and you're going to dread coming into work and be thinking about it when you get home from work. If it's a negative experience and then, when you come to work and you're dreading it already I don't think you're in the right mindset. So I think if you like the work that you're doing then overall you'll feel better"* ***(Participant 18, PICU)***.

Work Engagement

Within the theme of work engagement three subthemes were identified: the work itself; investment in growth and development; and finding meaning in the work.

The Work Itself

Participants found strengths to be in the variety of the work, the challenge of the patient acuity, the collaboration with the interprofessional team, and the opportunity to engage in the most cutting-edge evidence-based practice. " *. . .first of all I love the variety of what I see, and I find that not every day is the same, which keeps me eager to work because I don't know what my day is going to be like*" **(Participant 10, NICU)**.

Challenges highlighted included the gravity of the work (dealing with morbidity and mortality regularly), the pace and pressure of the work, and resource issues such as poor staffing ratios. *". . . it's kind of just expected that you're doing it and then everybody knows that it's inappropriate, but you're stuck, because there's a nursing shortage. . ."* **(Participant 11, NICU)**.

Investment in Growth and Development

Many participants felt that there were multiple opportunities for growth and development offered through their work, which contributed to their satisfaction at work and mitigated burnout. However, a few reported feeling as though opportunities beget opportunities, which resulted in the organization seeming to invest in the same cohort of people. *". . .they kind of come to you, the more you branch, and I find if you're working harder that kind of gets noticed and then opportunities present themselves within that"* **(Participant 12, CCCU**). One stated, "*I feel like there's room for me to grow"* **(Participant 10, NICU).** Another participant spoke about the need to focus on development for those who stay at the bedside, "*Those people that stick around and teach the next generation. . .I think those people should be valued and given opportunities*" **(Participant 13, PICU)**.

Finding Meaning in the Work

The meaning of the work was highlighted as a major factor when it comes to feeling fulfilled and avoiding burnout. *"I think it's a lot of fulfillment with feeling accomplished in improving a patient's condition. So even if it's just getting a baby to start feeds, or going up on feed successfully, or weaning ventilator settings successfully, or getting a baby out to hold with a family, I think the little things are what brings me the most fulfillment and wanting to come back"* ***(Participant 11, CCCU)***. Inversely, many participants spoke of the struggle when they could not find meaning in the work due to ethical dilemmas, chronicity of patients, or not feeling like they could provide their best level of care due to issues with team dynamics, the patients' family, or availability of resources.

Self-Care

Within the theme of self-care, two subthemes were identified: Preparation and recovery, and separation as preservation.

Preparation and Recovery

Most participants referenced both proactive (routinely exercising, engaging in hobbies, formal therapy) and reactive (treating themselves, seeing friends) self-care techniques for mitigating burnout. ". . .*I usually make plans to either hang out with friends or go somewhere with family member. I try to create social events to look forward to. . .just do things for myself so I'll read a book or I'll watch a show"* ***(Participant 11, NICU)***. When feeling drained, the self-care goal was a restoration of balance, "*I like exercising, treating myself, whether it be going out for a coffee or something. . .finding balance"* ***(Participant 15, CCCU)***.

Separation as Preservation

Many participants brought up the necessity of having separation from work, both physically and mentally, as a protective factor. Physical separation included getting their entitled breaks during work, the benefits of the commute home to decompress, taking vacation time (paid time off), and the rotation out of stressful assignments. Mental separation included not engaging in work (checking emails, doing e-learning, etc.) on days off, and the concept of mentally leaving work at work in order to fully be present for other aspects of life. One participant shared, "*I took a personal day the next day because, I just felt like I had had 4 days with that child and they died on my fourth shift. . .I felt like I needed some time because, I know that if I were to have come back then, I wouldn't have been giving the next assignment my full self"* ***(Participant 10, NICU)***.

Participants' Recommendations for Improvements

Throughout the interviews, participants were asked to share ideas to address issues they brought forward as contributing to burnout in their workplace. Participants were eager to provide ideas for opportunities to reduce the negative workplace experiences and enhance experiences that promote well-being. These recommendations, from the participants themselves, are summarized in **Table 1** according to which of the subthemes listed above that they address.

TABLE 1 | Recommendations for Nursing Unit and Organizational Leadership.

The work itself, respect as a professional, and finding meaning
Intentional debriefs throughout complex cases to reduce the spread of false or unproductive info
Ongoing transparency around unit level and organizational level decision making that impacts frontline staff
Swift and transparent addressing of unit-based issues by management, particularly when it comes to staff safety/respect issues with patients and families
Regular debriefing with support from a bioethics team/consultation both during and after difficult cases
Thoughtful patient assignments taking into account the nurses' previous shift experience
Transparency in assignment selection
Benefits and compensation
Proper compensation for extra hours worked (particularly for charge/clinical support team members who regularly leave late)
Focus on fostering unit level relationships (among nurses as well as among nurses and the interdisciplinary team)
Recognition of critical care as a unique group of nurses when it comes to compensation, for example, providing increased compensation, more mental health days, formal mental health check-ins
Initiate compensation based retention strategies for nurses in order to keep talent within the organization
Separation as preservation
Ensuring nurses get breaks during their shifts
Ensure staffing levels are sufficient so there is a reduced need for staff to work overtime.
Provide the opportunity for, and reduce a culture of guilt around, taking mental health days
Make designated mental health days 12 h instead of 8 h in order to benefit the frontline staff who have to most exposure to stress/trauma
Ability to ask for an assignment change or break from a specific assignment
Provide an on-site 24/h wellness space where nurses can take a break when needed
Identity
Ensure nurses only float to other critical care areas rather than throughout the hospital
Implement a resource nursing team to assist with staffing needs throughout the hospital
Acknowledge that critical care work and workflow is different from other areas of the hospital by ensuring consultation with critical care nurses prior to implementation of hospital-wide policies and interventions
Investment in growth and development
Provide opportunities for task rotation (e.g., opportunities to engage in project work)
Provide opportunities for advanced training at the bedside (e.g., certify on Continuous Renal Replacement Therapy (CRRT) and Extracorporeal Membrane Oxygenation (ECMO)
Provide opportunities for professional development and advancement

DISCUSSION

Throughout these 18 interviews the key themes were the experience and identification of burnout, quality of work-life, work engagement, and self-care. Consistent with the Theory of Reasoned Action and the pathway to burnout, factors of the work environment (quality of work-life) seemed to influence work attitudes (work engagement), which, subsequently influenced work outcomes (burnout). It became clear early in the analysis that the experience of burnout was common in pediatric critical care nurses as has been previously noted in the literature (11, 17). The emphasis on burnout being elusive to self-identification is a strong reminder of the need to check in regularly with teammates and colleagues, both formally and informally, to facilitate early identification of burnout. Suggestions from the literature to facilitate identification of burnout include: manager check-ins, peer support programs, Employee Assistance Programs, and Spiritual Care programs, to name a few (23, 24).

Although we did not directly aim to explore self-care-based interventions, many participants identified both preventative and restorative self-care strategies that they employ to mitigate burnout. Although not addressed by the pathway in the Theory of Reasoned Action, self-care seems to be an external strategy that participants used to mitigate the work outcome of burnout. Participants highlighted the need for separation from work as an important component of self-preservation. Similarly from an organizational perspective, recent literature has highlighted that leadership can support employee self-care by modeling good work-life balance and healthy boundaries with work, including taking paid time off, leaving work on time, and avoiding being constantly engaging with work outside of work hours/emergencies (24).

According to the Theory of Reasoned Action, work engagement is influenced by the work environment and influences work outcomes, such as burnout (14). When it comes to the theme of work engagement, Herzberg (25) describes how to motivate an employee to do something: they must have the *opportunity* and the *ability* to do it (25). This concept came through in the nurses' discussion of their work. Opportunities for skill development/mastery, task variety, and the diversity of the patient population and technology where all highlighted as factors that improved their work engagement and, through that, their well-being. As supported by the literature, work engagement can mediate the relationship between quality of work-life and health care support workers' intent to stay employed (26) and that between the demands of the job and nurse burnout (27). Nurse work engagement has also been shown to impact the patients' experience of care (28). Additionally, increased work engagement has been shown to be inversely associated with nurses' burnout and intent to leave their current employment (29, 30). Tensions within the work stemmed from lack of transparency in planning and communication and the moral distress and ethical dilemmas shown to be inherent to intensive care work (31). Potential solutions for these issues offered by our participants and supported by the literature are: regular bioethical debriefs, care planning that is shared with the interprofessional team, and check-ins and debriefs on difficult cases to reduce the spread of misinformation (23, 32).

We also heard about concepts of identity. Nurses identified deeply with the role but struggled with not being recognized as having a unique and separate skillset from other nurses at the hospital. Nurses reported feeling undervalued due to the perceived lack of recognition that critical care nurses require unique considerations within provincial and organizational policies. Floating (having to work on a unit that is not your

home/specialty unit), which is a method of hospital resource allocation, has been recognized as a patient safety issue in the Registered Nurse Safe Staffing Act of 2015, where the American Nurses Association asserts that hospitals should not require nurses to float outside of their education/training/specialty to avoid harm to both the patients and nurses (33). One solution to the challenge of floating, suggested by O'Connor and Duggan (33), is to have designated nurse resource teams that have diverse experience and have trained in several areas of the hospital (33). Particularly within the context of the COVID-19 pandemic, it has come to light that nurses are not interchangeable (34). Critical care trained nurses are an extremely valuable and limited resource with many calling for revision of RN compensation regulations as thousands of nurses leave the field while policies like Ontario's Bill C124 caps their wage increases during an unprecedented pandemic (35). Additionally, lack of autonomy and respect by administrators was cited as a major factor in attrition in a 2013 ethnographic study of PICU nurses in British Columbia, Canada (36). Hollow praise (e.g., the empty words without action or being called "health care heroes") and clichéd gestures (e.g., break room "resiliency pizza")[1] are not what these nurses find helpful to mitigate or prevent burnout. Alternatives could be including nurses in unit and corporate decision-making, focusing on recognition strategies that support nurses in their work (like safe staffing ratios and incentives to stay in the field), regular performance feedback, and opportunities for growth and development (23, 24, 32).

On the positive side, we heard many stories about the nurses' identity within their team and what a protective factor their work relationships can be. The bonds built between colleagues are unique to both the context in which they are formed in and the stress they endure. Similar findings have been reported from studies on the concept referred to as "unit cohesion," particularly in military unit bonding where it is identified as a source of resilience and a mitigator of Post-Traumatic Stress Disorder and depression (37). Group cohesion has also been shown to improve nurse satisfaction and retention (38). These distinctive bonds also support the role of context-based peer support as a frequently cited source of respite in our sample. Group cohesion can be fostered with team building activities, unit social events outside of work, and peer-to-peer support networks (23, 24).

LIMITATIONS

This study used an explanatory qualitative approach which does not allow for generalizability of our findings. It is also limited by the location, time, and context in which the interviews were conducted. This study took place in the unique context of the COVID-19 pandemic which undoubtedly increased the workplace stress on the staff during this time (39, 40). However, this context may have allowed the nuances of workplace well-being to be further illuminated and thus brought forward in our results. There is possible bias in participant responses due to perceived social desirability, despite assured anonymity of how the findings would be shared (41). As well, potential bias may have been introduced by the order in which concepts were presented from the semi-structured interview guide. Participants self-selected to participate in both phases of the study; those with the most extreme feelings may be over-represented (41). Finally, although reflexivity was practiced throughout the study, the PI's identity as a pediatric critical care nurse who cares about the well-being of fellow pediatric critical care nurses may have shaped the findings.

[1]Resiliency pizza refers to the pizza given to nurses as a "thank you" from hospital administration for working under less-than-ideal working conditions. The gesture is often received as an insult to those working at the bedside.

FUTURE IMPLICATIONS

This was a particularly opportune time to conduct research on nurse well-being. As we proceed through the later phases of the COVID-19 pandemic, mitigation of nurse burnout is more important than ever (24). Evidence-based recommendations, such as the results presented in this study, should be disseminated to nursing leadership, hospital administration, professional organizations, and government officials. Further research is needed to explore how pediatric nurse quality of work-life and work engagement impacts their experience of burnout including implementing and evaluating burnout interventions. By using data gathered directly from the nurses, interventions can be crafted to not only mitigate burnout, but prevent it from occurring.

CONCLUSION

This study expands our understanding of the experience of burnout and contributing factors in the understudied population of pediatric critical care nurses. Pediatric critical care nurses carry the trauma of what is unthinkable to most, and they do it with steady hands, expert skill, and compassion. As nurse researchers we owe them our time and our interpretation to voice their concerns and share their solutions with the organization and higher levels of leadership. Further research is needed on the outcomes of well-being interventions in pediatric critical care nurses. They are dynamic professionals that must be fostered in order to keep them thriving in their complex work; they deserve to be well in the process.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Board at The Hospital for Sick Children in Toronto, Canada (REB #1000072502). It is also approved by the University of Toronto. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LB was involved in the study design, data collection, data analysis, data interpretation, and drafting and finalizing the manuscript. WB and KC were involved in data interpretation, and substantively revised the manuscript for important intellectual content. KW was involved in the study design, data interpretation, and substantively revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.851001/full#supplementary-material

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SYSTEMATIC REVIEW
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Continuous Magnesium Sulfate Infusions for Status Asthmaticus in Children: A Systematic Review

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Objectives: Magnesium sulfate is a second-tier therapy for asthma exacerbations in children; guidelines recommend a single-dose to improve pulmonary function and decrease the odds of admission to the in-patient setting. However, many clinicians utilize prolonged magnesium sulfate infusions for children with refractory asthma. The purpose of this review is to describe the efficacy and safety of magnesium sulfate infusions administered over ≥ 1 h in children with status asthmaticus.

Methods: Medline was searched using the keywords "magnesium sulfate" and "children." Articles evaluating the use of magnesium sulfate infusions for ≥1 h published between 1946 and August 2021 were included. Published abstracts were not included because of lack of essential details. All articles were screened by two reviewers.

Results: Eight reports including 447 children were included. The magnesium regimens evaluated included magnesium delivered over 1 h (*n* = 148; 33.1%), over 4–5 h (*n* = 105; 23.5%), and over >24 h (*n* = 194; 43.4%). Majority of patients received a bolus dose of 25–75 mg/kg/dose prior to initiation of a prolonged infusion (*n* = 299; 66.9%). For the patients receiving magnesium infusions over 4–5 h, the dosing regimen varied between 40 and 50 mg/kg/h. For those receiving magnesium infusions >24 h, the dosing varied between 18.4 and 25 mg/kg/h for a duration between 53.4 and 177.5 h. Only three reports including 186 patients (41.6%) included an evaluation of clinical outcomes including evaluation of lung function parameters, reduction in PICU transfers, and/or decrease in emergency department length of stay. Five reports including 261 patients (58.4%) evaluated magnesium serum concentrations. In most reports, the goal concentrations were between 4 and 6 mg/dL. Only 3 (1.1%) out of the 261 patients had supratherapeutic magnesium concentrations. The only reports finding adverse events attributed to magnesium were noted in those receiving infusions for >24 h. Clinically significant adverse events included hypotension (*n* = 74; 16.6%), nausea/vomiting (*n* = 35; 7.8%), mild muscle weakness (*n* = 22; 4.9%), flushing (*n* = 10; 2.2%), and sedation (*n* = 2; 0.4%).

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Conclusion: Significant variability was noted in magnesium dosing regimens, with most children receiving magnesium infusions over >4 h. Most reports did not assess clinical outcomes. Until future research is conducted, the use of prolonged magnesium sulfate infusions should be reserved for refractory asthma therapy.

Keywords: magnesium, infusion, status asthmaticus, children, pediatric intensive care unit

INTRODUCTION

In the United States of America, approximately 7.1 million children have asthma, and these children experience approximately 680,000 emergency department (ED) visits and >70,000 hospitalizations annually (1). Among children admitted to the pediatric intensive care unit (PICU), those with severe asthma exacerbations, also referred to as status asthmaticus or critical asthma, have increased morbidity and associated health-care costs compared to those with mild to moderate asthma exacerbations (2). Several organizations like the National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) and Global Initiative for Asthma (GINA) have published guidelines on the management of children with asthma exacerbations (3–5). However, these guidelines provide limited recommendations for children with status asthmaticus or critical asthma. In these patients, the standard of care includes intravenous (IV) corticosteroids and nebulized continuous short-acting beta-2-agonists (SABA). However, providers have utilized several second-tier pharmacologic therapies including heliox, IV aminophylline, IV ketamine, and IV terbutaline (6).

Another therapy that has been proposed as an option for a second tier is the use of IV magnesium sulfate infusions. The NAEPPCC and GINA guidelines provide recommendations for a single dose of IV magnesium sulfate in children with asthma exacerbation in the ED with refractory clinical manifestations 1 h after receipt of oral/IV corticosteroids and repeated doses of SABAs (4, 5). The dosing regimen recommended is between 25 and 75 mg/kg with a maximum of 2 g/dose over 20 min (4, 7). This regimen is associated with an improvement in pulmonary function and 68% decreased odds of admission to the hospital when administered in the ED setting (8, 9). However, some sources have provided recommendations on the use of continuous magnesium sulfate infusions in the ED or PICU setting for children with refractory status asthmaticus (6). The purpose of this review is to describe the efficacy and safety of magnesium sulfate infusions in children with asthma exacerbations or status asthmaticus who received magnesium sulfate infusions administered over ≥1 h.

MATERIALS AND METHODS

Relevant articles were identified from Medline (1946–August 2021) using the terms "magnesium sulfate" and "children." Results were limited to studies in humans. Published abstracts were not included because of lack of essential details. Thus, the search was limited to published studies. To be included, the reports had to include children receiving a magnesium IV infusion administered over ≥1 h for asthma exacerbations refractory to common treatments and had to be published in the English language.

RESULTS

The PRISMA diagram of the included studies is shown in **Figure 1**. The electronic search identified 203 reports for title and abstract review that were imported into Convidence® . All articles were screened by two reviewers, and all authors were involved in the final selection process. One hundred ten records were excluded as they were either non-English articles or were review articles or case reports or commentaries. Ninety-three full-text studies were assessed for eligibility. Eighty-five studies were excluded for several reasons including studies done in the adult population, focused on nebulized magnesium, or involved administration of magnesium sulfate over <1 h. One report evaluated the use of a prolonged magnesium sulfate infusion for refractory asthma exacerbation, but they did not provide clear details on their dosing regimen; therefore, it was excluded from further review (10) (**Figure 1**).

A total of eight reports including 447 children were included (11–18). These eight reports included evaluation of different approaches to magnesium infusions. Two of the reports discussed a magnesium infusion administered over a 1-h period (11, 12). Four reports evaluated the efficacy and safety of magnesium infusions administered over 4–5 h (13–16). The remaining two reports described the use of magnesium infusions administered over >24 h (17, 18). **Table 1** provides an overview of these reports including the type of report, demographics, place in therapy, dosage regimen, and main outcomes.

Magnesium Infusions Administered Over 1 h

DeSanti et al. conducted a retrospective matched cohort analysis in children admitted to a non-intensive care setting on continuous albuterol therapy (11). The goal of this study was to determine the effect of magnesium sulfate on the duration of continuous albuterol and hospital length of stay (LOS). They compared 33 patients receiving intravenous (IV) magnesium sulfate infusion versus a control group (n = 33) with similar respiratory assessment scores. The IV magnesium sulfate doses ranged from 25 to 75 mg/kg and were administered over 60 min. Four patients in each group received magnesium sulfate in the ED prior to being admitted to the hospital. The authors noted that patients who received IV magnesium sulfate once admitted, had longer durations of continuous albuterol therapy (p = 0.001)

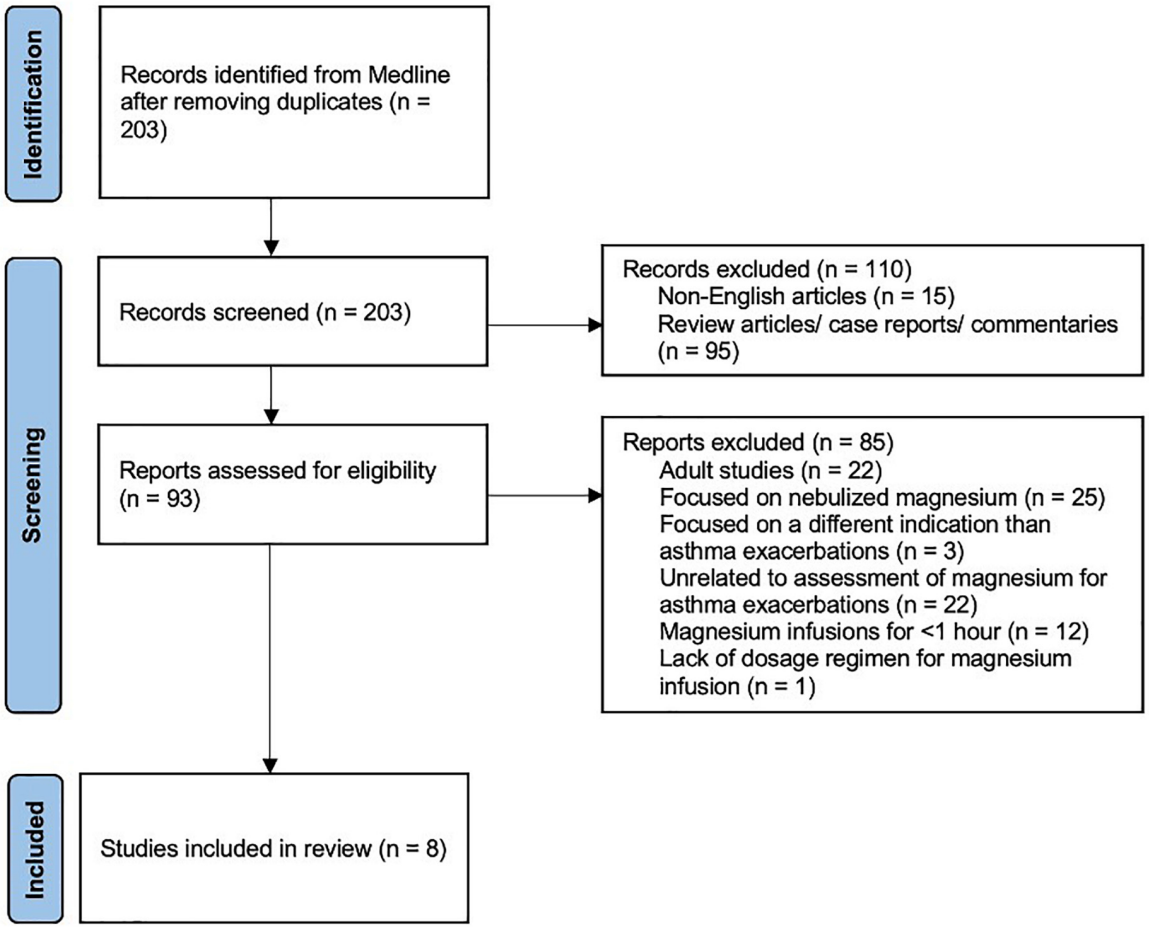

FIGURE 1 | PRISMA flow diagram of included studies.

and a longer hospital LOS ($p = 0.037$). In the magnesium sulfate group, the authors found no significant difference in adverse reactions including hypotension and respiratory depression between groups; the authors noted that neither of these adverse events were directly attributed to magnesium. They concluded that those who received magnesium sulfate did not have reduced continuous albuterol therapy duration or LOS. It is important to note that the patients' respiratory status was determined using a non-validated tool, limiting the external validity of their findings. Compared with other studies, they initiated magnesium sulfate later in the course of therapy, and they did not monitor magnesium sulfate concentrations, which may have been subtherapeutic.

Özdemir and colleagues conducted an open intervention study in children presenting to a pediatric pulmonary clinic with mild (Group 1) ($n = 50$) to moderate (Group 2) ($n = 65$) asthma to determine the effects of IV magnesium sulfate on patients' spirometry values (12). All patients received a 40–50 mg/kg IV infusion (maximum 1,500 mg/dose for patients >30 kg) of magnesium sulfate over 60 min. Fifteen minutes after the magnesium sulfate infusion, both mild and moderate asthma groups showed statistically significant increases in forced expiratory volume in 1 s over forced vital capacity (FEV_1/FVC), FEV_1, peak expiratory flow (PEF), and forced expiratory flow at 25–75% of forced vital capacity (FEF_{25-75}) ($p < 0.01$). There were no statistically significant differences in oxygen saturation, heart rate, and blood pressure before and after treatment with magnesium sulfate. The authors concluded that IV magnesium sulfate could aid spirometric parameters in children presenting with acute asthma without many adverse events. The authors did not report the number of patients that needed additional asthma therapy after IV magnesium sulfate administration, and they did not include a control group in their study. Additionally, patients were only included in the study if they had oxygen saturations >92% on room air.

Magnesium Infusions Administered Over 4–5 h

Irazuzta et al. conducted a retrospective study over a 3-year period evaluating the feasibility of a 4-h magnesium infusion protocol in 19 children with status asthmaticus (13). These patients had failed to improve with conventional therapy including at least one dose of magnesium sulfate 50 mg/kg IV

TABLE 1 | Overview of reports evaluating the use of magnesium infusions.

Reference (study type)	Sample size	Age (years)	Place in therapy for magnesium infusions	Magnesium dosing regimen (bolus/infusion and dosing)	Magnesium infusion duration	Results
Magnesium infusion administered over 1 h						
DeSanti et al. (11) (Retrospective matched cohort analysis)	Magnesium group (n = 33); control group (n = 33)	2–18 years (specific age not reported); 27 (81.8%) < 10 years	Added after patients received three doses of albuterol 2.5 mg with ipratropium 0.5 mg and systemic corticosteroids and at least 6 h of continuous albuterol 0.5 mg/kg/h	*Bolus*: None *Infusion*: >1 dose of 25–75 mg/kg/dose (standard 50 mg/kg/dose); max 2,000 mg/dose	1 h	Patients receiving magnesium had longer median duration of continuous albuterol than controls (34 versus 18 h; p = 0.001) and longer length of stay (72 versus 49 h; p = 0.037). More patients in magnesium group transferred to PICU compared to controls (9 versus 2 patients, p = 0.065). No significant difference in ADEs in each group; both had patients with hypotension (n = 3 magnesium; n = 3 controls) and respiratory depression (n = 8 magnesium; n = 3 controls)
Özdemir and Doðruel (12) (Open intervention study)	115	6–17 years (specific age not reported)	Included patients with no SABA use in past 3 h, no oral/IV steroids in last 12 h who were on room air. FEV1 was between 40 and 75% of predicted FEV1	*Bolus*: None *Infusion*: 40–50 mg/kg × 1 dose (max 1,500 mg for patients >30 kg)	1 h	Lung function parameters (FEV1/FVC ratio, FEV1, PEF, FEF_{25-75}) pre and post treatment showed statistically significant improvement with the magnesium infusion in children with mild and moderate asthma exacerbations. Mean change in FEV1 with magnesium infusion was 7.7% in the mild group and 10.9% in the moderate group
Magnesium infusions administered over 4–5 h						
Irazuzta et al. (13) (Retrospective chart review)	19	Mean 9.3 ± 4.6 years	Administered after nebulized albuterol, IV corticosteroids, two doses of nebulized ipratropium, and one dose of IV magnesium sulfate in the ED	*Bolus*: 50 mg/kg in ED; followed by 75 mg/kg (≤30kg) or 50 mg/kg (> 30kg) over 30–45 min *Infusion*: 40 mg/kg/h for 4 h	4 h	Serum magnesium concentrations at end of infusion were 4.4 ± 0.8 mg/dL Three patients noted discomfort with the infusions but received them as ordered. No patients needed to discontinue the infusion due to ADEs. No episodes of hypotension, respiratory failure, neurologic problems, or nausea
Egelund et al. (14) (Prospective cohort study)	Magnesium group (n = 19); control group (n = 38)	Mean 8.9 ± 4.2	Included patients admitted to the PICU with status asthmaticus	*Bolus*: one dose of 75 mg/kg (≤30 kg) or 50 mg/kg (> 30kg) over 30–45 min *Infusion*: 40 mg/kg/h infusion (utilized ideal body weight if body mass index >30 kg/m^2)	4 h	Three patients had mild infusion-related reactions with magnesium, but no significant ADEs were noted. No difference between groups in systolic and diastolic blood pressure or oxygen saturation. Heart rate and respiratory rate were lower in the magnesium group (heart rate p = 0.03, respiratory rate p = 0.01) but not clinically significant. Mean serum magnesium concentration post infusion was 4.4 ± 0.98 mg/dL
Vaiyani and Irazuzta (15) (Retrospective study comparing two magnesium infusion regimens)	Standard high-dose infusion group (n = 19); simplified infusion group (n = 10)	1–17 years (specific age not reported)	Administered after IV corticosteroids, two doses of nebulized ipratropium, and 5 mg of nebulized salbutamol every 20 min after 2 h of treatment	Standard high-dose infusion: *Bolus*: ≤30 kg—75 mg/kg or >30kg—50 mg/kg over 30–45 min *Infusion*: 40 mg/kg/h for 4 h (utilized ideal body weight if body mass index > 30 kg/m^2) Simplified infusion group: *Bolus*: None *Infusion*: 50 mg/kg/h for 5 h	4–5 h (depending on group)	No significant difference in magnesium concentration between groups. No significant difference in hemodynamic parameters, oxygen saturation, or respiratory rate between groups. No significant difference in ADEs between groups

(Continued)

TABLE 1 | (Continued)

Reference (study type)	Sample size	Age (years)	Place in therapy for magnesium infusions	Magnesium dosing regimen (bolus/infusion and dosing)	Magnesium infusion duration	Results
Irazuzta et al. (16) (Prospective, randomized, open-label study)	Magnesium prolonged bolus group (n = 19); High-dose magnesium infusion group (n = 19)	Magnesium prolonged bolus: 9.0 ± 2.9 years; High-dose magnesium infusion: 11.1 ± 3.8 years	Administered after IV corticosteroids and 5 mg of nebulized salbutamol every 20 min for 2 h	Prolonged magnesium bolus: *Bolus*:50 mg/kg bolus over 1 h High-dose magnesium infusion: *Bolus*: None *Infusion*: 50 mg/kg/h (max 8,000 mg) for 4 h	1 h (prolonged bolus group) 4 h (high-dose infusion group)	More patients discharged from ED within 24 h in the infusion versus bolus group, 47 versus 10%, p = 0.032; with absolute risk reduction of 37% (95% CI: 10–63%). Total length of stay was lower in the infusion versus bolus group, 34.13 ± 19.54 h versus 48.05 ± 18.72 h, p = 0.013. No ADEs noted in either group
Magnesium infusion administered over > 24 h						
Glover et al. (17) (Retrospective chart review)	40	Mean 6.8 ± 5.4 years	Administered after nebulized albuterol, ipratropium bromide, and IV methylprednisolone; 28 patients received aminophylline and four patients received ketamine	*Bolus*: Administered in 21 patients; overall mean 29.6 ± 13.2 mg/kg; administration time not defined *Infusion*: Overall mean 18.4 ± 6.5 mg/kg/h	Overall mean: 75.2 ± 74.9 h ≤30 kg: 93.8 ± 89.2 h >30 kg: 49.9 ± 39.3 h	Significant difference between those ≤30 kg versus >30 kg for initial bolus dose, 35.3 ± 12.7 versus 21.9 ± 12.7 mg/kg ($p < 0.05$) and maintenance infusion, 21.6 ± 6.0 versus 14.6 ± 4.2 mg/kg/h ($p < 0.05$). No difference in serum magnesium concentrations between those ≤30 kg versus >30 kg, 3.9 ± 0.6 versus 3.6 ± 0.5 mg/dL ($p > 0.05$). No cardiovascular ADEs noted with magnesium; one magnesium infusion was stopped in a patient who was experiencing over-sedation
Graff et al. (18) (Retrospective chart review)	154	Median 8 years (IQR 5–11.8 years)	Nebulized albuterol continuously or every 2 h, ipratropium bromide, and systemic corticosteroids; 40 patients received adjunctive therapies (aminophylline, terbutaline, and/or theophylline) while on the magnesium infusion	*Bolus*: 50–70 mg/kg (max 2,000 mg/dose) over 20 min *Infusion*: 25 mg/kg/h (max 2,000 mg/h), titrated in 5 mg/kg/h increments to maintain serum magnesium concentration between 4 and 6 mg/dL (i.e., drawn every 6 h during infusion)	Median 53.4 h (range 24–177.5 h)	82.5% of patients reached the therapeutic range by the 2nd concentration and 95% by the 3rd concentration. 48.1% of patients experienced hypotension that was primarily diastolic hypotension (94%). Five patients with hypotension events required interventions: 0.9% saline bolus (n = 2), maintenance IV fluids (n = 1), and reduction in magnesium infusion rate (n = 2). Nine of those without hypotension also received fluid boluses. Non-cardiovascular non-severe ADEs included nausea/emesis (22.7%), transient weakness (14.9%), flushing (6.5%); severe ADEs included hypotonia (0.65%), escalation of respiratory therapy (1.9%), and sedation (0.65%). Supratherapeutic concentrations >6 mg/dL occurred in 2% of patients and not associated with ADEs

ADEs, adverse drug events; SABA, short acting beta agonist; IV, intravenous; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF_{25-75}, forced expiratory flow at 25–75% of forced vital capacity; ED, emergency department; PICU, pediatric intensive care unit; IQR, interquartile range.

in the ED. Their magnesium infusion protocol in the PICU consisted of an IV magnesium sulfate loading dose of 75 mg/kg if ≤30 kg or 50 mg/kg if >30 kg over 30–40 min followed by a 40 mg/kg/h infusion for 4 h. Patients that were mechanically ventilated or received non-invasive ventilation were not eligible to receive magnesium infusions. During the infusion, none of the patients discontinued magnesium sulfate infusion due to adverse events, and there were no reported symptoms of hypotension, flushing, or nausea and vomiting. Twelve (63.2%) patients had serum concentrations of magnesium and electrocardiograms performed; both of which were within normal limits. By the end of the infusion, serum magnesium concentrations were 4.4 ± 0.8 mg/dL and ionized magnesium concentrations were 0.95 ± 0.2 mmol/L. The predictive value of serum magnesium and ionized magnesium concentrations was only moderate, with r^2 = 0.541. The authors concluded that magnesium infusions were feasible in the PICU, and serum magnesium concentrations did not predict ionized magnesium concentrations. This study was limited in that it was a retrospective study, so it is difficult to determine the timing of the magnesium sulfate infusion and adverse events. In addition, these findings lacked an assessment of clinical outcomes.

Egelund et al. performed a follow-up prospective cohort study of the report by Irazuzta et al. in 57 patients admitted to the PICU with status asthmaticus (13, 14). They compared the safety of magnesium sulfate infusion in 19 children receiving a magnesium infusion versus 38 children in the control group. In addition, they utilized magnesium concentrations to determine the pharmacokinetic parameters of patients receiving magnesium sulfate. Patients that had an instrumented airway or tracheotomy or history of renal dysfunction were not eligible for inclusion in the study. The patients in the treatment group received the same magnesium infusion regimen as in the initial study by Irazuzta et al. (13). However, in this study, the magnesium doses for patients with a body mass index (BMI) >30 kg/m^2 was based on their ideal body weight. They compared vital signs and magnesium concentrations before bolus, after bolus, mid-infusion, and at the end of the infusion. There was a significant difference in the age between the magnesium infusion and control groups (p = 0.0038); no other differences in demographics were noted. There were statistically significant differences between treatment and control groups in heart rate (-5.95 beats per min, 95% CI: -11 to -0.73; p = 0.03) and respiratory rate (-4.69 breaths per min, 95% CI: -7.79 to -1.60; p = 0.01), but these results were not clinically significant. In addition, there were no significant differences in systolic and diastolic blood pressures and oxygen saturations between groups. Three patients in the treatment group (15.8%) experienced nausea, vomiting, flushing, and injection site pain that the authors attributed to magnesium sulfate therapy. The mean serum magnesium concentration at the end of infusion was 4.4 ± 0.98 mg/dL, and the estimated volume of distribution was 0.4 ± 0.13 L/kg with a clearance of 1.58 ± 0.24 mL/kg/min. The authors noted that magnesium was associated with a lower heart rate and respiratory rate than controls, but no significant adverse events were noted. They also commented that the serum concentrations at the end of infusion were within the range to achieve smooth muscle relaxation based on data from previous studies. This study was limited in that there was no description of matching performed for the control and treatment groups, and no comparison of clinical outcomes was performed between groups.

As a follow up to the initial feasibility study, Vaiyani et al. conducted a retrospective study in children comparing vital signs and magnesium concentrations between patients receiving two different magnesium infusion regimens in the ED setting (15). Patients with a history of renal dysfunction or chronic respiratory compromise or instrumented airway were excluded from the magnesium infusion protocols. They compared patients receiving the magnesium sulfate regimen from their standard high-dose infusion utilized in previous studies, which consisted of magnesium sulfate IV bolus of 75 mg/kg if ≤30 kg or 50 mg/kg if >30 kg over 30–40 min followed by a 40 mg/kg/h infusion for 4 h (n = 19) versus a simplified infusion of 50 mg/kg/h for 5 h with no initial bolus (n = 10) (13, 14); for obese patients, magnesium sulfate dosing was determined using ideal body weight. The authors found no significant difference in vital signs or serum magnesium concentrations between groups. No adverse events were noted, and no patients had their magnesium infusion discontinued. The authors determined that patients receiving the simplified magnesium infusion without a loading dose produced similar magnesium concentrations compared to their standard high-dose magnesium infusions with loading doses. They postulated that a simplified dosing regimen could reduce potential for medication errors without changing serum magnesium concentrations. However, it should be noted that this study's findings are limited by its retrospective design and lack of comparison of clinical outcomes between groups.

Irazutzta et al. conducted a prospective study comparing a prolonged magnesium sulfate bolus versus a high dose simplified magnesium infusion in children 6–16 years of age with status asthmaticus on the rate of patient discharges from the ED at 24 h, LOS, and healthcare costs (16). Patients in this study were randomized to receive either a prolonged IV magnesium sulfate bolus of 50 mg/kg over 1 h (n = 19) or a high-dose IV magnesium infusion of 50 mg/kg/h for 4 h (maximum 8,000 mg/4 h) (n = 19). Along with the magnesium therapy, patients received standardized additional management strategies including supplemental oxygen via Venturi or rebreathing masks for a goal oxygen saturation of >90%, nebulized albuterol every 2 h, and IV dexamethasone 0.2 mg/kg every 6 h. As patients clinically improved, they were transitioned to oral prednisone 2 mg/kg/dose (maximum 60 mg/dose) every 8 h, nebulized albuterol every 4 h, and switched to nasal canula as their oxygen requirements decreased. Compared to the prolonged bolus group, the high-dose magnesium infusion group had a statistically significant greater chance of being discharged from the ED within 24 h (p = 0.032) and a shorter hospital LOS (p = 0.013). Additionally, the hospital cost per patient was significantly different between the high-dose infusion and prolonged bolus groups ($603.16 ± 338.47 versus $834.37 ± 306.73 respectively; $p < 0.016$). Similar to their previous studies, there were no clinical hypotension events, and no patient in the study needed to discontinue magnesium sulfate due to adverse events. No patients in the study needed PICU

admission or mechanical ventilation. The authors concluded that, for patients with asthma exacerbations unresponsive to conventional therapies alone, high-dose magnesium infusions are superior as adjunctive therapy compared to a prolonged IV bolus of magnesium. Compared to the previous studies, this study did not include an assessment of magnesium concentrations, and there was no description if the magnesium dosing was adjusted for patients who were obese.

Magnesium Infusions Administered Over >24 h

Glover et al. conducted a retrospective chart review of 40 children who presented with refractory wheezing that received a magnesium sulfate infusion in the PICU (17). The goal of the study was to identify dosing strategies and the safety profile of magnesium. Fifteen patients (36.6%) were mechanically ventilated before receiving magnesium infusions. Twenty-one patients (52.5%) received a mean IV magnesium sulfate dose of 29.6 + 13.2 mg/kg (time of administration not provided), and there was a significant difference in the bolus dose between children ≤30 kg versus >30 kg ($p < 0.05$) (**Table 1**). The overall mean infusion dose was 18.4 ± 6.5 mg/kg/h, and there was a significant difference in the infusion dose between groups, $p < 0.05$ (**Table 1**). There was also a significant difference between the duration of magnesium infusions between those ≤30 versus >30 kg ($p < 0.05$) (**Table 1**). Despite the differences in the dosing between groups, there was no significant differences between magnesium serum concentrations between those ≤30 versus >30 kg (3.9 ± 0.6 versus 3.6 ± 0.5 mg/dL, $p > 0.05$) (**Table 1**). There were no adverse cardiovascular events during magnesium therapy; one patient had their magnesium infusion discontinued secondary to over-sedation which they attributed to magnesium. The authors concluded that magnesium sulfate infusions are safe in pediatric patients and could be an option for refractory asthma treatment in the PICU. It is important to note that the authors did not assess the impact on clinical outcomes. In addition, the authors did not report when magnesium concentrations were obtained during therapy, so it may be difficult to compare these findings to other studies assessing magnesium concentrations.

Graff et al. performed a retrospective study of 154 children who received magnesium sulfate infusions for >24 h for the treatment of refractory status asthmaticus in the PICU; their primary focus was evaluation of non-cardiac and cardiac adverse events and supratherapeutic magnesium concentrations (18). Their magnesium sulfate infusion regimen included an IV bolus of 50–70 mg/kg (maximum 2,000 mg/dose) over 20 min followed by an infusion at 25 mg/kg/h (maximum 2,000 mg/h); their infusion was titrated by 5 mg/kg/h to obtain magnesium concentrations between 4 and 6 mg/dL. Forty patients (26.0%) received additional adjunctive agents with their magnesium infusion including terbutaline, aminophylline, and/or theophylline. The mean duration of therapy was 53.4 h, and a mean of 7 (range 4–10) magnesium concentrations per patient were obtained during their magnesium infusion. Supratherapeutic concentrations (>6 mg/dL) occurred in 2% of patients and were not associated with adverse events. In terms of safety, there were 170 hypotensive events in 74 patients (48.1%), of which the majority (94%) had primarily diastolic hypotension on one blood pressure reading. Only five hypotensive events required interventions. The authors did not find a significant difference in development of hypotension between patients who received magnesium infusions alone and those who received magnesium infusions and other adjunctive agents ($p = 0.08$). In addition, they did not find a difference in hypotensive events among those who had supratherapeutic concentrations, therapeutic concentrations, or around times of infusion initiation/changes ($p = 0.57$). They noted other non-cardiac adverse events including nausea/emesis (22.7%), transient weakness (14.9%), and flushing (6.5%). Five patients (3.2%) experienced severe adverse events such as hypotonia (0.65%), escalation to continuous or bilevel positive pressure (1.9%), and sedation (0.65%); all of these were attributed to the patient's underlying condition and not their magnesium infusion. No patient required endotracheal intubation. The authors concluded that magnesium infusions were well tolerated; they did note that diastolic hypotension was common but only a few patients required interventions. While the authors concluded that magnesium is safe, they did not study its efficacy or place in acute asthma therapy.

DISCUSSION

The use of a short magnesium sulfate infusion administered over 20 min is a common option for children with asthma exacerbations to improve lung function and decrease the odds of hospital admission (4, 7–9). However, many clinicians have opted to utilize longer infusions of magnesium sulfate over ≥1 h for children with refractory asthma exacerbations or status asthmaticus who fail conventional treatments. As noted in our systematic review, there was wide variability in the dosage regimens utilized. The majority ($n = 299$; 66.9%) received magnesium sulfate infusions ≥4 h, with 43.4% of them receiving them >24 h (13–18). Most of these patients ($n = 261$; 58.4%) received these infusions in the PICU, with the remaining patients receiving these agents in the pulmonary clinic, ED, or the in-patient wards (13, 14, 17, 18). Only three reports including 186 patients (41.6%) documented the impact of magnesium infusions on clinical outcomes including lung function parameters or PICU transfers (11, 12, 16).

There was significant variability in the dosing regimens utilized in these reports. Approximately 33.1% of patients received a magnesium sulfate infusion over 1 h with the majority receiving 40–50 mg/kg/dose (11, 12). This dosage regimen is consistent with previous studies that have evaluated the simulated pharmacokinetics of different magnesium sulfate bolus doses. Rower et al. simulated the pharmacokinetics of 54 children receiving magnesium sulfate 50 mg/kg (maximum 2,000 mg/dose) over 20 min to determine the dosage regimen to achieve target magnesium concentrations between 2.5 and 4.0 mg/dL (7). They found that doses between 50 and 75 mg/kg were necessary to achieve serum magnesium concentrations within their targeted range. However, given this study assessed

the pharmacokinetics of magnesium sulfate administered over 20 min, it is difficult to elucidate the impact of magnesium sulfate regimens administered ≥1 h like the studies by DeSanti and Özdemir et al. (11, 12).

For the remaining 66.9% (n = 299) of patients who received a magnesium infusion over ≥4 h, the majority of these patients (n = 251; 56.2%) received a bolus dose of 50–75 mg/kg/dose prior to receiving their subsequent magnesium infusion (13–18). In four reports, patients received 40–50 mg/kg/h of magnesium sulfate over 4–5 h infusion (13–16). Whereas, in two reports assessing magnesium infusions >24 h, patients received 18.4–25 mg/kg/h for a duration of 53.4–177.5 h (17, 18). Only two of these studies compared clinical outcomes and adverse events among patients who received different dosage regimens (15, 16). Given the different dosing regimens and study designs of these reports, it is difficult to compare these studies.

Two studies reported that patients' doses were determined by ideal body weight rather than actual body weight, but they did not articulate any clinical differences in non-obese versus obese children (14, 15). Previous studies have identified pharmacokinetic alterations in obese children including an increase in fat mass compared to lean body mass leading to an altered volume of distribution for certain medications in obese children and additional alterations in hepatic and renal function (19, 20). As a result, obese children may have an increased risk for adverse events if they receive a dose based on their actual body weight versus an adjusted dosing weight like ideal body weight (20). A previous study by Tudela et al. assessed the effect of body mass index on magnesium concentrations in pregnant women with pre-eclampsia (21). They noted that increased body mass index was associated with sub-therapeutic magnesium concentrations, and they hypothesized that it was associated with an increase in volume of distribution in these patients. In aforementioned pharmacokinetic study by Rower et al., they were not able to assess the impact of obesity on magnesium concentrations in children (7).

Five reports including 261 patients (58.4%) evaluated magnesium serum concentrations (13–15, 17, 18). It is important to note that one study by Irazuzta et al. evaluated both ionized and serum magnesium concentrations, while the other reports included assessments of serum magnesium concentrations only (13). Irazuzta and colleagues determined that the positive predictive value of serum and ionized magnesium concentrations was moderate and concluded that serum concentrations did not predict ionized concentrations (13). In most of these reports, the desired serum magnesium concentration was 4–6 mg/dL. Only one study evaluated the magnesium pharmacokinetics and noted that volume of distribution was 0.4 ± 0.13 L/kg with a clearance of 1.58 ± 0.24 mL/kg/min; these data are similar to other studies assessing magnesium pharmacokinetics (7, 14). Out of the 261 patients who had magnesium serum concentrations, only three patients (1.1%) were supratherapeutic with a serum concentration >6 mg/dL, and the authors did not attribute any adverse events to their elevated concentrations (18).

The only studies reporting adverse events attributed to magnesium were noted in those receiving infusions over >24 h (17, 18). Clinically significant adverse events included hypotension (n = 74; 16.6%), nausea/vomiting (n = 35; 7.8%), mild muscle weakness (n = 22; 4.9%), flushing (n = 10; 2.2%), and sedation (n = 2; 0.4%). For those with hypotension, 170 events occurred in the 74 patients, with most of these episodes associated with diastolic hypotension (n = 165; 97.1%) (18). Only five of these patients (6.6%) required an intervention to resolve the hypotension including a fluid bolus (n = 2), initiation of intravenous maintenance fluids (n = 1), or a decrease in magnesium infusion rate (n = 2). The only other adverse event that required intervention was nausea/vomiting; thirty of these patients (n = 85.7%) required treatment with ondansetron.

Several practical considerations must be noted when utilizing magnesium sulfate infusions. First, there are limited recommendations for IV concentrations of magnesium sulfate for continuous administration. Magnesium is commercially available as a 50% (500 mg/mL) solution; however, current recommendations are to dilute in dextrose 5 or 0.9% sodium chloride (United States Pharmacopeia) to a usual concentration of 60 mg/mL with a maximum of 200 mg/mL (22). Anecdotally, we currently utilize 40 and 80 mg/mL concentrations; clinicians may need to utilize a more concentrated solution for obese children to minimize volume in patients who may be fluid restricted. Another consideration is related to the drug library for IV smart pump technology for intravenous administration (23). Many institutions may have, in their drug library administration, considerations for intermittent magnesium sulfate boluses for electrolyte replacement. However, their drug library may need to be adjusted to ensure appropriate administration considerations for patients receiving prolonged magnesium sulfate infusions. At this time, due to the limited data pertaining to clinical outcomes, we recommend that the use of prolonged magnesium infusions should be reserved for refractory asthma therapy following other therapies with more robust clinical outcomes, including terbutaline and aminophylline (6). However, if clinicians consider this therapy, given the variability in dosing from these reports, we recommend an initial bolus of magnesium sulfate of 25 mg/kg/dose for those patients with an initial magnesium sulfate concentration <3.5 mg/dL. In addition, we recommend an initial starting dose of 15 mg/kg/h in those <40 kg and 10 mg/kg/h in those >40 kg to achieve a target magnesium sulfate concentration between 4 and 6 mg/dL. Further, we would recommend use of ideal body weight in those ≥2 years of age with a body mass index >95th percentile for weight and sex. We also recommend checking serum magnesium concentrations every 4 h based on the published half-life of approximately 2.5 h and titrate up and down by 5 mg/kg/h to achieve the target magnesium concentrations (7).

In conclusion, there was significant variability in the dosage regimens of those children who received prolonged magnesium sulfate infusions >1 h. Most reports described extended courses of magnesium for ≥4 h for children with refractory asthma treatment. Few reports described the impact of magnesium sulfate on clinical outcomes. Most reports evaluated magnesium serum concentrations and targeted a desired serum concentration between 4 and 6 mg/dL. The only patients who had a documented adverse event were those receiving magnesium >24 h and

included hypotension, nausea/vomiting, mild muscle weakness, flushing, and sedation. Based on the limited clinical evidence available, the use of prolonged magnesium sulfate infusions should be reserved as an option for refractory asthma therapy. Future clinical studies should evaluate the difference in clinical outcomes in those who received prolonged magnesium infusions with other therapies (e.g., aminophylline, terbutaline).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

PNJ, ASD, and NG contributed to the conception, writing, and final edits of this manuscript. All authors contributed to the article and approved the submitted version.

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Multiple Organ Dysfunction Interactions in Critically Ill Children

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Introduction: Multiple organ dysfunction (MOD) is a common pathway to morbidity and death in critically ill children. Defining organ dysfunction is challenging, as we lack a complete understanding of the complex pathobiology. Current pediatric organ dysfunction criteria assign the same diagnostic value—the same "weight"— to each organ system. While each organ dysfunction in isolation contributes to the outcome, there are likely complex interactions between multiple failing organs that are not simply additive.

Objective: Determine whether certain combinations of organ system dysfunctions have a significant interaction associated with higher risk of morbidity or mortality in critically ill children.

Methods: We conducted a retrospective observational cohort study of critically ill children at two large academic medical centers from 2010 and 2018. Patients were included in the study if they had at least two organ dysfunctions by day 3 of PICU admission based on the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) criteria. Mortality was described as absolute number of deaths and mortality rate. Combinations of two pediatric organ dysfunctions were analyzed with interaction terms as independent variables and mortality or persistent MOD as the dependent variable in logistic regression models.

Results: Overall, 7,897 patients met inclusion criteria and 446 patients (5.6%) died. The organ dysfunction interactions that were significantly associated with the highest absolute number of deaths were cardiovascular + endocrinologic, cardiovascular + neurologic, and cardiovascular + respiratory. Additionally, the interactions associated with the highest mortality rates were liver + cardiovascular, respiratory + hematologic, and respiratory + renal. Among patients with persistent MOD, the most common organ dysfunctions with significant interaction terms were neurologic + respiratory, hematologic + immunologic, and endocrinologic + respiratory. Further analysis using

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classification and regression trees (CART) demonstrated that the absence of respiratory and liver dysfunction was associated with the lowest likelihood of mortality.

Implications and Future Directions: Certain combinations of organ dysfunctions are associated with a higher risk of persistent MOD or death. Notably, the three most common organ dysfunction interactions were associated with 75% of the mortality in our cohort. Critically ill children with MOD presenting with these combinations of organ dysfunctions warrant further study.

Keywords: critical care, pediatrics, mortality, multiple organ dysfunction, data science

INTRODUCTION

Multiple organ dysfunction (MOD) is a final common pathway for death and long-term morbidity in critically ill children for many etiologies and pathophysiologic processes (1). Approximately 20% of children have two or more organ dysfunctions at the time of pediatric intensive care unit (PICU) admission (2), while an additional 23% of patients develop new MOD during their PICU course (3). Given that PICU mortality rates are low, various definitions of organ dysfunction are often used as a surrogate for morbidity in the PICU (4). Additionally, survivors of MOD frequently suffer long-term functional impairment and disability (4–6). However, defining single and MODs is challenging, as we lack a complete understanding of the complex pathobiology underlying most cases of MOD (7).

Various diagnostic criteria for pediatric organ dysfunction have been developed, validated, and applied clinically, including those by Wilkinson, Proulx, and the International Pediatric Sepsis Consensus Conference (IPSCC) (8–10). Recently, the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) investigators developed novel consensus criteria for single and MOD based on systematic literature reviews (11). These criteria were validated using electronic health record (EHR) data and they showed improved performance in discriminating mortality compared to the widely used IPSCC criteria for organ dysfunction (12). However, in the PODIUM criteria and in other MOD classification systems, the same "weight" is given to each organ system. While each organ dysfunction in isolation contributes to poor outcomes, there are likely complex pathophysiological interactions between failing organs with effects that are not simply additive. We do not know which combinations of organ dysfunction have the strongest association with poor outcomes. Identifying MOD patients with the most lethal combinations of organ dysfunctions may have important implications for focusing research efforts and personalizing clinical care. Therefore, the objective of this study was to use a data-driven approach to better describe the combinations of organ dysfunctions that are seen critically ill children with MOD, to evaluate the impact of interactions between organ dysfunctions, and to evaluate whether those interactions are significantly associated with persistent MOD or mortality in this population.

Abbreviations: CART, classification and regression tree; EHR, electronic health record; IPSCC, International Pediatric Sepsis Consensus Conference; MOD, multiple organ dysfunction; PICU, pediatric intensive care unit; PODIUM, pediatric organ dysfunction information update mandate; pSOFA, pediatric sequential organ failure assessment.

MATERIALS AND METHODS

Study Design and Population

We conducted a retrospective observational cohort study of patients aged 0–17 years of age admitted to the PICU between 2010 and 2018 (Ann & Robert H. Lurie Children's Hospital of Chicago) or between 2010 and 2016 (University of Chicago Comer Children's Hospital) who had at least two organ dysfunctions by day 3 of PICU admission. Patients were excluded if they had congenital heart disease or if their primary reason for admission was cardiac surgery. Data were extracted from the two institutional EHR databases using structured queries and underwent quality checks for conformity, completeness, and plausibility (13). Only data from the first PICU encounter in each hospitalization was included. Each hospitalization was treated independently. The Institutional Review Boards at Ann & Robert H. Lurie Children's Hospital of Chicago and The University of Chicago approved this study with a waiver of informed consent.

Definitions of Organ Dysfunction

We considered nine different organ dysfunctions in all patients per the PODIUM consensus criteria (cardiovascular, coagulation, respiratory, neurologic, renal, hematologic, immunologic, liver, and endocrinologic). The methods used to calculate these organ dysfunctions from EHR data have been previously published (11). Missing values were assumed to be within the normal range, and therefore negative for organ dysfunction.

Outcomes

We assessed two primary outcomes: development of persistent MOD and death. Death was defined as in-hospital mortality and classified as absolute number of deaths and mortality rate. MOD was defined as the presence of $\geq$2 concurrent organ dysfunctions regardless of cause, and persistent MOD was defined as the presence of MOD on day 7 after PICU admission (14–16).

Statistical Analysis and Classification and Regression Trees

Data were analyzed using R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria) (17). Interaction for

combinations of 2 or 3 organ dysfunctions was analyzed using interaction terms in logistic regression models, with a p-value < 0.005 considered significant (18). We did not examine interactions between coagulation and hematologic dysfunction or coagulation and liver dysfunction given the overlap in their PODIUM diagnostic criteria.

Organ dysfunctions were then incorporated as predictors in a Classification and Regression Tree (CART) model for the outcomes of mortality or persistent MOD to study the non-linear relationship between MOD combinations. The model was derived using 80% of patients in the cohort and validated in the remaining 20%. We used 10-fold cross-validation of the derivation set to prune and fit the CART model. Weighting of cases and costs for misclassification were not used. The performance of this model was assessed using the area under the receiver operating characteristic curve (AUROC).

RESULTS

Overall, 7,897 patients among the two PICU populations met the inclusion criteria. The median age on admission was 6.5 years (interquartile range [IQR] 1.6–13.0). Across both centers, 446 patients (5.6%) died, while 1,002 patients (12.7%) were alive with persistent organ dysfunction by day 7. We examined the incidence of nine different organ dysfunctions in all patients and in patients who died (**Table 1**). The most common organ dysfunctions among all patients were endocrinologic (61%), cardiovascular (51%), immunologic (49%), and neurologic (48%). However, non-survivors had a greater proportion of liver (28%), coagulation (15%), respiratory (11%), and hematologic (10%) dysfunction (**Table 1**). Organ dysfunction severity by 28 days is describe in **Supplementary Table 1**.

Interaction Analysis

Mortality

The organ dysfunction interactions that were significantly associated with the highest absolute number of deaths were cardiovascular + endocrinologic (329 deaths; interaction $p < 0.001$), cardiovascular + neurologic (323 deaths; $p < 0.001$) and cardiovascular + respiratory (316 deaths; $p < 0.001$), while the interactions associated with the highest mortality rates were liver + cardiovascular (35.9% mortality; $p = 0.001$), respiratory + hematologic (21.1% mortality; $p < 0.001$), and respiratory + renal (17.5% mortality; $p < 0.001$) (**Table 2** and **Figure 1**). The effect sizes for organ dysfunction interactions associated with mortality are displayed in **Figure 2**. The result for all combinations of two organ dysfunction interactions are presented in **Supplementary Table 2** and **Supplementary Figure 1**. The median length of stay for survivors with these organ dysfunction interactions was: 10.0 days (IQR 4.9–20.4) for cardiovascular + endocrinologic; 13.3 days (IQR 7.0–24.9) for cardiovascular + neurologic; 14.1 days (IQR 7.8–26.4) for cardiovascular + respiratory; 22.9 days (IQR 12.9–41.4) for liver + cardiovascular; 18.0 days

TABLE 1 | Demographics of patients with organ dysfunction by day 3 of PICU admission.

	All patients ($n = 7897$)	Survivors ($n = 7431$)	Non-survivors ($n = 466$)	p-value**
Age, median [IQR*] (years)	6.5 (1.6–13.0)	6.5 (1.6–13.0)	4.7 (1.0–11.9)	0.002
Sex, male (n, %)	4274 (54.1%)	4014 (54.0%)	260 (55.8%)	0.48
Race				
Black/African American	2586 (32.7%)	2440 (32.8%)	146 (31.3%)	0.04
White	2536 (32.1%)	2392 (32.35)	144 (30.9%)	
Hispanic/Latino	2021 (25.6%)	1907 (25.7%)	114 (24.5%)	
Other/Unknown	754 (9.5%)	692 (9.3%)	62 (13.3%)	
LOS, median [IQR] (days)	7.7 (4.1–15.1)	7.8 (4.3–15.1)	4.3 (1.5–19.0)	<0.001
Mechanical ventilation days, median [IQR]	1.0 (0–5.0)	1.0 (0.0–5.0)	4.0 (1.0–13.0)	<0.001
PRISM III score, median (IQR)	6.0 (2.0–11.0)	6.0 (2.0–10.0)	19.0 (9.0–28.0)	<0.001
Organ dysfunction incidence by day 3 (n, %)				
Endocrinologic	4790 (60.7%)	4414 (59.4%)	376 (80.7%)	<0.001
Cardiovascular	4015 (50.8%)	3634 (48.9%)	381 (81.8%)	<0.001
Immunologic	3878 (49.1%)	3617 (48.7%)	261 (56.0%)	0.002
Neurologic	3800 (48.1%)	3440 (46.3%)	360 (77.3%)	<0.001
Respiratory	3292 (41.7%)	2933 (39.5%)	359 (77.0%)	<0.001
Hematologic	2799 (35.4%)	2519 (33.9%)	280 (60.1%)	<0.001
Renal	2505 (31.7%)	2273 (30.6%)	232 (49.8%)	<0.001
Coagulation	808 (10.2%)	689 (9.3%)	119 (25.5%)	<0.001
Liver	562 (7.1%)	403 (5.4%)	159 (34.1%)	<0.001

IQR, interquartile range.
***Chi-squared performed for categorical variables. Kruskal–Wallis performed for continuous variables.*
p-value > 0.05 considered significant.

TABLE 2 | Top three organ dysfunction interactions associated with increased mortality, by **(A)** absolute number of deaths and **(B)** mortality rate.

	A. Highest absolute number of deaths, *N* (%)			B. Highest mortality rate, *N* (%)		
	2-Way Interactions	**Total *N* (%)**	**Died *N* (%)**	**2-Way Interactions**	**Total *N* (%)**	**Died *N* (%)**
1.	CV + Endo	2603 (33.0%)	329 (12.6%)	Liver + CV	432 (5.5%)	155 (35.9%)
2.	CV + Neuro	2154 (27.3%)	323 (15.0%)	Resp + Heme	1060 (13.4%)	224 (21.1%)
3.	CV + Resp	2007 (25.4%)	316 (15.7%)	Resp + Renal	964 (12.2%)	169 (17.5%)

N = 7897.

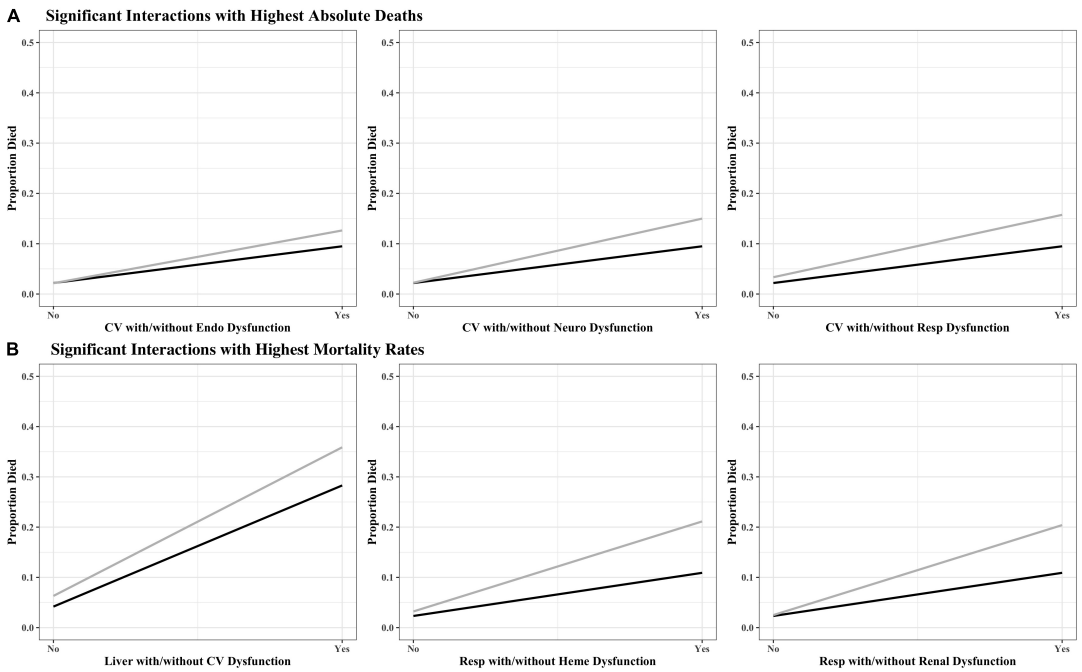

FIGURE 1 | Interaction plots for high-risk organ dysfunction pairs associated with **(A)** the highest number of absolute deaths and **(B)** highest mortality rates. The black line represents single organ dysfunction, while the gray line represents the interaction with the second organ dysfunction. Coag, coagulation; CV, cardiovascular; Endo, endocrinologic; Immuno, immunologic; Heme, hematologic; Neuro, neurologic; Resp, respiratory.

(IQR 10.3–31.5) for respiratory + hematologic; and 16.3 days (IQR 9.8–32.1) for respiratory + renal. When examining interactions for patient with three organ dysfunctions, two interaction terms were significantly associated with mortality: endocrinologic + immunologic + neurologic (164 deaths [15.6% mortality]; $p = 0.003$) and endocrinologic + immunologic + respiratory (171 deaths [17.2%]; $p = 0.002$) (**Supplementary Table 3**).

Persistent Multiple Organ Dysfunction

Among patients who had persistent MOD, the most common organ dysfunctions with significant interaction terms were neurologic + respiratory (557 patients [55.6% of persistent MOD]; interaction $p < 0.001$), hematologic + immunologic (492 patients [49.1%]; $p = 0.007$), and endocrinologic + respiratory (484 patients [48.3%]; $p < 0.001$) (**Supplementary Table 2**). The median length of stay for patients with these organ dysfunction interactions was: 14.0 days (IQR 7.8–25.5) for neurologic + respiratory; 9.7 days (IQR 5.4–18.4) for hematologic + immunologic; and 14.0 days (IQR 7.8–25.9) for endocrinologic + respiratory. Additionally, we examined interactions for patients with three organ dysfunctions. The most frequent organ dysfunctions that had significant interaction terms were endocrinologic + neurologic + respiratory (422 patients [42.1%]; $p = 0.005$), cardiovascular + hematologic + immunologic (279 patients [27.8%]; $p < 0.001$), and endocrinologic + renal + respiratory (215 patients [21.5%]; $p = 0.009$).

Classification and Regression Trees Model

The CART model for mortality is shown in **Figure 3**. This model discriminated death with an AUROC of 0.75 (95% confidence interval [CI] 0.69–0.82) in the validation set. The organ dysfunctions closest to the root node and with the strongest impact in the CART model for mortality were respiratory and liver. The CART model for persistent MOD performed with

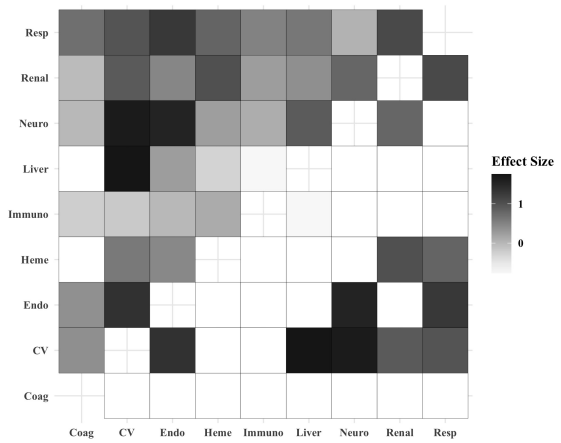

FIGURE 2 | Heatmap displaying the effect size of organ dysfunction interactions and association with mortality. The boxes in the top-left half of the heatmap include the effect size for all of the organ dysfunction interactions based on their coefficients. The boxes in the bottom-right half of the heatmap display only the effect size for the statistically significant organ dysfunction interactions. The white boxes in this half of the heatmap were non-significant and therefore not shaded. Increased box shading indicates a stronger effect size. Coag, coagulation; CV, cardiovascular; Endo, endocrinologic; Immuno, immunologic; Heme, hematologic; Neuro, neurologic; Resp, respiratory.

an AUROC of 0.74 (95% CI 0.70–0.78) in the validation set (**Supplementary Figure 2**). The organ dysfunctions with the strongest impact in the CART model for persistent MOD were hematologic and respiratory.

DISCUSSION

Critically ill children with single organ dysfunction are at risk of developing MOD, persistent MOD, and death (15). Additionally, certain phenotypes of MOD are associated with increased risk of morbidity and mortality (14). In this study, we demonstrate that certain organ dysfunctions significantly interact with each other, increasing the risk for persistent MOD and death. The three most common significant organ dysfunction interactions associated with mortality (cardiovascular + liver, respiratory + hematologic, and respiratory + renal dysfunctions) were associated with 75% of the deaths in our cohort. Additionally, the three most common significant organ dysfunction interactions associated with persistent MOD (neurologic + respiratory, hematologic + immunologic, and endocrinologic + respiratory) were associated with 36.3% of the cases of persistent MOD.

Many of the interactions detailed in our results have been individually described in the literature, with some studies evaluating targeted therapies for specific phenotypes characterized by organ dysfunction combinations. For example, liver with cardiovascular dysfunction has been described in the sepsis-associated macrophage activation syndrome (MAS) phenotype, characterized by shock, hepatobiliary dysfunction, and disseminated intravascular coagulation (DIC) (19). In these high-risk patients with MAS, targeted anti-cytokine therapies have been shown to reduce mortality (20). Another high-risk organ dysfunction interaction in our cohort, respiratory and renal dysfunction, has been described in critically ill children, particularly in the context of fluid overload. Existing literature has linked fluid overload with respiratory failure (particularly in the form of increased ventilator days) and mortality (21, 22).

Classification and regression trees models have previously been used to reveal non-linear interactions between variables in disease states like pediatric sepsis, acute respiratory distress syndrome, and acute kidney injury (23–25). Our CART analysis illustrates which organ dysfunctions tend to drive the association with the outcome. To our knowledge, this is the first CART analysis examining interactions in pediatric MOD. For non-survivors in our cohort, respiratory and liver dysfunction were shown drive the association with mortality, as these were the first nodes in the classification tree. For example, patients with MOD that have no respiratory or liver dysfunction in the first 3 days of PICU admission have the lowest risk for death at 2% mortality, compared to patients with liver but no respiratory dysfunction (8%), respiratory but no liver dysfunction (7%) or with both dysfunctions (38%). For persistent MOD, the association was driven by hematologic and respiratory dysfunction. Critically ill children without hematologic or respiratory dysfunction in the first 3 days of admission have the lowest risk for developing persistent MOD (2%) compared to when both dysfunctions are present (34%).

Our study has several strengths and limitations. Patient data was extracted from EHR databases corresponding to two large, urban, academic PICUs. The size and heterogeneity of the patient population is an advantage from a generalizability standpoint. However, our cohort may not be representative of all PICU populations, particularly in smaller, less urban, or non-academic settings. Expanding to other centers would provide us with increased power to detect other statistically significant interactions in organ dysfunction and death. Additionally, this retrospective study only describes the association of organ dysfunction interactions that occur within 3 days of PICU admission; we were unable to link this with admission diagnoses or assess longitudinal change in organ dysfunction. For example, if a patient is admitted with cardiovascular dysfunction and later develops liver dysfunction, is that patient's trajectory different from someone who first develops liver dysfunction, followed by cardiovascular dysfunction? Similarly, the PODIUM criteria do not differentiate between acute or chronic organ dysfunction. It is plausible that patients with existing, chronic organ dysfunction who then develop acute-on-chronic dysfunction may have a higher risk for a poor outcome compared to patients with only acute organ dysfunctions. As our diagnostic tools improve, criteria like PODIUM will be better equipped to diagnose organ dysfunction in a timely and specific way. Third, our analysis did not control for factors such as age, comorbidities, or genetic factors, although age is accounted for in the PODIUM consensus criteria. It is plausible that these factors could be influential in organ dysfunction interactions, especially related to progressive morbidity or mortality (26).

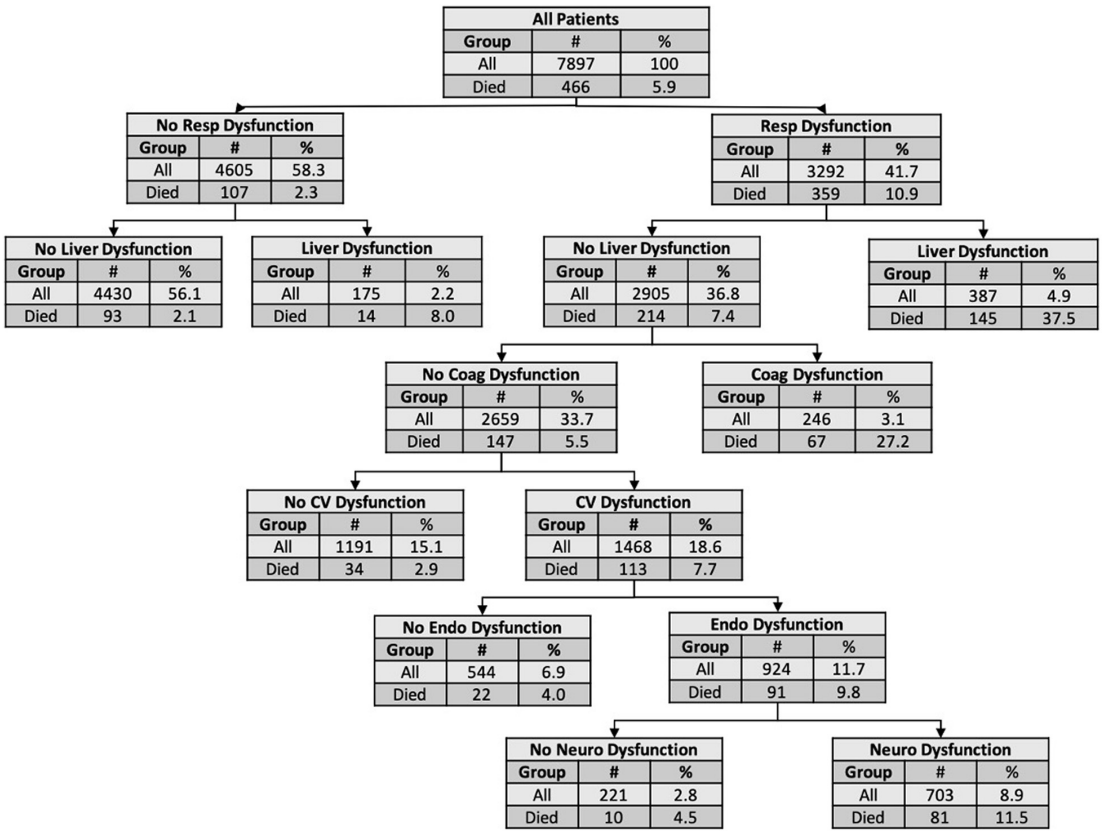

FIGURE 3 | Classification and regression tree for mortality. The nodes and leaves were based on 10-fold cross validation in the derivation set but the numbers presented are for the entire cohort. The top node of the decision tree (the root node) shows the total number of subjects in the cohort and the number and proportion of non-survivors. Each subsequent node shows the criterion for subsequent decisions, along with the number and proportion of patients with or without the organ dysfunction and the proportion who died. Terminal nodes show the risk for an individual with the preceding organ dysfunctions. AUROC: 0.75 (95% CI 0.69–0.82). Coag, coagulation; CV, cardiovascular; Endo, endocrinologic; Neuro, neurologic; Resp, respiratory.

In conclusion, organ dysfunction interactions occur frequently in critically ill children and specific interactions are significantly associated with persistent MOD and mortality. Patients presenting with these high-risk organ dysfunction combinations early in their PICU course warrant additional study, as earlier identification of these high-risk patients may impact treatment decisions and clinical outcomes. The high absolute number of deaths associated with certain organ dysfunction combinations warrant further focused research efforts, as targeted interventions on these patients may be able to have a higher clinical impact. Additionally, understanding which organ dysfunction interactions are associated with the highest risk for death may enhance situational awareness and prioritize resource utilization in the intensive care unit, in addition to supporting prognostication of outcomes at the patient level.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ann & Robert H. Lurie Children's Hospital of Chicago Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CB and LS-P designed the study and performed the data analysis. All authors made substantial contributions to drafting and final approval of the manuscript, and agree to be accountable for the content of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.874282/full#supplementary-material

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OPINION
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On Heidis, Howards, and Hierarchies: Gender Gap in Medicine

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Keywords: women, gender, inequality, gap, diversity, inclusion

As a young child, I was always known as a *tomboy*. The Merriam-Webster dictionary defines *tomboy* as a girl who behaves in a manner usually considered boyish. I loved climbing trees, scaling everything in sight, and playing with dirt, and I was never afraid to be just me. Growing up in a small fishing village, I was fortunate to be surrounded by mountains, trees, and beaches that formed the perfect landscape for my adventures. Aunties often gave me disapproving looks as I did not meet their standards of a quiet, obedient girl who was seen but not heard. I was expected to always smile and be perfect. Scrapes and bruises were seen as a reflection of my disobedience; I was supposed to learn how to cook and sew, not take risks with the boys as they jumped headfirst into the water and off cliffs. These unforgiving expectations continued into adulthood, made worse by a society that was biased against women.

While gender inequality can be seen across economic, social, political, intellectual, and numerous other domains, my experience in medicine made me realize that unless we act singularly and collectively, the gap will only continue to widen for our sisters and daughters. Even though more than 50% of medical students in the United States are female[1], gender parity is still not reflected in academia and medical leadership. When female physicians enter the workforce, they find themselves with lower compensations and less institutional support compared to their male counterparts, even when their productivity is higher or comparable. The disparity becomes even more striking in top executive positions that are mission critical such as department chairs, deans, presidents, or even hospital CEOs.

In a recent study involving ∼1.3 million patients, female patients were less likely to experience complications and to die if treated by a female rather than a male surgeon (1). Investigators also found that patients treated by female internists had significantly lower mortality and readmission rates compared with those cared for by male internists within the same hospital, even after adjusting for potential confounders (2). Likewise, numerous other studies have also demonstrated that women physicians tend to be more collaborative and are stronger communicators than their male colleagues–attributes that can lead to improved patient outcomes and satisfaction. Yet, the workplace remains unconducive for the retention and advancement of women. For the same position, the administrative work burden is often higher for women, with a pay gap seen between women and men physicians within all medical specialties. On a micro level, gender biases also continue to prevail, whether conscious or otherwise. I can recount the numerous times when I was introduced by my first name while male peers were introduced within the same setting by their titles. In other instances, the assumption was made that I was the trainee or nurse, and the male trainee was assumed to be the attending or physician in charge, when in fact it was exactly the opposite. I would have comments made regarding my Asian features and youthfulness, minimizing the intellect and skills that I brought to the table. This seems especially true in more technical disciplines, such as surgery or critical care when people tend to view women who look feminine as less competent.

[1]Available online at: https://www.aamc.org/news-insights/press-releases/majority-us-medical-students-are-women-new-data-show (accessed March 18, 2022).

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As a child, and into adulthood, I found myself wired such that I was always leaning in, always competing to accomplish a goal, to be the best, and going the distance to prove myself. In my drive to excel, I have been called intense and assertive, in ways that did not always come across as compliments. In a classic case study by Professor Frank Flynn at Columbia Business School, we saw how changing the name of a successful Silicon Valley venture capitalist, Heidi Roizen to Howard Roizen, impacted how she was judged as a person[2]. Although students rated Howard and Heidi as equally competent, they much preferred Howard and liked him significantly more. Heidi was thought to be selfish and too aggressive, with few wanting to work for or hire her. On the other hand, Howard was regarded as someone that they would want to hang out with, who would make a great colleague and even as a boss. Gender bias penalizes women for behaving in a certain way, especially when it violates what society regards as gender norms. The dominant, assertive, and authoritative behaviors that we associate with leadership tend not to be viewed as attractive in women. Rather, women are supposed to be kind, friendly, deferential, and socially skilled. The incongruity between our biases on gender and leader stereotypes inherently leads to a prejudice where our female leaders are judged more harshly even when they outperform their male counterparts.

If we do not act now, we will continue to have an exodus of female physicians from our profession. We are losing them in the workforce and missing out on having them in leadership positions. We need to disrupt gender stereotypes and insist on systemic and cultural change that will make gender equity and inclusion more than just words. In our day to day, we need to speak up when we witness gender bias. We need to push against comments that are made about our looks and personality, emphasizing, rather our intellect and skillset. We need to stand up for each other and be the other women's sponsors. It is important to share opportunities and always invite other women to the table. We need to be vocal and champion their recognition and advancement. Perhaps it is as simple as taking the opportunity when a woman voices her opinion in a meeting to acknowledge her contribution specifically and restate the point made. We need to amplify the other woman. By taking these small yet tangible steps, we can begin to effect change where we are at this very moment. For those who are in leadership positions, we need to be not just mentors but sponsors of other women. This means using political influence and personal clout to advocate for and place a more junior person in a key position.

Gender inequality is hurting us all as a society. Unless we have true equity, diversity, and inclusion in our workplace, leadership, and culture, we will never achieve the best version of our world. This is a gap that we cannot afford to ignore.

[2]Available online at: https://www.gsb.stanford.edu/experience/news-history/gender-related-material-new-core-curriculum (accessed March 18, 2022).

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Nutritional Support for Pediatric Severe Traumatic Brain Injury

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In critically ill children with severe traumatic brain injury (sTBI), nutrition may help facilitate optimal recovery. There is ongoing research regarding nutritional practices in the pediatric intensive care unit (PICU). These are focused on identifying a patient's most appropriate energy goal, the mode and timing of nutrient delivery that results in improved outcomes, as well as balancing these goals against inherent risks associated with nutrition therapy. Within the PICU population, children with sTBI experience complex physiologic derangements in the acute post-injury period that may alter metabolic demand, leading to nutritional needs that may differ from those in other critically ill patients. Currently, there are relatively few studies examining nutrition practices in PICU patients, and even fewer studies that focus on pediatric sTBI patients. Available data suggest that contemporary neurocritical care practices may largely blunt the expected hypermetabolic state after sTBI, and that early enteral nutrition may be associated with lower morbidity and mortality. In concordance with these data, the most recent guidelines for the management of pediatric sTBI released by the Brain Trauma Foundation recommend initiation of enteral nutrition within 72 h to improve outcome (Level 3 evidence). In this review, we will summarize available literature on nutrition therapy for children with sTBI and identify gaps for future research.

Keywords: nutrition, traumatic brain injury, pediatric intensive care unit, neurocritical care, enteral nutrition

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INTRODUCTION

Nutritional support is an important component of the comprehensive care for critically ill children. Evidence shows that appropriate delivery of energy and macronutrients maximizes the potential for positive outcomes in the pediatric intensive care unit (PICU), while over- or underfeeding may place patients at risk for increased morbidity and mortality (1–9). Guidelines from the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) suggest using indirect calorimetry (IC) to determine an appropriate caloric goal, initiating enteral nutrition (EN) within 24–48 h of PICU admission, and reaching two-thirds of the caloric goal by 7 days (10, 11).

However, questions remain about the optimal prescription of nutrition for children that have suffered a severe traumatic brain injury (sTBI). Prescribing nutrition therapy that is targeted for this population is important because inadequate nutrition results in loss of lean body mass and reduced functional capacity, both of which are uniquely important for recovery from sTBI (12, 13). Additionally, the pathophysiology underlying secondary injury cascades could be modulated through nutritional targets (14).

Here we will present available data regarding nutrition for pediatric patients in the acute period after sTBI, the potential impact of nutrition on patient outcome, and identify gaps for future research.

ENERGY EXPENDITURE AFTER TBI

In the PICU, nutrition support should be individualized to each patient's unique needs because both overfeeding and underfeeding are associated with deleterious effects (15, 16). However, estimating energy and protein requirements is a complex task. In healthy children, nutritional needs vary greatly depending on age, growth velocity, body composition, current nutritional status, and level of physical activity (17). When children become critically ill, the number of variables grows to include fever, sepsis, sedative/neuromuscular blockade, pharmacotherapy, and duration and stage of critical illness (18). Predictive equations are frequently used to estimate energy expenditure and guide prescription of nutrition in critically ill children, but they may over- or underestimate the true metabolic demand (18). The gold standard for measuring resting energy expenditure is indirect calorimetry.

Several studies have applied this technique to sTBI patients to determine their energy expenditure in the acute post-injury period. Original data from several decades ago suggested that sTBI induced a state of hypermetabolism with energy expenditure up to 170% of expected (19, 20). However, these studies were performed before contemporary neurocritical care practices were firmly established, and it has been shown that neuroprotective strategies such as temperature control (21), sedation (22), neuromuscular blockade (23), and burst suppression (24) result in decreased energy expenditure in sTBI patients. In support of this notion, recent studies of energy expenditure after sTBI do not show the same degree of hypermetabolism, with some studies even showing hypometabolism during the acute post-injury period (25, 26). In a prospective observational study by Mtaweh et al. (27), 13 pediatric patients in their first week after sTBI had intermittent measurements of energy expenditure (MEE) by indirect calorimetry. All patients were intubated and sedated with opiates, nearly all were receiving neuromuscular blockade, and none were febrile or seizing during testing. MEE was then compared to predicted resting energy expenditure (pREE) as calculated by two commonly used predictive equations: the Harris-Benedict equation and the Schofield equation. The result was an average MEE/pREE ratio of 70.2 $\pm$ 3.8% and 69 $\pm$ 4.5% expected, respectively.

These data support the notion that contemporary neurocritical care practices may be acting to blunt any expected hypermetabolism. This results in a hypometabolic state during the first week post-injury. Because of this difficulty in predicting energy expenditure after sTBI, indirect calorimetry remains the gold standard for determining caloric need and should be used whenever feasible.

MODE OF NUTRITION DELIVERY

In addition to determining total energy requirement, clinicians must decide the safest and most appropriate mode of nutrient delivery. EN is increasingly considered as the preferred mode of delivery. Compared to parental nutrition (PN), EN may decrease the risk of metabolic derangements, hepatobiliary dysfunction, and infection. EN is also considerably less costly compared to PN (28, 29). In a multicenter, randomized controlled trial of 1,440 critically ill pediatric patients, Fivez et al. showed that delaying the initiation of PN until the 8th day of hospitalization was superior to initiation of PN within 24 h of admission. Patients with delayed initiation of PN had lower rates of new infections, shorter durations of mechanical ventilatory support, and shorter durations of PICU stay (30). A similar result was seen in a large international study of nutrient delivery in mechanically ventilated children by Mehta et al. The study found that intake of a higher percentage of the prescribed dietary energy goal enterally is associated with improved 60-day survival, while mortality is higher in patients who received any amount of PN compared to those that received none (5).

With regard to studies specifically examining TBI patients, a small, randomized control trial of adult patients with moderate TBI by Meirelles et al. showed no difference in mortality, length of ICU stay, and days of mechanical ventilation based on mode of energy delivery (31). However, the authors did report significantly higher serum glucose in the PN group compared to the EN group (102.4 vs. 133.3 mg/dL). To our knowledge, there are no studies evaluating mode of nutrient delivery in pediatric sTBI.

TIMING OF SUPPORT

Delays in nutrition initiation and frequent interruptions to feeding commonly result in largely insufficient macronutrient delivery in PICU patients (5). Numerous studies have shown benefit for patients who receive early EN and for those who achieve adequate energy and protein delivery within 7–10 days (3, 5, 6, 8, 32). Although there is evidence that early EN is feasible and safe in the PICU (33–35), sTBI patients experience many barriers to reaching EN goals, including but not limited to need for vasoactives, high doses of sedatives, and fasting for procedures (36).

In a large adult retrospective cohort study with sTBI patients by Härtl et al. there was significantly higher two-week mortality among patients who were not fed within 5–7 days after TBI. This result represented a 2- and 4-fold increased likelihood of death respectively compared to those who were fed within 5 days of injury (37). In addition, every 10-kcal/kg decrease in caloric intake over the first 5 days was associated with a 30–40% increase in mortality rates.

Similar data have been reported for pediatric TBI patients. In a retrospective analysis of 109 children aged 8–19 years with sTBI, starting nutritional support within 72 h of admission and achieving goal caloric intake by day 7 was correlated with shorter ICU length of stay and improved clinical outcome at discharge (38). Similarly, Meinert et al. showed that patients who had nutritional support initiated within 72 h post-injury had lower mortality and improved functional outcome (favorable GOS-E Peds at 6 months and 12 months) when compared to those who received no nutritional support over the first 7 days post-injury (39). And most recently, a retrospective multicenter study of pediatric TBI patients of all severities showed that initiation of EN later than 48 h after admission was correlated with worse functional status at ICU discharge (change in POPC and change

TABLE 1 | Nutrition for pediatric severe traumatic brain injury.

Reference	Study design	Population			Study aim	Results/conclusions
		N	Inclusion criteria*	Exclusion criteria*		
Balakrishnan et al. (40)	Retrospective	Total N = 416 (N with GCS < 9 = 107)	-Age 0 to 18 -Head injury associated ICD9 diagnosis code	-Head abbreviated ISS of <2 -Died <48h from admission	To compare patients who received enteral nutrition early (≤48h) and late (>48h)	-Lower GCS and higher ISS were associated with delayed initiation of enteral nutrition -Delayed enteral nutrition was associated with worse functional status (POPC/PCPC) at PICU discharge ($p = 0.02$), but not mortality or increased length of stay
Meinert et al. (39)	Secondary analysis of RCT	N = 90	-Age 0 to 18 -Post-resuscitation GCS < 9	-Normal head CT -GCS = 3 with unreactive pupils -Hypotension for >10 min -Hypoxia for >30 min -Penetrating injury	To understand the relationship between the timing of initiation of nutritional support in children with severe traumatic brain injury (TBI) and outcomes	Initiation of nutritional support before 72 hours after TBI was associated with decreased mortality ($p = 0.01$) and favorable outcome (GOS-E Peds) at 6 months ($p = 0.03$) and 12 months ($p = 0.04$)
Mtaweh et al. (27)	Prospective observational study	N = 13	*Same as Meinert et al. (39)* -Weight > 10 kg -Mechanically ventilated	*Same as Meinert et al. (39)*	To evaluate energy expenditure in a cohort of children with sTBI	-MEE/pREE averaged 70.2 ± 3.8%, suggesting that contemporary neurocritical care practices may blunt a hypermetabolic response -Mean MEE/pREE in the favorable outcome group was 76.4 ± 6% vs. 64.7 ± 4.7% in the unfavorable outcome group ($p = 0.13$)
Malakouti et al. (68)	Retrospective	sTBI N = 101 control N = 92	-Age 0 to 15 -GCS < 9	-Admitted to PICU for <7 days	To examine nutritional support in severe pediatric traumatic brain injury patients (cases) and non-traumatic brain injury patients (controls) at a single center	-Nutrition was started 53 ± 20 hrs (range 12–162) after PICU admission -Patients whose intake met nutritional goals on PICU day 7 had earlier initiation of nutrition support than patients who never met the goals; both $p < 0.001$ -Average caloric and protein intakes for PICU days 0-7 were less for the TBI group (52% ± 16% caloric goal and 42% ± 18% protein goal) than for the non-traumatic brain injury group (65% ± 11% of caloric goal and 51% ± 20% of protein goal); both $p < 0.01$
Taha et al. (38)	Retrospective	N = 109	-Age 8 to 18 -GCS < 9	-Multisystem trauma	To examine the timing of nutritional supplement initiation and the timing of achieving full caloric intake in pediatric sTBI	-Starting nutritional support within 72 h of and admission and achieving goal caloric intake by day 7 was correlated with shorter ICU length of stay ($p < 0.01$) and improved clinical outcome (modified PCPC) at discharge ($p < 0.05$)
Briassoulis et al. (41)	RCT	*N* = 40 (*n* = 20 for immune-enhancing diet, n = 20 for standard enteral diet)	-GCS < 9 -Age 0 to 18 6 -Enteral feeds starting within 12h of admission	-Renal or gastrointestinal disease	To analyze the effect of an immune enhancing (IE) diet on infection and metabolic indices in children with sTBI	-Interleukin-8 levels were lower in the IE group compared with the regular formula group by day 5 ($p < 0.04$) -Less gastric cultures were positive in the IE group compared with the regular formula group (26.7 vs. 71.4%; $p < 0.02$) -Nosocomial infections (15 vs. 25%), length of stay (16.7 vs. 12.2 days), length of mechanical ventilation (11 vs. 8 days), and survival (80 vs. 95%) did not differ between groups
Havalad et al. (26)	Retrospective	*N* = 30	-GCS < 9 -Mechanically ventilated	-Required inotropes or pentobarbital	To determine if pREE varies significantly from MEE in a population of head-injured children	-More than half of the estimates of REE differed from measured REE by >10% and there was no correlation between severity of illness and measured REE to explain these inaccuracies, which suggests that nutrition should be prescribed to children with sTBI based on REE to avoid consequences of overfeeding or malnutrition

**Selected criteria relevant for understanding sample characteristics. TBI, traumatic brain injury; sTBI, severe TBI; ISS, illness severity score; GCS, glascow coma scale; MEE, measured energy expenditure; pREE, predicted resting energy expenditure.*

in PCPC) (40). Of note, this correlation did not hold when patients were stratified by TBI severity.

SITE OF ENTERAL NUTRITION DELIVERY

Feeding intolerance, though hard to define, is common in critically ill children. PICU patients that are unable to tolerate gastric feeding may receive EN that is delivered to the small bowel via naso-duodenal or naso-jejunal feeding tube. A randomized controlled trial of pediatric patients receiving mechanical ventilation showed that the percentage of daily caloric goal achieved was less in patients receiving gastric EN vs. small-bowel EN (30 ± 23% vs. 47 ± 22%) (42). There was no significant difference in signs or symptoms of feeding intolerance such as abdominal distension, vomiting, or diarrhea between groups.

sTBI patients may be more susceptible to feeding intolerance due to altered gastric motility, prolonged immobilization, and medication-related ileus (43). Due to this concern, one study in adult patients examined the tolerability of bolus vs. continuous gastric feeds and found that the patients receiving continuous feeds achieved their nutritional goals faster and had less frequent feeding intolerance (44). There are currently no pediatric studies comparing sites of EN delivery in sTBI patients.

IMMUNONUTRITION

Given the complex interplay of the intestines with the immune system, there is emerging interest in the effect of diet beyond its strictly nutritional value (45). The acute period after sTBI is characterized by neuroinflammation that paradoxically perpetuates secondary injury while also promoting repair (46). Due to their roles in cellular metabolism and the inflammatory cascade, substances such as amino acids, electrolytes, and antioxidants have been proposed as dietary supplements that could aid in modulating this delicate balance (47). In a randomized controlled trial with pediatric sTBI patients, patients who were given an immune-enhancing diet supplemented with glutamine, arginine, antioxidants, and omega-3 fatty acids showed no difference in outcomes when compared to patients who were on a regular formula regimen (41).

Based on emerging knowledge about the gut-brain axis, it has been hypothesized that alterations in gut microbiota could influence post-traumatic neuroinflammation (48). A recent study of children with sTBI by Rogers et al. characterized the temporal and spatial alterations in the microbiome during their initial ICU admission (49). Compared to healthy controls, sTBI patients quickly developed dysbiosis. They showed depletion of beneficial bacterial species and enrichment of pathogenic bacterial species over time. Additional studies are needed to determine how these changes impact clinical outcomes.

GLYCEMIC CONTROL

Hyperglycemia is a commonly observed response to the stress of critical illness, which is mediated by alterations in glucose metabolism that are caused by increases in pro-inflammatory and counter-regulatory hormones, such as cortisol and epinephrine (50). This stress hyperglycemia (SH) represents a common secondary insult to the brain after sTBI (51), and has been associated with increased morbidity and mortality in adult and pediatric patients (52–56). Studies examining the effect of tight glycemic control in PICU patients have yielded inconsistent results, with most studies showing no benefit or concern for harm from severe hypoglycemia (57–59).

In a large international RCT in adults with TBI, patients receiving intensive glucose control (target range 80–110 mg/dL) and patients receiving conventional glucose control (target of less than 180 mg/dL) had similar long-term outcomes (60). However, intensive glucose control resulted in more frequent episodes of moderate to severe hypoglycemia, suggesting possible harm. In addition, several small studies in adult sTBI patients have used cerebral microdialysis to demonstrate tight glycemic control is associated with critical reduction in glucose and elevation of lactate/pyruvate ratio in the brain (61, 62). This increase in markers of cellular distress suggests that tight glycemic control results in damaged brain tissue being unable to access the glucose that is necessary for cellular repair and survival (62). There have been no studies evaluating glucose control in pediatric sTBI patients.

DISCUSSION

Adequate nutrition is essential for all critically ill children because malnutrition contributes to immune dysfunction and infections (63), weakness (64), and delayed healing and recovery (65). However, delivering nutrition to patients with sTBI is not a straightforward task. Nutrition therapies for sTBI patients must take into account hydration and electrolyte goals to prevent fluid shifts that could worsen cerebral edema (66). In addition, sTBI is accompanied by unique physiologic derangements. Damage to axons in the autonomic nervous system can lead to delayed gastric emptying and intestinal hypomotility (43). These symptoms are compounded by the use of sedatives and barbiturates (67), which lead to feeding intolerance and the subsequent withholding of enteral nutrition.

Despite these factors, few studies have attempted to identify nutritional interventions that could improve outcome for this patient population (**Table 1**). In general, high-quality nutrition studies are scarce and studies that focus on sTBI are even more uncommon. Most studies to date have been limited by small sample size, retrospective or observational design, and inconsistent inclusion or exclusion criteria. This leads to reduced statistical power, poor generalizability, and difficulty in assessing correlation vs. causation.

In 2019, the Brain Trauma Foundation released updated guidelines for the management of pediatric sTBI, which include a section on nutrition (69). Based on available evidence the authors were able to make two primary recommendations: (1) early initiation of EN (within 72 h of injury) to decrease mortality and improve outcomes, and (2) immune-modulating diet is not recommended to improve outcomes. These recommendations are largely consistent with established guidelines for all critically

ill pediatric patients. The currently available data are insufficient to warrant making further statements about nutritional goals that are unique to sTBI patients; providers should continue to prescribe nutritional support according to the previously mentioned SCCM/ASPEN guidelines.

Further studies are needed to elucidate nutritional recommendations for sTBI patients. It is important that future studies are designed in a manner that generates high-quality data. These studies should optimally be large, prospective trials, and should seek to identify unique nutrition targets for pediatric sTBI patients. This includes identifying an appropriate caloric goal and identifying a threshold for the initiation of targeted glucose control. Additional studies should also seek answers to questions about the timing, mode, and composition of macronutrient delivery and their effect on outcome.

Beyond the strictly caloric value of a sTBI patient's diet, nutritional supplementation may present an opportunity to mediate the effects of brain injury on a cellular level (14, 47, 66). Future clinical and pre-clinical studies should examine how supplementation of certain electrolytes, vitamins, minerals, or amino acids could interact with cellular processes to mediate the inflammatory cascade and restore normal metabolic activities.

Another important consideration when designing future studies is the choice of outcome measure. Although mortality is a traditional primary outcome, functional status is equally important and may be more pertinent in pediatric research (70). Future studies should examine how nutrition combined with early mobilization and rehabilitation impacts deconditioning, muscle wasting, and change in overall functional status. Completion of high-quality studies that answer these questions will maximize the potential for positive outcomes in survivors of sTBI.

Of note, the Approaches and Decisions for Acute Pediatric TBI (ADAPT) Trial recently completed enrollment of 1,000 pediatric patients with sTBI. This trial was designed to use comparative effectiveness to examine the acute medical management of infants, children, and adolescents with severe TBI. Several of the a priori hypotheses put forward by the ADAPT investigators addressed nutrition questions, including many of those raised in this article. We anticipate new data will emerge from ADAPT and from other innovative trial designs, and we look forward to additional studies that will allow for more robust recommendations in the future.

AUTHOR CONTRIBUTIONS

EE, MS, MB, and KW contributed to the writing and editing of this manuscript. All authors contributed to the article and approved the submitted version.

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Predictive Value of Optic Nerve Sheath Diameter for Diagnosis of Intracranial Hypertension in Children With Severe Brain Injury

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Background and Aims: Intracranial Hypertension (ICH) is a life-threatening complication of brain injury. The invasive measurement of intracranial pressure (ICP) remains the gold standard to diagnose ICH. Measurement of Optic Nerve Sheath Diameter (ONSD) using ultrasonography is a non-invasive method for detecting ICH. However, data on paediatric brain injury are scarce. The aim of the study was to determine the performance of the initial ONSD measurement to predict ICH occurring in children with severe brain injury and to describe the ONSD values in a control group.

Methods: In this cross-sectional study, ONSD was measured in children aged 2 months-17 years old with invasive ICP monitoring: before placement of ICP probe and within the 60 min after, and then daily during 3 days. ONSD was also measured in a control group.

Results: Ninety-nine patients were included, of whom 97 were analysed, with a median (IQR) age of 8.7 [2.3–13.6] years. The median (IQR) PIM 2 score was 6.6 [4.4–9.7] and the median (IQR) PELOD score was 21 [12–22]. Aetiologies of brain injury were trauma (n = 72), infection (n = 17) and stroke (n = 8). ICH occurred in 65 children. The median (IQR) ONSD was 5.58 mm [5.05–5.85]. ONSD performed poorly when it came to predicting ICH occurrence within the first 24 h (area under the curve, 0.58). There was no significant difference between the ONSD of children who presented with ICH within the first 24 h and the other children, with a median (IQR) of 5.6 mm [5.1–5.9] and 5.4 mm [4.9–5.8], respectively. Infants aged less than 2 years had a median (IQR) ONSD

of 4.9 mm [4.5–5.2], significantly different from children aged more than 2 years, whose median ONSD was 5.6 mm [5.2–5.9]. Age, aetiology or ICP levels did not change the results. Thirty-one controls were included, with a median age of 3.7 (1.2–8.8) years. The median (IQR) of their ONSD measurement was 4.5 mm [4.1–4.8], significantly lower than the patient group.

Conclusion: In a paediatric severe brain injury population, ONSD measurement could not predict the 24 h occurrence of ICH. Severity of patients, timing and conditions of measurements may possibly explain these results.

Keywords: children, brain injury, intracranial hypertension, ultrasonography, optic nerve

INTRODUCTION

Intracranial hypertension (ICH) is a severe complication of paediatric acute brain disorders that can be life-threatening. Establishing a clinical diagnosis of ICH is, at times, difficult due to the lack of cooperation from infants, the lack of specificity of ICH clinical manifestations and because sedation is often necessary for disease management. To confirm a diagnosis of ICH, the invasive measurement of intracranial pressure (ICP) is performed using an intraparenchymal probe or intraventricular catheter. This invasive device remains the gold standard to diagnose ICH and to monitor ICP. Several non-invasive tools have been also developed to detect ICH, including the ultrasound measurement of the Optic Nerve Sheath Diameter (ONSD). The optic nerve is an extension of the central nervous system (CNS) surrounded by a sheath. This sheath, which is an extension of the dura mater and contains cerebrospinal fluid, can indeed distend depending on ICP changes (1–3).

There is an extensive amount of literature available regarding adult patients that shows a good correlation between ONSD and ICP measurement (4–6). However, no threshold measurement has currently met general approval. Aletreby et al. have recently found, in an adult meta-analysis, a cut-off of ONSD between 4.8 and 6.4 mm to detect ICH (7). However, in adults with severe trauma brain injury (TBI), another meta-analysis found a cut-off of 5.8 mm to predict ICH (8). In children, data are much scarcer, with results as well as sensitivity and specificity values varying greatly. A recent paediatric meta-analysis has reviewed the diagnostic performances of ONSD and found sensitivities between 39 and 100% and specificities between 22 and 100% (9). Some studies found a good correlation between ONSD and ICP, such as Kerscher (10) or Padayachy (11), whereas others do not find this correlation, such as Biggs (12) and Sharawat (13). It is noteworthy that few paediatric studies used invasive measurement of ICP (10, 11, 13, 14).

The main objective of the present study was to determine the performance of the ONSD measurement to predict ICH occurring within the first 24 h of placing an invasive ICP measurement probe in severe brain-injured children hospitalised in paediatric intensive care units (PICUs). The secondary objectives were to compare infants to children aged over 2 years old, to compare the ONSD measurement depending on the aetiology of brain injury, to describe the evolution of the ONSD measurement over a period of 3 days and to describe the ONSD values in sedated, ventilated children without brain injury (control group). We hypothesised that ONSD measurement would identify ICH in severe brain-injured children with sufficient precision.

MATERIALS AND METHODS

Setting and Patients

This prospective, cross-sectional and multicentre study was conducted in the Lyon and Grenoble PICUs, in France. We included consecutively children aged from 2 months to 17 years old, hospitalised for severe brain injury requiring invasive ICP monitoring according to the physician in charge of the patient. Children with a history of ocular disease, brain malformation or brain tumour, or chronic ICH were not included.

Moreover, we included a control group of children of the same age range who were sedated, intubated-ventilated and who did not have any brain injury. Before the inclusion of a child, an informed consent form was signed by both parents. A favourable opinion from the Comité de Protection des Personnes (CPP) Sud Est II (the research ethics committee for South-East of France) was granted on January 5, 2011. An authorisation from the AFSSAPS (former French National Agency for Medicines and Health Products Safety) was granted on December 20, 2010. The study was reported on clinicaltrials.gov (NCT01796015) and funded by the invitation to tender Actions Incitatives HCL 2009 N° D50705. Promotion was performed by the Hospices Civils de Lyon (HCL - n°2010-A00890-39).

In the PICUs participating in the study, invasive ICP monitoring is commonly performed (Camino, Integra LifeSciences, San Diego, CA, United States) for severe acute brain injury, such as severe TBI, CNS infection with coma, or severe stroke as suggested by some national or international guidelines (15–18).

Design and Data Collection

Optic Nerve Sheath Diameter measurement by ultrasonography is well defined and standardised (19): the diameter is measured 3 mm behind the eyeball, using the electronic calliper of the ultrasonography machine along a two-dimensional axis perpendicular to the optic nerve, with a linear probe. For each optic nerve, one sagittal measurement and one transversal

measurement are taken. The final measurement constitutes the mean of the four measurements taken during each examination. For the patient group, the first examination was performed within the 15 min prior to ICP probe placement. A second examination was performed within the 60 min after ICP probe placement. The examinations were then repeated once a day for 3 days, and performed long before or after any care procedure that may alter ICP. For the control group, a single ultrasound examination was performed.

All the examinations were performed by practitioners trained in this procedure. The ultrasound machines used were the HD11XE (Philips Medical Systems, Bothell, WA, United States) with a 7.5 MHz linear probe in Lyon and the Vivid S6 (GE Healthcare, Milwaukee, WI, United States) with a 9 MHz linear probe in Grenoble. All the examinations were recorded and systematically reread by a first reader (F.C.A. or E.J. if F.C.A. performed the recorded examination), blinded from the ICP value, after all inclusions. If the difference between the reread value and the value initially collected by the practitioner was higher than 0.6 mm, a second rereading between both readers, blinded from the ICP value and the measurement of the first reader, was performed to reach a consensus. The measurement used for the statistical analysis was the one found during rereading. The ICH definition was based on the ICP values with a 15-mmHg threshold for infants aged less than 2 years and a 20-mmHg threshold for children aged over 2 years old. These thresholds were chosen because they were used in clinical practice in both participating centres and because physiological values of ICP are lower in infants compared to older children (15).

Clinical data were collected in a prospective way: demographical data (age, genre, weight), aetiologies of the brain disorders (trauma, CNS infection, stroke) and severity scores (Paediatric Index of Mortality score [PIM-2] at admission and Paediatric Logistic Organ Dysfunction [PELOD] 24 h after admission).

Statistical Analysis

The accuracy of ONSD for the diagnosis of ICH was quantified by the Area Under the ROC Curve (AUC).

A sample size of 97 patients was determined in order to estimate the AUC with a precision of 7% for a 95% confidence interval (CI), under the assumption of an ICH prevalence equal to 50% in the studied population and for an expected AUC of 91%.

The empirical ROC curves were built using the ONSD measured within the 15 min prior to ICP probe placement. The ICH status was determined using the ICP measured during the first 24 h following the ICP probe placement. The AUC estimate and the 95% CI were obtained using the non-parametric method of Delong.

The sensitivity and specificity of ONSD were estimated using the positivity thresholds defined by Padayachy (20). The 95% CI was built using the method of Wilson.

The overall intra-patient correlation between ONSD and ICP measured together several times during the follow-up was estimated using the method allowing to take into account the repeated measures. The non-parametric test of Mann and Whitney was used to compare quantitative variables. The Chi-square test or the Fisher exact test were used to compare qualitative variables.

All the analyses were carried out using the statistical software R, version 3.6.3. The ROC curves and the AUC estimates were obtained using the package pROC (21).

RESULTS

Between April 2011 and February 2017, 99 patients were included (**Figure 1**), 97 of whom were retained for the statistical analysis. Patients' characteristics are described in **Table 1**. During the study period, 404 measurements were performed and 34 examinations were not recorded, which means that rereading was not feasible. Therefore, 269 measurements were reread once and 101 needed a second rereading for consensus. The median (interquartile range [IQR]) of the time interval between the first ONSD measurement and the ICP probe placement was 15 min [10–30]. The median (IQR) of the ICP measurement at baseline was 18.5 mmHg [10.7–28]. The median (IQR) of the ONSD measurement before placing the ICP probe was 5.58 mm [5.05–5.85]. The overall intra-patient correlation between ONSD and ICP was estimated at 0.07 (95% CI −0.07–0.21). ICH occurred in 65 children (67%) within the first 24 h. There was no significant difference between the ONSD of children who presented with ICH within the first 24 h and the other children, with a median (IQR) of 5.6 mm [5.1–5.9] and 5.4 mm [4.9–5.8], respectively ($p = 0.42$). The AUC was estimated at 58% (95% CI 45–70%) and the ROC curve is presented in **Figure 2**. Infants aged less than 2 years ($n = 20$) had a median ONSD (IQR) of 4.9 mm [4.5–5.2], significantly different from children aged more than 2 years ($n = 77$), whose median ONSD was 5.6 mm [5.2–5.9] ($p < 0.001$) (**Figure 3**). Based on the thresholds proposed by Padayachy (20), the diagnostic performance of ONSD at the 5.16 mm threshold in infants aged less than 1 year and at the 5.5 mm threshold in older children showed a 60% sensitivity (95% CI: 48–71%) and a 53% specificity (95% CI: 36–69%). Moreover, we performed a subgroup analysis depending on the age of the children and the aetiology of the brain disorders. ONSD did not differ according to the aetiology (CNS infection, severe TBI or stroke) (**Figure 4**). The diagnostic performance of ONSD to predict the occurrence of ICH was similar in children aged less or more than 2 years with an AUC (95% CI) of 52% (22–82%) and 58% (43–72%), respectively, and comparable whatever the aetiology with an AUC (95% CI) of 65% (34–97%) in children presenting with a CNS infection and of 54% (39–68%) in children with severe TBI. Finally, the distribution of ONSD was very similar regardless of the measurement time during the 4 days of the study (**Figure 5**).

Between April 2011 and March 2015, 31 children were included in the control group. Their demographic characteristics are described in **Table 1**. The median (IQR) of their ONSD measurement was 4.5 mm [4.1–4.8], significantly lower than the patient group ($p < 0.0001$) (**Figure 6**). In this control group, the ONSD in children aged more than 2 years was larger than the ONSD in children aged less than 2 years, with a median (IQR) of 4.6 mm [4.4–4.9] and 4.1 mm [4.0–4.5], respectively.

All examinations were performed uneventfully.

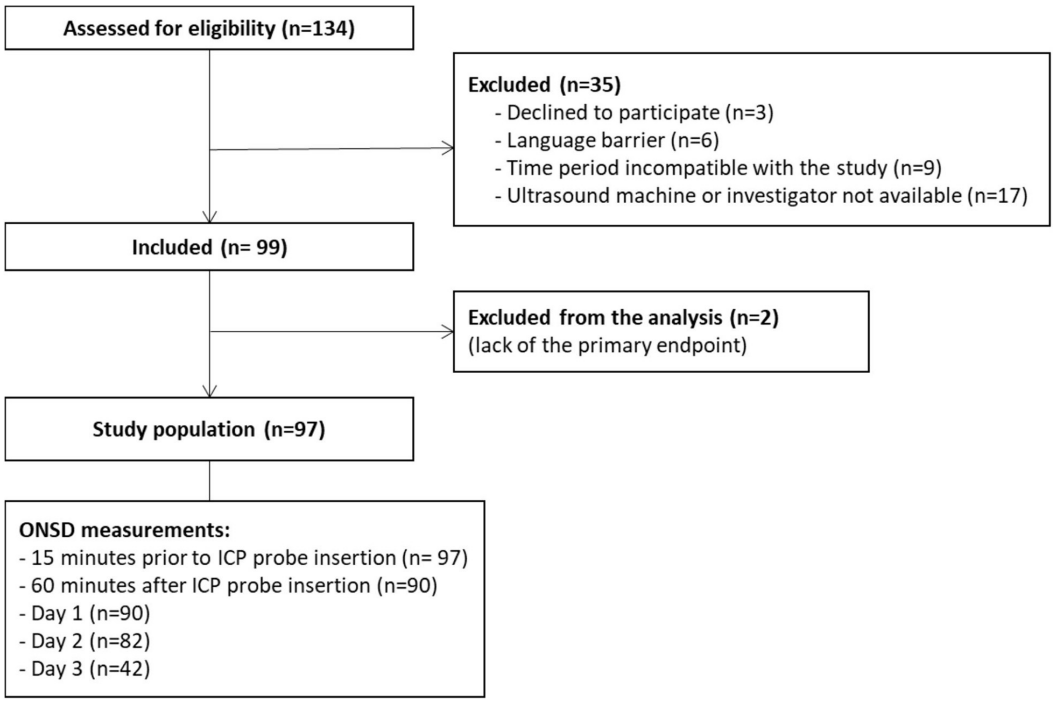

FIGURE 1 | Patients' flow diagram. ONSD, Optic Nerve Sheath Diameter; ICP, intracranial pressure.

TABLE 1 | Patient and control characteristics.

Variable	Overall patient population (*n* = 97)	With ICH (*n* = 65)	Without ICH (*n* = 32)	Control group (*n* = 31)
Demographics				
Age, year, median (IQR)	8.7 (2.3–13.6)	8.6 (2.4–13.1)	9.0 (2.1–14.6)	3.7 (1.2–8.9)
Male, n (%)	63 (64.9)	42 (64.6)	21 (65.6)	19 (61.3)
Weight, kg, median (IQR)	25 (15–50)	25 (15.5–49)	25.2 (14.5–52)	15.5 (10–30) †
Height, cm, median (IQR)	127 (93–156)	128 (98.5–155)	126 (89.5–159)	101 (75.5–131)
Severity scores				
PIM2, median (IQR)	6.6 (4.4–9.7)	7.1 (4.4–11.6)	6.5 (4.3–8.4)	–
PELOD, median (IQR)	21 (12–22)	21 (12–22)	17 (12–21.3)	–
Reason for ICP monitoring				
CNS infection, n (%)	17 (17.5)	13 (20)	4 (12.5)	–
Traumatic brain injury, n (%)	72 (74.2)	45 (69.2)	27 (84.4)	–
Stroke, n (%)	8 (8.2)	7 (10.8)	1 (3.1)	–
ONSD*, median (IQR)	5.58 (5.05–5.85)	5.58 (5.10–5.88)	5.36 (4.88–5.76)	4.51 (4.11–4.83) †
Mortality, n (%)	8 (8.2)	7 (10.8)	1 (3.1)	0 (0)

**For patients, within the 15 min prior to the placement of the ICP probe. Dashes indicate variables only reported for patients. †Indicate significantly results between control and overall patient population. ICH, intracranial hypertension; PIM2, Paediatric Index of Mortality 2; PELOD, Paediatric Logistic Organ Dysfunction; ICP, intracranial pressure; CNS, central nervous system.*

DISCUSSION

In this multicentre study including PICU children, the ONSD was not able to predict ICH occurring within 24 h of ICP probe placement. These data are concordant with those described by Biggs et al. (12), even if their population seemed to be less severely affected with a prevalence of ICH in only 6% of their patients, compared to 67% in our study. A paediatric meta-analysis performed by Bhargava et al. (9) concluded on the inability to identify a threshold for ONSD to predict ICH, with pooled sensitivity of 93% but specificity of only 74%. Our results, however, diverge from those described by other authors in paediatrics. Kerscher et al. (10) found a good correlation between ONSD and ICP in neurosurgical patients, of whom 7% were in ICUs. Our patients were all in ICUs in more severe and acute conditions. This element may modify the ONSD physiology and distensibility. Padayachy et al. also found a good correlation between ONSD and ICP at the time of a neurosurgical

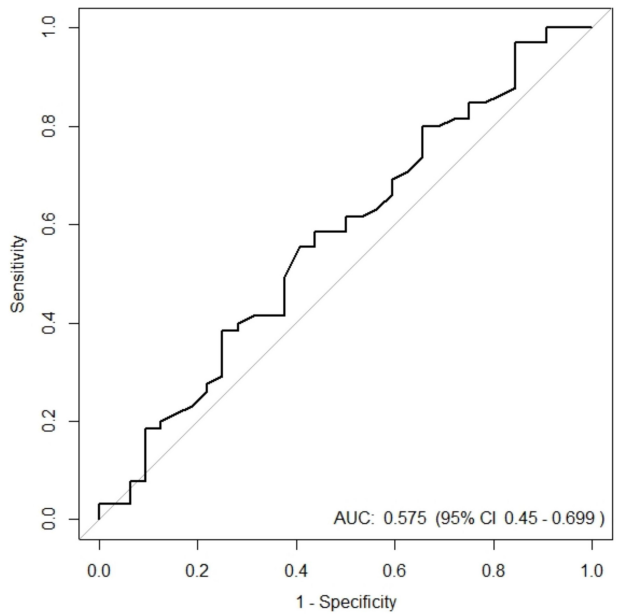

FIGURE 2 | Empirical ROC curve of Optic Nerve Sheath Diameter (ONSD) used to diagnose an intracranial hypertension occurring within the first 24 h following the measurement of ONSD in a paediatric brain injury population. AUC, area under the curve.

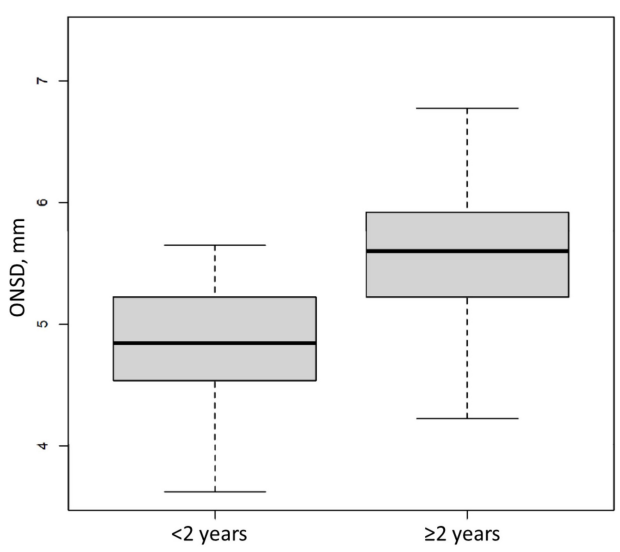

FIGURE 3 | Initial Optic Nerve Sheath Diameter (ONSD) in a paediatric brain injury population according to the age. Box and whisker plots represent interquartile range and 95% CI, respectively, and the horizontal bar indicates the median, $p < 0.001$.

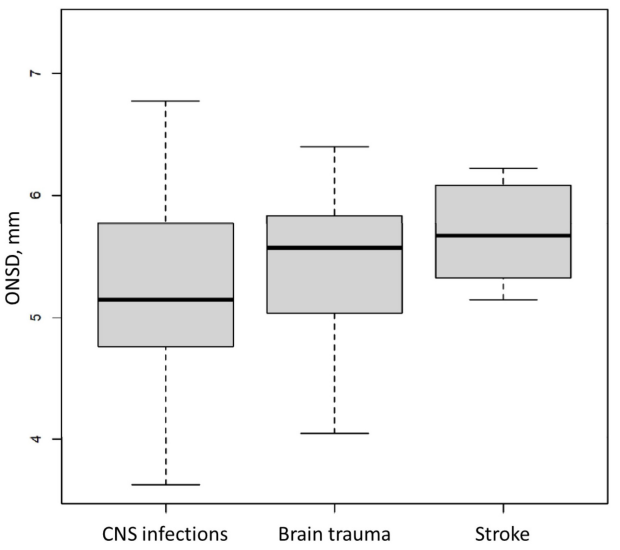

FIGURE 4 | Initial Optic Nerve Sheath Diameter (ONSD) in a paediatric brain injury population according to the aetiology. CNS, central nervous system. Box and whisker plots represent interquartile range and 95% CI, respectively, and the horizontal bar indicates the median.

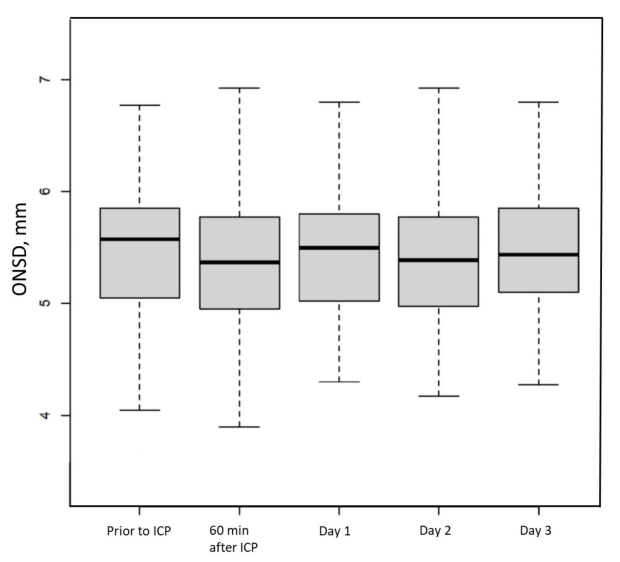

FIGURE 5 | Time course of Optic Nerve Sheath Diameter (ONSD) in a paediatric brain injury population. Box and whisker plots represent interquartile range and 95% CI, respectively, and the horizontal bar indicates the median. ICP, intracranial pressure.

procedure (11, 20). Their patients were included during surgical procedure with an ICH prevalence of 42%. Moreover, aetiologies varied from our population. They included 17% of traumatic brain injury versus 74% in our population, and they did not include CNS infection. These points could lead to differences in ICH mechanism and ONSD physiology, which may explain various results.

The ONSD values were significantly higher in patients compared to those of controls. This result was already found in a usual way, both in adults (8, 19, 22, 23) and in children (1, 13, 24–26).

In the patient group, as in the control group, children under 2 years of age have an ONSD significantly smaller compared to

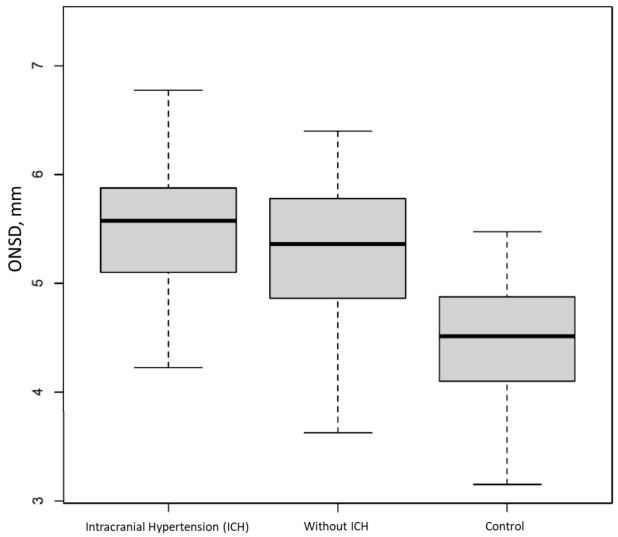

FIGURE 6 | Initial Optic Nerve Sheath Diameter (ONSD) in a paediatric brain injury population. Comparison between patients with or without Intracranial Hypertension (ICH) and the control group. Box and whisker plots represent interquartile range and 95% CI, respectively, and the horizontal bar indicates the median.

children over 2 years of age. There is indeed a growth in the optic nerve sheath, described by Fontanel et al. (25), found up until 10 years of age, but it is particularly pronounced during the first year of life (27). In our study, the children in the control group were younger (median age of 3.7 years) than the patient group (median age of 8.7 years), which may lead to a bias in the interpretation of our results. Fontanel et al. nevertheless described a very moderate growth in this age group (25). It is therefore conceivable that our results may well be a consequence of the neurological condition of our population, rather than related solely to age. However, our results obtained concerning variation with age suggest that age should be taken into account in the analysis of measurements, and that patients included in studies on ONSD should be stratified according to age.

In our patients, the ONSD results were comparable regardless of the cause of the brain injury. This analysis is hardly found in the literature. To our knowledge, only Padayachy et al. described different results depending on aetiology, with higher ONSD values in tumour or craniosynostosis patients (11). In these conditions, the mechanism of ICH is much slower than the causes of brain injury in our patients with different pathophysiological mechanisms that can alter the dynamics of evolution of ONSD.

Moreover, we did not observe a difference in ONSD over a period of 3 days in our patients with enlarged ONSD. We found enlargement at the outset without return to normal at a distance from acute ICH. In our study, the ONSD measurement therefore does not appear to be a relevant tool for monitoring our severe brain-injured patients. This result contradicts what has been observed by other authors. In other adult studies, changes in ICP led to correlated changes in ONSD in real time (28–30). In paediatrics, Vijay et al. also found rapid changes in ONSD in a very specific population having suffered from acute liver failure during acute episodes of ICH, with even a prognostic effect if the return to the baseline value occurred within 2 h (24). On the contrary, other authors found that changes in ICP were poorly correlated with changes in ONSD (10, 31).

The variability of results in the abundant literature on the subject could be explained by effects on the elasticity of the optic nerve sheath, as already described by Padayachy et al. (11), for which physiological studies would be useless. Stevens has recently taken an interest in the many methodological differences in ONSD measurement, which may explain the significant differences in our results, and has suggested four recommendations to follow in order to standardise the measurements in future studies (32). Although our measurements were collected after the publication of Steven's article, they matched three of the four recommendations, i.e., to measure outside the hyperechoic band if visible, to use the papilla as the starting point of the 3-mm depth and to use a high-frequency linear probe. The last recommendation suggests a mechanical index smaller than or equal to 0.3. We do not possess this information *a posteriori*.

The patients included in our study were particularly severely affected, as shown by their high severity scores, with a median PIM2 score of 6.6 and a PELOD score of 21, and the occurrence of ICH in 67% of them. This severity appears to be more significant than that of patients in the other paediatric studies (10, 12, 33). This point may explain part of our results. Indeed, the neurological severity of patients included in the study resulted in an active therapeutic management aiming to decrease ICP, even before ICP probe placement. In the group of patients without ICH, some of them may have presented with ICH, but it was treated and controlled from the start. Therefore, it seems to us that the ONSD measurement does not appear to be a relevant tool for discriminating severe brain-injured patients from the outset. Other authors such as Aletreby et al. (7) and Kerscher et al. (10) also suggested that ONSD may be a complementary tool in emergency departments rather than in ICUs, without replacing invasive measurements.

Regarding the blind rereading of all examinations, the methodology used was rigorous and systematic, allowing us to give value to our results. Even if one of the readers was able to perform the measurement themselves, rereading was performed after all inclusions, which were spread over more than 6 years, allowing concomitant ICP to be forgotten. In this way, the process of blinding was respected.

Our study has nevertheless some limitations. Although the number of inclusion was consistent with the calculation of the number of subjects needed to answer the primary objective, the number of patients per subgroup, and particularly for children younger than 2 years, is limited. As with any ultrasound examination, there is inter-rater variability. The training of the investigators was, however, standardised and they should have performed a minimum of 20 supervised ultrasound examinations in order to limit variability as much as possible. Any rereading of ultrasound examination remains a static measurement of an examination that is, by definition, dynamic thus resulting in inaccuracies. We conducted the analyses of the primary

endpoint by taking into account the measurement collected by the investigators (data not shown). The results were similar. Finally, there is no general consensus on the definition of ICH in the paediatric population. The thresholds chosen in the study are, however, accepted by several teams (34) and already used in the literature concerning ONSD (10, 11, 20).

CONCLUSION

The ONSD measurement is not associated with ICH occurring within 24 h in a paediatric population with severe brain injury. Brain injury results in an increased ONSD, which continues at least 3 days and is present at any age. The thresholds predicting ICH may probably be adjusted to the age of the patients. Further studies using rigorous measurement methodology are still needed to target the population for whom this feasible, inexpensive and rapid examination may be useful.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Comité de Protection des Personnes (CPP) Sud Est II (the Research Ethics Committee for South-East of France). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FC-A, AP, BK-K, TG, and EJ involved in the study design, data collection, and data interpretation. IW, FB, BC, CD, RP, FV, and SC-T involved in the data collection. MR performed the statistical analysis. FC-A wrote the first draft of the manuscript. AP, EJ, TG, and BK-K contributed to interpretation of the data and revising the manuscript. GS revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Myeloid-Derived Suppressor Cells and Clinical Outcomes in Children With COVID-19

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Background: Although children with COVID-19 account for fewer hospitalizations than adults, many develop severe disease requiring intensive care treatment. Critical illness due to COVID-19 has been associated with lymphopenia and functional immune suppression. Myeloid-derived suppressor cells (MDSCs) potently suppress T cells and are significantly increased in adults with severe COVID-19. The role of MDSCs in the immune response of children with COVID-19 is unknown.

Aims: We hypothesized that children with severe COVID-19 will have expansion of MDSC populations compared to those with milder disease, and that higher proportions of MDSCs will correlate with clinical outcomes.

Methods: We conducted a prospective, observational study on a convenience sample of children hospitalized with PCR-confirmed COVID-19 and pre-pandemic, uninfected healthy controls (HC). Blood samples were obtained within 48 h of admission and analyzed for MDSCs, T cells, and natural killer (NK) cells by flow cytometry. Demographic information and clinical outcomes were obtained from the electronic medical record and a dedicated survey built for this study.

Results: Fifty children admitted to the hospital were enrolled; 28 diagnosed with symptomatic COVID-19 (10 requiring ICU admission) and 22 detected by universal screening (6 requiring ICU admission). We found that children with severe COVID-19 had a significantly higher percentage of MDSCs than those admitted to the ward and uninfected healthy controls. Increased percentages of MDSCs in peripheral blood mononuclear cells (PBMC) were associated with CD4+ T cell lymphopenia. MDSC expansion was associated with longer hospitalizations and need for respiratory support in children admitted with acute COVID-19.

Conclusion: These findings suggest that MDSCs are part of the dysregulated immune responses observed in children with severe COVID-19 and may play a role in disease pathogenesis. Future mechanistic studies are required to further understand the function of MDSCs in the setting of SARS-CoV-2 infection in children.

Keywords: myeloid-derived suppressor cell (MDSC), pediatric, COVID-19, respiratory disease, T cell, immune function

INTRODUCTION

At the end of 2019, SARS-CoV-2 originated a pandemic that is anticipated to remain endemic. Although adults account for the vast majority of hospitalizations and fatalities attributed to SARS-CoV-2, children also develop severe disease requiring hospitalization. Of those children admitted to the hospital, almost one-third require admission to the intensive care unit (ICU) (1). In adults, severe coronavirus disease of 2019 (COVID-19) induces a dysregulated host immune response that is characterized by concurrent hyperinflammatory and anti-inflammatory responses. The inflammatory cytokine profiles in adults with COVID-19 requiring ICU admission are similar to those elicited in patients with acute respiratory distress syndrome or sepsis (2). Additionally, T cell lymphopenia and functional impairment are also common among critically ill adults infected with SARS-CoV-2 and are associated with more severe illness and increased risk of death (3, 4). The underlying immunological mechanisms that contribute to the heterogenous phenotypes of SARS-CoV-2 infection in children are ill-defined.

Myeloid-derived suppressor cells (MDSCs) are immature, heterogenous cells that appear to be a major determinant of the dysregulated host response to SARS-CoV-2 in adults. MDSCs are expanded during inflammatory conditions and potently suppress T cell proliferation and cytokine production contributing to adaptive immune suppression (5, 6). In adult patients with malignant tumors, inhibition of MDSCs is associated with improved T cell function, decreased tumor burden, and improved clinical outcomes (7, 8). The two predominant subsets of MDSCs, granulocytic (G-MDSCs) and monocytic (M-MDSCs), each suppress T cells by a variety of mechanisms, including upregulation of cell surface marker programmed death-ligand 1 (PD-L1) (9, 10). MDSCs also mediate immune suppression through induction of T regulatory cells and inhibition of natural killers (NK) cells (11, 12). In adults with severe COVID-19, MDSC expansion has been associated with increased risk of death (13–15). It is unknown if MDSCs are also expanded in children with acute SARS-CoV-2 infection and if they play a role in disease pathogenesis. We hypothesize that children with severe COVID-19 will have an expansion of MDSC populations that will be associated with clinical outcomes.

MATERIALS AND METHODS

Study Population and Design

This is a prospective, observational study conducted at Nationwide Children's Hospital (NCH) in Columbus, OH, a free-standing children's hospital. We enrolled a convenience sample of children with COVID-19. Subjects of all ages were eligible if they were admitted to the ward or pediatric intensive care unit (PICU) at NCH from November 2020 to December 2021 and diagnosed with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR). Subjects were approached if their native language included one of the following: Arabic, Chinese, Croatian, French, German, Spanish, Nepali, Polish, Russian, Somali, and Kinyarwanda. A hospital-employed or approved interpreter was used to review the full consent process and the families were also provided a short form to read in their native language (**Supplementary Figure 3**). Exclusion criteria included children with a limitation of care order in place at the time of enrollment, a diagnosis of malignancy or primary immunosuppression, or those with multi-system inflammatory syndrome in children (MIS-C) as defined by the Center for Disease Control (16), as MIS-C reflects a post-acute sequelae of SARS-CoV-2 infection. Initial disease severity for subjects admitted to the PICU was measured using Pediatric Risk of Mortality (PRISM) III (17) and Pediatric Logistic Organ Dysfunction (PELOD)-2 scores (18).

A cohort of pre-pandemic uninfected healthy controls (HC) presenting to the hospital for imaging studies were also included for comparative purposes. HC samples were collected from July 2018 to December 2019, subjects were excluded if febrile within 24 h prior to enrollment, receiving antibiotic treatment, had an oncologic diagnosis, were a transplant recipient, or were prescribed immunomodulatory medications. Data from the healthy control cohort has not been previously published. Informed consent was obtained from the subjects' legal guardians and, when appropriate, assent was obtained from the subject. The protocol was approved by the Institutional Review Board at Nationwide Children's Hospital (IRB STUDY00000921).

Data and Sample Collection

Data and Blood Samples

Demographic and clinical data for study subjects were collected using a dedicated database built for the study and from the electronic healthcare records. All data were recorded and stored in password protected electronic case report forms as part of Research Electronic Data Capture (REDCap). Data collected included demographic information and comorbidities, complete blood count (CBC), respiratory support, COVID-19-directed therapies received, and duration of hospitalization. Protected health information was kept separate from clinical data. The initial blood sample for hospitalized subjects was obtained at time of consent within 48 h of hospital admission to the ward or ICU. SARS-CoV-2 infection was diagnosed per standard of care using a PCR assay in nasopharyngeal (NP) samples including: GeneXpert Xpress SARS-CoV-2; Cepheid, Sunnyvale, California, the FilmArray Respiratory Viral Panel (BioFire, Salt Lake City, Utah), or SARS-CoV-2 PCR using US centers for Disease Control and Prevention 2019-nCoV_N1 primers and probes (19). Blood sampling from HC was performed at the time of intravenous catheter placement for imaging studies.

Peripheral Blood Mononuclear Cells Staining

Blood was collected in acid citrate dextrose (ACD) tubes and, within 2 h of sampling, peripheral blood mononuclear cells (PBMC) were isolated from whole blood by density gradient centrifugation at 530 g for 30 min at room temperature (Ficoll-Hypaque; Sigma-Aldrich, St. Louis, MO). If sufficient

quantity available, one million cells were reserved for myeloid-derived suppressor cell (MDSC) staining for flow cytometric analysis. Cells were stained for 20 min at 4°C for the following cell surface markers: CD45 conjugated to BUV 395 (BD Biosciences, San Jose, CA), HLA-DR conjugated to BV 711, CD3 conjugated to FITC, CD4 conjugated to PerCP-Cy55, CD127 conjugated to BV 421, CD14 conjugated to BV 510, CD38 conjugated to BV605, CD11b conjugated to BV785, PD-L1 conjugated to PE, CD56 conjugated to PE Cy5, CD33 conjugated to PE Cy7, CD25 conjugated to APC, CD15 conjugated to AF700, and CD8 conjugated to APC Fire 750 (all except CD45 from BioLegend, San Diego, CA). Cells were washed and then fixed using 4.21% paraformaldehyde fixation buffer for 30 min at 4°C (BD Biosciences, San Diego, CA). Samples were stored at 4°C and acquired using a BD LSRFortessa Flow Cytometer (BD Biosciences) within 4 days of staining. Compensation control beads were used to correct for fluorescence spectral overlap. Flourescence Minus One (FMO) controls were used to optimize gating strategy. Data analysis was performed using FlowJo 10.7.1 (BD Biosciences).

MDSCs were identified using the following gating strategy: CD45 positive, HLA-DR negative, and both CD33 and CD11b positive; MDSC subsets were further identified as M-MDSCs (CD14 positive, CD15 negative) or G-MDSCs (CD15 positive, CD14 negative) (**Supplementary Figure 1**). MDSCs were quantified as a percentage of total PBMC; G-MDSC and M-MDSC were quantified as a percentage of total MDSCs. A cutoff of greater than 3% MDSC was used to define the upper limit of normal MDSC proportion based on previously published data demonstrating that healthy donors have less than 2% MDSC of circulating PBMC (20). T cells were identified as CD45+ and CD3+, CD3 + T cells were then used as the parent gate to identify CD4+ and CD8 + T cells. T regulatory cells were defined as CD3+/CD4+/CD25+ and CD127 low (**Supplementary Figure 2**). CD4+, CD8+, and T regulatory (Tregs) T cells were quantified as percentage of total CD3 + T cells. Activated T cells were defined as positive for CD38 and HLA-DR and quantified as percentage of respective CD4+, CD8+ or T regulatory cells. NK cells were identified as CD3−/CD56+ (**Supplementary Figure 2**) and quantified as a percentage of total PBMC.

Statistical Analysis

Data are summarized using frequencies and percentages for categorical variables and medians with 25–75% interquartile range for continuous variables. Differences between groups were evaluated using chi-square or Fisher's exact tests for categorical variables and rank-sum tests for continuous variables. For all tests, a two-tailed p-value < 0.05 was considered significant. Associations with MDSCs were evaluated using Spearman correlation coefficients. Values from $\pm$ 0.1 to 0.3 indicate a marginal association, from $\pm$ 0.3 to 0.5 represent a moderate association, and > 0.5 indicate a strong association. Effect sizes are summarized using standardized differences. Because the sample size within groups is small and there are many comparisons, p-values may not detect true differences among groups. Instead, it is recommended to focus on standardized differences (21). In addition, comparisons by high MDSCs (using the threshold of $> 3\%$) were evaluated using chi-square or Fisher's exact tests for categorical variables and rank-sum tests for continuous variables. We used GraphPad Prism Version 7.0 for Windows (GraphPad Software, La Jolla, California, United States) for statistical analyses.

RESULTS

Study Subjects

We enrolled a convenience sample of 138 subjects (ages 3 weeks to 21 years) hospitalized between November 2020 and December 2021 with positive SARS-CoV-2 PCR, of which 86 were excluded for insufficient blood sample and 2 with an MIS-C diagnosis (**Figure 1**). Of the remaining 50 subjects enrolled, 28 children were diagnosed with symptomatic COVID-19 (18 were admitted to the inpatient ward and 10 children had severe illness defined by the need for intensive care level treatment) and 22 were identified *via* universal screening. Two subjects in the symptomatic COVID-19 group had a diagnosis of adrenal insufficiency requiring chronic steroid treatment. In the screening cohort, 6 subjects were admitted to the PICU: severe trauma ($N = 2$, including gunshot wound and high speed motor vehicle crash), infective endocarditis ($N = 1$), acute diabetic ketoacidosis ($N = 1$), post-operative monitoring ($N = 1$), and intentional ingestion ($N = 1$). Those admitted to the ward found to be incidentally SARS-CoV-2 positive included children with abscesses ($N = 2$), appendicitis ($N = 3$), MVC ($N = 1$), pelvic inflammatory disease ($N = 1$), eczema herpeticum ($N = 1$), bone fracture ($N = 1$), pituitary adenoma ($N = 1$), failure to thrive ($N = 1$), intentional ingestion ($N = 1$), inflammatory bowel disease ($N = 1$), chronic parotitis ($N = 1$), moyamoya complications ($N = 1$), and functional neurologic disorder ($N = 1$). Children admitted to the PICU with either acute COVID-19 or incidentally positive as part of the screening cohort had similarly low severities of illness indicated by PRISM III and PELOD-2 scores (1.5 [0, 5] vs. 3 [0, 10], $p = 0.5$, and 3 [2, 7.5] vs. 5 [2, 8], $p > 0.99$, respectively). Children in the screening cohort (ICU and ward) were older (median age 13 [9, 16] years) and had longer hospitalizations (median 99 [50, 186] days) compared with children with acute COVID-19 (**Table 1**). There were no significant differences in sex, race/ethnicity, or SARS-CoV-2 vaccination status among the three groups (**Table 1**).

Children with acute COVID admitted to the ICU had similar duration of symptoms as those admitted to the floor but were more likely to receive steroids or remdesivir as part of COVID-directed treatment (**Table 1**). In all children with acute COVID-19 (including subjects admitted to ICU and ward), obesity and genetic/neurologic diseases were the most prevalent underlying chronic conditions, ($N = 7$ of 28, for each disease). However, there was not a significant difference in underlying conditions when comparing subjects with symptomatic COVID-19 admitted to the ICU vs. the ward. Additionally, asthma and chronic lung disease were common in children with symptomatic COVID-19,

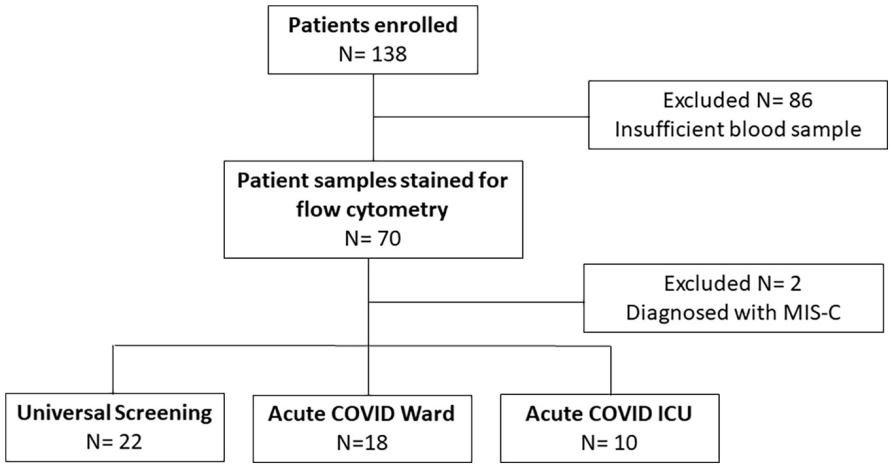

FIGURE 1 | Enrollment flow diagram. This flow chart diagrams enrollment, reasons for exclusion, and final numbers for three comparison groups.

TABLE 1 | Characteristics of children with SARS-CoV-2 and healthy controls.

Characteristics	COVID ICU (*N* = 10)		COVID ward (*N* = 18)		Universal screening (*N* = 22)		Healthy controls (*N* = 30)		
	Median or *N*	IQR or %	Median or *N*	IQR or %	Median or *N*	IQR or %	Median or *N*	IQR or %	*p*-value
Age, years	8.8	[1.0, 22.3]	3.2	[0.7, 11.9]	13	[9,16]	6.1	[4.1, 8.1]	**0.0084**
Female	4	40%	7	39%	13	59%	11	36.7	0.62
Race									
White	8	80%	10	55%	13	59%	24	80%	
Black	2	20%	4	22%	4	18%	2	7%	>0.99
Multiracial			2	11%	2	9%	1	3%	
Other			1	6%	3	14%	1	3%	
Ethnicity									>0.99
Hispanic or latino	0	0%	1	5%	4	18%	2	7%	
Not hispanic or latino	10	100%	17	95%	18	82%	28	93%	
Underlying conditions									
Obesity	3	30%	4	22%	8	36%	1	3%	
Respiratory	2	20%	4	22%	1	5%	6	20%	
Cardiac	2	20%	1	6%	2	6%	5	17%	>0.5
Genetic/Neurologic	4	40%	3	17%	2	6%	10	33%	
Other[a]	0	0%	5	28%	2	6%			
Days of Symptoms	2.5	[2, 5.8]	4	[2.3, 7]	NA		NA		0.35
Vaccination Status							NA		
Vaccinated	2	20%	2	11%	5	23%			
Unvaccinated	5	50%	10	55%	3	14%			0.63
Not known	3	30%	6	33%	14	64%			
Initial PRISM III Score	1.5	[0, 5]	NA		3[#]	[0,10]	NA		0.5
PELOD-2 Score*	3	[2, 7.5]	NA		5[#]	[2,8]	NA		>0.99
COVID-directed therapy									
Steroid	80^	80%	3^^	17%	NA		NA		**0.0005**
IVIG	0	0	1	6%					>0.99
Remdesivir	5	50%	0	0					**0.0026**
Hospitalization, days	9.9	[5.4, 22.2]	1.4	[0.9, 2.1]	99	[50, 186]	NA		**<0.0001**

*PRISM III, Pediatric Risk of Mortality score; PELOD, Pediatric Logistic Organ Dysfunction score, IVIG, intravenous immune globulin; *highest value within first 48 hours of admission. [#]Represent the PRISM III and PELOD 2 scores of the 6 universal screening subjects admitted to the ICU. ^Indicates 6 subjects received prior to blood sample; ^^indicates 3 subjects received prior to blood sample. Values in bold indicate significant P-values.*

[a]Other includes renal disease (n = 2), inflammatory bowel disease (n = 1), diabetes (n = 1), and sickle cell disease (n = 1) in the COVID-19 cohort, and renal disease (n = 1) and autoimmune disease (n = 1) in the universal screening cohort.

including 20% of those admitted to the ICU and 22% of those admitted to the ward. Of the children with acute COVID-19 admitted to the ICU, 6 (60%) received steroids before the initial sample compared with 3 (17%) subjects admitted to the ward. Duration of hospitalization was longer in children admitted to the ICU compared with that of children hospitalized on the ward. In the universal screening and healthy control cohorts, 36 and 3% of children were obese, respectively.

Differences in Myeloid-Derived Suppressor Cells According to Study Groups

Overall percentages of MDSCs were significantly higher in children with COVID-19 compared to healthy controls. Furthermore, children with COVID-19 requiring admission to the PICU had a significantly increased proportion of MDSCs compared to children admitted to the ward (10.2% [8.23, 23.0] vs. 1.21% [0.8, 3.5], $p = 0.02$; **Figure 2A**), with granulocytic (G)-MDSCs being the predominant subtype (58.7% [22, 90] vs. 8% [0, 39], $p = 0.005$; **Figure 2B**). Monocytic (M)-MDSCs were increased in children admitted to the ward with acute COVID-19 and in those identified by universal screening compared to uninfected controls (**Figure 2C**). In the screening cohort, there were no significant differences in% total (T)- MDSC or subsets between children admitted to the ICU compared to the ward **(Figure 3**). In all children with acute COVID-19 (ward and ICU), expression of the cell surface marker programmed death-ligand 1 (PD-L1) was almost exclusively identified on G-MDSC compared to monocytic (M)-MDSC (100% [74, 100] vs. 1.4% [0.6, 6.3], $p < 0.0001$).

Myeloid-Derived Suppressor Cells, T Cells, and Natural Killers Cells in Children With Symptomatic COVID

Children with increased percentage of T-MDSC, defined as > 3% total MDSC of PBMC (20), were associated with a decreased percentage of CD4 + T cells ($p = 0.002$) (**Figure 4A**), and increased percentage of CD8 + T cells and NK cells (both $p < 0.001$) compared with to children with < 3% MDSCs (**Figures 4B,C**). There was not a significant difference in the percentage of T regulatory cells in children stratified by low or high MDSC (**Figure 4D**).

In children with severe COVID-19, there were stronger associations between the percentage of G-MDSC and other immune cells compared to those admitted to the ward. Notably, in children admitted to the ICU the percentage of G-MDSC was negatively associated the percentage of CD4 + T cells and positively associated with the percentage of CD8 + T cells and NK cells (**Table 2**). Both CD4 + and CD8 + T cells demonstrated increased expression of cell surface markers of activation (CD38 + and HLA-DR+) associated with G-MDSCs in children with acute COVID-19 requiring admission to the ICU ($r = + 0.63$, $r = + 0.67$, respectively). These associations between percentage of G-MDSC and particular immune cells were not observed in children admitted to the ward with symptomatic COVID-19. Of note, samples from four children admitted to the ward with acute COVID-19 were not available for T cell analysis due to processing error.

Associations With Myeloid-Derived Suppressor Cells and Clinical Outcomes

Next, we calculated the receiver operating curve (ROC) characteristics to determine the association between% T-MDSC and the need for respiratory support. As shown in **Figure 5**, increased T-MDSC in children with acute COVID-19, admitted to both the ward and ICU, was significantly associated with a higher likelihood of requiring respiratory support (AUC 0.92, $p = 0.0007$). Of the 8 children requiring respiratory support, 4 children required intubation, 3 required non-invasive biphasic PPV (BiPAP), and 1 received supplemental oxygen *via* nasal cannula. Additionally, children with acute COVID-19, and > 3% T-MDSC had a longer duration of hospitalization compared to children with circulating MDSC closer to normal frequencies (**Figure 6**).

DISCUSSION

Since the beginning of the pandemic, over 100,000 children have been hospitalized and more than 1,000 have died in the United States alone due to SARS-CoV-2 infection (22, 23). The immune factors that are associated with severe COVID-19 in children are not well understood. Severe COVID-19 disease in adults has been characterized by lymphopenia and suppressed immune function (24). MDSC expansion is known to cause T cell lymphopenia and suppression and could be an important contributor to clinical outcomes in children with COVID-19. In this study, we found that children with COVID-19 have significantly increased percentages of MDSC that were associated with CD4 + T cell lymphopenia and worse clinical outcomes defined by increased need for respiratory support and prolonged hospitalization.

Initial investigations into the pathogenesis of SARS-CoV-2 infection in adults described a hyperinflammatory host response with associated cytokine storm as a key driver for disease severity and mortality (25). However, subsequent studies demonstrated that patients with severe COVID-19 have profound lymphopenia and decreased functional capacity of immune cells that was associated with increased risk of nosocomial infection and mortality (24, 26). MDSCs are increased as a result of host inflammatory conditions and suppress T cells and NK cells (27), and MDSCs have been found to be greatly increased in adults with severe COVID and associated with increased risk of mortality (15, 28, 29). Similar to studies in adults, we found that MDSCs were significantly increased in circulating peripheral blood of children, particularly G-MDSCs, and the expansion of these cells was associated with increased need for respiratory support, suggesting that they may play a role in COVID-19 lung disease.

A unique feature of our study was the inclusion of two other groups for comparison: uninfected healthy controls and children with COVID-19 identified by universal screening.

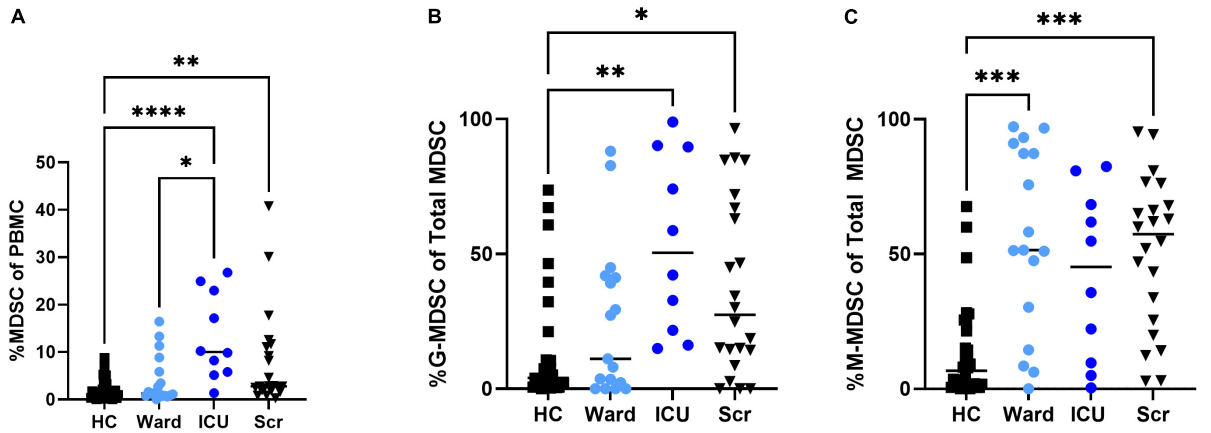

FIGURE 2 | Total MDSC and G- and M-MDSC subsets in children with acute COVID-19 compared to healthy controls and universal screening (Scr) subjects. Children critically ill due to acute COVID-19 had increased proportion of **(A)** Total (T-) MDSCs and **(B)** granulocytic (G-) MDSCs compared to those with less severe illness and healthy controls; T-MDSC were also increased in the Scr cohort compared to HC. **(C)**There was no significant difference in the proportion of monocytic (M)-MDSC between those children admitted to the floor or ICU with symptomatic COVID-19, but children admitted to the ward and in the Scr cohort had an increased proportion of M-MDSC compared to healthy controls. Kruskal-Wallis test was performed, data represent median with IQR. HC ($N = 30$), Ward ($N = 18$), ICU ($N = 10$), Scr ($N = 22$). *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001, ****p-value < 0.0001.

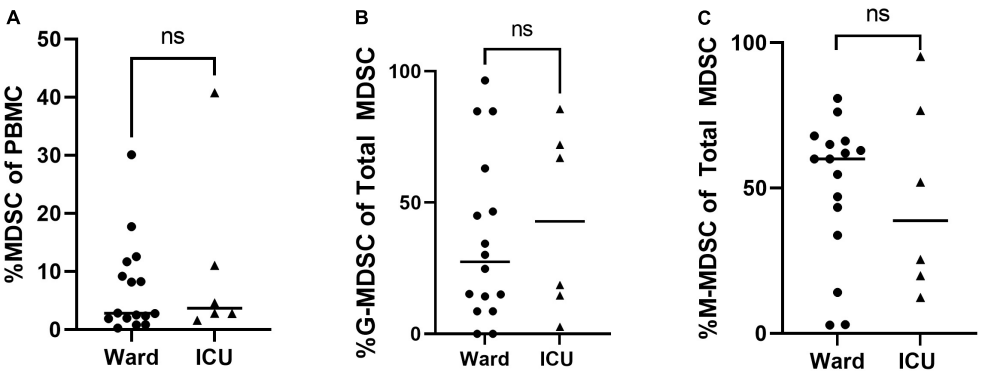

FIGURE 3 | Total MDSC and G- and M-MDSC subsets in children positive on universal screening. In children SARS-CoV-2 positive but asymptomatic for symptoms of acute COVID, there were no significant differences in subjects admitted to the floor vs. ICU in **(A)** Total (T-) MDSCs and **(B)** granulocytic (G-) MDSCs or **(C)** monocytic (M-) MDSCs. Mann-Whitney test was performed, data represent median with IQR. Ward ($N = 22$), ICU ($N = 6$). NS indicates p-value > 0.05.

Consistent with previous studies in adults, we found that children with severe COVID-19 had significantly increased proportions of circulating MDSCs compared to those admitted to the ward and the uninfected healthy controls. There were no significant differences in percentages of T-MDSC and G-MDSC between children in the ICU with COVID-19 and those identified by universal screening, likely because the screening group included children admitted to the ICU for various disease conditions that can be associated with significant increase in MDSCs [including severe trauma and diabetic ketoacidosis (30, 31)]. Additionally, the universal screening group was observed to have a significantly longer length of hospitalization, this was driven by several subjects that required inpatient rehabilitation following trauma, prolonged psychiatric counseling, or developed complications related to inflammatory bowel disease. When MDSC comparisons were made in the screening group between those admitted to the ICU and those to the ward, there was a similar trend for higher percentages of T-MDSCs and G-MDSCs in the ICU group, but the differences were not significant, likely related to being underpowered. However, our results indicate that MDSC, specifically G-MDSC, are significantly increased in children with critical illness. This is in agreement with previous reports demonstrating that G-MDSCs are prevalent in acute illnesses while M-MDSCs are prevalent in chronic inflammatory conditions such as cancer or chronic infections (31–35).

Intriguingly, our data also showed that increased circulating MDSCs in children with acute COVID-19 were associated with decreased percentage of CD4 + T cells but increased percentages of CD8 + T cells and NK cells. Both CD4 + and CD8 + T cells also showed higher proportions of activated cells indicated by increased cell surface expression of CD38 and HLA-DR. There was not a significant difference in T regulatory cells between children with < 3% or > 3% MDSC. These findings

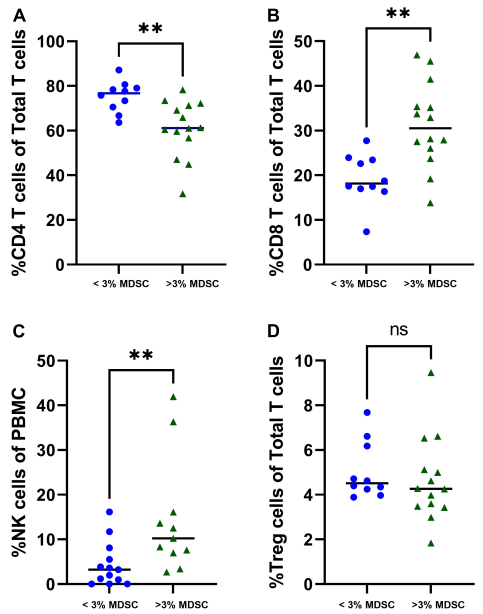

FIGURE 4 | Associations with T-MDSC and immune cells in patients with symptomatic COVID-19. Increased frequencies of T-MDSC were associated with **(A)** decreased percentage of CD4 + T cells, and increased percentages of **(B)** CD8 + T cells and **(C)** NK cells. **(D)** There were no significant associations between T-MDSC frequency and percentage of T regulatory cells. < 3% MDSC ($N = 10$), > 3% MDSC ($N = 14$). Mann-Whitney test was performed, data represent medians with IQR values. $^{**}p$-value < 0.01.

TABLE 2 | Correlations with% G-MDSC in children with acute COVID.

	All		ICU		Ward	
Immune cell	**rho**	***p*-value**	**rho**	***p*-value**	**rho**	***p*-value**
%CD4 T cells	−0.48	0.023	**−0.55**	0.125	−0.06	0.835
% CD4 T cells CD38 + HLA-DR +	0.39	0.073	**0.63**	0.067	0.06	0.842
%CD8 T cells	**0.60**	0.003	**0.72**	0.030	0.42	0.149
%CD8 T cells CD38 + HLADR +	0.41	0.059	**0.67**	0.050	−0.24	0.425
%T regulatory cells	−0.14	0.543	−0.35	0.356	0.17	0.573
CD4:CD8 ratio	**−0.57**	0.005	**−0.58**	0.099	−0.38	0.198
% NK cells	0.23	0.260	**0.60**	0.088	−0.15	0.588

CD, cluster domain; HLA-DR, human leukocyte antigen-DR isotype; NK, Natural Killer. Values in bold indicate moderate or large effect size.

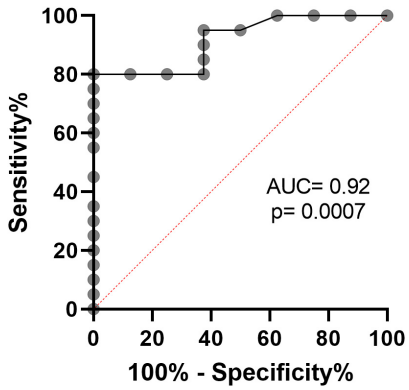

FIGURE 5 | Receiver operating characteristics curve demonstrates that% T-MDSC is associated with need for respiratory support in children with symptomatic COVID. In all children with COVID, admitted to both ICU and the ward, increased % T-MDSC was associated with higher likelihood of requiring respiratory support ($N = 8/28$), AUC = 0.92, $p = 0.0007$.

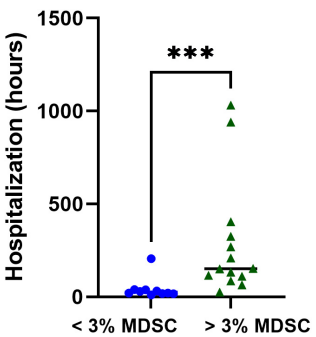

FIGURE 6 | Associations with T-MDSC and duration of hospitalization in children with symptomatic SARS-CoV-2. Increased initial% T-MDSC was associated with longer hospitalization in children admitted with COVID compared to those with lower circulating % T-MDSC. Mann-Whitney test was performed, data represent medians with IQR values. $^{***}p = 0.003$.

suggest that in children with COVID-19, MDSCs appear to have a more specific effect on CD4 + T cells, which are crucial for overall orchestration of antiviral immunity and viral clearance (36). MDSCs are known to suppress T cells and inhibit NK cells through direct cell-cell contact and production of chemokines, but those interactions occur at the tissue level (12, 27). Interactions between MDSCs and their target immune cells are complex and dependent on the microenvironment (7, 37, 38). Thus, it is possible that quantifying T cell subsets and NK cells in circulating PBMC does not provide a complete assessment of the overall effect of MDSCs, as it will be important to also assess the presence and function of this cell population in tissue, particularly in the lungs of patients with acute COVID-19. Indeed, while the majority of studies have focused on MDSCs circulating in peripheral blood in these patients, G-MDSCs have also been identified in the lungs of adults who died of COVID-19-related complications (39).

Although confirmatory studies are needed, our preliminary data showed that early circulating MDSCs in children with symptomatic COVID-19 are associated with the need for respiratory support. Of all children hospitalized with acute COVID-19, increased MDSCs were also associated with a significantly longer duration of hospitalization. These data suggest that MDSCs appear to contribute to the pathogenesis and clinical outcomes of severe COVID-19 in children.

Our study has several limitations. First, patients included represent a convenience sample which might have introduced enrollment bias. Nevertheless, patients were enrolled prospectively, and the same approach was used for children

hospitalized in the ward and those requiring ICU care, making comparisons fair. Second, we characterized MDSCs by their cell surface markers and we were not able to perform functional studies due to limited blood volume available from children. Third, steroids and other immunomodulatory medications may effect MDSC expansion and function (40). Six of the eight children in the ICU that received COVID-19- directed steroid therapy received this treatment prior to initial blood sample, and all three children admitted to the ward that received steroid treatment had the initial blood sample after treatment as well. Glucocorticoids have been shown to induce MDSC expansion in murine models and may contribute to MDSC expansion observed in our study. Previous studies have indicated that steroid administration is associated with worse outcomes in immunosuppressed phenotypes (41), and it may be that MDSCs play an important role in determining clinical outcomes related to steroid treatment.

A fourth limitation was that our study was not powered to compare differences in immune responses of children who have and have not received vaccinations against COVID-19. During the period of sample enrollment, several SARS-CoV-2 variants, notably delta and omicron- emerged, and effective vaccination programs became available for adults and later children (42). Although previously published data suggest that vaccinations are more effective when adjuvant MSDC-depleting therapies are used (43), it remains unknown what effect the current COVID-19 vaccines have on inflammation-driven MDSC expansion.

Future studies are required to further understand the relationships between MDSCs and target immune cell subsets, such as T cells and NK cells, at the tissue level in the lungs. Earlier and more frequent sampling is needed to explore MDSC dynamics and associations with clinical outcomes in children with COVID-19. MDSCs may have long term effects, including contributing to "long haul COVID," as this cell population has been found to persist even 3 months after SARS-CoV-2 infection (44). The current methods for identifying MDSC, including PBMC isolation and flow cytometry analysis, are cumbersome, additional studies are needed to identify a reliable serum marker indicating MDSC expansion in children that may be used to stratify patients according to severity of illness. Identifying MDSCs as a potential therapeutic target could allow the development of more personalized treatments plans with already available therapies targeting MDSCs (45). The notably high expression of PD-L1 on G-MDSC and significant increase in this MDSC subset in critically ill children in this study suggests that anti-PDL1 therapy may be a viable option for MDSC inhibition.

CONCLUSION

In conclusion, these results indicate that increased MDSCs are part of the immune response of children to SARS-CoV-2 infection. Children with severe COVID-19 had greatly increased total and G-MDSC proportions that were associated with decreased percentage of CD4 + T cells, prolonged hospitalization, and the need for respiratory support, suggesting that this cell population contributes to the pathogenesis of SARS-CoV-2 infection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Nationwide Children's Hospital Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KB designed, performed experiments, and wrote the manuscript. AA, SM, and FY performed experiments. VB and ZM assisted with flow cytometry panel design. RS, CT-S, and AQ collected clinical data. MM-C and RG assisted with data analysis. AM and OR reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Foremost, we would like to thank the patients and their families for participating in this study. We also want to express our appreciation for the dedicated research nursing staff at Nationwide Children's Hospital Clinical Research Services for their efforts in patient recruitment and sample collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.893045/full#supplementary-material

Supplementary Figure 1 | Gating strategy for Myeloid Derived Suppressor Cells (MDSCs). MDSCs were identified in fresh PBMC by flow cytometry. After gating on live cells and excluding doublets by FSC-A vs. FSC-H plot, leukocytes were gated by CD45 + vs. SSC-A. MSDCs were then identified by HLA-DR low/− and CD33b+/CD11b+. Subsets were then identified by CD15+/CD14− (G-MDSCs) and CD14+/CD15− (M-MDSCs). Green boxes indicate positive selection.

Supplementary Figure 2 | Gating strategy for T cell subsets and NK cells. After gating on lives cells and excluding doublets by FSC-A vs. FSC-H plot, leukocytes were gated by CD45 + vs. SSC-A. T cells were identified by gating on CD3 + cells and then subsets were identified by CD4+/CD8− and CD8−/CD4+. T regulatory cells were CD4 + CD25 + CD127 low. NK cells were identified as CD3-/CD56+. Green boxes indicate positive selection.

Supplementary Figure 3 | Example of PD-L1 expression on MDSC subsets. Expression of PD-L1 on both granulocytic-MDSC and monocytic-MDSC subsets identified by PD-L1 vs. SSC-A. Green boxes indicate positive selection.

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Efficacy and Safety of Prolonged Magnesium Sulfate Infusions in Children With Refractory Status Asthmaticus

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Objectives: There is a paucity of data on the use of intravenous magnesium sulfate infusion in children with refractory status asthmaticus. The purpose of this study was to evaluate the efficacy and safety of prolonged magnesium sulfate infusion as an advanced therapy.

Methods: This is a single center retrospective study of children admitted to our pediatric intensive care unit (PICU) with status asthmaticus requiring continuous albuterol. Treatment group included patients receiving magnesium for ≥4 h and control group included those on other therapies only. Patients were matched 1:4 based on age, sex, obesity, pediatric index of mortality III and pediatric risk of mortality III scores. Primary outcomes included PICU length of stay (LOS) and mechanical ventilation (MV) requirement. Secondary outcomes included mortality, extracorporeal membrane oxygenation (ECMO) requirement, analyses of factors associated with PICU LOS and MV requirement and safety of magnesium infusion. Logistic and linear regressions were employed to determine factors associated with MV requirement and PICU LOS, respectively.

Results: Treatment and control groups included 27 and 108 patients, respectively. Median initial infusion rate was 15 mg/kg/hour, with median duration of 28 h. There was no difference in the MV requirement between the treatment and control groups [7 (25.9%) vs. 20 patients (18.5%), $p = 0.39$]. Median PICU LOS and ECMO use were significantly higher in treatment vs. control group [(3.63 vs. 1.09 days, $p < 0.01$) and (11.1 vs. 0%, $p < 0.01$), respectively]. No mortality difference was noted. On regression analysis, patients receiving ketamine and higher prednisone equivalent dosing had higher odds of MV requirement [OR 19.29 (95% CI 5.40–68.88), $p < 0.01$ and 1.099 (95% CI 1.03–1.17), $p < 0.01$, respectively]. Each mg/kg increase in prednisone equivalent dosing corresponded to an increase in PICU LOS by 0.13 days (95% CI 0.096–0.160, $p < 0.01$). Magnesium infusions were not associated with lower MV requirement or lower PICU LOS

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after controlling for covariates. Fourteen (51.9%) patients in the treatment group had an adverse event, hypotension being the most common.

Conclusion: Magnesium sulfate infusions were not associated with MV requirement, PICU LOS or mortality.

Keywords: magnesium, continuous infusion, status asthmaticus, children, pediatric intensive care unit

INTRODUCTION

In the United States of America, children with asthma experience >70,000 hospitalizations and ∼700,000 emergency department (ED) visits for asthma exacerbation or status asthmaticus (1). Children with status asthmaticus have high morbidity and healthcare costs and are frequently admitted to the pediatric intensive care unit (PICU) (2). To achieve a rapid improvement in severe asthma exacerbations, concomitant administration of short acting beta-2 agonist and steroids with or without ipratropium is recommended. The National Asthma Education and Prevention Program Coordinating Committee and Global Initiative for Asthma guidelines also recommend the use of a single-dose intravenous (IV) magnesium sulfate of 25–75 mg/kg (maximum of 2 grams/dose) over 20 min in children with asthma exacerbation in the ED with refractory clinical manifestations 1 h after receipt of oral/IV corticosteroids and repeated doses of beta-2 agonists (2, 3). This single dose of magnesium sulfate has been associated with improvement of pulmonary function and decreased odds of hospital admission when administered to children in the ED (2, 4). Other recommended therapies for refractory status asthmaticus include ketamine, terbutaline, and/or aminophylline infusions and heliox. Use of a prolonged IV magnesium infusion for management of refractory asthma exacerbation has also been described in the literature (5).

Eight reports including 447 children have evaluated the use of a prolonged magnesium infusion over ≥1 h (6–13). Most of these studies ($n = 261$; 58.4%) focused on the use of magnesium infusions in the PICU, included patients receiving magnesium sulfate for >4 h (299; 66.9%), and did not evaluate both efficacy and safety. As a result, there remains an existing gap in the literature on the safety and efficacy of prolonged magnesium sulfate infusions. The purpose of this study was to evaluate the efficacy and safety of these prolonged magnesium infusions as an advanced therapy when compared to children receiving other therapies only (terbutaline, aminophylline, ketamine and/or heliox) for refractory status asthmaticus.

MATERIALS AND METHODS

Study Design and Population

This is a retrospective cohort study of children admitted to our 34-bed PICU at a tertiary care academic center from January 1, 2013 to August 31, 2020 with diagnosis of status asthmaticus. Patients were identified using ICD-9 or ICD-10 codes for diagnosis of "asthma" in the Virtual Pediatric Systems (14), and the hospital electronic medical record, Meditech® (Medical Information Technology, Inc., Westwood, MA). Patients were included in the study if they were >37 weeks postmenstrual age and <18 years of age at the time of admission and received continuous albuterol. Patients were included in the treatment group if they received a magnesium sulfate infusion ≥4 h for refractory status asthmaticus. The control group consisted of patients that did not receive magnesium sulfate infusions; controls were matched in a 1:4 fashion using propensity scoring based on age, biological sex, obesity status, pediatric index of mortality (PIM) III and pediatric risk of mortality (PRISM) III scores. Obesity has been previously associated with a significantly higher rate of hospital admissions and a longer hospital and PICU length of stay (LOS) compared with normal weight children (15, 16). Patients were excluded if they received magnesium infusions for indications other than status asthmaticus or if they had incomplete medical records. The study was approved by our institutional review board and waiver of consent was obtained.

Data Collection and Study Objectives

Demographics and clinical data, including vital signs, age, weight, sex, PIM III and PRISM III scores, PICU LOS, non-invasive and invasive mechanical ventilation (MV) use and use of extracorporeal membrane oxygenation (ECMO), were collected for the treatment and control groups. Non-invasive ventilation included high flow nasal canula, continuous positive airway pressure, and/or bilevel positive airway pressure. Obesity status was determined based on the Centers for Disease Control and prevention calculator for children ≥2 years of age that calculated body mass index (BMI) for age and sex (17). The World Health Organization criterion was used for defining obesity in children <2 years of age (18). Children ≥2 years of age were classified as obese if BMI was ≥95th percentile, while children <2 years of age were classified as obese if weight-for-length was ≥97.7th percentile.

All asthma therapies received by the patients were collected. Corticosteroid total dose was converted and reported as total prednisone dosing equivalents in milligrams (mg) (19). It was also noted if the treatment and control groups received additional advanced treatment options for refractory status asthmaticus. At the time of this study, the advanced treatment options in our PICU's status asthmaticus protocol included terbutaline, aminophylline, ketamine, heliox and magnesium sulfate infusions. Our protocol includes guidance for dosing and monitoring of these therapies. However, selection of agents was based on clinician discretion, and patients may have been initiated on ≥1 therapy based on their clinical status. For magnesium sulfate infusions, the protocol is listed in **Supplementary Appendix I**. Per the protocol, serum magnesium concentrations were assessed every 4 h, and the

magnesium sulfate infusions were titrated to a target goal of 4–6 mg/dL. For the treatment group, the number of patients with hypermagnesemia (serum magnesium level >6 mg/dL), and adverse events (i.e., hypotension, flushing, nausea/vomiting, and infusion related reactions) were collected. Hypotension was defined as systolic blood pressure (SBP) <60 mm Hg in term neonates, SBP <70 mm Hg in infants from 1 to 12 months, SBP <70 mm Hg + (2 × age in years) in children >1 to 10 years, and SBP <90 mm Hg in children over 10 years old (20). Magnesium sulfate data included infusion doses (mg/kg/hour), duration of magnesium infusion (hours), additional magnesium boluses administered (mg and mg/kg), and serum magnesium concentrations (mg/dL).

Outcomes

Primary outcomes included comparisons of PICU LOS and MV requirement between the treatment and control groups. Secondary outcomes included comparisons of the duration of MV and non-invasive ventilation, patients requiring ECMO and PICU mortality between the treatment and control groups. Another secondary outcome was to determine factors associated with PICU LOS and MV requirement. Additional secondary outcomes focused on a description of the magnesium sulfate infusion dosing regimen and its safety. Last, a sub-analysis was performed for the treatment group to compare the outcomes among children who received magnesium infusions as their first advanced therapy vs. those who received magnesium infusions after another advanced therapy (i.e., 2nd, 3rd, or 4th line).

Statistical Analysis

Descriptive and inferential statistics were employed. Categorical variables were compared using Chi-square test and were reported as frequency (percentage). Continuous data were compared using independent *t*-test or Mann-Whitney *U*-test depending on if data was normally distributed or not and were reported as mean (standard deviation) or median (interquartile range). Shapiro-Wilk tests were used to determine distributional assumptions. Propensity score matching was conducted using the Matchlt package version 4.3.2 in the R statistical program version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Logistic and linear regressions were employed to determine the associations for MV requirement and PICU LOS, respectively, while controlling for independent variables including continuous albuterol duration, cumulative prednisone equivalent dosing, ketamine exposure and magnesium infusion exposure. A generalized estimating equation was added to the regression models to account for matching *via* propensity scores. Model estimates and 95% confidence intervals are reported for models. Data management and analyses were conducted using SAS software version 9.4 (Statistical Analysis System, Cary, NC) with the alpha set at 0.05.

RESULTS

A total of 921 patients with asthma were identified during the study period. Sixty of these patients were initiated on magnesium sulfate; however, thirty-three were excluded as they received magnesium sulfate for <4 h. Twenty-seven patients were included in the treatment group. A total of 861 patients were eligible to be considered as controls. There were 516 of these patients who did not receive continuous albuterol and were excluded, leaving 345 remaining eligible patients. After 1:4 ratio propensity score matching was performed, 108 patients were included in the control group.

TABLE 1 | Patient demographics at PICU admission comparing treatment and control groups ($n = 135$).

Variables	Treatment group ($n = 27$)	Control group ($n = 108$)	*p*-value
	Number (%) or Median (IQR)		
Age (years)	8.5 (6.23–11.94)	9.05 (6.24–13.56)	0.53[a]
Weight (kg)	32.5 (24–55)	39.8 (20.6–63.8)	0.55[a]
BMI[b]			
BMI (kg/m^2)	19.8 (16.8–22.6)	19 (15.9–25.4)	0.92[a]
BMI percentile for age and sex	83.9 (58.6–96.1)	80.0 (44.8–95.7)	0.57[a]
Weight-for-length percentile	99.9[c]	80.0 (44.8–95.7)	
Obesity status	9 (33.3)	29 (26.9)	0.50[d]
Male gender	16 (59.3)	59 (54.6)	0.67[d]
Race/ethnicity			0.14[d]
African American	15 (55.6)	48 (44.4)	
White/Caucasian	6 (22.2)	24 (22.2)	
American Indian/Alaska Native	2 (7.4)	6 (5.6)	
Hispanic	2 (7.4)	4 (3.7)	
Asian American	0 (0)	2 (1.9)	
Mixed	2 (7.4)	2 (1.9)	
Unknown/unspecified	0 (0)	22 (20.4)	
Mortality scores			
PIM III	−4.66 (−6.12 to −4.53)	−5.29 (−6.05 to −4.60)	0.98[a]
PRISM III	5 (0–10)	4 (0–7)	0.55[a]

IQR, Interquartile range; BMI, Body mass index; PIM III, Pediatric Index of Mortality III; PRISM III, Pediatric Risk of Mortality III.
[a] *Wilcoxon two-sample test.*
[b] *BMI assessed in 26 children ≥2 years of age.*
[c] *Weight-for-length assessed in one child <2 years of age.*
[d] *Chi-square test.*

Baseline demographics of the 135 patients (27 in the treatment group and 108 in the control group) are presented in **Table 1**. The median age at PICU admission for the treatment and control groups were 8.5 and 9.05 years, respectively, $p = 0.53$. There was no difference in the number of patients classified as obese between the groups, $p = 0.50$. There was no statistical difference in the median PIM III and PRISM III scores or race/ethnicity between the treatment and control groups.

All patients in the treatment group and 88 (81.5%) patients in the control group received ≥1 magnesium sulfate bolus dose in either the ED and/or PICU (**Table 2**). There was statistical difference in the number of patients receiving magnesium sulfate boluses, number of boluses received, and median cumulative

TABLE 2 | Characteristics of magnesium sulfate boluses and infusion in treatment and control groups ($n = 135$).

Variables	Treatment group ($n = 27$)	Control group ($n = 108$)	*p*-value
	Number (%) or Median (IQR)		
Magnesium sulfate boluses			
Received magnesium boluses	27 (100.0)	88 (81.5)	**0.01**[a]
Number of magnesium boluses administered	3 (2–4)	1 (1–2)	<**0.01**[b]
Cumulative bolus dose (mg)	4,000.0 (2,750.0–6,000.0)	2,000.0 (1,400.0–2,295.0)	<**0.01**[b]
Cumulative bolus dose (mg/kg)	93.8 (68.8–158.3)	49.6 (34.6–87.1)	<**0.01**[b]
Magnesium sulfate infusions			
Rate to achieve the target serum concentration (mg/kg/h)[c]	19.9 (15.8–22.4)	–	–
Duration (hours)	28 (17–58.5)	–	–
Number of infusion rates increased	2 (0–3)	–	–
Number of infusion rates decreased	0 (0–1)	–	–
Cumulative infusion dose (mg)	19,939.0 (9,360.0–56,056.0)	–	–
Cumulative infusion dose (mg/kg)	560.0 (240.0–1,594.0)	–	–

IQR, Interquartile range.
[a] *Fisher's exact test.*
[b] *Wilcoxon two-sample test.*
[c] *Target magnesium serum concentration was 4–6 mg/dL.*

TABLE 3 | Primary and secondary outcomes comparing patients in treatment vs. control groups ($n = 135$).

Variables	Treatment group ($n = 27$)	Control group ($n = 108$)	*p*-value
	Number (%) or Median (IQR)		
Primary outcomes			
PICU LOS (days)	3.63 (1.70–7.80)	1.09 (0.66–1.95)	<0.01[a]
MV[b]	7 (25.9)	20 (18.5)	0.39[c]
Secondary outcomes			
Duration of MV (days)	4.96 (2–13)	1.60 (0.69–4.75)	0.02[a]
Non-invasive ventilation			
Received non-invasive ventilation[d]	27 (100)	98 (90.7)	0.21[e]
Duration of non-invasive ventilation (days)	2.92 (2.04–8.29)	1.44 (0.88–2.67)	<0.01[a]
ECMO			
Received ECMO	3 (11.1)	0 (0)	<0.01[e]
Duration on ECMO (days)	2.6 (0.4–12.4)	–	–
Mortality	1 (3.7)	4 (3.7)	1.00[e]

IQR, Interquartile range; PICU LOS, Pediatric intensive care unit length of stay; MV, Mechanical ventilation; ECMO, Extracorporeal membrane oxygenation.
[a] *Wilcoxon two-sample test.*
[b] *In the treatment group, four out of seven patients were mechanically ventilated before starting magnesium continuous infusion.*
[c] *Chi-square test.*
[d] *Non-invasive ventilation included high flow nasal canula, continuous positive airway pressure, and/or bilevel positive airway pressure.*
[e] *Fisher's Exact test.*
[f] *Exact Chi-square test.*

dose (mg and mg/kg) between the treatment and control groups. In addition, general characteristics of the magnesium sulfate infusion regimen and concentrations are reported in **Table 2**. The overall median rate to achieve the target serum concentration was 19.9 mg/kg/h, and patients continued with a median duration of 28 h. Based on our institutional protocol, a median of two increases in the magnesium sulfate infusion were required to achieve the target serum magnesium concentration.

Primary and secondary outcomes are shown in **Table 3**. There was a significant difference in the median PICU LOS between the treatment and control groups, 3.63 vs. 1.09 days, $p < 0.01$. There was no significant difference in the number of patients that received MV between the treatment and control groups, 7 (25.9%) vs. 20 (18.5%), $p = 0.39$. It should be noted that four of these seven patients in the treatment group who received MV, were placed on mechanical ventilation prior to initiation of their magnesium sulfate infusion. Of the patients who received MV, the treatment group had significantly higher median duration of MV compared to control group (4.96 vs. 1.60 days, $p = 0.02$). There was no significant difference in the number of patients in the treatment vs. control group who received non-invasive ventilation, but the median duration of non-invasive ventilation was significantly higher in the treatment vs. control group, $p < 0.01$. There was a significant difference in the number of patients in the treatment vs. control group who received ECMO, 3 (11.1%) vs. 0, $p < 0.01$. For the treatment group, the median duration of ECMO was 2.6 days. Overall, 5 (3.7%) patients expired during their PICU admission, but there was no difference in mortality between groups ($p = 1.00$). One of the patients in treatment group was initiated on ECMO for a total of 12.4 days before expiring.

Table 4 provides a summary of the additional adjunctive status asthmaticus therapies that patients in the treatment and control groups received. There was a significantly higher median duration of continuous albuterol in the treatment vs. control group, 2.08 vs. 0.69 days, $p < 0.01$. The majority ($n = 133$; 98.5%) of patients in the treatment and control groups received IV methylprednisolone with a frequency of every 6 h ($p = 0.01$). Patients in the treatment group had a longer median duration of corticosteroids versus the control group, 5.4 vs. 2.5 days, $p < 0.01$. The patients in the treatment group also had a significantly higher cumulative and daily prednisone equivalent doses than the control group. Other advanced therapies including ketamine, terbutaline and aminophylline were also used significantly more often in patients in the treatment vs. the control group (**Table 4**). The only significant difference in duration of these advanced therapies between the treatment and control groups was for terbutaline

infusions, 2.81 vs. 0.75 days, $p = 0.01$. In addition to this, the actual number of advanced therapies for status asthmaticus were numerically higher in patients in the treatment vs. the control group, though statistical analysis for this could not be performed. Timing of initiation of all therapies is shown in **Supplementary Table 1**.

Prior to initiation of the magnesium infusion, the median (IQR) baseline concentration was 2.7 (2.3–3.2) mg/dL. The median (IQR) number of serum magnesium concentrations obtained while on an infusion was 5 (3–13). The median (IQR) minimum and maximum magnesium serum concentrations while on the infusion were 3.1 (2.7–3.4) and 4.6 (3.5–5.4) mg/dL. Hypermagnesemia, defined as a serum magnesium concentration >6 mg/dL, was reported in 3 patients (11.1%). None of these patients were noted to have an adverse event. The magnesium infusion was discontinued in one patient, and two patients had their rate of magnesium infusions decreased but continued therapy.

Fourteen (51.9%) patients in the treatment group had an adverse event; four (14.8%) patients experienced ≥1 adverse event. The most identified adverse effect in the treatment group was hypotension, reported in 13 patients (48.1%). Three of these patients with hypotension required an intervention. The magnesium infusions were discontinued in two patients and an IV fluid bolus was given to the third patient. The remaining patients did not require any interventions. Only 1 (3.7%) patient complained of nausea and vomiting and received three doses of ondansetron. There was no documentation of any infusion related reactions or flushing.

Regression Analysis

A generalized estimating equation logistic and linear regressions were conducted to determine the effect of various factors (i.e., continuous albuterol duration, cumulative prednisone equivalent dosing, ketamine infusion exposure, and magnesium infusion exposure) on MV requirement and PICU LOS, respectively (**Table 5**). After adjusting for other variables in the model, the odds of being MV were 19.3 times higher for those that received ketamine infusions (95% CI: 5.40–68.88; $p < 0.01$). In addition, the odds of being MV were 10.9% higher for each mg/kg increase in the prednisone equivalent dosing (OR 1.09; 95% CI: 1.03–1.17; $p < 0.01$). Use of mechanical ventilation and duration of continuous albuterol were not independently associated with MV. Use of magnesium and ketamine infusions, and continuous albuterol duration were not associated with an increase in PICU LOS. After adjusting for other variables in the model, each mg/kg increase in total prednisone equivalent dose corresponded to an increase of 0.128 days in the PICU LOS (95% CI 0.096–0.160; $p < 0.01$).

Subgroup Analysis

A subgroup analysis was performed to compare the outcomes of the patients in the treatment group who received magnesium infusions as their first advanced therapy ($n = 16$) vs. those who received magnesium infusions after another advanced therapy (i.e., 2nd, 3rd, or 4th line) ($n = 11$) (**Supplementary Table 2**). There were no significant differences in the demographics, primary, and secondary outcomes between groups. There were no significant differences in the number of magnesium boluses, total mg/dose, and mg/kg of magnesium boluses, but there was

TABLE 4 | Comparison of medications received by patients in treatment vs. control groups ($n = 135$).

Variables	Treatment group ($n = 27$)	Control group (n=108)	*p*-value
	Number (%) or Median (IQR)		
Continuous albuterol			
Duration (days)	2.08 (1.00–5.33)	0.69 (0.42–1.38)	<0.01[a]
CORTICOSTEROIDS			
Agents			
Methylprednisolone	27 (100)	106 (98.2)	1.00[b]
Prednisolone	11 (40.7)	46 (42.6)	0.86[c]
Prednisone	9 (33.3)	41 (38)	0.66[c]
Dexamethasone	4 (14.8)	26 (24.1)	0.30[c]
Hydrocortisone	1 (3.7)	2 (1.9)	0.49[c]
Methylprednisolone IV frequency			
Every 6 h	23 (85.2)	57 (53.8)	0.01[c]
Every 8 h	2 (7.4)	8 (7.6)	
Every 12 h	1 (3.7)	38 (35.9)	
Every 24 h	1 (3.7)	3 (2.8)	
Dosing regimen			
Duration (days)	5.4 (3.6–10.3)	2.5 (1.8–3.9)	<0.01[a]
Cumulative dose in mg[d]	693.8 (426.0–1,350.0)	306.3 (178.8–452.5)	<0.01[a]
Cumulative dose in mg/kg[d]	19.0 (13.1–41.3)	7.89 (5.73–11.7)	<0.01[a]
Daily dose in mg/kg/day[d]	3.8 (2.7–4.4)	3.0 (2.3–4.0)	0.02[a]
ADVANCED THERAPIES OTHER THAN MAGNESIUM SULFATE			
Ketamine			
Received ketamine	11 (40.7)	16 (14.8)	<0.01[c]
Duration (days)	2.5 (0.6–6.0)	1 (0.6–1.3)	0.15[a]
Terbutaline			
Received terbutaline	12 (44.4)	8 (7.4)	<0.01[b]
Duration (days)	2.81 (0.83–3.88)	0.75 (0.21–0.88)	0.01[a]
Aminophylline			
Received aminophylline	12 (44.4)	3 (2.8)	<0.01[b]
Duration (days)	2.27 (1.29–5.17)	0.96 (0.21–1.38)	0.07
Heliox	3 (11.1)	2 (1.9)	0.05
Number of advanced therapies administered			–[e]
Zero	–	86 (79.6)	
One	11 (40.7)	18 (16.7)	
Two	4 (14.8)	3 (2.8)	
Three	5 (18.5)	1 (0.9)	
Four	7 (25.9)	0 (0)	

IQR, Interquartile range.
[a] *Wilcoxon two-sample test.*
[b] *Fisher's Exact test.*
[c] *Chi-square test.*
[d] *Calculated as prednisone equivalent dose.*
[e] *Statistical analysis was not applicable.*
[f] *Exact Chi-square test.*

TABLE 5 | Logistic and linear regression models looking at mechanical ventilation requirement and PICU LOS.

Variables	Reference value	GEE logistic regression for mechanical ventilation ($n = 115$*)		Variables	Reference value	GEE linear regression for PICU length of stay (days) ($n = 135$)	
		Odds ratio (95% confidence interval)	*p*-value			Model parameter estimate (95% confidence interval)	*p*-value
Intercept		0.013 (0.003–0.063)	<0.01	Intercept		−0.091 (−0.593 to 0.411)	0.72
Received magnesium infusion ($n = 23$)	No magnesium infusions ($n = 92$)	0.031 (0.001–1.201)	0.06	Received magnesium infusions ($n = 27$)	No magnesium infusions ($n = 108$)	−0.148 (−1.09 to 0.793)	0.76
Received ketamine infusions ($n = 18$)	No ketamine infusions ($n = 97$)	19.294 (5.404–68.882)	<0.01	Received ketamine infusions ($n = 27$)	No ketamine infusions ($n = 108$)	0.852 (−0.219 to 1.92)	0.12
Total prednisone equivalent dose (mg/kg)	Mean = 12.24, any 1-unit increase	1.099 (1.029–1.173)	<0.01	Total prednisone equivalent dose (mg/kg)	Mean = 14.11, any 1-unit increase	0.128 (0.096–0.160)	<0.01
Continuous albuterol duration (days)	Mean = 1.43, any 1-unit increase	1.053 (0.696–1.592)	0.81	Continuous albuterol duration (days)	Mean = 1.54, any 1-unit increase	0.297 (−0.014 to 0.609)	0.06

Patients who received magnesium were optimally matched 1:4 to those who did not receive magnesium using propensity scores generated on sex, obesity, age at admission, PIM III and PRISM III scores. Propensity scores were used in both models to account for matching process.

**Four patients received magnesium after mechanical ventilation and were excluded from the logistic regression model along with their matched controls.*

a significant difference in the magnesium infusion rate and duration between groups. There was a significant difference in the median number of advanced therapies administered between those who received magnesium infusions as their first advanced therapies vs. those who received it in addition to another advanced therapy, 1.0 vs. 3.0, $p < 0.01$.

DISCUSSION

To our knowledge, this is the first study evaluating both clinical outcomes and adverse events in children receiving magnesium sulfate infusions for ≥4 h for refractory status asthmaticus. Our study noted that the use of magnesium sulfate infusions was not associated with lower odds of MV requirement or PICU LOS when controlling for various independent covariates. In addition, we noted that 14 (51.9%) patients in the treatment group had ≥1 adverse event(s) while on their magnesium sulfate infusion. Several studies have evaluated the clinical outcomes of magnesium sulfate boluses (25–75 mg/kg over 20 min) in the ED setting in children with acute asthma exacerbation, but there are limited reports evaluating impact of magnesium sulfate infusions in children with refractory status asthmaticus (2–5).

Our study focused on relevant outcomes in the PICU including PICU LOS and MV requirement/duration. Of the previously mentioned eight studies in children with refractory status asthmaticus ($n = 447$) evaluating the efficacy and/or safety of magnesium sulfate infusions over >1 h, only three of these studies ($n = 186$; 41.6%) evaluated clinical outcomes (6–13). Only one study by Irazuzta and colleagues evaluated a clinical outcome relevant to our study population (11). They prospectively evaluated the use of a prolonged IV magnesium infusion of 50 mg/kg over 1 h ($n = 19$) vs. an infusion of 50 mg/kg/h over 4 h in the ED setting (11). They found a significantly shorter mean ED LOS with the prolonged infusion vs. the bolus group (34.1 ± 19.5 vs. 48.1 ± 18.7 h, $p = 0.01$). While this study did not assess outcomes in the PICU, the impact on overall LOS is more relevant to our study's findings as we noted a significant increase in PICU LOS in the treatment vs. the control group, 3.63 vs. 1.09 days, $p < 0.01$. However, unlike their study, we controlled for covariates, and in this analysis, magnesium infusions were not associated with increased PICU LOS or MV requirement.

Our study also assessed other secondary outcomes including non-invasive ventilation requirement/duration, ECMO requirement/duration and mortality between groups. We noted no statistical difference in the number of patients in the treatment vs. the control group who received non-invasive ventilation. However, we found a significant difference in the median duration of non-invasive ventilation between the treatment and control groups, 2.92 vs. 1.44 days, $p < 0.01$. Several studies have evaluated the use of non-invasive ventilation in children with status asthmaticus, but it is difficult to compare our study to these reports (21, 22). In our study, we noted a significant difference in the number of patients in the treatment vs. the control group who received ECMO during their PICU stay, 3 (11.1%) vs. 0, $p < 0.01$. For these patients in the treatment group, the median (IQR) duration was 2.6 days (0.4–12.4) or 62.4 h (9.6–297.6). Several studies have reported the use of ECMO for refractory status asthmaticus in children, with a median duration of ECMO of 93–144 h and survival rate of 95–100% (23–25). One of our patients in the treatment group who was initiated on ECMO expired after a prolonged ECMO run of 297.6 h. It is difficult to comment on the impact of magnesium sulfate infusions on the requirement of ECMO given our small sample size and retrospective study design. Overall, we noted that 3.7% of patients in the treatment and control groups expired

during their PICU admission, but no difference in mortality was noted between the groups. Other studies evaluating the mortality in children with status asthmaticus have noted a comparable mortality rate to our study of 3.4–4.3% (21, 26).

To account for the impact of other therapies on clinical outcomes, we also collected continuous albuterol duration, prednisone equivalent dosing, and receipt of additional advanced therapies (e.g., aminophylline, terbutaline, ketamine and heliox). We noted a significant difference in the median duration of continuous albuterol between the treatment and the control groups, 2.08 vs. 0.69 days, $p < 0.01$. However, continuous albuterol duration was not significantly associated with the odds of MV requirement or PICU LOS. Several other studies in children with status asthmaticus have assessed the duration of continuous albuterol as one of their primary outcomes; it is difficult to compare our study to these studies given that these studies did not employ prolonged magnesium infusions (21, 27). The treatment group had a significantly higher duration and cumulative and daily prednisone equivalent dosing compared with the control group. It is difficult to compare these findings given that initiation and dosing of corticosteroids was at prescriber discretion. A paucity of data exists on the dosing and impact of corticosteroids on outcomes in children with status asthmaticus. According to one study, many intensivists have been reported to utilize 2–4 times higher corticosteroid dosing compared to the published guidelines for children with asthma exacerbations (28). To account for confounding variables including the cumulative prednisone equivalent dosing, logistic and linear regressions were conducted to assess the odds of MV requirement and factors associated with PICU LOS, respectively. Higher cumulative prednisone equivalent dosing was associated with a higher MV requirement and longer PICU LOS. Previous studies have shown an association between the use of corticosteroids and the development of ICU-acquired weakness; thus, one plausible explanation is that patients receiving a higher cumulative prednisone equivalent dosing had a prolonged duration in MV duration and a corresponding increase in PICU LOS (29).

We also collected additional advanced therapies that the treatment and control groups received. In our study, we found a higher number of patients in the treatment group received an additional advanced therapy. Several previous studies have assessed outcomes in children receiving these advanced therapies (22, 30, 31). However, these authors only assessed outcomes of patients receiving one advanced therapy whereas we evaluated outcomes of children receiving more than one advanced therapy (22, 30, 31). One recent study by Stulce et al. evaluated outcomes in 1,144 children with status asthmaticus, in the Pediatric Health Information System database from 2016 to 2019, that received terbutaline and aminophylline as a second-tier therapy (29). They found a significantly higher odds of intubation and mechanical ventilation in African American children receiving terbutaline vs. those receiving aminophylline (OR, 12.41; 95% CI: 1.61–95.0). This study did not include any information on the number of children receiving prolonged magnesium infusions, so it is difficult to compare to our study. To account for the impact of these advanced therapies on clinical outcomes, we included the number of children receiving ketamine infusions in regression analyses. Both ketamine and magnesium infusions were received by 27 children. Due to the limited numbers of patients receiving heliox, terbutaline, and aminophylline infusions, we were unable to include them in the analyses. After controlling for various covariates, we noted that ketamine infusions were associated with 19.3 times higher odds of MV requirement but had no impact on PICU LOS. It is difficult to completely explain these findings, but it may reflect that ketamine infusions have been employed as a treatment for status asthmaticus and a sedative in patients receiving non-invasive and invasive mechanical ventilation (32).

All the patients who received magnesium sulfate infusions, were initiated at a rate of 15 mg/kg/h and were titrated to a goal serum magnesium concentration of 4–6 mg/dL. We noted a median duration of 28 h, and the median dose to achieve a serum concentration of 4–6 mg/dL was 19.9 mg/kg/h. Five previous studies including 261 children reported on the use of prolonged magnesium infusions over ≥4 h (8–10, 12, 13). It should be noted that all these reports utilized different dosing regimens, but they all utilized the same serum concentration goal of 4–6 mg/dL (33). Since the median duration of magnesium infusions in our study was 28 h, our findings can be compared to two previous reports that described the use of prolonged magnesium infusions over >24 h (12, 13). Patients in our study received comparable dosing and duration to those noted in these studies, with a median infusion rate of 18.4–25 mg/kg/h for a total duration of 53.4–177.5 h. Out of the five studies evaluating magnesium serum concentrations with prolonged magnesium infusions, only three patients (1.1%) developed hypermagnesemia, defined as a concentration >6 mg/dL (8–10, 12, 13). In these reports, no adverse events were attributed to magnesium infusion (13). We noted that 3 (11.1%) patients in the treatment group developed hypermagnesemia. While the percentage of children with hypermagnesemia in our study was higher than these previous reports, we also noted that the supratherapeutic concentrations were not associated with adverse events.

We noted 14 (51.9%) patients in the treatment group had an adverse event, most common adverse events included hypotension ($n = 13$; 41.8%) and nausea/vomiting ($n = 1$; 3.7%). Only two studies evaluating prolonged magnesium infusions reported adverse events (12, 13). The incidence of hypotension in our study was similar to the rate reported by Graff et al. (13). They evaluated adverse events in 154 children receiving magnesium infusions for ≥24 h and noted 170 episodes of hypotension that occurred in 74 of the 154 children (48.1%). Only five (6.8%) of these patients required an intervention with a fluid bolus, reduction in magnesium infusion rate, or initiation of IV maintenance fluids. In our study, we noted that 3 (21.4%) of the 14 patients with hypotension required similar interventions. The only other adverse event we noted in our study was nausea/vomiting in 1 patient. In the two previous studies evaluating magnesium infusions, 7.8% patients ($n = 35$) developed nausea and vomiting; 30 (85.7%) of these patients received ondansetron therapy (12, 13). Similar to these reports, nausea and vomiting in this one patient in our study resolved with ondansetron.

Our study has some limitations. First, the nature of retrospective design may have resulted in some missing or undocumented information. As a result, we were not able to establish a causal relationship between the outcomes and magnesium infusions. To account for this, we did employ the use of regression analyses to evaluate the factors associated with MV requirement and PICU LOS. Second, this study was conducted at a single center. As a result, the results may not be generalizable to other institutions. Third, our study included a limited sample size of children who received prolonged magnesium infusions. However, our sample size of the treatment group was comparable to many other reports analyzing the use of prolonged magnesium infusions in children with status asthmaticus (8–12). Fourth, our institution's refractory status asthmaticus protocol provided guidance on dosing and monitoring of advanced therapies. However, the selection of the therapies was at discretion of the providers. Therefore, we were unable to determine how the selection of advanced therapies may have affected the clinical outcomes. To account for the order of advanced therapies, we conducted a subgroup analysis comparing patients in the treatment group who received magnesium infusions as their first advanced therapy vs. those who received magnesium infusions after another advanced therapy (i.e., 2nd, 3rd, or 4th line). We found no difference in clinical outcomes between groups, but our sample size was small and further exploration is needed.

In conclusion, magnesium sulfate infusions were not associated with MV requirement or PICU LOS when controlling for covariates. Higher prednisone equivalent dosing was associated with an increase in MV requirement and PICU LOS. Overall, 14 (51.9%) patients in the treatment group developed an adverse event but were not associated with hypermagnesemia. Further prospective studies are needed to compare the impact of prolonged magnesium infusions vs. other advanced therapies on outcomes in children with refractory status asthmaticus.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Oklahoma Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KWT collected the clinical data and drafted this manuscript. SBN performed the statistical analysis for this study. PNJ, JLM, SBN, and NG critically revised the manuscript and approved the final version. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.860921/full#supplementary-material

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Chest Compressions in Pediatric Patients With Continuous-Flow Ventricular Assist Devices: Case Series and Proposed Algorithm

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Patients with continuous flow ventricular assist devices (CF-VAD's) in the systemic ventricle (left ventricle or single ventricle) often have no palpable pulses, unreliable pulse oximetry waveforms and non-pulsatile arterial waveforms despite hemodynamic stability. When circulatory decompensation occurs, standard indicators to begin cardiopulmonary resuscitation (CPR) which are used in other pediatric patients (i.e., significant bradycardia or loss of pulse) cannot be applied in the same fashion. In this population, there may already be pulselessness and development of bradycardia in and of itself would not trigger chest compressions. There are no universal guidelines to dictate when to consider chest compressions in this population. As such, there may be a delay in decision-making or in recognizing the need for chest compressions, even in patients hospitalized in intensive care units (ICU) and cared for by experienced staff who perform CPR regularly. We present four examples of pediatric cardiac ICU patients from a single center who underwent CPR between 2018 and 2019. Based on this case series, we propose a decision-making algorithm for chest compressions in pediatric patients with CF-VADs in the systemic ventricle.

Keywords: pediatric, chest compression (CC), ventricular assist device (VAD), continuous flow ventricular assist device, cardiopulmonary resuscitation (CPR), cardiac intensive care unit, left ventricular assist device (LVAD)

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BACKGROUND

The implantation of ventricular assist devices (VADs) in pediatric patients has become relatively widespread and has increased with time over the past decade (1–3). According to the most recent annual report from the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs), there were over 1,200 device implantations in 1,011 pediatric patients <19 years by North American hospitals between September 2012 and December 2020 (1). The most common devices used were intracorporeal continuous flow devices, accounting for 41% of patients from this time period. An additional 26% were paracorporeal continuous flow devices. Thus, the majority (67%) of pediatric VADs implanted during this time period were continuous flow devices. In considering only the younger non-adolescent pediatric population (<10 years of age), continuous flow device use was still substantial. There were 355 continuous flow VADs implanted (233 paracorporeal, 122 intracorporeal) of 627 device implantations; 56.6% (1).

While Pedimacs and other registries (1–6) collect data on adverse events in pediatric patients with mechanical circulatory support (MCS), there is no published data on the frequency of resuscitation necessitating chest compressions in this population. Though the frequency of discharge home in pediatric patients with VADs has increased over the past decade, a significant number of these patients still have prolonged hospital stays prior to discharge or never get discharged home (5).

Pediatric patients with continuous flow ventricular assist devices (CF-VAD's) in the systemic ventricle (left ventricle or single ventricle) often have no palpable pulses, unreliable pulse oximetry waveforms and non-pulsatile arterial waveforms despite hemodynamic stability. When circulatory decompensation occurs, standard indicators to begin cardiopulmonary resuscitation (CPR) which are used in other pediatric patients (i.e., significant bradycardia or loss of pulse) (7) cannot be applied in the same fashion. In this population, there may already be pulselessness and development of bradycardia in and of itself should not trigger chest compressions. There are no universal guidelines to dictate when to initiate or consider chest compressions in this pediatric population. Further, it is unclear whether existing adult algorithms for CPR in CF-VAD patients (8–10) can be applied in blanket fashion to adolescents, akin to how the American Heart Association's (AHA) algorithm for adult basic life support (BLS) is used in post-pubertal pediatric patients (11). Studies of hospitalized adult CF-VAD patients in cardiovascular emergencies have shown that there is often uncertainty about when to initiate chest compressions leading to delays in resuscitation (8, 9).

We present four cases of pediatric patients with CF-VADs from a single center who underwent in-hospital CPR between 2018 and 2019. Based on this case series, we propose a decision-making algorithm for chest compressions in pediatric patients with CF-VADs in the systemic ventricle.

CASE SERIES

Table 1 summarizes the four pediatric (<18 years old) patients in this case series. Each patient had a CF-VAD in the systemic ventricle, and each received chest compressions while admitted within the cardiac intensive care unit.

Patient #1 was a 16-year-old, 70 kg (1.8 m^2) male with muscular dystrophy and dilated cardiomyopathy, who underwent placement of a HeartMate-3™ (Abbott®, Abbott Park, Illinois) left ventricular assist device (LVAD) as destination therapy. On post-operative day 10, he developed significantly decreased VAD flows associated with worsening right ventricular function and the development of pericardial tamponade. He was initially planned for an urgent pericardiocentesis. Asystole occurred upon induction of anesthesia, and chest compressions were initiated shortly after, as the VAD flows declined. He instead underwent an emergent subxiphoid pericardial window. Duration of chest compressions was 15 min. There was evidence of significant neurologic injury after the event, which led to withdrawal of life support.

Patient #2 was a 3-year-old, 14 kg (0.56 m^2) girl with congenital heart block who developed pacemaker-induced cardiomyopathy. As a bridge to heart transplant, she underwent placement of a Jarvik 2015 LVAD (JarvikHeart™, New York, New York) in addition to a PediMag™ (Thoratec®, Pleasanton, California) right ventricular assist device (RVAD). On post-operative day 6, while mechanically ventilated, there were low-flow alarms from her RVAD. It was quickly noted that she had had accidental disconnection of her RVAD inflow cannula. This quickly resulted in significant blood loss and hypotension. Her RVAD cannula was quickly reconnected and pump speed resumed. She received 4 min of CPR prior to resumption of full flows. She suffered no neurologic injury and ultimately underwent heart transplantation six months after VAD placement.

Patient #3 was a 17-year-old, 110 kg (2.1 m^2) male with dilated cardiomyopathy who underwent placement of a HeartMate-3™ LVAD. On post-operative day 9, he was noted to have rising central venous pressures (CVP) and elevated lactate levels, as well as a drop in hemoglobin. He soon developed altered mental status, hypotension, and low-flow alarms from his VAD. Over the course of minutes, he had progressively lower flows. When flows dropped below 0.5 L/min, chest compressions were initiated. He received 2 min of chest compressions, with simultaneous administration of an intravenous fluid bolus and a dose (0.01 mg/kg) of epinephrine. VAD flows were restored, as was mean arterial pressure (MAP). He underwent an emergent mediastinal exploration, which revealed hemopericardium and a hemothorax.

Patient #4 was a 15-year-old, 53 kg (1.5 m^2) female with dilated cardiomyopathy. She underwent placement of a HeartWare™ HVAD™ (Medtronic®, Dublin, Ireland) LVAD. On post-operative day 14, her VAD flows acutely dropped to 0.8 L/min, MAP dropped from 60 to 65 mmHg to <30 mmHg and she became suddenly unresponsive. Prior to this, she had been awake, alert, sitting up, receiving non-invasive mechanical ventilation. Chest compressions were initiated, immediately followed by the administration of an epinephrine dose (0.01 mg/kg) and an intravenous fluid bolus. After a 2-min cycle of CPR, VAD flows increased and MAP normalized. She was subsequently confirmed to have pericardial tamponade, and underwent mediastinal exploration with hematoma evacuation. On post-operative day 24, now sedated and intubated, this patient had another acute drop in VAD flow after administration of a fosphenytoin dose for new-onset seizures. VAD flows again dropped below 1 L/min, and MAP dropped below 30 mmHg. With this second event, mental status changes could not be assessed as she was receiving sedative infusions. She did not receive chest compressions. She was given a dose of epinephrine (0.01 mg/kg) and an intravenous fluid bolus. VAD flows and MAP normalized.

Three of these four patients (#2, #3, and #4) initially came to clinician attention due to low-flow alarms (**Table 1**). In patient #4, who had two separate but similar low-flow events, the decision to initiate chest compressions only occurred with her first event, and this decision was informed by the acute change in mental status. In patients #1, #3, and #4, there was initial clinician

TABLE 1 | Summary of patient data.

Patient	Age	Diagnosis	Type of left VAD	Reason for clinician attention	Reason chest compressions initiated by clinician	Duration of chest compressions	CPR outcome
#1	16 years	Cardiomyopathy, muscular dystrophy	HeartMate-3™ (Abbott®, Abbott Park, Illinois)	Telemetry	Asystole	15 min	Neurologic injury, death.
#2	3 years	Pacemaker-induced cardiomyopathy	Jarvik 2015 (JarvikHeart™, New York, New York)	Low-flow alarm	Disconnected RVAD cannula	4 min	Restored MAP and VAD function. No direct sequalae.
#3	17 years	Dilated cardiomyopathy, idiopathic	HeartMate-3™ (Abbott®, Abbott Park, Illinois)	Low-flow alarm	Altered mental status; progressive decline of VAD flow until <0.5 L/min	2 min	Restored MAP and VAD function. No direct sequalae.
#4	15 years	Dilated cardiomyopathy, idiopathic	HeartWare™ HVAD™ (Medtronic®, Dublin, Ireland)	Low-flow alarm	Altered mental status; progressive decline of VAD flow; MAP < 30 mmHg	2 min	Restored MAP and VAD function. No direct sequalae.

CPR, cardiopulmonary resuscitation; MAP, mean arterial pressure; VAD, ventricular assist device.

uncertainty about when it was the appropriate time to initiate chest compressions in this population with hemodynamically-stable pulseless electrical activity (PEA) at baseline.

DECISION-MAKING ALGORITHM

Using the knowledge of sequence of events in these 4 cases, we created an algorithm to guide the decision about initiation of chest compressions in pediatric patients with CF-VADs in the systemic ventricle (**Figure 1**). We decided to focus simply on an algorithm that informs the decision to begin chest compressions.

Our decision-making algorithm starts with a response to a low-flow alarm. We chose to start here since 3 out of 4 patients in our case series came to clinician attention due to low-flow alarms. Our algorithm is initiated once the indexed VAD flow falls below 1 liter per minute per square meter. We did not start with a patient symptom first (such as change in mental status or hypotension), because in all of our 4 cases, the low-flow alarm preceded every symptom in drawing attention to the patient.

We considered complete VAD failure and the absence of a palpable pulse to be a clear indication for chest compressions. In cases where there is VAD dysfunction but the presence of a pulse, we recommend that the decision to initiate chest compressions be based on poor perfusion associated with a heart rate <60 beats per minute, in alliance with the American Heart Association (AHA) pediatric basic life support guidelines (11).

In patients with low flows with no evidence of VAD dysfunction, the next decision-making steps should be confirmation of non-pulsatile flow (no palpable pulse), followed by determination of mean arterial blood pressure (MAP). MAP measurement can be accomplished invasively *via* intra-arterial catheter or non-invasively *via* the Doppler opening pressure (DOP). Confirmation of non-pulsatile flow prior to MAP measurement by cuff is important since the DOP may over-estimate the MAP and may more closely correlate with systolic pressure if the patient is pulsatile (12). The steps in the algorithm can still be followed if the patient has a narrow pulse pressure, and some studies have demonstrated that DOP is an accurate assessment of MAP even in pulsatile LVAD patients (13).

Excessively high MAP's should be treated to restore flows. For low MAP's, we set cut-off points by weight, which we call the "drop-off MAP." In those low-flow patients whose MAP's fall below the "drop-off MAP" cutoff, we propose that the decision point for initiation of chest compressions should be acute change in mental status (for non-intubated non-sedated patients) or a drop in invasive end-tidal carbon dioxide ($ETCO_2$) to <20 mmHg (for intubated patients).

Supplementary Table S1 summarizes some patient- and device-related problems to consider in patients with CF-VAD in the left ventricle who develop low-flow or evidence of decreased tissue perfusion.

DISCUSSION

To our knowledge, no pediatric algorithms exist in the literature to determine the initiation of chest compressions during cardiovascular emergencies in this unique population. CPR algorithms for adult patients with CF-VAD's have been proposed and published in the literature (8–10). In addition, a 2017 AHA statement provides an algorithm for emergency medical personnel responding to unresponsive VAD patients in the field (14).

Studies have demonstrated that chest compressions may be safe and effective in patients with intracorporeal VADs (15, 16). Chest compressions can be performed on all patients with VADs, with the exception of the Total Artificial Heart (TAH) (SynCardia Systems, LLC; Tucson, Arizona). Patients with a TAH have had their ventricle(s) excised at the time of implantation, and therefore do not benefit from chest compressions, defibrillation, pacing or cardioactive medications; the plastic artificial ventricle is incompressible (14, 17, 18). A large study of adult LVAD patients with cardiac arrest between 2010 and 2018 did show

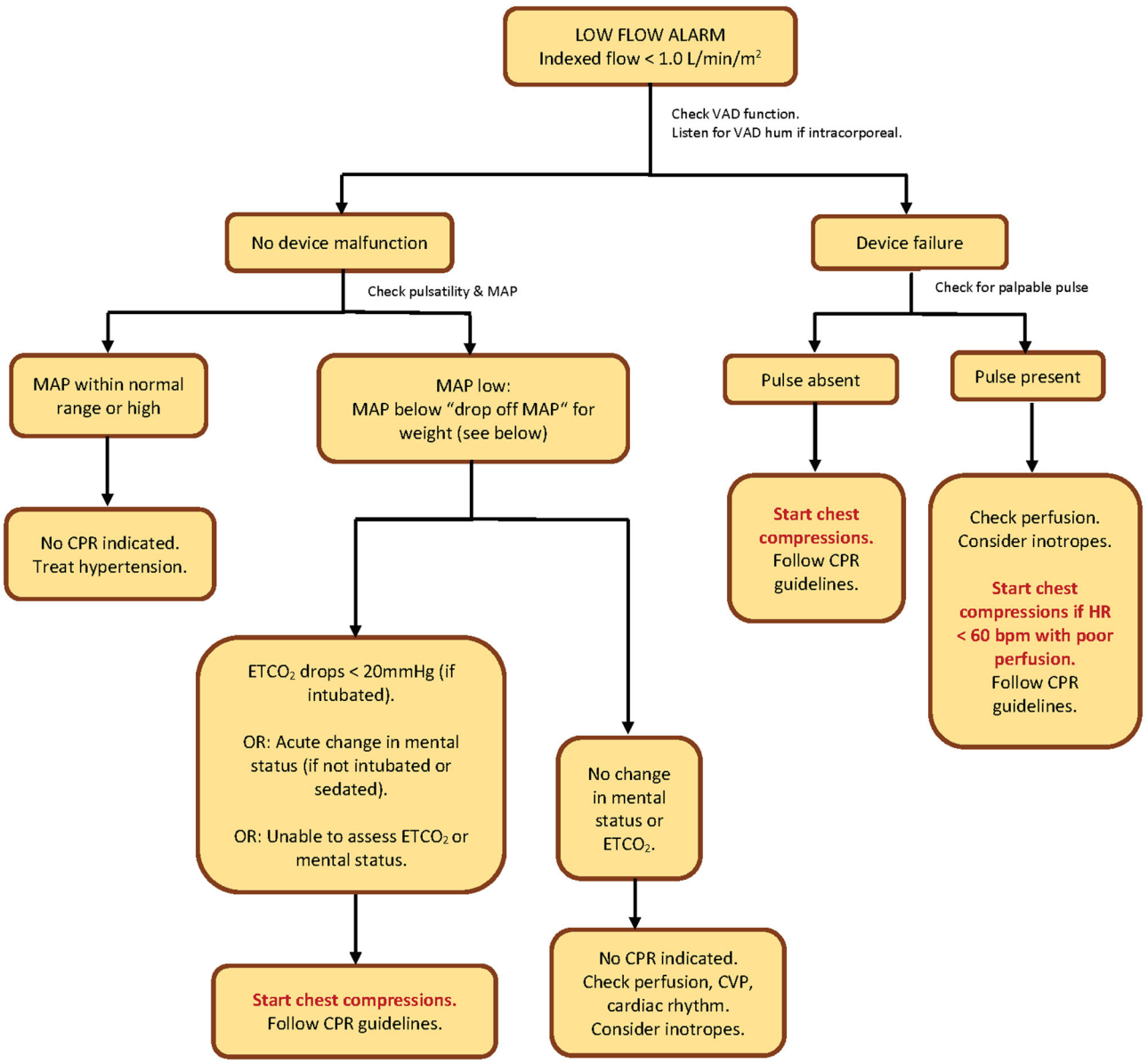

FIGURE 1 | CPR algorithm to determine initiation of chest compressions in pediatric patients with continuous-flow ventricular assist devices in the systemic (left/single) ventricle. "Drop-off MAP" by patient weight: If weight <15 kg = 25 mmHg; if weight 15–30 kg = 30 mmHg; if weight >30 kg = 35 mmHg. VAD, ventricular assist device; MAP, mean arterial pressure; CPR, cardiopulmonary resuscitation; $ETCO_2$, end-tidal carbon dioxide; HR, heart rate; bpm, beats per minute; CVP, central venous pressure.

a higher mortality in those who received CPR compared to those who did not. But the authors advise that this finding must be interpreted with caution since the two groups differed based on several variables that were independent risk factors for mortality. Of note, the authors also reported a declining rate of utilization of chest compressions over the time period studied, and this was hypothesized to be due to increasing uncertainty regarding the safety and efficacy of chest compressions in the VAD population (19).

Without the ability to rely on traditional cutoff points such as the loss of a pulse or a drop in heart rate below 60 beats per minute, clinical assessment and judgement of a profound decline in perfusion should serve as the indicator for when to initiate chest compressions in pediatric CF-VAD patients who have an acute circulatory decompensation. Guidelines for CPR, which can be used in all other patients, will not apply in pediatric CF-VAD patients. Thus, even experienced ICU staff who perform CPR regularly have demonstrated uncertainty regarding timing of initiation of chest compressions in CF-VAD patients. In the face of declining continuous variables such as MAP or near infrared spectroscopy (NIRS), clinicians may be uncertain about what

cutoff points should trigger chest compressions, or whether to use inotropes alone.

Garg et al. reviewed a series of adult patients with continuous-flow left ventricular assist devices (LVADs) who underwent in-hospital CPR, and compared them to patients without VADs at the same hospital who suffered in-hospital cardiac arrest. They found a statistically significant difference in time to initiation of chest compressions, with the VAD patients experiencing a delay in initiation. They attributed this delay to clinician uncertainty about when to start compressions in this group of patients who are pulseless at baseline. They coined the term "hypotensive electrical activity" (HEA), and created an algorithm to establish cut-off points beyond which chest compressions should be initiated (8). Yuzefpolskaya et al. also published a proposed algorithm for CPR in adult CF-VAD patients, after presenting a case report that demonstrated delayed initiation of chest compressions in a hospitalized adult LVAD patient (9).

Similar to these adult cases, our pediatric cases involved clinician uncertainty about timing of initiation of chest compressions, leading to short delays in resuscitation. Our cases were from a pediatric cardiac intensive care unit at a single large tertiary center that provides a broad range of advanced cardiac therapies. Our proposed CPR algorithm for pediatric CF-VAD patients is written for hospitalized patients in intensive care units. This algorithm was presented several times before multidisciplinary groups for feedback as well as education.

Categorical decision-points we used in our algorithm include determination of VAD function, determination of presence of a palpable pulse, determination of MAP, and assessment for acute change in mental status or drop in $ETCO_2$. The published adult VAD CPR algorithms (8–10) recommend use of Doppler to determine presence of (pulseless) arterial blood flow in emergencies. Of note, those algorithms start with a response to an unresponsive patient. Our algorithm starts with response to a low-flow alarm, and initially addresses VAD function, and we account for those with presumed preserved flow by using hemodynamic and clinical parameters to determine need for compressions. Our patients were all hospitalized in intensive care, and their circulatory emergencies first came to clinician attention due to low-flow alarms. Also in contrast, the AHA guidelines for CPR in patients with mechanical circulatory support targets use by emergency medical personnel in the field (14).

Our cut-offs for drop-off MAPs by weight need to be validated in further studies. Even in non-VAD patients, determination of the blood pressure below which chest compressions are indicated (in the absence of non-perfusing rhythm or bradycardia) remains a controversial topic. This is true even in adult medicine where it is more likely (than in pediatrics) that one blood pressure number chosen may apply to most patients. Harper et al., in an editorial in 2020, proposed a systolic blood pressure <50 mmHg as a trigger to initiate chest compressions in the anesthetized adult patient (20).

Our choice of $ETCO_2 < 20$ mmHg also needs to be further studied, but is extrapolated from existing resuscitation literature that associates an $ETCO_2 < 20$ mmHg during CPR with poor cardiac output from poor CPR quality (21).

Our algorithm is intentionally simple, and does not include details on how to perform CPR. Users of this algorithm are thus referred to existing guidelines for pediatric basic and advanced life support, once the decision tree has suggested to start chest compressions. Also for simplicity, our algorithm does not provide extensive guidance on how to resuscitate pediatric VAD patients with low-flows who do not require chest compressions.

CONCLUSION

There is minimal existing literature demonstrating the scope of the problem of circulatory collapse requiring chest compressions in patients with CF-VADs. Published literature does not include pediatric patients. Our case series of 4 pediatric CF-VAD patients demonstrates the significant morbidity and mortality that can occur. The already published literature as well as our case series demonstrate that there may be delays in resuscitation due to clinician uncertainty about when to begin chest compressions in this population that would have "hemodynamically-stable PEA" at baseline.

A CPR algorithm, such as we have proposed, that guides decision-making may lead to earlier and more appropriate resuscitation in pediatric CF-VAD patients with cardiovascular emergencies. Further investigation is necessary to determine the applicability of our algorithm across different pediatric centers, as well as its use in reducing time to initiation of appropriate chest compressions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UT Southwestern Medical Center IRB. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IE: data collection (case series), data collation, creation of algorithm, and writing of manuscript. PY: editing of algorithm, review of literature, and review of manuscript. Both authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.883320/full#supplementary-material

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Early Changes in Near-Infrared Spectroscopy Are Associated With Cardiac Arrest in Children With Congenital Heart Disease

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Background: The association of near-infrared spectroscopy (NIRS) with various outcomes after pediatric cardiac surgery has been studied extensively. However, the role of NIRS in the prediction of cardiac arrest (CA) in children with heart disease has yet to be evaluated. We sought to determine if a model utilizing regional cerebral oximetry (rSO2c) and somatic oximetry (rSO2s) could predict CA in children admitted to a single-center pediatric cardiac intensive care unit (CICU).

Methods: We retrospectively reviewed 160 index CA events for patients admitted to our pediatric CICU between November 2010 and January 2019. We selected 711 control patients who did not have a cardiac arrest. Hourly data was collected from the electronic health record (EHR). We previously created a machine-learning algorithm to predict the risk of CA using EHR data. Univariable analysis was done on these variables, which we then used to create a multivariable logistic regression model. The outputs from the model were presented by odds ratio (OR) and 95% confidence interval (CI).

Results: We created a multivariable model to evaluate the association of CA using five variables: arterial saturation (SpO2)- rSO2c difference, SpO2-rSO2s difference, heart rate, diastolic blood pressure, and vasoactive inotrope score. While the SpO2-rSO2c difference was not a significant contributor to the multivariable model, the SpO2-rSO2s difference was. The average SpO2-rSO2s difference cutoff with the best prognostic accuracy for CA was 29% [CI 26–31%]. In the multivariable model, a 10% increase in the SpO2-rSO2s difference was independently associated with increased odds of CA [OR 1.40 (1.18, 1.67), $P < 0.001$] at 1 h before CA. Our model predicted CA with an AUROC of 0.83 at 1 h before CA.

Conclusion: In this single-center case-control study of children admitted to a pediatric CICU, we created a multivariable model utilizing hourly data from the EHR to predict CA.

At 1 h before the event, for every 10% increase in the SpO2-rSO2s difference, the odds of cardiac arrest increased by 40%. These findings are important as the field explores ways to capitalize on the wealth of data at our disposal to improve patient care.

Keywords: near-infrared (NIR) spectroscopy, cardiac arrest, prediction, children, congenital heart disease

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a method of non-invasive real-time continuous monitoring of tissue oxygenation. The use of NIRS has been studied extensively in children with congenital heart disease (CHD) (1). There have been studies looking at the association between NIRS and various outcomes after pediatric cardiac surgery, such as low cardiac output syndrome, acute kidney injury, necrotizing enterocolitis, neurodevelopmental outcome, and mortality (2–5). In particular, multisite NIRS, which refers to simultaneously monitoring cerebral oxygen saturation (rSO2c) as well as somatic oxygen saturation (rSO2s), can be performed by placing NIRS sensors over the brain and kidney, liver, or intestines. Since the body's response to decreased cardiac output is to decrease perfusion to somatic sites to preserve perfusion to the brain, it can be helpful to monitor multisite NIRS as an early predictor (1). Monitoring regional tissue oxygen extraction (using arterial oxygen saturation-rSO2 difference) can also be useful in the pre- and post-operative periods of children with CHD. In a study of children with CHD during the pre-operative period, it has been shown that those lesions with diastolic runoff compared to lesions without runoff have the most cerebral oxygen extraction indicating less cerebral blood flow. There is also evidence that cerebral tissue oxygen extraction can be predictive of mortality in the children with HLHS after Stage 1 Palliation (6, 7). While the ability of NIRS to predict various outcomes has been well-studied, the role of NIRS in the prediction of cardiac arrest (CA) in children with heart disease has yet to be studied. In fact, this gap in the literature does not only apply to children with CHD. There is literature looking at the association of NIRS with intra-arrest and post-cardiac arrest outcomes in adults (8, 9), although this consists of case reports and case series (10–15). There are no data on the use of NIRS to predict cardiac arrest in adults. Our goal therefore was to determine if regional, cerebral, and somatic oxygen saturations (rSO2c and rSO2s) could predict cardiac arrest in children admitted to a single-center pediatric cardiac intensive care unit (CICU).

METHODS

The Institutional Review Board's approval was obtained before this study. We queried our local Get With the Guidelines Resuscitation (GWTGR) Registry database for children admitted to the Children's Medical Center Dallas pediatric CICU between November 2010 and January 2019 who developed a cardiac arrest during their CICU admission. Our pediatric CICU is a 26-bed unit that admits surgical and non-surgical patients with heart disease. The GWTGR Registry database defines cardiac arrest as pulselessness or pulse with inadequate perfusion requiring chest compressions and/or defibrillation. From the GWTGR Registry database, we retrospectively reviewed all events by chart review of the electronic health record (EHR) to confirm the diagnosis of cardiac arrest. For our study, we chose to only include patients who developed a cardiac arrest that resulted in chest compressions. We excluded cardiac arrests that resulted in defibrillation alone without chest compressions. We chose to analyze only the index events. We identified 160 index CA events during the study period. We attempted to find a method to match controls to cases. Although there exist multiple severities of illness scoring systems that have been validated in the general pediatric ICU population to predict mortality, such as Pediatric Risk of Mortality (PRISM)-3 and Pediatric Index of Mortality (PIM)2, unfortunately, no scoring system has been validated for the population of children with congenital heart disease (16, 17). Jeffries et al. published a scoring tool to predict the risk of mortality, the Pediatric Index of Cardiac Surgical Intensive Care Mortality (PICSIM), that has been validated in children after cardiac surgery (18). Unfortunately, this score is unique to the post-surgical population and cannot be used in non-surgical patients. As there was no validated tool to match cases and controls in total, we selected our control patients at random using the following criteria: 1. Patients admitted to the CICU between November 2009 and December 2019; 2. patients who did not have a cardiac arrest during the admission; 3. patients who were not in the cardiac arrest dataset; and 4. patients who were not on extracorporeal membrane oxygenation (ECMO) already at the time of admission; and 5. patients who were admitted to the CICU within 12 h of hospital admission.

NIRS monitoring was done using Medtronic INVOS oximeter probes and monitors. Our standard of care for all patients who are admitted to our CICU is to place INVOS oximeter probes on the forehead and flank to measure regional cerebral and somatic (kidney) oxygen saturation. We collected various data from the electronic health record (EHR). The study period consisted of up to 48 h before CA for patients who had a cardiac arrest, and up to the first 48 h of ICU admission for the control patients. Demographic data (age, weight, gestational age, ventricular status) were collected from the EHR. Single ventricle physiology is defined as those patients with a mixture of systemic venous and pulmonary venous return, with total cardiac output partitioned into pulmonary and systemic blood flow (19). Therefore, this definition would include patients who are intended to undergo a single ventricle palliation pathway as well as patients palliated initially with a shunt before two ventricle repairs (such as Tetralogy of Fallot). Surgical information (date of surgery, STS-European Association for Cardiothoracic Surgery (STS-EACTS) mortality category (STAT category), cardiopulmonary bypass

(CPB) times, and cross-clamp (Xclamp) times were collected from the STS database and EHR).

We had previously created a machine-learning algorithm to predict the risk of CA in our center (manuscript currently under preparation). The machine-learning algorithm was created using XG-boost, or extreme gradient boosting, a type of decision tree algorithm. The machine-learning algorithm was trained on the same dataset. A total of 11 variables were selected that were most important to the machine learning algorithm (**Table 1**). VIS was defined by the equation: Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + [100 × Epinephrine dose (mcg/kg/min)] + [10 × Milrinone dose (mcg/kg/min)] + [10,000 × Vasopressin dose (units/kg/min)] + [100 × Norepinephrine dose (mcg/kg/min)]. The data values of HR, SpO2, DBP, rSO2c, rSO2s, and ETCO2 levels are automatically carried over from the patient monitor to the EHR with the bedside nurse confirming the value before it is finalized in the EHR. The missing values were carried forward from the last documented value. The 11 variables in order from most to least missing data were the following: anion gap, FiO2, base excess, ETCO2, rSO2s, rSO1c, DBP, SpO2, HR, urine output, and VIS (**Supplementary Table 1**). The average of all available values within each hourly interval from hours 1 to 15 before CA was used for analysis. Univariable analysis was performed on each of those 11 variables, and we selected the variables that were found to have an association with CA in our multivariable analysis. We created multivariable logistic regression models to include these variables to predict CA as a function of time. The output from models was presented by odds ratio (OR) and 95% confidence interval (CI).

For some variables, we used absolute values, while for others, we used the relative change from baseline (**Table 2**). We defined a patient's baseline for a given variable as the average value over the first 4 h of the study period. The relative change of a given variable X at hour Y was defined as [X (at hour Y)-X (baseline)]/X(baseline. Given the population of children admitted to our CICU have both cyanotic and non-cyanotic heart disease, which can affect the baseline SpO2, rSO2c, and rSO2s, we chose to analyze the changes in these values compared to the patient's baseline rather than their absolute values. In patients with single ventricle physiology, changes in rSO2 can influence the SpO2. Similarly, since baseline HR and DBP can be age-dependent, we elected to analyze changes in HR and DBP compared to the patient's baseline. We elected to use absolute VIS. Values for VIS were not normally distributed therefore could not be represented as a continuous variable in our logistic regression model but rather as categories. When we analyzed the distribution of the VIS data, 75% of the VIS values were 0. Therefore, we elected to classify values for VIS into two categories: VIS 0 and VIS > 0. We also elected to evaluate absolute values of the surrogates of arteriovenous difference: SpO2-rSO2s difference and SpO2-rSO2c difference. We attempted to use simultaneous values of SpO2 and rSO2s and rSO2c to calculate these differences, however, the number of values containing simultaneous values was too small to do an analysis. Therefore, we instead used the average of SpO2 values within a specific hour and the average of rSO2s and rSO2c for that specific hour to calculate the SpO2-rSO2s difference and SpO2-rSO2c difference. All other variables (FiO2, urine output, base excess, anion gap, ETCO2) were represented as absolute values rather than standardized to the patient's baseline. FiO2 was represented as a categorical instead of a continuous variable with all values broken down into tertiles. All values for a given variable over a given hour were averaged and the average value was used in the model. We defined the patient's baseline as the first 4 h of the study period, we excluded any patient who had <6 h of available data. The original contributions presented in the study are publicly available. These data can be found here [link/accession number]. Odds for CA were examined by univariable and multivariable logistic regression models for hours 1 through 15 before CA.

TABLE 1 | Clinical features most important to the XG-boost algorithm.

Heart rate (HR)
Oxygen saturation level measured by pulse oximetry (SpO2)
Diastolic blood pressure (DBP)
rSO2c
rSO2s
End tidal carbon dioxide (ETCO2)
Urine output (cc/kg/hr)
Base excess
Anion gap
Fraction of inspired oxygen (FiO2)
Vasoactive inotrope score (VIS)

TABLE 2 | Clinical features: absolute value vs. relative change from baseline.

Variable	Absolute value or relative change
Heart rate (HR)	Relative change
Oxygen saturation level measured by Pulse oximetry (SpO2)	Relative change
Diastolic blood pressure (DBP)	Relative change
rSO2c	Relative change
rSO2s	Relative change
End tidal carbon dioxide (ETCO2)	Absolute value
Urine output (cc/kg/hr)	Absolute value
Base excess	Absolute value
Anion gap	Absolute value
Fraction of inspired oxygen (FiO2)	Absolute value
Vasoactive inotrope score (VIS)	Absolute value

Statistical Analysis

Categorical data are presented as counts and proportions and compared between groups using a chi-square test. Mean and std, or Medians and interquartile ranges are used to summarize continuous data and are compared with the *t*-test or Wilcoxon's rank-sum test, based on the distribution of data. Data distribution was assessed by the Shapiro–Wilk's normality test and normal probability plots. Optimal predicted probability

cutoffs were determined by Youden's index from the receiver-operating characteristic (ROC) analysis and displayed as median and 95% confidence intervals. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided, and $P < 0.05$ was considered as significant.

RESULTS

During the defined study period 160 patients had cardiac arrest and 711 control patients. **Table 3** shows the demographics of those patients who had a cardiac arrest vs. no cardiac arrest. Patients who had a cardiac arrest tended to be younger, of lower weight, younger gestational age at birth, more likely to have single ventricle physiology, higher STAT category, and longer CPB and cross-clamp times. The dataset for case and control groups and their corresponding 11 variables for hours 1 to 15 is provided.

Univariable Analysis

Univariable analysis of the different variables with their association with risk of cardiac arrest at 1 h before CA is displayed in **Table 4**. FiO2, DBP, anion gap, HR, VIS, SpO2, SpO2-rSO2c difference, and SpO2-rSO2s difference were all significantly associated with the risk of cardiac arrest on univariable analysis.

Multivariable Analysis

Based on the univariable analysis results, we created a multivariable model consisting of FiO2, DBP, anion gap, HR, VIS, SpO2-rSO2c difference, and SpO2-rSO2s difference. **Table 5** shows which variables were associated with CA with a multivariable logistic regression model. All the variables except FiO2, anion gap, and SpO2-rSO2c difference were significantly associated with CA. FiO2 and anion gap were removed from the model given their non-significance and low numbers (only 26 patients in the CA group had those variables to analyze). **Figure 1** shows the graph of the multivariable logistic model with the AUROC at each hour before CA using the variables HR, VIS, SpO2-rSO2s difference, SpO2-rSO2c difference, and DBP. The AUROC increased as time moved closer to the CA and was 0.83 1 h before the CA. **Table 6** displays the odds ratios for CA for each variable in the multivariable model 1 h before CA. The SpO2-rSO2s difference was independently associated with the risk of CA with an OR of 1.40 (1.18, 1.67), $P < 0.001$. The odds ratios for CA for all other hours before CA can be found in **Supplementary Table 2**.

Changes in Individual Variables in the Multivariable Model Over Time

Since the rSO2s values are affected by SpO2 values, we wanted to evaluate if it was the SpO2-rSO2s difference that was different between cases and controls, since this was taken to be a surrogate of arteriovenous oxygen difference and thus the amount of oxygen extraction. **Figures 2**, **3** show the mean SpO2- rSO2s difference and SpO2-rSO2c difference, respectively, over time. The SpO2-rSO2s difference values in cases were higher than in controls. The average optimal cutoff which differentiated cases and controls between hours 1 and 15 before CA was 29% [26–32%]. The SpO2-rSO2c difference values were higher in cases compared to controls as well. The average optimal cutoff which differentiated cases and controls between hours 1 and 15 before CA was 31% [30–33%]. **Figures 4**, **5** show changes in HR and DBP, respectively, over time. Of note, the control group's HR and DBP do not start at baseline at hour 15. By definition, we chose the baseline HR and DBP to be calculated using an average of the first 4 h of data, which for the majority of patients was before hour 15. **Figure 4** shows that the control group's HR started at a higher baseline and by hour 15 came down significantly, whereas the arrest group's HR had levels at hour 15 which was similar to their baseline. **Figure 5** shows that the control group's DBP baseline was similar to levels seen at hour 15, whereas the arrest group's

TABLE 3 | Patient prearrest characteristics: cardiac arrest vs. no cardiac arrest.

Characteristic	Cardiac arrest $n = 160$ (%)	No cardiac arrest $N = 711$ (%)	*P*-value
Gender (male)	84 (52.50%)	367 (51.62%)	0.84
Age (day) Median [IQR]	54 [1, 908]	217 [30, 1,563]	<0.0001
Number of days from admission to cardiac arrest	10.90 [2.38, 32.80]	N/A	N/A
Single ventricle physiology	64 (40.0)	91 (12.80)	<0.0001
Weight (kg) Median [IQR]	5.17 [3.30, 11.0]	7.30 [4.32, 15.65]	0.0001
Gestational age Median [IQR]	38.0 [36.0, 39.3]	39.0 [37.0, 40.0]	0.0009
For surgical patients: (below variable were analyzed on surgical yes patients only)	$N = 94$	$N = 337$	
Number of post-operative days at arrest Median [IQR]	10.16 [1.68, 26.63]	N/A	
Stat category 1	4 (4.35%)	145 (43.6%)	<0.0001
Stat category 2	17 (18.48%)	109 (32.83%)	
Stat category 3	7 (7.61%)	33 (9.94%)	
Stat category 4	46 (50.00%)	37 (11.14%)	
Stat category 5	16 (17.39%)	5 (1.51%)	
No stat category assigned (stat category = 0)	2 (2.17%)	3 (0.90%)	
CPB times Median [IQR]	118.0 [93.0, 163.0]	77.0 [53.0, 111.0]	<0.0001
X clamp times Median [IQR]	70.0 [39.0, 116.0]	49.5 [24.0, 80.0]	0.003

TABLE 4 | Univariate predictors of cardiac arrest.

Variable	OR, CI {95%}	*P*-value	AUROC
FiO2 (tertile 3 vs. 1)	0.78 (0.41, 1.51)	0.47	0.63
(tertile 3 vs. 2)	2.63 (1.59, 4.37)	<0.001	
Urine output	0.98 (0.96, 1.01)	0.30	0.48
DBP	0.91 (0.87, 0.95)	<0.001	0.62
Anion gap	11.20 (3.30, 38.30)	<0.001	0.68
Base excess	0.84 (0.51, 1.40)	0.51	0.51
ETCO2	0.86 (0.68, 1.09)	0.21	0.58
HR	1.16 (1.10, 1.23)	<0.001	0.64
VIS	9.14 (6.18, 13.52)	<0.001	0.71
SpO2	0.80 (0.70, 0.90)	<0.001	0.58
rSO2c	0.97 (0.93, 1.01)	0.25	0.53
rSO2s	1.04 (0.999, 1.096)	0.05	0.55
SaO2-rSO2c difference	1.31 (1.11, 1.53)	0.001	0.61
SaO2-rSO2s difference	1.40 (1.21, 1.60)	<0.001	0.64

All units of change are 10 except HR, DBP, SpO2, rSO2c, and rSO2s which are 5.

TABLE 5 | Variables associated with cardiac arrest in multivariable logistic regression model.

SaO2-rSO2s difference
HR
VIS
DBP

DBP at hour 15 was lower than their baseline. At around hour 5 before CA, changes in HR and DBP start to develop. HR shows a steady increase above baseline. DBP shows a steady decline below the baseline.

Confounding Variables

Since we were unable to match cases to controls as described previously in our Methods section, we attempted to account for confounding variables in our multivariable analysis.

The patients who had a CA compared to controls were more likely to have SV physiology, therefore, we wanted to evaluate if the diagnosis of SV physiology was a potential confounder. We also created a multivariable model that included the diagnosis of SV physiology as a covariate in addition to the other variables. Even after controlling for SV physiology diagnosis, the variable SpO2-rSO2s difference remained a significant risk factor for odds of CA.

The surgical patients who had a CA compared to the controls had higher STAT categories, longer CPB times, and longer X clamp times, therefore, we created a model for the surgical patients that included CPB times as a variable in addition to the other 4 variables. We had originally attempted to use the STAT category as a variable in our multivariable model however there was an imbalance of STAT categories in this cohort with a larger proportion of lower STAT categories. Therefore, in the multivariable analysis, we had to divide the STAT categories into two groups: those with STAT categories 1–2 vs. 3–5. Since we did not believe a dichotomous grouping adequately stratified the risk of surgical complexity, we decided to use CPB time (a variable that could be evaluated as a continuous variable) as a surrogate for surgical complexity since those patients with surgeries of higher surgical complexity tended to have higher CPB times. The CPB time was classified into 3 categories: Group 1: 0–60 min, Group 2: >60–120 min, and Group 3: >120 min. This model shows that even when controlling for CPB time, increases in the SpO2-rSO2s difference increase the odds of CA.

DISCUSSION

In this case-control study of children admitted to a single-center pediatric CICU, FiO2, DBP, anion gap, HR, VIS, SpO2, SpO2-rSO2c difference, and SpO2-rSO2s difference were all significantly associated with the risk of CA on univariable analysis. The multivariable analysis found that the variables HR, VIS, SpO2-rSO2s difference, and DBP were independently associated with CA. Multivariable logistic regression model to predict CA with the variables HR, VIS, SpO2-rSO2s difference, SpO2-rSO2c difference, and DBP had a good performance of an AUROC that improved over time with the highest AUROC at hour 1 before arrest of 0.83 (**Figure 1**). When looking at the individual components of our model over time, the SpO2-rSO2s difference and SpO2-rSO2c difference between case and control patients remained relatively constant (**Figures 2**, **3**), whereas the HR and DBP showed steady increases and decreases, respectively, as the time approached the CA (**Figures 4**, **5**). Interestingly, changes in HR and DBP showed similar changes at around hour 5 before CA. For the variable DBP, control patients started off and remained with values close to their baselines with CA patients having DBP values that were lower than their baseline values, but at hour 5 before CA, the split between case and control patients becomes more prominent with case patients having declines in their DBP. In contrast, with the variable HR, CA patients started with their baseline HR, while control patients started with significantly lower HR values than their baseline. Again, at hour 5 before CA, the split between the two groups becomes more prominent with case patients having HR values that increase.

Studies have shown there is usually a widening of the arteriovenous oxygen (AVO2) difference in settings of shock or poor oxygen delivery to the body. Thus, the decision to choose to use the variables SpO2-rSO2s and SpO2-rSO2c in our model. Although in our multivariable model changes in SpO2-rSO2c difference were not significant for CA, changes in SpO2-rSO2s were. Typically, when cardiac output is limited, somatic perfusion is limited to preserve cerebral perfusion (20). Therefore, when cerebral perfusion is impaired, it is often a late sign of impaired cardiac output when the body has lost its compensatory mechanism to preserve cerebral blood flow. A study by Hanson et al. showed that in moderately dehydrated children, rSO2c is preserved while rSO2s often decreases. Rehydration resulted in a significant increase in rSO2s with no changes in rSO2c (21). We only analyzed the performance of the model up to 1 h before CA. It is possible if we had

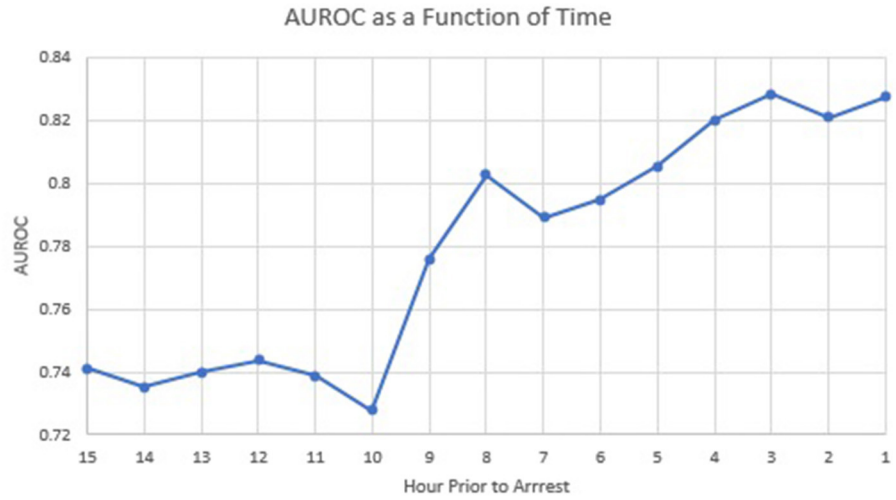

FIGURE 1 | Multivariable model prediction of cardiac arrest.

TABLE 6 | Odds ratio of cardiac arrest of individual variables of multivariate model at 1 h prior to cardiac arrest.

Variable	OR [CI]	*P*-value
SaO2-rSO2s difference	1.40 (1.18, 1.67)	<0.001
SaO2-rSO2c difference	1.12 (0.90, 1.38)	0.30
HR	1.17 (1.08, 1.27)	<0.001
VIS	10.01 (6.12, 16.36)	<0.001
DBP	0.95 (0.90, 0.997)	0.037

Units of changes for HR are 5 bpm; Units of change for DBP are 5 mm Hg; SaO2-rSO2c and SaO2-rSO2s are 10% points.

evaluated rSO2c in the minutes preceding CA, we could have detected changes.

As expected, the cases had overall higher SpO2-rSO2s values compared to controls. The average optimal cutoff which differentiated cases and controls between hours 1 and 15 before CA was 29%. This optimal cutoff can be valuable for the provider taking care of children with CHD when used in conjunction with other patient factors. It was unexpected that there were no changes in SpO2-rSO2s difference closer to the arrest of cases compared to controls. We hypothesize that this could be secondary to clinician intervention. A clinician may notice early on a widened SpO2-rSO2s difference and make interventions to correct what is perceived to be a state of impending deterioration, such as administration of fluid, packed red blood cell (prbc) transfusion, or titration of vasoactive infusions. We did not investigate the administration of any medications for this study other than vasoactive infusions. Future studies should evaluate other factors that could affect SpO2-rSO2s differences, such as administration of packed red blood cell transfusions, volume expanders, sedative medications, and neuromuscular blockade. Why those patients despite stable SpO2-rSO2s differences continued to go on to have a CA is unknown. Some patients will have a CA that is unpredictable, such as from a sudden respiratory arrest from a mucus plug occluding an airway. There are other subgroups of cardiac patients who are at high risk of sudden cardiac arrest without any preceding changes, such as single ventricle physiology patients, those with coronary artery abnormalities, or primary arrhythmias. Data from the Single Ventricle Reconstruction Trial have shown that 18% of deaths during hospitalization post the Norwood procedure were sudden and unexpected (22). We did not do subgroup analysis on patients who were found to have a non-sudden CA, but perhaps future studies could delve into that subset of patients who are not thought to have a sudden event, and evaluate the changes in their SpO2-rSO2s difference.

To our knowledge, this is the first case-control study to show that a multivariable model using NIRS can be used to predict CA. There have been various case reports and case series reporting the use of NIRS as a predictor of CA. Mebius et al. published a case report of two infants with CHD who demonstrated a change in NIRS before the onset of CA (15). Tume et al. published a case report of an infant after cardiac surgery who demonstrated a decline in NIRS before the onset of CA (14). Lanks et al. published a case report of an adult who demonstrated a decrease in his cerebral NIRS before the onset of CA (10).

Although not specific to CA, prior studies have shown an association between NIRS and mortality in children with CHD which is consistent with the findings of our study. Hoffman et al. found that the use of rSO2c and rSO2s in the post-operative period could predict mortality and ECMO use in patients with hypoplastic left heart syndrome (6). Phelps et al. found that low rSO2c in the first 48 h after the Norwood procedure had a strong association with adverse outcomes, defined as hospital death, need for ECMO, or CICU stays >30 days (23).

We chose to only analyze data from the EHR rather than continuous physiologic data. It is very likely that with more

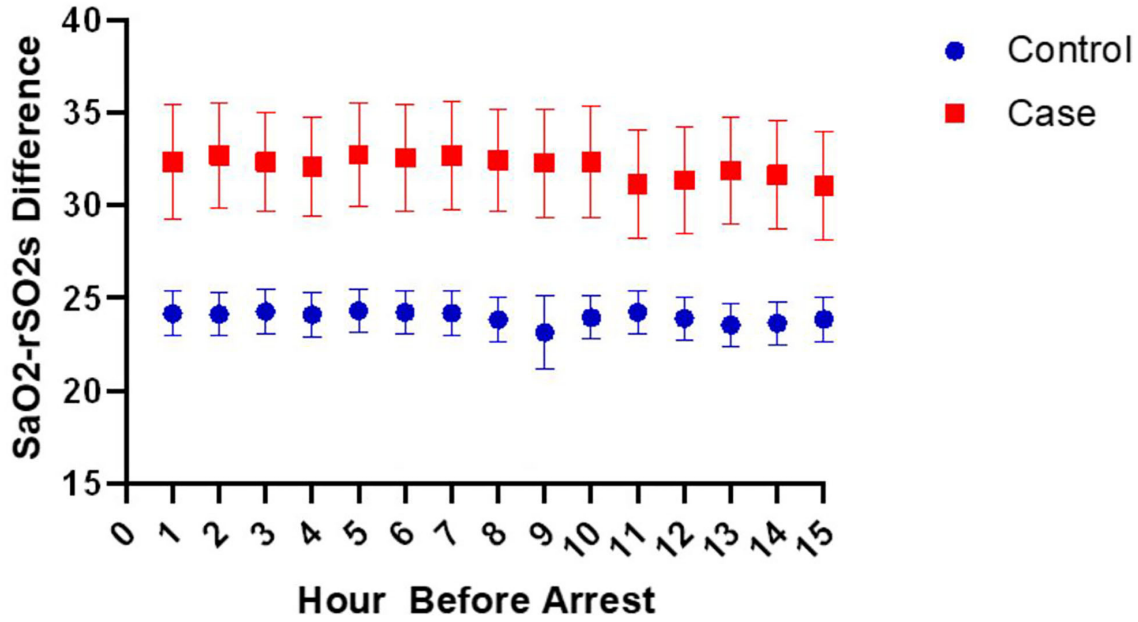

FIGURE 2 | Changes in the SaO2-rSO2s difference over time.

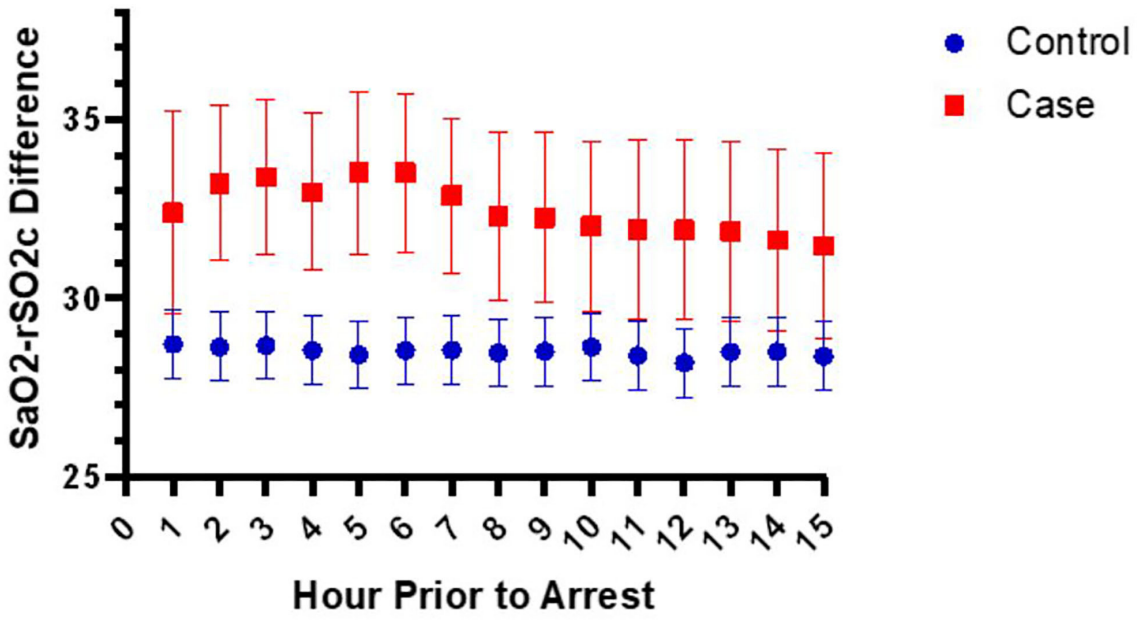

FIGURE 3 | Changes in the SaO2-rSO2c difference over time.

granular data, our model performance would improve. Although not quite ready for bedside use, the goal would be to program a prediction model into our existing EHR to flag clinicians to patients with concerning trends. Our next step will be to use continuous physiologic data to see if this improves our model performance.

Limitations

One of the main limitations of our study is that we only chose to study the first 48 h of the ICU admission of control patients. This would likely give us a skewed sample of patients that would not include higher post-operative stat categories from neonatal surgical repairs, such as the Norwood procedure, since it is not

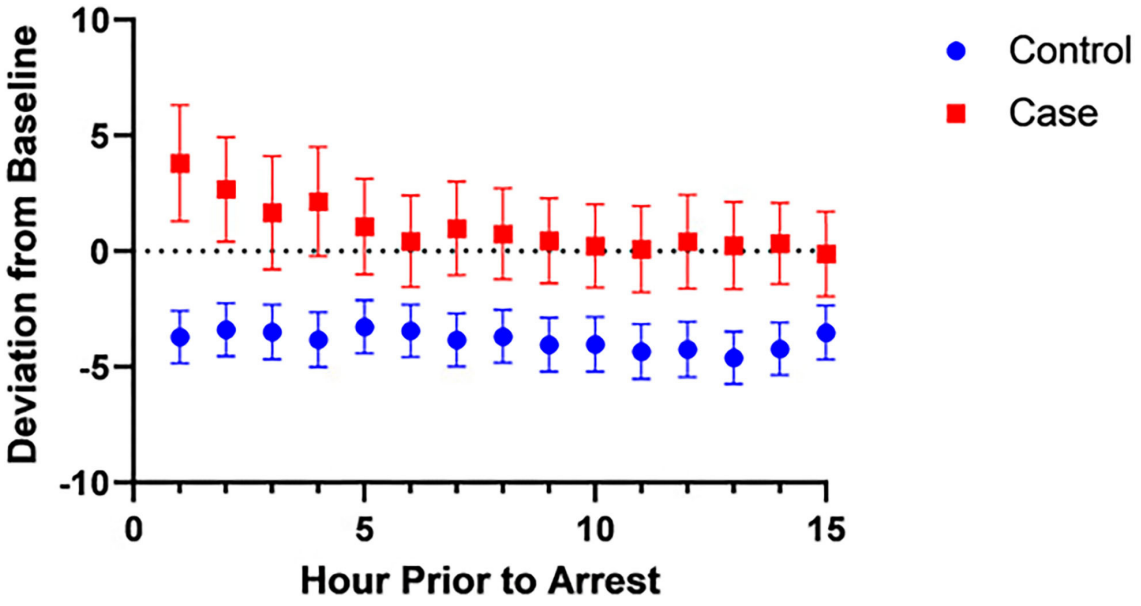

FIGURE 4 | Changes in heart rate over time.

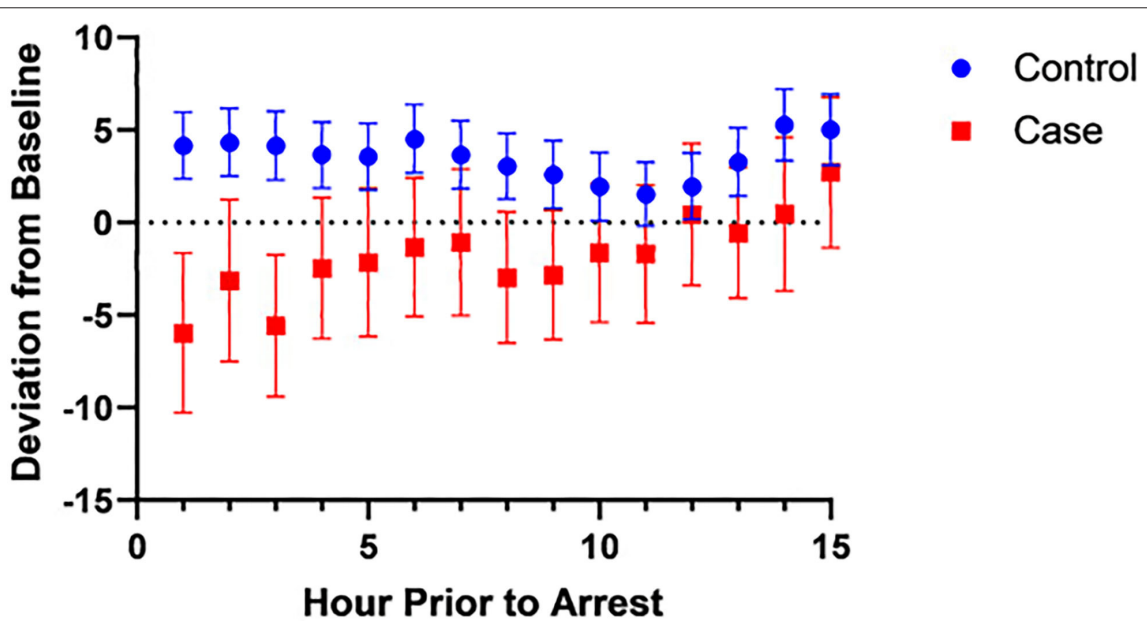

FIGURE 5 | Changes in diastolic blood pressure over time.

our center's norm to do these procedures within the first 48 h of admission given the elevated PVR and transitional physiology. The bigger changes in VIS, HR, DBP, and SpO2-rSO2s difference could be reflective of more complex surgeries and longer surgical times in patients with higher stat categories rather than a marker of impending cardiac arrest. We chose the first 48 h of admission for control patients to compare to the CA patients since we believed that for most patients (whether it was post-surgical or a medical admission), the first 48 h of admission tend to be their most unstable.

The prearrest characteristics were different in the case vs. control patients. Currently, there is no severity of illness score that has been validated in both the surgical and non-surgical pediatric heart disease population that would allow us to match cases with control patients. We believe that the large sample size of our control group will make up for this limitation. We were unable to include stat category as a covariate in our model since there was a relatively smaller number of patients with higher STAT category operations. Instead, we used CPB time as a covariate since usually operations with higher STAT categories

have higher CPB times. We elected to use CPB time as a surrogate for the STAT category.

This is also a single-center study, therefore, our results may not apply to other centers. This is also a heterogeneous group of patients with various age ranges, cardiac anatomy, and physiology.

CONCLUSION

In this case-control study of children admitted to a single-center pediatric CICU, we were able to show that a multivariable model consisting of SpO2-rSO2s difference, and SpO2-rSO2c difference, HR, DBP, and VIS was able to predict CA with an AUROC of 0.83 1 h to the CA. Furthermore, at 1 h before CA, for every 10% increase in the SpO2-rSO2s difference, the odds of cardiac arrest increased by 40%. The average optimal cutoff which differentiated cases and controls was 29%. Future studies should validate this model using continuous physiologic rather than hourly data to see if the model performance would be enhanced.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PY, IE, and LR contributed to the conception and design of the study. XL performed the statistical analysis. PY wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.894125/full#supplementary-material

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The Neglected Price of Pediatric Acute Kidney Injury: Non-renal Implications

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Preclinical models and emerging translational data suggest that acute kidney injury (AKI) has far reaching effects on all other major organ systems in the body. Common in critically ill children and adults, AKI is independently associated with worse short and long term morbidity, as well as mortality, in these vulnerable populations. Evidence exists in adult populations regarding the impact AKI has on life course. Recently, non-renal organ effects of AKI have been highlighted in pediatric AKI survivors. Given the unique pediatric considerations related to somatic growth and neurodevelopmental consequences, pediatric AKI has the potential to fundamentally alter life course outcomes. In this article, we highlight the challenging and complex interplay between AKI and the brain, heart, lungs, immune system, growth, functional status, and longitudinal outcomes. Specifically, we discuss the biologic basis for how AKI may contribute to neurologic injury and neurodevelopment, cardiac dysfunction, acute lung injury, immunoparalysis and increased risk of infections, diminished somatic growth, worsened functional status and health related quality of life, and finally the impact on young adult health and life course outcomes.

Keywords: acute kidney injury, pediatric critical care medicine, acute lung injury, cardiac dysfunction, functional status, growth, neurologic injury, immunoparalysis

INTRODUCTION

Acute kidney injury (AKI) is common in critically ill children, occurring in up to 25% of the general pediatric intensive care unit (PICU) population and up to 40–60% of the pediatric cardiac intensive care unit (CICU) population (1–6). Although most studies are in children from high-income countries in the context of intensive care settings, AKI is a global problem associated with considerable morbidity and mortality (7). Once thought to be an isolated syndrome, emerging

evidence suggests that AKI has far reaching effects in the body that affect short and long term outcomes in critically ill children. Recent evidence suggests that, with AKI, molecular and biologic mediators are involved in organ crosstalk at a cellular and genomic level in critical illness.

Hospitalized children who develop AKI have increased morbidity and mortality. Specifically, patients who develop AKI have longer length of mechanical ventilation, longer ICU and hospital lengths of stay, as well as increased health resource utilization (4, 8–13). AKI is an independent risk factor for mortality in pediatric patients with critical illness, after cardiac surgery, sepsis, acute respiratory distress syndrome, recent surgery, and oncologic disorders (6, 9, 14–17). Furthermore, the risk of mortality extends beyond the hospital admission: patients with AKI during acute illness have higher mortality rates years after discharge compared to patients without AKI (18, 19). The independent association of AKI with morbidity and mortality, with or without the presence fluid overload, may be mediated by the effects of AKI on other organ systems.

Current standardized definitions of AKI only focus on rapid creatinine elevations from baseline and varying degrees of oliguria with an "or" logic. By the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI severity is stratified based on fold-increase of creatinine or duration of oliguria (20). These definitions are agnostic to etiology, course, rate and degree of recovery, and timing of onset in relation to critical illness. Evidence is rapidly accumulating to indicate that severity is not the only dimension that has outcome implications; rather, timing of onset, duration, number of episodes, and rate of recovery, have discrete impacts on organ and global outcomes (21–25).

Renal recovery after AKI episodes is not always complete. Certain risk factors, such as extent of pre-morbid kidney health, repeat events, and underlying risk factors contribute to impaired recovery with long term consequences (22, 23, 25). About 10% of AKI survivors develop chronic kidney disease (CKD) (26–29). Emerging preclinical evidence suggests that organ crosstalk in AKI leads to short and long term adverse events on all organ systems, with remote consequences (**Figure 1**) (30). For the practicing intensivist, an understanding of the non-renal effects of AKI can help them tailor treatment strategies and follow-up plans that are focused on preventing these sequelae and ultimately, death. This review aims to discuss the non-renal effects of AKI both in the acute critical illness and long-term recovery phases.

AKI AND THE EFFECTS ON OTHER ORGAN SYSTEMS

AKI and the Brain

In recent years, an intriguing crosstalk between the kidneys and the brain has been discovered. In a murine model of ischemia/reperfusion (I/R) AKI, the blood-brain-barrier was disrupted with increased levels of proinflammatory chemokines in the cerebral cortex and corpus callosum, as well hippocampal neuronal dysfunction and apoptosis 24 h later (31, 32). These changes translated into reduced cognitive performance and memory loss in the mice (32, 33). There is accumulating evidence from diverse pediatric cohorts supporting the concept of kidney-brain crosstalk leading to long-term neurocognitive dysfunction that extends beyond critically ill populations and includes children hospitalized with community-acquired AKI (29, 32, 34, 35).

Mechanistically, endothelial activation in the context of AKI may contribute to blood-brain-barrier dysfunction resulting in brain injury through exposure to uremic toxins and inflammatory mediators. These changes, in turn, may contribute to neurodevelopmental delay in critically ill children. One pathway implicated in AKI-related brain injury is the angiopoietin (angpt)-Tie-2 axis that regulates endothelial integrity. Angpt-1 is a growth factor that maintains a quiescent resting state of the vascular endothelium, whereas its counterpart, Angpt-2 is rapidly released by activated endothelium (36). Angpt-2 primes the endothelium to respond to inflammatory cytokines, upregulates cellular adhesion molecules, and promotes remodeling, but can also lead to vascular leak and endothelial cell apoptosis (37). A higher ratio of Angpt-2/Angpt-1 is thought to contribute to the pathogenesis of organ injury seen in AKI, critical illness, cardiopulmonary bypass, and severe malaria (38–40). Elevated Angpt-2 levels and the resultant altered Angpt-2/Angpt-1 ratio is linked to increased vascular permeability and inflammation that compromise the tight junctions of the blood-brain-barrier (38). This imbalance is independently associated with worse cognitive function in patients with severe malaria who develop AKI with deficits in fine and gross motor skills, visual reception, receptive and expressive language, and learning (38). Other insults such as inflammatory processes, neurotransmitter derangement, and oxidative injury that are associated with cognitive impairment have also been seen in critically ill children with AKI (41).

Emerging evidence confirms a link between AKI and worse neurocognitive outcomes. In a large retrospective multicenter PICU database study of almost 30,000 patients from 24 PICUs, it was found that cognitive disability was present in 12.2% of patients who received continuous renal replacement therapy (CRRT). This was consistent with a decline in cognitive function at hospital discharge (OR 1.76) (42). Recurrent AKI after distinct cardiac surgeries in children with congenital heart disease has been shown to be associated with worse neurodevelopmental outcomes, specifically in language, motor, and cognitive domains, and most pronounced in the language domain (34). In a cohort of pediatric patients with diabetic ketoacidosis, after adjusting for demographics and severity, those who developed AKI had lower IQ scores and worse short term memory 6 months after recovery (35).

AKI is common in patients with malaria and is associated with neurologic deficits in several patient populations (19, 25, 29, 34). In prospective cohort studies of children with malaria, 25–37% of children with AKI had acute neurologic deficits compared to 2–13% of those patients without AKI. Risk factors for neurologic deficits in children with severe malaria associated AKI include elevated blood urea nitrogen and persistent AKI (25). In persons with malaria, AKI, and acute neurologic deficits, neurocognitive differences persisted for up to 2 years following illness. The

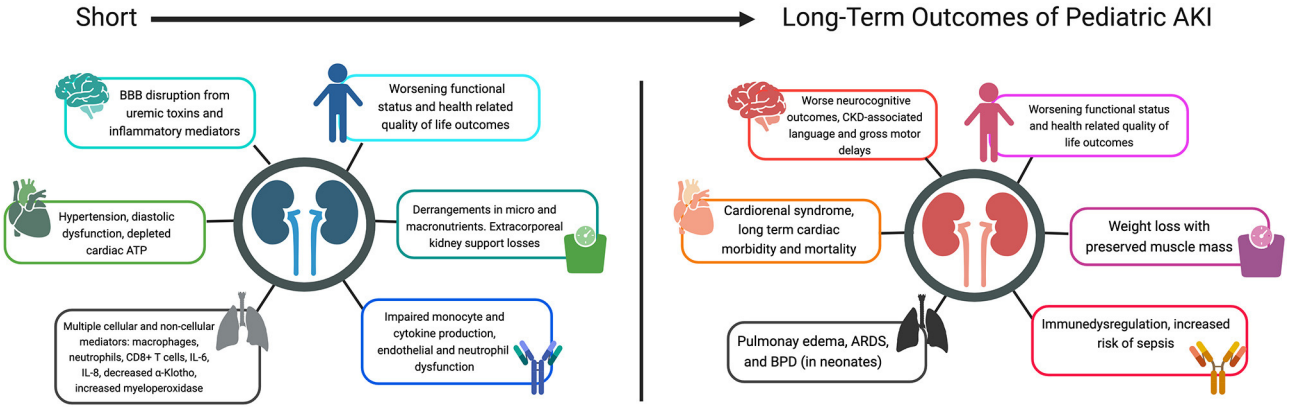

FIGURE 1 | Short and long term outcomes of pediatric AKI. BBB, blood-brain-barrier; ATP, adenosine triphosphate; CD8+, cluster of differentiation 8; IL-, interleukin; CKD, chronic kidney disease; ARDS, acute respiratory distress syndrome; BPD, bronchopulmonary dysplasia.

relationship was independent of socioeconomic and nutritional status, parental and child education, enrichment in the home environment, and disease severity during hospitalization (29). Furthermore, in children ≥6 years of age with malaria, those who developed AKI while hospitalized had worse scores in socio-emotional function and behavioral regulation up to 2 years following illness (43).

Finally, AKI is a risk factor for CKD which has been associated with poor neurocognitive outcomes including language and gross motor skills, as well as executive function and decision making abilities (28, 44–46). Lower academic achievement is also present in 34% of children with CKD, with the worst scores in mathematics (47).

AKI and the Heart

The organ cross-talk between the kidneys and heart has been well-established, with five distinct cardiorenal syndromes currently described (48). Cardiorenal syndrome type 3 (CRS3) specifically encompasses AKI that results in acute cardiac dysfunction. However, the description of CRS3 has not included an evaluation on long-term cardiovascular outcomes after AKI recovery. Growing epidemiological evidence in adults suggest associations of AKI events with long-term cardiovascular morbidity and mortality, even in those who have complete kidney recovery. In adults, after adjusting for confounders, AKI is associated with cardiovascular events, especially heart failure by 1 year after hospital discharge (49–52). The effect of AKI on cardiovascular function in children has not been reported. There are several ongoing retrospective evaluations in discrete populations.

A causal mechanism is yet to be established between AKI and cardiovascular dysfunction in adults (53). Recent reports using a murine model of bilateral ischemia-reperfusion AKI in intact adult C57BLK/6J male mice demonstrated diastolic dysfunction that preceded hypertension and was characterized by abnormal cardiac metabolism and depleted cardiac adenosine 5'-triphosphate (ATP) reserves (53, 54). In fact, the cardiac metabolites affected in AKI were noted to be remarkably similar to that of direct myocardial ischemia (53). Importantly, the cardiovascular dysfunction demonstrated after I/R AKI in mice persisted 1 year after the AKI (54). In the long-term murine AKI model, treatment with ITF2357, a non-specific histone-deacetylase inhibitor, prevented the development of diastolic dysfunction, hypertension and reduced cardiac ATP levels (54). In a secondary analysis of AKI and cardiac outcomes by sex, female mice maintained normal diastolic function and cardiac ATP levels compared to male mice with matched AKI severity. However, female mice developed hypertension and renal fibrosis comparable to male mice (55). Analysis of the cardiac metabolome 1 year after injury implicates sex differences in oxidative stress as a potential mechanism to explain the differential cardiorenal outcomes between males and females. Translational studies are needed to establish the mechanistic derangements of cardiorenal syndrome in humans and to evaluate if there is a protective effect in women. In pediatric patients, the potential role of pubertal status on long-term cardiorenal outcomes also warrants investigation.

AKI and the Lungs

Cellular and molecular mediators of lung injury have been described in the setting of AKI. The initial response to ischemic and nephrotoxic renal injury is mediated by macrophages and neutrophils and may lead to an unchecked pro-inflammatory state resulting in distant pulmonary injury (56–64). Ischemic renal injury in mice leads to an increase in circulating CD8+ T-cells in the lung along with increased markers of T-cell activation. These mice also had increased levels of caspase-3 which mediates pulmonary epithelial cell apoptosis (65). The non-cellular pro-inflammatory mediators of lung injury include interleukin-6 (IL-6) and interleukin-8 (IL-8). Both molecules are found to be elevated in the serum of patients with AKI and are also implicated in lung injury (66–69).

AKI leads to other changes in the concentrations of circulating mediators that may lead to lung injury as well. Uremic toxins are increased in the setting of AKI and are known to cause endothelial cell dysfunction, increased gene

expression of IL-6, and decreased pulmonary sodium clearance via downregulation of aquaporins and sodium-channels resulting in pulmonary edema (66, 70–78). The production of α-Klotho occurs exclusively in the kidney. The absence of this molecule has been associated with emphysematous changes in the lung. Patients with AKI have markedly reduced levels of circulating α-Klotho suggesting it may play a role in protecting the lung from kidney mediated injury (79–90).

Newer animal models have also shown increased markers of inflammatory reactive oxidant species generating myeloperoxidase activity in subjects with AKI compared to sham cohorts up to 14 days after initial injury (30). In a secondary analysis of the Assessment of Worldwide Acute Kidney injury Epidemiology (AWAKEN) retrospective cohort trial, neonates born between 29 and 32 weeks gestation who developed AKI in the Neonatal ICU had a four-fold higher odds of developing moderate or severe bronchopulmonary dysplasia in multivariable analyses (91). Given that premature neonates in this age growth are at a critical point of pulmonary angiogenesis coupled with altered vascular growth factors in AKI, it is hypothesized that the disrupted physiologic processes in AKI may potentiate lung injury in this fragile cohort of patients (91). Furthermore, in infants born at ≥32 weeks gestation, AKI is independently associated with worse lung outcomes including higher likelihood of chronic lung disease and longer dependence on oxygen and respiratory support (92). For an in-detail review of the complex interaction between the lungs and kidney, the readers are referred to Alge et al. (56).

AKI and the Immune System

More recently, the kidney-immune system cross talk has begun to take shape such that the development of AKI is considered to be an immunocompromised state (93). The concept that the kidney plays a role in immune regulation is not new. In fact, it has now been nearly 2 decades since it was noted that there is impaired monocyte cytokine production in critically ill patients with AKI (94). A secondary analysis of the Program to Improve Care in Acute Renal Disease (PICARD) (95) and a single center study in the United Kindom both demonstrated that patients with AKI experience high rates of infectious complications, including sepsis, occurring at a median of 5 days after AKI diagnosis (96). More recently, these results have been recapitulated in homogenous and heterogenous groups of patients across the age spectrum (97–100). Interestingly, the immune effect of AKI appears to be prolonged, even in the presence of complete recovery of AKI. This was demonstrated in a propensity matched analysis where there was a 4.5-fold greater odds of infection within 30 days of discharge in critically ill adults with complete recovery of AKI (100). The association between AKI and infection remained significant at 31–90 and 91–365 days. In children, the association between AKI and subsequent infection was assessed after the Norwood operation, the most complex palliative procedure for newborns with a single ventricle and ductal dependent systemic blood flow. In this study, after adjusting for confounding variables, the was a 3.6-fold greater odds of subsequent infection in neonates with postoperative AKI (98). In a single center retrospective cohort study, a higher odds of infection in a single center study of 5,000 critically ill children: there was a non-linear increase in risk for sepsis based on AKI severity, with stage 3 AKI patients incurring the greatest risk for sepsis (99). A small single center study of pediatric patients receiving CRRT also found an association with infection, that occurred a median of 11 days after CRRT initiation (101).

Little is known about the mechanisms by which the inflammatory cascade that results from AKI may contribute to the development of subsequent sepsis, and this is certainly the focus of substantial research. In an observational study to examine the impact of renal disease on patients with critical illness, patients with AKI developed a reduction in 7 primary amino acids that have been implicated in endothelial and immune dysfunction (102). New data suggest an interaction between the kidney and intestinal microbiome. The intenstinal microbiota are directy involved in immune homeostasis through regulation and induction of both arms of the immune system (103). In addition, in experimental models, neutrophil function is impaired early on in the evolution of AKI, and uremic toxins, such as resistin, may contribute to immune dysfunction (104). More work is needed to enhance our understanding of the the role AKI plays in the sepsis causal pathway. Until we identify the mechanistic derangements, therapeutic targets are limited. Indeed, for now, we can only anticipate the inevitable septic episodes and provide supportive care.

AKI and Growth

The impact of AKI on long term growth outcomes has been scarcely described in the pediatric literature. Even after initial recovery from induced I/R AKI in animal models, growth parameters in mice with AKI were affected long-term compared to those without AKI: mice in the AKI cohorts weighed significantly less than healthy and sham controls, which occurred irrespective of sex. There was no apparent reduction in muscle mass, indicating a potential decrease in fat and/or bone (30, 55). Macro- and micronutrient derangements, as well as alterations to vital minerals, vitamins, and growth factors have been described in AKI (105). In fact, AKI is a risk factor for protein-energy debt in critically ill children and might be augmented by extracorporeal kidney support related losses (106–108). A recent review discusses the deleterious impacts of AKI on dysregulation of mineral metabolism and its direct effects on bone health (109). The investigation of anthroprometic outcomes following pediatric AKI is warranted.

AKI and Sex as a Biological Variable

The NIH released the notice "Consideration of Sex as a Biological Variable in NIH-funded Research" in 2015; however un-pooled gender-based investigations of sex as a biological variable in the study of kidney disease remain lacking. Animal models demonstrate a protective effect of female sex in ischemia-reperfusion AKI (110, 111), however conflicting data remain in humans. Clinically, females do better than males with regards to AKI development, CKD progression, and the need for dialysis treatment in hospital-acquired AKI (112–116). Yet controversies remain—the KDIGO supplemental guidelines state that female sex confers a higher risk in developing AKI after cardiac surgery

and nephrotoxin exposure despite several studies by Neugarten et al. demonstrating improved outcomes in women compared to men (116–118). Women tend to have slower progression of CKD compared to men, however some studies present conflicting data, likely owing to the inclusion of a mix of pre- and post-menopausal women (119–121). The effect of pubertal development in boys and girls and its impact on the development of AKI, recovery from AKI, and progression to CKD have yet to be determined.

AKI and Functional Status, Health-Related Quality of Life

Mortality is not the only important metric to assess the impact of critical illness in childhood. Most children who are admitted to ICU survive their critical illness, albeit with varying degrees of acquired morbidity (122). Functional outcomes of survivors after critical illness are core outcome indicators for clinical care benchmarking, developmental research, and ensuring adequate follow-up post ICU stay (123, 124). Children who have new physical disabilities and limitations may not be able to interact with their environment or participate in school at the level they did prior to their illness. This can result in a decline in their health-related quality of life as well as emotional and social functioning. Long-term outcome cohort studies in the general PICU population such as the Wee-Cover (125) and the Survivor Outcomes Study (126) did not assess the risk of functional declines due to AKI or kidney support. Current evidence linking AKI events and functional outcomes are largely restricted to septic AKI cohorts and CRRT survivors. In a secondary analysis of the cross-sectional epidemiology of sepsis (SPROUT) study, 24% of patients with severe AKI (KDIGO 2 and 3) developed new morbidity compared to only 15% of patients without severe AKI, based on the Pediatric Overall Performance Category (POPC) scale (127). More recently, the Life After Pediatric Sepsis Evaluation (LAPSE) study showed similar results using the more granular Functional Status Scale (FSS). In this study, patients with severe septic AKI were more likely to have new morbidity at hospital discharge compared to patients without kidney injury or stage 1 AKI (8). At the 3-month follow-up, 31% of patients with severe AKI had a decline in health-related quality of life by 25% or more from baseline and was mostly due to declines in physical function (8). The association of renal dysfunction and poor functional outcomes was also seen in a cohort of PICU patients with respiratory failure. The Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study showed that more patients with global functional decline at 6-month follow-up had renal dysfunction during admission than those without decline at 6-month follow-up (11 vs. 5%) (128).

Children who require CRRT during PICU admission may be at higher risk for developing functional decline after critical illness than patients with AKI that do not require dialysis. In a retrospective review of patients who received CRRT at a single tertiary center, 51% developed new morbidity based on FSS at hospital discharge. This cohort had high utilization of rehabilitation therapies and many required new technology at hospital discharge (129). In a larger cohort including survivors at 24 different PICUs, 24.8% of patients that required kidney replacement therapy had a new global functional disability at hospital discharge as determined by a change in POPC from baseline (OR 2.43) (42).

Our understanding of how AKI impacts functional outcomes and health-related quality of life in other at-risk populations, such as post cardiac surgery, remains incomplete. Pediatric survivors with low cardiac output post cardiac surgery have lower functional abilities and worse health-related quality of life at age 4 compared to those without low cardiac output in the post-operative period (130, 131). Although there is a known causal linkage between low cardiac output syndrome and AKI, there is a paucity of research on the independent association of AKI and long-term outcomes in survivors of congenital cardiac surgery. Rigorous ongoing research into long-term functioning and health-related quality of life for patients with congenital cardiac disease should include exposure to other risk factors, such a severity and number of episodes of cardiac surgery associated AKI.

Longitudinal Impact on Adult Health and Life Course Outcomes

Young adults, aged 16–25 years, are a unique population whose physiology is not that of a child nor that of an aging adult. Unlike neonates, who are often at a higher risk of AKI due to their immature nephron function, and adults, who are at higher risk of AKI due to comorbidities, the young adult age group is typically thought to be healthy. However, it has been shown that even in critically ill patients aged 16–25 years admitted to a general adult ICU, the frequency of AKI (40%) exceeds that of the general PICU population (4, 132). Furthermore, in young adults the development of AKI in the ICU was found to be a significant predictor of hospital and ICU mortality, as well as mortality 1 year after discharge (132).

Young adults with congenital heart disease represent a particularly vulnerable group for AKI and its consequences, given their risk for repeated AKI events across a lifetime (133, 134). Importantly, the young adult congenital heart disease population is a growing population due to advances in cardiac care (135). In young adults with congenital heart disease that are diagnosed with AKI in the Cardiac ICU and have persistent kidney dysfunction 7–28 days after hospital discharge, there is a 12-fold increased odds of mortality at 5 years, independent of illness severity (134).

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Pediatric critical illness is frequently a dynamic state of complex interactions between every organ in the body responding and reacting to one another. Although once thought to be an isolated syndrome, it is clear that the implications of AKI have far reaching consequences that significantly affect ICU morbidity and mortality, as well as long term quality of life in survivors. Recent evidence has begun to elucidate how non-renal organs may be impacted by changes in fluid

balance and the proinflammatory state secondary to the resulting AKI in critical illness. AKI is associated with both an immune dysregulated state and a proinflammatory state. The altered cytokine signature and endothelial dysfunction mediate most organ crosstalk in AKI, including brain and lung dysfunction. Abnormal cellular energy metabolism, similar to acute myocardial ischemia, can be demonstrated in the myocardium in AKI. Interestingly, the short and long term impact of AKI seems to have a sex predilection, with females being relatively protected from progression to CKD and dialysis.

In addition to the acute effects of AKI on other organ function, AKI impacts survivor functional outcomes, health-related quality of life, growth, and post-discharge mortality. Survivors of AKI represent a vulnerable population that require long-term, multi-disciplinary follow-up regardless of their discharge renal function. Prospective cohort studies designed to better understand the long-term impact of AKI on childhood development and growth are needed. Future research should focus on the identification of the mediators of organ cross-talk between the kidneys and the brain, heart, lung, and the immune system.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Association Between Language Use and ICU Transfer and Serious Adverse Events in Hospitalized Pediatric Patients Who Experience Rapid Response Activation

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Background: Hospitalized patients and caregivers who use a language other than English have worse health outcomes, including longer length of stay, more frequent readmissions, and increased rates of in-hospital adverse events. Children who experience clinical deterioration (as measured by a Rapid Response Team event) during a hospitalization are at increased risk for adverse events and mortality.

Methods: We describe the results of a retrospective cohort study using hospital records at a free-standing, quaternary children's hospital, to examine the association of language of care with outcomes (transfer to intensive care, adverse event, mortality prior to discharge) following Rapid Response Team event, and whether increased interpreter use among patients who use a language other than English is associated with improved outcomes following Rapid Response Team event.

Results: In adjusted models, Rapid Response Team events for patients who use a language other than English were associated with higher transfer rates to intensive care (RR 1.1, 95% CI 1.01, 1.21), but not with adverse event or mortality. Among patients who use a language other than English, use of 1-2 interpreted sessions per day was associated with lower transfer rates to intensive care compared to use of less than one interpreted session per day (RR 0.79, 95% 0.66, 0.95).

Conclusion: Rapid Response Team events for hospitalized children of families who use a language other than English are more often followed by transfer to intensive care, compared with Rapid Response Team events for children of families who use English. Improved communication with increased interpreter use for hospitalized children who use a language other than English may lead to improvements in Rapid Response Team outcomes.

Keywords: disparities, hospital medicine, critical care, language interpretation, interpreter use

BACKGROUND

Several studies have shown that children of families with limited English language proficiency, or those who use a language other than English (LOE) for medical care, have worse health outcomes, (1, 2) receive lower quality care, (2, 3) and report worse patient experiences of care (4–6) compared with children of English-speaking families. Among hospitalized children, studies have shown increased serious adverse events, (7) and increased likelihood to transfer to the intensive care unit within 24 hours of admission, (8) for children of families who use a LOE compared with English-speaking children and families. Language spoken does not have a biological mechanism to explain these disparities, suggesting that inequitable provision of care may contribute. In fact, differences in treatment have been demonstrated in pediatric populations; children of families who use LOE, compared with English-speaking children, receive different treatment, including worse post-operative pain management, (3) and increased testing such as chest x-rays and blood tests for children with bronchiolitis (2).

The reasons for these disparities in care and outcomes are likely multifactorial, with pre-hospital health and in-hospital social determinants of health both playing important roles (9). The factors contributing to these disparities in treatment during a hospitalization are also multifactorial, with evidence showing that barriers to effective communication between the healthcare team and family may also play a role. Among patients who use LOE, increased rates of interpretation use by provider teams are associated with improved outcomes, improved quality of care, and better patient satisfaction among adult and pediatric patients (5, 8, 10, 11). Despite this, interpretation is underutilized, with rates reported at 39–45% of conversations with patients and families who use LOE (8, 12).

Effective communication between a caregiver and provider team may be particularly salient for hospitalized children who require activation of a rapid response system, as these represent patients with a higher likelihood of clinical deterioration. During these events in a hospital stay, often referred to as Rapid Response Team events, or "RRT", children are evaluated with a pediatric intensive care unit (ICU) team for possible admission to the ICU. Our study objective was to determine whether outcomes for hospitalized pediatric patients who experienced an RRT were associated with patient language preference. We evaluated three primary outcomes: rate of transfer to the ICU following an RRT, rate of serious adverse event following an RRT, and mortality prior to discharge. We hypothesized that among patients who experienced an RRT, children of families who use LOE (henceforth, "patients who use LOE") are associated with worse outcomes, and that for patients who use LOE, frequency of interpreter use would mitigate these disparities.

METHODS

Study Design and Sample

We conducted a retrospective single-site cohort study of all pediatric patients hospitalized in an urban, pediatric tertiary institution's acute care wards including medical, rehabilitation, cancer and surgical units, between October 2016 and October 2019 who experienced at least one RRT. In our institution, an RRT can be called by any member of the medical team, including a patient's caregiver. There are no automatic or scoring system-based ways for an RRT to be called. The RRT team includes an ICU nurse, an ICU provider, a respiratory therapist, and the patient's floor medical team. Patients were excluded if they were admitted to the inpatient psychiatry facility or if there was missing data for our measured outcome variables (1.9% of all patients). The Seattle Children's Institutional Review Board approved this study.

Outcomes

We examined three binary outcome variables: (1) transferring to the ICU following an RRT, (2) having a serious adverse event following an RRT, and (3) mortality prior to discharge. The first two outcomes were measured at the level of the RRT event (more than one RRT per hospitalization encounter was possible) whereas we measured mortality at the hospitalization encounter level (each hospitalization could have a single mortality outcome). Transfer to the ICU was defined by the date and time stamp in the electronic medical record between acute care and an ICU of <4 h following activation of the index RRT. For the outcome of rate of serious adverse event following an RRT, we used chart data on the number of "rescue events", defined as the requirement of new non-invasive or invasive positive pressure ventilatory support, or initiation of inotropic support within 2 h of ICU transfer. Patients who experience a rescue event have higher mortality, and this was used as a proxy for measurement of other types of adverse events (13). For the rest of the text, we will use the term "adverse event" to mean an event that met any of those criteria.

Exposure

The primary exposure variable was a binary variable, and measured whether, on admission, parents identified English as their language for communication (and thus were considered to be English-speaking) or identified a language other than English as their language for communication (and thus were considered to use LOE).

Covariates

Covariates anticipated to confound the relationship between language use and transfer to the ICU, adverse event, or mortality were considered when designing our multivariable model. The Pediatric Medical Complexity Algorithm (PMCA) (14) is a publicly available algorithm for identifying children with medical complexity, as these patients are at higher risk of mortality (15, 16). In our analysis we categorized patients based on PMCA: no chronic disease, non-complex chronic disease (NC-CD), or complex chronic disease (C-CD), as previous studies have done (15–17). Patient public insurance status has been shown to be associated with higher all-cause in-hospital mortality, (18) and in our study was measured as a binary variable (private insurance vs. public or no insurance (0.25% of encounters were for uninsured patients). A patient's experience of racism from provider teams has been shown to impact outcomes in several clinical domains,

(19–21) and thus could also impact outcomes following an RRT, so we examined the potential to include race/ethnicity as a covariate in our models as well.

Statistical Analysis

Descriptive statistics were used to characterize the demographics of the overall study population, as well as of the two study populations. Data are presented as frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for numeric variables.

For the RRT level outcomes (whether a patient transferred to ICU following an RRT and whether a patient had an adverse event following an RRT), a preliminary fitting of the data with random effect models showed that patient random effects contributed <4% of the total variation in these outcomes and suggested including just the hospitalization random effects would be sufficient. On the other hand for the hospitalization-level outcome "survival to discharge," the data suggested random effects at patient level would be needed. However, fitting mixed models on the data led to non-convergence in some situations. Therefore, we instead employed generalized estimating equations (GEE) to analyze the data while leveraging the knowledge about correlations from our preliminary random effect model fitting. Specifically, we used GEE Poisson regression models to analyze (1) the RRT-level outcomes assuming exchangeable correlations within hospitalizations and (2) the hospitalization-level outcomes assuming exchangeable correlations within patients. Adjusted models controlled for PMCA category and insurance category.

To understand whether frequency of interpreter use by providers caring for the patients who use LOE in the study population was associated with differences in our outcome variables among this sub-population, we conducted an analysis limited only to hospitalizations for patients who use LOE. A measure of interpretation rate was calculated by counting all interpreted sessions within one patient's hospitalization (phone, video, and in-person), and dividing that by the length of hospital stay in days. This was then categorized into a binary variable, with a cutoff of 1 interpreted session per day of hospital stay ($\leq$1 vs. >1).

To model the incidence rate ratio (IRR) of each outcome among patients who use LOE who experienced different categories of daily interpretation, we again used Poisson regression models with GEE method to account for correlations due to multiple RRTs during the same hospitalization for the RRT-level outcomes, or multiple hospitalizations for the same patient for the hospitalization-level outcome.

RESULTS

Characteristics of Study Population

A total of 2,040 unique hospitalizations with at least one RRT, between October 2016 and October 2019 were included in this study. Of these hospitalizations, there were 1,730 unique patients, and 2,823 unique RRTs. The top diagnoses represented by the study subjects are in **Supplemental Table 1**. The majority of hospitalizations were for English-speaking patients (n = 1,751; 86%), and complex chronic patients (n = 1,532; 75%). The proportion of complex chronic patients was higher among patients who used LOE (83% for those who used LOE vs. 74% for English-speaking patients, $p = 0.003$; **Table 1**). More patients who used LOE had either public or no insurance compared to English-speaking patients (85% compared to 49%, $p < 0.001$).

More than half (54%) of hospitalizations were for patients who had public or no insurance, and 42% of hospitalizations were for patients who self-identified as White race/ethnicity, 7% for patients who identified as Black or African American, 23% as Latinx, 8% Asian, 4% Native American, Alaskan Native, or Native Hawaiian, and 11% other race or two or more races (**Table 1**). The majority of hospitalizations were for patients who survived to discharge (1,954; 96%). Adjusted models controlled for PMCA category and insurance category. Our adjusted models did not include race/ethnicity, because we found a very small number of patients who use LOE in some race/ethnicity categories.

Association Between Language Use and Outcome Measures

Among the 2,040 hospitalizations, 16 hospitalizations and 100 RRTs were missing either the exposure variable, a covariate, or an outcome measure, and were excluded from analysis, leaving 2,783 RRTs from 2,024 hospitalizations and 1,717 patients. The distributions of each outcome across the English-speaking group and the group using LOE are shown in **Table 2**. In adjusted models, an RRT for a patient who used LOE was more likely to result in a transfer to the ICU than RRTs for English-speaking patients (IRR 1.10, 95% CI 1.01, 1.21; **Table 3**). There was no association between language use and experiencing an adverse event, or death prior to discharge (**Table 3**). Our study was powered to detect a 7.5% difference in transfer rates, a 4.2% difference in adverse event rate, and a 3.7% difference in mortality (22).

Secondary Analysis: Association Between Daily Interpreter Use Frequency and Outcome Measures

Among hospitalizations for patients who use LOE, the median number of interpreted sessions per day was 1.5 (IQR 0.6, 2.7), which included in-person, video, and phone interpreted sessions. Our three outcome measures for patients who use LOE, stratified by number of interpreted sessions per day of hospital stay, can be found in **Table 4**. In adjusted models, >1 interpreted session per day was associated with reduced rates of ICU transfer (IRR 0.83, 95% CI 0.73, 0.95; **Table 5**), compared with $\leq$1 interpreted sessions per day. Rate of interpreter use was not associated with adverse event rate or mortality prior to discharge in either model (**Table 5**).

DISCUSSION

In this retrospective study of hospitalizations in a tertiary pediatric hospital, RRTs for patients who use LOE were more likely to be followed by a transfer to the ICU than RRTs for English-speaking patients. RRTs for patients who use LOE were

TABLE 1 | Demographics of 2,040 hospitalizations during the study period.

Variable	Level	Overall	English-speaking patients	Patients who use LOE	*P*-value
All hospitalizations		2,040	1,751	289	
Patient Race/Ethnicity					<0.001
	White	860 (42%)	843 (48%)	17 (6%)	
	Black or African American	150 (7%)	129 (7%)	21 (7%)	
	Latino or Latina	460 (23%)	284 (16%)	176 (61%)	
	Asian	160 (8%)	115 (7%)	45 (16%)	
	Native American, Alaskan Native, or Native Hawaiian	87 (4%)	84 (5%)	3 (1%)	
	Two or more races	114 (6%)	113 (6%)	1 (<1%)	
	Other race	99 (5%)	84 (5%)	15 (5%)	
Insurance Type					<0.001
	Private	926 (46%)	892 (51%)	34 (12%)	
	Public or Uninsured	1,103 (54%)	856 (49%)	247 (85%)	
PMCA					0.003
	Non-chronic	225 (11%)	204 (12%)	21 (7%)	
	Non-complex chronic	283 (14%)	255 (15%)	28 (10%)	
	Complex chronic	1,532 (75%)	1,292 (74%)	240 (83%)	

Data are shown as n (%).

TABLE 2 | RRT-level summary of each of the three RRT-level measured outcomes, for 2,783 included RRTs.

Variable	Overall ($n = 2,783$)	English-speaking patients ($n = 2,371$)	Patients who use LOE ($n = 412$)	*P*-value
Survival to discharge	2,648 (95%)	2,260 (95%)	388 (94%)	0.383
Adverse event following the RRT	205 (7%)	168 (7%)	37 (9%)	0.209
Transfer to ICU following the RRT	1,482 (53%)	1,245 (53%)	237 (58%)	0.067

TABLE 3 | Results of adjusted and unadjusted Poisson regression models associating language use with each measured outcome.

Outcome Measure	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Survival to discharge[a]	0.99 (0.96, 1.01)	0.99 (0.96, 1.02)
Adverse event following the RRT	1.28 (0.9, 1.81)	1.16 (0.8, 1.69)
Transfer to ICU following the RRT	1.11 (1.02, 1.21)	1.1 (1.01, 1.21)

[a] *Survival to discharge was measured at the hospitalization-level using hospitalization-level covariates, with all other outcome variables measured and analyzed at the RRT-level.*

TABLE 4 | Outcome measures stratified by the category of interpreter use per day of hospital stay during 412 RRTs and 281 hospitalizations from 229 patients who use LOE in the study population.

Outcome	Adjusted IRR (95% CI)	
	≤1 interpreted sessions per day ($N = 144$)	>1 interpreted sessions per day ($N = 268$)
Survival to discharge[a]	140 (97%)	248 (93%)
Adverse event following the RRT	17 (12%)	20 (7%)
Transfer to ICU following the RRT	90 (63%)	147 (55%)

[a] *Survival to discharge was measured at the hospitalization-level using hospitalization-level covariates, with all other outcome variables measured and analyzed at the RRT-level.*

not more likely to result in adverse event, and hospitalizations for patients who use LOE who experienced an RRT were not associated with higher mortality prior to discharge. Among patients who use LOE who experienced an RRT, rates of interpretation use were low. RRTs among patients who use LOE with lower rates of interpretation were more likely to result in ICU transfer. Our findings add to existing literature showing differences in outcomes for children who use LOE compared to English-speaking children, and our findings raise concern for communication barriers contributing to these disparities (1–3, 8).

Our finding that RRTs for patients who use LOE were more likely to be followed by a transfer to the ICU is consistent with previous work that shows pediatric patients who use LOE in the ED are more likely to transfer to the ICU within 24 h of admission to the hospital (8). The goal of RRTs is to recognize clinical change early enough to act and improve outcomes, and we did

TABLE 5 | Results of adjusted Poisson regression models associating number of interpreted sessions per day (as a binary variable) of hospital stay with each of our measured outcomes during 412 RRTs and 281 hospitalizations from 229 patients who use LOE in the study population.

Outcome	Adjusted IRR (95% CI)	
	≤1 interpreted sessions per day (*N* = 144)	>1 interpreted sessions per day (*N* = 268)
Survival to discharge[a]	(ref)	0.97 (0.92, 1.03)
Adverse event following the RRT	(ref)	0.7 (0.38, 1.28)
Transfer to ICU following the RRT	(ref)	0.83 (0.73, 0.95)

[a] *Survival to discharge was measured at the hospitalization-level using hospitalization-level covariates, with all other outcome variables measured and analyzed at the RRT-level.*

not find any disparities in adverse events or deaths after ICU transfer. However, our findings suggest either that at time of RRT call, patients who use LOE are sicker and more likely to require ICU transfer than English-speaking patients, or that for similar clinical presentations, providers are more likely to choose to transfer patients who use LOE to the ICU compared to English-speaking patients. Potential inadequate communication during and preceding an RRT for patients who use LOE compared to English-speaking patients may contribute to differential decision for ICU transfer. Supporting this, interpreter use in our study population who use LOE was low, and there was an association with higher rates of transfer to the ICU among hospitalizations for patients who had less than one interpreted session per day compared to those who had more than one per day.

If at the time of an RRT, patients who use LOE are more likely to be more acutely and severely ill compared to English-speaking patients, our findings would support the hypothesis that RRTs are called later in an illness course for patients who use LOE compared to English-speaking patients. This supports a hypothesis that signs of illness may have been missed and appropriate care may not have been instituted as early in the illness courses of patients who use LOE. Further, if patients who use LOE are sicker at the time of RRT call, this may be influenced by inadequate communication with families who use LOE, such that medical teams are less aware of clinical changes at early stages. Previous work has also posited that under-triage for patients who use LOE may be due to poor communication with families about symptoms due to the language barrier, (7) and that for patients who are triaged at lower acuity levels, interpretation is less likely to be used (8). Differential transfer to the ICU may also be due to inadequate communication influencing team decision-making at the time of RRT call, which is supported by growing evidence among pediatric populations that provider teams make different clinical decisions for patients who use LOE compared to English-speaking patients (2, 3, 7, 8, 23, 24).

These findings suggest that interventions aimed at increasing interpretation use may improve patient outcomes. Future work should explore reasons for low interpretation use, and factors associated with increased interpreter use, to inform interventions. Potential interventions include increasing access to interpretation resources, (5, 11) process changes to identify patients who may benefit from interpretation and communicate interpretation need and use, (8, 12) education of providers and nurses, (1) standardized and protocolized processes for clinical team communications during RRTs, and changes to clinical workflow such as adjusting nursing assignments and rounding schedules to make use of interpretation less of a barrier. It is important that future work includes perspectives of families who use LOE, with the ultimate goal to address their communication needs and barriers.

Limitations

Results of this single center study may not be generalizable to all other hospital settings, and the retrospective design limits ability to evaluate causation or mechanism. Most patients who use LOE in this study identified Spanish as their language for care, limiting generalizability for patients who use other languages. Because of our sample size, and because most families who use LOE identified as one race (Latino/Latina), we were unable to use race/ethnicity in our model as a proxy for experiencing racism. Our sample was limited to hospitalizations with an RRT, which allowed us to examine differential outcomes of RRT, but limited our ability to understand whether and when an RRT is utilized for patients who use LOE compared to English-speaking patients. There is potential for under-counting of interpreted sessions per day, as we were unable to include instances where a bilingual provider cared for a family using LOE. Further, we only have data on number of interpreted sessions per day, and thus were not able to evaluate outcomes with respect to length or content of sessions, or factors related to family communication preferences or presence at the beside. Our outcomes focused on mortality, ICU transfer, and adverse event rate; we did not consider other outcomes, such as hospitalization cost or family mental health. Additionally, our model could be impacted by unmeasured confounding, specifically for severity of illness at time of RRT or for ICU capacity (both of which we were unable to include due to lack of data availability). Many factors during a hospitalization may affect adverse events and mortality, limiting our ability to draw conclusions about the lack of differences in these outcomes for our two study populations.

CONCLUSIONS

We found that the decision to transfer a patient to the ICU following an acute evaluation for deterioration on the floor (via RRT) varied by patient language use, with RRTs for patients who use LOE more likely to be followed by a transfer to the ICU. We also found that among patients who use LOE, increased use of interpreters was associated with reduced rates of transfer to the ICU following RRT. Together, these findings suggest improved communication between provider teams and families who use LOE with more consistent interpreter use may help to mitigate disparities in patient outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Seattle Children's Hospital Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AO and JM conceptualized and designed the study, carried out analysis, drafted the initial manuscript, and reviewed and revised the manuscript. JRa collected data, carried out analysis, and reviewed and revised the manuscript. TC, SB, JRo, and AA conceptualized and designed the study, provided oversight for the analysis, and reviewed and revised the manuscript. PQ performed statistical analysis, provided feedback regarding study design and data analysis, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.872060/full#supplementary-material

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Adverse Childhood Experiences and Patient-Reported Outcome Measures in Critically Ill Children

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Adverse childhood experiences (ACEs) are linked to adverse health outcomes for adults and children in the United States. The prevalence of critically ill children who are exposed to ACEs is not known. Our objective was to compare the frequency of ACEs of critically ill children with that of the general pediatric population of Georgia and the United States using publicly available National Survey of Children's Health (NSCH) data. The impact of ACEs on patient-reported outcome measures of emotional, social, and physical health in critically ill children is not known. We sought to determine whether a higher total number of ACEs was associated with poorer patient-reported measures of emotional, social, and physical health. We conducted a prospective cross-sectional study of children $<$ 18 years of age who were admitted to a 36-bed free-standing, quaternary academic pediatric intensive care unit in Atlanta, Georgia from June 2020—December 2021. Parents of patients who were admitted to the pediatric intensive care unit completed a survey regarding their child's ACEs, health care use patterns, and patient-reported outcome measures (PROMIS) of emotional, social, and physical health. Prevalence estimates of ACEs were compared with national and state data from the NSCH using Rao-Scott Chi-square tests. PROMIS measures reported within the PICU cohort were compared with population normed T-scores. The association of cumulative ACEs within the PICU cohort with patient-reported outcomes of emotional, social, and physical health were evaluated with a *t*-test. Among the 84 participants, 54% had $\geq$ 1 ACE, 29% had $\geq$ 2 ACEs, and 10% had $\geq$ 3 ACEs. Children with $\geq$ 2 ACEs had poorer anxiety and family relationship T-scores compared to those with $\leq$ 1 ACE. Given the high burden of ACEs in critically ill children, screening for ACEs may identify vulnerable children that would benefit from interventions and support to mitigate the negative effects of ACEs and toxic stress on emotional, social, and physical health.

Keywords: adverse childhood experiences, pediatric, intensive care unit, patient-reported outcome measures, social determinants of health, anxiety, family relationships, national survey of children's health

Abbreviations: ACE, adverse childhood experiences; eMR, electronic medical record; IQR 25th to 75th, percentile interquartile range; NSCH, National Survey of Children's Health; PICU, pediatric intensive care unit; PROMIS, Patient-Reported Outcomes Measurement Information System.

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INTRODUCTION

Adverse childhood experiences (ACEs) are potentially traumatic events that occur in childhood. ACEs include witnessing or being a victim of violence in the home or community, being abused, neglected, or discriminated against, living in a household with substance abuse or mental health problems, or experiencing household instability due to parental separation, incarceration, or death (1, 2). Nearly half of all U.S. children have experienced at least one ACE; over 20% have experienced at least two ACEs (3). ACEs are linked to worse health outcomes in adulthood, including heart disease, cancer, asthma, traumatic brain injury, obesity, depression, substance abuse, and premature death (1, 2, 4–11). Adults with higher ACE exposures may attain lower educational and economic potential (8, 12). Data now links ACE exposure with poor health outcomes as early as childhood and adolescence (13, 14). While social determinants of health are associated with childhood admission to an intensive care unit and being more severely ill upon admission (15–18), there are no published studies that explicitly examine the link between ACEs and patient-reported outcome measures in critically ill children. Whether critically ill children have higher exposure to ACEs than the general pediatric population in Georgia and the U.S. is not known. Additionally, whether ACEs are associated with patient-reported outcome measures of emotional, social, and physical health in critically ill children is not known.

The primary objective of this study was to determine whether children admitted to an Atlanta, Georgia pediatric intensive care unit (PICU) had a higher exposure to ACEs compared to the general pediatric population in Georgia and the United States as reported by the National Survey of Children's Health (NSCH) (19). We hypothesized that a higher proportion of children in the PICU would have more ACEs compared to Georgian or U.S. children. A secondary objective was to determine whether higher total ACE exposure was associated with poorer patient-reported outcomes of emotional, social, and physical health in the PICU cohort using the validated, population-normed PROMIS measures (20). We hypothesized that children with a higher total ACE exposure would have poorer patient-reported outcome measures of emotional, social, and physical health.

MATERIALS AND METHODS

Study Design

This prospective, observational study was performed in the 36-bed academic medical/surgical Pediatric Intensive Care Unit (PICU) at Emory University/Children's Healthcare of Atlanta at Egleston from June 2020 through December 2021.

Ethics Statement

The study was approved by the Institutional Review Board at Children's Healthcare of Atlanta (IRB00000643) and all methods were carried out in accordance with relevant guidelines and regulations in the Declaration of Helsinki. Informed consent was obtained from the parents of all subjects and assent was obtained from all patients 6–17 years old prior to data collection.

Inclusion/Exclusion Criteria

All children aged 0–17 years old admitted to the PICU at our large, urban, academic, quaternary care center for critical illness or injury were eligible for this study and represent a convenience sample. Children were excluded from the study if they had any end-of-life care limits (i.e., Do Not Resuscitate or Withdrawal of Life-Sustaining Treatment orders) in place, if they were admitted to the PICU for routine post-operative monitoring, if they had never lived in a home setting (i.e., ex-premature or medically complex infants who had never been discharged from the hospital), if the PICU attending did not wish them to be enrolled, or if they had previously been enrolled in the study. All patients in the PICU were screened on days that trained study staff were available to enroll patients. No questionnaires were administered until written informed consent was given. Study materials were available in English and Spanish.

National Survey of Children's Health Sample

The 2018–2020 NSCH is directed by the Health Resources and Services Administration (HRSA) Maternal and Child Health Bureau (MCHB). The NSCH is a nationally representative survey of children ages 0–17 years of age living in non-institutional settings in the 50 states and the District of Columbia (21–23). The NSCH questionnaire is a valid measure of ACEs and a standardized assessment of health status and health care access (24). NSCH data is publicly available and deidentified; thus, it did not qualify as human subjects research and did not require institutional review board approval.

Participant Characterization

Demographic information, comorbidities, and healthcare use were obtained by parent report and medical history from the electronic medical record (eMR) using the same question format as that used in the NSCH (19). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Children's Healthcare of Atlanta. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources (25, 26).

Study Measures

The eight-item validated ACE questionnaire was used from the NSCH. The eight ACE questions were self-reported by medically and developmentally able participants who were 12—17 years old and proxy-reported by parents for children 0—17 years old.

We chose nine validated and population-normed Patient-Reported Outcomes Measurement Information System (PROMIS) short forms containing a total of 44 items across the domains of emotional, social, and physical health. We used PROMIS questionnaires to measure life satisfaction, meaning and purpose, positive affect, psychological stress experiences,

anxiety, depressive symptoms, sleep disturbances, family relationships, and peer relationships. PROMIS measures were only measured from the PICU cohort and are not part of the NSCH; however, the PROMIS measures are normalized to population values. The population mean PROMIS T-score is 50 with a standard deviation of 10; a higher PROMIS T-score indicates that more of the concept being measured is present (20). The PROMIS measures were administered to medically and developmentally able patients ages 12–17 years old and/or their parents using the proxy forms for 6–17-year-olds. Validated PROMIS measures for children 0–5 years old across the selected domains were not available at the time of study initiation.

Comparison of Self- and Proxy-Reported Outcome Measures

Self-reported and parent-proxy ACE and PROMIS measures within the PICU cohort were compared using a Pearson correlation coefficient. When both self- and proxy-reported PROMIS T-scores were available, self-reported measures were used in the analysis (27).

Statistical Analysis

Statistical analyses were performed using SAS v9.4 (Cary, NC). Using complex survey design methodologies recommended by the NSCH (22, 28), ACE frequencies in the study cohort were compared to Georgia (GA) and U.S. population data, available from the NSCH, using appropriate GA- and U.S.-weighted percentages and compared to the PICU frequencies *via* Rao-Scott Chi-square tests. T-scores for the PICU sample were calculated for PROMIS measures following automated scoring in REDCap. Only participants with complete ACE or PROMIS data were analyzed. In addition to the complete case analysis, we performed a sensitivity analysis where we assumed that missing ACE data in the NSCH dataset meant that a particular ACE was not experienced. PROMIS T-scores were compared for children with ≤ 1 vs. ≥ 2 ACEs in the PICU sample using two-sample *t*-tests and Cohen's *d* effect sizes, interpreted as small (0.2), moderate (0.5), and large (0.8). Missing values for demographic and medical history occurred in fewer than 10% of participants. All statistical tests were performed two-sided, and p-values < 0.05 were considered statistically significant.

RESULTS

Study Population

A total of 731 children were screened for enrollment; 207 of those did not meet inclusion criteria or were excluded (**Figure 1**). There were 104 patients with parents/legal guardians who were available for consent in this convenience sample; a total of 85 patients were enrolled, with median time to enrollment of 2 days (IQR: 2–3.5) after PICU admission (**Table 1**). One patient less than 6 years of age did not have ACE data collected, leaving 84 patients available for analysis.

Demographic and clinical history of the participants are shown in **Table 1**. Participants were compared with the demographic and clinical history of both Georgia and U.S. children surveyed in the NSCH. Notable differences in the PICU population studied compared with the NSCH GA and USA cohorts included a higher proportion of children who were in the 0 – 5 age range, male, Black or African American, non-Hispanic or Latino, and/or publicly insured (**Table 1**). Children in the PICU cohort had higher frequency of comorbid conditions such as asthma, hematologic or oncologic disorders, diabetes mellitus, and epilepsy or seizures as compared with the GA or USA NSCH cohorts (**Table 1**).

Healthcare Use

A higher proportion of PICU children were never seen by a health care professional (13%) compared with children in GA (3.0%) and USA (4.1%) NSCH cohorts (**Table 2**). Of the children within the PICU cohort with no comorbidities, 42.9% of them had ≥ 2 ACEs compared to 57.1% of them who had < 2 ACEs (**Supplementary Table 7**). A higher proportion of PICU children were seen two or more times (56.1%) in the 12-months prior to PICU admission compared with children in the GA (37.6%) and United States (36.9%) NSCH cohorts (**Table 2**). Children within the PICU cohort with 2 or more comorbidities were more likely to be seen two or more times in the 12-months prior to PICU admission (77.8%) compared to those with one (51.4%) or no (35%) comorbidities (**Supplementary Table 1**). Of the children within the PICU cohort with two or more comorbidities, 28.6% experienced ≥ 2 ACEs compared to 71.4% who experienced < 2 ACEs (**Supplementary Table 7**). Children in the PICU were more likely to access medical care in a hospital emergency department or hospital outpatient center than children in the GA and U.S. NSCH cohorts (**Table 2**). Reasons for PICU admission are shown in **Supplementary Table 2**.

Adverse Childhood Experience Prevalence and Cumulative Burden in the Pediatric Intensive Care Unit vs. National Survey of Children's Health Cohorts

We screened children admitted to the PICU for individual ACEs. As shown in **Figure 2**, children in the PICU were more likely to report experiencing parental/guardian separation or divorce, parental incarceration, witnessing or being a victim of neighborhood violence, or living with someone with a mental illness compared to children in the GA or U.S. NSCH populations (**Figure 2**). We next summed the number of ACEs experienced by each participant to determine whether children in the PICU had a higher cumulative ACE burden compared to the general pediatric population of GA and the U.S. surveyed in the NSCH. We found that a higher percentage of children in the PICU experienced ≥ 1 (vs. 0) and ≥ 2 (vs. ≤ 1) total ACEs compared with children in the GA or U.S. NSCH populations (**Figure 3**).

The age distribution of ACEs by age are shown in **Supplementary Table 3**. Older children in the PICU were more likely than younger children to report experiencing parental/guardian separation or divorce, parental incarceration, domestic violence, or witness or be a victim of neighborhood violence (**Supplementary Table 3**). Similarly, older children were

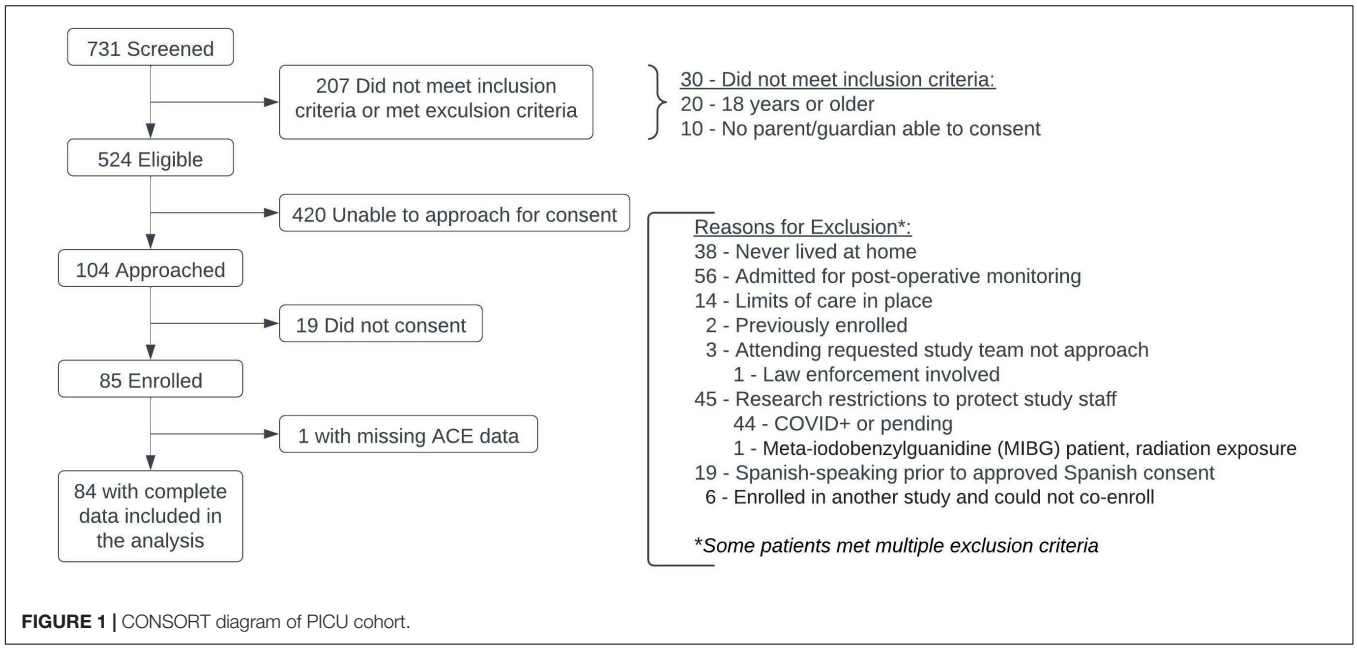

FIGURE 1 | CONSORT diagram of PICU cohort.

more likely than younger children to have a higher total ACE burden (**Supplementary Table 3**).

Only complete cases in the NSCH were analyzed in our initial ACE analysis. To assess the degree of bias by analyzing only complete cases, we performed a sensitivity analysis where we assumed that missing ACE responses indicated no experience of an ACE. The results of this sensitivity analysis for the type and distribution of the total number of ACEs reported was the same as the complete case analysis (**Supplementary Table 4**).

Patient Reported Outcome Measures

For children ages 6–17 years in the PICU cohort, we next evaluated nine domains of emotional, social, and physical health using the parent proxy- and/or self-reported PROMIS questionnaires (20). There were forty-three children ages 6–17 years with complete PROMIS measures available for analysis. There were 12 participants with both self- and proxy-reported PROMIS measures. We determined the correlation between the proxy- and self-reported PROMIS T-scores. In general, there was moderate linear association between the proxy- and self-reported PROMIS measures with Pearson correlation coefficients ranging from 0.55 to 0.76 (**Supplementary Table 5**). Measures with higher correlation ($\geq$ 0.65) included meaning and purpose, positive affect, psychological stress, depressive symptoms, family relationships, and peer relationships (**Supplementary Table 5**). Measures with correlation $<$ 0.65 included life satisfaction and anxiety (**Supplementary Table 5**). We report the summarized T-scores for the self- and proxy-reported PROMIS measures along with the combined overall cohort PROMIS T-score data, where self-reported T-scores were used if both self- and proxy-reported T-scores were available in **Supplementary Table 6**. The PROMIS T-scores for the overall PICU cohort were similar to the U.S. population normed T-score of 50 (*SD*: $\pm$ 10) with values ranging from 45.9 to 55.1; however, the standard deviation for each measure was somewhat variable and ranged from 8.0 to 11.2 (**Supplementary Table 6**).

We next assessed the PROMIS measures by total exposure to ACEs by splitting children into two groups that included children with $\leq$ 1 (n = 25) vs. $\geq$ 2 ACEs (n = 18) (**Figure 4**). The demographic and clinical characteristics by total ACE exposures are summarized in **Supplementary Table 7**. The subgroup of children with $\geq$ 2 ACEs was older and reported more financial insecurity, but there were no significant differences between the two subgroups with respect to sex, race, ethnicity, insurance type, comorbidities, illness severity, length of stay, or discharge disposition (**Supplementary Table 7**). Amongst children admitted to the PICU, those who had $\geq$ 2 ACEs had worse PROMIS scores than those with $\leq$ 1 ACE across multiple domains; however, significant differences were only seen in anxiety and family relationships (**Figure 4**). Mean differences and Cohen's d criteria effect size were small (0.2) to moderate (0.5) for all of the PROMIS measures. The PROMIS measures with the largest Cohen's d effect sizes when comparing $\leq$ 1 vs. $\geq$ 2 total ACEs were life satisfaction (0.45), positive affect (0.49), anxiety (0.64), depressive symptoms (0.57), family relationships (0.55), and sleep disturbances (0.56).

DISCUSSION

In this study, we compared the type and total number of ACEs in a cohort of critically ill children to publicly available National Survey of Children's Health data from children living in Georgia and the United States. Consistent with our hypothesis, we found that a higher proportion of children in the PICU experienced ACEs compared to GA and U.S. children. We also used validated, population-normed patient-reported outcome measures with

TABLE 1 | Patient demographics and clinical characteristics.

Characteristic, *n* (%)[a]	PICU[b,c] *n* = 84	NSCH[d] GA *n* = 2,027	NSCH USA *n* = 102,740
Age (y), *n* (%)			
0–5	41 (48.8)	536 (29.9)	28,891 (32.1)
6–11	21 (25.0)	621 (36.9)	31,493 (33.6)
12–17	22 (26.2)	870 (33.2)	42,356 (34.4)
Sex, *n* (%)			
Female	37 (44.1)	954 (49.0)	49,336 (48.9)
Male	47 (55.9)	1,073 (50.9)	53,404 (51.1)
Race, *n* (%)			
White	28 (33.3)	1,340 (52.4)	79,360 (66.6)
Black or African American	53 (63.1)	390 (33.7)	7,348 (13.9)
American Indian or Alaska	0 (0.0)	13 (1.7)	945 (1.7)
Native	0 (0.0)	129 (3.7)	5,418 (4.9)
Asian	0 (0.0)	3 (0.3)	582 (1.8)
Native Hawaiian/other Pacific	0 (0.0)	22 (1.7)	834 (2.1)
Islander	3 (3.6)	130 (6.5)	8,253 (9.0)
Other			
Multiple			
Ethnicity, *n* (%)			
Hispanic or Latino	4 (4.8)	210 (14.9)	12,946 (25.5)
Not Hispanic or Latino	80 (95.2)	1,817 (85.2)	89,794 (74.5)
Insurance, *n* (%)			
Public	56 (68.3)	435 (30.9)	21,021 (30.1)
Private	26 (31.7)	1,338 (53.7)	71,372 (58.4)
Private and public	0 (0.0)	64 (4.7)	3,956 (4.6)
Not insured	0 (0.0)	155 (10.8)	4,873 (6.9)
Missing	2	35	1,518
Financial insecurity, *n* (%)			
Never	49 (58.3)	1,133 (50.9)	57,919 (53.2)
Rarely	19 (22.6)	610 (32.3)	30,915 (31.9)
Somewhat often	13 (15.5)	197 (13.5)	9,695 (11.7)
Very often	3 (3.6)	41 (3.3)	2,216 (2.9)
Missing	0	46	1,995
Comorbidities[e], *n* (%)			
0	21 (25.0)	1,157 (61.7)	61,292 (64.5)
1	35 (41.7)	459 (20.9)	21,429 (18.8)
2 +	28 (33.3)	411 (17.4)	20,019 (16.8)
PRISM score, median (IQR)	2 (0, 5)	n/a[f]	n/a
Length of stay, median (IQR)			
ICU days	3 (2, 6)	n/a	n/a
Hospital days	5 (3, 9)		
Discharge disposition, *n* (%)			
Inpatient rehabilitation	4 (4.8)	n/a	n/a
Inpatient psychiatric facility	3 (3.6)		
Home	77 (91.7)		
Time to Enrollment (days), median (IQR)	2 (2, 3.5)	n/a	n/a

[a] *Column percent does not account for missingness.*
[b] *Weight and stratum of 1 applied.*
[c] *PICU, pediatric intensive care unit.*
[d] *NSCH, National Survey of Children's Health.*
[e] *Includes 28 comorbidities; missing comorbidities were coded as "no."*
[f] *n/a, not applicable.*

PROMIS questionnaires. We found wide variability in the PROMIS scores amongst children in the PICU; however, the PROMIS scores were similar to the mean population T-score. When we assessed PROMIS scores by total number of ACEs (≤ 1 vs. ≥ 2), we found that the anxiety and family relationship T-scores were worse for children with a higher ACE burden. Over half of the children in the PICU experienced at least one ACE, nearly 30% experienced two or more ACEs, and 10% experienced three or more ACEs. Children with a higher number of ACE exposures prior to their critical illness reported worse

TABLE 2 | Healthcare use for the children admitted to the pediatric intensive care unit compared with the general pediatric population in georgia or the united states from the national survey of children's health.

Health care use, *n* (%)[a]	CHOA PICU[b,c] *n* = 84	NSCH[d] GA *n* = 2,027	NSCH USA *n* = 102,740
Visit to health care professional in past 12 months			
No–0 visit	11 (13.4)	58 (3.0)	3,726 (4.1)
Yes–1 visit	25 (30.5)	1,066	55,098 (58.9)
Yes–2 or more visits	46 (56.1)	(59.3)	27,349 (36.9)
Missing (*n*)	2	581 (37.6)	16,567
		322	
Has a place where usually receives sick care			
Yes	78 (93.9)	1,630	84,308 (76.9)
No	5 (6.0)	(76.7)	17,988 (23.1)
Missing (*n*)	1	390 (23.3)	444
		7	
Place where usually receives sick care			
Doctor's office	53 (69.7)	1,476	72,626 (86.4)
Hospital ER	16 (21.1)	(88.4)	739 (1.8)
Hospital outpatient	4 (5.3)	23 (2.9)	452 (0.8)
Clinic or health center	3 (3.9)	3 (0.1)	8,317 (9.4)
Retail store clinic	0 (0.0)	71 (5.9)	774 (0.9)
School	0 (0.0)	25 (1.3)	271 (0.3)
Some other place	0 (0.0)	6 (0.2)	437 (0.5)
Missing (*n*)	8	17 (1.1)	19,124
		406	
Has a place where receives preventive care			
Yes	78 (95.12)	1,867	95,850
No	4 (4.88)	(90.90)	(91.05)
Missing (*n*)	2	144 (9.10)	6,318 (8.95)
		16	572
Receives sick and preventive care in same place			
Yes	73 (93.6)	1,773	91,066 (95.9)
No	5 (6.4)	(95.6)	4,282 (4.1)
Missing (*n*)	6	85 (4.4)	7,392
		169	

[a] *Column percent does not account for missingness.*
[b] *Weight and stratum of 1 applied.*
[c] *PICU, pediatric intensive care unit.*
[d] *NSCH, National Survey of Children's Health.*

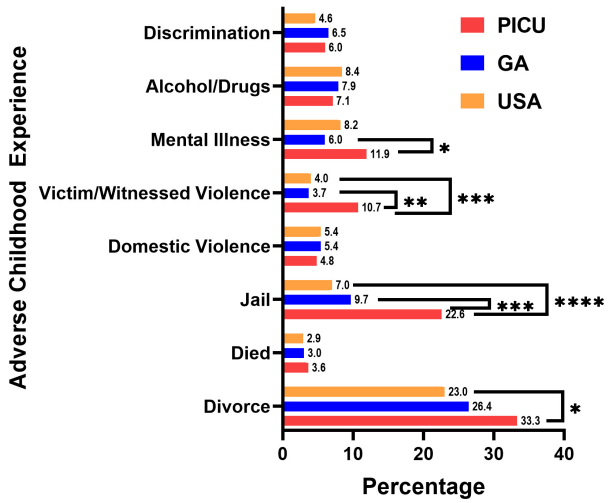

FIGURE 2 | Adverse childhood experiences by type. Children admitted to the pediatric intensive care unit (PICU) had a higher percentage of divorced or separated parents, had a parent who served time in jail, witnessed or was a victim of neighborhood violence, and has lived with a person with mentally illness. Children admitted to the PICU (red bars, $n = 84$); weighted responses of children living in Georgia from the National Survey of Children's Health (blue bars, $n = 1,889$); weighted responses of children throughout the United States (USA) from the National Survey of Children's Health (orange bars, $n = 97,173$). Numbers at the top of the bars are the percentage of children experiencing that adverse childhood experience. Only complete cases were included in the analysis. Rao-Scott Chi-square tests were used to compare differences between groups. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

levels of anxiety and poorer family relationships than those with one or no ACEs.

Adverse childhood experiences are toxic stressors with long-term, negative consequences on health and life opportunities such as education and job potential (1, 2). The lasting, harmful risks associated with ACEs are well-known in adults with a higher cumulative ACE burden (1, 2). ACEs are associated with over forty different health, education, and employment opportunity (life) outcomes. Each cumulative ACE confers higher risk of worse health and life outcomes (2, 11).

The negative consequences of ACEs are not just limited to adults. Children who experience a higher total number of ACEs can have delayed brain development and weakened immune and stress-response systems (4, 29, 30). As a result, a child's attention, decision-making, learning, and peer relationships may suffer (2). Our findings of worse PROMIS scores in critically ill children with 2 or more ACEs is consistent with published data showing worse mental health outcomes in adults who have more ACEs (1, 9, 10). The children in our PICU population are a vulnerable population at high risk for negative, lasting consequences of ACEs. We do not know whether a high baseline level of toxic stress affects susceptibility to critical illness, nor how critical illness interacts with ACEs to result in even greater levels of toxic stress and negative health outcomes. We do know that all children with critical illness are at high risk for significant morbidity and mortality even after initial recovery and hospital discharge (31, 32). We hope to further study the interactions between ACEs, critical illness, and outcomes in further studies; this includes the question of whether non-elective ICU admission itself should be considered an ACE.

As expected, the highest median cumulative ACE burden was seen in the oldest age group, as older children had more time to accrue ACEs. The PROMIS measures used in our analysis have been tested in children from 5 to 17 years of age with the measures showing factor invariance across age groups (33). Therefore, we did not adjust for age in our analysis of total ACE exposure with PROMIS measures. We did not include the PROMIS measures in the 0–5 age group due to the lack of availability of proxy-reported PROMIS measures in this age group at the time we began enrolling children into our study. Proxy-reported PROMIS

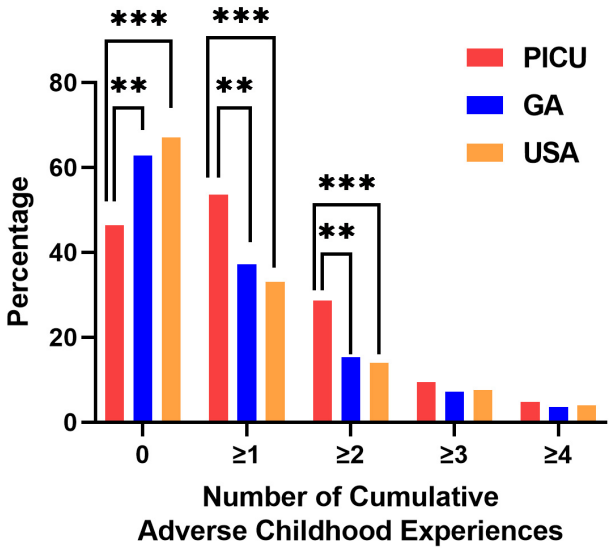

FIGURE 3 | Number of cumulative adverse childhood experiences. Children admitted to the pediatric intensive care unit (PICU) had a higher percentage of experiencing ≥ 1 or ≥ 2 adverse childhood experiences compared to the general population of children living in Georgia or the United States. Children admitted to the PICU (red bars, $n = 84$); weighted responses of children living in Georgia from the National Survey of Children's Health (blue bars, $n = 1,889$); weighted responses of children throughout the United States (USA) from the National Survey of Children's Health (orange bars, $n = 97,173$). Only complete cases were included in the analysis. Rao-Scott Chi-square tests were used to compare differences between groups. $^{**}p < 0.01$, $^{***}p < 0.001$.

questionnaires are now available for some measures, and future work should use these measures. The participants in our PICU cohort had similar overall levels of financial insecurity as reported for children in the GA and USA NSCH cohorts; however, there were large differences in health care use including greater use of a hospital emergency department as a primary place to seek both sick and well care. Our findings echo the results from a pediatric emergency department-based study of ACEs and healthcare use patterns from our Children's Healthcare of Atlanta healthcare system (34). In this pediatric emergency department study of children who did not require acute stabilization, 28% of children reported experiencing 1 ACE and 18% experienced ≥ 2 ACEs. A greater proportion of children admitted to the PICU had even higher numbers of ACEs compared to the pediatric emergency department cohort. These findings underscore the importance of understanding the link between ACEs, severity of illness, and recovery from critical illness.

We believe it likely that ACE exposure of children in our PICU population is underestimated. First, we had a higher proportion of children 5 years and younger in our study cohort compared to the distribution of children in the NSCH. Older children have more time to accumulate ACEs. Second, we were not able to enroll children without a parent or guardian at the bedside, nor were we able to enroll children who were taken into state custody due to abuse, neglect, or other family instability. Third, some parents may have declined study participation out of the fear that disclosure of ACEs would result in legal ramifications and/or impact on their child's medical care. There were also instances where parents acknowledged the presence of multiple ACEs to study staff but declined study participation citing the fear of reliving the trauma of the event(s) and experiencing post-traumatic stress. Lastly, some parental (proxy) ACE survey responses were discordant with additional ACEs reported to the medical team caring for the participant and recorded in the eMR.

The pediatric intensive care unit may be an effective and efficient place to implement ACE screening given the high proportion of critically ill children who reported experiencing at least one ACE. So, what can a pediatric intensivist do for the child and family once ACEs are disclosed? A growing body of research shows that there are effective interventions to prevent ACEs and mitigate their effects (2, 4, 30, 35). While the overall benefit of universal screening for ACEs in health care settings remains uncertain due to potential re-traumatization as well as limited understanding of best practices to address ACEs once they are identified, we suggest that screening is warranted if effective mitigation strategies can be employed. The Center for Disease Control and Prevention (CDC) has published a National Center for Injury Prevention and Control strategy aimed at identifying children with ACEs and preventing the accumulation of more ACEs using trauma-informed and evidence-based approaches (35). Pediatric intensivists can work to refer at-risk patients and families to programs and services including home visitation programs, enhanced primary care programs, mentoring programs, and trauma-focused cognitive behavioral therapy and multisystem therapy (2, 36). In addition, all pediatric providers can advocate for and support population-level interventions such as accessible early childhood education, violence prevention programs, youth-serving organizations, and multi-sector partnerships that work to identify and address ACEs (2, 35, 36). The pediatric ICU may serve as an important setting to trial whether ACE prevention and mitigation strategies can be implemented during hospitalization to improve the long-term outcomes and maximize the life opportunity potential of critically ill children. We believe it is especially important.

Patient reported outcome measures using PROMIS questionnaires have been validated for use in children with traumatic brain injury (37). The Common Data Elements project out of the National Institutes of Health National Institute of Neurological Disorders and Stroke encourages researchers to demonstrate the validity and utility of standardized instruments such as the PROMIS measures and to seek funding to support the validation and use of these metrics (38). Clinicians are adopting these measures into clinical practice, and PROMIS measures are integrated into some Epic eMR systems (39, 40). There is interest in expanding the use of validated and standardized patient-reported outcome measures and health-related quality of life questionnaires in pediatric critical care medicine (41–46). Further studies, such as ours, are needed to determine the most appropriate measures of overall health in the pediatric critically ill population (42, 45).

Our study has several limitations. First, children were enrolled at a single, quaternary academic medical center in Atlanta. Our hospital serves a predominantly minority, publicly insured

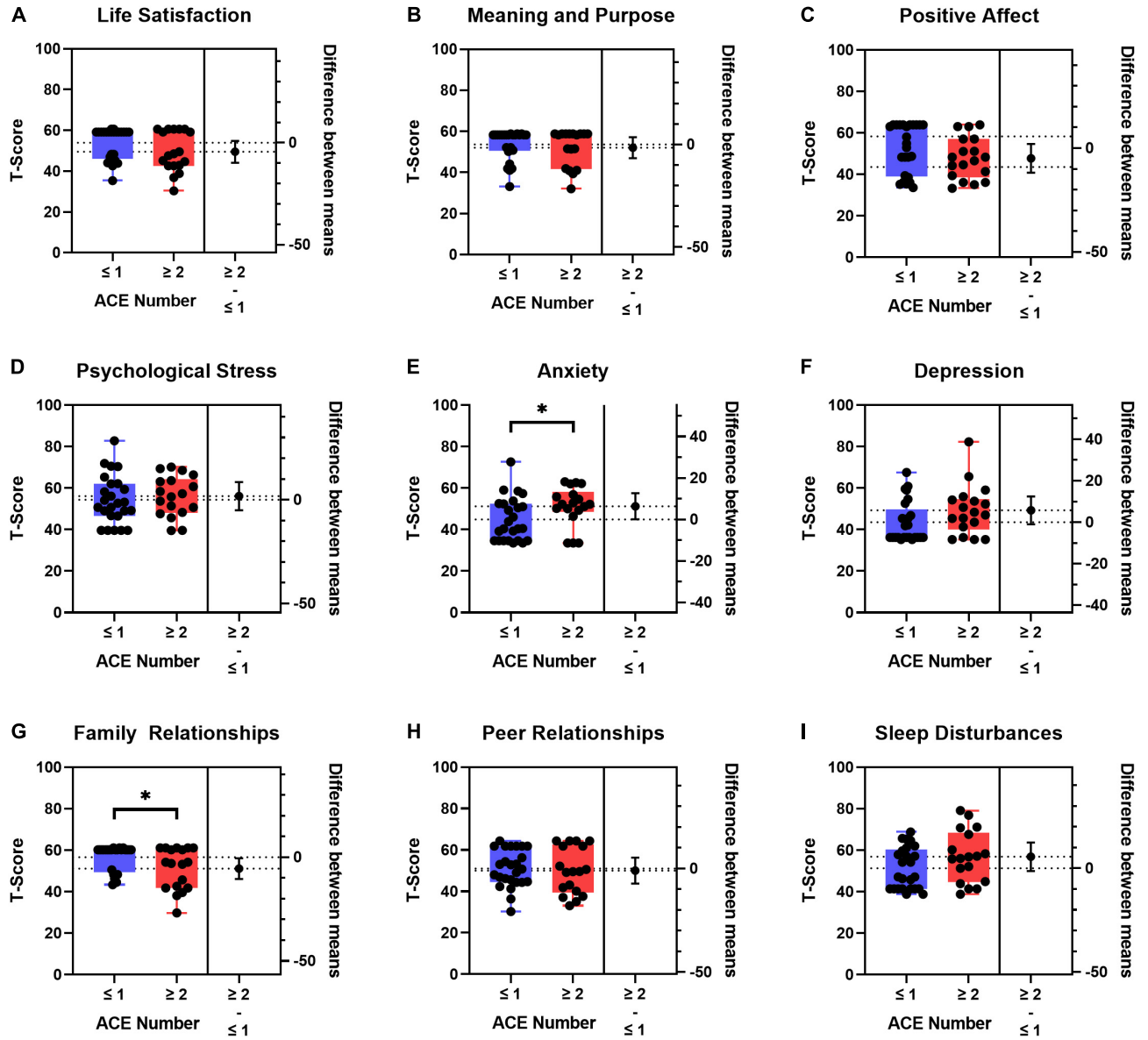

FIGURE 4 | Boxplots of patient reported outcome measures (PROMIS) T-scores and difference between means by ≤ 1 (n = 25) vs. ≥ 2 (n = 18) adverse childhood experiences (ACEs). **(A)** Life Satisfaction, **(B)** meaning and purpose, **(C)** positive affect, **(D)** psychological stress, **(E)** anxiety, **(F)** depression, **(G)** family relationships, **(H)** peer relationships, and **(I)** sleep disturbances. *T*-tests were used to compare differences between groups. Self-reported PROMIS T-scores were used preferentially in children who also had proxy-reported PROMIS T-scores. If no self-reported PROMIS T-score was available, the proxy-reported T-score was used. Blue boxes denote ≤ 1 ACE; red boxes denote ≥ 2 ACEs. The population normed T-score is 50 with a standard deviation of 10. The higher the T-score means that there is more of the concept you are testing. Dotted horizontal lines are the means for the two groups. The lower and upper edges of the boxplots are the 25th and 75th percentiles, respectively. The whisker lines are the minimum and maximum values. The black circle to the right of each boxplot is the difference between means for the two groups with the 95% CI denoted by the whisker line. *$p < 0.05$.

population and our results may not be generalizable to other populations. Our study highlights the demographic differences in our PICU sample compared to the Georgia and national-weighted samples. We did not adjust for this in our descriptive analysis, and future work evaluating comparative ACE outcomes with regression adjustment or sample stratification may be used to account for demographic differences. ACEs are a sensitive topic that can induce stress when remembering past traumatic events. We were unable to enroll any children admitted due to immediate sequela of non-accidental trauma or children who are in the custody of the state. As a result, our cohort likely underestimates the frequency of ACEs in our PICU population due to selection bias. We were not able to approach a large proportion of eligible study participants for consent because the entire recruitment period occurred during the COVID-19 pandemic with associated limitations to

non-COVID-19-related clinical research, restrictions on non-essential clinical research personnel working in-person, visitor restrictions, and the constraint of obtaining in-person consent from a parent/legal guardian. Analyses related to race/ethnicity within our PICU cohort are limited by collection of this data by hospital registration staff at the time of admission without subsequent verification by study staff at the time of enrollment. This may have led to simplified classification and/or misclassification of some subjects (47); however the participants in our study accurately reflect the demographics of children for whom we care in our PICU. It is known that a parent or guardian's childhood exposure to ACEs can affect their children (12, 48, 49). We did not ask parents or guardians about their childhood ACE exposures to look for correlation with their child's ACE and PROMIS measures. Exploring the interaction between a parent/guardian and child's ACE exposure is a potential future direction of our work. Finally, Early Childhood Parent-Report PROMIS measures are now available for several of the domains including depressive symptoms, anxiety, positive affect, sleep disturbances, and family relationships. Future studies that can be expanded to incorporate PROMIS measures in children ages 0–5 years.

In summary, children admitted to the pediatric intensive care unit are exposed to higher-than-average ACEs. Hospitalization of a high-risk group of critically ill children provides a contact point whereby identification of ACEs *via* universal screening can be employed. Furthermore, strategies to mitigate the downstream effects of ACEs can be deployed to provide necessary family support for high-risk children. Better identification and understanding of ACEs could inform interventions aimed at reducing morbidity from toxic stress to narrow the disparity gaps in health and life outcomes in vulnerable children experiencing critical illness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Children's Healthcare of Atlanta Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AR, JG, and AF conceived and developed the study. AR and JG supervised the data acquisition and analyzed and interpreted the data, drafted and edited the manuscript. CO, MV, and AR enrolled participants and acquired the data. JG, TW, and SG performed the statistical analyses and edited the manuscript. All authors edited and approved the final version of this manuscript and agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.923118/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A review of key strategies to address the shortage of analgesics and sedatives in pediatric intensive care

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Importance: Targeted analgosedation is a challenge in critically ill children, and this challenge becomes even more significant with drug shortages.

Observations: Published guidelines inform the provision of analgosedation in critically ill children. This review provides insights into general approaches using these guidelines during drug shortages in Pediatric Intensive Care Units as well as strategies to optimize both pharmacological and non-pharmacological approaches in these situations.

Conclusions and relevance: Considering that drug shortages are a recurrent worldwide problem, this review may guide managing these drugs in critically ill children in situations of scarcity, such as in pandemics or disasters.

KEYWORDS

pediatrics, COVID-19, sedation, analgesia, delirium

Introduction

In 1955, the pioneer dedicated Pediatric Intensive Care Unit (PICU) was established in Europe, and pediatric critical care medicine has only been accepted as a distinct specialty since 1981 (1). Many pediatric critically ill patients in these units require life-saving measures, including mechanical ventilation (MV), continuous renal replacement therapy, and extracorporeal membrane oxygenation therapy. These interventions are associated with a protracted PICU stay and the need for analgosedation (2).

Unfortunately, several essential analgesic and sedative agents have been depleted globally primarily due to increased needs and the disruption of manufacturing and supply chains (3). In 2016, the World Health Organization proactively took a stand about the lack of essential medicines, reported in low, middle, and high-income countries. The

scarcity of drugs poses risks to the patient's health due to non-treatment, undertreatment, and failure to find suitable alternatives (4).

This review aims to: (1) provide the reader with information regarding drug supply chain issues; (2) highlight the levels of service for dispensing medicines: conventional, contingency and crisis, emphasizing the role of pharmacists in the rationing of them; (3) address the relevance of appropriate management of analgesia and sedation in the PICU; and (4) present dose optimization strategies regarding analgo-sedative choices in addition to considering different approaches to preventing medication overuse.

Drug shortages: A global issue

Numerous definitions for drug shortages have been widely used, as shown in Table 1. Unfortunately, there is a lack of a standardized definition. Moreover, the low and middle-income countries have the absence of an official description (5).

Drug shortages are recognized as a global issue (4) and are usually due to several factors. Drug shortage affects high, middle, and low-income countries. In high-income countries, it has more attention when compared to other regions of the globe. The supply chain for delivering raw materials to patient use is complex and involves multiple entities, including manufacturers, group purchasing associations, wholesalers, and healthcare systems. On the manufacturing side, drug shortages occur due to lack of raw materials, regulatory problems, manufacturing interruptions, voluntary and involuntary recalls, promotion reduction (such as patent expiration or generic drug profitability), or manufacturer consolidations. Moreover, drug shortages also occur due to improper stocking practices, changes in clinical practice (resulting in increased demand), and even supply chain disruption due to natural disasters. Otherwise, low-middle income countries have some novel reasons for drug shortage, comprising licensing of manufacturers/products, shortage of raw material for a local producer, drug smuggling, and lodging tax government practices. These countries have insufficient research and lack policies to deal with this problem (5–7).

During a major disaster, such as a pandemic or war, for example, it is necessary to forecast and manage the shortage of drugs essential to critical care from global, national, regional, and institutional perspectives. Drug shortages can be expected to coincide with an interruption of other necessary resources such as personnel, availability of personal protective equipment, and medical devices. Supplies for drug preparation and administration can also be scarce (3).

Burry et al. summarized the main strategies that stakeholders must consider for future steps during a global disaster from the worldwide level to the institutional approach:

TABLE 1 Definitions of drug shortages according to different institutions.

Institution	Definition
ASHP and UUDIS	"A supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternate agent."
EFPIA	"A crisis situation caused by any ability of any MAH to supply a medicine with a specific API to market over an extended period of time resulting in the unavailability of this medication for patients."
FIP	"A drug supply issue requiring a change. It impacts patient care and requires the use of alternative agents."
Health Canada	"When a manufacturer/importer anticipates that they cannot supply a drug to meet projected demand."
ISPE	"A situation in which total supply of an approved medicine is inadequate to meet the current projected demand at the user level."
US FDA (three definitions)	1. "A period of time when the demand or projected demand for drug exceeds the supply of drug." 2. "When demands exceeds supply at any point in the supply chain may ultimately create a "stock-out" at the point of appropriate service delivery to the patient if the cause of shortage cannot be resolved in a timely manner relative to the clinical needs of the patients." 3. "A situation in which the total supply of all clinically interchangeable versions of an FDA regulated drug product is inadequate to meet the projected demand at the user level."

API, active pharmaceutical ingredients; ASHP, American Society of Hospital Pharmacists; EFPIA, European Federation of Pharmaceutical Industries and Associations; FIP, International Pharmaceutical Federation; ISPE, International Society of Pharmaceutical Engineering; MAH, Market Authorization Holder; US FDA, Food and Drug Administration (United States); UUDIS, University of Utah Drug Information Service (5).

- Global: Proactively plan for shortages *via* substitution and conservation strategies; establish transnational networks with national and regional sharing arrangements; develop recommendations on essential supplies.
- National and Regional Manufacturing: create usage prediction models; couple with inventory management; engage manufacturers; improve pharmaceutical processes; eliminate redundant critical production steps; recommendations on essential supplies; collaborative

dashboards; sharing arrangements; decentralize production to multiple sites. Supply disruption is exacerbated if there are limited manufacturing capacity, market concentration, or just-in-time inventory practices that result in minimal product inventory on hand at any given time. However, the Food and Drug Administration (FDA) cannot prevent manufacturing concentration, require redundancy of that capability, require a company to manufacture a drug, maintain a certain level of inventory of the drug, or reverse a business decision to stop manufacturing. Manufacturers may consider opportunities to increase redundant manufacturing capacity, maintain idle capacity, or increase inventory levels to reduce shortage risks, and other stakeholders can explore how to encourage such practices.

- Institutional: Balance drug inventory; identify drugs at risk of shortage; develop drug conservation guidelines; rotate stock; identify therapeutic alternatives (3, 8).

Given this situation, the role of pharmacists in alleviating the current crisis and future challenges is a central one. Notably, among the pharmacist's actions is advocacy for implementing the *Interagency Drug Shortage Task Force* recommendations by participating in dedicated drug shortage task forces or rationing committees to guide management strategies and keeping informed regarding drug shortages (9).

Finally, Ammar et al. suggest that drug escalation capacity and response be measured based on three levels: **conventional care**, **contingency care**, and **crisis care**. Contingency care comprises all the practices that may be outside usual care notwithstanding they attempt to keep traditional care. On the other hand, crisis care approaches are outside of standard of care, however, provide the best feasible care when resources are severely limited (10).

Children have unique illnesses and are at a singular developmental stage that may need specific medications for which there may not be therapeutic alternatives. Additionally, the evidence supporting **the use of substitutes may be limited in pediatric patients and may raise concerns for adverse events**. Therefore, a comprehensive and multidisciplinary approach is necessary to ensure that drug shortages do not lead to unfavorable patient outcomes (11).

The challenges of analgesia and sedation in pediatrics

Alleviating pain and anxiety in critically ill children may be quite challenging. Patient admission and daily care processes within PICUs can be frightening and painful for pediatric patients and their families. Pain can result from the underlying disease or trauma and can be exacerbated by anxiety and emotional stress, two common elements of the PICU stay. The condition in which children find themselves in this environment, surrounded by strange people and machines, separated from their parents, in a hostile, noisy, and bright place most of the time, leading to the interruption of the circadian cycle, causes more anxiety and vulnerability to pain. Pain may also result from diagnostic and therapeutic interventions to which patients are submitted during the hospitalization period. In intensive care, children, and newborns (NB) are often subjected to numerous potentially uncomfortable or painful procedures, such as arterial and venous punctures, thoracic drainage, and endotracheal intubation. These therapeutic interventions place an enormous burden on these patients, affecting the successful performance of these procedures and the patient's recovery (12–16).

An effective analgesia approach facilitates invasive procedures or interaction with invasive equipment such as MV and enhances rehabilitation of the critically ill patient (12). Accurate assessment of pain and comfort using validated scales with targeted, measured goals is central to excellent clinical management (13).

Adequate analgesia and sedation minimize the stress response and improve clinical and psychological outcomes. When inadequate, negative outcomes include undertreated pain or persistent agitation leading to accidental removal of invasive devices. On the other hand, oversedation results in prolonged PICU and hospital stay, prolonged MV, and the development of tolerance, physical dependence, iatrogenic withdrawal syndrome (IWS), and delirium. Accurate assessment of pain, distress, IWS, and delirium in critically ill children can be challenging as these conditions often overlap. The use of validated assessment scales as outlined in the recent PANDEM guidelines facilitates assessment guiding proper care and mitigating their development (12, 17).

The *2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU* (PADIS Guidelines) have recommended the approach to sedation as "analgesia first" (before sedation) or analgesia-based sedation, which implies that an analgesic (usually an opioid) is used before a sedative to achieve the desired sedative goal. Institutions should have protocols that include periodic evaluations of pain and sedation using validated tools and provide clear guidance on the choice and dose of the drug, ensuring that pain treatment is a priority over the administration of sedatives (18). Recently, Smith et al. developed Society of Critical Care Medicine (SCCM) clinical practice guidelines for critically ill pediatric patients, including pain, sedation/agitation, iatrogenic withdrawal, neuromuscular block, delirium, PICU environment, and early mobility. Key areas included the need for routine monitoring of pain, agitation, withdrawal, and delirium using validated tools in children; improved use of protocol sedation and analgesia, and recognition of the importance of non-pharmacological interventions to

improve patient comfort and provision of comprehensive care (17).

The SCCM developed a multicomponent and evidence-based six-step strategy to liberate patients from the ICU. This approach, called "the ABCDEF bundle," represents **A**: Assess, prevent, and manage pain; **B**: Both Spontaneous Awakening Trials (SATs) and Spontaneous Breathing Trials (SBTs); **C**: Choice of sedation; **D**: Delirium assessment, prevention, and management; **E**: Early mobility and exercise; and **F**: Family engagement and empowerment. The conceptualization of the proposed "ICU Liberation" achieved notable recognition in adult critical care research and has become prominent in PICU. In a recent survey of 161 PICUs in 18 countries, Ista et al. observed that, unfortunately, the A-F bundle items have been adopted with substantial variability internationally (19).

We should emphasize that providing analgosedation is not restricted to the PICU environment. Currently, with the exponential growth in the number of procedures in children and adolescents experience outside the operating room, there has been a greater need for awareness and guidance on procedural sedation by professionals who are not anesthesiologists, including emergency departments, wards, outpatient clinics, imaging centers, and dental offices (20, 21).

Regarding drug shortages, in the specific case of analgosedation, one of the recommended approaches to conserving intravenous analgesic supplies during contingency care is to implement protocols where clinicians would initially use intermittent analgesic boluses before patients transition to continuous infusion. In addition, enteral delivery of opioids and analgesics may help to conserve the supply of intravenous (IV) agents. However, this strategy should be limited to patients with adequate gastrointestinal motility and function. Other situations can also be considered. For example, ketamine has analgesic properties and may spare the use of IV opioids. Furthermore, it is not known to cause significant respiratory depression at moderate doses, and this is advantageous when trying to transition the child off MV (10).

With regard to benzodiazepines, they can also be administered in intermittent doses or as a continuous infusion to obtain mild sedation. However, they should only be considered as first-line sedatives in contingency care settings. When used, IV lorazepam, midazolam, or diazepam in scheduled doses or as needed, can help to conserve drug stocks in the scenario of ongoing shortages. This approach can limit overall sedative exposure while still providing appropriate light sedation, preserving the need for high doses and continuous infusions known to be associated with accumulation. However, if this is not sufficient for adequate sedation, continuous infusion of benzodiazepines can be started. Still intermittent doses may be reconsidered again when continuous infusion is no longer needed and transition from continuous infusion to a less aggressive dose is appropriate (10).

Dose optimization strategies

Analgo-sedative regimen selection should take into consideration patient-specific risk factors, targeted level of sedation, anticipated duration, analgesic needs, physician familiarity, and institutional formulary availability. The following strategies that ensure comfort and optimize dosing of analgesics and sedatives. Applying these strategies can be challenging for teams unfamiliar with these measures, particularly when human resources are scarce, and family presence is restricted.

Set a goal and reassess regularly and as patient condition changes

It is highly relevant for the interdisciplinary team to actively participate and discuss the goals of analgesia and sedation when necessary. When determining a sedative and analgesic regimen for a critically ill patient, the first step is to choose the desired degree/depth of sedation.

Moreover, the "Pediatric Brain Roadmap" contributes like a script to disseminate delirium assessment results and crucial information to guide delirium management discussion during interdisciplinary rounds. Its components are pain assessment, target, and actual LOC, delirium assessment, and sedative/analgesic/antipsychotic medications previously received:

- Where is the patient going? → Sedation targets and therapy goals.
- Where is the patient now? → Actual level of consciousness (RASS)/Delirium assessment/Pain assessment.
- How did they get there? → Shock, hypoxia, fever, drug exposure (18, 22).

Whenever possible, target a patient with RASS 0 (alert and calm)

There are few current indications for continuous deep sedation. These include the treatment of intracranial hypertension, severe respiratory failure, refractory status epilepticus, and prevention of consciousness in patients treated with neuromuscular blocking agents (18, 22).

Consider non-pharmacological strategies for analgesia and sedation

Non-pharmacological interventions can reduce the total requirement and associated side effects of sedation

TABLE 2 Alternatives for pediatric analgesics and sedatives according to the desired sedation level.

Alternatives for pediatric analgesics		
First-line analgesics—Conventional care		
Light sedation	→	**Deep sedation**
Fentanyl or morphine AN		Fentanyl or morphine CI
Scheduled acetaminophen, PO, or IV		Scheduled acetaminophen, PO, or IV
Scheduled gabapentin or pregabalin (in case of neuropathic pain)		Scheduled gabapentin or pregabalin (in case of neuropathic pain)
Second-line analgesics—Conventional care		
Light sedation	→	**Deep sedation**
Ketamine AN		Ketamine CI▼
Hydromorphone AN		Hydromorphone CI
Oxycodone immediate release AN		Scheduled oxycodone immediate release
Third-line analgesics—Contingency care		
Light sedation	→	**Deep sedation**
Remifentanil CI ▲		Scheduled methadone, PO, or IV
Fourth-line analgesics—Crisis care		
Light sedation	→	**Deep sedation**
Lidocaine IV'		Sufentanil CI
Nefopam PO[		
ALTERNATIVES FOR PEDIATRIC SEDATIVES		
First-line sedatives—Conventional care		
Light sedation	→	**Deep sedation**
Dexmedetomidine CI▼		Ketamine CI▼
Ketamine *bolus* IV		Propofol CI□
Second-line sedatives—Conventional care		
Light sedation	→	**Deep sedation**
Clonidine PO scheduled every 6 h		Clonidine CI
Midazolam *bolus* IV		Midazolam CI
Third-line sedatives—Contingency care		
Light sedation	→	**Deep sedation**
Lorazepam PO or IV scheduled every 4–6 h		Lorazepam CI
Diazepam PO AN		Diazepam PO or IV scheduled every 6–8 h
Fourth-line sedatives—Crisis care		
Light sedation	→	**Deep sedation**
Phenobarbital PO or IV scheduled every 6–8 h		Thiopental CI
Hydroxyzine PO scheduled every 8 h		
Clonazepam PO AN or scheduled		
Atypical antipsychotics# (risperidone, quetiapine, and olanzapine) PO AN		
Typical antipsychotics# (haloperidol, chlorpromazine, or levopromazine) PO or IV AN		
Chlormethiazole PO AN		

AN, as needed; CI, continuous infusion; IV, intravenous line; PO, orally. ▲ Remifentanil has single pharmacokinetic and pharmacodynamic profiles. Unfortunately, it is expensive compared to other conventional opioids (33). ' Current literature has demonstrated that an infusion of lidocaine effectively treats acute perioperative pain and various circumstances of chronic pain in pediatrics, particularly pain refractory to conventional regimens (34, 35). [Data on nefopam use in children are lacking. However, it is mentioned in the 2018 PADIS Guidelines as an opioid-sparing pharmacological option for pain management (17, 36). ▼ As in adults, the use of benzodiazepines in pediatric intensive care is associated with an increased risk of delirium (can be up to four times higher than in children who do not receive them). Therefore, the early addition of dexmedetomidine or ketamine infusion may reduce or even prevent the regular use of benzodiazepines and/or opioids (26, 37). □ According to Koriyama et al., propofol infusions in critically ill children appear to be safe by limiting doses to 4 mg/kg/h and for <24 h; however, adequate follow-up for adverse effects has not yet been carried out due to a lack of solid evidence. Studies show that higher doses and for longer periods are associated with propofol infusion syndrome (38). # In general, typical antipsychotics mainly trigger extrapyramidal syndrome (hyperpyrexia, dystonias, akathisia, Parkinsonism) and hyperprolactinemia. Atypical ones can lead to weight gain and metabolic disorders. Other side effects include malignant hyperthermia, hypotension, laryngospasm, lipid changes, glucose disturbances, and anticholinergic effects. Sedation, increased appetite, and weight gain are more commonly observed with the use of olanzapine (39–44). All antipsychotics carry a risk for QT interval prolongation, with the possibility of torsades de pointes. Risk factors for torsades de pointes include inherent risk of the drug, higher doses, rapid upward titration, rapid IV infusion, female gender, electrolyte disturbance, bradycardia, concomitant QT-prolonging drugs, ion-channel polymorphisms, and patients with congenital long QT syndrome caused by ion channel mutations (45, 46). Moreover, the use of the antipsychotic chlorpromazine in pediatric patients causes numerous drug interactions, ineffectiveness, inappropriate doses, and side effects (47). → For procedural sedation, nitrous oxide is a practical adjunct widely used in dental procedures. It has effective anxiolytic, amnestic, and analgesic, with few side effects associated with its use. Some authors highly recommend its application as part of the sedative arsenal for minor procedures (10, 24, 26, 38, 48–53).

and analgesia medications and have been recommended by international sedation guidelines. In addition to addressing risk factors, these strategies include daily screening for delirium; environmental orientation; maintaining normal hydration; regulation of bladder and bowel function; early establishment of normal diet; correction of metabolic disorders; cardiorespiratory optimization; early identification of infection; effective treatment of pain; daily mobilization; avoidance of antipsychotic drugs, benzodiazepines, and anticholinergics; sleep promotion; light and noise reduction; early removal of invasive devices; avoidance of physical restraints; attention to the parameters and modes of ventilation; cluster care (18, 22–24).

Use the "analgesia first" or "analgesia-based sedation" approach

Consider pain assessment and treatment with opioid-sparing measures using a multimodal analgesia strategy, including non-opioid analgesics such as acetaminophen, dipyrone (metamizole), nefopam, ketamine, lidocaine, neuropathic agents, and NSAIDs (18).

Patient-specific drug therapy

Once the depth of sedation is chosen, it is essential to focus on selecting specific sedatives and pain relievers. In recent years, numerous studies have shown that benzodiazepines are independently associated with the incidence of delirium. Therefore, benzodiazepines should not be used as first-line sedatives in critically ill children. In the last decade, the use of alpha agonists such as dexmedetomidine has increased in PICUs. It may shorten the duration of MV and reduce the need for opioids and the incidence of delirium. In addition, attention should be paid to the individual characteristics of each patient. Care should be taken concerning obese patients and those with organ dysfunction and arrhythmias (18, 24, 25).

Medication rotation

Some authors suggest establishing a sedation rotation regime based on the hypothesis that replacing sedative and analgesic drugs targeting different receptors for shorter periods may decrease the incidence of tolerance and IWS (26).

A-F bundle

This bundle promotes fast recovery and ICU liberation, with satisfactory evidence in adults and children.

- *[A] Assessment and management of pain.*
- *[B] Both awakening and breathing trials.*
- *[C] Choosing the optimal sedative (avoiding benzodiazepines when possible) and titrating to the lightest sedation level possible.*
- *[D] Delirium assessment and management.*
- *[E] Early mobility and exercise.*
- *[F] Family engagement and empowerment when possible* (27–31).

The inclusion of the letter R (respiratory-drive-control" "ABCDEF"R") was suggested by Chanques et al. and should be considered to prioritize the management of factors related to the MV and the respiratory unit, avoiding the unnecessary use of medications that can delay ventilator release and worsen other patient outcomes (32).

In Table 2, we summarize the pharmacological options for providing analgesia and sedation in conditions of scarcity.

Conclusion

Care of critically ill children during conditions of scarcity of analgesic and/or sedative drugs has presented numerous challenges globally. Effective approaches to managing drug shortages, implementing evidence-based guidelines for evaluating pain and delirium, and understanding alternative pharmacological and non-pharmacological options for analgesia and sedation will ensure safe and effective management of pain and delirium in the setting of limited resources or future disasters.

Author contributions

RC conceptualized and wrote the first draft of the review. MR-R, MM-B, AP-B, and JH made substantial contributions to the conception, design, literature data, and content of the tables. PK and AS drafted the article and revised it critically for important intellectual content. All authors approved the final version to be published.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Why women say no to leadership positions

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I am a pediatric critical care physician who followed the academic roadmap by being a strong clinician, trailblazer in research, skilled educator and advocate for my patients. I am no unicorn. I know dozens of women in pediatric critical care who are just like me or better. They are my peers, my academic crushes and my friends. Several of us have considered leadership positions that would require a seismic shift in our lives due to geographical moves, rebalancing of work demands or ceding of our academic joys. Let me be clear: these women are not afraid of change, embrace hard work and are already seen as superwomen who slay challenges. Yet, many of us will not take the leap because the academic ladder was not built for us.

As I considered a leadership position, I searched for women who were succeeding in that role. I struggled to find many role models who were mothers of young children who had relocated to accept that position. When I chatted with a recruiter, she asked, "What will it take for me to move you?" I responded, "The question you should be asking is what motivates me?" She then asked and I responded "Anything I do has to validate my role as a good mother. Secondly, I am motivated by purpose, not fame, not money, not power. Do not obscure my position, I will be compensated for my labor, but if you do not find out what makes me whole it will be a futile process."

This is not to say men do not care about purpose and family. This is to say that my job as a mother is woven into the fabric of all I do. A geographic move is a heavy undertaking for women because of our outsized role at home. Women bear the onus of resettling the family, establishing the village that makes work-life integration seamless, and managing the emotional toll of disrupting the children's lives. Is there a strong swim team? How long will it take to travel to my parents in an emergency? Will we find a French-speaking nanny? And as a woman of color an extra layer of questions arise around safety. Can my son walk in this neighborhood wearing a hoodie? If I do not know the answers to these questions and the hundreds of other questions playing out in my head, I cannot decide if this job is the right fit. So, while it is important to meet the high-profile, often male decision-makers on that first visit, it is equally important to address these concerns.

My research program centers around teaching communication skills to clinicians and one pearl I teach is that if you approach a family meeting with an agenda and fail to find out what is most important to the family, you will miss an opportunity to learn who they are, how they make decisions and what they value most. Effective goals of care decision making requires asking value-based questions then making recommendations based on the family's values. Without that information you cannot make complex medical decisions, such as placing a tracheostomy. The same is true for life decisions.

A decision as important as a geographic move for a new academic role is complex. The absence of women in front of you adds an additional layer of complexity. Academia has a long history of excluding women from leadership. While pediatrics is dominated by women, the upper ranks are populated by men. In 2019 a gender disparities report on the pediatric critical care workforce revealed that only 32% of division directors and 25% of Department of Pediatrics Chairs are women (1). Women are often overlooked for leadership positions because society has acculturated us to not be seen as innovators. Women are told we are not ready for leadership, so we wait to be selected, to be deemed worthy, to have the door cracked, while men may get an opportunity to stretch for a position in which there is growth. This disparity results in women being considered for leadership positions after they have arrived, have checked all the boxes and are often overqualified for the position. The threat in this approach is that the excitement for the position can be fleeting, the growth in skills incremental and the staying power compromised. In response to these delays, we are told to "lean in," negotiate for more money, speak up in meetings, or essentially, behave like men. While these strategies work well for men, they are often detrimental for women's careers who are then labeled as aggressive or ungrateful. The system puts the burden on women to change, when most of the challenges we face are systemic and need to be addressed by the organizations we serve. Women do not need to adapt to the system, the system needs to become inclusive and equitable for women such that women have early opportunities to rise into leadership.

A consequence of women not being in the pipeline for leadership positions is that we are shielded from the realities of leadership. We are unacquainted with the negotiation palate of options; is housing a possibility? Can I work remote? What signal does it send if I leave early on Thursdays to attend soccer matches? Can I be my authentic self and still succeed? Women need to be in the room to gain this knowledge while preparing for leadership positions. The system needs transparency. We deserve to know what is possible.

The good news is that many institutions have begun to incorporate some of these elements into recruitment. I remember as I was listening to a Department Chair list the research staff that would be available to me, I dreamed of personal staff who could comparably set me up for success. I fantasized about a personal assistant who could navigate the school landscape, sign me up for local neighborhood listservs, find vets, doctors, and dentists and automate my life similarly to how I curated it in my current setting. I said this out loud and the Chair responded, we have a work-life office that handles that. While the work-life office would not address all the personal tasks, it was a great start. I have also seen institutions begin to set metrics for diversity of race, ethnicity, and gender of applicant pools for leadership positions. These are positive developments, but more needs to be done. If we want more women in academic leadership, especially women of color, academia must bend—speak our language, recruit women earlier in their career, retain them at their home institution, offer salary transparency and recognize the unique challenges of leading while mothering. We can do the job, make us WANT the job.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

TO confirms sole responsibility for the study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The longitudinal course of pediatric acute respiratory distress syndrome and its time to resolution: A prospective observational study

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Background: The longitudinal course of patients with pediatric acute respiratory distress syndrome (PARDS) is not well described. In this study, we describe the oxygenation index (OI) and oxygen saturation index (OSI) in mild, moderate, and severe PARDS over 28 days and provide pilot data for the time to resolution of PARDS (T_{res}), as a short-term respiratory-specific outcome, hypothesizing that it is associated with the severity of PARDS and clinical outcomes.

Methods: This prospective observational study recruited consecutive patients with PARDS. OI and OSI were trended daily over 28 days. T_{res} (defined as OI < 4 or OSI < 5.3 on 2 consecutive days) were described based on PARDS severity and analyzed with Poisson and logistic regression to determine its association with conventional outcomes [mechanical ventilation (MV) duration, intensive care unit (ICU) and hospital length of stay, 28-day ventilator-free days (VFD), and 28-day ICU-free days (IFD)].

Results: There were 121 children included in this study, 33/121(27.3%), 44/121 (36.4%), and 44/121(36.4%) in the mild, moderate, and severe groups of PARDS, respectively. OI and OSI clearly differentiated mild, moderate, and severe groups in the first 7days of PARDS; however, this differentiation was no longer present after 7days. Median T_{res} was 4 (interquartile range: 3, 6), 5 (4, 7), and 7.5 (7, 11.5) days; $p < 0.001$ for the mild, moderate, and severe groups of PARDS, respectively. T_{res} was associated with increased MV duration, ICU and hospital length of stay, and decreased VFD and IFD.

Conclusion: The oxygenation defect in PARDS took progressively longer to resolve across the mild, moderate, and severe groups. T_{res} is a potential

Abbreviations
AUC, area under the curve; CI, confidence intervals; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; HFNC, high flow nasal cannula; ICU, intensive care unit; IFD, intensive care unit free days; IRR, incidence rate ratio; MV, mechanical ventilation; OI, oxygenation index; OSI, oxygen saturation index; OR, odds ratio; PARDS, pediatric acute respiratory distress syndrome; PELOD, Pediatric Logistic Organ Dysfunction score; PICU, pediatric intensive care unit; PIM 2, Pediatric Index of mortality 2 score; PCPC, pediatric cerebral performance category; POPC, pediatric overall performance category; ROC, receiver operating characteristic; VFD, ventilator-free days.

short-term respiratory-specific outcome, which may be useful in addition to conventional clinical outcomes but needs further validation in external cohorts.

KEYWORDS

non-invasive ventilation, oxygen inhalation therapy, acute lung injury, acute respiratory distress syndrome, pediatric intensive care unit, critical care outcomes, artificial respiration

Introduction

Pediatric acute respiratory distress syndrome (PARDS) is characterized by severe hypoxemia (1). Clinical definitions of PARDS (or ARDS) invariably incorporate some measure of oxygenation [e.g., oxygenation index (OI), oxygen saturation index (OSI), partial pressure of arterial oxygen to fraction of inspired oxygen (PF) ratio, and oxygen saturation to the fraction of inspired oxygen (SF) ratio] with cut-offs delineating mild, moderate, and severe groups (1, 2). However, most conventional outcomes [e.g., mortality, ventilator duration, and pediatric intensive care unit (PICU) duration] in PARDS are often affected by confounders (3) and are frequently not due to refractory hypoxemia (4, 5). There is a lack of a more direct and specific respiratory outcome for PARDS. Oxygenation measures are associated with outcomes and the ability to stratify patients into prognostic groups (6, 7). As such, it is intuitive that the resolution of this oxygenation defect may result in a positive short-term respiratory-specific outcome (8). In adult patients, the presence or absence of resolution of ARDS (defined as improvement in $P/F > 200$ for at least 48 h) was shown to be associated with lower hospital mortality (8).

Most previous studies in PARDS focused on the first few days of illness and rarely examined the course of illness to its resolution in detail (6, 9). Indeed, PARDS may progress in severity after diagnosis and this trajectory may be associated with worse outcomes (10). It is also possible that patients with PARDS are vulnerable to further respiratory insult necessitating escalation of respiratory support. The understanding of the course/trajectory of PARDS is lacking and is an unmet medical need. To address these gaps in the medical literature, we undertook this study with the aims of (1) describing the extent and longitudinal course of lung injury in mild, moderate, and severe PARDS by ascertaining the OI and OSI trends over 28 days and (2) demonstrating proof of concept of time to resolution of PARDS (T_{res}) as a short-term respiratory-specific outcome. We hypothesized that T_{res} is associated with the severity of PARDS and clinical outcomes.

Methods

Design, setting, and patients

This study was conducted in a 16-bedded multidisciplinary PICU from September 2018 to July 2021. All PICU admissions were screened daily for PARDS and informed consent was obtained under the centralized Singhealth institutional review board reference number: CIRB 3076/2017/E. The Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria were applied to identify patients with PARDS and oxygenation criteria were met on two separate blood gases 4 h apart (11, 12). All patients were ventilated according to a lung-protective mechanical ventilation protocol (13). Reporting was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary appendix). (14).

Measurement and data collection

Clinical data were collected which included admission severity scores [Pediatric Index of mortality (PIM) 2 and Pediatric Logistic Organ Dysfunction (PELOD) scores] (15, 16). Comorbidities were defined by the presence of complex chronic conditions and categorized into the most clinically affected system (17). Sepsis and organ dysfunction were defined by the International Pediatric Sepsis Consensus Conference (18). Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) were scored at PICU admission and discharge (19). Mechanical ventilation (MV) settings and their corresponding blood gas measurements were recorded at 0600-0800H daily—these were used for calculation of daily OI and OSI up to 28 days after diagnosis PARDS.

Outcomes and statistical analysis

Patients were analyzed in three groups: mild, moderate, and severe PARDS. The highest severity over the first 7 days of PARDS was used to categorize patients into their severity groups (e.g., if a patient was recruited on day 1 with mild PARDS but progressed to develop severe PARDS on day 3, he/she was analyzed as severe PARDS). This was done to capture all patients who developed severe disease who will likely have poorer outcomes compared to patients who remain in the mild/moderate category throughout their illness (10). Patients who remained on non-invasive ventilation throughout the course of PARDS were empirically categorized into the mild group. Data were summarized as counts

(percentages) and median (interquartile range) for categorical and continuous variables, respectively. Comparisons between severity groups were done using the Chi-square test and Kruskal–Wallis tests for categorical and continuous variables, respectively.

The primary outcome was time to resolution of PARDS (T_{res}) defined as OI < 4 or OSI < 5.3 for two consecutive days —this was treated as time-to-event data. T_{res} based on PARDS severity was plotted using a Kaplan–Meier curve and compared using the Log-rank test. We also established the relationship between T_{res} with PARDS severity, PIM2, and PELOD scores using Cox regression to determine if the general severity of illness impacts the resolution of PARDS. T_{res} (treated as a continuous variable) was further analyzed to quantify its association with conventional PARDS outcomes using Poisson [for ICU length of stay, hospital length of stay, 28-intensive care unit free days (IFD), duration of MV, 28-ventilator-free days (VFD)] and Cox regression (for change in POPC and PCPC from admission discharge). These associations were expressed as an incidence rate ratio (IRR), hazard ratio (HR), or odds ratio (OR), whichever is appropriate, with corresponding 95% confidence intervals (CI). After a review of the causes of death, a sensitivity analysis was performed excluding patients who at PICU admission, had a poor overall diagnosis (e.g., terminal malignancy) or poor neurologic prognosis (e.g., brainstem dysfunction). Both survivors and non-survivors were included in the analysis of T_{res} with censoring of non-survivors at the time of death. A sensitivity analysis for the primary outcome (T_{res}) was done using conventional stratification of PARDS within 24 h of diagnosis.

Analysis was performed on STATA software, version 15.1 (StataCorp, College Station, TX) and SAS version 9.3 software (SAS Institute, Cary, NC). All tests were two-tailed and a p-value <0.05 was accepted as statistically significant.

Results

One hundred and twenty-one patients were identified for this study, with 33/121 (27.3%, 44/121 (36.4%), and 44/121 (36.4%) in the mild, moderate, and severe groups, respectively. The majority of patients in this cohort had pneumonia [78/121 (64.5%)] as the inciting factor for PARDS followed by sepsis [20/121 (12.4%)] (**Table 1**). Most patients had underlying comorbidities [85/121 (70.3%)], of which neuromuscular [29/121 (27.1%)] and genetic/congenital [21/121 (19.6%)] were the most common.

Almost all patients [115/121 (95.0%)] required invasive MV (**Supplementary Figure S1**). Throughout the first 7 days of PARDS, the OI, OSI and alveolar-arterial oxygen gradient (AaDO2) were higher and PF ratio, SF ratio were lower with greater severity of PARDS (**Supplementary Table S1**). Differences in OI and OSI (as well as the other oxygenation measures) were not statistically significant after the first week of PARDS (**Figure 1**). There was a stepwise increase in the use of pulmonary (e.g., high-frequency oscillation, pulmonary vasodilators, prone positioning) and non-pulmonary (e.g., neuromuscular blockade, diuretics, and red blood cell transfusions) therapies, across severity groups (**Supplementary Table S2**). A stepwise increase in the vasoactive inotrope scores and other PICU support therapies was also evident across severity groups (**Supplementary Table S3**).

MV lasted longer and VFD lasted shorter across severity groups (**Table 2**). Patients with severe PARDS required more time to be liberated from the ventilator (Log-rank test $p = 0.0294$), whereas there was no difference between the mild and moderate groups (**Supplementary Figure S2**). Change in the PCPC score from admission to discharge was higher in severe PARDS compared to moderate or mild PARDS [(1 (0, 2) vs. 0 (0, 1) and 0 (0, 1), respectively; $p = 0.045$], but there was no significant difference for the change of POPC score. PICU duration was longer and IFD shorter across severity groups. Time to PICU discharge was successively longer with increasing PARDS severity (Log-rank test $p = 0.0003$) (**Supplementary Figure S3**). Hospital duration was increased across severity groups and the Kaplan–Meier plot showed that the time to hospital discharge was different across severity groups (Log-rank test $p = 0.0008$) (**Supplementary Figure S4**). There was no difference in PICU and hospital mortality across severity groups (**Supplementary Figures S5, 6**). Death due to refractory hypoxemia occurred only in the severe group, whereas, deaths due to multiorgan dysfunction occurred in all groups (**Supplementary Table S4**).

The median (interquartile range) T_{res} demonstrated a stepwise increase from the mild to severe PARDS categories [mild 4 (3, 6), moderate 5 (4, 7) vs. severe 7.5 (7, 11.5) days; $p < 0.0001$] (**Table 2** and **Figure 2**). There was a decreased likelihood of PARDS resolution in moderate [HR 0.35 (95%CI 0.16, 0.76); $p = 0.008$] and severe [HR 0.17 (95%CI 0.08, 0.39); $p < 0.001$] PARDS compared to mild PARDS. However, there was no association between PIM 2 [HR 1.01 (95%CI 0.99, 1.02); $p = 0.253$] and PELOD [HR 1.02 (95%CI 0.99, 1.05); $p = 0.326$] scores and T_{res}. T_{res} was associated with an increased duration of MV [IRR 1.10 (95%CI 1.05, 1.15); $p < 0.001$], PICU length of stay [IRR 1.11 (95%CI 1.06, 1.16); $p < 0.001$], and hospital length of stay [IRR 1.06 (95%CI 1.01, 1.11); $p = 0.018$]. In addition, T_{res} was associated with decreased VFDs [IRR 0.93 (95%CI 0.87, 1.00); $p = 0.046$] and IFDs [IRR 0.84 (95%CI 0.76, 0.92); $p < 0.001$]. There was no association between T_{res} and the change in POPC [HR 1.05 (95%CI 0.83, 1.33); $p = 0.688$] and PCPC [HR 1.13 (95%CI 0.84, 1.52); $p = 0.424$] scores. The sensitivity analysis for the primary outcome (T_{res}) according to severity classification within 24 h of diagnosis showed a similar direction of effect.

TABLE 1 Characteristics of patients with pediatric acute respiratory distress syndrome.

Characteristics	Mild PARDS ($n = 33$)	Moderate PARDS ($n = 44$)	Severe PARDS ($n = 44$)	Total ($n = 121$)	p-Value
Age, years	4.5 (0.8, 12.6)	3.3 (0.6, 9.4)	1.5 (0.5, 5.1)	2.8 (0.6, 9.4)	0.227
Male gender	19 (57.6)	25 (56.8)	31 (70.5)	75 (62.0)	0.348
Weight, kg	13.9 (8.6, 32.3)	12.6 (6.7, 30.2)	9.7 (6.2, 14.3)	12 (6.9, 29.2)	0.183
BMI, kg/m^2	16.5 (13.6, 20.0)	16.8 (13.7, 19.1)	16.9 (15.2, 19.2)	16.7 (13.8, 19.3)	0.996
Comorbidity					0.328
Neuromuscular	6 (19.4)	14 (37.8)	9 (23.1)	29 (27.1)	
Respiratory	2 (6.5)	2 (5.4)	4 (10.3)	8 (7.5)	
Heme-oncology	2 (6.5)	3 (8.1)	5 (12.8)	10 (9.4)	
Genetic/congenital	5 (16.1)	10 (27.0)	6 (15.4)	21 (19.6)	
Neoplastic	2 (6.5)	1 (2.7)	4 (10.3)	7 (6.5)	
Others	3 (9.7)	4 (10.8)	3 (7.7)	10 (9.4)	
PIM 2	5.5 (2.8, 22.2)	6.2 (3.2, 15.8)	11.3 (4.4, 24.3)	7.1 (3.3, 20.9)	0.269
PELOD	9 (1, 11)	2 (1, 14)	10 (1.5, 20)	10 (1, 13.5)	0.489
Risk factor					
Pneumonia	21 (63.6)	26 (59.1)	31 (70.5)	78 (64.5)	0.422
Aspiration	3 (9.1)	7 (15.9)	4 (9.1)	14 (11.6)	
Sepsis	4 (12.1)	9 (20.5)	7 (15.9)	20 (16.5)	
Others	5 (15.2)	2 (4.6)	2 (4.6)	9 (7.4)	
Bacteremia	2 (6.1)	6 (13.6)	7 (15.9)	15 (12.4)	0.410
Respiratory pathogen					
Bacterial	10 (30.3)	14 (31.8)	21 (47.2)	45 (37.2)	0.192
Viral	15 (45.5)	22 (50.0)	24 (54.6)	61 (50.4)	0.730
Fungal	2 (6.1)	3 (6.8)	9 (20.5)	14 (11.6)	0.069
None	8 (24.2)	8 (18.2)	9 (20.5)	25 (20.7)	0.809
Air leak	1 (3.0)	2 (4.6)	5 (11.4)	8 (6.6)	0.273
Multiorgan dysfunction	18 (56.3)	27 (61.4)	36 (81.8)	81 (67.5)	0.035
POPC admission	1.5 (1, 4)	3 (1, 4)	2 (1, 4)	2 (1, 4)	0.297
POPC discharge	4 (1, 4)	4 (4, 4)	4 (4, 4)	4 (3, 4)	0.253
PCPC admission	1.5 (1, 4)	3 (2, 4)	2 (1, 4)	2 (1, 4)	0.166
PCPC discharge	3 (1, 4)	4 (3, 4)	4 (3,4)	4 (3,4)	0.046

Continuous and categorical variables summarized in medians (interquartile ranges) and counts (percentages), respectively.
BMI, body mass index; PIM 2, Pediatric Index of Mortality 2; PELOD, pediatric logistic organ dysfunction; PARDS, pediatric acute respiratory distress syndrome; POPC, pediatric overall performance category; PCPC, pediatric cerebral performance category.

Discussion

Our study described OI and OSI trends in patients with PARDS over the course of 28 days, as well as the time to resolution. OI and OSI provided a clear separation between mild, moderate, and severe groups in the first week of PARDS. We demonstrated pilot data that T_{res} lengthened with increasing severity of PARDS and that the likelihood of PARDS resolution was lower in moderate and severe PARDS compared with mild PARDS. In contrast, increased overall severity of illness (PIM2 and PELOD) was not associated with a lower likelihood of PARDS resolution. We went on to demonstrate that a longer T_{res} was associated with clinical outcomes such as duration of MV and length of stay.

We examine in detail the longitudinal course of PARDS with respect to the oxygenation trends. This is important because patients with mild/moderate PARDS may progress to severe PARDS after the first 24 h (20). Patients who progress to severe PARDS, even if this occurs days later, may benefit from therapies for severe PARDS and may have similar poorer intermediate/long-term outcomes (e.g., mortality, MV duration, or long-term respiratory support) as severe PARDS. There are data in adult ARDS that approximately 20% of patients progress in severity and this may be associated with poorer prognosis (10). Future studies are needed to compare the outcomes of patients who progress in severity vs. those who remain in their severity groups or resolve, in order to confirm whether these patients actually perform worse. The

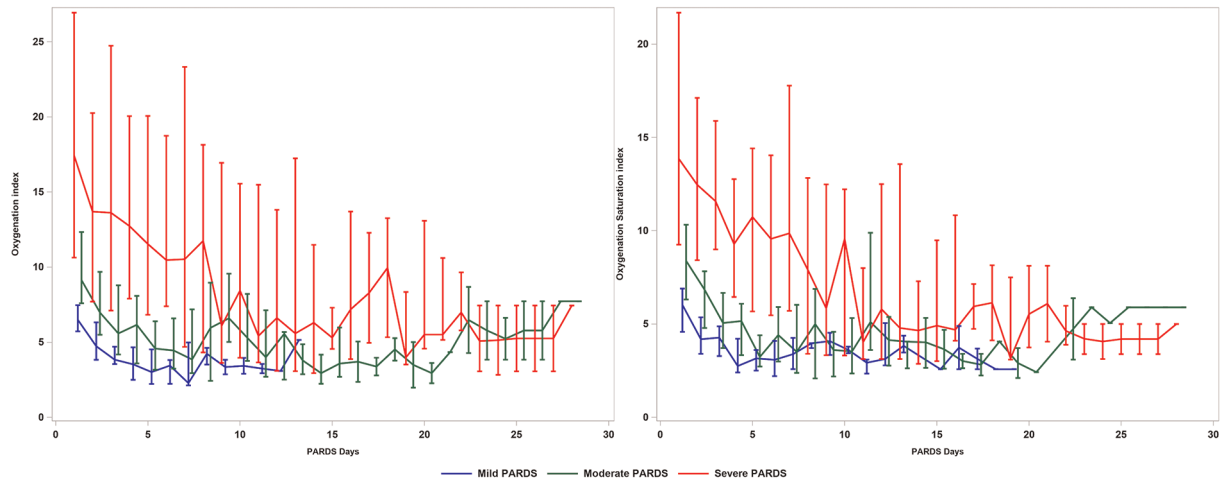

FIGURE 1
Oxygenation index and oxygenation saturation index in patients with PARDS across 28 days. PARDS, pediatric acute respiratory distress syndrome.

TABLE 2 Short and intermediate term outcomes in patients with pediatric acute respiratory distress syndrome.

Outcomes	Mild PARDS ($n = 33$)	Moderate PARDS ($n = 44$)	Severe PARDS ($n = 44$)	Total ($n = 121$)	*p*-Value
Time to resolution of PARDS, days	4 (3, 6)	5 (4, 7)	7.5 (7, 11.5)	6 (4, 8)	<0.001
Ventilator duration, days	5 (3, 10)	7 (4, 13)	11.5 (8, 19.5)	8 (4, 13)	0.001
28-day VFD	21.5 (0, 24)	21 (12, 23.5)	13 (0, 18)	17 (0, 22)	0.004
PICU mortality	6 (18.2)	4 (9.1)	8 (18.2)	18 (14.9)	0.401
PICU duration, days	5.5 (3.5, 10.5)	11 (6, 16)	15 (9.5, 30)	11 (6, 19)	<0.001
28-day IFD	21 (0, 24)	16 (0, 21)	2.5 (0, 13.5)	14 (0, 21)	<0.001
Hospital duration, days	16 (6, 24)	27 (17, 60)	31 (17.5, 69)	23 (12, 56)	0.007
Hospital mortality	7 (21.2)	4 (9.1)	10 (22.7)	21 (17.4)	0.190

Continuous and categorical variables summarized in medians (interquartile ranges) and counts (percentages), respectively.
IFD, PICU free days; PARDS, pediatric acute respiratory distress syndrome; PICU, pediatric intensive care unit; VFD, ventilator free days.

discovery that oxygenation measures were useful in disease stratification within the first 7 days of PARDS suggests that this critical period should be minimally included in future PARDS studies. It is unclear why there was such poor differentiation in OI/ OSI between the severity groups after 7 days, but it could be due to the smaller number of patients who remained intubated and had data for OI/OSI calculation.

There is currently no physiologic marker that indicates recovery from lung injury. Here, the oxygenation defect that characterizes PARDS, which was demonstrated to improve with time, could be used as a respiratory-specific outcome corresponding to the physiologic recovery of lung injury. We demonstrated that T_{res} was specifically associated with the severity of PARDS but not with the general severity of illness (PIM2 and PELOD scores) and how it related to other clinical outcomes. We highlight the bias by using conventional outcomes (**Supplementary Figure S7**). Conventional outcomes are confounded by patient factors (e.g., pneumonia is a common terminal event in end-stage malignancies and will inevitably be associated with poor survival outcomes) and therapeutic factors (e.g., use of prolonged neuromuscular blockade and systemic corticosteroids for any indication may result in adverse functional outcomes independent of PARDS course), many of which are not respiratory in nature (3). Indeed, mortality due to refractory hypoxemia accounts for only approximately 20% of deaths in pediatric and adult cohorts of ARDS (i.e., 80% of patients with ARDS die from other causes) (4, 5, 21, 22)—this would also confound other outcome measures where mortality was included as part of that composite outcome (e.g., VFD, IFD and PARDS-free days). Whereas, the duration of MV may be confounded by

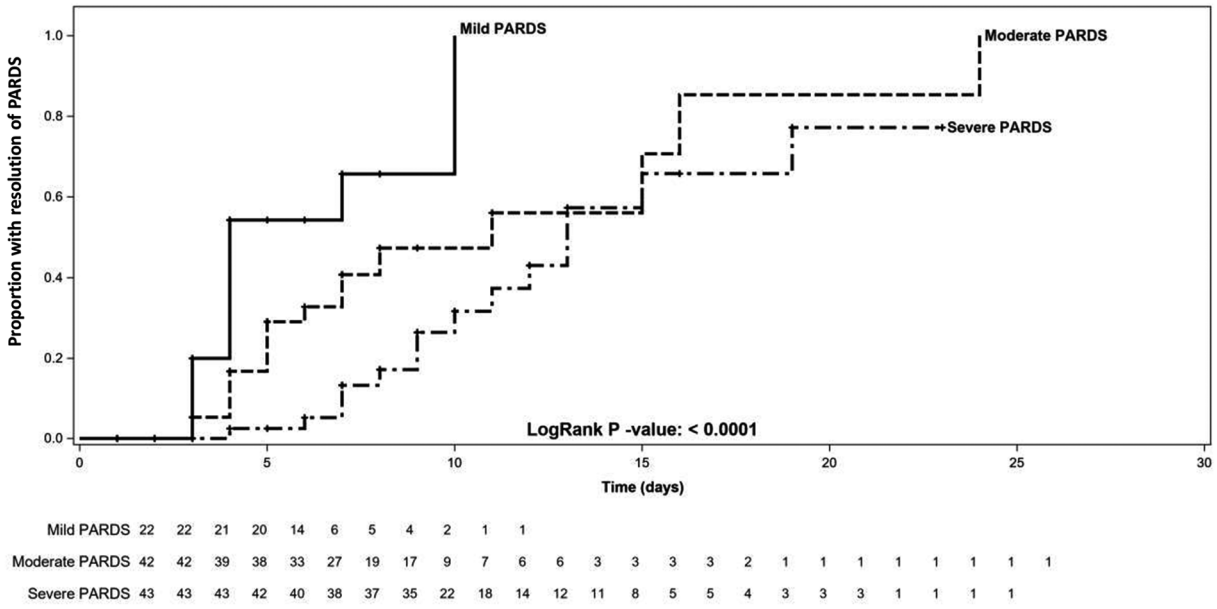

FIGURE 2
Kaplan–Meier curve of time to resolution of pediatric acute respiratory distress syndrome in patients with mild, moderate, and severe disease. PARDS, pediatric acute respiratory distress syndrome.

non-pulmonary disease (e.g., a patient with PARDS who has underlying neurological comorbidity may remain on ventilation long after resolution of lung disease). It is evident from **Supplementary Figure S7** that many patients remain intubated/admitted to the PICU for days/weeks after the resolution of PARDS, presumably due to factors other than acute lung injury. T_{res}, therefore, may be useful in addition to conventional patient-important outcomes when studying PARDS specific therapies.

There are limitations to this study. Despite routine and complete screening of all PICU admissions, our cohort had a small sample size. The single-center nature of this study also limits its generalizability. A future multicenter study will address both these limitations. Because this study is only proof of concept, a separate study with larger and independent cohort of PARDS patients is needed to validate T_{res} as a useful clinical and research outcome measure. From our data, a post hoc sample size calculation to detect a difference in T_{res} of 3.5 days between severe and non-severe PARDS will require a sample size of 44 and 77, respectively (based on the following parameters: recruitment period of 36 months, follow-up for 28 days, allocation ratio severe to non-severe 1:1.5, alpha 5%, power 80%). Another limitation was that we did not evaluate the relationship between T_{res} and longer-term outcomes in PARDS, e.g., duration of non-invasive respiratory support or follow-up lung function—this should be evaluated in future studies.

Conclusion

The oxygenation defect associated with PARDS was demonstrated to subside towards the end of the first week of illness, with severe disease taking longer to resolve than mild or moderate disease. We propose T_{res} as a surrogate outcome measure for PARDS (specifically indicating resolution of the oxygenation defect occurring in PARDS), in addition to conventional outcomes like mortality and duration of MV which are less specific for PARDS. External validation of these findings in a larger and independent cohort is necessary to evaluate T_{res} as a relevant clinical outcome measure.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the centralized Singhealth institutional review board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JJMW, RS, and JHL contributed substantially to the conception and design of the study. JJMW, HLT, SWL, YJM, and AA were responsible for the execution of the study and acquisition of data. JJMW, RS, and PK performed the analysis of data. JJMW drafted the manuscript. JJMW, SWL, HLT, YHM, and JHL contributed substantially to the interpretation of data and revising the manuscript critically for important intellectual content. All authors approved the version submitted for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.993175/full#supplementary-material.

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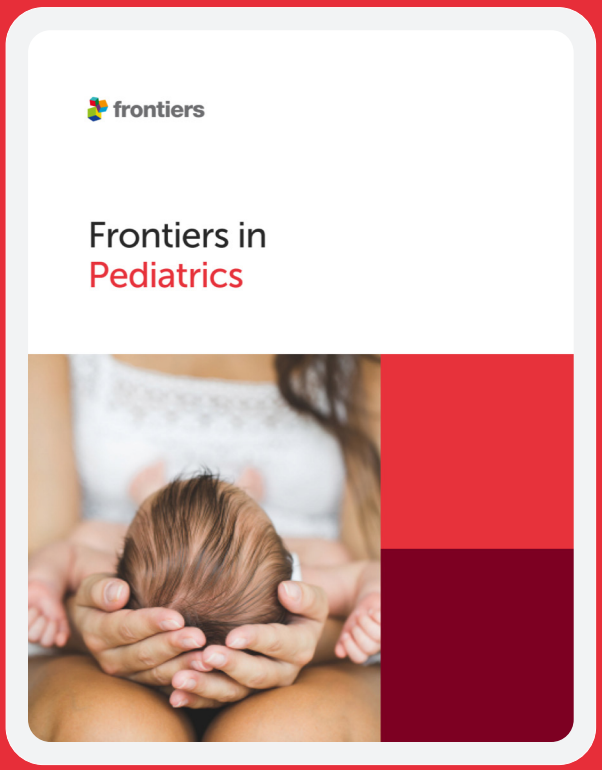

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