INSIGHTS IN PEDIATRIC CRITICAL CARE: 2021

EDITED BY: Niranjan Kissoon and Jhuma Sankar
PUBLISHED IN: Frontiers in Pediatrics

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-83250-770-4
DOI 10.3389/978-2-83250-770-4

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INSIGHTS IN PEDIATRIC CRITICAL CARE: 2021

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Citation: Kissoon, N., Sankar, J., eds. (2022). Insights in Pediatric Critical Care: 2021. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-770-4

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frontiers | Frontiers in Pediatrics

TYPE Editorial
PUBLISHED 31 October 2022
DOI 10.3389/fped.2022.1057991

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

RECEIVED 30 September 2022
ACCEPTED 04 October 2022
PUBLISHED 31 October 2022

CITATION
Sankar J and Kissoon N (2022) Editorial: Insights and advances in pediatric critical care. Front. Pediatr. 10:1057991. doi: 10.3389/fped.2022.1057991

Editorial: Insights and advances in pediatric critical care

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KEYWORDS

insights and advancements, insights, pediatric critical care, pediatric intensive care, artificial intelligence, fluids, cardiac critical care

Editorial on the Research Topic
Insights and advances in pediatric critical care

By Sankar J, Kissoon N. (2022) Front. Pediatr. 10: 1057991. doi: 10.3389/fped.2022.1057991

Future progress in paediatric critical care (PCC) will be accelerated by harnessing the collective wisdom of our colleagues globally. It is for this reason that we invited participation in this collection of Frontiers on Insights in Pediatric Critical Care. In this collection we have put together a unique collection of contemporary research work encompassing varied critical care conditions and what the future holds for these conditions.

The year 2020 saw the dawn of another era in medicine with the arrival of SARS CoV-2. Sooman et al. in eight Swiss PICUs during the pandemic which had eight Pediatric Multisystem Inflammatory Syndrome- Temporally associated with SARS CoV-2 (PIMS-TS) patients observed higher workload, different organisational issues due to temporary regulations by the government. While some of the PICUs admitted PIMS-TS patients, others did not and this resulted in poor bed occupancy rates and skewed utilisation of resources. We learn from their experience that differences between PICUs within a country are substantial and distribution of resources should be addressed.

The disease profile in PCC has changed over time with fewer but severe infections, caring for children with complex surgical procedures, acute multisystem involvement, chronic co-morbidities and more severe conditions necessitating greater complexity of services (1, 2). As a result, we have graduated from early "rudimentary" support to complex therapies such as extracorporeal therapies in lung and heart problems, use of targeted therapies like mono clonal antibodies and use of biomarkers for individualised approach.

As survival rates improved, long term morbidities increased and survival of those with chronic illnesses improved. Pediatric palliative care (PC) is slowly emerging as a major component of supportive therapy in pediatric critical care and is recommended in life threatening illness and not only life limiting illness. In the article by

Buang et al., the authors highlight the importance and principles of palliative care and provide the pyramid model framework of integrating PC into ICU.

While optimising ventilation takes care of the primary lung condition, optimising fluid, electrolyte and nutritional support and preventing infections are key to successful ventilation and survival. Appropriate fluid management in mechanically ventilated critically ill children remains an important challenge and in this issue Arrahmani and team with an aim to understand the current fluid therapy practices in mechanically ventilated children survey 107 intensivists with more than 10 years experience. About 75% administered restrictive fluids (80%), greater than 5% fluid overload% prompted diuretic administration and only about 50% of participants used lung ultrasound to identify pulmonary edema. Further studies addressing restrictive fluid strategies are the need of the hour.

Resuscitation in septic shock in 1991 revealed the need for generous fluid resuscitation to improve outcomes (3). Boluses of 20 mls/kg repeated several times became accepted practice and was the basis of the Early Goal Directed Therapy (4, 5), and septic shock guidelines including that for paediatrics (6). However, PCC is practiced in environments endowed with high technology and at the other extreme austere settings. The finding that bolus fluid can be harmful in resource poor settings (FEAST) (7) has led to investigations of less aggressive fluid resuscitation (SQUEEZE) (8). Fluid bolus administration requires careful monitoring for features of fluid overload and use of point-of-care ultrasonography (POCUS) to aid in clinical decision making in determining fluid responsiveness and cardiac output. Ultrasonography has evolved as a useful tool in the PICU and Emergency Department (ED). Burton et al. in the present series describe the current state, challenges and future direction of POCUS in the PICU and highlight the importance of training, standardisation of usage and competency while using POCUS.

Determining fluid responsiveness using only clinical parameters has been found to be unreliable in the ED. Awadhare P et al. in 40 patients with shock evaluated the utility of a relatively new non-invasive monitoring device (ICON monitor) in a before and after bolus study. A 15% increase in stroke volume after a bolus had an excellent AUC. The monitor looks promising due to its non-invasive nature and in providing useful information to the clinical in the ED.

Despite advances in the management of pediatric acute respiratory distress syndrome (PARDS) and shock, once refractory to conventional treatment these patients have very high risk of death. Extracorporeal therapies have shown promise in such cases with increased survival rates in refractory shock and PARDS (9). Survival with ECMO in neonates has improved over the decades. However, many of these survivors develop chronic lung disease. In a retrospective series of 91% neonates by Ortiz et al. from a neonatal ECMO centre, the authors report 76% of survivors developing CLD and factors such as prolonged ECMO, early initiation of ECMO (<24 h of life) and Congenital diaphragmatic hernia as risk factors for the same.

Pediatric cardiac critical care one of the most challenging disciplines in medicine has come a long way and in the article by Pollack et al., the authors describe seven key elements including but not limited to education, personalised medicine, newer surgical techniques, nanomedicine, machine learning and quality and safety that will expand the horizon of Pediatric cardiac critical care.

It has been periodically observed that it takes an average of 17 years for adoption of research into practice and this is known as delayed adoption (2). Significant advances have been made in our understanding of the pathophysiology, disease markers and targeted therapies in various critical care conditions and it is continuously evolving. There have been key advances in technology such as use of bed side ultrasound, intra-arterial and intracranial pressure monitoring devices, continuous oximetry, electronic health records and big data. Use of artificial intelligence which is common in surgical conditions is increasingly being used by emergency and critical care specialities and has been reported to be useful in rapid recognition, initiating treatment protocols, continuous monitoring and for prognostication. In this series we have three interesting studies highlighting the use of machine learning, artificial intelligence and big data.

In the first of the three articles published, Kim YT and team attempted to use automated densitometric CT parameters augmented by a machine learning algorithm in 58 children to prognosticate traumatic brain injury in children. About 1/5th of the study population had unfavourable outcome and the prognostic value of brain CT was augmented by the machine learning algorithm. This study provides useful information on use of this algorithm for immediate outcomes during hospitalisation. However, this requires further validation in large scale datasets and whether it has value in predicting long term outcomes also need to be seen.

Abbas et al. similarly compared the utility of a commercially available risk analytic tool T3 (IDO2) in the cardiac intensive care unit with mixed venous saturation (SvO_2). The AUC for predicting SvO_2 of <40% was excellent (0.87). Testing the utility of the tool in taking informed clinical decisions and in diverse patient settings would test its true utility and ease of use.

Ehrmann et al. highlight the importance of understanding big data and its interpretation especially by the trainees. While we are moving towards integration of complicated data and developing AI algorithms that would make decision making quick and accurate, the first step towards the clinical utility of such complicated data sets is empowering the

trainees with basic understanding of how to use and interpret this data.

Concerted efforts to advance knowledge as well as addressing inequities and resource allocation is needed globally for critically ill children. The insights from our global community is a contribution to this endeavour (10).

Author contributions

NK and JS conceptualised the topic collection and edited the article submission and selection process. JS and NK wrote the commentary and approved the final version. All authors contributed to the article and approved the submitted version.

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

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frontiers in Pediatrics

ORIGINAL RESEARCH
published: 02 November 2021
doi: 10.3389/fped.2021.750272

Intracranial Densitometry-Augmented Machine Learning Enhances the Prognostic Value of Brain CT in Pediatric Patients With Traumatic Brain Injury: A Retrospective Pilot Study

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OPEN ACCESS

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: 30 July 2021
Accepted: 07 October 2021
Published: 02 November 2021

Citation:
Kim Y-T, Kim H, Lee C-H, Yoon BC, Kim JB, Choi YH, Cho W-S, Oh B-M and Kim D-J (2021) Intracranial Densitometry-Augmented Machine Learning Enhances the Prognostic Value of Brain CT in Pediatric Patients With Traumatic Brain Injury: A Retrospective Pilot Study. Front. Pediatr. 9:750272. doi: 10.3389/fped.2021.750272

Background: The inter- and intrarater variability of conventional computed tomography (CT) classification systems for evaluating the extent of ischemic-edematous insult following traumatic brain injury (TBI) may hinder the robustness of TBI prognostic models.

Objective: This study aimed to employ fully automated quantitative densitometric CT parameters and a cutting-edge machine learning algorithm to construct a robust prognostic model for pediatric TBI.

Methods: Fifty-eight pediatric patients with TBI who underwent brain CT were retrospectively analyzed. Intracranial densitometric information was derived from the supratentorial region as a distribution representing the proportion of Hounsfield units. Furthermore, a machine learning-based prognostic model based on gradient boosting (i.e., CatBoost) was constructed with leave-one-out cross-validation. At discharge, the outcome was assessed dichotomously with the Glasgow Outcome Scale (favorability: 1–3 vs. 4–5). In-hospital mortality, length of stay (>1 week), and need for surgery were further evaluated as alternative TBI outcome measures.

Results: Densitometric parameters indicating reduced brain density due to subtle global ischemic changes were significantly different among the TBI outcome groups, except for need for surgery. The skewed intracranial densitometry of the unfavorable outcome became more distinguishable in the follow-up CT within 48 h. The prognostic model augmented by intracranial densitometric information achieved adequate AUCs for various outcome measures [favorability = 0.83 (95% CI: 0.72–0.94), in-hospital mortality = 0.91 (95% CI: 0.82–1.00), length of stay = 0.83 (95% CI: 0.72–0.94), and need for

surgery = 0.71 (95% CI: 0.56–0.86)], and this model showed enhanced performance compared to the conventional CRASH-CT model.

Conclusion: Densitometric parameters indicative of global ischemic changes during the acute phase of TBI are predictive of a worse outcome in pediatric patients. The robustness and predictive capacity of conventional TBI prognostic models might be significantly enhanced by incorporating densitometric parameters and machine learning techniques.

Keywords: pediatric traumatic brain injury, computed tomography, densitometric analysis, prognostic modeling, machine learning

INTRODUCTION

Pediatric traumatic brain injury (TBI) accounts for over 500,000 emergency department visits in the United States each year (1). The anatomical and physiological properties (e.g., thinner cranium, less myelinated tissue) of the pediatric brain can result in more rapid and severe development of secondary ischemic-edematous insults after head injury (2–4), and hence worse outcomes, than in adults (5). Given that cerebral edema is the fundamental pathophysiological mechanism underlying TBI, assessing the extent of cerebral edema may be crucial for evaluating the risk of intracranial hypertension and predicting outcomes (6).

Magnetic resonance imaging (MRI) is of significant diagnostic value for identifying pathological diffuse brain swelling; however, it requires children to be stationary and often sedated during a long acquisition time. Therefore, brain computed tomography (CT) remains the gold standard imaging modality during the acute phase of TBI for rapidly evaluating TBI and developing an appropriate intervention strategy (7, 8). The degree of brain swelling is generally evaluated by CT classification systems [i.e., Marshall (9) and Rotterdam score (10)] based on the status of the mesencephalic cisterns or midline shift; this classification is easily applicable and is considered useful for predicting outcomes after TBI (9–12). The efficacy of CT classification systems makes them important prognostic factors in well-known TBI prognostic models (i.e., Corticosteroid Randomization after Significant Head Injury [CRASH] or International Mission for Prognosis and Analysis of Clinical Trials [IMPACT] models) (13, 14). However, the classification system relies on manual visual inspection of CT images by clinicians and hence has been criticized for its intrinsic inter- and intrarater variabilities (10, 15).

It is well-known that there is a linear relationship between edema-induced water accumulation and Hounsfield unit (HU) values (16); a 1% increase in tissue water content causes a 2-3 HU reduction in attenuation on CT images (17). This dose-responsive relationship could be applied to quantitatively evaluate edematous changes by using HU distribution via densitometric CT analysis in patients with TBI (18). Accordingly, densitometric analysis could be an appropriate tool for evaluating the majority of early-stage pediatric TBIs that show no visually identifiable abnormalities on CT images. Moreover, by performing whole-cerebrum densitometric analysis in a fully automated manner, the degree of secondary edematous accumulation following TBI could be objectively measured without inter- or intrarater variability (18). These advantages of densitometric CT analysis could be exploited to construct a more robust prognostic model for TBI.

The past few years have seen a surge in attempts to use machine learning to construct prognostic models. Traditional logistic regression may have low robustness for explaining multivariate non-linear relationships (19), whereas machine learning can better apprehend non-linear relationships and interactions through more flexible modeling (20). Gradient-boosted decision trees (GBDTs), a widely used machine learning algorithm, produce an interpretable prognostic model that is an ensemble of decision trees, which are in high demand in the medical domain (21). Among GBDT variants, CatBoost has recently been introduced and has shown notable robustness and highly accurate generalizability (22). This study hypothesized that combining CT densitometry and a machine learning technique (i.e., CatBoost) would enhance the prognostic value of brain CT with a more robust prognostic model for pediatric TBI. The objectives of this study are 2-fold: (1) to investigate the association between intracranial densitometry based on brain CT and various outcomes in pediatric TBI patients and (2) to evaluate the prognostic value of brain CT by constructing a densitometry-augmented TBI prognostic model based on a robust machine learning method.

Abbreviations: ANN, artificial neural network; cEs, cerebral edema score; CRASH, corticosteroid randomization after significant head injury; CT, computed tomography; dGx, proportions of normal-density gray matter; dWx, proportions of normal-density white matter; GBDT, gradient-boosted decision tree; GM, gray matter; HU, Hounsfield unit; IMPACT, international mission for prognosis and analysis of clinical trials; LOOCV, leave-one-out cross-validation; MRI, magnetic resonance imaging; PCA, principal component analysis; SHAP, Shapley additional explanations; SVM, support vector machine; TBI, traumatic brain injury; WM, white matter.

MATERIALS AND METHODS

Study Design and Setting

This retrospective pilot study investigated the relationship between intracranial densitometry based on brain CT and the outcome of pediatric patients with TBI. Furthermore, TBI prognostic models were constructed using the CatBoost model (22), a cutting-edge gradient boosting algorithm optimized in

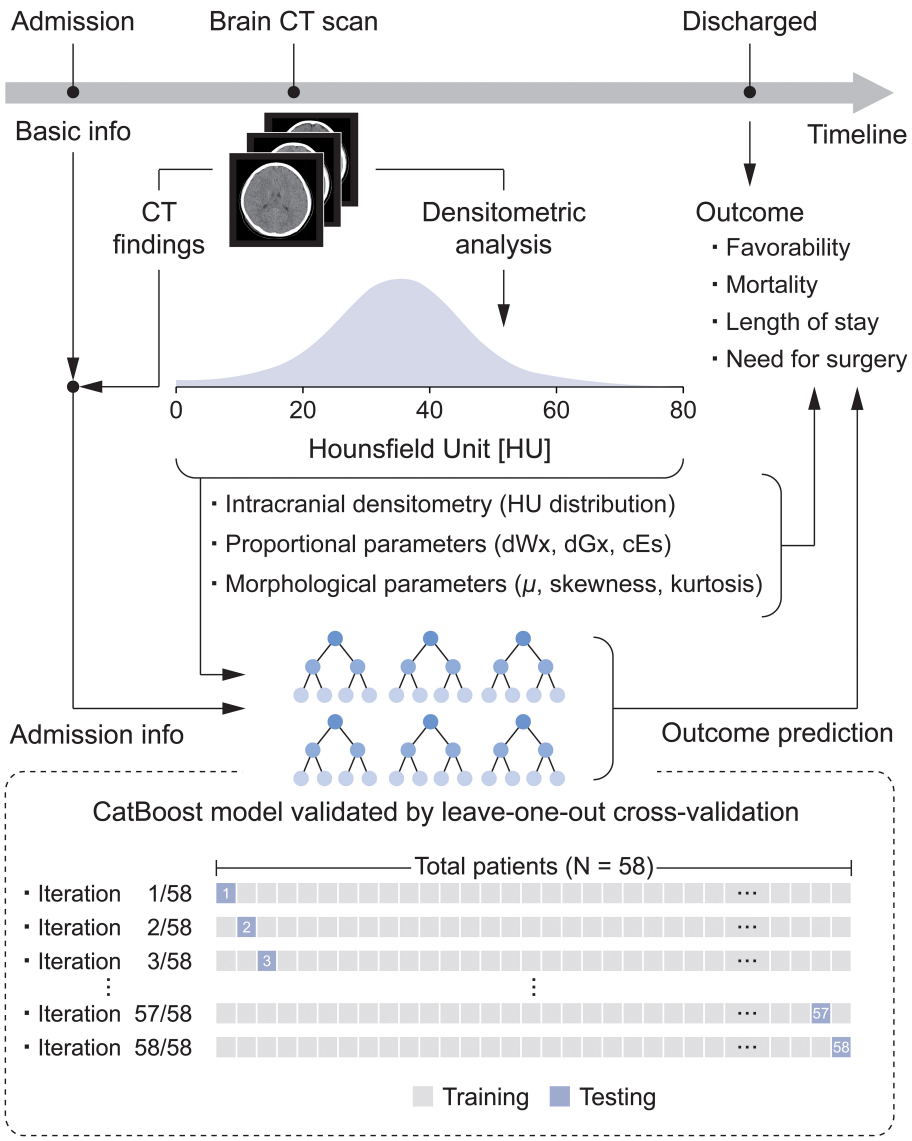

FIGURE 1 | Flow diagram for the development of the densitometry-augmented prognostic model based on brain CT.

a small dataset and robust to overfitting, based on intracranial densitometric information. The prognostic models were evaluated through leave-one-out cross-validation (LOOCV), which is appropriate for small datasets. An overview of this study is shown in **Figure 1**.

The setting of this study is at a single trauma center (i.e., the Trauma Center of Seoul National University Hospital). Basic clinical information of TBI patients, such as brain CT images and Glasgow Coma Scale (GCS) scores, was obtained during the same period. Anonymized clinical information obtained on admission to the emergency room, radiology reports, and brain CT images were retrospectively reviewed and collected from the institutional database of Seoul National University Hospital from 2013 to 2017. This study was approved by the Ethics Committee of Seoul National University Hospital (IRB H-1706-144-862). The requirement for informed consent was waived due to the retrospective nature of this study.

Study Population

The subjects were enrolled according to the following inclusion criteria: (a) direct admission for TBI through the emergency medicine department (not transferred from another hospital); (b) age $\leq$ 19 years; (c) underwent non-enhanced brain CT scan; and (d) eligible CT acquisition conditions (tube voltage $=$ 120 kVp, tube current $\geq$ 150 mA) for analysis of HU values (23). Additionally, the following exclusion criteria were applied: (a) significant image artifacts (e.g., beam-hardening effects) in the CT images and (b) outcome unrelated to traumatic head injury (e.g., acute respiratory failure, myocardial contusions). Furthermore, patients with significant infratentorial hemorrhage

were excluded because even a small infratentorial lesion may be fatal, which would significantly affect the outcomes and skew the data (24).

These criteria were entered into the institutional clinical data warehouse of Seoul National University Hospital, SUPREME®. Consequently, a total of 58 pediatric TBI patients who underwent head CT examinations were retrospectively included in this pilot study. Enrolled subjects were directly transferred to the trauma center. The Glasgow Outcome Scale (GOS) score was recorded at the time of discharge. Additionally, alternative outcome measures such as in-hospital mortality, length of stay (LOS) and need for surgery were used as reference standards.

Densitometric Analysis of Brain CT

Densitometric CT analysis utilizes HU values obtained by brain CT to derive intracranial densitometric data as a distribution representing the material density. It can provide a quantitative evaluation of brain density alterations caused by edema-induced water accumulation without inter- or intrarater variability. This study utilized the methods proposed by Kim et al. (18), which allow the quantitative derivation of intracranial densitometric data of the whole cerebrum. To implement the method, in-house software was written in Java (Oracle, Inc., Redwood Shores, California, USA), providing a fully automatic method for the densitometric analysis of head CT images. To analyze only the major intracranial components (e.g., cerebrospinal fluid, parenchyma, blood), a threshold limit of 0–79 HU was applied (18). The intracranial densitometry was derived from Equation 1:

$$p(\lambda) = \frac{\sum_{k=1}^{n} \lambda_k}{\sum_{k=1}^{n} \sum_{\lambda=0}^{79} \lambda_k} \quad (1)$$

where λ_k is the number of pixels having an HU value of λ from the k^{th} CT image in a series of CT scans showing the supratentorial brain region, the denominator of the equation is the entire number of pixels having an HU value of 0 to 79 in the whole cerebrum, and $p(\lambda)$ is the proportion of pixels having an HU value of λ in the whole cerebrum. The graph of the intracranial densitometric data was derived by plotting the $p(\lambda)$ in the range of 0–79 HU.

In this study, densitometric analysis was based on initial brain CT scans at admission and follow-up CT scans acquired within 48 h of initial CT scans. Brain CT scans were obtained with a Brilliance 64 scanner (Philips Medical Systems, Eindhoven, Netherlands). The CT acquisition parameters were as follows: tube voltage = 120 kVp, tube current $\geq$ 150 mA, and image matrix = 512 by 512, with a 5-mm slice thickness. Follow-up CT scans were also performed with the same acquisition settings.

Quantitative Evaluation of Intracranial Densitometry

There are two paradigms to quantitatively evaluate intracranial densitometry: one for evaluating the proportion of a specific HU region and the other for evaluating the morphology of the HU distribution.

In evaluating the proportion of a specific HU region, three parameters, dWx, dGx, and cEs, proposed in previous studies were used in the study (18, 25). Excessive water accumulation caused by cerebral edema or ischemia lowers the material density of the brain parenchyma and consequently affects both white matter (WM) and gray matter (GM). In addition, the presence of space-occupied lesions with high density (e.g., subdural, epidural, and intracerebral hemorrhage) also decreased the relative proportion of normal density parenchyma in the cranium. Accordingly, the proportions of normal-density WM (dWx) and GM (dGx) were quantitatively assessed. dWx and dGx were defined as the proportions of pixels of 26–30 and 31–35 HU, respectively, among pixels depicting the entire cerebrum (25). In addition, Kim et al. suggested the use of the cerebral edema score (cEs), ranging from 17 to 24 HU, as an indicator of cerebral edema severity to compensate for the CT classification system (18).

The presence of a hypodense lesion (e.g., ischemic-edematous lesion) or hyperdense lesions (e.g., intracranial hemorrhage) in the intracranial area can contribute to the left- and right-sided dominance of the densitometry, respectively. Such pathological brain changes can be identified by assessing the intracranial densitometric morphology, which was evaluated as the proportional HU distribution by calculating μ, skewness and kurtosis, where μ is the mean HU value of the distribution, and skewness and kurtosis are the measure of the asymmetry and the tail of the distribution, respectively.

Intracranial densitometry reveals pathological changes in the material density of the whole cerebrum. Thus, it may be suggestive of various TBI pathologies (e.g., cerebral ischemia, edema, intracranial hemorrhage). **Figure 2** shows some intuitive examples of intracranial densitometry affected by various TBI pathologies. The color bar at the bottom shows the HU area on densitometry, where cerebral ischemia [3–27 HU] (26), edema [17–24 HU] (18), and intracranial hemorrhage [40 HU∼] (27) are primarily affected. Compared with the patient without significant visible pathology (**Figure 2A**), the patient with massive brain edema following severe ischemic insults (**Figure 2B**) showed a leftward shift of the densitometry center with an increase in both skewness and kurtosis due to excessive water accumulation. On the other hand, in the patient with a large degree of acute subdural hemorrhage (**Figure 2C**), the center of the densitometry shifted to the right due to the space-occupied lesion. In addition, both **Figures 2B,C** show that the proportion of parenchyma within the normal density range was also affected by the occurrence of intracranial pathology.

Lesions with partially overlapping HU ranges (e.g., subacute subdural hemorrhage) may skew the interpretation of the densitometric parameters, but only patients during the acute stage were involved in this study.

Prognostic Model Construction

Prognostic models were constructed based on the four outcome measures (i.e., favorability, mortality, LOS and need for surgery) with CatBoost (22), which is a state-of-the-art gradient-boosted decision tree. CatBoost mitigates the overfitting problem and shows robustness and generalizability. In addition, CatBoost has various advantages of (1) having a swift training speed through parallel processing, (2) being appropriate for small sample sizes

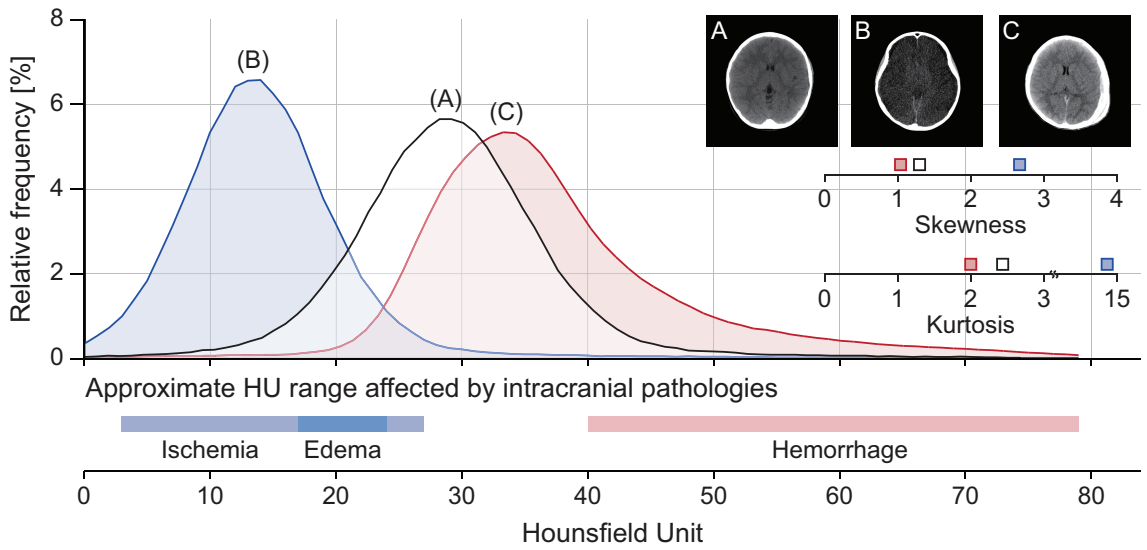

FIGURE 2 | Representative cases of intracranial densitometry affected by various TBI pathologies. **(A)** A 7-year-old male patient with no visible pathology, **(B)** A 10-year-old female patient with massive brain edema, **(C)** A 7-year-old male patient with acute subdural hemorrhage. The color bar at the bottom shows the HU range on densitometry, which mainly affects intracranial pathologies.

and unbalanced data, and (3) exhibiting higher accuracy than other gradient boosting algorithms. The IMPACT model was excluded from this study because the IMPACT model does not consider patients under the age of 14 years (14).

In this study, a total of three types of prognostic models were constructed. (1) CatBoost-based CRASH-CT (i.e., CRASH-$CT_{CatBoost}$) is the model based on admission characteristics (i.e., age, GCS, pupil reaction, and presence of extracranial injury) and initial CT findings (i.e., presence of petechial hemorrhage, obliteration of the third ventricle or basal cisterns, subarachnoid hemorrhage, midline shift, and non-evacuated hematoma). These are the same input of the conventional CRASH-CT model (13). (2) The densitometry-augmented model (i.e., D/CRASH-$CT_{CatBoost}$) was constructed with the intracranial densitometric information (i.e., dWx, dGx, cEs, μ, skewness, kurtosis, and HU distribution) and the CRASH-CT input. (3) The reference model was the conventional CRASH-CT model (i.e., CRASH-CT_{LR}) established by logistic regression.

Prognostic models for outcome favorability were derived from both initial and follow-up CT to assess the changes in prognostic value during the acute phase of TBI. Undoubtedly, the model based on the follow-up CT data uses input variables derived from the follow-up CT. On the other hand, prognostic models for mortality, LOS, and need for surgery were all established only based on initial CT data at admission.

The prognostic value of CatBoost was optimized by a grid search with the variation of three hyperparameters: Iteration [50, 100, 200, 300, 400], depth [4, 5, 6, 7, 8, 9, 10], and loss function [log loss, cross-entropy]. Likewise, the logistic regression model was optimized with iterations [50, 100, 200, 300, 400] and C [0.001, 0.01, 0.1, 1, 10, 100] as hyperparameters.

Principal component analysis (PCA) was used to reduce the dimensions of the input variables that still contain most of the information to alleviate the dimensionality and overfitting problems that can occur in machine learning procedures. Accordingly, the high dimensions of admission characteristics, initial CT findings, and HU distribution were reduced by PCA.

SHAPs (Shapley Additional exPlanations) of the tree ensemble model were derived to assess the importance of the model input variables. Based on this, it is possible to conveniently examine the importance of individual input variables used in the CatBoost-based prognostic model and to determine how the input variables contribute to the prediction of the outcomes.

The predictive performance of all prognostic models was assessed by LOOCV (**Figure 1**), which results in unbiased and reliable estimates of model performance; iterative validations were performed 58 times by separating training ($N = 57$) and testing subjects ($N = 1$). These machine learning models were developed by scikit-learn 0.24.1 and CatBoost library 0.25.1 in the Python 3.7 environment.

Statistical Analysis

The calculation of the sample size was performed by Viechtbauer's formula developed for the pilot study (28); the calculated sample size was 45, with a confidence level of 0.90 and a probability of 0.05. Considering that the dropout rate was 30%, 58 subjects were enrolled in this study. Non-parametric statistical methods were employed due to the sample size. The Mann-Whitney U-test was applied to compare continuous data between outcome groups. The discrimination of the prognostic models was assessed by receiver operating characteristic (ROC) curve analysis. The optimal cutoff values for discriminating outcomes were calculated using the maximal Youden's J statistic (sensitivity + specificity – 1) (29) in the ROC curve. Hanley's test

(30) was performed to compare the area under the ROC curve (AUC). In this study, four reference standards against AUC of all prognostic models were used: (1) dichotomous outcome measured at discharge [i.e., GOS score 1–3 (positive) vs. 4–5 (negative)], (2) in-hospital mortality [i.e., deceased (positive) vs. survived (negative)], (3) LOS in hospital [i.e., >1 week (positive) vs. ≤ 1 week (negative)], and (4) need for surgical intervention [i.e., underwent TBI-related surgery during hospitalization (positive) vs. no need for surgical procedure (negative)]. In this study, there was no need to reassign the LOS outcome of the deceased patients because no patients died in the group with LOS of <1 week (31). The sensitivity, specificity, positive predictive value, and negative predictive value with 95% confidence interval of each prognostic model were determined at the optimal cutoff. The analyses were considered statistically significant at two-sided $p < 0.05$. Statistical analyses were conducted using commercial software (SPSS 24, IBM Corp., Chicago, Illinois, USA).

RESULTS

Demographics

Fifty-eight pediatric TBI patients were included in this study. Of the 58 patients, 46 (79.3%) were assigned to the favorable outcome group, and 12 (20.7%) were assigned to the unfavorable outcome group. The detailed demographics are listed in **Table 1**.

TABLE 1 | Baseline characteristics.

	Total ($N = 58$)	Favorable outcome group ($N = 46$)	Unfavorable outcome group ($N = 12$)
Age, years			
Median, interquartile range	6 (1.75–13)	7 (2–14.25)	5 (1–9.25)
Sex, no. (%)			
Male	32 (55.2)	27 (58.7)	5 (41.7)
Female	26 (44.8)	19 (41.3)	7 (58.3)
Cause of injury, no. (%)			
Motor vehicle accident	17 (29.3)	15 (32.6)	2 (16.7)
Fall	24 (41.4)	22 (47.8)	2 (16.7)
Blunt trauma	17 (29.3)	9 (19.6)	8 (66.7)
Glasgow Coma Scale on admission, no. (%)			
3–8	9 (15.5)	5 (10.9)	4 (33.3)
9–12	3 (5.2)	2 (4.3)	1 (8.3)
13–15	46 (79.3)	39 (84.8)	7 (58.3)
Pupil reactivity, no. (%)			
Both	53 (91.4)	42 (91.3)	11 (91.7)
One	3 (5.2)	3 (6.5)	0 (0)
None	2 (3.4)	1 (2.2)	1 (8.3)
Extracranial injury, no. (%)			
Extracranial hematoma	7 (12.1)	6 (13.0)	1 (8.3)
Facial injury	8 (13.8)	7 (15.2)	1 (8.3)
Lower extremity injury	4 (6.9)	4 (8.7)	0 (0)
Spinal cord injury	3 (5.2)	3 (6.5)	0 (0)
None	36 (62.1)	26 (56.5)	10 (83.3)
Surgical intervention, no. (%)			
Burr hole trephination	4 (6.9)	4 (8.7)	0 (0)
Craniectomy/Craniotomy	9 (15.5)	7 (15.2)	2 (16.7)
External ventricular drain	1 (1.7)	0 (0)	1 (8.3)
None	44 (75.9)	35 (76.1)	9 (75.0)
Elapsed time between initial CT acquisition and trauma, hours			
Median, interquartile range	11.50 (4.38–27.79)	10.09 (4.00–26.33)	12.50 (6.88–65.37)
Follow-up CT scan within 48 h, no. (%)	34 (58.6)	28 (60.9)	6 (50.0)
Imaging findings, no. (%)			
Skull fracture	18 (31.0)	16 (34.8)	2 (16.7)
Petechial hemorrhage	10 (17.2)	8 (17.4)	2 (16.7)
Obliteration of basal cisterns	9 (15.5)	7 (15.2)	2 (16.7)
Midline shift > 5 mm	25 (43.1)	19 (41.3)	6 (50.0)
Length of stay, days			
Median, interquartile range	9 (3–25)	6 (2.75–16.5)	20.5 (12.5–153.75)
In-hospital mortality, no. (%)	6 (10.3)	0 (0)	6 (50.0)

Changes in Intracranial Densitometry at the Acute Phase of Pediatric TBI

For initial CT acquired at admission and follow-up CT acquired within 48 h later, the changes in intracranial densitometry according to the outcome were evaluated. **Figure 3A** shows the density distribution obtained from the initial CT scan at admission, which skewed to the right in the unfavorable outcome group compared to the density distribution of the favorable outcome group, indicating brain density alteration in the acute phase of TBI. These morphological disagreements resulted in significant differences between the outcome groups in the specific HU range. Contrary to the intracranial densitometry of the favorable outcome relatively analogous to the normal distribution, the skewed distribution of the unfavorable outcome became more distinguishable in the follow-up CT (**Figure 3B**). This deformation suggests that the change in brain density due to secondary insults became more substantial.

The intracranial densitometric morphology was further assessed through densitometric parameters in a quantitative manner. **Table 2** shows the densitometric parameters in both outcome groups. Among the proportional densitometric parameters from the initial CT, cEs showed a significant difference, whereas dWx and dGx, indicating the proportion of normal-density WM and GM, showed no significance. Nevertheless, only the dGx from the follow-up CT showed a significant difference. As the intracranial morphology of the unfavorable outcome group showed a distorted distribution, all of the morphological densitometric parameters differed significantly between outcome groups both in initial and follow-up CT. On the other hand, the CT classification systems (i.e., Marshall and Rotterdam score) did not significantly distinguish outcome favorability in either initial or follow-up CT.

Prognostic Model at the Acute Phase of Pediatric TBI Augmented by Intracranial Densitometry

The predictive performance of the prognostic models constructed from the variables acquired during the acute phase was assessed by LOOCV based on the outcome favorability (**Figure 4**). As the reference model, the CRASH-CT model

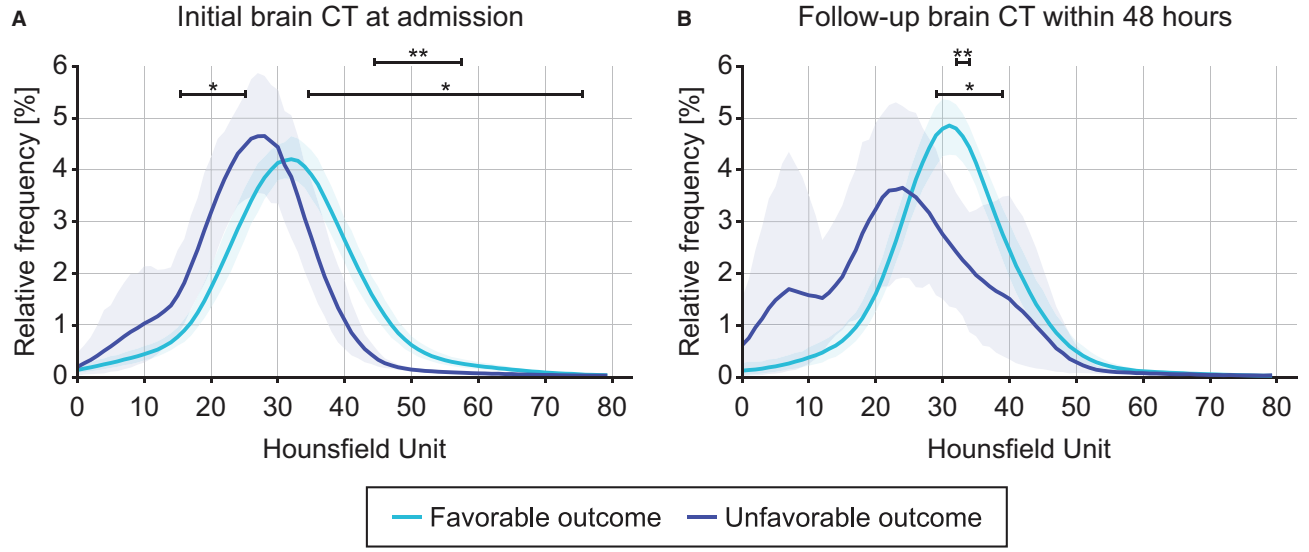

FIGURE 3 | Comparison of intracranial densitometry by outcome favorability based on the initial brain CT at admission **(A)** and follow-up brain CT within 48 h **(B)**. Blue = favorable outcome group, purple = unfavorable outcome group. The bold line and shaded area denote the mean and range of the 95% confidence interval, respectively. Significance at $p < 0.05$* and $p < 0.001$**.

TABLE 2 | Comparison of densitometric parameters and conventional CT classification systems by outcome favorability based on the initial and follow-up brain CT.

	Median (interquartile range)		*P*-value
	Favorable outcome	Unfavorable outcome	
Initial brain CT at admission (*N* = 58; favorable = 46, unfavorable = 12)			
Proportional densitometric parameters			
dWx	18.94 (13.43–25.17)	24.00 (15.31–27.90)	0.19
dGx	20.48 (14.92–24.48)	18.87 (7.08–22.07)	0.28
cEs	12.40 (7.15–19.40)	24.26 (15.58–39.71)	0.008
Morphological densitometric parameters			
μ	32.89 (27.73–35.78)	28.32 (22.39–29.51)	0.005
Skewness	0.55 (0.09–1.17)	1.43 (0.76–1.73)	0.006
Kurtosis	2.28 (1.15–4.74)	4.46 (4.08–7.79)	0.002
CT classification systems			
Marshall score	6 (2.75–6)	4 (2.50–6)	0.33
Rotterdam score	2 (2-2)	2 (1.25–2.75)	0.97
Follow-up brain CT within 48 h (*N* = 34; favorable = 28, unfavorable = 6)			
Proportional densitometric parameters			
dWx	22.71 (15.15–27.59)	14.88 (6.75–26.07)	0.11
dGx	23.45 (19.99–26.23)	13.03 (2.63–18.50)	0.001
cEs	13.12 (8.35–19.00)	31.38 (5.09–40.09)	0.30
Morphological densitometric parameters			
μ	31.65 (29.14–34.26)	26.67 (16.20–30.11)	0.037
Skewness	0.69 (0.06–1.07)	1.57 (0.69–1.86)	0.022
Kurtosis	3.05 (1.56–4.39)	5.01 (3.89–8.61)	0.015
CT classification systems			
Marshall score	5.5 (4–6)	5 (3.75–6)	0.95
Rotterdam score	2 (1.25–3)	2.5 (2–3)	0.39

based on logistic regression (i.e., CRASH-CT_{LR}) showed an AUC of 0.56. By using the CatBoost model, an AUC of 0.63 was derived from the model using only the CRASH-CT input (i.e., CRASH-$CT_{CatBoost}$). The densitometry-augmented model (i.e., D/CRASH-$CT_{CatBoost}$) showed significant enhancement in the AUC compared with the CRASH-CT_{LR} model. Specifically, the AUC of the model that included densitometric information was improved to 0.83 ($p < 0.03$ by Hanley's test). Alternating the variables from the initial CT to the follow-up CT further enhanced the prognostic value of the CatBoot models (**Figure 4B**). Accordingly, the difference in the AUC between the CRASH-CT_{LR} and the D/CRASH-$CT_{CatBoost}$ became more significant ($p < 0.02$ by Hanley's test) despite the smaller number of subjects. The performance of the prognostic models at the optimal cutoff point for predicting the outcome was further evaluated (**Table 3**).

The feature importance of the input variable and SHAP of the tree ensemble of the best model from the initial CT, D/CRASH-$CT_{CatBoost}$, was derived (**Figure 5A**). In the D/CRASH-$CT_{CatBoost}$ model, morphological parameters (i.e., kurtosis, skewness, and μ) and dGx were the main contributors to the prediction. As kurtosis and skewness increased, the prediction of unfavorable outcomes increased. Additionally, lower μ and dGx values contributed to the prediction of unfavorable outcomes. D/CRASH-$CT_{CatBoost}$ from the follow-up CT also showed that dGx and skewness mainly contributed to the outcome prediction (**Figure 5B**), which is similar to the model from the initial CT. This may reflect the shift in the center of intracranial densitometry toward lower HUs with morphological distortion in patients with an unfavorable outcome.

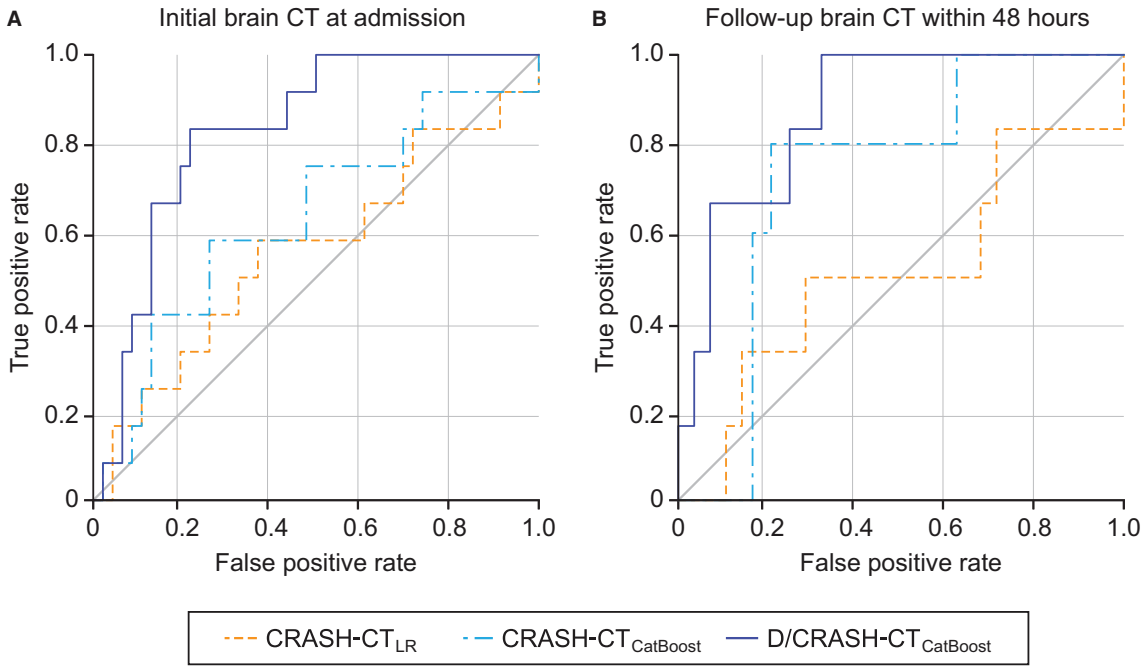

FIGURE 4 | ROC curves of the prognostic models for the differentiation of favorable and unfavorable outcomes based on the initial brain CT at admission **(A)** and follow-up brain CT within 48 h **(B)** by the LOOCV. Orange = CRASH-CT_{LR}, blue = CRASH-$CT_{CatBoost}$, indigo = D/CRASH-$CT_{CatBoost}$.

TABLE 3 | Comparison of prognostic models for predicting outcome favorability based on the initial and follow-up CT-based LOOCV.

	AUC	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]
Initial brain CT at admission (*N* = 58)					
CRASH-CT_{LR}	0.56 (0.36–0.76)	58.33 (31.95–80.67)	63.04 (48.60–75.48)	29.17 (14.91–49.17)	85.29 (69.87–93.55)
CRASH-$CT_{CatBoost}$	0.63 (0.44–0.83)	58.33 (31.95–80.67)	73.91 (59.74–84.4)	36.84 (19.15–58.96)	87.18 (73.29–94.4)
D/CRASH-$CT_{CatBoost}$	0.83 (0.72–0.94)	83.33 (55.20–95.30)	78.26 (64.43–87.74)	50.00 (29.93–70.07)	94.74 (82.71–98.54)
Follow-up brain CT within 48 h (*N* = 34)					
CRASH-CT_{LR}	0.51 (0.21–0.82)	50.00 (18.76–81.24)	71.43 (52.94–84.75)	27.27 (9.75–56.56)	86.96 (67.87–95.46)
CRASH-$CT_{CatBoost}$	0.73 (0.51–0.96)	80.00 (37.55–96.38)	79.17 (59.53–90.76)	44.44 (18.88–73.33)	95.00 (76.39–99.11)
D/CRASH-$CT_{CatBoost}$	0.88 (0.74–1.00)	83.33 (43.65–96.99)	75.00 (56.64–87.32)	41.67 (19.33–68.05)	95.45 (78.20–99.19)

AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

Comparative Assessment of Intracranial Densitometry According to Alternative TBI Outcome Measures

Intracranial densitometry acquired at admission was further compared for alternative outcome measures for TBI (i.e., in-hospital mortality, LOS, and need for surgical intervention). Intracranial densitometry in the deceased group showed considerable skewness, suggesting that low-attenuated pixels dominate (**Figure 6A**). On the other hand, when the groups were dichotomized based on the LOS (1 week), the intracranial densitometry of the worse outcome group was transversely shifted to the left without noticeable deformation (**Figure 6B**). However, there was no association between need for surgery and intracranial densitometry; the morphology between the outcome groups (i.e., need for surgery vs. no surgery) was indistinguishable (**Figure 6C**). In addition, **Table 4** further describes the densitometric parameters and CT classifications that depend on the three outcome measures. Outcome groups based on in-hospital mortality and LOS revealed significant morphological parameters, although proportional parameters and CT scores showed limited significance.

Prognostic Model for Alternative TBI Outcome Measures Augmented by Intracranial Densitometry

For the three alternative outcome measures, the performance of the prognostic models was evaluated through LOOCV (**Figure 7**). **Figure 7A** shows exceptionally superior performance of the D/CRASH-$CT_{CatBoost}$ than that of the CRASH-CT_{LR} for predicting in-hospital mortality ($p < 0.018$ by Hanley's test). On

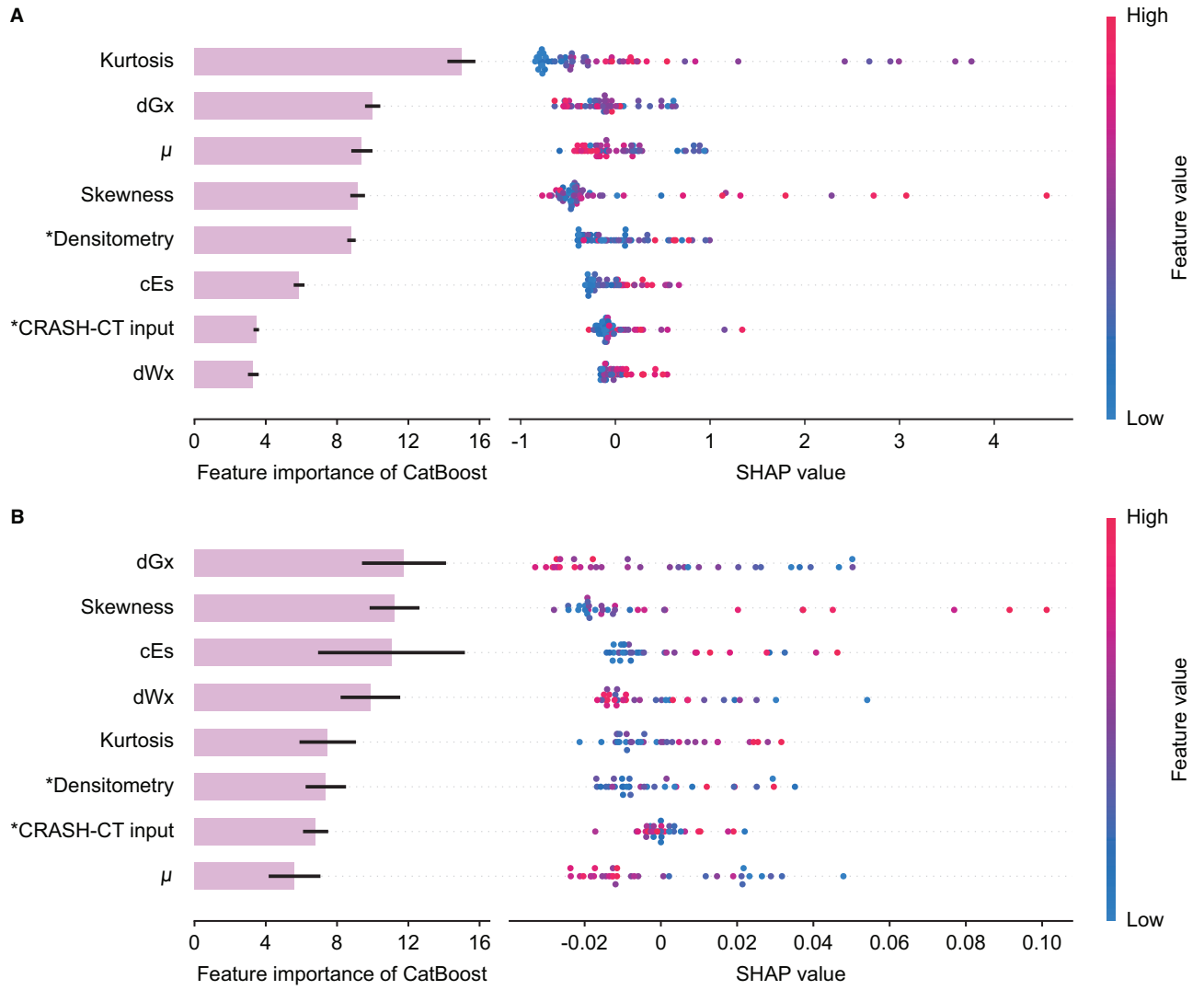

FIGURE 5 | Feature importance and SHAP value of the D/CRASH-$CT_{CatBoost}$ model for the differentiation of favorable and unfavorable outcomes based on the initial brain CT at admission **(A)** and follow-up brain CT within 48 h **(B)**. Each row shows the distribution of SHAP values assigned to a model input. Asterisks denote input variables that have undergone dimensionality reduction by principal component analysis.

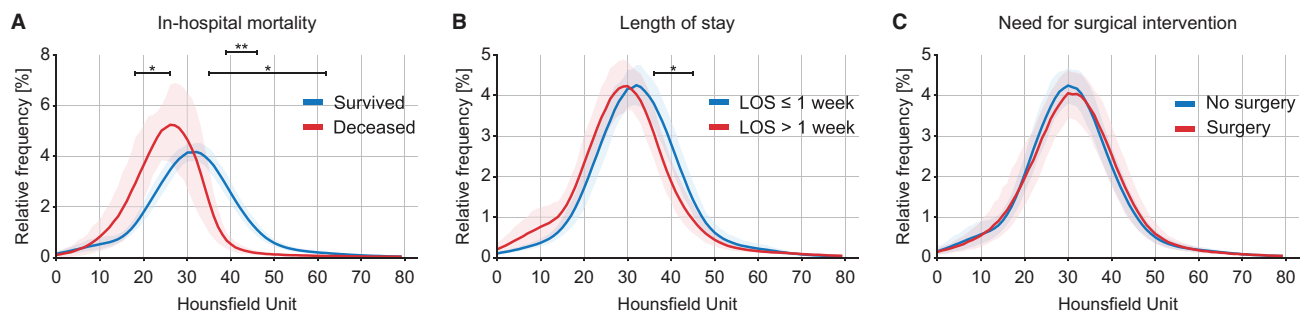

FIGURE 6 | Comparison of intracranial densitometry by alternative outcome measures: in-hospital mortality **(A)**, length of stay **(B)** and need for surgical intervention **(C)**. The bold line and shaded area denote the mean and range of the 95% confidence interval, respectively. Significance at $p < 0.05$* and $p < 0.001$**.

TABLE 4 | Comparison of densitometric parameters and conventional CT classification systems by alternative outcome measures.

	In-hospital mortality			Length of stay			Need for surgical intervention		
	Median (interquartile range)		*P*-value	Median (interquartile range)		*P*-value	Median (interquartile range)		*P*-value
	Survival (*N* = 52)	Deceased (*N* = 6)		LOS ≤ 1 week (*N* = 28)	LOS > 1 week (*N* = 30)		No need for surgery (*N* = 44)	Need for TBI-related surgery (*N* = 14)	
Proportional densitometric parameters									
dWx	19.27 (13.64–25.22)	26.22 (13.48–34.85)	0.19	18.84 (14.24–24.28)	21.86 (11.92–27.42)	0.52	19.48 (14.53–27.09)	19.93 (13.04–24.33)	0.57
dGx	20.32 (14.82–24.23)	18.38 (3.14–24.21)	0.32	20.48 (16.61–24.55)	18.90 (13.79–23.00)	0.37	20.03 (13.78–24.85)	20.51 (17.68–22.99)	0.81
cEs	13.25 (7.47–20.72)	26.87 (20.64–45.44)	0.011	10.90 (7.29–18.89)	17.55 (9.11–27.72)	0.13	14.71 (7.54–26.53)	15.14 (8.40–22.52)	0.96
Morphological densitometric parameters									
μ	32.15 (27.31–35.64)	27.51 (20.43–29.36)	0.022	33.25 (28.49–35.78)	29.24 (26.41–33.72)	0.06	30.47 (26.66–34.81)	31.16 (27.04–35.62)	0.61
Skewness	0.57 (0.10–1.18)	1.67 (0.91–1.78)	0.007	0.4 (−0.05 to 0.98)	1.08 (0.46–1.57)	0.003	0.89 (0.15–1.28)	0.45 (0.10–1.04)	0.37
Kurtosis	2.45 (1.22–4.66)	7.14 (4.49–9.63)	0.003	2.31 (1.12–4.06)	4.10 (1.77–6.02)	0.07	3.39 (1.50–5.41)	1.96 (1.12–4.07)	0.17
CT classification systems									
Marshall score	6 (3–6)	3 (2–4.5)	0.034	6 (2.25–6)	6 (2.75–6)	0.76	6 (2–6)	6 (4–6)	0.50
Rotterdam score	2 (2)	1.5 (1–2.25)	0.20	2 (1.25–2)	2 (2)	0.75	2 (1.25–2)	2 (2–3)	0.10

the other hand, prognostic models for LOS prediction showed consistent capacity without a significant difference between the prognostic models (**Figure 7B**). The prognostic ability of the model to predict the need for surgery showed a moderate AUC of 0.71. **Table 5** indicates detailed statistical measures for the performance of the prognostic model.

The feature importance and SHAP of the tree ensemble of the D/CRASH-$CT_{CatBoost}$ were derived based on the three outcome measures (**Figure 8**). The in-hospital mortality prediction model possessed the skewness of intracranial densitometry as a significant contributor, but in the models predicting LOS or need for surgery, the conventional CRASH-CT input, not the densitometric parameter, made the most dominant contribution to the prediction. This result was related to the weak statistical significance of the input variables from the intracranial densitometry.

DISCUSSION

The efficacy and practicality of the conventional CT classification system for evaluating injury severity after TBI have long been acknowledged; however, this method suffers from high inter- and intrarater variability (10, 15). Non-etheless, the system has been incorporated into well-known prognostic models for TBI, which may significantly affect the robustness of the models. This study utilized a recently developed interpretable machine learning model (CatBoost) to build a TBI prognostic model and employed CT densitometry, which is fully automated and thus does not suffer from inter- and intrarater variability (18), to compensate for the subjective CT classification system. The results indicate that (1) densitometric parameters are independently associated with various TBI outcome measures (i.e., favorability, mortality, and LOS) but not the need for surgery, (2) the prognostic capacity of the conventional CRASH model could be enhanced by employing CatBoost rather than traditional logistic regression, and (3) the capacity can be further increased by supplementing densitometric parameters as model inputs. The novelty and importance of the utilized methods and derived findings of this study warrant a detailed discussion.

The Rationale of Densitometric CT Analysis in TBI Pathologies

The inter- and intrarater variability of conventional CT classification systems mainly stems from the wide heterogeneity of injury types and severity (15) and the dependence on arbitrary estimations based on visual inspection (10). Densitometric CT analysis aims to overcome such limitations by quantitatively evaluating the density of brain structures and/or lesions based on brain CT scans. The technique has been widely applied in evaluations of various pathological brain changes [e.g., early cerebral edema (18, 32) or ischemic changes (33), lesion water uptake (34), parenchymal compression (35), and hemorrhage growth (36)] and for predicting outcomes (18, 25, 37, 38) in acquired brain injury. There are two approaches to applying densitometry: region of interest-based analysis (33–36, 38) and whole-cerebrum analysis (18, 25, 37). This study adopted the

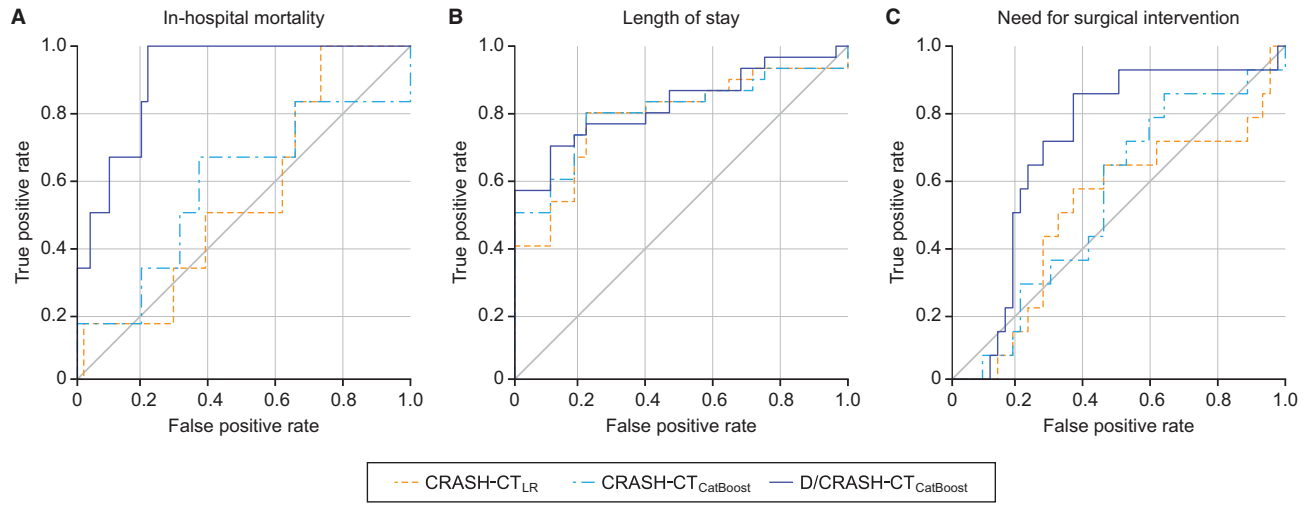

FIGURE 7 | ROC curves of the prognostic models for the differentiation of alternative outcome measures: in-hospital mortality **(A)**, length of stay **(B)** and need for surgical intervention **(C)** based on LOOCV. Orange = CRASH-CT$_{LR}$, blue = CRASH-CT$_{CatBoost}$, indigo = D/CRASH-CT$_{CatBoost}$.

TABLE 5 | Comparison of prognostic models for predicting alternative outcome measures based on LOOCV.

	AUC	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]
In-hospital mortality					
CRASH-CT$_{LR}$	0.55 (0.32–0.79)	50.00 (18.76–81.24)	61.54 (47.96–73.53)	13.04 (4.54–32.13)	91.43 (77.62–97.04)
CRASH-CT$_{CatBoost}$	0.58 (0.29–0.87)	66.67 (30–90.32)	63.46 (49.87–75.2)	17.39 (6.98–37.14)	94.29 (81.39–98.42)
D/CRASH-CT$_{CatBoost}$	0.91 (0.82–1.00)	100 (60.97–100)	78.85 (65.97–87.76)	35.29 (17.31–58.70)	100 (91.43–100)
Length of stay					
CRASH-CT$_{LR}$	0.79 (0.67–0.91)	80.00 (62.69–90.49)	78.57 (60.46–89.79)	80.00 (62.69–90.49)	78.57 (60.46–89.79)
CRASH-CT$_{CatBoost}$	0.80 (0.68–0.92)	80.00 (62.69–90.49)	78.57 (60.46–89.79)	80.00 (62.69–90.49)	78.57 (60.46–89.79)
D/CRASH-CT$_{CatBoost}$	0.83 (0.72–0.94)	76.67 (59.07–88.21)	78.57 (60.46–89.79)	79.31 (61.61–90.15)	75.86 (57.89–87.78)
Need for surgical intervention					
CRASH-CT$_{LR}$	0.51 (0.33–0.70)	57.14 (32.59–78.62)	63.64 (48.87–76.22)	33.33 (17.97–53.29)	82.35 (66.49–91.65)
CRASH-CT$_{CatBoost}$	0.54 (0.37–0.71)	64.29 (38.76–83.66)	54.55 (40.07–68.29)	31.03 (17.28–49.23)	82.76 (65.45–92.40)
D/CRASH-CT$_{CatBoost}$	0.71 (0.56–0.86)	85.71 (60.06–95.99)	63.64 (48.87–76.22)	42.86 (26.51–60.93)	93.33 (78.68–98.15)

AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

latter approach (1) to ensure the robustness of the prognostic model to be constructed and (2) because it was originally designed to be applied for pediatric TBI (18).

Whole-cerebrum analysis-based intracranial densitometry can respond to two major intracranial pathologies of TBI: ischemic-edematous insults and intracranial hemorrhage. However, there is a discrepancy in the sensitivity of intracranial densitometry for the two pathologies. According to volumetric CT measurements, the proportion of parenchyma in pediatric subjects accounts for 93–94% of the cranium (39). Undoubtedly, parenchyma also occupies the equivalent proportion in intracranial densitometry. Therefore, intracranial densitometry derived from whole-cerebrum analysis benefits from the sensitive response to diffuse ischemic injury that contributes to global changes in parenchymal density, despite subtle alterations (18, 25). Of course, the significant amount of hyperdense lesion (e.g., crescent-shaped acute subdural hemorrhage) also markedly expanded the proportion of the intracranial densitometry area above 40 HU (**Figure 2C**). On the other hand, whole-cerebrum densitometry shows a limited response to focal lesions occupying a relatively small proportion. For example, intracranial densitometry may be less sensitive for focal lesions such as petechial hemorrhages or focal brain ischemia. Accordingly, consideration of focal lesions in the whole-cerebrum densitometric analysis may be restricted, and this study thus focused on the interpretation of TBI pathologies involved in global parenchymal changes.

Quantitative Assessment of Secondary Ischemic-Edematous Insults in the Acute Phase of TBI

Intracranial densitometry offers a wide variety of quantitative parameters, i.e., morphological parameters (μ, skewness, and

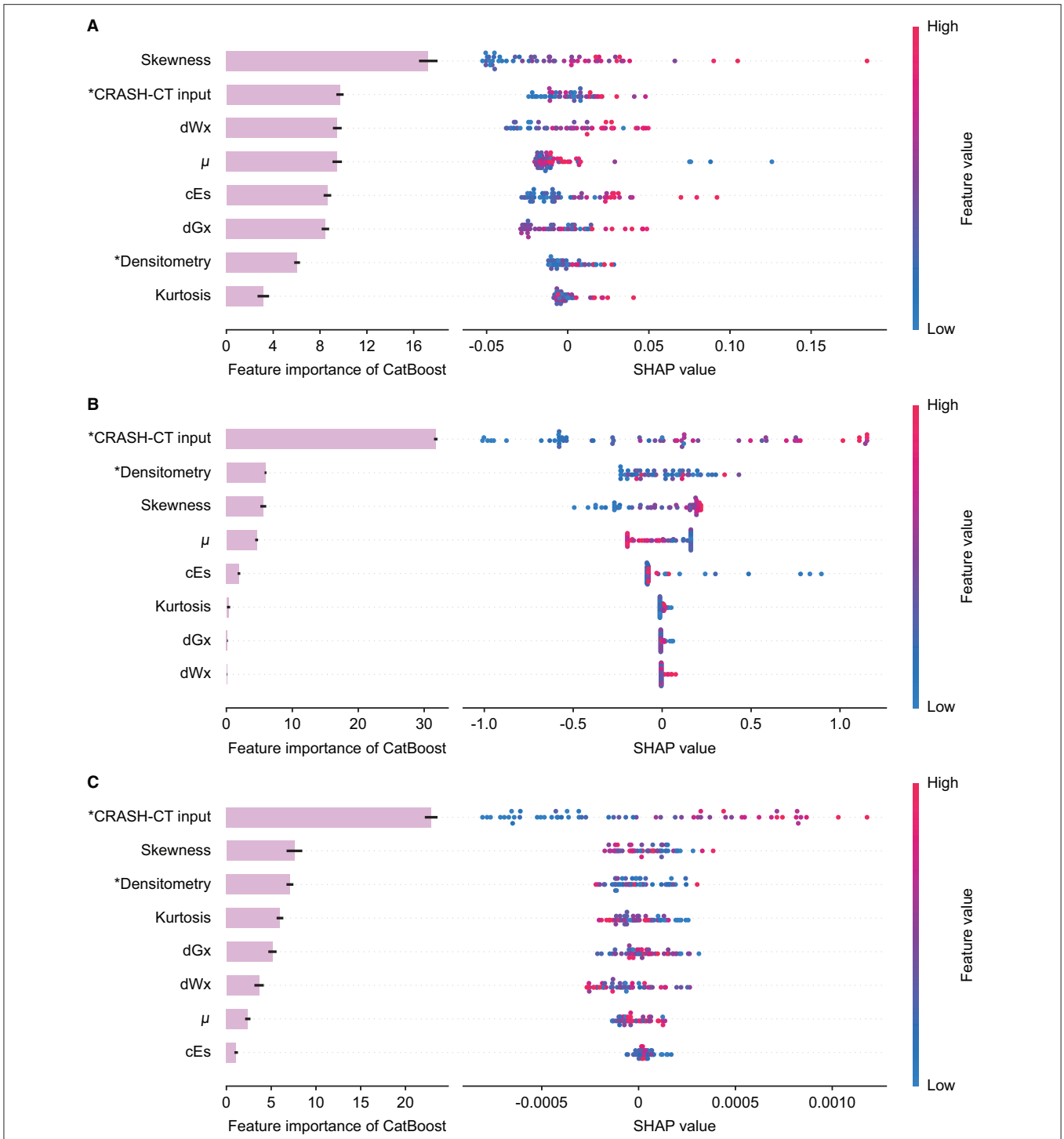

FIGURE 8 | Feature importance and SHAP value of the D/CRASH-$CT_{CatBoost}$ model for the differentiation of alternative outcome measures: in-hospital mortality **(A)**, length of stay **(B)**, and need for surgical intervention **(C)**. Each row shows the distribution of SHAP values assigned to a model input. Asterisks denote input variables that have undergone dimensionality reduction by principal component analysis.

kurtosis) and proportional parameters (dWx, dGx, and cEs). The morphological parameters are derived from a whole-cerebrum density distribution (**Figure 3**). Based on the dichotomized outcome favorability, the averaged density distribution of patients with an unfavorable outcome was determined to be significantly right-skewed in distribution with a leftward shift of

the center compared to that of patients with a favorable outcome. The distortion of the intracranial densitometry in the unfavorable outcome group became further apparent in the follow-up CT. These morphological characteristics are reflected as an increase in skewness and a decrease in μ, respectively, and suggest that the overall density of the parenchyma was reduced due to a subtle global ischemic change after TBI (37). The unfavorable outcome group also showed a higher kurtosis value in their density distributions than the favorable outcome group. Kurtosis, which has often been wrongfully interpreted as a measure of the "peakedness" of distribution graphs, is actually a measure of outliers (40). Localized hyper- or hypodense lesions result in significant increases in a specific range of HU values, i.e., they are outliers that contribute to increased kurtosis of the density distribution (**Table 2**). Although the statistical power was limited due to the small number of subjects in the follow-up CT subgroup, this group exhibited the same trend as the outcome group in terms of the morphological parameters from the initial CT. These morphological parameters were the main contributors to the outcome prediction of the proposed model (**Figure 5**).

Unlike morphological parameters, which mainly reflect whole-cerebrum density distribution, proportional parameters reflect the density distribution of specific, major intracranial entities, and can be interpreted in relation to the pathophysiology of cerebral edema. Cerebral edema is divided into vasogenic and cytotoxic types. In general, cytotoxic edema affects both WM and GM (41), whereas vasogenic edema primarily affects WM and easily spreads to other locations via WM tracts (42). In the acute phase of TBI, vasogenic, and cytotoxic edema often coexist (43). Thus, reduced brain tissue density mediated by cerebral edema can be simultaneously reflected by lower WM and GM density values on CT. The increased proportion of hypodense pixels in CT images is reflected as an increase in the cEs (18), whereas changes in WM and GM densities are reflected as changes in dWx and dGx (37). Intriguingly, the conventional statistical analysis indicated that only cEs was significant in differentiating favorable and unfavorable outcome groups based on the initial CT (**Table 2**), whereas the machine learning model indicated that dGx had the highest importance among the proportional parameters, followed by cEs and dWx (**Figure 5**). Nonetheless, inferential statistics are influenced by effect size or sample size (44), and statistical significance does not guarantee high feature importance in the prognostic model. Indeed, dGx, the proportion of normal-density GM, which did not differ significantly between the two outcome groups, was considered a significant predictor of the outcome by the utilized machine learning model. Nevertheless, in follow-up CT within 48 h, dGx showed a significant difference between the outcome favorability. Despite the shortage of statistical power, this would suggest that brain density alternation even affected the relative proportion of GM with normal density.

In addition to the densitometric analysis, quantitative CT classification systems (i.e., Marshall and Rotterdam score) have been evaluated for use in assessing the severity of TBI. In pediatric TBI, the Rotterdam score has better discriminatory power than that of Marshall (45). However, neither the Marshall nor the Rotterdam scores classified outcomes well in our cohort (**Tables 2**, **4**), which may be attributed to the cohort characteristics of this pilot study. Originally, the Rotterdam score was developed for only moderate or severe TBI, excluding mild head injury (10). Liesemer et al. reported that although the Rotterdam score was initially developed for use in the adult population, the prognostic function worked well in the pediatric TBI population (46); however, ∼80% of the subjects had moderate or severe TBI (GCS, 3–8). A study in which the Marshall score showed adequate prognostic ability in pediatric TBI was also composed of moderate or severe TBI in 60% of the cohort (45). Consequently, the conventional CT classification systems could not work properly in this study, where ∼70% of mild TBI patients are composed.

Responsiveness of Intracranial Densitometry to Alternative Outcome Measures

Mortality, LOS, and the need for surgical procedures are primary outcome measures for pediatric TBI in clinical practice (47). In addition to outcome favorability, we investigated how intracranial densitometry responds to these outcome measures. LOS was closely associated with mortality in TBI patients (48); nevertheless, mortality is the worst consequence of TBI. Therefore, undoubtedly, the most sensitive response of intracranial densitometry was mortality. The averaged densitometry between the survival and deceased groups showed the most distinguishable difference among the alternative outcome measures. This finding suggests that deceased patients enter an irreversible state in which the brain densitometry was significantly different from the normal state. On the other hand, the morphology of intracranial densitometry was relatively similar between groups based on the LOS, a less severe outcome. However, the dichotomized LOS revealed a significant difference in the GM-related HU range. In contrast to mortality and LOS, no statistically significant difference in intracranial densitometry was observed between the groups classified by surgery necessity. This non-significance implies that, as mentioned above, the focal lesions that require surgical intervention may have a limited effect on the deformation of whole-cerebrum densitometry.

Machine-Learning-Based Prognostic TBI Model Augmented by Densitometric Information

This study proposed a novel prognostic model based on GDBTs augmented with CRASH-CT and intracranial densitometric information. Based on various outcome measures, the proposed models (i.e., D/CRASH-$CT_{CatBoost}$) achieved enhanced prognostic capacity compared with the conventional model; this consistent improvement can be contributed by a combination of (1) densitometric information and (2) machine learning models. Intracranial densitometry is a quantitative input variable that responds to global pathological changes in the intracranial region (18, 25). The proposed model included additional densitometric information, enhancing prognostic values, especially for GOS-related outcome measures (**Figures 5**, **6A**). On the other hand, in terms of LOS and surgery necessity, CRASH-CT input variables

(e.g., age, GCS, pupil reaction, extracranial injury, CT findings) played a more substantial contribution than the densitometric information (**Figures 6B,C**). In this case, it can be assumed that machine learning itself contributed to increasing the prognostic value rather than adding the densitometric variables. Logistic regression does not consider the correlation between the input variables and has multicollinearity problems (49), whereas CatBoost can lead to better performance by reducing information loss by creating a combination considering the correlation between the input variables (50).

The significant factors contributing to the decreased prognostic capacity of the conventional CRASH-CT model are 2-fold, namely, interrater variability, and validation method. The CRASH-CT model is a widely used prognostic TBI model (13), and its variables are based on the injury status and initial CT findings. The radiological findings used as the input of the CRASH-CT model are based on the Marshall CT classification, which has been reported to have ∼12.7% interrater variability (51). Interrater variability changes the results of a prognostic model and thus lowers its reliability. In addition, CRASH-CT yielded low accuracy for pediatric TBI patients in this study, unlike reports in the literature (25, 52). It can be assumed that it is not properly fitted to predict the outcome at discharge since the original CRASH-CT model predicts outcome favorability after 14 days (13). In addition, the LOOCV method, a stricter validation method than others reported in the literature (25, 52), also contributed to the low prognostic capacity of the CRASH-CT model. Previous studies (13, 25, 52) in which the training and testing of logistic regression models were performed with the same cohort without external validation have the potential to overestimate the prognostic capacity, and it is complicated to resolve the overfitting problem oriented to the cohort. In this study, individual and iterative validations were performed 58 times by separating training and testing subjects through LOOCV. Despite the more rigorously evaluated results, improvements in prognostic value were observed by adding densitometric information to the CRASH-CT input. A significantly enhanced prognostic value could be achieved compared with CRASH-CT when only initial brain CT data were used, suggesting that machine learning-based automated densitometry is a useful prognostic tool that can minimize unnecessary radiation exposure in children with TBI.

In several recent studies, prognostic models using machine learning have been proposed to predict the outcome favorability of patients with pediatric TBI more accurately (53–55). Kayhanian et al. proposed a support vector machine (SVM)-based prognostic model using admission laboratory variables (53). Hale et al. developed an artificial neural network (ANN) model using laboratory values, GCS scores, and initial CT findings (54). Tunthanatip et al. compared the prognostic value of various machine learning models using comorbidity and radiological finding information and concluded that the SVM-based model showed the highest performance (55). These studies consistently reported that machine learning outperformed conventional logistic regression (53–55), and the same results were obtained in the present study. However, unlike the GBDT used in this study, the ANN and SVM models used in previous studies are "black box" models that are difficult to interpret (56). Interpretability of the model is an important issue when using machine learning in the medical domain (21). A black box-based prognostic model that lacks an explanation of how much an input variable contributed to the prediction may have limited application in the clinical environment (57). It is complicated to convince a clinician of the results of a model when they are presented without any explanation. On the other hand, the proposed GBDT-based model showed reliable prognostic capacity and could explain how the input variables contribute to the prediction. Consequently, unlike the previous ML-based prognostic models for pediatric TBI, which entail a trade-off between interpretability and prognostic capacity (53–55), the proposed model accomplished both.

Limitations and Suggestions

Several limitations should be considered. First, this study was a single-center, retrospective pilot study with a small cohort size. The small cohort size hampered the appropriate distribution of TBI severity; mild TBI patients were the most dominant in this study. Thus, the proposed model should be validated by a large-scale dataset, and a prospective, multicenter study is required for generalization of the model proposed in this study. Second, this study used only the in-hospital outcome measures because there was no long-term outcome information in our institutional database. The model's prediction of long-term outcomes should also be validated. Third, except for intracranial densitometry, elaborative modalities for assessing cerebral edema in TBI patients were not used in this study. The extent of cerebral edema would have been better assessed and cross-validated using MRI (e.g., diffusion-weighted imaging and apparent diffusion coefficient mapping). In future validation studies, the benefits of the proposed method will be investigated to address the following issues: (1) changes in physician decision-making as the result of utilizing densitometric analysis; (2) estimation of other intracranial pathologies (e.g., intracranial hypertension); and (3) prognostic capacity of the proposed models for predicting long-term outcomes.

CONCLUSION

This study revealed that intracranial densitometric information derived from initially acquired brain CT scans performed at admission was highly associated with worse outcomes in pediatric TBI patients. Contrary to the conventional TBI prognostic model (i.e., CRASH-CT model), which mainly uses arbitrary measures (i.e., Marshall classification) that suffer from inter- and intrarater variability, fully automated densitometric analysis of the whole cerebrum was supplemented in the construction of the prognostic model. Accordingly, the prognostic value of brain CT was significantly enhanced by augmenting densitometric information with a cutting-edge GBDT-based machine learning model. In conclusion, intracranial densitometry information could improve the reliability of brain CT-based clinical decision-making during the acute phase of TBI and may serve as the basis for enhancing the TBI prognostic model.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because sharing data outside is not available according to the policy of our institution. Requests to access the datasets should be directed to http://hrpp.snuh.org/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Seoul National University Hospital (IRB H-1706-144-862). 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

Y-TK drafted and revised the manuscript, carried out clinical data analysis and interpretation, and contributed to the design of the study. HK critically revised the manuscript and contributed to the design of the study. C-HL performed prognostic modeling via machine learning. C-HL, BY, JK, YC, W-SC, and B-MO critically revised the manuscript. B-MO performed data collection. D-JK conceptualized and designed the study, critically revised the manuscript, and oversaw the creation of the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT, MSIT) (Grant number 2019R1A2C1003399 and Grant number 2020R1C1C1006773) and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C1561).

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frontiers in Pediatrics

ORIGINAL RESEARCH
published: 28 January 2022
doi: 10.3389/fped.2022.761815

The SARS-CoV-2 Pandemic Impacts the Management of Swiss Pediatric Intensive Care Units

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OPEN ACCESS

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *31 August 2021*
Accepted: *03 January 2022*
Published: *28 January 2022*

Citation:
Soomann M, Wendel-Garcia PD, Kaufmann M, Grazioli S, Perez M-H, Hilty MP, André MC and Brotschi B (2022) The SARS-CoV-2 Pandemic Impacts the Management of Swiss Pediatric Intensive Care Units. Front. Pediatr. 10:761815. doi: 10.3389/fped.2022.761815

The impact of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic on pediatric intensive care units (PICUs) is difficult to quantify. We conducted an observational study in all eight Swiss PICUs between 02/24/2020 and 06/15/2020 to characterize the logistical and medical aspects of the pandemic and their impact on the management of the Swiss PICUs. The nine patients admitted to Swiss PICUs during the study period suffering from pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and constituting 14% (9/63) of all SARS-CoV-2 positive hospitalized patients in Swiss children's hospitals caused a higher workload [total Nine Equivalents of nursing Manpower use Score (NEMS) points, $p = 0.0008$] and were classified to higher workload categories ($p < 0.0001$) than regular PICU patients ($n = 4{,}881$) admitted in 2019. The comparison of the characteristics of the eight Swiss PICUs shows that they were confronted by different organizational issues arising from temporary regulations put in place by the federal council. These general regulations had different consequences for the eight individual PICUs due to the differences between the PICUs. In addition, the temporal relationship of these different regulations influenced the available PICU resources, dependent on the characteristics of the individual PICUs. As pandemic continues, reflecting and learning from experience is essential to reduce workload, optimize bed occupancy and manage resources in each individual PICU. In a small country as Switzerland, with a relatively decentralized health care local differences between PICUs are considerable and should be taken into account when making policy decisions.

Keywords: pediatric intensive care unit, children, SARS-CoV-2 pandemic, pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2, PIMS-TS, management

INTRODUCTION

Children have been reported to be affected by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2–8% of all reported cases (1–4). In addition, they seem to experience milder disease courses, as only 0.2–2% of all affected children have been severely or critically ill (1, 4–6). In the course of the pandemic clusters of severely affected pediatric patients with symptoms similar, although distinctively different from severe Kawasaki disease were reported in Europe and North America (7–13). This new syndrome was named pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) (3, 9). It's clinical and laboratory presentations have been described in depth in a series of case reports and case series by now (7–16). Most of the patients diagnosed with PIMS-TS have been treated according to protocols with corticosteroids or immunoglobulins or both, but a high need for organ supportive measures has been reported (3, 8, 17–20). In addition to having to care for patients with this new syndrome, Swiss PICUs were confronted with organizational issues arising from temporary regulations put in place by the federal council due to the pandemic.

There are eight PICUs in Switzerland, distributed all over the small country of 41,285 square kilometers with 8.6 million inhabitants (21, 22). Two PICUs are located in the French speaking part, six PICUs in the German speaking part and none in the Italian speaking part of Switzerland. The aim of our study is to describe the different logistical and medical challenges facing the Swiss PICUs during the first wave of the SARS-CoV-2 pandemic.

MATERIALS AND METHODS

PICU Burden

All eight Swiss PICUs provided data on organizational characteristics and the situation in their units during the study period. These included general characteristics (total number of beds, total number of admissions, and affiliation to adult hospitals) and characteristics related to the SARS-CoV-2 pandemic (percentage of scheduled admissions, cancellation of interventions, staff recruited to adult wards, and percentage of PIMS-TS patients).

For comparing workloads the Nine Equivalents of nursing Manpower use Score (NEMS) and Riker Sedation-Agitation Scale (SAS) as well as a Swiss derivative of the two, the Swiss Society of Intensive Care Medicine (SSICM) shift categories were used (23–25). These scores are used as standard practice in all PICUs in Switzerland and filled out per patient per shift immediately after every nursing working shift. The routine length of a nursing staff shift is 9 h and planned or unplanned double shifts were not practiced. If unplanned absences occurred, units reduced their bed availability for this shift. NEMS score is well-validated and easier to use than the Therapeutic Intervention Scoring System, therefore the Swiss society of intensive care medicine has established using this scoring system nationwide (26–30). NEMS includes data on interventions as well as of therapies and reflects the workload of nurses and physicians. The score includes the following nine items: basic monitoring, intravenous medication, mechanical ventilator support, supplementary ventilator care, single vasoactive medication, multiple vasoactive medication, dialysis techniques, specific interventions in the intensive care unit (ICU), and specific interventions outside the ICU (23). The higher the NEMS Score, the more nursing manpower was needed during a certain shift or during the whole ICU stay. SAS is used to evaluate a patient's level of sedation and agitation. During each shift each patient is given a score from one to seven ranging from an unarousable patient to a dangerously agitated patient (24). SSICM shift categories integrate NEMS and SAS, category 1A of the SSICM defines the most, and category 3 the least, work-load intensive shift for ICU nurses (25). Details SSICM shift categories are shown in **Table 1**.

TABLE 1 | Classification criteria for the Swiss Society of Intensive Care Medicine (SSICM) shift categories.

Category	1A	1B	2	3
Criteria	NEMS > 30 or NEMS ≥ 21 and SAS > 5	NEMS 21–30 and SAS ≤5 or NEMS 13–20 and SAS >5	NEMS 13–20 and SAS ≤ 5 or NEMS < 13 and SAS > 5	NEMS < 13 and SAS ≤ 5

NEMS, Nine Equivalents of nursing Manpower use Score; SAS, Riker Sedation-Agitation Scale.

Patient and Population Data

In order to compare the critically ill SARS-CoV-2 pediatric patients to the regular PICU population, data on all patients hospitalized in the eight Swiss PICUs in 2019 was used. The whole year instead of the corresponding time period in 2019 was used to avoid a seasonal bias in the group representing regular PICU patients. This data was drawn from the Minimal Dataset of the Swiss Society of Intensive Care Medicine (MDSi) (31). The Pediatric Index of Mortality 2 (PIM2) was used as an indicator of predicted case severity of the patients with PIMS-TS and the general PICU population (32). Data of the patients with PIMS-TS was retrospectively gathered in all eight Swiss PICUs on patients hospitalized from February 24, 2020, the date on which the first SARS-CoV-2 PCR positive patient was reported in Switzerland, up until the June 15, 2020. Included were all patients with age below 20 years and a positive SARS-CoV-2 polymerase chain reaction (PCR) result or the diagnosis of PIMS-TS according to either the Royal College of Child Health

Abbreviations: ARDS, acute respiratory distress syndrome; FOPH, Federal Office of Public Health; ICU, intensive care unit; IQR, interquartile range; MDSi, Minimal Dataset of the Swiss Society of Intensive Care Medicine; MIS-C, multisystem inflammatory syndrome in children; NEMS, Nine Equivalents of nursing Manpower use Score; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2; pRIFLE, pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease; RISC-19-ICU, Risk Stratification in COVID-19 patients in the ICU; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SAS, Sedation-Agitation Scale; SSICM, Swiss Society of Intensive Care Medicine.

TABLE 2 | General characteristics and characteristics related to the pandemic of the eight Swiss pediatric intensive care units between 02-24-2020 and 06-15-2020.

Characteristics	PICU 1	PICU 2	PICU 3	PICU 4	PICU 5	PICU 6	PICU 7	PICU 8
General characteristics								
Children hospital associated with adult hospital	No	Yes	Yes	Yes	Yes	Yes	No	No
Number of PICU beds	8	12	9	7	12	11	10	25
ECMO center	No	Yes	No	Yes	Yes	No	No	Yes
Perform hemodiafiltration	No	Yes	No	Yes	Yes	Yes	No	Yes
Characteristics related to the pandemic								
Total number of admissions	115	224	99	265	168	156	136	365
Total NEMS points per patient	237	219	262	186	466	164	305	294
Percentage of scheduled admissions	24%	49%	9%	16%	51%	24%	27%	49%
Cancellation of scheduled interventions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Staff recruited to adult wards	Yes	No	Yes	Yes	Yes	Yes	No	No
Percentage PIMS-TS patients of all admissions	0.9%	0	0	1.5%	1.8%	0	0	0.3%
Number of positive SARS-CoV-2 PCR patients without PIMS-TS	0	0	0	0	0	0	0	0

ECMO, extra corporal membrane oxygenation; NEMS, Nine Equivalents of nursing Manpower use Score; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

and Pediatrics (33), the World Health Organization (34) or the Centers for Disease Control and Prevention case definitions (35), during the PICU stay. Patient data was collected from chart notes and anonymized in the respective centers with a custom made questionnaire, one center's data was obtained from the Risk Stratification in COVID-19 patients in the ICU (RISC-19-ICU) registry (36). Information was gathered also on the use of anti-inflammatory medications including corticosteroids, intravenous immunoglobulin, anakinra, and tocilizumab, which all have been licensed for use in other conditions but were used off label for PIMS-TS.

General epidemiological data on the SARS-CoV-2 pandemic in Switzerland was drawn from the official website of the Swiss Federal Office of Public Health (FOPH) (37). As no reliable serological data was available at the whole population level, the total number of SARS-CoV-2 PCR positive tests in Switzerland was used in calculations to represent number the SARS-CoV-2 cases despite our PIMS-TS group mostly being PCR negative and seropositive. Data on the demographics of Switzerland was obtained from the website of the Swiss Federal Statistical Office (21).

Definitions of Organ Dysfunction

Acute respiratory distress syndrome (ARDS) was defined according to the Pediatric Acute Lung Injury Consensus Conference definition for pediatric acute respiratory distress syndrome (38). Shock was defined as an arterial systolic blood pressure below the age adapted 5th percentile or a systolic blood pressure below two standard deviations of the age adapted mean, and/or the need for vasoactive support to maintain blood pressure in the range (39, 40). Myocardial injury was defined as ejection fraction reduced below 55% measured using the biplane Simpson method according to the current pediatric echocardiographic recommendations (41, 42). Renal dysfunction was defined according to the pRIFLE classification (43). Hepatic dysfunction was defined as the elevation of liver enzymes above the age adapted reference and elevation of prothrombin time (44). An abnormal prothrombin time or activated partial thromboplastin time (according to age adapted reference values of the local laboratories) was classified as a coagulation disorder (45).

Ethical Approval

The study proposal (KEK: 2020-00720), as well as the RISC-19-ICU (KEK: 2020-00322, ClinicalTrials.gov Identifier: NCT04357275) registry have been evaluated by the Cantonal Ethics Committee of Zurich, a member of the Swiss Association of Research Ethics Committees—Swissethics and in line with the Swiss Federal Human Research Act deemed exempt from the need for additional ethics approval. The study complies with the Declaration of Helsinki, the Guidelines on Good Clinical Practice (GCP-Directive) issued by the European Medicines Agency as well as the Swiss law and Swiss regulatory authority requirements and has been designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Statistical Analysis

Statistical analysis was conducted employing the R environment for statistical computing version 4.0.2. Comparisons of population characteristics were performed using Wilcoxon rank-sum test for continuous not normally distributed and the chi-squared test for categorical variables. Continuous not normally distributed data is presented as median with interquartile ranges (IQR) and nominal data as counts and percentages.

TABLE 3 | Comparison of PIMS-TS patients and all PICU patients hospitalized in 2019 based on quantitative and qualitative measures of case complexity.

Characteristics	PIMS-TS patients *n* (patients) = 9 *n* (shifts) = 273	All patients in 2019 *n* (patients) = 4,881 *n* (shifts) = 63,015	*p* value
Quantitative measures, median (IQR)			
Length of stay in days	10 (9-11)	1.6 (0.8–3.9)	<0.0001
Duration of positive pressure ventilation in hours	72 (0–99)	0 (0–24)	0.025
PIM2 on admission	4.3 (1.5–7.2)	1.4 (0.6–3.2)	0.07
Total NEMS points	569 (496–736)	92 (51–239)	0.0008
Qualitative measures, number of shifts (percentage)			
SSICM shift categories			
1A + 1B	156 (57.1)	23,557 (37.4)	0.0001
2 + 3	117 (42.9)	39,458 (62.6)	
Riker SAS			
SAS ≥ 5	33 (12.1)	6,523 (10.4)	0.35
SAS < 5	240 (87.9)	56,492 (89.6)	

IQR, interquartile range; NEMS, Nine Equivalents of nursing Manpower use Score; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2; SAS, Sedation-Agitation Scale; SSICM, Swiss Society of Intensive Care Medicine.

RESULTS

PICU Burden

The Swiss PICUs varied in general characteristics as well as in characteristics related to the pandemic. The different medical and logistical aspects affecting the PICUs are listed in **Table 2**. In addition to some PICUs having to care for patients with this new syndrome, all PICUs were confronted with organizational issues arising from temporary regulations put in place by the federal council due to the pandemic. These general regulations had different consequences for the eight PICUs due to their different characteristics. As shown in **Table 2**, there were units (PICU 8) not affiliated to adult hospitals and without staff recruitment to adult wards, where nevertheless scheduled interventions were canceled due to regulations set by the federal council. As a consequence, this PICU was not fully occupied and had a relatively low workload. Other PICUs (PICU 5), however, were affiliated to an adult ward and staff recruitment to the adult wards was required. Therefore, cancellation of scheduled interventions was essential to have enough manpower and staff for the emergency admissions to these PICUs (PICU 5). Other PICUs (PICU 1) were also influenced by local circumstances with staff being recruited to adult wards due to staff shortage in the area despite the PICU not being affiliated with an adult hospital.

TABLE 4 | General characteristics of patients with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2 (PIMS-TS), details on organ dysfunction and applied therapies.

Characteristic	*n* (%)	Median (IQR)
General characteristics		
Age in years		11 (9–11.5)
Gender		
Female	2 (22%)	
Male	7 (78%)	
Body mass index in kg/m^2		20 (16.8–26.4)
Organ dysfunction		
Acute respiratory distress syndrome	2 (22%)	
Shock	8 (89%)	
Myocardial injury	4 (44%)	
Renal dysfunction	6 (67%)	
Hepatic dysfunction	4 (44%)	
Coagulation disturbances	6 (67%)	
Supportive measures		
Any type of respiratory support	9 (100%)	
Highest level of respiratory support		
Invasive ventilation	5 (56%)	
Non-invasive ventilation (NIV)	1 (11%)	
Continuous positive airway pressure (CPAP)	0 (0%)	
High-flow nasal cannula (HFNC)	1 (11%)	
Low-flow nasal cannula (LFNC)	2 (22%)	
Duration of respiratory support per patient in days		
Invasive ventilation ($n = 5$)		3.8 (3–8)
NIV ($n = 3$)		1 (0.4–4)
CPAP ($n = 0$)		0
HFNC ($n = 2$)		3 (2–4)
LFNC ($n = 3$)		1 (1–6.3)
Vasopressors or inotropes	8 (89%)	
Duration in days		3.5 (3-4.8)
Extracorporeal membrane oxygenation (ECMO)	0	
Continuous renal replacement therapy	1 (11%)	
Duration in days		3
Cytokine absorption therapy	1 (11%)	
Drug therapies		
Hydroxychloroquine	3 (33%)	
Intravenous immunoglobulin (IVIG)	6 (67%)	
Steroids	6 (67%)	
Biological agents	6 (67%)	
Anakinra	6 (67%)	
Tocilizumab	2 (22%)	
Combinations of immunotherapies		
None	1 (11%)	
IVIG only	1 (11%)	
Anakinra only	1 (11%)	
Steroids and anakinra	1 (11%)	
Steroids and IVIG	1 (11%)	
IVIG, steroids, and anakinra	2 (22%)	
IVIG, steroids, anakinra, and tocilizumab	2 (22%)	
Outcome		
Patients alive on discharge	9 (100%)	

IVIG, intravenous immunoglobulins.

Four out of eight PICUs had patients admitted with PIMS-TS between February 24, 2020 and June 15, 2020. Patients with PIMS-TS constituted 0.6% of all Swiss PICU admissions (9/1,528) during this time period and 0.3–1.8% of the PICU admissions of PICUs treating patients with PIMS-TS. A comparison of patients with PIMS-TS and general pediatric intensive care unit patients hospitalized in 2019 is shown in **Table 3**, based on quantitative and qualitative measures of case complexity. Patients with PIMS-TS had higher total NEMS scores ($p = 0.0008$) and were classified to higher SSICM workload categories more frequently than general PICU patients hospitalized in 2019 ($p < 0.0001$).

Epidemiology of SARS CoV-2 Positive Patients

The total of 1,113 children and young adults under the age of 20 were tested positive for SARS-CoV-2 infection between February 24, 2020 and June 15, 2020 in Switzerland, of which 6% (63/1,113) had to be hospitalized [Swiss FOPH (37)]. Ten pediatric patients with a concurrent positive SARS-CoV-2 PCR result or with PIMS-TS were hospitalized in PICUs. The only patient not diagnosed with PIMS-TS was admitted to the PICU due to an acute necrotizing encephalopathy. As the role of SARS-CoV-2 in the pathogenesis and disease progression remained unclear in this case, this patient's data was excluded from the present analysis. The nine remaining patients with PIMS-TS hospitalized in Swiss PICUs constituted 14% (9/63) of all SARS-CoV-2 positive hospitalized and 1% (9/1,113) of all SARS-CoV-2 positive children and young adults under the age of 20 in Switzerland during that period [Swiss FOPH (37)]. The incidence of severe PIMS-TS requiring hospitalization at a PICU was, therefore, 0.5 per 100,000 people under the age of 20 during the study period. No information is available on seropositivity in the general population during the study period. The general characteristics of all the PIMS-TS patients, details on organ dysfunction and applied therapies are presented in **Table 4**.

DISCUSSION

In this observational study, we describe different aspects of the first wave of the SARS-CoV-2 pandemic impacting the management of Swiss PICUs. Many of these aspects are difficult to measure and especially their temporal relationship complicates the analysis. Although, initially the disease was thought to affect predominantly adult departments, in the course of the pandemic, pediatric units and PICUs were more and more affected. Most of the staff were confronted with a pandemic, a new and unknown situation, for the first time in their life.

The absolute number of pediatric patients requiring intensive care due to severe SARS-CoV-2 and PIMS-TS during the study period was low. Similar results of hospitalized children and adolescents admitted to PICUs have been reported in other studies as well (46, 47). Although Switzerland is a small country, eight independent PICUs treat critically ill children. Each PICU is quite small, operating a relatively small number of beds. Although cooperation between the PICUs exists in several forms, every day professional exchange is not common. These circumstances explain why it took time for the PICU staff to learn about the new disease. However, in the course of the first wave of the pandemic, the PICUs recognized, that it is important to cooperate and to exchange experiences with each other to learn fast about the new disease and to improve patient outcome. As a consequence, Swiss consensus guidelines to treat pediatric patients with PIMS-TS for best practice were established by a multidisciplinary group of Swiss pediatric clinicians with expertise in intensive care, immunology, rheumatology, infectious diseases, and hematology during the second wave of the pandemic at the end of 2020 (http://transfer.imk.ch/f.php?h=3R2LIfFV&d=1).

Apart from the challenge of treating this unknown severely ill patient group, there were different logistical and organizational issues influencing the management of the PICUs. At the beginning of the pandemic a variety of measures to prepare the Swiss hospital network for the pandemic were instituted on federal level. Nationwide, scheduled interventions were canceled to reduce the need for post-interventional intensive care and to increase resources for emergency admissions. The federal government did not differentiate between adult and children's hospitals, provided services or bed occupancy of the individual PICUs. In some regions staff recruitment to the adult wards was required, a measure adopted by regional governments. Our data illustrates the effects of those measures on PICUs. For example, the comparison of PICU 5 with PICU 8 shows the different impact of the policy measures on the workload of individual PICUs. PICU 5 and 8 had almost the same, relatively high, percentage of scheduled admissions. At the same time PICU 8 was not associated to an adult hospital, lost no staff to adult wards and treated very few patients with PIMS-TS, whereas PICU 5 was associated to an adult hospital, a part of its staff was recruited to adult wards and treated significantly more children with PIMS-TS. These clearly different circumstances led to different workloads, to some extent illustrated by the difference in average total NEMS points per patient during the study period (466 vs. 294, **Table 2**). Although small in numbers, PIMS-TS patients admitted to PICUs were severely ill, caused a higher workload then average PICU patients (total NEMS points per patient 569 vs. per general PICU patient 92, **Table 3**)The total impact of these patients on total PICU workload during this period can unfortunately not be quantified based on our data.

Different measures influenced the workload and the bed occupancy of the individual PICUs differently, depending on the presence or absence of the single factors and their temporal relationships. Due to their complexity, the exact quantification and comparison of the impact of all these factors was unfortunately not possible. However, thanks to the observations and experiences of the first wave, we recognize that the individual PICUs should be organized primarily by a regional and not federal level and in accordance with but not the same to the surrounding adult hospitals. A timely analysis of the burden and duties of the individual PICU is essential to reduce the workload of the PICU and simultaneously ensure optimal bed occupancy for economic reasons. During a pandemic timely customization

of measures is also essential to adapt the usual available resources to the present requirements. Although it is very important to learn of the experiences of the different countries regarding management of a PICU during a pandemic, there is not much literature. Zeng et al. give insights on the management of a PICU in the SARS-CoV-2 pandemic in southwest China. They focus on measurements ensuring the safety of both patients and medical staff (48). This paper proposes and optimizes a strategic plan for the management of SARS-CoV-2 outbreak in PICU and use risk management and process control to effectively manage the department as well as to protect both the patients and the staff (48).

Our study has some limitations. The retrospective design restricts the range of data available from the study population, this applies for both the historical comparison cohort as well as the epidemiological PIMS-TS data. The logistical aspects are difficult to measure and their temporal relationship has impact on their influence on the management of a single PICU. However, the aim of this study was to describe the different issues of the pandemic influencing the PICUs in Switzerland, a small country organized in a decentralized manner.

In conclusion, the SARS CoV-2 pandemic does not exclusively affect adult ICUs, with PICUs also having to face a variety of eventualities with a plethora of consequences. As pandemic continues, reflecting and learning from experience and cooperate with other PICUs is essential to reduce the workload, optimize the bed occupancy and dispose the resources in each individual PICU. In a small country as Switzerland, the different PICUs should be organized dependent of the local and not federal health care policy due to their different characteristics.

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

The studies involving human participants were reviewed and approved by Cantonal Ethics Committee of Zurich, Stampfenbachstrasse 121, 8090 Zurich. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MS and BB made the conception and the design of the study and draft the manuscript. PW-G and MK performed all statistical analyses of the study, interpreted results, and critically revised the manuscript. SG, M-HP, MH, and MA helped with acquisition of data and critical review of the manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

We would like to thank the contributors of all the Swiss PICUs for their effort and help in data collecting: Tilman Humpl (University Hospital of Bern, Department of Pediatric Intensive Care), Thomas Riedel (Cantonal Hospital Graubuenden, Department of Pediatrics), Peter Rimensberger (University Hospital of Geneva, Division of Neonatology and Pediatric Intensive Care, Department of Pediatrics), Bjarte Rogdo (Children's Hospital of Eastern Switzerland, Neonatal, and Pediatric Intensive Care Unit), Martin Stocker (Children's Hospital Lucerne, Neonatal, and Pediatric Intensive Care Unit). We also thank the RISC-19-ICU collaborators represented by Thierry Fumeaux (Hospital of Nyon, Switzerland, Intensive Care Unit), Philippe Guerci (University Hospital of Nancy, France, Department of Anesthesiology and Critical care Medicine), Jonathan Montomoli (Erasmus medical Center, Rotterdam, Netherlands, Department of Intensive Care Medicine), Reto Schüpbach (University Hospital of Zurich, Zurich, Switzerland, Institute of Intensive Care Medicine).

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frontiers in Pediatrics

REVIEW
published: 01 February 2022
doi: 10.3389/fped.2021.830160

Point-of-Care Ultrasound in the Pediatric Intensive Care Unit

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Ultrasonography has been widely used in medicine for decades but often by specific users such as cardiologists, obstetricians, and radiologists. In the last several years, the use of this imaging modality has moved to the bedside, with clinicians performing and interpreting focused point of care ultrasonography to aid in immediate assessment and management of their patients. The growth of point of care ultrasonography has been facilitated by advancement in ultrasound-related technology and emerging studies and protocols demonstrating its utility in clinical practice. However, considerable challenges remain before this modality can be adopted across the spectrum of disciplines, primarily as it relates to training, competency, and standardization of usage. This review outlines the history, current state, challenges and the future direction of point of care ultrasonography specifically in the field of pediatric critical care medicine.

Keywords: POCUS, point of care, ultrasound, pediatrics, critical care

OPEN ACCESS

Edited by:
Jhuma Sankar,
All India Institute of Medical Sciences, India

Reviewed by:
Maninder Dhaliwal,
Medanta the Medicity Hospital, India
Veena Raghunathan,
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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *06 December 2021*
Accepted: *29 December 2021*
Published: *01 February 2022*

Citation:
Burton L, Bhargava V and Kong M (2022) Point-of-Care Ultrasound in the Pediatric Intensive Care Unit. Front. Pediatr. 9:830160. doi: 10.3389/fped.2021.830160

INTRODUCTION

Point-of-care ultrasound (POCUS) describes the acquisition and interpretation of images by the treating clinician, the end-user, at the bedside (1). It allows for real-time, data-informed clinical decisions, without dependence on a specialist to obtain the images or to interpret them. In pediatric critical care, this ultrasound framework lends itself perfectly as it allows for procedures to be done safely and for rapid, convenient serial reassessments aimed at improving diagnosis and monitoring (2).

In the past decade, significant advancements have been made in pediatric critical care POCUS (3). However, as with most significant advancements, it is not without controversy. The rise of POCUS has been rapid, and many questions remain unanswered, including those related to competency and training. Usage can alter workflow, increase the financial burden, and incorrect interpretations made by inadequately trained users can pose significant risks to patients. However, when POCUS is used as a supplement to existing clinical aids, or as an extension of the physical exam, rather than an independent tool to overrule or replace other diagnostic modality, its benefits are immense, and can provide critical information and guidance in taking care of our patient (4, 5).

In this review, we discuss the origins, current state and evolution of POCUS within pediatric critical care, as well as the future direction and the obstacles that must be overcome to continue its advancement.

HISTORY OF CRITICAL CARE POINT-OF-CARE ULTRASOUND

Medical ultrasound was derived from World War I SONAR technology and then adapted by radiology, cardiology, and obstetrics over the ensuing decades. The first case series of 150 critically ill patients, demonstrating the utility of POCUS was published by Lichtenstein and Axler in 1993

(6), POCUS altered the therapeutic plan in up to one quarter of these patients. However, early point-of-care machines provided poor image quality and were cumbersome to move around and operate, limiting the widespread use of POCUS. For the next two decades, ultrasound machines became smaller, less expensive, more portable and allowed for improved image quality (7). **Table 1** gives an overview of the different ultrasound probes that are currently being used, and their general applications. As the technology advanced, POCUS developed rapidly in parallel, largely spearheaded by adult emergency medicine and critical care (8).

The earliest application of POCUS in pediatric critical care was for central venous catheter placement (9). The transition to ultrasound guided vascular access was motivated by the recommendations from the Agency for Healthcare Research and Quality (AHRQ) as one of the twelve most highly rated practices to prevent medical errors (10). The safety and efficacy of ultrasound guided central venous cannulation allowed for expansion of procedural guidance to arterial line placement, lumbar puncture, peritoneal, pleural, and even pericardial fluid drainage (11). Today, ultrasound guidance in performing procedures is widely accepted and practiced.

On the other hand, diagnostic POCUS implementation and adoption into practice remains variable. A national survey of 128 academic pediatric critical care units in the United States confirmed low and variable rates of implementation, mostly from a lack of user training, competence and confidence (12). In 2014, pediatric POCUS pioneers issued a call to action for responsible and widespread implementation into practice (13). The first reported pediatric critical care focused institutional POCUS training program was implemented in 2015 (14). Since then, POCUS education, training and clinical application have improved in both pediatric critical care and emergency medicine (15). Finally, the growth of pediatric POCUS is also evident in the development of practice guidelines. Although guidelines were published for adult patients by the Society of Critical Care Medicine in 2015, (16, 17) pediatric recommendations have been limited until recently, when the European Society for Pediatric and Neonatal Intensive Care (ESPNIC) published comprehensive, evidence-based guidelines for pediatric intensivists (3).

CURRENT STATE OF CRITICAL CARE POINT-OF-CARE ULTRASOUND

The following sections discuss an overview of the various diagnostic and procedural POCUS applications specific to the pediatric critical care and their impact on patient management.

Procedural Ultrasound

Pediatric critical care practice relies heavily on diagnostic and therapeutic procedures. Utilization of bedside imaging in performing procedures improves accuracy, overall success, and patient satisfaction. It decreases time to successful completion of the procedure and complications (18, 19).

Vascular Cannulation

Central line placement is a commonly performed procedure in the pediatric intensive care unit (PICU). Ultrasound guidance for internal jugular central line placement is the current standard of care in pediatric and adult patients (20). Ultrasound guidance for central venous cannulation increases overall success rate, decreases number of mean attempts required and arterial punctures, especially for internal jugular vein cannulation (18, 21). The evidence is limited for femoral vein and subclavian vein cannulation but supports similar improvement in success and decrement in complications when ultrasound guidance is used (21). The two most common orthogonal planes of central venous cannulation are longitudinal (in plane) and transverse (out-of-plane) (**Figure 1**). There is no consensus as to the superiority of either approach. Vezzani et al. in their study of adult cardiac patients undergoing subclavian cannulation by an experienced anesthesiologist, reported superiority of transverse approach. The cannulation in transverse approach group was associated with higher overall success, first puncture success and lower time to cannulation, failed attempts, and complications (22). In contrast, trained emergency medicine physicians in a simulation study found the longitudinal approach to be superior

TABLE 1 | Ultrasound probes and their general applications.

Probe	Configuration	Frequency (MHz)	Applications
Standard linear	Long, narrow rectangular probe face	5–13	To visualize superficial structures (such as the pleural space, vascular structures and soft tissue) and for procedural guidance)
Neonatal/pediatric linear	Long, narrow rectangular probe face or hockey stick configuration	7–22	Same as standard linear with a smaller footprint for procedural purposes and for a better fit in between rib spaces
Phased array	Small, square probe face	1–5	For visualization of cardiac anatomy and abdominal compartment
Neonatal/pediatric phased array	Smaller square/rectangular probe face	4–8	Same as standard phased array but with smaller footprint for a better fit in between rib spaces
Curvilinear	Curved/rectangular probe face	1–5	Allows for a deeper penetration with a wide field of view. Used for visualization of the abdominal and thoracic space, as well as for procedural guidance

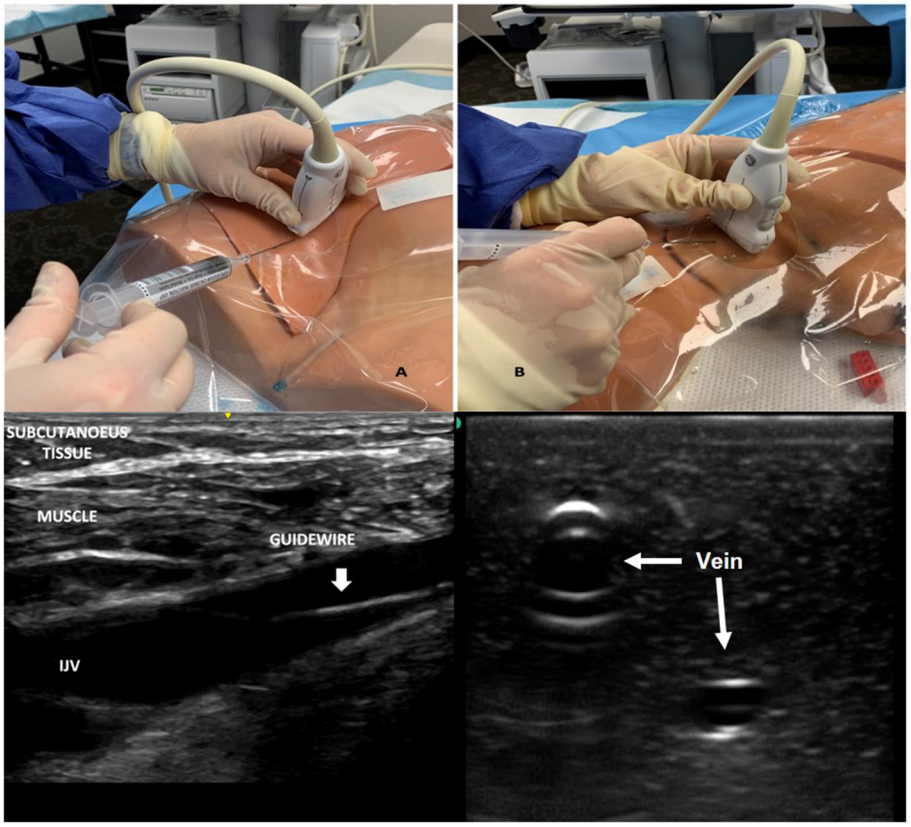

FIGURE 1 | Image demonstrating vascular imaging in short and longitudinal access and probe placement for obtaining images in the two planes. **(A)** Shows probe placement and imaging in longitudinal axis. **(B)** Demonstrating probe placement and imaging in short axis.

(23). Currently, there are no pediatric studies comparing the superiority of the two approaches.

Ultrasound guidance has also been shown to aid in peripheral venous access. Vinograd et al. demonstrated that use of ultrasound guided peripheral intravenous access in children was associated with increased first attempt success rates and increased line longevity compared with traditional placement technique (24). Similarly, Peripherally Inserted Central Catheter (PICC) placed with ultrasound guidance resulted in increased first attempt success rate, overall success rate, and decreased procedure time (25). POCUS can also be used to confirm catheter tip location in venous vascular cannulation. Ultrasound confirmed catheter tip location has been deemed to be safe and effective in midline catheters in adults, umbilical venous catheter and PICC lines in neonates, and to have good agreement with chest x-ray in central venous catheters in pediatric patients (26–29).

For arterial cannulation, there is limited but high-quality evidence (5 RCT's) in pediatric patients suggesting that ultrasound guidance improves first attempt success rate (risk ratio 1.96; 95% CI 1.34–2.85) and decreases complications (risk ratio 0.20; 95% CI 0.07–0.60) (19).

Although concerns were raised regarding the decrease in proficiency of landmark-based methods after adoption of ultrasound by trainees, they were not substantiated by a recent prospective observational study (30). Lastly, there is also skepticism regarding the utility of ultrasound guidance in the hands of experienced providers. In a study by Froehlich et al., ultrasound guided cannulation by experienced physicians were not superior to landmark guided placement even though a robust improvement was noticed in the resident and fellow group (31).

Pleural and Peritoneal Drainage

Thoracentesis, paracentesis, chest tubes, and abdominal drains are important diagnostic and therapeutic procedures performed frequently in the PICU using both real-time and static ultrasound guidance. These procedures are discussed below in greater detail in the abdominal and lung ultrasound sections.

Lumbar Puncture

Lumbar puncture is another commonly performed procedure in the PICU. The incidence of failed procedure and traumatic tap can be as high as 50% (32). Evidence suggesting the utility of ultrasound guidance in lumbar puncture especially for infants and neonates is rapidly emerging. It is a feasible approach to identifying landmarks and interspaces prior to performing the lumbar puncture (33). Ultrasound guidance

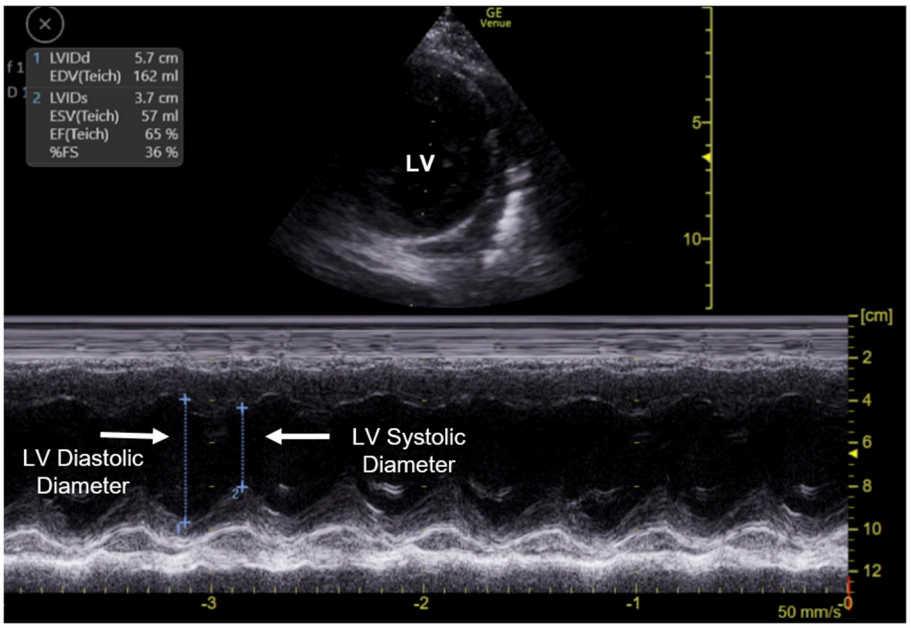

FIGURE 2 | Quantitative estimation of left ventricle (LV) function using fractional shortening. The upper half of the image displays the placement of M-mode line through the left ventricle in a parasternal short axis view of the heart. The lower half of the image displays the M-mode output. Left ventricle systolic and diastolic diameters are measured to calculate fractional shortening. The scale represents the depth of imaging. LV, Left ventricle.

increased the overall number of successful taps, while decreasing the number of traumatic taps, shortened the time to procedure completion, caused fewer needle passes and enhanced patient satisfaction (34, 35). There was a high rate of procedural success even in patients where a previous lumbar puncture using landmarks approach had been previously attempted (36).

Cardiovascular Ultrasound

Hemodynamic instability with and without myocardial dysfunction are common in critically ill children. Focused cardiac ultrasound (FCU) helps in the rapid assessment of myocardial function, fluid status and signs of an obstructive physiology in patient with hemodynamic instability. It can be integrated with clinical assessment to differentiate the etiology of shock as well as to make decisions regarding fluid administration, vasopressor or inotrope usage, and other treatment modalities (37, 38). Although much of the early advancement in FCU was achieved in adults, cardiac images obtained in children have better resolution, encouraging the use of this tool in pediatric patients with hemodynamic instability (39). As the knowledge of expanded applications for critical care POCUS has increased, the number of critical care clinicians employing FCU has also increased (15).

Evaluation of Cardiac Function

Critical care clinicians can examine the systolic and diastolic function of both the ventricles using FCU. While both ventricles can be examined, left ventricular systolic function is more readily assessed. In FCU, the heart is imaged in several different views and the left ventricle systolic function is "eyeballed," or assessed qualitatively (37). Questions are often raised regarding the ability of non-cardiology clinicians to accurately assess myocardial function using echocardiography. In a study by Spurney et al., focused echocardiography performed and interpreted by non-cardiologists using a portable machine in a pediatric population yielded >90% accuracy in the assessment of ventricular function, ventricular size, and the presence or absence of pericardial effusion. Qualitative assessment of left ventricular contractility by intensivists had 96% concordance with cardiologist's interpretations for "clinically significant diagnosis" (40). Conlon et al., reported that a group of POCUS-credentialed pediatric intensivists achieved >90% agreement on ventricular function with cardiologists (38). Critical care clinicians can also employ several quantitative methods of assessing left ventricle systolic function to augment their assessment such as fractional shortening (FS), end point septal separation (EPSS) and fractional area change (FAC) (37) (**Figure 2**). Right ventricle function can also be assessed using FCU. However, the lack of uniform geometry and the contraction of the right ventricle in more than one axis makes it much more challenging to assess its function. Nonetheless, using several different views, the right ventricular wall motion, volume and wall thickness can be assessed, and pulmonary artery systolic pressure can be estimated (41). Guidelines recommend that critical care physicians should use qualitative and semi-quantitative measures to assess for pulmonary hypertension and right ventricle dysfunction (3). Taken together, all these studies suggest that pediatric critical care physicians can perform FCU safely.

TABLE 2 | Assessments of Volume Responsiveness (VR).

Parameter	Definition/explanation	Adult cut-off suggesting VR
IVC collapsibility index	Volume Status Assessment in spontaneously breathing patients (Min IVC diameter-Max IVC diameter)/ Max IVC diameter	>50–55%
IVC distensibility index	Volume Status Assessment in Mechanically Ventilated Patients (Max IVC diameter-Min IVC diameter)/ Min IVC diameter	>18%
Aortic flow velocity variability	Measurement of peak velocity of flow *via* pulsed wave Doppler proximal to aortic valve	>12–15% variability
Left ventricular outflow tract velocity time integral	Doppler ultrasound measurement of blood flow proximal to the aortic valve. It is measured as the area under the velocity time curve obtained from doppler waveform	≥15% variability

Evaluation of Volume Status and Fluid Responsiveness

The accurate assessment of volume status (preload) and fluid responsiveness is challenging in critically ill pediatric patients. Although POCUS has been applied to this question in many different ways, the best application is yet to be determined. **Table 2** provides an overview of volume responsiveness assessment using ultrasound guidance with suggested adult and pediatric cutoff values. The inferior vena cava (IVC) assessment using both *static* measures, in which a single view of IVC at a discrete point in time is obtained and *dynamic* measures, whereby changes in IVC size over a period of time are obtained, have been an ultrasound target for assessment of volume status for a long time. However, both the static measures and dynamic IVC measurements such as IVC collapsibility index (IVCCI) and distensibility index (IVCDI) are affected by cardiopulmonary interactions, such as in the setting of increased spontaneous breathing efforts. In critically ill patients on the mechanical ventilator, the reliability of these values is further decreased, particularly in the setting of high mean airway pressures (42, 43).

In adults, an IVCCI >50% predicts hypovolemia and fluid responsiveness in adults, (37) but this has not proven to be predictive of volume status or fluid responsiveness in children (37, 44). An IVCDI >18% predicts fluid responsiveness in adults with a sensitivity of 80% and a specificity of 94% (37, 45). In contrast, a recent study in mechanically ventilated children did not find IVCDI to be a predictor of fluid responsiveness, instead, the authors found a positive correlation between IVC distensibility and percent fluid overload by weight (46).

Two other dynamic measures of fluid responsiveness, velocity time integral (VTI) and aortic flow variability (AFV) index are much more reliable measures of volume status and fluid responsiveness in children (**Figure 3**). They have consistently predicted fluid responsiveness in mechanically ventilated children with good sensitivity (92%) and specificity (85.5%) (47). However, these measures are technically more challenging to obtain and require a deeper understanding of the principles of doppler, limiting its clinical application.

Evaluation of the Pericardial Space

Pericardial Tamponade is a life-threatening process in children admitted to the PICU especially after cardiac surgery. FCU allows for rapid evaluation of pericardial effusion (39). Evidence of effusion is typically most visible in a subxiphoid four chamber view. In the presence of effusion, tamponade can be sensitively indicated by right atrial collapse (42, 43). A study by Conlon et al., showed that credentialed pediatric intensivist-performed POCUS had a 95% concordance rate for the evaluation of pericardial effusion with a pediatric cardiologist (38). In another study by Spurney et al., the presence or absence of pericardial effusion diagnosed by pediatric intensivists with bedside echocardiogram was diagnosed with 91% accuracy (40). Ultrasound guidance in pericardiocentesis decreases complications and enhances first attempt success (48). Subxiphoid and apical approaches are preferred and the drainage is performed either in the short/out-of-plane axis or long/in-plane axis (49).

FCU in the PICU changes diagnosis and management (2, 50). Arnoldi et al. recently demonstrated that the incorporation of FCU in patients with presumed septic shock changed the intensivists' understanding of hemodynamics in 67% of the patients, suggesting that alignment of clinical management with a cardiac hemodynamic algorithm may improve outcomes in children with suspected septic shock (51). Additionally, a recent pilot study in adults demonstrated that critical care ultrasound-guided, goal-directed therapy in the setting of septic shock resulted in improved clearance of lactic acid at 6 hours and decreased fluid infusion volume at 12 and 24 h compared to the standard, early goal-directed therapy (52).

Finally, the purpose of hemodynamic POCUS is not to replace the formal echocardiogram (5). Rather, it uniquely equips the trained intensivist to answer focused questions with images and interpretations in the clinical context of the patient in the moment (43). It is best used as an adjunct to the physical exam and in conjunction with other means of assessing hemodynamic function that are available to intensivists (43). With the expansion of hemodynamic POCUS in pediatric critical care, there are now numerous guidelines and algorithms available to guide the focused application of echocardiography (3, 39, 53, 54).

Lung Ultrasound

Acute respiratory failure, often secondary to pneumonia, bronchiolitis, and asthma exacerbation is the most common reason for admission to the PICU with pneumonia being the leading cause of death in children worldwide (55). The most commonly used radiographic test, standardized by the World Health Organization is the chest X-ray (CXR) (56). However, the CXR has been found to have relatively low sensitivity and specificity in differentiating etiologies in pediatric acute respiratory failure, suggesting the need for a tool with better diagnostic values. Lung ultrasound is a rapid, radiation free modality and when performed with a focused assessment, allows

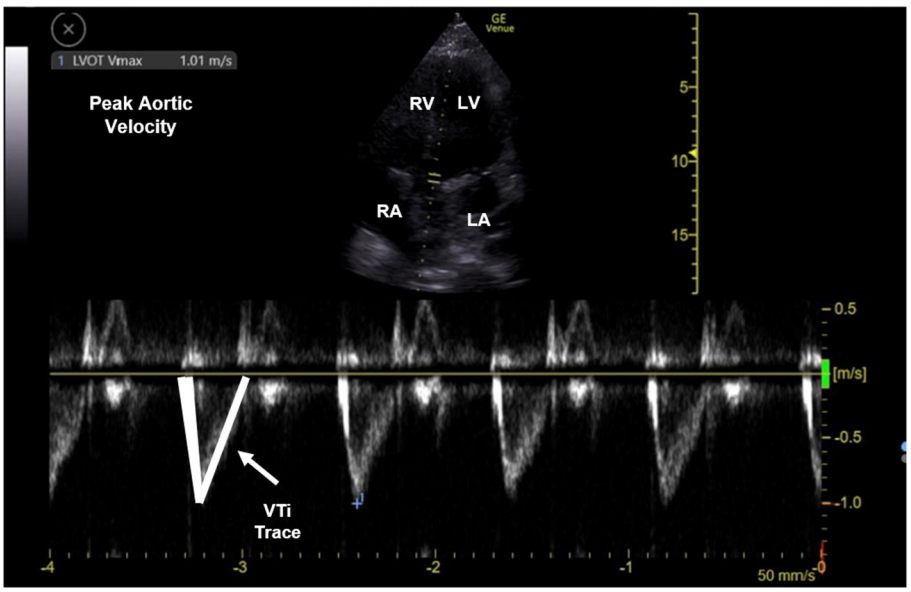

FIGURE 3 | Pulse doppler waveform measuring peak aortic velocity and velocity time integral (VTi). The upper half of the image displays an apical 5 chamber view with pulse doppler gate at the aortic outflow tract. The lower half of the image displays doppler waveform (m/sec). The waveform is traced to estimate VTi and measure peak aortic velocity. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; VTi, velocity time integral.

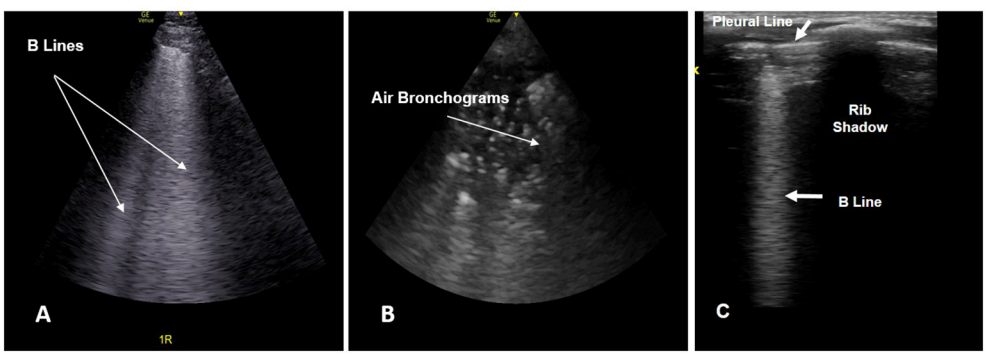

FIGURE 4 | (A) Lung ultrasound image showing multiple B lines (arrow). **(B)** Lung ultrasound image showing air bronchograms (arrow) giving a "speckled" appearance. **(C)** Lung ultrasound image obtained using a linear probe showing a single B line.

the clinician to rule in or out quickly and accurately diagnose certain clinical conditions (57).

Due to the high degree of impedance between soft tissue and air, well-aerated lungs are not well-visualized on ultrasound. Many pulmonary disease processes develop adjacent to the pleura and involve increasing pulmonary fluid or consolidations which provide enhanced ultrasound transmission, and cause alteration or disappearance of normal artifacts in pathologic ultrasound patterns (4). As a result, much of lung ultrasound relies on the interpretation of artifacts. These principles provide the foundation for lung ultrasound. To date, numerous protocols have been published, including the BLUE protocol which provides a standard approach for image acquisition and an algorithmic methodology to synthesize interpretation (58). Lung ultrasound can be used in the pediatric critical care to detect pneumonia, pneumothorax, pleural effusions, lung edema, and atelectasis, as well as guidance for chest tube placement and thoracentesis (3).

Evaluation of Lung Parenchyma

In the evaluation of parenchymal lung disease, a variety of lung ultrasound patterns (pleural line abnormalities, consolidation, dynamic air bronchograms, and sometimes pleural effusion) aid in the diagnosis of pneumonia. B-lines (**Figure 4**) are vertical reverberation artifacts that indicate increased interstitial lung density. The distribution of B-lines have been shown to correspond with sub-pleural thickened interlobular septa, and

are absent under normal conditions. More than two B-lines in a given ultrasound field is considered pathologic and indicative of alveolar-interstitial disease processes.

Lung ultrasound has a much higher diagnostic accuracy compared to CXR in the diagnosis of pneumonia with a pooled sensitivity of 96% and specificity of 93% in pediatric patients (57, 59). Recently, the severity of SARS-COV-2 pneumonia as determined by lung ultrasound performed by intensivists based on alveolar and interstitial consolidation was found to have a strong association with severity as assessed by chest CT (60). Lung ultrasound is also useful in the evaluation of other lung diseases such as bronchiolitis and atelectasis. Studies have demonstrated the ability for users to differentiate pneumonia from bronchiolitis and atelectasis with >85% sensitivity and specificity (61, 62). Lung ultrasound can also predict the need for oxygen and prognosis in patients with bronchiolitis presenting to an emergency room (63).

Evaluation of Pleural Space

Lung ultrasound detects pneumothorax in adults with a sensitivity and specificity >90%; (58) and in neonates with 100% sensitivity and specificity (64). The ultrasound pattern seen in pneumothorax involves an absence of lung sliding at the pleural line, which can be further elucidated in motion (M) – mode, the presence of A-lines, the absence of B-lines, and the visualization of a lung point. Lung point is a specific indicator of pneumothorax characterized by segments of lung sliding and abolished lung sliding in the same ultrasound image (58). Lung ultrasound is also the gold standard for the diagnosis of pleural effusion (**Figure 5**); it detects smaller volumes of pleural fluid compared to CXR and spares radiation associated with CT (65). Ultrasound guided evacuation of pneumothorax and pleural effusion is recommended in neonates, children, and adults to improve success of the procedure and to limit complications (3, 66, 67). While real-time ultrasound guided pleural fluid drainage is safe and easy, the free air associated with pneumothorax makes direct needle and landmark visualization difficult due to poor ultrasound transmission. Therefore, ultrasound is best employed as static guidance in pneumothorax evacuation (67). The use of ultrasound guidance in identification of thoracic landmarks prior to performing thoracentesis or the use of ultrasound guidance for real time thoracentesis in adult patients have been shown to decrease complications such as pneumothorax, inadvertent placement into the abdominal viscera and failed attempts (68, 69). The procedure can be safely performed even in patients on mechanical ventilation with a low rate of pneumothorax (70).

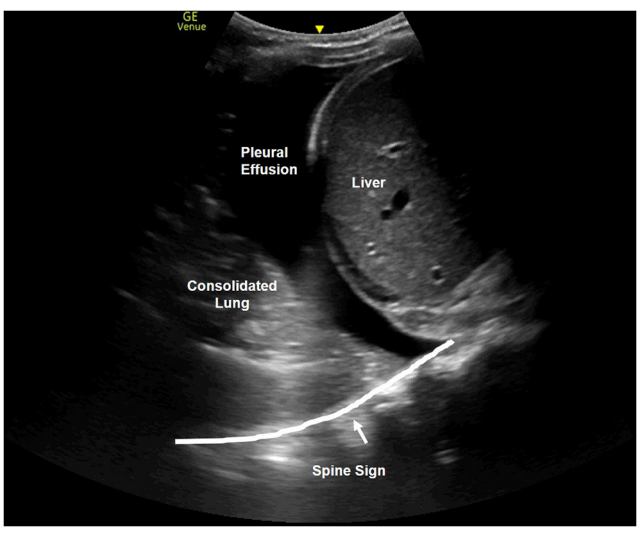

FIGURE 5 | Right upper quadrant view of thoracic-abdominal cavity demonstrating liver, pleural effusion, consolidated lung and the spine sign.

Diaphragm Ultrasound

The diaphragm is easily identified on ultrasound due to its curved, dome-like muscular structure lined superiorly and inferiorly by parietal pleura and peritoneum, respectively. Diaphragmatic ultrasound has been a recent area for innovation with important critical care applications. Much of the work done involves diaphragmatic thickness and diaphragm thickening fraction. Diaphragmatic thickness is a static measure of the distance between the pleural and peritoneal layers. Thickening fraction of the diaphragm, which is used to assess diaphragmatic contractility, is the increase in thickness during inspiration expressed as a percentage (71, 72).

Diaphragmatic dysfunction is a loss of the muscular force generation of the diaphragm that has been associated with longer duration of mechanical ventilation and extubation failure (71–73). Ultrasound determined diaphragmatic thickness and thickening fraction has shown that diaphragmatic atrophy is greater in patients on neuromuscular blockade and that diaphragmatic contractility was linearly correlated with patients' degree of spontaneous breathing (72, 74). Ultrasound determined diaphragmatic atrophy has also been proven to be associated with prolonged post-extubation non-invasive positive pressure ventilation (73). These studies demonstrate the utility of diaphragmatic ultrasound as a tool to help identify patients who are at risk for diaphragmatic dysfunction-mediated morbidity. Similarly, in two pediatric studies, the investigators found an association between diaphragmatic thickening fraction during spontaneous breathing trials and successful extubation (75, 76). Diaphragmatic ultrasound has also been used in children to predict outcomes in both pneumonia and bronchiolitis using various diaphragmatic ultrasonographic metrics (77, 78).

Abdominal Ultrasound

The focused assessment with sonography in trauma (FAST) examination is one of the original applications of resuscitation ultrasound, particularly in the emergency department (ED). It assesses for the presence of free fluid in the peritoneal cavity, and may be useful in the serial evaluation of blunt abdominal trauma in pediatric patients who are hemodynamically stable (79) (**Figure 6**). FAST exam has been shown to decrease the time to intervention in adult patients with blunt abdominal trauma (80). However, in a large randomized controlled trial of 925 pediatric patients treated in an ED following blunt torso trauma, the use of FAST compared with standard care only did not

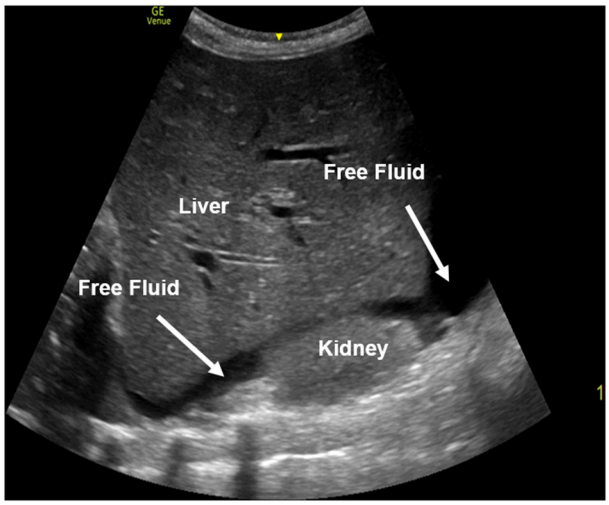

FIGURE 6 | A right upper quadrant view performed in a FAST exam with free fluid present between the liver and the kidney. The free fluid appears black (anechoic) on ultrasound.

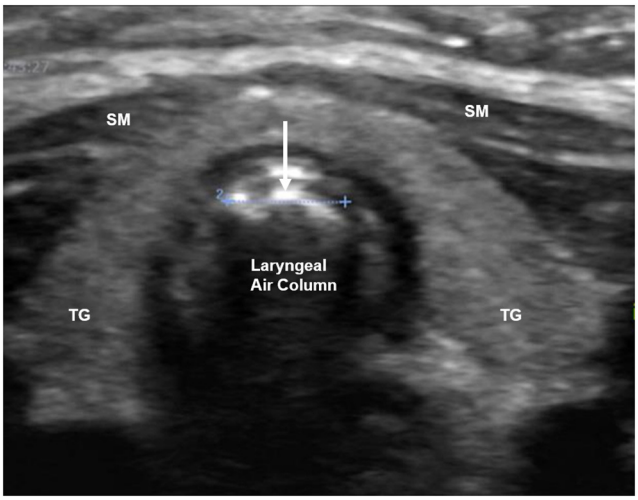

FIGURE 7 | Airway ultrasound image at the level of thyroid gland demonstrating laryngeal air column width (arrow). TG, thyroid gland; SM, strap muscles.

improve clinical care nor did it change the length of ED stay (81). In this study, there was no harm to the patients, including delay in care, missed findings or increased in number of computed tomography (CT) scans obtained because of the FAST exam. Since the FAST exam can be performed rapidly and repeated serially without much risk, it is prudent for providers to develop expertise in FAST even when the expected yield might be low. The traditional FAST has also been augmented to evaluate the lungs for hemothorax and pneumothorax, known as the extended FAST examination (eFAST) (82).

Point-of-care abdominal ultrasound can also be used for rapid estimation of bladder volume in oliguric/anuric critically ill children. Although it underestimates the true bladder volume compared to bladder catheterization (83), abdominal ultrasound is more accurate and reliable than the portable automated bladder ultrasound devices (84), especially at low bladder volumes. Use by bedside nurses is also a feasible approach, making this tool easily accessible for use (85).

Ultrasound guidance is frequently used in performing paracentesis and placement of abdominal drains. Mercardi et al., found that ultrasound guided paracentesis decreased the rate of complications such as bleeding and the associated patient care costs (68).

Airway Ultrasound

Airway ultrasound is a novel point of care application in pediatric critical care (86). Clinicians are often challenged with questions such as vocal cord dysfunction, prediction of post-extubation stridor, anticipation of a difficult airway, and correct size and depth of endotracheal tube placement that are inadequately answered by current imaging or require invasive procedures.

The diagnosis of vocal cord dysfunction requires a flexible scope that is not always readily available and can be uncomfortable for the patient. A single view of the vocal cords obtained using bedside ultrasound can be used to diagnose vocal cord dysfunction in patients. A recent meta-analysis of eight observational studies, including 290 pediatric patients showed robust test characteristics of using bedside ultrasound to diagnose vocal cord dysfunction: pooled sensitivity of 91%, specificity of 97%, and a diagnostic odds ratio 333.56 (87). Adaptation by clinicians from diverse backgrounds, methodological and equipment similarities, rapid learning curve and a low risk of bias makes this an attractive bedside procedure (87).

Post extubation stridor complicates the clinical course of patients. Accurately predicting which patients will develop post extubation stridor allows clinicians to intervene both before and after development of stridor to minimize its clinical impact. Laryngeal air column width is measured using a single view obtained at the level of vocal cords (**Figure 7**). The difference in the width of the air column with the balloon cuff of the endotracheal tube inflated and deflated predicts post extubation stridor more accurately than the cuff leak test (accuracy 91% vs. 53%) (88).

Video laryngoscopy and the use of end tidal capnography are widely available and reliably predict endotracheal vs. esophageal intubation. However, when these are not available or in certain clinical scenarios, for instance in a patient with prolonged cardiac arrest or large pulmonary embolism when capnography is not reliable, bedside ultrasound can rapidly and accurately differentiate between esophageal vs. endotracheal intubation. A single view of trachea and esophagus at the level of cricothyroid membrane, while performing laryngoscopy and intubation predicts tracheal intubation with a sensitivity of 92–100% and a specificity of 100% (89, 90). The clinician can further measure the width of the air column at the level of cricoid cartilage to predict the correct size of cuffed

(98% accuracy) and uncuffed (95% accuracy) endotracheal tubes (91).

Airway ultrasound can also be used to determine the depth of the endotracheal tube, and if the tube is in the right main stem bronchus. Because direct visualization of the endotracheal tube and the cuff is difficult (as they are both radiolucent), investigators have used indirect methods of cuff detection and depth of endotracheal tube placement. These include visualizing saline inflated cuff (sensitivity 98.8%, specificity 96.4%) (92), evaluating pleural sliding on both sides of the chest, (90) and assessing diaphragmatic movement on both sides simultaneously (93). Recently, clinical protocols combining these methods have been deployed with promising results in adults but validating studies are lacking in pediatrics (94). Although direct visualization of the endotracheal tube is feasible in neonates and infants, (95) this technique is much more challenging and only recommended for providers with experience in bedside ultrasound.

Airway ultrasound is promising in the prediction of a difficult laryngoscopy. A recent meta-analysis found robust test characteristics for prediction of a difficult laryngoscopy with significant sensitivity and specificity in adult patients using ultrasound (96). Ultrasound metrics evaluating anterior neck soft tissue thickness and mobility of the neck were found to be important predictors of a difficult laryngoscopy (96). To date, only one pediatric study evaluating ultrasound for difficult laryngoscopy has been performed that demonstrated good sensitivity (100%) and negative predictive value (100%) but with modest specificity (62%) and positive predictive value (19%) (97).

Neurosonology

Traumatic brain injury is associated with significant morbidity and mortality in patients admitted to the PICU. Improving diagnosis and non-invasive monitoring of increased intracranial pressure and adequacy of cerebral perfusion remain attractive targets for clinical use and future research in neurocritical care (98). The two most common measurements used in cerebral ultrasound are the optic nerve sheath diameter (ONSD) and transcranial doppler estimation (99). Optic nerve sheath communicates with the subarachnoid space and increased intracranial pressure is transduced from the space to the sheath thereby causing sheath distention (**Figure 8**). Ultrasound measured ONSD above a certain threshold can predict increased intracranial pressure. Currently, most pediatric studies use ONSD >4.5 mm to predict increased intracranial pressure, which is a metric derived from adult studies (100). Isolated measurements at the time of patient presentation have been used to predict increased intracranial pressure due to a wide variety of etiologies such as hydrocephalus, shunt dysfunction, cerebral malaria, meningitis, intracranial mass and traumatic brain injury in pediatric patients (101). In these diverse patient populations, ONSD estimation performs well with a high sensitivity (pooled sensitivity 93%) and modest specificity (pooled specificity 74%) (101). However, a wide variation in the optimal threshold of

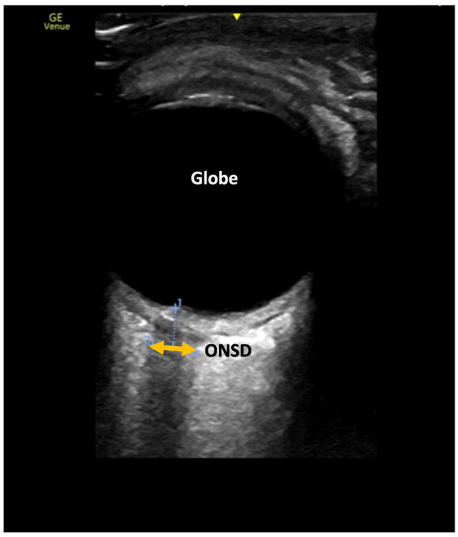

FIGURE 8 | Ocular ultrasound demonstrating optic nerve sheath diameter measurement (ONSD). The sheath appears as a less bright (hypoechoic) structure compared to the surrounding tissue.

ONSD and a modest specificity have prevented its applicability to clinical practice. There are also concerns that the plasticity of the sheath changes over time in patients with chronic elevation of intracranial pressure. Recently, serial measurements of ONSD performed in pediatric patients with traumatic brain injury and invasive intracranial monitoring failed to demonstrate co-relation between ONSD and increased intracranial pressure (102). Further work indexing ONSD to pediatric head size needs to be done before this metric can be integrated in clinical settings.

Transcranial doppler (TCD) has been used in the care of children for over three decades. TCD relies on the estimation of peak systolic, end diastolic and mean cerebral blood flow velocities from large cerebral arteries. These measurements are then used to derive physiological parameters to answer relevant clinical questions. Its utility in the outpatient management of patients with sickle cell disease is well-known (103). Its utility in neurocritical care is limited to evaluation of cerebral autoregulation, increased intracranial pressure, cerebral vasospasm, midline deviation and brain death (104). The availability and the utilization of this novel point of care tool remains restricted to a few specialized centers with resources and expertise in TCD. A recent survey of 29 pediatric neurocritical care centers found 20 centers utilizing TCD in their clinical practice to guide patient management. However, the adaptation was limited by the presence of equipment and trained physicians capable of performing and interpreting these studies, and the lack of standardized protocols across institutions (105). Consensus recommendations on standardizing these practices have since been proposed (106), but much work needs to be done before this can be integrated into current critical care practice.

PRACTICAL POCUS CONSIDERATIONS

PICU patients are typically compromised, at least to some extent, and can be fragile and difficult to position. Additionally, many are connected to ventilators, extracorporeal circuits, or any number of different monitors at their bedside. Taken together, these factors can pose barriers to adequate POCUS access and image acquisition. Over the last few years, as POCUS technology has improved, clinicians now have access to smaller and more portable machines, mitigating some of these ergonomic issues (1). However, in certain circumstances, optimal positioning cannot be achieved, and the clinician must be flexible and trained in obtaining important information in less than ideal situations. The clinician must also be prudent in determining when the effort of POCUS is not in the patient's best interest, and therefore should be avoided or delayed.

POCUS equipment also has the potential to be a significant fomite (107). Infectious organisms such as staphylococcus aureus, pseudomonas aeruginosa, and vancomycin-resistant enterococci have been cultured from POCUS equipment, (108–112) and the ability of SARS-CoV-2 to survive on plastic emphasize the potential infectious threat (113). The importance of preventing POCUS from causing harm to already critically ill patients cannot be understated. To that end, numerous professional groups have published POCUS disinfection guidelines (114–117). Aseptic cleaning techniques have been shown to significantly reduce infectious organism burden on ultrasound equipment (118, 119). Emphasis on and adherence to these practices are important to prevent the benefit of POCUS from being outweighed by infectious consequences.

TABLE 3 | Glossary of terms.

Air Bronchograms	Air filled bronchi surrounded by alveoli filled with fluid, pus or other material. These appear as alternate areas of bright and dark structures on ultrasound
Aortic Flow Variability (AFV)	Change in the velocity of blood flow during respiratory cycle, measured over the aortic valve
B-lines	Vertical artifact on lung ultrasound signifying pleural or parenchymal pathology
B-mode	Brightness Mode - standard ultrasound that generates 2-dimensional gray scale images
Doppler	Measurement of velocity and direction of moving structures using ultrasound
End Point Septal Separation (EPSS)	Assessment of mitral valve leaflet movement toward interventricular septum using Motion (M) - mode
Fractional Area Change (FAC)	The change in left ventricle area between systole and diastole expressed as a percentage
Fractional Shortening (FS)	The change in left ventricle diameter size between systole and diastole expressed as a percentage
Impedance (acoustic)	The resistance to the propagation of ultrasound waves through the tissue.
IVC Collapsibility Index (IVCCI)	The change in the diameter of IVC in a spontaneously breathing patient over the respiratory cycle
IVC Distensibility Index (IVCDI)	The change in the diameter of IVC in a mechanically ventilated patient over the respiratory cycle
Laryngeal Air Column Width (LACW)	The width of the column of air as determined by ultrasound
Longitudinal axis	The evaluation of a structure along its length. Also referred to as In-plane or long axis approach
Lung sliding	Dynamic movement seen on ultrasound at the pleural line as visceral pleura slides along the parietal pleura
M-mode	Motion mode - narrows to a single line of B-mode that permits a still image to demonstrate motion and allows for measurements of rapidly moving structures
Pulsed-wave doppler	Doppler principle of sending pulses of ultrasound and analyzing reflected sound waves between the pulses
Transverse axis	The evaluation of a structure in a plane orthogonal to its length. Also referred to as the out of plane or short axis approach.
Velocity Time Integral (VTi)	Doppler ultrasound measurement of blood flow. It is measured as the area under the velocity time curve obtained from doppler waveform

CURRENT STATE OF TRAINING AND COMPETENCY STANDARDS

Bedside ultrasound educators and program directors from several pediatric critical care fellowship programs conducted a detailed needs assessment that laid the foundation for programmatic development in the U.S. (15). They highlighted five core elements: training, credentialing, image storage, documentation, and quality assurance. Universally accepted standards for these core elements are lacking due to limited availability of high-quality evidence. Most large and small fellowship programs in the United States utilize diagnostic ultrasound and 79% of these programs provide formal fellow ultrasound training. However, only a small number of programs have quality assurance and credentialing processes in place. Image storage and appropriate documentation were also limited in the surveyed programs. The consensus among the survey participants was that having all five core elements in place would facilitate more effective implementation of bedside ultrasound.

Currently, a variety of training programs and curricula serve the educational needs of pediatric critical care physicians and trainees. National, regional, and institutional courses and longitudinal educational series are available at multiple centers. These courses can be expensive and limited in their availability. There is also a dearth of published curricular resources, thus making bedside ultrasound implementation difficult for programs without extensive infrastructure and personnel in place. The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) published expert consensus guidelines on bedside ultrasound applications defining the scope of pediatric and neonatal critical care physicians; however several of these recommendations are expert opinions supported only by moderate quality evidence (3). Lack of infrastructure, personnel, training opportunities and well-defined scope of practice are barriers to education and widespread adaptation of bedside ultrasound.

Assessment of competency in bedside ultrasound is critical to its safe and effective application at the bedside. The current standards for competency are often defined by the number of examinations performed and are guided by limited

evidence. The American college of Emergency Physicians recommends 25–50 high quality scans in each POCUS domain, while the Society of Critical Care Anesthesiologists recommends a higher number at 50 exams per domain (120, 121). However, it is important to recognize that the learning curve is different for each learner. Multi modal assessment tools that avoid the "one size fits all" approach such as direct observations, written examinations, structured clinical examinations and periodic quality assurance image review and feedback are necessary to effectively evaluate competency (122).

Lastly, credentialing allows a clinician who has demonstrated competency to integrate a new skill into their practice. It ensures the maintenance of a standard of care for both the patients and the physicians. The lack of published guidelines has contributed to difficulties in establishing credentialing pathways. Institutions have used a collaborative approach to bring together the major stakeholders and provide oversight as well as develop credentialing pathways (5). One such example is the implementation of ultrasound curriculum in a large academic pediatric critical care unit by Conlon et al., (14). Experiences from other institutions in the future will help further strengthen the development of standardized credentialing pathways.

FUTURE DIRECTIONS FOR POINT OF CARE ULTRASOUND

POCUS is beneficial in skilled hands, and emerging evidence suggest improved outcomes with its deployment. However, there are several challenges to its safe and efficacious implementation. First, there is a lack of adequate training, competency standards and evidence-based scope of practice. In 2020, the Joint Commission on Accreditation of Healthcare Organizations and the Emergency Care Research Institute cited POCUS without appropriate oversight as a major health technology hazard (123). This emphasizes the need for training and certification standards, oversight processes, and imaging and interpretation protocols to prevent adverse outcomes associated with POCUS implementation (124). As standardization practices are being developed, it is important that they are pediatric critical care-specific. Uniformity across individual programs at a professional society level would serve both as a safeguard and as a tool to optimize performance (125, 126). Also, there is a large variability in the level of expertise, the scanning protocols used, the heterogeneity of the patients and clinical conditions, and the lack of systematic approach that prevents consistent integration into clinical practice.

Ultrasonographic technological advances will help POCUS innovation and implementation (1). Smaller, more versatile handheld ultrasound devices with Doppler, M-mode, and other quantitative abilities are more readily available (127–129). Convenience without compromising capability will improve application and consistent informed decision making. Artificial intelligence is also being applied to ultrasound technology to flatten the learning curve and improve image acquisition (1). Deep-learning algorithms applied to POCUS have the potential to be transformative as it allows the ultrasound machine to guide image acquisition (130) and to detect certain pathologies in point-of-care images (131, 132). Although emerging work in ultrasound artificial intelligence could be the driving force behind POCUS training and application advancement, it could also pose challenges to the development and enforcement of competency and safety measures.

CONCLUSION

In its current state, pediatric critical care POCUS lags behind other areas of critical care in implementation and expertise. The application of training and certification standards in parallel with emerging technology will improve competency and confidence among clinicians (8). As more skilled practitioners become available, it will be important that an appropriate scope of practice is defined and applied. Evidence based pediatric critical care-specific literature to support and validate practices will be crucial (4, 9, 13). The ultimate goal of improving and increasing POCUS use in the specialty is not to increase the ultrasound footprint in pediatric critical care; but rather to optimize the care that patients receive in the PICU. A glossary of important terms used can be found in **Table 3**.

AUTHOR CONTRIBUTIONS

LB, VB, and MK contributed to the conception and writing and final edits of this manuscript. All authors contributed to the article and approved the submitted version.

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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.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 23 February 2022
doi: 10.3389/fped.2022.828637

Current Practice of Fluid Maintenance and Replacement Therapy in Mechanically Ventilated Critically Ill Children: A European Survey

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Edited by:
Jhuma Sankar, All India Institute of Medical Sciences, India

Reviewed by:
Guoping Lu, Fudan University, China
Zaccaria Ricci, University of Florence, Italy

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *03 December 2021*
Accepted: *24 January 2022*
Published: *23 February 2022*

Citation:
Arrahmani I, Ingelse SA, van Woensel JBM, Bem RA and Lemson J (2022) Current Practice of Fluid Maintenance and Replacement Therapy in Mechanically Ventilated Critically Ill Children: A European Survey. Front. Pediatr. 10:828637. doi: 10.3389/fped.2022.828637

Appropriate fluid management in mechanically ventilated critically ill children remains an important challenge and topic of active discussion in pediatric intensive care medicine. An increasing number of studies show an association between a positive fluid balance or fluid overload and adverse outcomes. However, to date, no international consensus regarding fluid management or removal strategies exists. The aim of this study was to obtain more insight into the current clinical practice of fluid therapy in mechanically ventilated critically ill children. On behalf of the section of cardiovascular dynamics of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) we conducted an anonymous survey among pediatric intensive care unit (PICU) specialists in Europe regarding fluid overload and management. A total of 107 study participants responded to the survey. The vast majority of respondents considers fluid overload to be a common phenomenon in mechanically ventilated children and believes this complication is associated with adverse outcomes, such as mortality and duration of respiratory support. Yet, only 75% of the respondents administers a lower volume of fluids (reduction of 20% of normal intake) to mechanically ventilated critically ill children on admission. During PICU stay, a cumulative fluid balance of more than 5% is considered to be an indication to reduce fluid intake and start diuretic treatment in most respondents. Next to fluid balance calculation, the occurrence of peripheral and/or pulmonary edema (as assessed including by chest radiograph and lung ultrasound) was considered an important clinical sign of fluid overload entailing further therapeutic action. In conclusion, fluid overload in mechanically ventilated critically ill children is considered an important problem among PICU specialists, but there is great heterogeneity in the current clinical practice to avoid this complication. We identify a great need for further prospective and randomized investigation of the effects of (restrictive) fluid strategies in the PICU.

Keywords: fluid balance, edema, mechanical ventilation, children, pediatric intensive care unit

INTRODUCTION

Increasing evidence shows that overzealous use of (intravenous) fluids in critically ill patients beyond the resuscitation phase is associated with adverse outcome (1–3). A recent systematic review and meta-analysis showed that fluid overload in critically ill children admitted to the pediatric intensive care unit (PICU) was associated with fewer ventilator free days, a higher risk of acute kidney injury and even an increased risk of mortality (4). To our knowledge, no clinical trials comparing liberal vs. restrictive fluid therapy strategies in critically ill children have been published.

Restricting the amount of fluids is a daily clinical challenge, particularly in critically ill children undergoing invasive mechanical ventilation. Specifically, because the administration of fluid is necessary to provide hemodynamic support and to ensure appropriate caloric/protein intake while at the same time it functions as a vehicle for drug delivery (fluid creep) (5, 6). As a result, a positive (cumulative) fluid balance and the formation of edema are very common in these children (3, 4, 7, 8). However, fluid maintenance strategies and the use of diuretic medications in the PICU environment may vary. More insight into the current clinical practice of fluid therapy in critically ill children is necessary. This information can be used to design and guide future trials that might lead to international consensus and evidence-based guidelines.

The main goal of this study was to gain insight into the current clinical practice and attitudes of PICU clinicians regarding fluid maintenance and replacement therapy in mechanically ventilated critically ill children.

METHODS

Survey Design

This web-based, anonymous survey was designed using Surveymonkey®. The survey was composed using the contribution of all authors. In the process, besides email contact, we organized two discussion sessions and multiple dry runs. The conceptual survey questions were sent to an independent colleague with expertise regarding the subject, for review concerning clarity, relevance and topic coverage.

The survey was written in English and comprised of a total of 47 questions divided over eight sections (Demographic information, Statements regarding fluid management and overload, Monitoring fluid balance, Interventions, Nutrition and enteral feeding and Future studies). As stated in the survey (**Supplementary Material**) the questions focused on "general" invasive mechanically ventilated (expected duration >48 h) PICU patients, excluding post-transplant patients, post-cardiothoracic surgery patients and patients with pre-existing cardiac and kidney dysfunction prior to admission to PICU. The survey consisted of a combination of multiple-choice questions, Likert-scales and free text responses. The full questionnaire of this survey can be found as an online supplement to this article (**Supplementary Material**).

Participants were asked for consent at the start of the survey and were given the opportunity to leave comments and demographic information on a voluntary basis. A waiver from the local ethical committee for the distribution of the survey was obtained (W21-388). The survey was created and distributed following current available recommendations where possible and appropriate (9).

Target Respondents and Survey Distribution

Only (fellow-) pediatric-intensivists and PICU nurse practitioners were asked to fill in the survey. Furthermore, it was also required for the participants to work in a European country. The survey invitation was distributed through the European Society of Pediatric Neonatal Intensive Care (ESPNIC) newsletter and by email personally directed to all members of the section of cardiovascular dynamics of ESPNIC. In the Netherlands, the survey was also distributed via email to the members of the Dutch Society of Pediatric Intensive Care. Finally, in order to increase the response rate, the survey was also distributed to other colleagues using the authors' personal contact list. Official email reminders were sent twice, at 1 and 3 months after the initial distribution of the survey. In addition, monthly reminders were sent out through social media platforms of ESPNIC (e.g., official ESPNIC Facebook page, twitter, LinkedIn).

Data Collection

Data from the online survey were collected from November 2020 until April of 2021.

Statistical Analysis

Statistical analysis was performed using IBM statistics SPSS v26.0. Data were analyzed with descriptive measures and presented as proportion, percentage and median (interquartile range, IQR). For each question, the total number of respondents may due to an incomplete survey response leading to missing answers. Therefore, we present the number of respondents per survey question throughout the paper. Data from Likert scales were enumerated as ordinal data ranging from 1 to 5, with 1 = strongly disagree and 5 = strongly agree.

RESULTS

Demographic Information

After exclusion of those respondents that were not eligible to participate, a total of 107 respondents were included in the final analysis (**Figure 1**). 82/107 (76.6%) of the respondents completed all the mandatory questions of the survey. 55/107 (48.6%) of the respondents came from the Netherlands, 17/107 (15.9%) from Germany and 16/107 (15.0%) from the UK (**Table 1**).

As depicted in **Table 1**, 95/107 (88.5%) of the respondents were practicing pediatric-intensivists and had over more than 10 years (N = 65/107, 60.7%) of clinical experience working in a PICU. The respondents stated to work in a general-, cardiac-, or mixed PICU in 49/107 (45.7%), 1/107 (0.9%), and 45/107 (42.1%) of the cases, respectively. 12/107 (11.2%) reported to work in a combined PICU-neonatology (N)ICU.

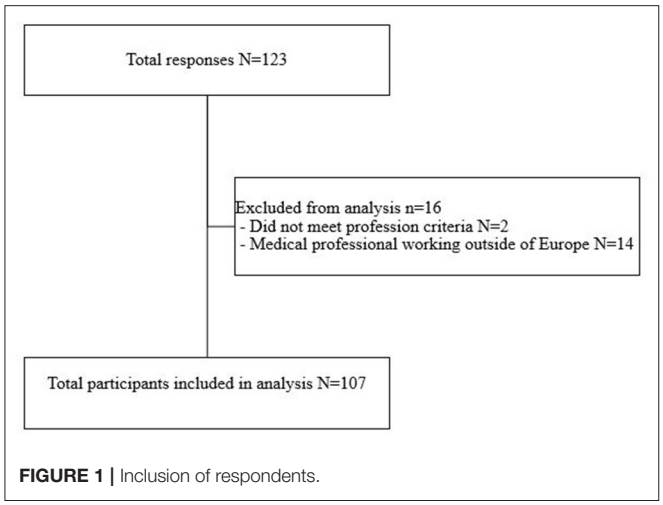

FIGURE 1 | Inclusion of respondents.

TABLE 1 | Demographics.

	N (%)
Total number of respondents after exclusion	107 (100)
Country of PICU location	
Netherlands	55 (48.6)
Germany	17 (15.9)
UK	16 (15)
Belgium	1 (0.9)
Czech Republic	1 (0.9)
France	2 (1.9)
Greece	2 (1.9)
Hungary	1 (0.9)
Italy	4 (3.7)
Norway	1 (0.9)
Spain	5 (4.7)
Switzerland	2 (1.9)
Ukraine	2 (1.9)
Macedonia	1 (0.9)
Medical profession	
Pediatric-intensivist	95 (88.5)
Fellow pediatric-intensivist	7 (6.5)
PICU nurse-practitioner	4 (3.7)
Years of experience working in PICU	
>10 years	65 (60.7)
5–10 years	16 (15.0)
0–5 years	26 (24.3)
PICU facility	
General PICU	49 (45.7)
Cardiac PICU	1 (0.9)
Mixed cardiac and general PICU	45 (42.1)
Mixed PICU-neonatology (N)ICU	12 (11.2)

View on Fluid Management

Respondents were asked to give their view on several statements concerning the topic fluid overload and management. As shown in **Figure 2**, 82/86 (95.7%) respondents considered fluid overload to be a common problem in invasive mechanically ventilated children admitted to the PICU. In addition, 76/86 (88.3%) respondents agreed or strongly agreed with the argument that positive fluid balance is associated with a poor outcome in these patients. In line with this, 56/86 (64.9%) respondents believed that a conservative fluid management approach will be beneficial. The results of all statements are shown in the **Supplementary Figure 1**.

Determining Total Fluid Maintenance Requirement

In the survey, fluid maintenance was defined as all fluids administered during the course of mechanical ventilation, including medication, nutrition, fluid challenges. 57/86 (66.3%) of the respondents reported the presence of a local written protocol concerning total fluid management in invasive mechanically ventilated patients. In 55/86 (63.9%) of cases, the existing protocol was intended for all admitted patients, while in the other cases the protocol was primarily intended for a specific PICU population (e.g., post-cardiac surgery, post general surgery, septic patients).

55/86 (63.9%) of the respondents reported that they use the Holiday-Segar formula (4 ml/kg/h for the first 10 kg + 2 ml/kg/u for the second 10 kg + 1 ml/kg/u>20 kg) to determine the normal daily total fluid volume requirement in healthy children (non-critically ill, non-mechanically ventilated patients). For PICU patients at the start of invasive mechanical ventilation, 64/86 (74.4%) of the respondents reported to give less fluids (median (IQR) 20% (20–30)] based on the calculated normal daily total fluid volume. The remainder of the respondents 21/86 (24.4 %) stated to give the full 100% of calculated normal maintenance fluid.

Balanced crystalloid solutions were the preferred choice during intravenous fluid therapy followed by crystalloid solutions. A small minority [3/82 (3.7%)] preferred colloid solutions, such as albumin and hydroxyethyl starch.

Table 2 depicts the response concerning fluid resuscitation and hypovolemia. When asked about the way the respondents determined the need for fluid resuscitation in invasive mechanically ventilated children, 79/82 (96.3%) of the participants reported clinical signs (e.g., central capillary refill, color, peripheral temperature) as a marker for hypovolemic state. Heart rate, blood pressure, urine production and fluid responsiveness were also frequently (in >90% of the responses) considered as markers for a hypovolemic state.

When administering a fluid bolus, 59/82 (72.0%) of the participants preferred a fluid bolus of 10 ml/kg in invasive mechanically children without signs of cardiac failure. 11/82 (13.4%) of the respondents reported the use of a fluid bolus of 20 ml/kg.

Monitoring Fluid Overload and Interventions

The choice of fluid overload monitoring in invasively mechanically ventilated children was divided between the

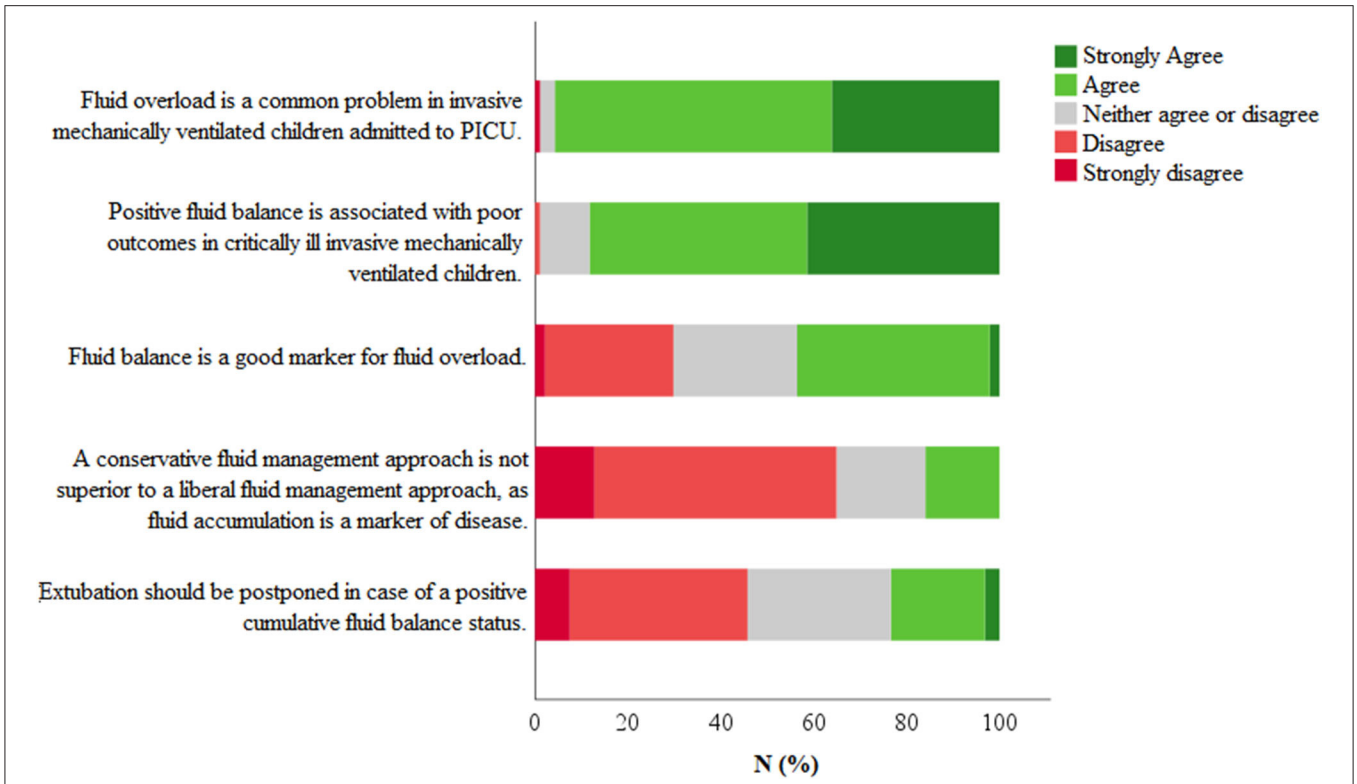

FIGURE 2 | Statements regarding fluid management. Respondents were asked to give their opinion on several statements using a 5-point Likert scale (strongly disagree–strongly agree). Total number of respondents $N = 82$.

respondents of the survey. More than one third of the respondents claimed that NET or cumulative fluid balance was monitored hourly, followed by every six ($N = 21/82$, 25.6%) or eight ($N = 14/82$, 17.1%) hours.

Figure 3 illustrates the reported clinical signs of an excessive fluid state (as considered to be in need of fluid removal therapy). Peripheral edema, signs of pulmonary edema and a positive total fluid balance, as clinical signs of an excessive fluid state, were reported in 77/82 (93.9%), 79/82 (96.3%), and 76/82 (92.7%) of the responses, respectively. On the other hand, peripheral edema, signs of pulmonary edema and a positive total fluid balance, as clinical signs addressing the need for fluid removal therapy and /or fluid restriction, were reported in 61/82 (74.4%), 78/82 (95.1%), and 51/82 (62.2%) of cases, respectively.

Table 3 depicts tools (clinical, radiological and/or laboratory) used for diagnosing fluid overload. For this purpose, laboratory findings (e.g., urea, creatinine, NT-pro BNP), chest-X-ray and lung ultrasound were reported to be utilized in 60/82 (73.1%), 57/82 (69.5%), and 42/82 (51.2%) of the responses, respectively.

As presented in **Table 4**, there was a considerable variation in clinical practice regarding the threshold of positive cumulative fluid balance at which fluid management adjustments were accomplished. While a small majority (51.2%) of the respondents would change the fluid management above 5% positive cumulative fluid balance, 28% of the clinicians reported to make adjustments only when clinical signs of fluid overload were observed. Decreasing the amount of maintenance fluidas was reported to be the primary intervention in case of an excessive fluid state of the patient by 67/82 (81.7%) respondents. Starting diuretic drug therapy as the initial approach was reported by 72/82 (87.8%) of the cases. Initial diuretics prescribed included intermitted loop diuretics (reported by 73/82 (89.0%) of the respondents), potassium sparing drugs in 36/82 (43.9%) of the cases, and 20/82 (24.4%) of the respondents preferred continuous loop diuretic drip infusion. Thiazide diuretics were reported to be used in only 9/82 (11.0%) of the responders. Early initiation of continuous renal replacement therapy (CRRT) was reported to be the initial approach in 4/82 (4.8%) of the cases while 55/82 (67.1%) of the respondents indicated that CRRT is never or rarely used to manage fluid overload as the sole indication. In 27/82 (32.9%) of the cases, CRRT is reported to be used as treatment for fluid overload as the sole indication.

Nutrition and Enteral Feeding

In order to maintain an acceptable fluid balance, 37/82 (45.1%) of the survey respondents (strongly) agreed that energy requirements of the patients can be decreased. On the other hand, 32/82 (39.0%) (strongly) disagreed with this statement. Enteral administration of fluid by feeding (non-resuscitation) was considered the preferred method in 75/82 (91.5%) of the cases.

TABLE 2 | Fluid resuscitation and hypovolemia.

	N (%)
Total number of respondents	82 (100)
How do you determine if your patient is in need of fluid resuscitation? (please check ALL that apply)	
Based upon clinical signs (like refill, colour, peripheral temperature)	79 (96.3)
Based upon heart rate and or blood pressure	75 (91.5)
Based upon urine production	74 (90.2)
Based upon additional diagnostics (ultrasound, advanced hemodynamic monitoring, etc.)	60 (73.2)
Based upon laboratory diagnostics like urea	35 (42.7)
Based upon increased lactate level	66 (80.5)
Based upon a measure of fluid responsiveness	74 (90.2)
Other, please specify*	5 (6.1)
In case of a hypovolemic state, what volume of fluid bolus do you typically give to an invasive mechanically ventilated child that is hemodynamically stable without cardiac disease?	
None	3 (3.7)
5 ml/kg	8 (9.8)
10 ml/kg	59 (72.0)
15 ml/kg	1 (1.2)
20 ml/kg	11 (13.4)
Do you determine fluid responsiveness before administering a fluid bolus	
Always	9 (11.0)
Often	32 (39.0)
Sometimes	32 (39.0)
Rarely	7 (8.5)
Never	2 (2.4)
If you determine fluid responsiveness, what method do you use most often? (please check ALL that apply)	
N/A	4 (4.9)
Passive leg raising	32 (39.0)
Arterial pressure variations	44 (53.7)
Peak flow variations in aorta using ultrasound/Doppler	6 (7.3)
Mini fluid bolus	31 (37.8)
CVP	21 (25.6)
Diameter of the inferior vena cava using ultrasound	37 (45.1)
Liver compression	47 (57.3)
Other, please specify**	4 (4.9)
If you deliver a fluid bolus as fluid resuscitation, how do you establish its beneficial effect? (please check ALL that apply)	
An increase in blood pressure	57 (69.5)
A decrease in heart rate	80 (97.6)
An increase in urine production	64 (78.0)
An increase in cardiac output	29 (35.4)
Improved clinical signs	78 (95.1)
Improved NIRS measurement	17 (20.7)
Other, please specify***	5 (6.1)

**Other: central venous oxygen saturation n = 2, passive leg raising test n = 1, based on pathophysiology n = 2.*

*** Other: heart rate changes n = 2, PiCCO n = 2.*

**** Other: decrease in pulse pressure variation n = 2, improved serum lactate/base excess n=2, Not specified n = 1.*

CVP, central venous pressure; NIRS, Near-infrared spectroscopy; PiCCO, Pulse index Continuous Cardiac Output.

Future Trial Design

When asked whether future research in fluid management is essential to improve our understanding and tailoring medical care in invasive mechanically ventilated patients in the PICU, 78/82 (95.1%) respondents agreed or strongly agreed with the statement. None of the respondents disagreed or strongly disagreed (**Figure 4A**).

There is also a high willingness (N = 71/82, 86.6%) among participants to include patients in a future clinical trial investigating possible benefits of a conservative fluid approach. Some respondents who answered "no" believe there is already enough evidence to justify a conservative fluid management approach in invasive mechanically ventilated children. The other respondents argued allocating to a "liberal fluid management"

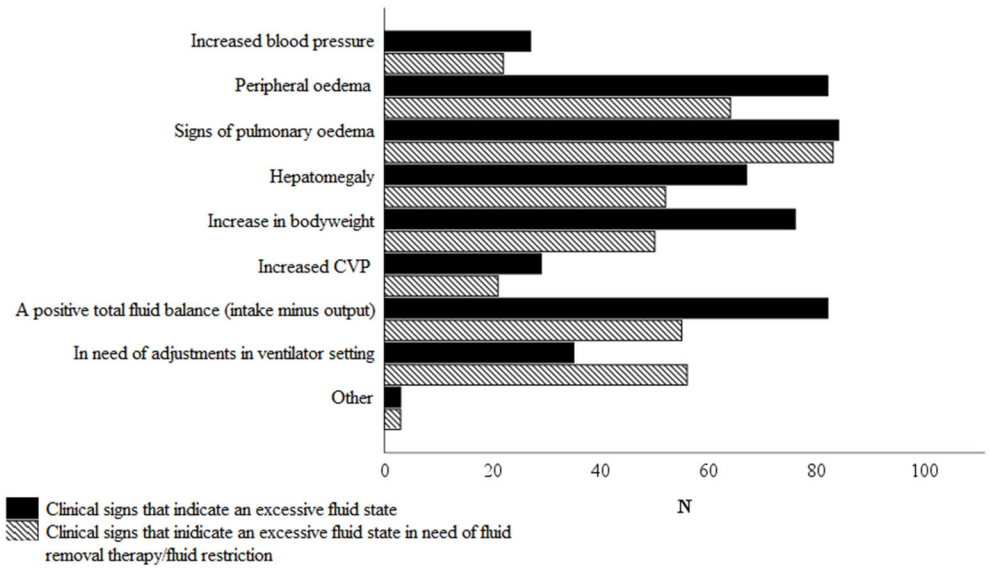

FIGURE 3 | Clinical symptoms and signs that indicate an excessive fluid state with or without the need of fluid removal therapy and/or fluid restriction, according to the respondents. Total number of respondents $N = 82$.

TABLE 3 | Tools (clinical, radiological and/or laboratory) used regularly diagnosing fluid overload.

	N (%)
Total number of respondents	82 (100)
Lung ultrasound	42 (51.2)
Cardiac ultrasound	40 (48.8)
Chest-X-ray	57 (69.5)
PiCCO (transpulmonary thermodilution)	9 (11.0)
Laboratory findings (e.g., ureum, creatinin, NT-proBNP)	60 (73.1)
Other*	13 (17.1)

**Other: based on clinical/physical examination of the patient (N = 10, 13.0%), Fluid overload in percentage (N = 1, 1.2%).*
PiCCO, Pulse index Continuous Cardiac Output.

arm would not be ethical, as a conservative approach has already been integrated in their current fluid management protocol.

When it comes to the preferred trial design, 34/82 (41.5%) of the respondents preferred a pragmatic clinical trial, whereas 32/82 (39.0%) preferred patient allocation to strict, detailed intervention protocols (**Figure 4B**).

The duration of mechanical ventilation was often reported as an important primary outcome of a future clinical study ($N = 59/75$, 78.7%). Other possible important primary outcomes, reported by respondents, were: PICU length of stay ($N = 35/75$, 46.7%), mortality ($N = 20/75$, 26.7%) and renal failure/ need for renal replacement therapy ($N = 17/75$, 22.7%).

DISCUSSION

The primary aim of this study was to obtain information regarding daily clinical practice and the opinion of clinicians concerning fluid maintenance and replacement therapy in critically ill children undergoing invasive mechanical ventilation. The results show that in the opinion of many PICU specialists, fluid overload is a serious problem and a possible threat to these patients. However, there seems to be no clear agreement in the recognition, prevention or treatment of fluid overload in the PICU.

Maintaining an optimal fluid status in critically ill patients is one of the challenging aspects of (P)ICU care. During critical illness, the blood circulation can be compromised due to several factors, including a (widespread) pro-inflammatory response. Inflammation may cause capillary leakage, with subsequent hypovolemia, and a reduced cardiac function, both leading to circulatory insufficiency. Invasive mechanical ventilation itself can also reduce the cardiac output by increasing the afterload, while also decreasing the preload of the right ventricle. In these circumstances fluid loading can be lifesaving, and is therefore recommended in the acute phase of severe disease states like septic shock (10, 11). In contrast, fluid overload my also develop as a result of overzealous fluid administration and/or a continuous high fluid intake in combination with a concomitant inappropriate production of ADH (SIADH) or kidney failure. This often leads to the accumulation of extravascular fluid, further aggravated by degradation of the glycocalyx, culminating in the formation of edema in several tissues including the lung (7, 12, 13). The tissue edema, which may co-exist with both hyper- and hypovolemic intravascular volume, is considered to be the main cause of adverse effects of fluid overload. This could explain the consistent finding that positive cumulative fluid balance is associated with poor outcomes in both critically ill adults and children (3, 7, 14–20).

TABLE 4 | Fluid balance and indication of fluid removal therapy.

	N (%)
Total number of respondents	82 (100)
What cumulative fluid balance (%) (since admission in PICU AND start of mechanical ventilation) is a reason for making fluid management changes?	
Even fluid balance, one should strive for a negative fluid balance	14 (17.1)
0–5% fluid positive	3 (3.7)
5%−10% fluid positive	29 (35.4)
10%−15% fluid positive	22 (13.4)
15%−20% fluid positive	2 (2.4)
Other*	23 (28.0)
What is the preferred initial drug therapy used for fluid removal in case of positive fluid balance or signs of fluid overload in invasive mechanically ventilated PICU patients?	
Intermittent loop diuretics	73 (89.0)
Continuous loop diuretics drip infusion	20 (24.4)
Thiazide diuretic (e.g., hydrochlorothiazide)	9 (11.0)
Potassium sparing (e.g., spironolactone)	36 (43.9)
I do not use diuretics for fluid removal therapy	0 (0.0)
Other	0 (0.0)
In case of changing fluid management, due to positive fluid balance or clinical signs of fluid overload, what is the initial intervention used for fluid removal?	
Lowering fluid maintenance	67 (81.7)
Avoidance of maintenance fluid and minimization of drug diluents	40 (48.8)
Start diuretic drug therapy	72 (87.8)
Early start of renal replacement therapy	4 (4.9)
Watchful waiting	3 (3.7)
No intervention	0 (0.0)
Other**	2 (2.4)
How often is continuous renal replacement treatment (CRRT) used to manage fluid overload as the sole indication?	
Always	0 (0.0)
Usually	6 (5.6)
Sometimes	21 (19.6)
Rarely	41 (38.3)
Never	14 (13.1)

Other: Changes in fluid management only in combination with clinical signs (N = 23, 28.0%).
Other: switch to enteral feeding (N = 1, 1.2%), not further specified (N = 1, 1.2%).

The theoretical concept mentioned above, has clearly been embraced by the critical care community, fueling a large number of studies on fluid management over the last years. In our survey, the vast majority of respondents indeed considered fluid overload to be a common problem in the PICU, associated with a poor outcome (**Figure 2**). This is on par with published reports from both pediatric and adult intensive care medicine (17, 18).

Considering fluid replacement, the majority of respondents used a volume of 10 ml/kg as a fluid bolus. This is in conjunction with current guidelines and studies (11, 21) although 20 ml/kg is still used by some. Fluid therapy was guided most frequently by clinical signs and symptoms, although research has shown that these do not always predict fluid responsiveness in a reliably way (22, 23). Fluid responsiveness, defined as an increase in cardiac output as a result of fluid loading, was sometimes determined using various methods. Unfortunately, these methods have not been fully validated in (smaller) children, and the effect of fluid loading is often not tested against a reliable effect parameter like cardiac output (22). This can be a result of the sparse use of invasive tools for hemodynamic monitoring, such as central venous pressure or pulmonary artery catheters, in children as compared to adults. Therefore, in contrast to the adult ICU, fluid resuscitation is not always performed based upon valid parameters and might contribute to fluid overload (23, 24). Future research needs to identify more accurate parameters for guiding fluid resuscitation in critically ill children in order to prevent fluid overload.

The majority of respondents monitor the fluid balance and possible signs of fluid overload regularly. However, there was large variability in the clinical practice regarding the threshold of a positive cumulative fluid balance at which adjustments to the fluid management strategy were applied. A close majority

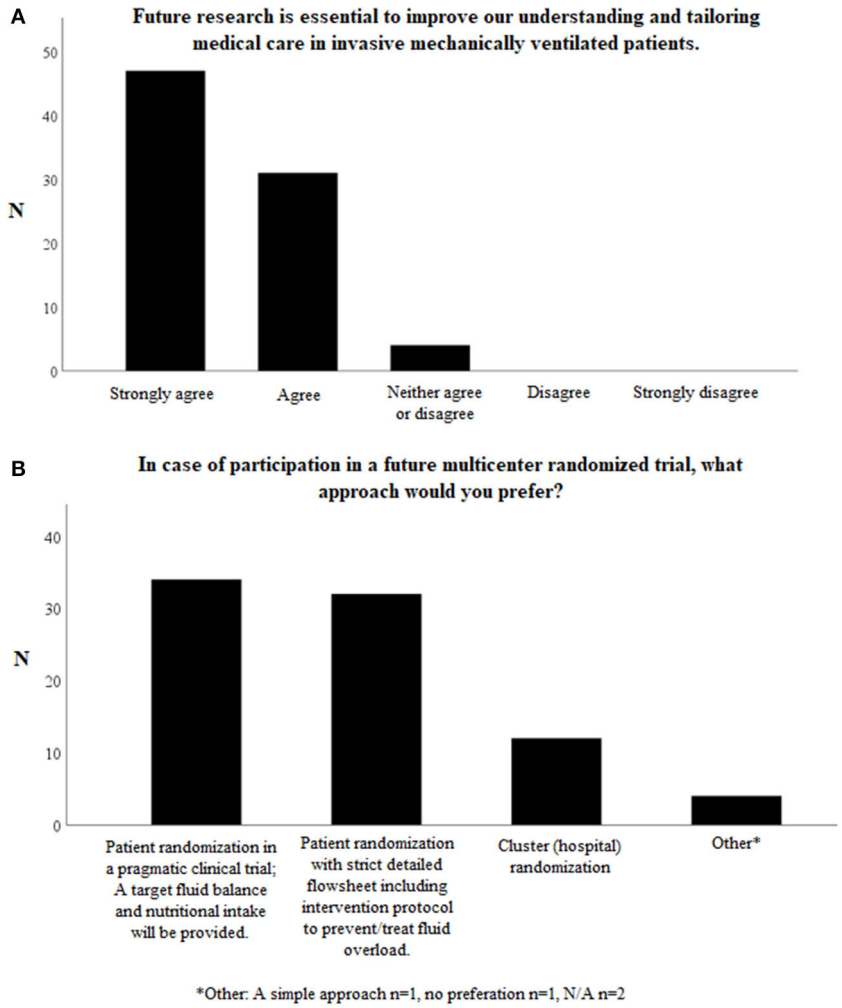

FIGURE 4 | Questions on possible future studies on fluid management in invasively mechanically children. Total number of respondents $N = 82$. **(A)** Further research in fluid management is essential to improve our understanding and tailoring medical care in invasive mechanically ventilated patients. **(B)** In case of participation in a future multicenter randomized trial, what approach would you prefer? *Other. A simple approach $n = 1$, no preferation $n = 1$, N/A $n = 2$.

considered an increase of more than 5% in cumulative fluid balance a reason for intervention. Advanced diagnostics, when used, were diverse, ranging from chest x-ray to laboratory tests. A recent systemic review showed that positive cumulative fluid balance is indeed a risk factor for increased mortality in adult ICU patients (18). The increasing body of evidence from both adult and pediatric studies displaying a consistent positive association between fluid overload and adverse outcomes seems to convince many PICU clinicians that fluid overload is a threat to critically ill children.

Although several studies have shown that a positive cumulative fluid balance is associated with a worse outcome as early as day 1 of PICU admission, in a recent study among children with pediatric ARDS this association was only apparent after day 4 of disease progression (4, 7, 14). Also, in adults, a negative cumulative fluid balance at day 4 of acute lung injury was associated with significantly lower mortality (25). Van Regenmortel et al. (26) aimed to quantify all fluid sources and assess fluid creep in adult ICU-patients. Maintenance and replacement fluids accounted for 24.7% of the total daily fluid volume, whereas fluid creep represented 32.6% of the total daily fluid volume. Therefore, to limit fluid intake, both fluid maintenance and creep during drug delivery needs to be addressed by clinicians. In our survey, the majority of participants reported to give less than 80% of the Holliday-Segar formula, but a protocol was present in only 64% of the cases. This can be explained by the absence of an international guideline concerning continuous fluid management in critically ill (ventilated) children.

Loop diuretics were mentioned in our survey as the predominant first line drug intervention. However, there was no uniform strategy to counteract pending fluid overload. Lowering maintenance fluids, diuretics or avoidance of maintenance fluid and minimizing drug diluents were all mentioned almost equally. Unlike to the adult ICU literature, no guidelines for de-resuscitation or protocols for diuresis after the resuscitation

phase in critically ill children have been published to our knowledge (16, 27). When loop diuretics do not increase urine production to the desired level, CRRT is the most efficient way to treat fluid overload. CRRT exploited solely for treating or preventing fluid overload is regarded as a relative indication, and timing and indications are still under debate (28). However, a recent survey showed that during pediatric extracorporeal life support (ECLS) an increasing number of centers use CRRT as a tool to prevent or treat fluid overload (29). Studies in adults have shown improved oxygenation indices and shorter ICU length of stay with a restrictive fluid strategy, however no survival benefit has been shown thus far (20). Trials for fluid therapy in children have been proposed for many years but still not accomplished (30). The general opinion seems to be that both hemodynamic and respiratory therapy needs to be personalized implying that a one-size-fits all strategy will not be realistic (20, 31).

FUTURE PERSPECTIVES

The current lack of randomized clinical trials hampers the development of widely accepted international guidelines. In terms of future research regarding fluid overload in the PICU, some problems have to be overcome.

First, current fluid strategies among participating centers will likely vary to a great extent and should thus be aligned. In particular, determining the volume of fluids in the liberal treatment arm might pose a difficulty, considering that centers, in which restriction of maintenance fluids is already common practice, may raise ethical concerns.

Second, there are questions related to timing, type and aggressiveness of interventions (e.g., fluid restriction, diuretic medication, CRRT) in a conservative fluid treatment arm complicating trial design (32). The ability to actually avoid fluid accumulation in critically ill children may be limited (5). This might require aggressive fluid restriction protocols directly following the resuscitation phase. As a result, incorporation of a broad set of safety parameters and long-term outcome measurements are therefore imperative.

Third, obtaining an appropriate sample size may be challenging. The adult ARDS FACTT-study enrolled 1,000 patients and had enough power to detect a 10% absolute reduction (from 31 to 21%) in mortality (1). In less prevalent pediatric ARDS, mortality is about half at 17.1% (SD 38.7), and thus a 5% absolute reduction in death rate would necessitate a sample size of more than 1,500 patients (12). This sample size would rise to above 6,000 patients for a trial including all critically ill children (also non-ARDS), in order to be able to detect a significant reduction in mortality, providing the case fatality of 3.1% (7). Such numbers are unrealistic for pediatric critical care research, and thus focus should lie on alternative primary outcomes such as duration of mechanical ventilation, as well as effects on a specific sub-groups of PICU patients (5).

Finally, the results of this survey show a high willingness among PICU clinicians to participate in a clinical trial in which children are to be randomized into a liberal vs. a conservative fluid strategy. Without such a trial, an evidenced based guideline cannot be accomplished.

There are several limitations to this study. First, the response did not follow an even distribution from the various European countries. There could be a bias as the majority of the respondents originated from the Netherlands, Germany and the UK. Second, the number of respondents was not very high and poses the question if the results reflect the opinion of the majority of European pediatric intensivists. Third, the results reflect the individual opinion of clinicians and not institutional or departmental policy. Fourth, intensivists that consider fluid overload a problem may have been more motivated to participate in the survey causing bias.

CONCLUSION

Pediatric intensivists consider fluid overload an important problem and a possible threat to invasive mechanically ventilated critically ill children. However, currently there seems to be no agreement on fluid-sparing strategies and interventions to avoid this complication. Therefore, clinical trials that address prevention and treatment of fluid overload in mechanically ventilated children in the PICU are highly needed.

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 Amsterdam University Medical Center. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

IA: study inception, survey design and conduction, analysis, and report writing. SI and JW: survey design and revision of the report. RB and JL: study inception, survey design, analysis, and report writing. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank our colleague Prof. Dr. M. de Hoog for his help and very useful feedback regarding the design of the survey.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.828637/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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ORIGINAL RESEARCH
published: 07 April 2022
doi: 10.3389/fped.2022.857106

Non-invasive Cardiac Output Monitoring and Assessment of Fluid Responsiveness in Children With Shock in the Emergency Department

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to
Pediatric Critical Care,
a section of the journal
Frontiers in Pediatrics

Received: 18 January 2022
Accepted: 04 March 2022
Published: 07 April 2022

Citation:
Awadhare P, Patel R, McCallin T,
Mainali K, Jackson K, Starke H and
Bhalala U (2022) Non-invasive
Cardiac Output Monitoring
and Assessment of Fluid
Responsiveness in Children With
Shock in the Emergency Department.
Front. Pediatr. 10:857106.
doi: 10.3389/fped.2022.857106

Introduction: The assessment of fluid responsiveness is important in the management of shock but conventional methods of assessing fluid responsiveness are often inaccurate. Our study aims to evaluate changes in objective hemodynamic parameters as measured using electrical cardiometry (ICON® monitor) following the fluid bolus in children presenting with shock and to evaluate whether any specific hemodynamic parameter can best predict fluid responsiveness among children with shock.

Materials and Methods: We conducted a prospective observational study in children presenting with shock to our emergency department between June 2020 and March 2021. We collected the parameters such as heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and hemodynamic data such as cardiac output CO), cardiac index (CI), index of contractility (ICON), stroke volume (SV), stroke index (SI), corrected flow time (FTC), systolic time ratio (STR), variation of index of contractility (VIC), stroke volume variation (SVV), systemic vascular resistance (SVR), and thoracic fluid content (TFC) using the ICON monitor before and after fluid bolus (FB). We assessed percent change (Δ) and used paired-sample Student's *t*-test to compare pre- and post-hemodynamic data and Mann–Whitney *U*-test to compare fluid responders and non-responders. *P*-Values < 0.05 were considered statistically significant.

Results: We recorded 42 fluid interventions in 40 patients during our study period. The median IQR age was 10.56 (4.8, 14.8) years with male/female ratio (1.2:1). There was a significant decrease in ΔRR [−1.61 (−14.8, 0); $p = 0.012$], ΔDBP [−5.5 (−14.4, 8); $p = 0.027$], ΔMAP [−2.2 (−11, 2); $p = 0.018$], ΔSVR [−5.8 (−20, 5.2); $p = 0.025$], and ΔSTR [−8.39 (−21, 3); $p = 0.001$] and significant increase in ΔTFC [6.2 (3.5, 11.4); $p = 0.01$] following FB. We defined fluid responders by an increase in SV by ≥10%

after a single FB of 20 ml/kg crystalloid. Receiver operating curve analysis revealed that among all the parameters, 15% change in ICON had an excellent AUC (0.85) for the fluid responsiveness.

Conclusion: Our study showed significant changes in objective hemodynamic parameters, such as SVR, STR, and TFC following FB in children presenting with shock. A 15% change in ICON had an excellent predictive performance for the fluid responsiveness among our cohort of pediatric shock.

Keywords: fluid responsiveness, shock, children, hemodynamic monitoring, electrical cardiometry

INTRODUCTION

Shock is a leading cause of morbidity and mortality in the pediatric patients worldwide (1, 2). The prevalence of sepsis and septic shock has been reported to be around 1–26% of shock cases with mortality rates ranging from 5 to 35% in hospitalized children globally (3, 4). Appropriate fluid resuscitation is crucial in the management of children with shock (5). The current American College of Critical Care Medicine (ACCM), Pediatric Advanced Life Support (PALS), and Surviving Sepsis Campaign Guidelines have focused on the implementation of early and goal-directed fluid therapy (6, 7). Many studies have shown that mortality in pediatric patients with septic shock has been significantly decreased with aggressive fluid administration (8, 9). However, overzealous fluid administration can also lead to fluid overload (FO) and has been associated with complications such as acute respiratory distress syndrome (ARDS), which results in poor outcomes including increased hospital length of stay and mechanical ventilator days (10–13). As a result, in the recent decades, a more restrictive approach for fluid resuscitation has emerged in adults and children vs. the usual aggressive fluid therapy (14–16).

Despite ongoing extensive research related to fluid management in septic shock, the optimal amount of fluid to administer in early resuscitation of pediatric shock remains uncertain (17). Therefore, it is imperative to assess the clinical and hemodynamic responses before and after each fluid bolus (FB) to guide resuscitation and to determine the presence or absence of FO. Traditional use of subjective findings such as pulse volume, capillary refill time, and clinical signs of hydration status to predict fluid responsiveness (FR) has been proven to be unreliable (18, 19). In the recent decades, objective hemodynamic parameters have gained popularity and have been shown to reliably predict FR in adults (20, 21). While there is a growing body of the literature on the use of non-invasive devices for objective hemodynamic monitoring, there is a paucity of the literature related to the assessment of FR using these measures in children with shock (22).

ICON monitor, which is based on a novel technology of electrical cardiometry (EC), is one such non-invasive hemodynamic monitoring device and has been studied for the assessment of FR in adult patients with the promising results (23, 24). EC technique uses signals generated by the surface electrodes to measure the alterations in thoracic impedance. The changes in bio-impedance to the flow of erythrocytes in the aorta are computed into an algorithm allowing continuous hemodynamic monitoring (25). In our pilot study, we aim to determine changes in subjective and objective measures of hemodynamic status before and after FB in children with shock using ICON monitor. We also sought to assess whether changes in objective parameters could predict FR in these children.

MATERIALS AND METHODS

Study Design and Selection of Participants

We conducted a prospective observational pilot study in children presenting with shock to our emergency department (ED) from June 2020 to March 2021. We conducted the study at the Children's Hospital of San Antonio (CHofSA), a freestanding, 200-bed, tertiary care children's hospital. The Baylor College of Medicine Institutional Review Board and CHofSA feasibility committee approved the study. Due to the prospective observational nature of the study, a waiver of informed consent was obtained.

In our study, we used ICON® non-invasive hemodynamic monitor to measure objective hemodynamic parameters before and after FBs in children with shock in the ED. ICON® monitor has been utilized to monitor patient hemodynamics in our pediatric intensive care unit (PICU) since 2018. Hence, we were interested to determine whether it may be feasible to expand the use of ICON® monitor to the ED. After a short training period for the research team and ED staff, we began using the monitor on ED patients with shock to explore the workflow and obtain fluid resuscitation responses by measuring subjective and objective parameters.

Inclusion Criteria

1. Children aged 0–17 years who presented in shock or presumed shock and required FB in our ED.
2. Children in whom all the hemodynamic parameters were available and feasible using ICON® monitor.

Exclusion Criteria

1. Children with suspected infection with SARS CoV-2 who were designated as patients under investigation (PUI).
2. Children in whom any hemodynamic data using ICON® monitor were not feasible or not available.

Unfortunately, during the study period, we were facing the COVID-19 pandemic wave. During the study period, our hospital policies required all PUI to be considered as suspected COVID 19 and did not allow trainees to be involved with the care of PUI and patients with COVID-19. We therefore excluded the PUI.

We defined shock *a priori* based on a combination of clinical and/or laboratory parameters such as hypothermia or hyperthermia, tachycardia or tachycardia out of proportion to the degree of fever, tachypnea, hypotension, delayed capillary refill time, dry mucosa, and elevated lactate levels which warranted fluid resuscitation. In our ED, it is a standard protocol for the triage nurse to alert the ED attending about any patient presenting in shock or presumed shock. The ED attending then decides about the administration of FB based on his/her assessment of the patient's clinical status suggestive of shock or presumed shock. Therefore, in our study, we included pediatric patients presenting with shock or presumed shock who were administered FB. In our ED, it is a routine practice to monitor the patients' clinical and hemodynamic parameters obtained *via* standard monitoring before and after FB interventions. We expanded the current standard of care with an application of the ICON® monitor to obtain additional hemodynamic parameters after the decision to administer fluid was made. The providers were blinded to the information collected by the monitor to reduce the risk of introducing bias into the treatment of the patients. We did not initiate or change real-time clinical management of the patient based on hemodynamic parameters obtained using the ICON® monitor.

Non-invasive Monitoring

ICON® monitor measurements require the placement of four skin sensors on the left side of the body as shown in **Figure 1**. After attaching the four sensors (two upper and two lower), we confirmed 100% signal strength before capturing hemodynamic parameters for accuracy. The upper sensors apply a harmless low amplitude, high-frequency alternating current. The changes in pulsatile red blood cell flow and change of thoracic electrical bio-impedance during the cardiac cycle are captured between the pair of the sensors. The complex mathematical algorithm built into the device calculates beat-to-beat parameters such as cardiac output, stroke volume, and many other hemodynamic parameters (25).

Hemodynamic Measurements

We collected hemodynamic variables before and within 10 min after each FB in children with shock. We obtained demographic characteristics such as age and gender, clinical parameters such as heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure

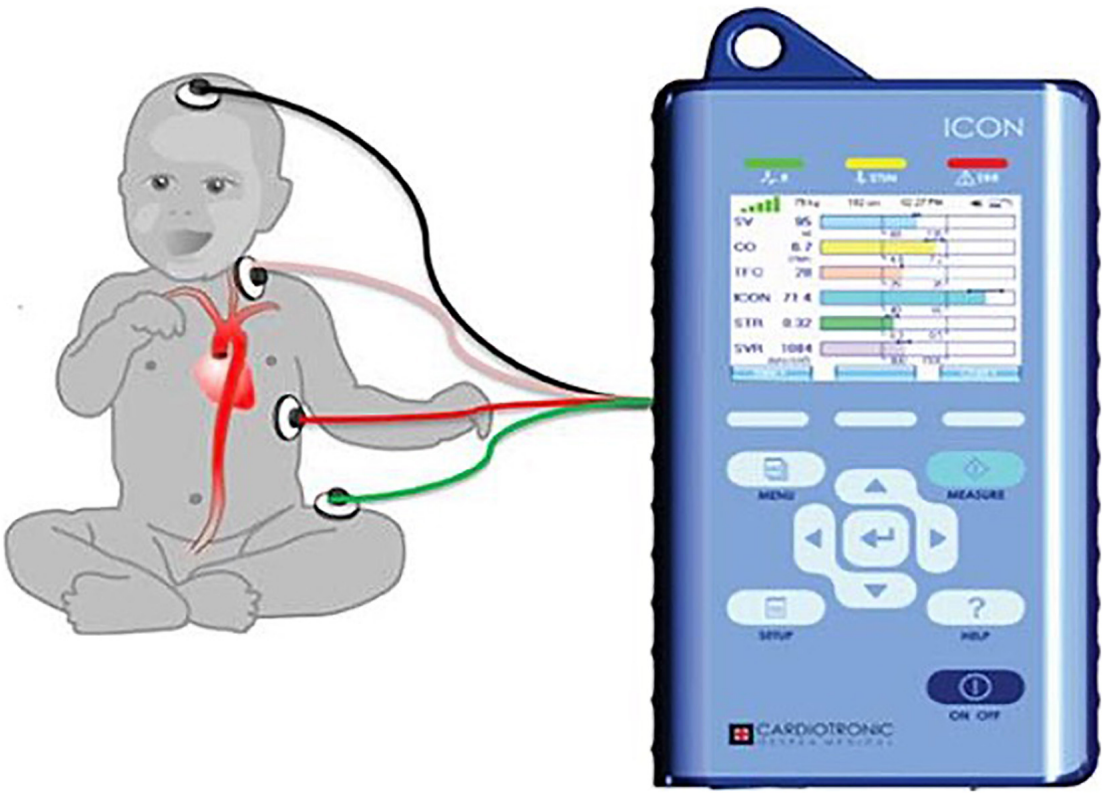

FIGURE 1 | The figure shows placement of ICON four sensors. One sensor placed on forehead, second sensor placed on left base of neck, third sensor placed on left thorax at the level of xiphoid, and fourth sensor placed on left thigh. Adopted from ICON user manual with due permission from Markus Osypka, Osypka Medical Inc., Germany.

(MAP), and hemodynamic parameters from ICON device such as cardiac output (CO), cardiac index (CI), index of contractility (ICON), stroke volume (SV), stroke index (SI), corrected flow time (FTC), systolic time ratio (STR), variation of index of contractility (VIC), stroke volume variation (SVV), systemic vascular resistance (SVR), and thoracic fluid content (TFC).

Similar to the prior studies in adults, we defined the fluid responders *a priori* as those who exhibited an increase in SV by $\geq$10% after a single FB of 20 ml/kg crystalloid (18).

Statistical Analysis

We conducted a statistical analysis using R–project (R Core Team, Vienna, Austria). We presented numeric data in median interquartile range (IQR) values. We calculated percent change (Δ) for pre- and post-hemodynamic data and compared the data using paired-sample Student's *t*-test. We used Mann–Whitney *U*-test to compare hemodynamic parameters between fluid responders and non-responders. Furthermore, we plotted sensitivity and specificity for the cut-off points 5, 10, 15, and 20% for all variables to create receiver operating characteristic (ROC) curves to assess their predictive performances. *p*-values < 0.05 were considered statistically significant.

RESULTS

During the study period between June 2020 and March 2021, total number of ED visits in our children's hospital was 23,060. Out of these patients, 1,792 presented with shock. During the Coronavirus disease 2019 (COVID-19) pandemic, the ICON device was not used in many patients who visited our ED during the study period. Therefore, in total, we were able to record 42 fluid interventions in 40 patients out of these 1,792 during our pilot study (**Figure 2**).

Patient's Characteristics

The median (IQR) patient age was 10.56 (4.8, 14.8) years with male/female ratio 1.2:1. Out of 40 patients included in our study, 32 (80%) had clinical findings and the remaining 8 (20%) had clinical and laboratory findings suggestive of shock. The hypovolemic shock was present to some degrees in 72% and septic shock in 28% of patients. The most common underlying etiology of shock was hypovolemia due to gastrointestinal condition (48%) (**Table 1**). All patients received FBs with crystalloids *via* infusion pump. The preferred crystalloid was normal saline in 32/42 (76%) and ringer's lactate in 10/42 (24%). The mean weight-based volume of fluid administration was 16.24 ml/kg (standard deviation 5.6) with a mean duration of 47.26 min (standard deviation 15.8) to bolus completion.

Effects of Fluid Therapy and Fluid Responsiveness

We observed a significant decrease in ΔRR [−1.61 (−14.8, 0); $p = 0.012$], ΔDBP [−5.5 (−14.4, 8); $p = 0.027$], ΔMAP [−2.2 (−11, 2); $p = 0.018$], ΔSVR [−5.8 (−20, 5.2); $p = 0.025$], and

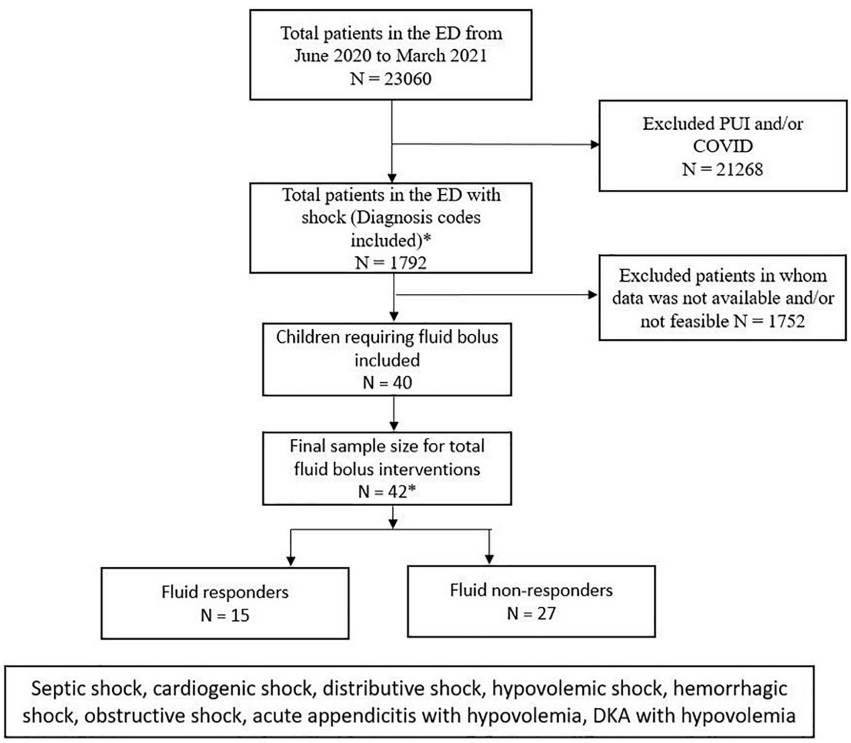

FIGURE 2 | Consort patient flow diagram showing the total number of ED visits in our study period and number of patients who were included and excluded in the study. PUI, patients under investigation, COVID, coronavirus disease.

TABLE 1 | Demographic data and clinical characteristics.

Patient's characteristics	Percentage (%) or Median (IQR)
Age (years)	10.56 (4.8, 14.8)
Gender (male: female)	1.2:1
Type of shock	
Hypovolemic	30 (72%)
Septic	12 (28%)
Underlying etiology/Primary diagnosis/System involved	
Gastrointestinal	20 (48%)
Endocrine/Metabolic	9 (22%)
Neurological	7 (16%)
Genitourinary	2 (6%)
Respiratory	1 (2%)
Musculoskeletal	1 (2%)
Hematology/Oncology	2 (4%)

IQR, interquartile range.

ΔSTR [−8.39 (−21, 3); $p = 0.001$] and a significant increase in ΔTFC [6.2 (3.5, 11.4); $p = 0.01$] following FB. About 35% of FBs led to > / = 10% change in TFC. There were no significant differences in HR, SBP, SV, SI, CO, CI, SVV, FTC, ICON, and VIC post-FB (**Table 2**).

Fluid responsiveness was seen in 15/42 interventions. Between responders vs. non-responders, fluid responders had a significant decrease in ΔHR [−3.7 (−16.6, −0.72) vs. 1.32 (−5.1, 9.9); $p = 0.002$], ΔSVV [−34 (−50, −2.9) vs. 25 (−19.5, 83.7); $p = 0.002$], ΔSVR [−12.8 (−22.7, −7.7) vs. 0 (−12.8, 9.2); $p = 0.31$], and ΔSTR [−19.3 (−24.6, −12) vs. −5 (−14.8, 8.8); $p = 0.03$]. Furthermore, fluid responders had a significant increase in ΔSI [16 (15.8, 24.2) vs. −3 (−9, 0.91); $p = 0.00000011$], ΔCO [14.2 (4, 23) vs. −2.2 (−12.9, 6.2); $p = 0.006$], ΔCI [14.5 (5.2, 23) vs. −3.5 (−12.8, 5.6); $p = 0.003$], ΔFTC [7.65 (2.6, 9.4) vs. 0 (−6, 3.8); $p = 0.002$], and ΔICON [16.7 (13.5, 25) vs. −9 (−23, 5.1), $p = 0.003$] as compared to non-responders. There were no significant differences between age, ΔRR, ΔSBP, ΔDBP, ΔMAP, ΔTFC, and ΔVIC between these two groups (**Table 3**).

Receiver Operating Characteristic Curve Analysis

We compared areas under ROC curves (AUCs) after fluid expansion for ΔHR, ΔSVR, ΔSVV, ΔSTR, ΔSI, ΔCO, ΔCI, ΔFTC, and ΔICON. The AUC denoted better classifiers for ΔSI (AUC–0.99), ΔICON (AUC–0.85), and ΔCI (AUC–0.73). The optimal threshold value for CI, SI, and ICON calculated by the ROC curve analysis was 15% (**Figure 3**).

DISCUSSION

Our prospective observational pilot study focused on subjective and objective methods of assessing hemodynamic status and FR in children presenting to the ED in shock. To our knowledge, this is the first pediatric report of the use of electrical cardiography which demonstrated a significant change in objective indices of hemodynamic status following FB in children with shock. Additionally, the study demonstrated the changes in specific hemodynamic indices such as CI, SI, and ICON as measured by electrical cardiography best-predicted FR in children with shock. The overall goal of fluid administration in patients with shock is to increase cardiac preload and subsequently stroke volume (15, 17). However, the studies in critically ill patients that examined FR demonstrated only 40–50% of patients responded to volume expansion (19, 26, 27). Furthermore,

TABLE 2 | Comparison between pre- and post-FB hemodynamic variables.

Parameters	Pre-FB median (IQR)	Post-FB median (IQR)	Δ Median (IQR)	*p*-values
HR (bpm)	107 (92, 131)	103.5 (85, 127)	−0.72 (−8, 4.2)	0.453
RR (/min)	22 (19, 24)	20 (18, 24)	−1.61 (−14.8, 0)	**0.012**
SBP (mmHg)	116 (105, 125)	112.5 (100, 123)	−5 (−14.5, 7)	0.104
DBP (mmHg)	73 (64, 84)	69 (55, 80)	−5.5 (−14.4, 8)	**0.027**
MAP (mmHg)	88 (83, 96)	84.5 (73, 93)	−2.2 (−11, 2)	**0.018**
SV (ml)	51.5 (27, 77)	54.5 (35, 72)	0.7 (−9, 15)	0.814
SI (BSA)	38 (35, 48)	41 (34, 48)	2.16 (−7.5, 16)	0.242
CO (l/min)	5 (3.5, 7.3)	4.7 (3.8, 6.3)	2.4 (−8.4, 16)	0.858
CI (BSA)	4.2 (3.2, 4.8)	4.2 (3.3, 5)	1.1 (−8, 16)	0.2577
SVV (%)	12.5 (8, 17)	13 (8, 17)	0.0 (−5, 4)	0.509
FTC (ms)	312 (298, 327)	323.5 (302, 333)	2.31 (−0.8, 8)	0.282
TFC	28.5 (20, 34)	31 (23, 37)	6.2 (3.5, 11.4)	**0.005**
SVR (dyn.s/cm$^{5)}$	1387 (958, 1913)	1374 (942, 1704)	−5.8 (−20, 5.2)	**0.025**
STR	0.37 (0.33, 0.45)	0.34 (0.3, 0.38)	−8.39 (−21, 3)	**0.001**
ICON	72.8 (56.6, 96.3)	71 (51, 103)	4 (−21.6, 16.6)	0.858
VIC (%)	13.5 (9, 27)	16.5 (11, 26)	0.0 (−33, 57)	0.433

FB, fluid bolus; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; FTC, corrected flow time; TFC, thoracic fluid content; SVR, systemic vascular resistance; STR, systolic time ratio; ICON, index of contractility; VIC, variation of index of contractility; Δ, percentage change; bpm, beats per minute;/min = per minute; ml, milliliters; BSA, body surface area; %, percentage; ms, milliseconds; dyn.s/cm^5, dynes/sec/cm^5; significant value, $p < 0.05$. (Paired-sample Student's t-test). Bold values correspond to significant p-values.

the conventional subjective parameters such as vital signs and physical examination pose several limitations and alone are not reliable in assessing FR, especially in children (28, 29). On the other hand, objective parameters such as CO, CI, SV, SI, and SVR may provide much more accurate hemodynamic status (30). More recently, non-invasive cardiac output monitors are also being utilized to provide continuous data of patients' hemodynamic status that could help in guiding fluid therapy and to predict FR (22, 31). Several studies have demonstrated the usefulness of these non-invasive devices in adults (23, 24, 32), yet the effectiveness of such devices remains controversial in pediatric patients. Some studies support the use of these newer non-invasive techniques in children. A study by Norozi et al. demonstrated a good correlation (r = 0.84) between CO measurements obtained by non-invasive cardiac output monitor and invasive direct Fick oxygen method in children with various congenital heart conditions (33). However, in another study that compares SVV measured by NICOM (non-invasive cardiac output monitor), traditional transesophageal echocardiography reported its ineffectiveness to predict FR in children undergoing cardiac surgery (34). In another study by Ballestero Yolanda et al. on a pediatric animal model with hemorrhagic shock, CI measured by bioreactance technique did not show significant changes after volume expansion (35).

TABLE 3 | Changes in hemodynamic variables in responders vs. non-responders.

Parameters	Responders n = 15 median (IQR)	Non-responders n = 27 median (IQR)	p-values
Age (years)	7.9 (2, 11)	12.3 (5.6, 15.6)	0.15
ΔHR (bpm)	−3.7 (−16.6, −0.72)	1.32 (−5.1, 9.9)	**0.002**
ΔRR (/min)	−6.2 (−15.5, 0)	0 (−12.7, 4.5)	0.169
ΔSBP (mmHg)	−0.85 (−4.9, 4.9)	−6.6 (−12, 7.5)	0.293
ΔDBP (mmHg)	−2.4 (−5.8, 8.9)	−9.8 (−16.2, 6.43)	0.253
ΔMAP (mmHg)	−1,1 (−4.6, 1.8)	−6.5 (−12.8, −0.6)	0.100
ΔSI (BSA)	16 (15.8, 24.2)	−3 (−9, 0.91)	**0.00000011**
ΔCO (l/min)	14.2 (4, 23)	−2.2 (−12.9, 6.2)	**0.006**
ΔCI (BSA)	14.5 (5.2, 23)	−3.5 (−12.8, 5.6)	**0.003**
ΔSVV (%)	−34 (−50, −2.9)	25 (−19.5, 83.7)	**0.002**
ΔFTC (ms)	7.65 (2.6, 9.4)	0 (−6, 3.8)	**0.002**
ΔTFC	6.6 (5.4, 12)	5.8 (1.5, 10.5)	0.216
ΔSVR (dyn.s/cm^5)	−12.8 (−22.7, −7.7)	0 (−12.8, 9.2)	**0.031**
ΔSTR	−19.3 (−24.6, −12)	−5 (−14.8, 8.8)	**0.003**
ΔICON	16.7 (13.5, 25)	−9 (−23, 5.1)	**0.0003**
ΔVIC (%)	0 (−39, 44)	0 (−23, 71)	0.617

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; FTC, corrected flow time; TFC, thoracic fluid content; SVR, systemic vascular resistance; STR, systolic time ratio; ICON, index of contractility; VIC, variation of index of contractility; Δ, percentage change; bpm = beats per minute;/min = per minute; millimeters of mercury, mmHg; ml, milliliters; BSA, body surface area; %, percentage; ms, milliseconds; dyn.s/cm^5, dynes/sec/cm^5; significant value, $p < 0.05$. Bold values correspond to significant p-values.

In our study, we observed a significant decrease in RR, MAP, SVR, and STR and an increase in TFC, while CO, CI, SV, and SI remained unchanged. TFC is a newer objective parameter that has shown to identify pulmonary congestion which might not be evident on chest x-rays (36, 37). One study in critically ill children with respiratory failure and shock demonstrated that high TFC values correlate with pulmonary plethora and predicted patient outcomes (37). Another study in patients with heart failure suggested that TFC may identify patients at risk for decompensation (38). TFC measurements using EC have shown to be correlated with the presence of respiratory distress in infants (39). Hence, our pilot study that determined a significant increase in TFC may identify this as an important area of future study. A significant increase in TFC following FB in our study may be related to increased pulmonary interstitial edema following FB.

Predicting FR in children can be challenging. The predictive abilities of various hemodynamic parameters have previously been evaluated in a systematic review (40). Our results show that ΔCI, ΔSI, and ΔICON had good predictability for FR in children. In our study, AUCs of CI, SI, and ICON were 0.73, 0.99, and 0.85, respectively. In a study on adult patients undergoing laparoscopic cholecystectomy, AUCs for CI and SI for FR were 0.83 and 0.90, respectively (41). In a study on post-operative pediatric patients, AUC for SI was 0.88 (42). Our findings of AUC for HR for FR correlate with the prior similar results (43, 44). Though commonly used as a parameter to assess fluid status, HR is a worse predictor of FR. In our study, changes in CI and ICON showed a high predictive performance for FR. It is possible that FB improved myocardial contractility through Frank–Starling mechanism, and therefore, CI and ICON showed an excellent predictive performance.

Limitations

Our study had several limitations. It is a prospective observational pilot study conducted in a single center, and our sample size is small. A major challenge we encountered that led to a smaller sample size was the necessary exclusion of patients with COVID-19 or PUI during the unprecedented pandemic due to PPE restrictions and institutional guidelines to protect students from potential exposure. In addition, this cohort does not represent consecutive patients due to the limitations of availability and feasibility to perform monitoring in the unpredictable ED setting. Furthermore, considering these limitations in patient recruitment, our sample included most patients with mild-to-moderate shock and may not be representative of the most critically ill patients. Additionally, this may have impacted the rate of fluid administration with the mean bolus duration longer than optimum for shock resuscitation guidelines. Therefore, the results of this study cannot be generalized to all patients with pediatrics with shock. Despite the limitations of our pilot, the parameters we found to be statistically significant demonstrate the promising results that using a non-invasive monitor to assess objective hemodynamic changes in children with shock has the potential to aid ED physicians in predicting FR and better guide fluid management.

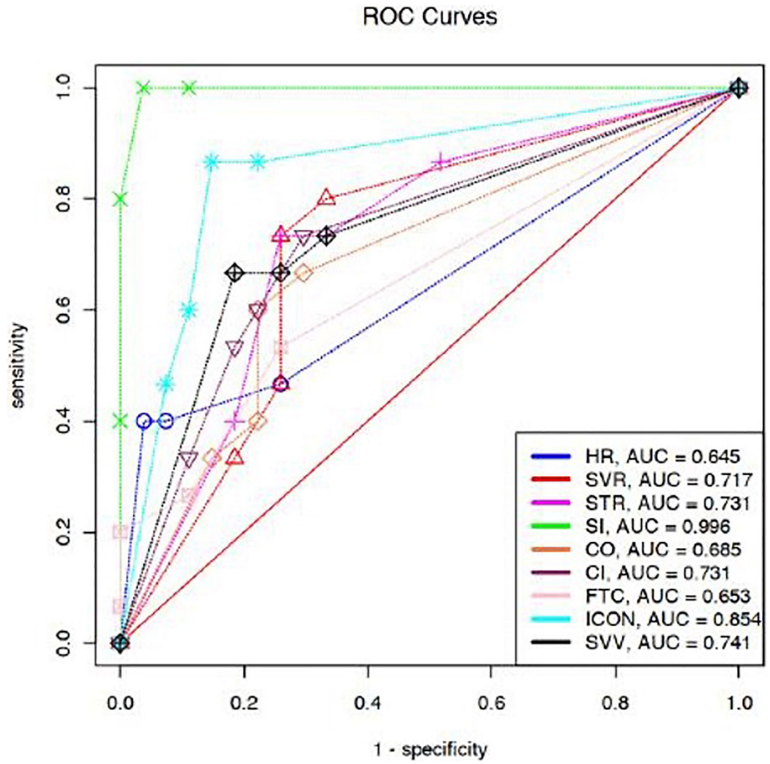

FIGURE 3 | Comparison of AUCs for prediction of FR after fluid expansion. ΔHR [0.64 (95% CI 0.55–0.72)], ΔSVR [0.71 (95% CI 0.62–0.79)], ΔSVV [0.74 (95% CI 0.65–0.82)], ΔSTR [0.73 (95% CI 0.64–0.81)], ΔSI [0.99 (95% CI 0.97–1)], ΔCO [0.68 (95% CI 0.59–0.76)], ΔCI [0.73 (95% CI 0.64–0.81)], ΔFTC [0.65 (95% CI 0.56–0.73)], and ΔICON [0.85 (95% CI 0.78–0.91)]. HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; FTC, corrected flow time; TFC, thoracic fluid content; SVR, systemic vascular resistance; STR, systolic time ratio; ICON, index of contractility; VIC, variation of index of contractility; Δ, percentage change.

CONCLUSION

The results of our pilot study suggest that integration of objective assessment with subjective data using advanced non-invasive monitoring could help to evaluate patients' hemodynamic status and FR in children with shock in ED settings. The findings of excellent predictive performance (AUC 0.85) of changes in ICON for FR could potentially aid treating physicians in avoiding fluid overload, developing optimal management plans, and using objective clinical decision-making for children with shock. Larger, multi-center, prospective, randomized studies are needed to further evaluate the validity of non-invasive devices in predicting FR in children.

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 Baylor College of Medicine 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

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

FUNDING

This study was supported by the University of The Incarnate Word School of Osteopathic Medicine Seed Grant.

ACKNOWLEDGMENTS

We would like to convey our special thank to ED physicians, residents, and nursing staff at the Children's Hospital of San Antonio Emergency Department, San Antonio, TX, United States.

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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.

frontiers | Frontiers in Pediatrics

PERSPECTIVE
published: 10 May 2022
doi: 10.3389/fped.2022.864755

Ignorance Isn't Bliss: We Must Close the Machine Learning Knowledge Gap in Pediatric Critical Care

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OPEN ACCESS

Edited by:
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Reviewed by:
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Samriti Gupta, All India Institute of Medical Sciences, India
Aditya Nagori, Indraprastha Institute of Information Technology Delhi, India

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *28 January 2022*
Accepted: *18 April 2022*
Published: *10 May 2022*

Citation:
Ehrmann D, Harish V, Morgado F, Rosella L, Johnson A, Mema B and Mazwi M (2022) Ignorance Isn't Bliss: We Must Close the Machine Learning Knowledge Gap in Pediatric Critical Care. Front. Pediatr. 10:864755. doi: 10.3389/fped.2022.864755

Pediatric intensivists are bombarded with more patient data than ever before. Integration and interpretation of data from patient monitors and the electronic health record (EHR) can be cognitively expensive in a manner that results in delayed or suboptimal medical decision making and patient harm. Machine learning (ML) can be used to facilitate insights from healthcare data and has been successfully applied to pediatric critical care data with that intent. However, many pediatric critical care medicine (PCCM) trainees and clinicians lack an understanding of foundational ML principles. This presents a major problem for the field. We outline the reasons why in this perspective and provide a roadmap for competency-based ML education for PCCM trainees and other stakeholders.

Keywords: artificial intelligence, machine learning, pediatric critical care medicine, medical education, learning curricula

INTRODUCTION

Pediatric intensivists are bombarded with more patient data than ever before. The density and complexity of data generated from patients, their monitoring devices, and electronic health records (EHR) pose significant cognitive challenges. Clinicians are required to integrate data from a variety of sources to inform medical decision-making, which is further challenged by high stakes, time-sensitivity, uncertainty, missing data, and organizational limitations (1, 2).

These constraints make critical care environments a compelling use case for artificial intelligence (AI) in medicine. AI is an umbrella term that contains multiple techniques and approaches. Modern advances in AI have largely been driven by machine learning (ML) methods such as supervised, unsupervised, deep, and reinforcement learning (3). ML has the potential to decrease cognitive load and enhance decision making at the point of care. Additionally, ML may be uniquely suited to analyzing the heterogeneous data generated during care and quantifying the complex determinants of the behavior of critically ill patients. Techniques, expectations, and infrastructures for developing and utilizing ML have matured, and there are many examples of ML algorithms published in the critically ill adult (4–8) and pediatric (9–16) literature that robustly predict morbidities and mortality.

However, these algorithms are at risk of being deployed in an environment where many intended end-users currently lack a basic understanding of how they work (17–20). We argue that the ML

education gap in pediatric critical care medicine (PCCM) presents a major problem for the field because it may contribute to either *distrust* or *blind trust* of ML, both of which may harm patients.

WHY LACK OF ML EDUCATION IS A PROBLEM FOR PCCM

Clinician distrust of ML is inversely associated with clinician engagement with the ML tool. Distrustful, disengaged clinicians are less likely to use even well-performing ML (21), limiting potential benefits to patients. Distrust may also manifest as missed opportunities to demystify the technology for trainees, recruit clinician champions for future ML projects, and realize the return on institutional and/or extramural investment. Distrust can therefore be enormously costly—in both non-monetary and monetary terms—and efforts to combat clinician distrust in ML through extensive pre-integration education have been successfully employed in both adult (22) and pediatric critical care (23).

Conversely, blind trust of ML is also problematic for PCCM. Humans are prone to automation bias whereby automated decisions are implicitly trusted, especially when end-users poorly understand the subject matter (24). Automation bias has been reported in the ML literature, especially among inexperienced end-users (25). In PCCM, blind trust of ML has the potential to harm patients. Clinicians may make flawed decisions when inappropriately using algorithms developed using biased training datasets (26). Furthermore, algorithms may degrade in performance over time (27) and across different care settings (28). These phenomena may be more prevalent in ML developed from relatively small training datasets (12), as in PCCM. Pediatric intensivists must be able to critically appraise ML literature and any ML-based tool. Identifying strengths and weaknesses of any potential ML intervention is vital to its proper application at the bedside, and critically ill pediatric patients deserve the same rigor applied to ML as other important topics in PCCM.

TABLE 1 | Proposed PCCM ML curriculum.

Curriculum objective	Enabling competencies	Possible educational strategies
A. Foundational ML concepts from development to deployment	A1. Describe and identify major classes of machine learning (e.g., supervised/unsupervised learning, deep learning, reinforcement learning) and the phases of applying ML in critical care settings from development through deployment A2. Describe key differences in data sources and structure required to build different classes of ML A3. Recognize limitations of training data common to pediatrics and PCCM (e.g., data sparsity) and possible mitigation strategies A4. Explain methodological concepts integral to ML model evaluation (e.g., validation, bias, variance, etc.) and performance (e.g., sensitivity, specificity, positive predictive value, precision, receiver operating characteristic curves, F-1 score, etc.) A5. Demonstrate appropriate application of different ML techniques to specific use cases in PCCM A6. Gain a foundational understanding of the "human" factors relevant to using ML at the bedside (e.g., cognitive biases, cognitive load, trustworthiness, uncertainty, explainability, etc.) A7. Learn specific strategies to discuss the results of ML systems with pediatric patients (when applicable) and families	Asynchronous online module with subsequent small group discussion (Competencies A1 and A4) Interprofessional discussion and case-based learning with data scientists and engineers (Competencies A2, A3, and A5) Simulation (Competencies A5, A6 and A7)
B. ML Ethical and legal considerations in clinical practice	B1. Explain the issues of bias and inequity in ML algorithms, including its potential etiologies and implications using published examples B2. Understand core concepts of data privacy and how they relate to building and using ML B3. Explain the challenges associated with using ML for shared decision making in PCCM with families and pediatric patients B4. Identify sources of liability when using ML outputs to guide decision-making and how to navigate liability with families and regulators	Bioethics case-based discussion (Competency B1) Case-based didactic learning with clinicians and administrators (Competencies B2 and B4) Simulation (Competency B3)
C. Proper usage of EHR and biomedical data	C1. Understand broadly how EHR data is used to build ML, including key benefits and limitations to the approach (e.g., data missingness, data incorrectness, lack of granularity, etc.) and how limitations are typically managed C2. Understand the limitations of applying ML to the common pathologies of PCCM (e.g., patient heterogeneity, age-specific variance, etc.) and strategies to mitigate limitations when possible C3. Explain some future directions of biomedical data and ML, including novel sources of healthcare data in critical care (e.g., imaging, genetic data, inflammatory profiles, unstructured/text data, wearable data, etc.)	Interprofessional discussion with data scientists, computer scientists, and health informatics specialists (Competencies C1 and C2) Asynchronous online module (Competency C3)
D. Critical appraisal of ML systems	D1. Appraise ML tools/literature based on evidence-based medicine principles (e.g., internal validity, generalizability, risk of bias) D2. Understand the core components of reporting guidelines for ML and its prospective evaluation	Case-based discussion with ML clinician champions and researchers (Competency D1) Asynchronous online module with subsequent small group discussion (Competency D2)

CLOSING THE GAP: A PROPOSED ML CURRICULUM FOR PCCM TRAINEES AND OTHER STAKEHOLDERS

After acknowledging that a ML knowledge gap exists in PCCM, we must make concerted efforts to close it for the benefit of our patients. Understanding foundational principles of ML will be required to effectively interact with many applications of ML, including diagnostic and therapeutic decision support systems (e.g., disease risk prediction models, treatment recommender systems, etc.). Published ML curricula for medical students (29, 30) and medical (31, 32) and surgical (33) subspecialities converge on several key domains such as the "critical appraisal of AI systems" and "ethical and legal implications" (34). We propose below an ML curriculum for PCCM trainees and stakeholders based on similar domains, but with key adaptations for clinicians caring for critically ill children where appropriate.

We used Kern's six step approach for curriculum development (35) as a guiding framework for our ML in PCCM curriculum (**Table 1**). After identifying the PCCM education gap problem above (Kern's Step 1), our group of experts in PCCM, medical education, and ML identified high-priority curricular needs (Kern's Step 2) based on previous literature (30) and group consensus using modified Delphi methodology (36). We determined specific curriculum objectives (Kern's Step 3), which were operationalized into measurable, enabling competencies. Competencies were designed to be checked "yes, achieved" or "no, not achieved" at the competition of the curriculum and/or PCCM training. We suggest educational strategies (Kern's Step 4) to achieve specific competencies.

Step 5 of Kern's approach relates to implementation, which is the practical deployment of the education strategies listed above within the context of PCCM training resources and modalities. Many of the forums/methods necessary to institute the ML in PCCM curriculum already exist in many programs, thereby increasing the feasibility of delivery. We outline implementation resources common to many PCCM training programs, organized by curriculum objective, in **Figure 1**. Implementation of the curriculum may be more challenging in institutions that lack these resources. Shared access to materials that can be delivered virtually (e.g., freely accessible online modules, ML conferences/webinars, discussion with computer scientists via video conference, etc.) may increase the feasibility of curriculum implementation at less resourced centers. Curriculum champions at early adopting centers can also provide mentorship and promote faculty development at centers that have the desire to implement the curriculum but lack ML experience or expertise.

The final step of Kern's approach relates to evaluation and assessment (35). We recommend a multifaceted approach. Traditional pre-post assessments using the Kirkpatrick outcomes hierarchy (37) can collect objective data such as knowledge of core ML concepts and subjective data such as trainee confidence applying those concepts.

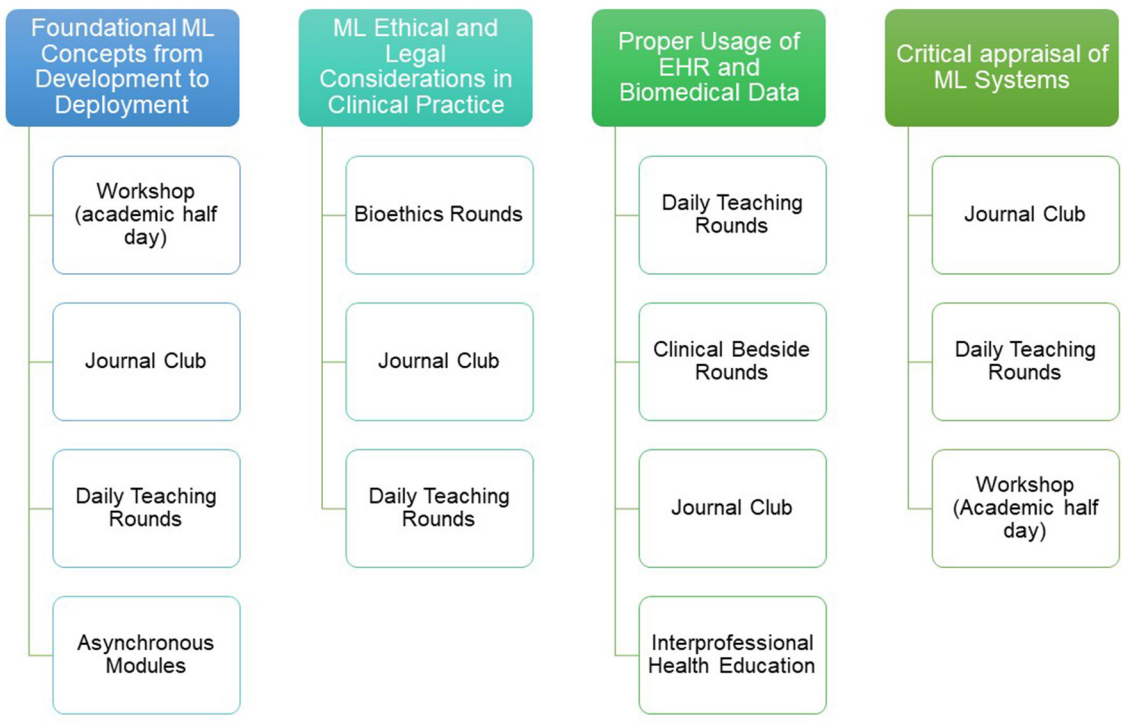

FIGURE 1 | One potential roadmap for leveraging existing curricular implementation resources common to many PCCM training programs. Resources are divided by the ML in PCCM curriculum objectives.

These assessments should be combined with open-ended discussions with key stakeholders (i.e., educational and institutional leaders, clinical faculty, trainees, interprofessional team/allied health members, course teachers, etc.) regarding key outcomes of interest. This multifaceted approach acknowledges the known limitations of pre-post assessments in richly understanding how a curriculum impacts learners. Evaluations should be repeated longitudinally to measure retention and identify new high-yield curricular objectives for PCCM that may arise in the fast-changing field of ML.

CONCLUSIONS

The promise of ML to improve medical decision making and patient outcomes is tempered by an incomplete understanding of the technology in PCCM. This education gap presents a major problem for the field because trainees and key stakeholders are at risk for developing distrust or blind trust of ML, which may negatively impact patients. However, this problem also presents an opportunity to effectively close the education gap by instituting an ML in PCCM curriculum. Our multidisciplinary group is the first to present such a curriculum in this perspective, focusing on key high-yield objectives, measurable enabling competencies, and suggested educational strategies that can utilize existing resources common to many PCCM training programs. We hope to empower PCCM trainees and stakeholders with the skills necessary to rigorously evaluate ML and harness its potential to benefit patients.

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.

AUTHOR CONTRIBUTIONS

DE, VH, and FM: literature search, background and rationale, writing all or part of the manuscript, critical revision of the manuscript, and editing of the manuscript. LR, AJ, and BM: critical revision of the manuscript and editing of the manuscript. MM: background and rationale, critical revision of the manuscript, and editing of the manuscript. All authors agree to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

FUNDING

VH was supported through an Ontario Graduate Scholarship, Canadian Institutes of Health Research Banting and Best Master's and Doctoral Awards, and Vector Institute Postgraduate Fellowship. LR was supported through a Canada Research Chair in Population Health Analytics (950-230702).

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frontiers | Frontiers in Pediatrics

ORIGINAL RESEARCH
published: 03 June 2022
doi: 10.3389/fped.2022.846074

Performance of a Risk Analytic Tool (Index of Tissue Oxygen Delivery "IDO2") in Pediatric Cardiac Intensive Care Unit of a Developing Country

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Objective: To determine the performance of a commercially available risk analytic tool (IDO2) to estimate the risk for SVO2 < 40% in patients admitted in cardiac intensive care unit (CICU).

Methods: Medical and T3 records of all patients (aged 1 day to 12 years, weight >2 kg) who received care in the CICU between October 1st, 2019 and October 1st, 2020, had SvO2 lab(s) drawn during CICU course and whose data was transmitted to T3, were included. The average IDO2 Index was computed in the 30-min period immediately prior to each SvO2 measurement and used as a predictor score for SvO2 < 40%.

Results: A total of 69 CICU admissions from 65 patients, median age 9.3 months (interquartile range 20.8) were identified. Surgical and medical patients were 61 (88%) and 8 (12%) respectively; 4 (5.7%) patients had single ventricle physiology. Tetralogy of Fallot $n = 23$ (33.3%) and ventricular septal defects 17 (24.6%) were major cardiac diagnosis. Sixty-one (89.9%) of the admissions were successfully discharged from the hospital. Of the 187-total included SvO2 labs, 17 (9%) were < 40%. The AUC of estimating SvO2 < 40% IDO2 was 0.87 [confidence interval (CI): 0.79–0.94]. Average IDO2 above 75 had the highest absolute risk (42.11, CI: 20.25–66.50) and highest RR (4.63, CI: 2.31–9.28, p-value < 0.0001) of SvO2 < 40%.

Conclusion: IDO2 performed well in estimating low SvO2 (<40%) in pediatric patients presenting to a CICU in a low resource setting. Future work is needed to determine the effect of this risk analytic tool on clinical outcomes in such a setting.

Keywords: children, cardiac intensive care unit, developing country, cardiac surgery, risk estimates

OPEN ACCESS

Edited by:
Jhuma Sankar, All India Institute of Medical Sciences, India

Reviewed by:
Devyani Chowdhury, Alfred I. duPont Hospital for Children, United States
Tavpritesh Sethi, Indraprastha Institute of Information Technology Delhi, India

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *30 December 2021*
Accepted: *16 May 2022*
Published: *03 June 2022*

Citation:
Abbas Q, Hussain MZH, Shahbaz FF, Siddiqui NuR and Hasan BS (2022) Performance of a Risk Analytic Tool (Index of Tissue Oxygen Delivery "IDO2") in Pediatric Cardiac Intensive Care Unit of a Developing Country. Front. Pediatr. 10:846074. doi: 10.3389/fped.2022.846074

INTRODUCTION

Postoperative care of children undergoing congenital heart disease (CHD) surgery demands constant interpretation of high velocity, high volume data coming from many sources (physiologic, laboratory data etc.) and subsequent decision making based on the interpretation of these inputs. In low middle income countries (LMICs), this is complicated due to a low provider to patient ratio, limited expertise, and the complex clinical states of patients' (i.e., delayed diagnosis or referral,

comorbidities like malnutrition and infections etc.) (1–6). All these factors make the postoperative period extremely vulnerable and complex, precluding early identification of inadequate tissue oxygen delivery which can lead to increased morbidity and mortality (2, 7). If this abnormal tissue oxygen delivery can be identified early coupled with a frame work of intervention to address it, the outcomes can be changed for the better (8). The high- frequency, velocity, and volume data originating from patients can be used for real-time analysis and continuous assessment of patients condition and risk estimation. Predictive modeling and continuous estimation of probabilities of a patients' physiologic state can be one way to integrate diverse, physiologic signals, and provide an early warning system related to the trajectory of a patient in response to their clinical state or their response to specific treatments. One such algorithm, recently FDA 510(k) cleared and displayed at the bedside by the T3 (tracking trajectory and trigger) Visualization Platform (Etiometry, Inc., Boston, MA), is the Inadequate oxygen delivery (IDO2) index (4).

T3 is a novel patient data aggregation, visualization, and risk analytic tool. It captures data from patients monitors, ventilators, and the laboratory information system (4). The IDO2 algorithm utilizes up to 10 physiologic values [heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, oxygen saturation on pulse oximetry (SpO2), right atrium pressure, central venous pressure, temperature, oxygen saturation in arterial blood gas (SaO2), oxygen saturation in venous blood gas (SvO2)] in the full dataset captured from the bedside monitor and laboratory values. It then sends the data to the T3 platform to compute the IDO2 index in real time. IDO2 calculation is based on a model-based risk assessment methodology described and validated previously (9). The index is calculated at 5 second intervals and provides a continuous probability between 0 and 100 of the measured mixed systemic venous saturation (SvO2) being lower than 40% in the preceding time (30 min in our study). Continuous venous oximetry has been shown to improve outcomes in the Cardiac intensive care unit (CICU) and is recommended to be used to monitor patients' trajectories (10–12). It also provided information on oxygen transport dynamics, oxygen extraction ratio (OER), cardiac output, and oxygen delivery. It has been shown that a SVO2 of $<$40% or an OER of $>$50–60% have been associated with shock, lactic acidosis, and other worse outcomes (11–15). Hence IDO2 provides continuous estimation of patients' risks of experiencing inadequate oxygen delivery with intermittent measurement of some of the data variables like blood gases and SVO2. The IDO2 index can continue to be computed based on previously acquired data even when data is missing at particular points in time. This approach uses non-linear stochastic dynamic models of human physiology and recursive Bayesian estimation (9) (see **Appendix** for details on the model in **Supplementary Materials**). IDO2 has been previously validated demonstrating a positive correlation with other indices of oxygen perfusion (serum lactate) and adverse events (8, 9, 16).

The performance of this risk analytic algorithm hasn't been tested in patients presenting in a low resource setting. We hypothesize that despite the different disease spectrum and physiological states, the principles behind the physiological states are same, so we expect IDO2 index will perform same way in a phenotypically different population. This may stem from differences in disease type, more prevalence of malnutrition, and delayed presentation (condition that can alter the physiological state), thus making our cohort more unique than the one on which IDO2 was first validated.

METHODS

Retrospective review of prospectively collected medical records and T3 records of all patients (aged 1 day to 12 years) who received care in the CICU between October 1st, 2019, and October 1st, 2020, was done after approval approval by the ethical review committee of the Aga Khan University (application #2020-4795-10506). Our hospital is a tertiary care center in city of Karachi catering to a population of 47 million (Sind) and 12 million (Baluchistan) with multi-disciplinary/specialty adult and pediatric hospital. Annually ∼250 open heart surgeries (including single and bi-ventricular repair) are done at our hospital. The CICU is a dedicated 4-bedded unit with 1:1 nurse-patient ratio. Average experience of bedside nursing care is 3 years with an attrition rate of 25%. The ICU is staffed by year 2 or 3 general pediatric post graduate trainees and four intensivists (one of them on call on a weekly basis). Our center is also part of international quality improvement collaborative (IQIC), and clinical data variables were extracted from this data. IQIC is a surgical database/registry that collects data from congenital heart disease surgical program in LMICs, for risk adjusted benchmarking of outcomes and quality improvement efforts.

Patients with SvO2 measurements with no associated IDO2 index in the preceding 30 min (minimum data set criteria for IDO2 index computation were not met), birth weight $<$2 kg, and who were born premature were excluded.

The T3 Data Aggregation and Visualization (T3) software is an FDA 510(k) approved application that collects, stores, and displays ICU data in near-real time. It employs proprietary data aggregation technologies developed by Etiometry (Etiometry Inc., Boston, MA) to enable the collection, segmentation, and patient binding of data to support care. T3 employs a web-based user interface to display data collected from monitoring devices as well as Etiometry algorithms anywhere within clinical workflows *via* a web browser. Data from patients' bedside monitor is continuously transferred to T3 platform every 5 s and it is stored in institutions' data warehouse which can be retrieved by authorized personnel.

T3 at Aga Khan University's CICU was implemented in November 2018. Initially only patient's bedside monitors and laboratory feed were connected and later data from ventilators were also captured. All stakeholders including physicians and nurses were trained on how to access and use T3. Nursing staff were also trained on appropriate labeling of blood samples for accurate feeding into the IDO2 algorithm. Regular spot checks and audits were done, which were verified by Etiometry Inc. as well. Once this routine practice was established, IDO2 calculation with full data set was started. During this period

access to the platform for visualizing patient's data was provided to nurse leads, trainee, and attending physicians (intensivists, cardiologists, and surgeons). In October 2019 we installed persistent displays of T3 in our unit, so everyone had access to this platform and data. However, there was no compulsion to use this data and thus the information around use of this platform for clinical decision making wasn't measured for the purpose of this study.

All SvO2 measurements and preceding IDO2 data were extracted from the Etiometry's platform. Each SvO2 value was taken as an independent assessment of a patient's state of oxygen delivery at the time the measurement sample was collected. SvO2 measurements were done based on patients' clinical conditions and at the discretion of caring team. There was no set protocol used to decide when to obtain these labs. However, a general rule in our unit is that when patients are at risk of low cardiac output syndrome (LCOS) (i.e., prolonged cardiopulmonary bypass pump time) and arrhythmias, or have developed LCOS, SvO2 is measured. The average IDO2 Index was computed in the 30-min period immediately prior to each SvO2 measurement and used as a predictor score for SvO2 $< 40\%$. The resulting receiver operating characteristic (ROC) curve was generated and the Area Under the Curve (AUC) was computed to demonstrate the overall discriminatory power of the index. AUC confidence intervals were generated using Bootstrapping, in which bootstrapped AUCs were calculated using random subsets of the data points selected with replacement from the original set. To test that increases in IDO2 values are associated with increased risk for SvO2 $< 40\%$, the 30-min IDO2 values and its corresponding SvO2 measurements were divided into four bins based on average IDO2 value. The bins, which were chosen were chosen to divide the range of possible IDO2 values [0, 100] into four equal ranges, were 0–25, 25–50, 50–75, and 75–100. The absolute and relative risks for SvO2 $< 40\%$ were calculated for each bin. Each relative risk of SvO2 $< 40\%$ was calculated by computing the absolute risk of encountering SvO2 $< 40\%$ in a particular IDO2 bin relative to the absolute risk in the whole population. Finally, the increase in risk between adjacent bins

TABLE 1 | Demographic details of study population ($n = 69$).

Demographics			Frequency (%)	Median (IQR)
Gender	Male		46 (66.7)	
	Female		23 (33.3)	
Age (month)				9.3 (20.8)
Admission Type	Medical		8 (11.6)	
	Surgical		61 (88.4)	
Diagnosis	Cardiac		64 (92.8)	
	1. Tetralogy of fallot		1. 23 (33.3)	
	2. Ventricular septal defect		2. 17 (24.6)	
	3. Transposition of great arteries		3. 5 (7.24)	
	4. Coarctation of aorta		4. 4 (5.80)	
	5. Atrial septal defect		5. 1 (1.45)	
	6. Others		6. 14 (20.3)	
	Non-cardiac		5 (7.2)	
Outcome	Survived		62 (89.9)	
	Expired		7 (10.1)	
Length of mechanical ventilation (hours)				43.5 (79)
Length of CICU stay (days)				6 (6)
Length of hospital stay (days)				9 (9)
CPR	Yes		9 (13.0)	
	No		60 (87.0)	
Duration of CPR ($n = 9$) (minutes)				7 (11)
Scoring of cardiac procedures ***(n = 60)***	RACHS	1	16 (26.7)	
		2	31 (51.7)	
		3	8 (13.3)	
		4	5 (8.33)	
	STAT	1	21 (30.4)	
		2	22 (36.7)	
		3	7 (11.7)	
		4	10 (16.7)	

IQR, interquartile range; CICU, cardiac intensive care unit; CPR, cardiopulmonary resuscitation; RACHS, risk adjustment in congenital heart surgery; STAT, The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

were calculated and checked for statistical significance using a parametric method. Specifically, to test statistical significance of the increase, a *p*-value was calculated using a normal approximation for the distribution of the algorithm of the ratio of risk in adjacent bins. Results are presented as median with interquartile range (IQR) for continuous data and frequencies with percentages for categorical variables. Relative risk along with *p*-value for SvO2 < 40% for different increasing values of IDO2 in the preceding 30-min average IDO2 value are reported.

RESULTS

A total of 69 CICU admissions were identified from 65 patients. Median age of the study population was 9.3 (IQR 4–24.7) months. Sixty-four (92.8%) admissions had a cardiac diagnosis; 61/64 (95.3%) were admitted after cardiac surgery. Admitting diagnosis included tetralogy of Fallot (23, 33.3%), ventricular septal defect (17, 24.6%), transposition of great arteries (5, 7.2%), coarctation of Aorta (4, 5.8%) and others (20, 27.5%). The median stay was 6 days in the CICU (IQR 1–6) and 9 days in the hospital (IQR 1–9). Mortality was 10.1%. There were a total of nine CPR events amongst the included patients. Of the seven patients who expired; three had CPR preformed on them while the remaining four were in comfort care with a do not resuscitate directive (**Table 1**).

A total of 194 SvO2 labs were taken during the study period. Seven (3.6%) SvO2 labs were excluded for insufficient data required for IDO2 calculation. Of the 187 (96.4%) total included SvO2 labs, 17 (9%) were < 40%. Sixty-three patients had IDO2 values in the bin of <25, 11 patients had values between 25 and 50, 10 between 50 and 75, 9 had IDO2 >75. The AUC of predicting SvO2 < 40% using 30-min average IDO2 was 0.87 (confidence interval: 0.79–0.94) (**Figure 1**). Average IDO2 ≤ 25 had the lowest risk of SvO2 < 40% (relative risk: 0.33, confidence interval: 0.11–0.96, *p*-value 0.042) relative to all other average IDO2 ranges. There was no significant difference in the relative risk of SvO2 < 40% when comparing IDO2 ≤ 25 with 25 < IDO2 ≤ 50 and 25 < IDO2 ≤ 50 with 50 < IDO2 ≤ 75 (**Table 2**).

Compared to all other IDO2 ranges, average IDO2 above 75 had the highest absolute risk (42.11, confidence interval: 20.25–66.50) and the highest relative risk (4.63, confidence interval: 2.31–9.28, *p*-value < 0.0001) of SvO2 < 40% (**Figure 2**).

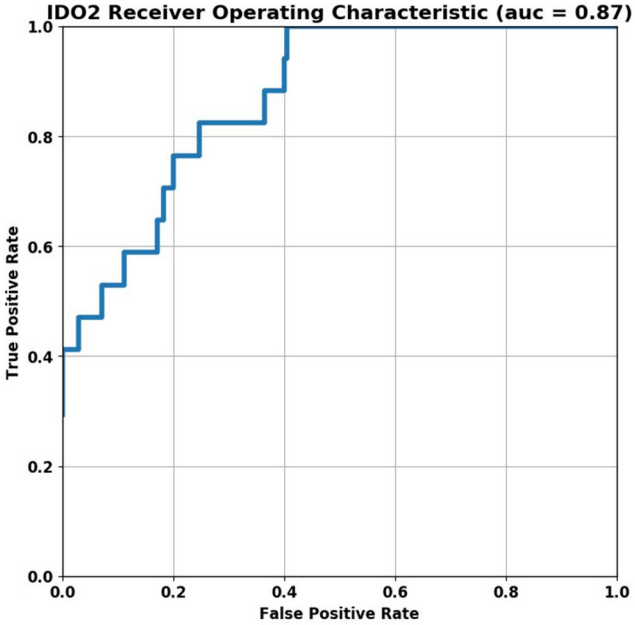

FIGURE 1 | ROC curve of detecting SvO2 < 40% using 30-min IDO2 average.

DISCUSSION

In pediatric post-operative CHD patients from a CICU in a low resource setting, IDO2 (an FDA approved algorithm) demonstrated modest ability to estimate the risk for low SvO2 (a surrogate of low cardiac output and tissue perfusion). The AUC value of 0.87 for predicting SvO2 <40% in our cohort is better than the previously published initial results where the AUC was 0.79 (CI 0.76–0.82). This could be due to the inherent property of iterative algorithms which improves as more data is provided and analyzed. The previous work of assessing the performance of IDO2 has been performed in centers present in high income regions (HIR) (8, 9, 17). To the best of our knowledge this is probably the first study demonstrating performance of this algorithm on post-operative patients in LMICs. CHD patients in LMICs are considered to have a very different spectrum of disease (2, 5, 6, 18, 19). These patients present late and majority of the time have associated co-morbidities like infections, severe malnourishment, and significant lung injury (especially in shunt lesions) due to repeated pneumonia (20–25). These patients thus have different physiological states than similar patients presenting in HIR (i.e., advanced pulmonary vascular obstructive disease, significantly elevated filling pressures due to prolonged volume load etc.) (26). IDO2 also has the ability to use minimum data set (heart rate, SpO2 and blood pressure) to continuously estimate the risk for SvO2 < 40%, all of which can be taken non-invasively. This is also very contextual for LMICs where cost of care is a huge issue. It is thus encouraging to see that the performance of IDO2 is modest even in a very different patient population thus adding to the geographical validation of this tool.

The ability of IDO2 in predicting adverse events like cardiac arrest has been demonstrated by Futterman et al. The IDO2 measured in the preceding 120 min of the event had an AUC of 0.74 which improved to 0.81 when single ventricle patients were included in predicting a cardiac arrest in these patients (17). We were unable to perform such analyses as there were only nine CPR events, and we only had a small proportion of single ventricle patients in our cohort.

Our results also depict that IDO2 < 25 had the lowest risk of having SvO2 < 40%, while this risk increases with increasing IDO2 values and reaches maximum with IDO2 > 75. These findings are similar to what has been shown by Futterman et al. (17). This can also be used to make a framework to trigger clinical teams for any intervention. So far we don't know which threshold of IDO2 value to get an alert or to act

TABLE 2 | Absolute risk and relative risk of experiencing SvO2 < 40% for each IDO2 bin.

Testing parameter	Averaging period (minutes)	Number of patients	IDO2 range	Absolute risk	# SvO2	# SvO2 < 40%	Relative risk	*p*-value
IDO2	30	69	All	9.09 (5.39–14.16)	187	17		
IDO2	30	63	0_to_25	3.01 (0.83–7.52)	133	4	0.33 (0.11–0.96)	0.042
IDO2	30	11	25_to_50	14.29 (1.78–42.81)	14	2	1.57 (0.40–6.13)	0.515
IDO2	30	11	50_to_75	14.29 (3.05–36.34)	21	3	1.57 (0.50–4.92)	0.4377
IDO2	30	9	75_to_100	42.11 (20.25–66.50)	19	8	4.63 (2.31–9.28)	<0.0001

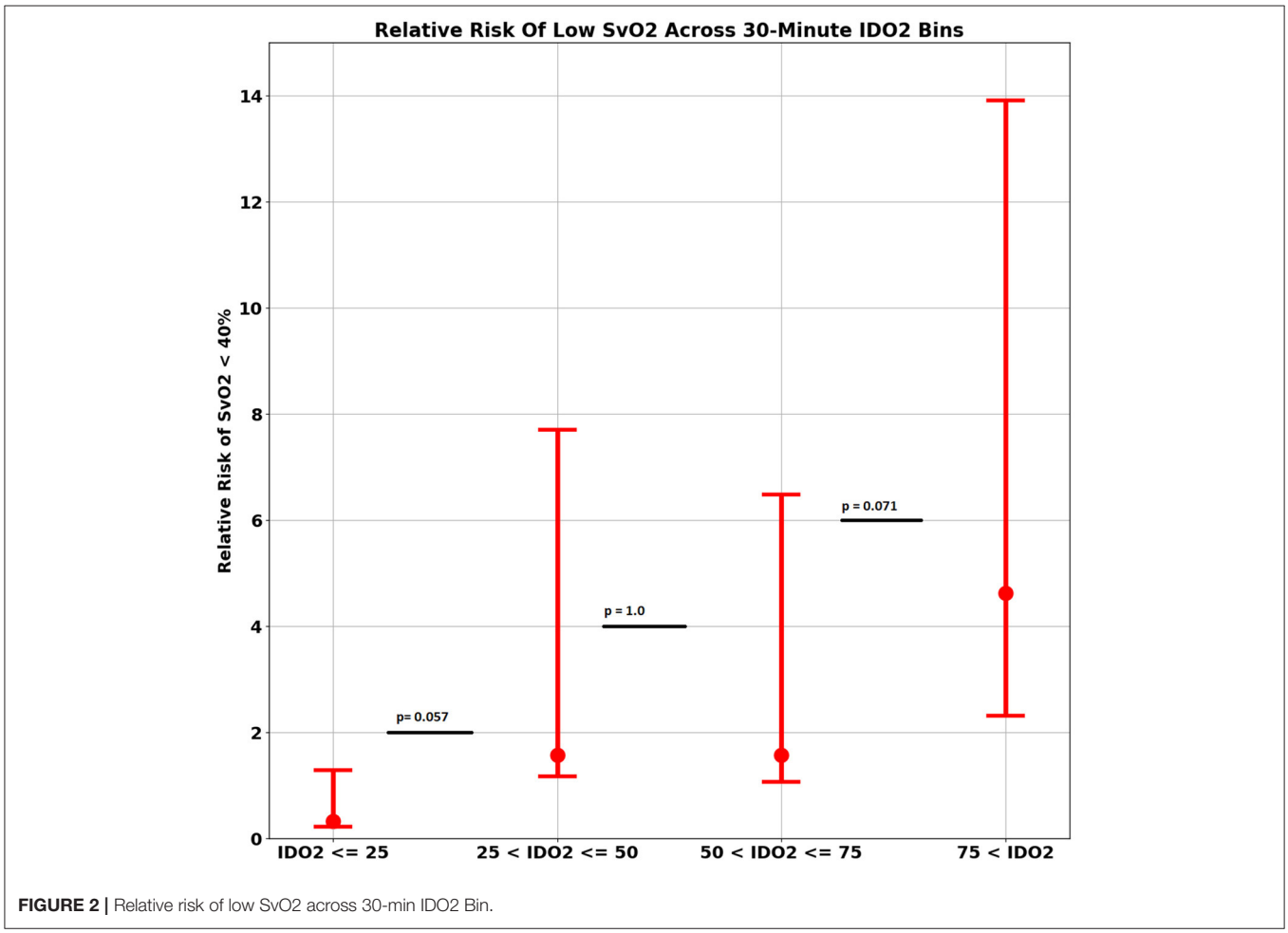

FIGURE 2 | Relative risk of low SvO2 across 30-min IDO2 Bin.

on, as it is very tough to decide at what IDO2 a particular intervention should be aimed at. Another study by Rogers et al.; who compared the IDO2 and LCOS score to predict adverse outcomes in their post CHD surgery patients; showed that LCOS score had a stronger association with specified medium term adverse outcomes compared to IDO2 (8). This might be due to very low frequency of adverse events in their population (7%). Further work will be needed to test the ability of IDO2 vs. other conventional measures of adverse event prediction (LCOS score, vasoactive inotropic score, pediatric risk of mortality etc.) especially in settings where such events have occurrences as high as we had in our population (i.e., 10% mortality rate).

Nearly 90% of all CHD patients are present in what is considered a low resource setting, especially LMICs (19). Each of these countries face similar challenges of lower expertise among staff which is compounded with additional complexities in patients (delayed presentation and or diagnosis, lack of awareness among primary physicians, less availability of treating facilities) and financial constraints; when compared to HIRs (5). As such, automated tools to help identify risks in critically ill patients may provide health care workers in LMICs with a decision support system, thus helping them deliver higher quality care. Since the mortality and frequency of adverse events in such settings is higher; such tools may have a better performance in helping

improve the care and translate in better patient outcomes. To make them useful in such settings, a clear framework of implementation, standard operating procedures, and above all, compliance to these management protocols centered around such risk analytic tools is critical and may be the missing piece in demonstrating the true benefit of such tools in improving patient outcomes. Previously such a beneficial effect on patient outcome has been demonstrated after implementation of the T3 platform in a high resource setting (27).

There are several limitations of our study. Firstly, it is a single center study with a small sample size and thus precluded more detailed analysis and demonstration of significance in some of the results. Since the number of patients in this study were low, we took each IDO2 value as an independent value for IDO2 estimation. Another limitation is that its effects on patient care processes, the ultimate goal of such algorithms, was not studied. Though majority of the cohort were post-operative CHD patients, there were some non-cardiac critically ill patients admitted to CICU who were also included. However, the results are still a giant leap in application of this algorithm beyond neonatal population and in a different geographic location with different characteristics. We understand that this is not a true validation study, rather a pilot study, but we strongly feel that once incorporated into the normal work-flow of patient care delivery, such a model based algorithm and data visualization platform can transform the care processes and outcomes in resource limited settings.

CONCLUSIONS

A physiologic model-based risk analytic algorithm performed well in a different population subset after successful implementation in low resource setting.

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 Ethical Review Committee of the Aga Khan University (Ref # 2020-4795-10506). 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

QA and BH conceived the idea and lead the implementation. QA trained all staff and did analysis. NS helped in sustaining the implementation. MH and FS collected data along with QA. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors would like to thank all PICU staff, Biomedical and IT staff of the hospital and Etiometry team who helped us in implementing this in our PICU.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.846074/full#supplementary-material

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frontiers | Frontiers in Pediatrics

MINI REVIEW
published: 10 June 2022
doi: 10.3389/fped.2022.907268

Palliative and Critical Care: Their Convergence in the Pediatric Intensive Care Unit

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Palliative care (PC) is an integral component of optimal critical care (CC) practice for pediatric patients facing life-threatening illness. PC acts as an additional resource for patients and families as they navigate through critical illness. Although PC encompasses end of life care, it is most effective when integrated early alongside disease-directed and curative therapies. PC primarily focuses on improving quality of life for patients and families by anticipating, preventing and treating suffering throughout the continuum of illness. This includes addressing symptom distress and facilitating communication. Effective communication is vital to elicit value-based goals of care, and to guide parents through patient-focused and potentially difficult decision-making process which includes advanced care planning. A multidisciplinary approach is most favorable when providing support to both patient and family, whether it is from the psychosocial, practical, emotional, spiritual or cultural aspects. PC also ensures coordination and continuity of care across different care settings. Support for family carries on after death with grief and bereavement support. This narrative review aims to appraise the current evidence of integration of PC into pediatric CC and its impact on patient- and family-centered outcomes. We will also summarize the impact of integration of good PC into pediatric CC, including effective communication with families, advanced care planning, withholding or withdrawal of life sustaining measures and bereavement support. Finally, we will provide a framework on how best to integrate PC in PICU. These findings will provide insights on how PC can improve the quality of care of a critically ill child.

Keywords: pediatric intensive care unit (PICU), integrative models, critical care, palliative care, framework

OPEN ACCESS

Edited by:
Niranjan Kissoon, University of British Columbia, Canada

Reviewed by:
Yves Ouellette, Mayo Clinic, United States

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *29 March 2022*
Accepted: *05 May 2022*
Published: *10 June 2022*

Citation:
Buang SNH, Loh SW, Mok YH, Lee JH and Chan YH (2022) Palliative and Critical Care: Their Convergence in the Pediatric Intensive Care Unit. Front. Pediatr. 10:907268. doi: 10.3389/fped.2022.907268

INTRODUCTION

Palliative care (PC) is recognized to be an integral component of optimal critical care (CC) practice for children facing life-threatening illness (LTI) or life limiting illness (LLI). Although it encompasses end of life (EOL) care, PC is most effective when integrated early alongside disease-directed and curative therapies. Professional organizations such as World Health Organization and the American Academy of Pediatrics endorse early integration of PC in management of seriously ill children, regardless of whether the patient is receiving disease-directed therapy and their expected outcome (1, 2). The primary goal of PC is to enhance quality of life, reduce suffering, optimize function and support both patient and families.

Pediatric intensive care units (PICUs) care for children with serious illnesses, complex medical conditions and technology dependence. While overall PICU mortality is low and declining, up to 80% of all inpatient pediatric deaths occurs in the PICU setting, often preceded by withdrawal of life-sustaining therapy (3–5). Improved PICU survival rate has also resulted in more acquired morbidities and chronic complex conditions (CCC) in survivors, shifting the focus of CC from aggressive life-sustaining therapy to one that maintains comfort and preserves quality of life in this group of patients (6). Timely and optimal management of distressing symptoms is important to reduce patient's suffering. It is also imperative to address families' emotional, psychological and spiritual distress while they make difficult decisions for their critically ill child. For these reasons, early integration of PC with CC is recommended (7). Despite its established benefits, PC utilization for critically ill children remains low with considerable variability across institutions (8, 9). This highlights the need to standardize integration and utilization of PC into CC.

This narrative review aims to summarize current literature to describe different models for integrating PC into CC and its impact on patient and family-centered outcomes. We will highlight the skills in PC that is required in PICU and the range of needs which arise from these children and their families. Finally, we will provide a framework on how best to integrate PC in the CC setting.

CHALLENGES OF PEDIATRIC PALLIATIVE CARE

Pediatric palliative care (PPC) is a multidisciplinary clinical approach which delivers patient and family centered care to children with LLI or LTI to minimize suffering while maximizing quality of life (1, 10). Although PPC is a rapidly growing field, PC for adults is comparatively far more established. There are several fundamental differences between the pediatric and adult population which preclude the generalisability of adult PC on children. **Table 1** summarizes the differences between adult and palliative population and its impact on PPC (6, 11–14).

The death of a child has been described as the most stressful of life events with significant implications (15). Parental grief after the loss of a child is more intense and prolonged compared to grief experienced by adults who has suffered the loss of a spouse or parent (16). Many studies reported that many bereaved parents suffer from long-standing mental health issues such as complicated grief, depression and post-traumatic stress disorder (PTSD) (17–20). Bereaved parents are also shown to have increased health risk for cancers, type 2 diabetes, myocardial infarction and acute illnesses (21–24). For these reasons, early PPC is advocated to provide additional support for both patient and families.

A growing body of literature describe direct benefits of PPC for patients, families and staff. Despite this, the adoption of PPC is still suboptimal. A prospective international multicenter study on PICU mortality showed that patients who died in PICU were less likely to have a DNR or PC consult compared to patients who died in another inpatient setting (25). Systemic integration of PPC into CC practice will likely improve this situation. This is demonstrated in a retrospective study in Taiwan where a standardized approach to EOL care resulted in increased willingness to accept withdrawal of life-sustaining interventions and lowered PICU care intensity, such as PICU utilization and use of catecholamines infusion in patients with the DNR status (26).

Impact of Palliative Care Interventions

Pain and Symptom Management

Pain, from the disease or interventions, is the most common symptom experienced by critically ill children in PICU (27, 28). Other commonly experienced symptoms are nausea, dyspnea and delirium. There are numerous barriers that may contribute to under-reporting of these symptoms. This includes communication difficulties by PICU patients due to severity of illness, unrecognized delirium, neurocognitive impairment and presence of invasive support such as endotracheal tube. Pain

TABLE 1 | Differences between adult and pediatric palliative patients.

Domain	Adult population	Pediatric population	Implication to PPC
Patients characteristic	Less diverse population • Age range tends to be narrower.	More diverse population • Age range tends to be wider (spanning from *in-utero* though young adulthood).	Management and communication need to be constantly tailored to child's level of comprehension, emerging autonomy, parental views and child's condition.
Underlying diagnosis and comorbidities	• Malignancy is the most common diagnosis.	• Large variety of congenital and acquired conditions with unknown trajectories and evolving treatment goals. • Growing proportion of children having complex chronic conditions	PPC specialists need a broad understanding of pediatric conditions and be able to address both chronic and acute end of life symptoms It is common for PPC specialists to provide symptom control and decision-making support while potential treatment is still being pursued.
Duration of PC needed	• Average duration of survival after initiation of PC: 1–3 months.	• Survivorship after initiation of PC can range from hours to years.	PPC should begin at time of LTI diagnosis and continue throughout disease trajectory.

PPC, pediatric palliative care; LTI, life threatening illnesses.

assessment in the pediatric population is also more challenging than in adults because patients of different age groups express pain differently. A wide range of pain rating scales for different age groups and verbal skills are readily available to achieve consistency of pain assessment (29). Initiatives to improve EOL care in PICU should include raising awareness of pain as a vital sign and standardizing guidelines for symptoms management.

The management of distressing EOL symptoms is of upmost importance in PC. Retained memories of unrelieved EOL symptoms have negative impacts on bereaved parents and siblings (30). A high index of suspicion and close monitoring assist with identification of symptoms, which can be quickly followed by aggressive interventions in collaboration with subspecialties like acute pain team and PC team. Early engagement of PC team positively impact patient and family-centered outcomes by facilitating better pain and EOL symptoms management. Alleviation of physical EOL symptoms also enables PC team to form a good rapport and better negotiate domains of psychological and spiritual care with the family and patient.

Effective Communication

Effective communication is an essential pillar of good pediatric CC. Parents of PICU patients are often overwhelmed with medical concepts and uncertainties and are required to make high-stake decisions for their child. Many PICU physicians and subspecialists function on a roster basis, making continuity of care challenging (7). In a qualitative study, many parents reported that the sheer number of physicians and the coordination of communication added on to their emotional burden and eroded their confidence as they needed to seek clarifications (31). PC specialists can act as a constant and strengthen the team's ability for effective communication in such instances.

The high stress environment of the PICU may predispose to conflicts between physician-family, among physicians and within family (32). Conflicts compromise quality of care and contributes to physicians' burnout (33). Commonly cited reasons for physician-family conflict are disagreement over care plans and poor communication (32, 34). Sources of conflict among physicians include disagreement in medical decisions such as pain management, lack of leadership and undervaluing each other's role in a multidisciplinary team, all of which fall under the umbrella of poor communication (35). Palliative specialists can help neutralize tension between all parties and redirect the focus toward advocating for the child's best interest.

End of life discussion in PICU is a delicate and challenging process for physicians, with uncertainty around prognosis of many pediatric conditions adding to the complexity of it. Even though communication is one of the core skills of PICU physicians, many are uncomfortable with EOL discussion and may delay these important conversations (36). This delay can result in missed opportunities for identification of emotional issues and negatively impair healing for the family (37). A cross-sectional study of family conferences held in the PICU of Children's National Hospital, United States reported that nearly three quarters of family conferences and 79% of physician speech was medically focused (38). This study also reported that a higher patient-centeredness score was associated with higher patient satisfaction (38). The family-centered model of PC helps forge a beneficial and supportive partnership between families and physicians.

Advanced Care Planning

Advanced Care Planning (ACP) aims to facilitate early planning of treatment goals, including EOL care, through professionally facilitated discussions with patients and families (39). Positive impacts of pediatric ACP include higher rating of EOL care in patients, decrease negative emotions in parents and enabling parents to be better informed and certain about their decisions (40, 41). A study on bereaved parents reported that all parents felt that ACP was important even though only 61% of the parents had finalized ACP prior to their child's death (42).

The answer to when, how and who to initiate ACP remains controversial. A study on clinical providers' attitudes on ACP identified unrealistic parent expectations, differences between clinical and patient/parent understanding of prognosis and lack of parent readiness as the top 3 barriers to ACP discussion (43). Despite having clarity of the barriers, 71% of the respondents believed that ACP happened too late in the patient's clinical course (43). Naturally, many physicians feel insecure about discussing ACP as they are worried about burdening families and destroying the therapeutic alliance with parents (44). PC specialists can step in to share this burden and ensure timely discussion of ACP in a sensitive manner. It is, however, important that ACP discussion should not be owned by a particular physician and should be shared by the entire medical care team.

Withdrawal, Withholding of Life Sustaining Therapy or Non-escalation

A framework by the Royal College of Pediatrics and Child Health, United Kingdom states that there are three sets of circumstances when withholding, withdrawal or non-escalation of life sustaining interventions (WWNLST) can be considered (i) when life is limited in quantity, (ii) when life is limited in quality, (iii) lack of ability to benefit (45). Transition in goals of care from curative to comfort should be made by clinical teams in partnership, and with the agreement of, the parents and patient. PPC can work together with PICU physicians to identify patients suitable for WWNLST and aid in timely open discussion with the family to achieve consensus. A large single center retrospective study in Spain reported that WWNLST was more frequently facilitated in suitable patients after the development of a PC unit (46).

The practice of WWNLST remains highly variable despite many published recommendations (47, 48). Poorly handled WWNLST can lead to confusion and distress for the patient, family and medical staff. The role of PC is to formulate a carefully thought-out plan, from planning to post withdrawal of care, to ensure a smooth process and an optimal experience for all involved stakeholders.

Compassionate extubation at home (CEAH) is a valuable service that PICU can offer and facilitate. The familiarity and comfort of home help families achieve a higher level of satisfaction and comfort with their child's EOL care (49). Medical staff involved in CEAH also reported it to be valuable despite

its complex orchestration (50). Despite being resource intensive and logistically challenging, reports have reaffirmed the feasibility of CEAH in the pediatric population with positive outcomes (51, 52). A recently published framework detailing processes from preparation to follow through acts as a good reference for PICU intensivists in their provision of CEAH as an option of EOL care (53).

Bereavement Care Services

The death of a child can lead to long-term adverse effects on parental and siblings' physical and psychological health (54, 55). Data also suggest that bereaved parents have higher mortality rates (56). The goals of bereavement support are to facilitate healing and adjustment of bereaved parents after the death or their child so that they can continue to live normal and meaningful lives, and also to carry out early intervention for individuals at risk of negative bereavement reactions (57). Despite the established benefits, hospitals lack coordinated and standardized bereavement programs (58).

A systematic review identified five key components of pediatric bereavement: (i) acknowledgment of parenthood and child's life; (ii) establishing keepsakes, (iii) follow-up contact, (iv) education and information, and (v) remembrance activities (59). However, only four out of 12 studies reported interventions that commenced before the death of the child, inconsistent with bereavement theories of facilitating the transition of parents toward a new reality (59). A qualitative study conducted in the United States reported that five out of nine bereaved parents experienced feelings of abandonment by the medical team after the death of their child, with some parents verbalizing their wish for follow up meeting or support (57). These highlight the need for improvement and standardization of bereavement care.

An anecdotal report by a PPC physician on primary medical providers after redirection of patient's care plan toward comfort stated "sudden loss of power of prescription" and "assumption that bereavement should be delegated to other team members" as challenges primary providers faced (60). Hence, PC specialists can help to ensure that important components of pediatric bereavements are met and to empower primary physicians in providing bereavement care, reducing the risks of adverse effects associated with the death of a child.

Other Outcomes

A systematic review of adult controlled trials reported a reduction in relative risk of ICU admission and ICU length of stay by 37 and 26%, respectively, in patients who received PC interventions and ACP discussion (61). A pediatric retrospective study conducted at St.Jude Hospital, United States reported that children who received PC intervention were significantly less likely to die in PICU and to receive invasive treatment (62). These outcomes have important economic implications and reduce the financial burden of some families. Indeed, an adult cohort study demonstrated that patients who received PC incurred significantly lower costs as a result of reduced length of hospital stay and number of investigations performed compared to patients who received usual care (63).

Integrating Palliative Care Into PICU: Models of Care

The integration of PPC in PICU is largely extrapolated from adult models. The traditional models for PC-CC integration can be broadly classified into "integrative," "consultative," and "mixed" models (64). The integrative model embeds standardized PC principles and interventions into daily CC practice by the ICU team for all patients and families facing critical illness. The consultative model incorporates the involvement of specialist PC team on a needs basis, reserved for those at highest risk for poor outcomes. Successful implementation of this model includes the use of clinical triggers for expert PC consult. Mixed models would feature aspects of both integrative and consultative models (**Figure 1**).

More recently, a tiered approach for PC-CC integration has been described (**Figure 1**) (65). In this model, interventions are categorized into primary, secondary and tertiary PC, with increasing PC specialists involvement across the levels. Primary PC is the provision of evidence-based PC interventions by critical care physicians. This is useful in institutions where dedicated PC teams are not available. Examples of primary PC interventions can be found in the Initiative for Pediatric Palliative Care (IPPC) curriculum which highlights six core constituents of quality PPC: holistic care of the child, support of family unit, involvement of the family and child in decision-making, communication and planning of care, treatment of pain and other symptoms, continuity of care and support of grief and bereavement (66). PICU physicians are also equipped with knowledge about EOL issues including pronouncing death and discussing need for autopsies. However, delivery of primary PC can be highly variable and is dependent on resources, manpower and critical care physicians' knowledge on PC. An international multicentre cross-sectional study including 34 PICUs of varying socio-economic settings reported heterogenous and incomplete fulfillment of IPPC domains in their delivery of primary PC, with better adherence in higher income groups and units with shorter shift lengths (67).

Secondary PC uses ICU-based champions who receive additional PC training through courses and subspecialty rotations. These ICU champions strengthen the delivery of PC in ICU by spearheading PC-based training for other ICU staff, advocating for earlier PC subspecialty involvement in suitable patients and also improving PC *via* quality improvement initiatives and protocols development. A recent report describes the integration of a pediatric palliative care-champion (PPCC) based model into the cardiac ICU in Boston Children's Hospital, United States (68). The PPCC model is expected to be more sustainable than other PC-CC integration models as the workload is shared with overextended subspecialty PC services, hence relieving the strain on PC teams while allowing early integration of PC principles in the ICU. However, provision of secondary PC will require commitment from ICU providers and a robust PPC team to support program development and education.

Tertiary PC involves consultation of a subspecialty PC team as an additional resource. This is helpful in specific situations where

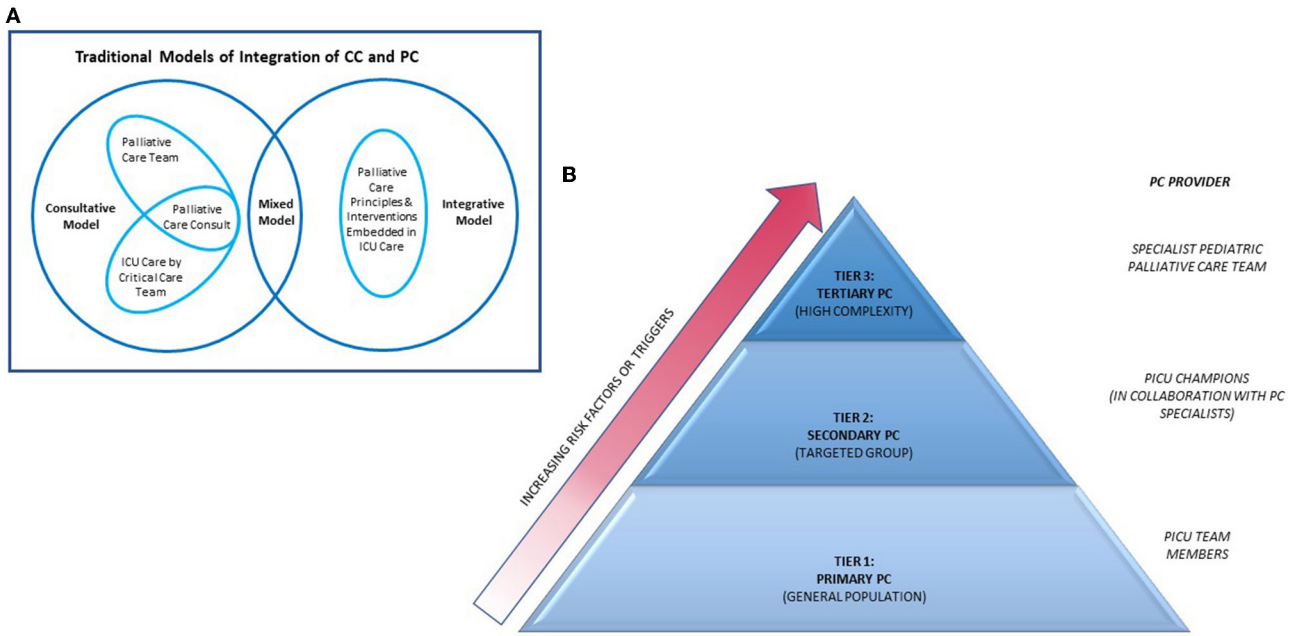

FIGURE 1 | Models of integration of PC into ICU. PC, palliative care; CC, critical care; ICU, intensive care unit. **(A)** Diagram depicting interactions of traditional models of integration of PC into ICU. Adapted from Nelson et al. (64). **(B)** Pyramid model of integrating of PC into ICU. Source—Public domain and adapted from Rothschild et al. (65).

PC team can facilitate more difficult communications, support complex decision making in the face of uncertainty or conflict while providing both emotional and spiritual support for both patient and family and assist with managing difficult symptoms. Added benefits include ensuring continuity in goals of care and care coordination across multiple providers and settings.

Defining clinical triggers for PC consultations ensures that palliative consults are made appropriately. In PICUs, common triggers criteria include baseline patient characteristics (e.g., extreme prematurity), selected acute or life-limiting diagnoses (e.g., severe traumatic brain injury, Trisomy 13), resource utilization based criteria (e.g., ECMO duration, number of ICU admissions over time), social risk factors or failure of initial ICU efforts to address PC needs of patients and families (64). However, variability in resources and systems of care limits the use of a fixed set of trigger criteria across institutions. Adaptation of triggers mapped to institution resources and needs is a more logical approach (69).

Choosing to adopt any of the above models can be an important initial step toward an initiative to incorporate PC practice into the PICU. Both primary and secondary PC have the same characteristics as the integrative model while tertiary PC is most alike to the consultative model. In reality, there is usually a large degree of overlap between models and no one model can suit the demands of all institutions. Careful and realistic assessment of available resources, attitude of stakeholders, cultural and value system of the institution would be required to find the best fit.

CONCLUSION

The integration of PC to CC has many positive impacts on patient and family-centered outcomes and is becoming the standard for high-quality care of critically ill children. PC also ensures both coordination and continuity of care across different care settings are met. Several models of integration have been proposed but the model of choice should be tailored to available resources, attitude of stakeholders, cultural context and value system of the institution.

AUTHOR CONTRIBUTIONS

SB and SL wrote sections of the manuscript. YM, JL, and YC contributed additional resources/journals and advice regarding content. All authors contributed to manuscript revision, read, and approved the submitted version.

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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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ORIGINAL RESEARCH
published: 08 July 2022
doi: 10.3389/fped.2022.909862

Chronic Lung Disease Following Neonatal Extracorporeal Membrane Oxygenation: A Single-Center Experience

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OPEN ACCESS

Edited by:
Niranjan Kissoon, University of British Columbia, Canada

Reviewed by:
Warwick Wolf Butt, Royal Children's Hospital, Australia
Daniel Dirnberger, Alfred I.duPont Hospital for Children, United States

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Specialty section:
This article was submitted to Pediatric Critical Care, a section of the journal Frontiers in Pediatrics

Received: *31 March 2022*
Accepted: *15 June 2022*
Published: *08 July 2022*

Citation:
Perez Ortiz A, Glauner A, Dittgen F, Doniga T, Hetjens S, Schaible T and Rafat N (2022) Chronic Lung Disease Following Neonatal Extracorporeal Membrane Oxygenation: A Single-Center Experience. Front. Pediatr. 10:909862. doi: 10.3389/fped.2022.909862

Objective: To assess the incidence and severity of chronic lung disease (CLD) after neonatal extracorporeal membrane oxygenation (ECMO) and to identify factors associated with its development.

Methods: A retrospective observational study in a neonatal ECMO center was conducted. All neonates who received support with ECMO in our institution between January 2019 and October 2021 were included and their pulmonary outcome was investigated.

Results: A total of 91 patients [60 with congenital diaphragmatic hernia (CDH), 26 with meconium aspiration syndrome, and 5 with other diagnoses] were included in this study. Sixty-eight (75%) neonates survived. Fifty-two (76%) ECMO survivors developed CLD. There was no statistical difference between patients with and without CLD with regard to gender or gestational age. Patients with CLD had lower birth weight, were younger at the initiation of ECMO, and required longer ECMO runs. Patients with CDH developed CLD more often than infants with other underlying diseases (94 vs. 60%). Seventeen ECMO survivors (25%) developed severe CLD.

Conclusion: The incidence of CLD after neonatal ECMO is substantial. Risk factors for its development include CDH as an underlying condition, the necessity for early initiation of ECMO, and the need for ECMO over 7 days.

Keywords: chronic lung disease, extracorporeal membrane oxygenation, respiratory failure, neonatal lung disease, congenital diaphragmatic hernia

INTRODUCTION

Neonatal extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique, which provides support to critically ill neonates suffering severe respiratory and/or cardiac failure refractory to conventional treatment with a high likelihood of mortality and a potentially reversible etiology.

Severe respiratory failure still remains the main indication for neonatal ECMO. The most common underlying diseases include congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), and persistent pulmonary hypertension (PPHN) (1).

The application of ECMO has improved the survival of neonates with severe respiratory failure but carries also a higher risk of long-term morbidity. Among neonatal ECMO survivors, long-term pulmonary sequelae are well described (2–6). The development of chronic lung disease (CLD) may be an early marker for future pulmonary morbidity (7). Obstructive patterns with bronchospasm, asthma, and decreased exercise tolerance are the most common conditions of long-term respiratory morbidity (8).

The aim of this study was to assess the incidence and severity of CLD in neonates after ECMO in patients treated in our institution, distinguished by the primary underlying condition. Furthermore, we aimed to identify perinatal characteristics associated with the development of CLD.

MATERIALS AND METHODS

Subjects

Neonates who received support with ECMO between January 2019 and October 2021 were selected from the neonatal intensive care unit (NICU) of the Department of Neonatology of the University Children's Hospital Mannheim, University of Heidelberg. The indication criteria for and the allocation to ECMO were based on the recommendations of the Extracorporeal Life Support Organisation (ELSO) (9) for all the underlying diagnoses, with the exception of CDH. ECMO initiation in neonates with CDH was based on the recommendations made by CDH EURO Consortium Consensus Guideline Update 2015 (10). All patients received veno-arterial ECMO. All gestational ages were included. Exclusion criteria were congenital heart defects (except patent ductus arteriosus and persistence of foramen ovale) and inborn errors of metabolism. This study was approved by the local ethics committee of the Medical Faculty Mannheim of the University of Heidelberg.

Chronic Lung Disease

The diagnosis of CLD was made as reported before (10, 11): if there was an additional need for oxygen supplementation on day 28 after birth, CLD was diagnosed. Target values for oxygen saturation at the moment of diagnosis were ≥92%. An oxygen reduction test was performed on day 28 of life to check the need for oxygen administration in not mechanically ventilated patients. The severity of CLD was differentiated into three grades according to the additional need for oxygenation at day 56 after birth or at discharge, whichever point came first: mild CLD with no need for supplemental inspired oxygen (fraction of inspired oxygen [FiO_2] $\leq$ 0.21), moderate CLD (FiO_2, 0.22–0.29), and severe CLD ($FiO_2 \geq 0.30$ and/or positive pressure).

Data Collection

Demographic, pre- and perinatal, as well as clinical and laboratory data, were collected from the patients' records, including demographic variables, diagnosis, prenatal parameters (if available), referral from another institution, highest oxygenation index prior to ECMO, age at initiation of ECMO, duration of ECMO, total duration of mechanical ventilation, duration of oxygen dependency, and type of respiratory support at discharge.

Statistical Methods

Statistical analysis was performed with SAS Version 9.4 (SAS Institute Inc., United States). Descriptive statistics were used to describe the demographic characteristics of the patients and the incidence of CLD. Neonates with CLD and neonates without CLD were compared with regard to gender, birth weight, prematurity, oxygenation index (OI) prior to ECMO, age at onset of ECMO, duration of ECMO, and underlying diagnosis. The chi-square or Fisher's exact test for categorical variables and the *t*-test or the Mann–Whitney U test for quantitative variables were applied to determine statistical differences between the two groups. For normally distributed variables, results were compared through means and standard deviations; when variables were not normally distributed, comparisons were made through medians and ranges. The development of CLD was also analyzed depending on the underlying condition. Logistic regression analyses were used to identify predictors of the development of CLD. A *p*-value of 0.05 or less was considered significant.

RESULTS

Demographic and Clinical Characteristics of the Study Cohort

Between January 2019 and October 2021, 93 neonates received ECMO support within the first week of life at the Neonatal ECMO Center of University Children's Hospital Mannheim. Complete data for analysis were available for 91 patients. Fifty-three neonates were born at our institution, whereas 38 patients (42%) were referred specifically to receive ECMO support. Severe respiratory failure was the indication for neonatal ECMO in all patients, CDH being the most common underlying disease (66%), followed by MAS (29%). Sixty-eight patients survived to be discharged (75%). CLD was present in 76% of ECMO survivors. Seventeen of these patients (33%) developed severe CLD, and 21 and 46% developed moderate and mild CLD, respectively. Patients with CDH developed CLD more often than infants with other underlying diseases (94 vs. 60%). Severe CLD was present in 42% of the CDH patients whereas only 7% of patients with other underlying conditions developed severe CLD.

Eleven surviving patients (16%) needed some kind of respiratory support at discharge, and three patients (4%) were discharged with invasive ventilation. The perinatal characteristics of the study population and its respiratory outcome, distinguished by the primary underlying condition are shown in **Table 1**.

Comparison of All Patients With and Without Chronic Lung Disease

Patients who developed CLD did not differ from those who did not in neither in gender nor gestational age. Patients with CLD had lower birth weight and OI prior to ECMO, they were younger at the initiation of ECMO and required longer ECMO runs. The same results were found when comparing patients with severe CLD and no CLD (**Table 2**). Place of birth was statistically significantly different between patients with and without CLD. Since our institution is a referral center for patients with CDH and especially severe CDH are already diagnosed before birth, this condition cannot be considered a risk factor for the development of CLD.

Consideration of all these perinatal characteristics showed good discrimination for predicting CLD in ECMO survivors [area under the curve (AUC) 0.86; $p = 0.002$]. Duration of ECMO was the only independent predictor of development of CLD (odds ratio = 1.39; 95% confidence interval = 1.02–1.90; $p = 0.04$). Seven days were established as the best cutoff point (sensitivity = 89%, specificity = 43%) for predicting CLD. An overview of all the perinatal characteristics of all patients with and without CLD is displayed in **Table 2**.

TABLE 1 | Clinical perinatal characteristics of the patients treated with neonatal extracorporeal membrane oxygenation (ECMO).

	All patients	CDH	MAS	Other
Subjects, n (male)	91 (49)	60 (30)	27 (15)	5 (4)
Preterm (<37 weeks)	7	7	0	0
Inborn	53	53	0	0
Age at ECMO-Onset, h	24 (3–146)	19 (3–146)	32 (10–113)	45 (27–66)
Duration of ECMO, days	9 (1–28)	9 (1–28)	9 (4–14)	10 (7–14)
Survivors, n	68	38	26	4
CLD	52	34	16	2
Mild CLD	24	8	16	0
Moderate CLD	11	11	0	0
Severe CLD	17	15	0	2
RS at discharge	11	9	0	2
Oxygen	1	0	0	1
HFNC	6	5	0	1
NIV	1	1	0	0
IV	3	3	0	0

Data are expressed as median (range) or n. Total group of patients and subgroups according to diagnosis are shown. CLD, chronic lung disease; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; IV, invasive ventilation; MAS, meconium aspiration syndrome; NIV, non-invasive ventilation; OI, oxygenation index; CLD, chronic lung disease; RS, respiratory support.

Comparison of Congenital Diaphragmatic Hernia Patients With and Without Chronic Lung Disease

There was a disproportionate number of infants with CDH in the group of patients who developed CLD (65 vs. 14% p 0.001) and severe CLD (88 vs. 11% $p < 0.0001$) when compared with the group which did not develop CLD. Nevertheless, no statistically significant differences regarding perinatal characteristics could be found when comparing CDH patients with and without CLD. All three patients who needed invasive respiratory support at discharge had CDH as an underlying disease. A comparison of the perinatal characteristics between patients with CDH discharged with invasive ventilation and discharged without respiratory support showed no statistically significant differences.

Comparison of Meconium Aspiration Syndrome Patients With and Without Chronic Lung Disease

Neonates with MAS developed no CLD (38%) or mild CLD (62%) after ECMO. When comparing neonates with MAS as an underlying condition, birth weight was the only perinatal characteristic that differed between the group with and without CLD: patients who developed CLD had lower birth weights (**Table 3**).

DISCUSSION

Neonatal ECMO has improved the survival of neonates with severe respiratory failure (2, 5, 11). However, improved survival might carry a higher risk of long-term morbidity among survivors depending on several factors, such as underlying conditions (7, 12). MAS, PPHN, and neonatal respiratory distress syndrome were historically the most common indications for neonatal ECMO (8). Due to perinatal care improvement, their incidence declined and to date, CDH represents one-third of neonatal ECMO diagnoses (8). Irrespective of the underlying disease, the development of CLD represents an important risk factor for impaired pulmonary outcomes in neonatal ECMO survivors (13).

Mechanical ventilation and supplemental oxygen contribute to the pathogenesis of CLD (2). The use of protective ventilation, and avoiding barotrauma and hyperoxia during the course of ECMO may mitigate ventilation-induced lung injury and may promote lung healing until the underlying disease heals. On the other hand, only critically ill neonates who otherwise would have died receive support with ECMO, so a poor respiratory outcome would be expected in these patients. In a prospective study of 219 neonates who met the criteria for ECMO, Vaucher et al. (14) showed that ECMO survivors had a 50% reduction in the incidence of CLD compared with patients with severe respiratory failure who survived after conventional or high-frequency ventilation. In a randomized controlled trial of 78 1-year-old infants after severe respiratory failure, Beardsmore et al. (15) showed that ECMO does not prevent sequelae of severe respiratory disease in the newborn period, but that

TABLE 2 | Comparison of clinical perinatal characteristics between patients with and without chronic lung disease.

	No CLD	CLD$^{\alpha}$	*P*-value	Severe CLD$^{\alpha}$	*P*-value
Subjects (male)	14 (7)	52 (28)	0.7100	17 (10)	0.6200
Preterm (<37 weeks)	0	3	1.0000	1	1.0000
Birth weight, g*	3581 (±480)	3107 (±424)	0.0006	3022 (±537)	0.0050
Inborn	1	31	0.0008	13	0.0001
Age at ECMO-Onset, h^{+}	28.5 (10–66)	19 (3–146)	0.0360	14 (3–48)	0.0320
Duration of ECMO, days^{+}	7.0 (4–13)	8.5 (5–16)	0.0490	10 (6–16)	0.0380
Highest OI prior to ECMO*	45 (±10)	36 (±15)	0.0440	34 (±14)	0.0330
Diagnoses					
CDH	2	34	0.0010	15	<0.0001
MAS	10	16		0	
Other	2	2		2	

Data are expressed as mean (standard deviation), median (range)$^{+}$, or n. Shown are comparisons from perinatal parameters between subgroups according to the presence and severity of chronic lung disease. $^{\alpha}$Patients with CLD and with severe CLD were compared with patients without CLD. CLD, chronic lung disease; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; MAS, meconium aspiration syndrome; OI, oxygenation index.*

respiratory function following ECMO was no worse and indeed appeared slightly better than following conventional treatment. Our institution is a national referral center for neonatal ECMO and neonates with CDH. In our study, the incidence of CLD after neonatal ECMO was clinically relevant (76%) and much higher than those reported in previous studies (14, 16). The number of infants with CDH in the group of patients who developed CLD was disproportioned (65 vs. 14%). The underlying condition may be an important factor associated with pulmonary morbidity after neonatal ECMO (7, 12) and the high prevalence of patients with CDH in our study population (56% diagnosis among ECMO survivors) may explain our high incidence of CLD. We found a significantly higher rate of CLD in patients with CDH than in all other patient populations, which is in accordance with previous studies (2, 14, 17) and comprehensible, since infants with other diagnoses (such as MAS or pneumonia) have a normal lung development, while the pathophysiology of CDH includes lung hypoplasia and PPHN. Furthermore, CDH patients that require ECMO concern the most severe cases (18). ECMO can rescue these severely ill patients, providing time for improvement of pulmonary hypertension and avoiding iatrogenic lung injury (10) until the surgery can be performed, but the sequelae of the severe pulmonary hypoplasia remain present, compromise the lung function in these patients, and contribute to a prolonged need of oxygen and invasive ventilation. Using data from the CDH Study Group registry, Van Den Hout et al. (19) described an incidence of CLD of 41% in patients with CDH. Similar results were found in a study of 255 patients with CDH conducted in our center: CLD was found in 45% of the subjects. However, the incidence of CLD in patients with CDH not treated with ECMO was 28% vs. 94% in those that required ECMO (20).

Within our population of neonates with severe respiratory failure that required ECMO support, patients who developed CLD and severe CLD had lower birth weights, were younger at the initiation of ECMO, and required longer ECMO runs compared to patients who did not develop CLD. Since hemodynamic problems and not only respiratory failure may be relevant for the ECMO initiation in neonates with CDH, the higher rate of CLD in neonates with CDH and a large number of CDH patients in our study population may explain the earlier ECMO requirement with lower oxygenation indexes in patients who developed CLD.

Of all perinatal characteristics examined, the duration of ECMO was the only parameter identified as an independent predictor of the development of CLD.

If patients with CDH and lung hypoplasia were excluded, the incidence of CLD was 60%. All these patients were outborn neonates with severe respiratory failure, who were referred to our institution when they met the inclusion criteria for ECMO. In contrast with Schwendeman et al. (21), we did not find differences between neonates with and without CLD regarding age at initiation of ECMO or highest oxygenation index prior to ECMO. Birth weight was the only perinatal characteristic that differed between the two groups. In our study, no MAS patients developed moderate or severe CLD. Different studies have evaluated long-term pulmonary sequelae in patients with an underlying condition different from CDH. A cross-sectional study conducted by Boykin et al. (22) in 10–15-year-old patients who underwent ECMO after MAS, revealed air trapping and

TABLE 3 | Comparison of clinical perinatal characteristics in patients with meconium aspiration syndrome between those with and without chronic lung disease.

	No CLD	CLD	*P*-value
Subjects (male)	10 (4)	16 (11)	0.23
Preterm (<37 weeks)	0	0	
Birth weight, g*	3666 (±537)	3273 (±307)	0.03
Inborn	0	0	
Age at ECMO-Onset, h^{+}	23 (10–37)	27.5 (10–113)	0.28
Duration of ECMO, days^{+}	6 (4–13)	9 (5–14)	0.14
Highest OI prior to ECMO*	44 (±8)	45 (±15)	0.87

Data are expressed as mean (standard deviation), median (range)$^{+}$, or n. Shown are subgroups according to the presence of chronic lung disease. CLD, chronic lung disease; ECMO, extracorporeal membrane oxygenation; MAS, meconium aspiration syndrome; OI, oxygenation index.*

persistent airflow obstruction. Hamutcu et al. (4) also found a high prevalence of respiratory symptoms, lung hyperinsuflation, and airway obstruction in 48 ECMO survivors at age of 11 years. However, they found a direct correlation between the amount and duration of elevated oxygen exposure and barotrauma with the frequency of long-term respiratory complaints, suggesting that ECMO and lung-rest ventilation strategies do not prevent the development of pulmonary morbidity in later childhood, but may reduce its severity. These findings could be in accordance with the lower incidence of CLD and no incidence of severe CLD found in our patients with a diagnosis different from CDH and lung hypoplasia. Further studies correlating the development of CLD and its severity and long-term pulmonary morbidity through childhood and age in patients with a diagnosis different from CDH following neonatal ECMO should be performed in order to verify this hypothesis.

In our study, nearly all CDH patients (94%) developed CLD after ECMO (22% mild, 30% moderate, and 42% severe). Nine patients with CDH (24%) needed respiratory support at discharge: five infants were discharged with a high-flow nasal cannula (HFNC), one with non-invasive ventilation (NIV) and three (8% CDH survivors) required long-term tracheostomy and invasive home mechanical ventilation. Our incidence of tracheostomy in CDH survivors is in line with those described in prior publications (17). In patients with CDH, the need for ECMO has been associated with the degree of long-term pulmonary morbidity with an increased likelihood of tracheostomy placement (22, 23). While prenatal risk stratification identifies severe cases, its correlation with long-term respiratory morbidity remains unknown (24) and postnatal identification of infants with irrecoverable lung hypoplasia that will develop severe CLD remains difficult (21). A few CDH patients without CLD made it impossible to identify statistically significant differences concerning perinatal characteristics when comparing CDH patients with and without CLD. However, the differences found when comparing patients with all diagnoses (early ECMO requirement despite lower oxygenation indexes and longer ECMO runs) might identify the most severe cases of CDH patients with a higher risk to develop CLD.

Respiratory long-term outcome in terms of lung function and exercise capacity in CDH patients is well described in the literature (3, 4, 12, 13, 15, 22, 25, 26). Although CLD is a risk factor for the development of pulmonary morbidity in later childhood, only few studies have described the incidence and severity of CLD following neonatal ECMO (14, 16), infants with CDH being unrepresented in those studies. Due to several factors such as lung hypoplasia and the need for prolonged ventilation and high oxygen supply in their neonatal period, infants with CDH are at risk of developing CLD (27). The development of CLD with a need for respiratory support on day 30 of life has shown to be a strong independent predictor of long-term morbidity (not only pulmonary but also developmental and in terms of future readmissions and surgical procedures) in patients with CDH (28), we believe that is very important to be aware of the very high incidence of CLD after ECMO in these patients in order to optimize their long-term care and the counseling of their families.

Limitations

Our study has several limitations: it is a retrospective, observational, single-center study. The high incidence of CLD and severe CLD in neonates with CDH made it impossible to identify statistically significant differences concerning perinatal characteristics when comparing CDH patients with and without CLD and we only found differences, when comparing patients with all diagnoses. However, since the underlying condition may be an important factor associated with pulmonary morbidity after neonatal ECMO, patients with different diagnoses should be analyzed separately. Because of the small number of patients, it was also impossible to identify perinatal factors associated with the need for respiratory support at discharge. A multicenter study with a greater number of patients should be performed in order to identify related perinatal characteristics for the development of CLD and the need for home mechanical ventilation, distinguished by the primary underlying condition.

CONCLUSION

The incidence of CLD after neonatal ECMO in this study was clinically relevant. CDH as an underlying condition, the necessity for early initiation of ECMO, and the need for ECMO over 7 days are factors associated with its development. Nearly all our patients with CDH requiring ECMO support developed CLD, one-third developed severe CLD, and 24% needed respiratory support at discharge. Since the development of CLD has shown to be a strong predictor of long-term morbidity in patients with CDH, these findings should be considered in order to optimize the long-term care of these patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in this 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 Local Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg. 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

AP, AG, FD, SH, and NR contributed to the concept and design, acquisition, interpretation of data, and drafting of the article. TD and TS contributed to the interpretation of data and revised the article for important intellectual content. All authors approved the final version of the article.

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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.

frontiers | Frontiers in Pediatrics

TYPE Review
PUBLISHED 16 September 2022
DOI 10.3389/fped.2022.863868

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Pediatric Critical Care,
a section of the journal
Frontiers in Pediatrics

RECEIVED 27 January 2022
ACCEPTED 22 August 2022
PUBLISHED 16 September 2022

CITATION
Pollak U, Feinstein Y, Mannarino CN,
McBride ME, Mendonca M, Keizman E,
Mishaly D, van Leeuwen G,
Roeleveld PP, Koers L and Klugman D
(2022) The horizon of pediatric cardiac
critical care. *Front. Pediatr.* 10:863868.
doi: 10.3389/fped.2022.863868

The horizon of pediatric cardiac critical care

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Pediatric Cardiac Critical Care (PCCC) is a challenging discipline where decisions require a high degree of preparation and clinical expertise. In the modern era, outcomes of neonates and children with congenital heart defects have dramatically improved, largely by transformative technologies and an expanding collection of pharmacotherapies. Exponential advances in science and technology are occurring at a breathtaking rate, and applying these advances to the PCCC patient is essential to further advancing the science and practice of the field. In this article, we identified and elaborate on seven key elements within the PCCC that will pave the way for the future.

KEYWORDS

training, personalized medicine, artificial intelligence, tissue engineering, safety and quality, pediatric cardiac critical care, minimally invasive cardiac surgery, mechanical circulatory support

Introduction

In 1671, Neils Stenson described the cardiac pathology of a stillborn fetus with multiple congenital anomalies including the cardiac lesion, which is now recognized as tetralogy of Fallot (1). The first palliative intervention for these patients was pioneered by Hellen Taussig and Alfred Blalock, in November 1944, with the assistance of Vivian Thomas, when the left subclavian artery was anastomosed to the pulmonary artery, with what now known as the Blalock-Thomas-Taussig shunt, in a severely cyanosed child with tetralogy of Fallot (2). A decade later, Sir Walter Lillehei performed the first complete repair for patients with tetralogy of Fallot using human cross-circulation technique (3).

During these procedures, children were hand-ventilated and endotracheal tubes were removed on the table at the end of the procedure (4). Following extubation, postoperative care proceeded in the hospital ward, where children were placed in a closed oxygen tent. No invasive monitoring or arterial blood gases were undertaken, and all medications such as morphine and penicillin, were administered by intramuscular injections (4).

The field of pediatric cardiac critical care (PCCC) has developed rapidly in the last 30 years. In the modern era, the partnership between congenital cardiac surgery and PCCC has resulted in dramatically improved outcomes, driven largely by transformative technologies and an expanding collection of novel pharmacotherapies. The exponential advances in science and technology are occurring at a breathtaking rate; applying these advances to the PCCC patient will be essential to advancing the science and practice of the field. In this article, we identified and elaborate on seven key elements within the PCCC that will pave the way to the coming decades (Figure 1).

Future perspectives of pediatric cardiac critical care

Education and training

In response to PCCC growing complexity, more hospitals are using dedicated pediatric cardiac units with highly trained multidisciplinary and inter-professional teams to oversee the management of children with heart disease (5, 6). This care model requires specialized training to provide high-quality care, keep up with evolving technologies, and to perform with optimal teamwork and communication in a complex environment (6–8).

In the circles of medical education, we recognize the need for standardized instruction and assessment so that learners are achieving and maintaining skills, knowledge and attitudes to ensure our highest standards of care. Competency-based medical education (CBME) has become the primary strategy in the United States (US) and other countries to provide a standardized education and assessment of trainees with the use of milestones and entrustable professional activities (EPAs) (9). Milestones, developed and implemented by the Accreditation Council for Graduate Medical Education (ACGME; organization that defines standards for US residency and fellowship programs), is a competency-based assessment tool used to help standardize the trainee experience (10). Milestones of trainees are assessed bi-annually in the domains of medical knowledge, patient care, professionalism, and system-based practice (11). EPAs are defined as measurable activities delineated by each discipline to observe that a trainee can perform a given task independently (12). Learners can then be assessed for each task, and with the provision of effective feedback, the learner builds graduated responsibility and competency in specific educational domains (9, 12).

Learning objectives offer further specificity, and these are noted for PCCC in the physician curriculum published by the Pediatric Cardiac Intensive Care Society (PCICS), as well as a recent publication by Tabbutt et al. (13, 14). Standardization and structured educational opportunities for nurses and advanced practice providers are also expanding; PCICS also recently published an advanced practice provider and a nursing curriculum to further the effort to standardize knowledge and skills for those disciplines (15–17).

Simulation-based training is a frequently used educational modality for trainees and staff in all levels and in different disciplines (18). There is growing evidence that simulation-based education strategies, including mastery learning curriculum can improve patient care practices as well as improved outcomes (19–21). Using principles of adult learning theory with methodology in simulation, the Simzones framework, was developed as a graduated learning system to develop simulation-based activities for adult learners, although the integration of mutli-modal simulation technologies has not been well explored (22–25). In the US, simulation curricula have been developed for first year pediatric critical care fellows and cardiology fellows respectively (26–28). PCCC simulation has focused on building understanding of physiology as well as multidisciplinary teamwork and systems of care through bootcamps and other simulation sessions (23). Multi-center creation of simulation scenarios may further help standardize learner training from different disciplines and institutions (13, 14).

Virtual reality (VR) has increasingly been utilized as an adjunctive educational tool in medical education training, particularly in non-technical skill building including communication and team building situations (29). VR-based training may provide improved accessibility by using a computer or virtual platform, allowing trainees to learn asynchronously and independently (30, 31). The use of VR simulations for junctional ectopic tachycardia and low cardiac output syndrome have been used for physician trainees, noting that participants had positive feedback using this interface (32). The Stanford Virtual Heart project has been developed as another resource for learners to interact with various congenital heart malformations, focus on their spatial relationships with other heart structures (31). Further research is needed to describe the effectiveness of learning with this new technology, including in PCCC (32).

Three-dimensional (3-D) printing models are another educational modality for multidisciplinary learners' use (33–35). Hussein et al. developed a 3-D printed heart model for surgical trainee practice for the arterial switch operation and demonstrated an improvement of time and trainee technical performance when using 3-D printed model before using a hands-on training congenital heart surgery tool (36). 3-D

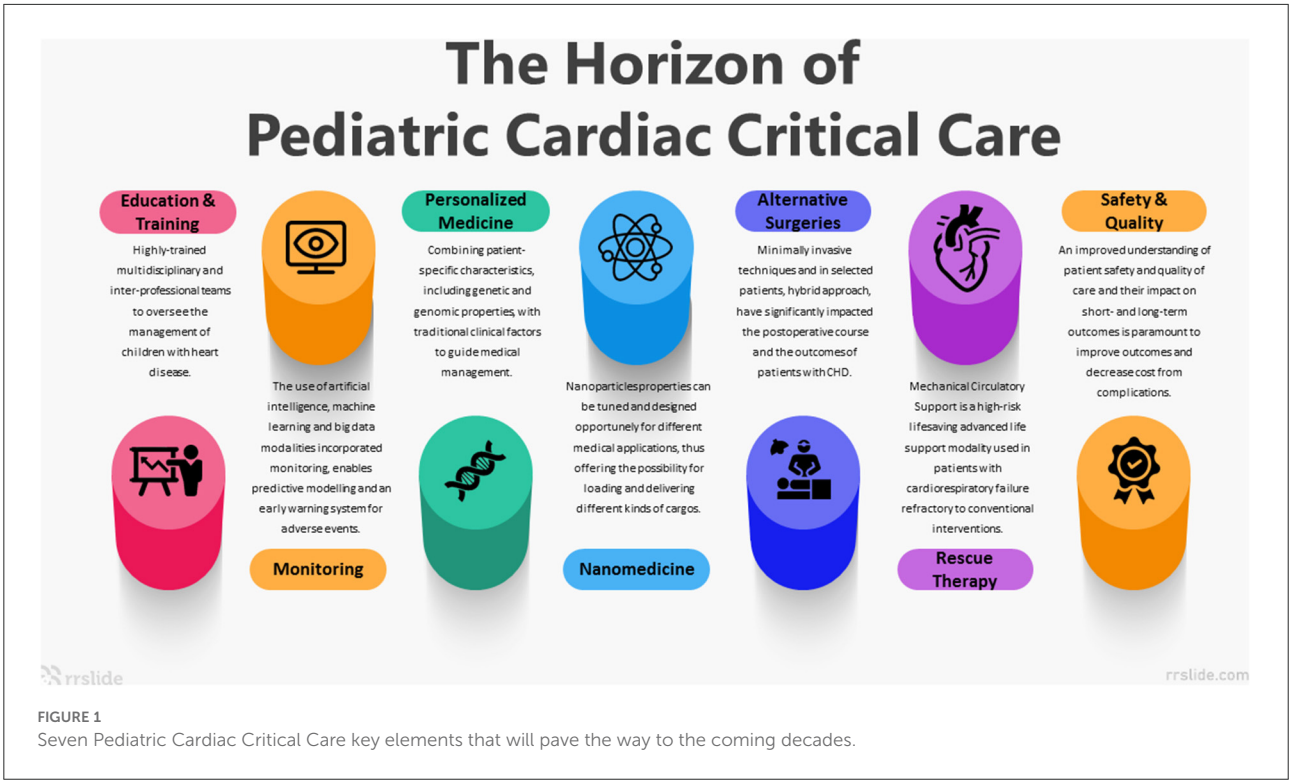

FIGURE 1
Seven Pediatric Cardiac Critical Care key elements that will pave the way to the coming decades.

printing requires special software and technology and is currently only available at specific institutions. Further research is needed to demonstrate improved educational effects and subsequent performance on patient outcomes.

Patient monitoring

Daily work in the PCCC unit involves multitasking, often with disparate teams and unpredictable high-risk events. These factors combine to produce an environment in which health providers must rely on knowledge and protocols/warning systems to guide the prioritization and performance of tasks (37). Due to the significant presence of and reliance on technology in such modern healthcare environments, the interaction between healthcare providers and these technologies may have a profound impact on the quality of care (37). In order to improve outcomes, significant effort has been dedicated to designing tools to help ICU providers manage the increasing influx of data, and facilitate the early identification of patient deterioration and risks.

Development of such algorithms has continued, and they now cover multiple data streams and are designed as risk assessment tools. An example of newer generation algorithms is the Rothman Index (RI), developed for adults, which is an illness-severity index embedded within the electronic medical record. Twenty-six variables are continuously tracked, and data is fed into a proprietary algorithm; the calculated score is designed to reflect patient illness severity (37).

Another pediatric prediction tool assesses imbalances between oxygen delivery and oxygen consumption, associated with organ dysfunction along with morbidity and mortality. The Inadequate Oxygen Delivery (IDO_2) Index (Etiometry, Boston MA) synthesizes patient physiologic and laboratory measures to continuously predict the risk of having a mixed venous oxygen saturation $< 40\%$, wherein an elevated IDO2 value indicates elevated risk in children following CPB surgery (38). This web-based tool captures and displays integrated data exported from continuous bedside physiologic data.

Lin et al. investigated the usability of data integration and visualization of T3 in the light of human factors and discovered several limitations to the easy implementation of the software (39). The observations from usability testing warn that without consistent exposure and integration into clinical practice, data interpretation aids may be ignored, and, thus, excluded from critical decision-making where they would be most useful. Furthermore, a study comparing low cardiac output score and IDO_2 for predicting adverse events in 72 h following congenital heart surgery showed that using the IDO_2 values had no association with occurrences of adverse events (40). A group from Boston Children's found that IDO_2 monitoring could identify critically ill children with sepsis at highest risk of adverse events or undesirable outcomes (41), and Dewan et al validated the IDO_2 index (IDO_2) to predict in-hospital

cardiac arrest in a general pediatric ICU (42). Additional specific congenital heart disease machine-learning (ML) approaches to identify risk factors for complications in the early postoperative phase (43), long-term complications (44), prediction of brain injuries in ECMO patients (45) are published as well. These ML algorithms were used to predict clinical deterioration, to classify surgical risk, or to classify the heart disease using patient characteristics. Early prediction of critical events in infants using a naïve Bayesian model was introduced by Ruiz et al. Thirty-four routinely collected data points, such as heart rate, CO2, and lactate, were integrated into the algorithm. The model was able to predict events up to 1 h prior to their occurrence with high sensitivity and specificity (46). Single ventricle lesions remain high risk for adverse events. A novel ECG algorithm utilizing ST segment instability for detection of cardiopulmonary arrest in single ventricle physiology was described by Vu et al (47).

Results of recent studies on AI algorithms in patients with CHD are encouraging. Nevertheless, patient monitoring algorithms remain in an early phase, and ongoing development is likely in the following realms: (I) scope of input (II). algorithm parameters, (III) human-machine interfaces, and (IV) training (how to use such indicators as decision support tools) (48). While perhaps promising, the costs of implementation are very high and the prospect of being universally available is not likely in the near future. These applications should only supplement standard monitoring but not substitute for current standards of ICU monitoring.

Genomic medicine

Personalized medicine refers to combining patient-specific genetic and genomic properties with traditional clinical factors to guide medical management. The use of the patient-specific data facilitates personalized management, tailored to address individual risk factors, severity of illness and assess response to treatment (49).

PCCC medicine will likely benefit significantly from increased integration and application of genomic medicine. The widely used molecular studies diagnose only about 20% of suspected genetic diseases, and in the Congenital Heart Disease Genetic Network Study designed by the Pediatric Cardiac Genomics Consortium, only 11% of cases had a genetic diagnosis (50). Technologies such as rapid whole genome sequencing (rWGS) of patients admitted in the PCCC units increase the rate of diagnosis and may reduce the cost of care (51). Genomics research also focuses on understanding and treating acquired diseases such as distinguishing viral and bacterial infections in cases of fever (52–54) and may support the decision to perform a semi-elective procedure in a febrile child. Additionally, genomics may also assist in assessing the severity of disease and likelihood of morbidity and mortality in various pathologies, particularly in patients with multiple genetic anomalies and comorbidities. For instance, fatal acute myocarditis has been previously shown to correlate with putatively damaging variants in genes related to cardiomyocyte structure and function (55).

The potential of multi-omics technologies to elucidate the complex interactions between genes, proteins, and biochemical reactions can hopefully fill gaps in our current PCCC knowledge. It can also provide accurate and rapid data to direct management considering the advances in technology and statistical processing power achieved during the last decade.

To date, genomic research provides a better understanding of why some patients develop critical care syndromes such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), or severe sepsis, whereas others do not (56, 57). These findings can be applied to the PCCC practices in several aspects. AKI is a common complication of post CPB patients and prediction models of high-risk patients using genomics will potentially modulate their postoperative course. Studies using genome-wide RNA transcriptome analyses of blood enable us to identify groups of children at high risk of mortality and differentiate those likely to benefit from early corticosteroid treatment (58–61). Weathington et al. focused on cell gene expression in severe asthma, revealing mechanisms of severe disease as well as the influences of medications and the identification of severity-related genes which may provide new diagnostic and therapeutic targets (62). Werner et al. reported a detectable signal in gene expression profiles for early detection of ventilator-associated pneumonia in ventilated children (63), a method that may influence the duration of mechanical ventilation in the post cardiac surgery pediatric patient.

Pharmacogenomic research investigates the patient's genetic information that influences their response to therapeutic drugs. One example is the use of pharmacogenomics to adjust sedation and analgesia in pediatric ARDS. Zuppa et al. revealed several factors affecting the pharmacokinetics of midazolam in children, using the Illumina HumanOmniExpress genome-wide single nucleotide polymorphism chip. These findings provide the basis for future implementation of a personalized approach to sedation (64, 65).

Cardiac critical care in general and specifically in the pediatric population provides broad operational leeway for genomics, where a genetic basis was found for an increasing number of congenital defects and pathologies once considered idiopathic (e.g., pulmonary arterial hypertension, Hypoplastic Left Heart Syndrome, and dilated cardiomyopathy) (66–70). Multigene next-generation sequencing panels that focus on cardiomyopathy- or arrhythmia-disease genes are available, and Ritter et al. reported that the results influenced the medical decision-making in 53% of all cases and up to 80% of cases with a positive result, especially when testing was expedited (71).

Most patients in PCCC units are admitted after cardiothoracic surgeries for congenital and acquired heart defects. Reed et al. reported a proteomic analysis of infants who underwent open heart surgery. Some patients experience a systemic response to CPB with significant derangements

in hemostasis and systemic inflammation that cause excess morbidity and mortality. This multifactorial response involves acute phase response, coagulation, and cell signaling pathways that are not fully understood yet. Reed et al. identified several biomarkers that improve our understanding of the phenomenon (72). Future implications include early identification and treatment of susceptible infants, likely leading to improved outcomes. However, more research is needed to enable these findings to become feasible tools for intensivists.

Despite the advances made in the field of orthotopic heart transplantation (OHT), there are still gaps in the understanding of the alloimmune response, the role of immunomodulation, development of tolerance, and xenotransplantation. Ongoing research is focused on improving outcomes post OHT using immunomodulation for children with pre-formed anti-HLA antibodies (PRA). Previous studies reported these children to have increased risk for rejection, coronary artery vasculopathy and mortality (73–75). Nowadays, with the increased incidence of Ventricular Assist Device (VAD) therapy which is associated with the development of PRA, improving immunomodulation is crucial as immunomodulation therapies showed better outcomes for PRA-positive children after OHT (76). Genomic research achieved advances in understanding the role of regulatory T cells, costimulatory signals and exosomes, all of which have clinical implications and may be leading targets to promote cardiac allograft tolerance and enable cardiac xenograft survival (77).

While genomic research is surging, ethical and translation challenges arise as well. There is a need to create a suitable model for incorporating genomic data in critical care management. Challenges include knowledge gaps among intensivists on how to interpret genetic results, concerns regarding the potential effect of genetic information on child-parent bonding, and the implications of such information on medical and family decisions (78, 79). Dimmock et al. reported that clinicians perceived rapid genomic sequencing (RGS) to be helpful in 77% of cases and that RGS changed clinical management in 28% cases. Clinicians also reported a low likelihood of harm of RGS of infants in ICUs with diseases of unknown etiology (80). This perception is supported by parents' responses in a study by Cakici et al., describing that most parents reported they had been adequately informed to consent, understood the genetic results, and denied having regrets or experiencing harm from the sequencing (81).

Regeneration, nanotechnology and tissue engineering

Regeneration of cardiomyocytes

Myocardial damage has been traditionally managed with medication or assist devices, depending on the etiology, extent and presentation of the dysfunction. With an estimated turnover rate of <1% per year, with most renewal events reported to occur in the first decade of life, revealing the heart's capacity for regeneration, and how to regulate it, are fundamentals to cardiovascular research (82).

Cardiomyocyte (CM) necrosis, as seen after myocardial infarction (MI) triggers a marked inflammatory response orchestrated mainly by cardiac fibroblasts, and the idea of converting a portion of these cells *in situ* to contractile cells is a transformative concept. Combinations of specific epigenetic modulators or pharmacological inhibition of signaling pathways can improve the conversion of fibroblasts to induced cardiomyocyte-like cells (iCMs). In the initial studies, using viral vectors loaded with cardiogenic transcription factors injected directly into the necrotic area, a modest proportion of CMs in the necrosis border zone was traced as progeny of infected fibroblasts, concomitant with reduced scar area and improved myocardial function (83). Although the robustness of the *in vivo* reprogramming process and the use of viral vectors are under debate, this technique provides a novel, cell-free platform for cardiac repair.

Another important element in the regeneration of CMs is the extracellular matrix (ECM). Extracellular biomechanical properties, such as matrix rigidity, that affect cytoskeletal integrity and sarcomere organization in CMs might act within signaling pathways to influence proliferation (e.g., the Hippo signaling cascade with its transcriptional coactivators YAP and TAZ) (84, 85). The link between Hippo signaling and the sarcomere was further elucidated by Bassat et al. (86) and Morikawa et al. (87) reporting that the dystrophin glycoprotein complex (DGC) inhibits YAP nuclear localization by sensing mechanical and biochemical inputs from the ECM. Agrin, a matrix glycoprotein, promotes CMs cell division *in vitro via* the DGC-YAP axis and is required for an effective regenerative response in the myocardium of neonatal mice. Administration of agrin facilitates cardiac regeneration in adult mice after MI. CMs division might also be modulated by emergence at birth from somewhat hypoxic environment *in utero* to atmospheric oxygen. Recent studies have reported proliferative effects of experimental hypoxia on CMs *in vivo*, making regulated hypoxia worthy of further exploration in the context of the regenerative response (88). The potential benefits of regeneration of damaged cardiac tissue after the direct effect of open heart surgery and the indirect effect of CPB, although still premature and futuristic, are promising and may alter the post-operative course in the PCCC unit.

Nanotechnology

Nanomedicine is the application of nanotechnology to medicine for diagnosis and therapy (89). Introducing nanoparticles (NPs) directing modulators of developmental pathways in CMs significantly advanced the concept of cell-level *in-vivo* cardiotherapy. Currently, nanoparticles properties

can be tuned and designed for different medical applications, thereby offering the possibility for loading and delivering a multitude of therapies. Special attention is being paid to NP-based system for cardiotherapy and their therapeutic cargos such as microRNAs, cardioprotective drugs or growth factors. The Hippo pathway is a promising target for nanoparticle based therapies (90), as it has emerged as a possible switch in CMs proliferation (91), being tightly connected to the onset and progression of cardiomyopathies (92).

In this context, Nguyen et al. (93) used matrix metalloproteinase (MMP)-responsive hydrogels with the ability to be retained at the necrotic area thus being potentially suitable for the sustained delivery of therapeutic molecules. Another recently reported strategy called *THEREPI* relies on the use of a biocompatible patch, which is placed on the epicardium at the border zone of the necrotic myocardial tissue to achieve the sustained delivery of drugs, macromolecules and possibly cells for cardiac therapy (94). Ideally, *THEREPI* can be efficiently used for the *in situ* administration of therapeutic nanoparticles, thereby increasing their retention at the diseased site and improving cargo delivery.

The potential of gene editing in the restoration of contractility along with the discovery that the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) system could be used to introduce sequence-specific DNA cleavage in human cells has revolutionized research (95). Nanomedicine-related sciences and different systems have been engineered for carrying the CRISPR/Cas9 apparatus and guide the genetic reprogramming inside the cells, based on lipid and inorganic nanoparticles (96, 97). While the exploitation of this technique in nanomedicine in the context of myocardial regeneration can be attractive in the case of genetically-determined cardiac pathologies, technical challenges connected to its specificity are still under investigation (98). A promising strategy to overcome these challenges involves utilizing organ-on-a-chip technologies, capitalizing on microfluidic advances which are combined with complex three-dimensional (3D) cell biology that provides organ-like physiology and pathophysiological cellular and tissue level responses (99, 100).

Tissue engineering

Current surgical procedures used in CHD are limited by the use of prosthetic materials used to replace heart valves, vascular grafts, and synthetic patches. Use of these materials is susceptible to complications such as infection, host immune response, and thrombotic complications. The lack of growth and remodeling potential is also a prominent limitation in children. The field of tissue engineering holds promise for surgical solutions for these patients (101). Tissue engineering, first described as a field by Langer and Vacanti in 1993, promotes using the body's natural growth and regeneration processes to repair and replace damaged and nonfunctioning organs with healthy, native tissue (102). Many approaches exist within tissue engineering, including the use of biodegradable polymeric scaffolds, decellularized extracellular matrix, stem cells, and harvested patient cells (103). The field of congenital cardiovascular tissue engineering that has advanced furthest to date is the tissue engineered vascular grafts such as cavo-pulmonary conduits during the final stage of the Fontan procedure, which express healing, remodeling and growth characteristics of native tissue (101).

Tissue engineered heart valves (TEHVs) remain another challenging field. *In vivo* and preclinical studies have been promising, but clinical translation requires improved performance of current prosthetic options (104). TEHVs have had a difficult history in the clinic, being used in patients after only limited animal models, and being limited by several complications in early studies. These difficulties led to a return to laboratory research to improve the designs, and mechanistic studies of tissue formation in TEHVs are required for further advancement (105).

Many congenital cardiac anomalies can be discovered and diagnosed *in utero* during routine physician appointments (106). If dysfunctional valve associated CHDs could be repaired *in utero* (e.g., balloon valvuloplasty in the fetus to open stenotic valves) there is the potential to provide curative treatment for CHD before birth, preventing the need for any surgeries (107). Combination of this idea of fetal intervention, tissue engineering and scar-free wound healing properties, holds potential to develop novel curative procedures for CHDs (108).

Finally, a group from Tel Aviv University reported on the development and application of advanced 3D printing techniques using the personalized hydrogel as a bioink. Combined with the patient own cells, the hydrogel may be used to print thick, vascularized, and perfusable cardiac patches that fully match the immunological, biochemical and anatomical properties of the patient. The personalized hydrogel was used to print volumetric, freestanding, cellular structures, including whole hearts with their major blood vessels (109).

As we look toward the horizon, novel technologies developed through nano-medicine and tissue engineering, can be expected to change the patient care in the PCCC. It will be important for pediatric cardiologists, cardiac intensivists and cardiac surgeons to accelerate this research and ensure that the new technologies are applied toward the treatment of the critically ill pediatric cardiac patient.

Alternatives to the traditional cardiac surgery

Minimally invasive cardiac surgery

During the last decades there has been tremendous advancement in minimally invasive techniques for most of the surgical fields, including congenital heart defects (CHD). While

only extracardiac defects, such as PDA, were correctable during the first years of minimally invasive approach, advancements in the field now allow some complex intracardiac defects to also be repaired or palliated with a minimally invasive approach (110).

The use of these techniques significantly impacts the postoperative course and the outcomes of patients with CHD. First, it allows earlier mobility and resumption of physical activity secondary to reduced pain and respiratory dysfunction and thereby shortens the length of hospital stay. Furthermore, it reduces the long-term morbidity related to sternotomy, such as chest wall asymmetry, rib fusion, scoliosis, shoulder girdle abnormalities, chronic pain syndrome and more. Lastly, it is associated with a number of cosmetics benefits (110, 111). Complete care of children with CHD does not concise of merely repairing or palliating their heart defect, but rather ensuring their psychosocial future wellbeing. A better cosmetic result has been associated with an improved self-body image and quality of psychosocial wellbeing.

Various approaches exist for minimally invasive pediatric cardiac surgery. The choice depends on the anomaly type and surgical preferences. Extracardiac malformations such as PDA, vascular ring, aortic coarctation, collateral vascular system closure and ligation and more, can be performed *via* left lateral thoracotomy, but also using video-assisted thoracoscopic (VATS) procedure (112). In recent years, more complex intracardiac malformations have also been addressed by minimally invasive approaches. Septal defects, atrioventricular canal defect, valvular lesions (such as mitral cleft), anomalous pulmonic venous drainage, and even tetralogy of Fallot can be performed by limited right anterior thoracotomy, or lower partial sternotomy (110). These procedures, however, require modification of the cardiopulmonary bypass (CPB) management, including cannulation strategy and myocardial protection. Cannulation can be achieved peripherally *via* femoral and jugular cannulation, however, peripheral cannulation can be complicated and not feasible for children under 8 kg. The procedures can be performed either on a fibrillating heart or by cardioplegia infusion, depending on the type of the defect and the repair (113).

Future perspectives of minimally invasive techniques rely on endoscopic tools and robotic surgery. Nonetheless, contemporary existing instruments in the field are yet too big for neonatal thorax. The application of novel technology in the field will undoubtfully have a significant impact on the management of patient with congenital anomalies, and will affect the early and long term outcome of the repair (114).

Hybrid procedures in pediatric cardiac surgery

Tight collaboration between cardiac surgeons, interventional cardiologists and pediatric cardiac intensivists, has always been the hallmark of a well-functioning congenital cardiac center. Historically, however, this collaboration in the management of CHD has occurred in sequence. Hybrid approach for some of the congenital malformations consists of a combined interdisciplinary intervention in a single procedure (115). The goal of a hybrid procedure is to reduce the number of interventions and/or their invasiveness, decreasing by that the magnitude of cardiac interventions. Hybrid procedures are usually performed on a beating heart off CPB, which allows a real-time intraoperative feedback of a given procedure by angiography or by transesophageal echocardiogram (TEE).

Hybrid procedures are utilized under various circumstances. The classical indication for hybrid approach is for high risk, or low weight neonates with HLHS. Recent studies have demonstrated that these patients may benefit from a shorter and less invasive procedure, which consists of bilateral pulmonary artery banding and PDA stenting (116). The primary advantage of such procedures is in delaying major surgery with CPB in small neonates while improving hemodynamics to optimize growth and development despite possible risks of stent migration and the need for pulmonary artery reconstruction. Nonetheless, in spite of improvement in Norwood outcomes in the recent years, the hybrid approach is most commonly the procedure of choice in high risk or low birth weight neonates (<2 kg).

Muscular VSD is another indication for a hybrid approach. When surgery alone or catheter-based alone are unable to reach satisfactory results of a given defect, a hybrid approach may provide the solution. Muscular VSDs that are unreachable by surgery may be closed by a proper device on a non-heparinized heart *via* direct ventricular puncture using TEE guidance (117).

In summary, hybrid approach may be an excellent choice in selected patients. Advancements in this field are still required to provide better technical tool in order to reach improved outcomes, which will surely impact the complex management of these small patients.

Mechanical circulatory support

Extracorporeal Life Support (ECLS) or Extracorporeal Membrane Oxygenation (ECMO) is a high-risk lifesaving advanced life support modality used in carefully selected patients with cardiorespiratory failure refractory to conventional therapeutic interventions. Despite ongoing evolution during the past 40 years, patient selection, minimizing ECMO/ECLS duration and complications, circuit pharmacology, and optimal anticoagulation remain some of the important challenges that ECMO/ECLS clinicians are aiming to overcome.

For cardiogenic shock, veno-arterial (V-A) ECMO can be utilized. Support is aimed at providing adequate systemic oxygen delivery, offloading the heart, and identifying/treating the underlying reason for cardiogenic shock as soon as possible. Future research should focus on optimizing patient selection

and timing, single-ventricle support, outcome predictors, and the identification and treatment of residual lesions (118).

Extracorporeal cardiopulmonary resuscitation (ECPR) is the rapid deployment of V-A ECMO to provide cardiovascular support and gas exchange in the context of cardiopulmonary arrest, and can be considered for children with heart disease who experience a witnessed in-hospital cardiac arrest (119, 120). There is insufficient data to recommend ECPR for out-of-hospital cardiopulmonary arrest events in children. To further improve outcomes in ECPR, patient selection, team organization, high-quality CPR, measure and benchmark patient and process metrics, and simulation for individuals and team practice are key elements (119).

Utilization of ECMO for pediatric septic shock has not become a mainstay of sepsis protocols in most centers, but the surviving sepsis campaign guidelines do recommend to consider V-A ECMO as a rescue therapy in children with septic shock only if refractory to all other treatments (121), but there is still the need for more consistency in the indication criteria (122).

As the duration of ECMO/ECLS support and the occurrence of complications are important negative determinants of outcome, current and future endeavors at minimizing these factors are paramount. Systemic anticoagulation can be notoriously difficult, especially in infants, and the most common complications in all types of ECMO/ECLS support remain bleeding and/or thrombosis-related (123). In an attempt to minimize these often devastating complications, new ways of anticoagulating the circuit without anticoagulating the patient are being developed (124, 125). Surface modifications, aimed at overcoming the blood-biomaterial surface interactions, are currently being developed that mimic endothelium and anti-thrombotic agents (126). Three major groups of surface modifications are already in use or on the horizon. First, biomimetic surfaces such as heparin coating already exist, but do not obviate the need for systemic anticoagulation. Nitric-oxide donors from within the ECMO tubing, targeting platelet and fibrin adhesion as well as having antibacterial properties seem hopeful but are not yet commercially available. Secondly, biopassive surfaces such as phosphoryl or poly-2-methoxyethylacrylate coating have been shown to have a favorable effect on platelets by mimicking a biomembrane due to hydrophilic properties (127). The third surface modification aims to mimic endothelial function or to induce endothelialization of the actual surface itself. In the future a combination of biomimetic and bio-passive properties with a living cellular interface will likely become available (126). Until then, the most common systemic anticoagulant, heparin, remains the mainstay; however, the use of bivalirudin, a direct thrombin inhibitor, is becoming more prevalent (125, 128).

Pediatric ECMO/ECLS would benefit from smaller, safer, and smarter equipment, which would ideally act on feedback directly from patient parameters (e.g., temperature, blood pressure waveforms, continuous blood gas monitoring, etc.) to avoid hyperoxia, sudden drops in pCO2 and provide the ideal amount of flow. As far as we aware these interactive biofeedback ECMO systems are not under development (yet), but could surely play a role in the future. Other exciting innovations on the, more near, horizon are the use of pumpless ECMO and the development of an implantable artificial pediatric lung as a bridge to transplantation or lung remodeling for children with end-stage lung failure with promising results in animal models (129–131). Furthermore, development of an artificial placenta for premature infants also seems promising, but is not within the scope of this review (132). ECMO/ECLS is highly technical, requires expertise from many different specialties, and deserves rigorous initial and ongoing training (including simulation). The ECMOed taskforce from the Extracorporeal Life Support Organization (ELSO) has outlined an educational agenda with recommendations promoting an international collaborative approach toward standardization of ECMO education. High-quality research will be necessary to support educational practices (133).

Children who survive ECMO can suffer from a wide range of physical and neurodevelopmental disabilities, which they can even develop long after their stay in PCCC (134). Current data to support neuromonitoring on ECMO is limited. Therefore, future studies are needed to be able to develop evidence-based guidelines for neuromonitoring and neuroprotection for children supported with ECMO/ECLS (135). Moreover, very importantly, in the future, all ECMO/ECLS centers should have a structured long-term follow-up program to identify these disabilities early as recommended by ELSO (134).

Ventricular assist devices (VADs) are mechanical pumps that take over the function of the failing ventricle and restore adequate blood flow. Over the last few decades, significant effort has been dedicated to developing ventricular assist devices for smaller children with increasingly complex anatomy.

Short-term VADs are used in the acute treatment of cardiogenic shock or ventricular dysfunction after cardiac surgery with the expectation of patient recovery. These devices are deployed for hours to days as a "bridge to recovery" or "bridge to decision". CentriMag (Thoratec Corporation, USA), and its pediatric version PediMag, are extracorporeal centrifugal pumps for short-term use as support for LV, RV or biventricular in children and adults. They have magnetically suspended rotors to minimize wear and the risk of hemolysis and thrombosis. Percutaneous devices such as Impella have been used successfully in bigger pediatric patients (more than 0.9 m^2 of BSA), including patients with single ventricle physiology (136).

The Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany) is a pulsatile paracorporeal long-term device that can support patients in a wide range of sizes, from infants to teenagers as a bridge to cardiac transplantation in children with severe left or biventricular dysfunction. Even though not prospectively studied in children, intracorporeal adult VADs

as Thoratec Heartmate II e III (Abbott corp, St. Paul, MN, USA), and Syncardia TAH (SynCardia Systems, Inc., Tucson, AZ, USA) can be used in older children and teenagers, with future perspectives for its usage as destination therapy.

VAD support for single ventricle physiology, especially after stage 1 and 2, is currently a challenge. However, it is possible to provide long term mechanical circulatory support for the Fontan population with end-stage heart failure to support the systemic circulation as a bridge to heart transplant (137). Moreover, the usage for long-term support for the pulmonary circulation in patients with univentricular physiology after Fontan procedure seems promising. Cysyk et al. reported a sheep study where a miniaturized device was successfully tested *in vivo* as a right heart replacement device demonstrating adequate circulatory support and normal physiologic pulmonary and venous pressures (138). Additional research is needed to continue to advance this promising approach.

Safety and quality

PCCC has become incredibly complex due to patient heterogeneity and advances in medical and surgical strategies that have enabled treatment options for patients with increasingly complex conditions. An improved understanding of patient safety and quality of care and their impact on short and long-term outcomes is paramount to improve outcomes and decrease cost from complications (139, 140). As it is a fast-paced, technical environment with many distractions, complications and adverse events are frequently observed in the PCCC unit (141). High-risk procedures are being performed in complex patients with challenging physiology and anatomy with diverse teams. This requires high levels of technical and cognitive performance from staff. Hand offs, medication dispensing and administration, and diagnostic errors are a particular source of potential patient harm (142). Reducing risk of adverse events requires a safety culture which learns from previous incidents and proactively assesses risk of future events.

Errors, latent threats, culture and learning to improve safety

Both active errors and latent conditions impact patient safety in the PCCC unit. Active errors, those with an immediate detrimental effect, can either happen unconsciously or are deliberate violations of existing rules. Reducing these types of errors should be done at system level—analyzing and improving systems and processes to make it easier to accomplish high risk tasks in complex systems. For example, rules to limit distractions for medication preparation and mandatory double checks will reduce medication error. Latent conditions are factors that increase the likelihood of adverse incidents. Latent conditions known to the PCCC unit (143) include lack of crowd control during emergencies, lack of role clarity during surgical procedures, different structures to handover patients, inadequate equipment, shortage of staff, absence of senior staff, structural staff fatigue due to disproportionate workload, compassion fatigue and burn-out. Occupational stress is common in pediatric critical care and burn-out prevalence has been reported in ranges of 42–77% (144). Interventions to augment staff resilience such as education in self-care and peer support are indispensable for improvement of staff wellbeing, the perception of greater teamwork and ultimately patient safety and quality of care.

Organizational culture and team dynamics also play a major role in patient safety. Hierarchy remains a threat to patient safety (a nurse might find it difficult to address unsafe behavior of a doctor). Negative behaviors of healthcare staff are furthermore associated with decreased productivity, employee satisfaction, engagement and retention, increased absenteeism, poor teamwork and worse patient outcomes (145). Rude behavior within neonatal intensive care teams has been shown to negatively affect the ability of a team to diagnose and treat critically ill neonates (146).

There have been many reports of improvement of patient safety after systematic evaluation of safety threats (147). However, relying solely on incident reporting systems is insufficient to improve patient safety as a substantial number of incidents are not reported. Barriers to incident reporting including fear of retribution, inadequate reporting systems, lack perceived importance of reporting, lack of knowledge regarding safety event definitions, and lack of multidisciplinary collaboration in this process (148). Morbidity and mortality conferences and discussion of cases with excellent performance also positively impact outcome (149). The latter is associated with a more positive effect on healthcare staff than only learning from mistakes and near-misses and this may change the perception of reporting systems and increase overall reporting.

Information technology to enhance patient safety

There is an increased interest in the use of information technology and artificial intelligence to improve performance and overcome human error. Information technology has the potential to improve communication (i.e., handover summary), increase medication safety (i.e., notice of important medication interactions) and increase monitoring safety (i.e., alerting abnormal vital signs). Artificial intelligence is capable of analyzing and integrating the large volumes of continuous physiological data from patients in PCCC unit, predicting adverse events and ideally provide decision support as has been outlined in detail in the monitoring section.

Quality improvement in the PCCC unit by standardization of care and quality improvement programmes

Standardization is a way of dealing with human error by limiting options in the execution of care. Care can be standardized using guidelines, bundles, protocols and checklists. These tools improve adherence to best practice and contribute to patient outcomes. Bundles, protocols and pathways facilitate the development of shared expectations and understanding of standards of care for certain diagnoses and patients locally. The shared expectations set the framework for multi-disciplinary care delivery and teamwork. Examples are bundles and checklists to reduce adverse events during tracheal intubation, unplanned extubation, central line infections, cardiac arrest and the use of a handover checklist (150–152). Cognitive aid bundles for critical events improve adherence to best practice in simulation trials of these emergencies and their use is recommended (153).

An important issue for quality improvement in the care of children with congenital heart disease is the size of the case load of single centers. Failure to rescue (FTR)—the ability to prevent mortality following complications—is a potential challenge associated with a lower case volume and may represent some of the foundation to support centralization of care (154). But even single centers with higher case volumes may struggle to aggregate sufficient outcome data derive meaningful analyses in the short term (140). International societies and collaboratives such as the Extracorporeal Life Support Organization (ELSO), European Association for Cardio-Thoracic Surgery (EACTS), the Association for European Pediatric and Congenital Cardiology (AEPC) and the Cardiac Neurodevelopmental Outcome Collaborative have therefore developed guidelines to standardize care for children in the PCCC unit. The recent growth of quality improvement collaboratives and registries, facilitated by the evolution of videoconferencing is transforming quality and outcomes. These registries/collaboratives have been established with a focus on data sharing, commitment to high quality data and inclusion of multidisciplinary teams. Collaboratives such as the Pediatric Acute Care Cardiology Collaborative (PAC-3) (155), that achieved a reduction in length of postoperative hospital stay, the Pediatric Cardiac Critical Care Consortium (PC4), that achieved a 24, 22, and 12% relative reduction in in-hospital mortality, postoperative mortality and major complications, respectively (141). The National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) successfully halved both mortality and growth failure in children with hypoplastic left heart syndrome between stage 1 and 2 palliation and demonstrate that there is a roadmap for multi-center collaborative quality improvement that results in sustained improvement in outcomes (156). Inclusion of developing countries in international collaboratives have also been successful (157) and increased international involvement must be a priority.

Congenital heart surgery outcome metrics have largely been defined in two domains, short and long-term mortality and short and long-term morbidity (158). As mortality rates have decreased over time, there is an increasing recognition of the importance of long-term neurodevelopmental and quality of life outcomes. Concurrently, there is growing recognition that survival in patients with complex, advanced illness may come at the cost of severe disability, negative quality of life of both patient and their family and increased healthcare costs (159). Benchmarking neurodevelopmental (intellectual, motor, developmental) and social outcomes for patients with CHD with the general population is an important tool to measure quality of care (160–162). There is a generally accepted multi-disciplinary set of long-term PICU outcome measures (163) and development of a similar set for patients in the PCCC unit should be considered.

The next steps to reduce mortality and make significant impact on long-term neurodevelopmental outcomes will require innovation and a keen focus on quality and safety. Learning from incidents, near-misses and excellence provides insight in ways to improve safety and care. Successful PCCC unit management highly depends on optimal multidisciplinary teamwork. Negative behaviors and other teamwork undermining factors should not be tolerated. Modern technology allows evaluation of practice through data sharing and machine learning algorithms and data integration remains an important next step in the advancement of our ability to utilize available data. Finally, long term outcome analysis should include considerations of means by which we can improve sustainability and cost of care delivery.

Discussion

The future of PCCC appears bright with the array of emerging technologies. Investment in the human capital with advanced training and education, exploit artificial intelligence modalities into patient monitoring and early warning systems, personalized medicine with regenerative goals, improved surgical capabilities including minimally invasive as well as hybrid procedures, rescue therapy with cutting-edge mechanical circulatory support, and above all, the shield dome of patient safety and improved quality of care interact in harmony with each other to create the future stage of PCCC. The exponential convergence of these scientific and technological advances holds great promise to mitigate the disease burden of children with congenital heart disease.

Author contributions

UP and DK contributed to conception, design, and integration of the manuscript. MEM and CM wrote the Education and training section. MM wrote the Patient monitoring section. YF wrote the Genomic medicine section. UP

wrote the Regeneration, nanotechnology and tissue engineering section. EK and DM wrote the Alternative to traditional cardiac surgery. GL and PR wrote the Mechanical circulatory support section. DK and LK wrote the Safety and quality section. All authors contributed to manuscript revision, read, and approved the submitted version.

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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