High Burden of Acquired Morbidity in Survivors of Pediatric Acute Respiratory Distress Syndrome

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Abstract

Introduction: With improving mortality rates in pediatric acute respiratory distress syndrome (PARDS), functional outcomes in survivors are increasingly important. We aim to describe the change in functional status score (FSS) from baseline to discharge and to identify risk factors associated with poor functional outcomes.

Methods: We examined clinical records of patients with PARDS admitted to our pediatric intensive care unit (PICU) from 2009 to 2016. Our primary outcome was acquired morbidity at PICU and hospital discharge (defined by an increase in FSS ≥3 points above baseline). We included severity of illness scores and severity of PARDS in our bivariate analysis for risk factors for acquired morbidity.

Results: There were 181 patients with PARDS, of which 90 (49.7%) survived. Median pediatric index of mortality 2 score was 4.05 (1.22, 8.70) and 21 (26.6%) patients had severe PARDS. 59 (65.6%) and 14 (15.6%) patients had acquired morbidity at PICU and hospital discharge, respectively. Median baseline FSS was 6.00 (6.00, 6.25), which increased to 11.00 (8.75, 12.00) at PICU discharge before decreasing to 7.50 (6.00, 9.25) at hospital discharge. All patients had significantly higher median FSS score at both PICU and hospital discharge compared to baseline. Feeding and respiratory were the most affected domains. After adjusting for severity of illness, severity categories of PARDS was not a risk factor for acquired morbidity.

Conclusion: Acquired morbidity in respiratory and feeding domains was common in PARDS survivors. Specific attention should be given to these two domains of functional outcomes in these children.

Introduction

Mortality rates from pediatric acute respiratory distress syndrome (PARDS) remains high at 24-33%, albeit with an overall decreasing trend over the last 3 decades (1, 2). Better understanding of the disease entity, early recognition and institution of specific and better supportive management has led to this improvement (3). However, this comes at the cost of survivors acquiring more morbidities after critical illness. To date, studies on PARDS have focused on clinical outcomes such as mortality, duration of invasive ventilation and pediatric intensive care unit (PICU) length of stay (4, 5). Little is known about the functional outcomes of PARDS survivors. Indeed, the Pediatric Acute Lung Injury Consensus Conference (PALICC) group of experts recognized the paucity of data on the morbidities from severe lung injury in children and highlighted that further studies are urgently required in this particular area (6).

One of the most commonly used scoring system for assessment of function in pediatric critical illness survivors is the functional status score (FSS) (7). As a scoring tool, FSS offers better granularity in documenting patients with moderate to severe disabilities compared to other functional scales such as Pediatric Overall Performance Category (POPC) and the Pediatric Cerebral Performance Category (PCPC) (8). FSS has been used as an objective measure of functional outcomes in other groups of critically ill children (e.g., congenital heart disease, traumatic brain injury and extra-corporeal membrane oxygenation) (9-11). Majority of studies examining pertinent outcomes in children with PARDS did not utilize FSS in their assessment (12, 13). Furthermore, there is lack of studies examining the risk factors for worse FSS scores in PARDS survivors. To address this gap in the current PARDS literature, we undertook this study with the aims to: (1) describe the change in FSS from baseline to PICU and hospital discharge in

children with PARDS; and (2) to identify risk factors associated with poor functional outcomes in PARDS survivors.

Materials and methods

This is a retrospective study of all patients (1 day-16 years old) with PARDS admitted to PICU in KK Women's and Children's Hospital, Singapore from January 2009 to December 2016. Our hospital is the largest of two tertiary and teaching pediatric hospitals in Singapore. Our PICU is a 16-bedded multidisciplinary facility that admits general medical, oncology, general surgical, neurosurgical and cardio-thoracic patients. Approval for this study was obtained from the SingHealth Centralized Institution Review Board (CIRB reference number: 2018/2455), with waiver of consent obtained.

Patients

A patient list was generated using International Classification of Disease [ICD9CM or ICD10AM (from 2012 onwards)] or the SCT code (SNOMED CLINICAL TERMINOLOGY) for a primary or secondary discharge diagnosis of ARDS. ARDS was first defined in 1994 by American European Consensus Conference (14) and validated for the pediatric population in 2012 (15). Definition of pediatric ARDS was refined in 2015 by PALICC work group (16). This new definition required the presence of new infiltrates on chest imaging and stratified patients into mild, moderate and severe ARDS based on oxygenation index. Clinical charts of identified patients were then examined to ensure that these patients fulfilled PALICC definition of PARDS. In addition, an independent search of the PICU's admission log was also performed to pick up cases who fulfilled definition of PARDS but was not coded.

We included all patients aged 1 day to 16 years old that had either a primary or secondary diagnosis of PARDS. Premature neonates (gestation age <35 weeks) and patients cared for in the neonatal intensive care unit (NICU) were excluded.

Data collection

Data pertaining to demographic profile, clinical outcomes, arterial blood gases, microbiological investigations and respiratory support were collected from case notes and electronic records. Severity of PARDS were graded into mild, moderate or severe according to PALICC classification (16). Paediatric index of mortality 2 (PIM2) score was calculated on admission to PICU (17).

FSS has six domains: mental, sensory, communication, motor, feeding and respiratory. Each domain has a scale from 1 (no dysfunction) to 5 (very severe dysfunction), with a total FSS score ranging from 6 to 30. FSS were retrospectively recorded within 24 hours of PICU admission, at PICU discharge and hospital discharge using information charted by both physicians and nurses. Acquired morbidity was defined as an increase of FSS score 3 points above a child's prehospitalization baseline at PICU or hospital discharge (8). FSS scores were also divided into a five-category rubric developed by Pollack et al from good to very severely abnormal functional status (8). Multiorgan dysfunction was defined as two or more organ dysfunction (18).

Statistical analysis

Patients were analyzed into two groups: No morbidity and acquired morbidity at PICU and hospital discharge. Categorical data were expressed as counts and percentages whereas

continuous data were expressed as median and interquartile ranges (IQRs). Differences between categorical data were analyzed by chi-square tests or Fisher's exact test (when cell sizes were less than 5). Differences between continuous data were analyzed by Mann-Whitney test. Differences between FSS at baseline and discharge points were analyzed by the Wilcoxon's signed rank test. Risk factors for acquired morbidity were adjusted for PIM2 score using bivariate analysis. All statistical tests were 2-tailed and P values of <0.05 were considered to be statistically significant. Statistical analysis was carried out using SPSS version 19 (IBM, Armonk, NY, USA).

Results

Demographics

There was a total of 4338 PICU admissions from January 2009 to December 2016. Of these, 181 (4.2%) patients fulfilled the PALICC definition of PARDS. Ninety patients (49.7%) in our cohort survived. The most common risk factors of PARDS in our survivor cohort were pneumonia (64 patients, 71.1%) and sepsis (15 patients, 16.7%). Median oxygenation index (OI) at day 1 of PARDS was 11.2 (7.8, 16.2). Twenty-one (26.6%) patients had severe PARDS. Median age of survivors was 2.2 [interquartile range (IQR) 0.4, 7.3] years and median PIM2 score was 4.05 (1.22, 8.70).

Fifty-nine (65.6%) and 14 (15.6%) patients had acquired morbidity at PICU and hospital discharge, respectively (Table 1). There was no significant demographic difference between survivors with no morbidity and acquired morbidity at both PICU and hospital discharge.

Change in FSS from baseline

All patients had higher FSS score at both PICU and hospital discharge compared to baseline. Figure 1 described the change in median FSS from baseline to hospital discharge in our PARDS survivors. Median baseline FSS of our PARDS survivors was 6.00 (6.00, 6.25). This increased to 11.00 (8.75, 12.00) at PICU discharge before decreasing to 7.50 (6.00, 9.25) at hospital discharge. The median change of FSS was 3.00 (2.00, 5.00) at PICU discharge and 0.00 (0.00, 2.00) at hospital discharge. Median FSS was significantly higher at PICU discharge ($Z= -7.95$ $p= <0.01$) and hospital discharge ($Z= -5.22$ $p= <0.01$) compared to baseline.

Pre-morbidly, only 9 (10.0%) patients had moderately to very severely abnormal FSS. At PICU discharge, more than half of the patients (63.3%) had moderately to very severely

abnormal FSS and one-quarter (24.4%) continued to have them even at hospital discharge. Eighty-three (92.2%) and 35 (38.9%) patients did not return to their premorbid status at PICU and hospital discharge, respectively.

FSS domains

Functional impairment in all 6 domains were present at both PICU and hospital discharge. At PICU discharge, functional impairment (domain score 1) was highest in the respiratory (81.1%) and feeding (78.9%) domains (Figure 2). At hospital discharge, functional impairment was also highest in the respiratory (22.2%) and feeding (41.1%) domains, with 3 being the most common abnormal score (moderate dysfunction).

Risk factors associated with poor functional outcomes in PARDS survivors

Severity categories of PARDS was not a risk factor for acquired morbidity in our cohort of survivors of PARDS (Table 2). There was no significant association between severity categories of PARDS and acquired morbidity after adjustment for PIM2 score at PICU [adjusted odds ratio 1.91 (95% CI 0.61 – 5.97] and hospital discharge [adjusted odds ratio 1.95 (95% CI 0.54 – 6.99]. There was also no significant difference in change in median FSS at both PICU and hospital discharge between patients with mild to moderate PARDS and severe PARDS.

Discussion

Our study demonstrated a high burden of morbidity in survivors of PARDS. All survivors had a higher FSS score at PICU and hospital discharge compared to the pre-hospital baseline. Acquired morbidity was present in 66% of PARDS survivors at PICU discharge and improved to 16% at hospital discharge. Respiratory and feeding domains were the most affected with the majority of survivors requiring some form of non-invasive ventilation at PICU discharge and assisted feeding which was persistent to hospital discharge. Severity of PARDS was not a risk factor for acquired morbidity.

Our study showed that nearly 20% of PARDS survivors had acquired morbidity at hospital discharge. A retrospective study conducted at the Children's Hospital of Philadelphia, United States (n=316) reported similar prevalence of acquired morbidity in PARDS survivors using FSS, with higher Pediatric Risk of Mortality III score, immunocompromised status and higher 24 hours arterial oxygen partial pressure to fractional inspired oxygen ratio being risk factors (19). Another follow up study of the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial (n=1330) looked at post-discharge functional status of 1330 pediatric survivors using PCPC and POPC scales (12). Similar to our study, 20% of the RESTORE trial subjects experienced a decline of functional status from baseline to follow up. In addition, the RESTORE investigators reported worse functional outcomes in children with underlying prematurity or malignancy and those who received longer duration of mechanical ventilation. Functional decline was significantly associated with moderate or severe PARDS in univariate analysis but not after adjustment for age and Pediatric Risk of Mortality III (PRISM-III) score in the RESTORE trial. This highlights that functional decline in children with respiratory failure is likely a result of complex interactions between a patient's comorbidities and

disease process. Compared to fore-mentioned 2 studies, our study did not identify any risk factors for FSS defined acquired morbidity at PICU and hospital discharge. This lack of findings may be secondary to our small sample size, lack of long-term follow-up in our study and the differences between FSS and POPC/PCPC scales. A large cohort study of 5000 pediatric ICU patients reported that POPC/PCPC scales were less precise compared to FSS, especially at indicating moderate to severe disability (8). Indeed, given the better granularity of FSS in scoring functional status, future studies to evaluate the trajectory of FSS in PARDS survivors are required.

Respiratory and feeding domains were the most affected in our PARDS survivors. These acquired morbidities can be due to direct complications from PARDS or consequences of PICU related care. One of the main long-term complications of PARDS is pulmonary dysfunction. Lung protective ventilation, being one of the key advances in ARDS management, has led to improvement in short-term survival but not in pulmonary function when compared with standard ventilation treatment (3, 20). In several adult ARDS studies, survivors were found to have abnormal spirometry results, lower diffusing capacity of the lung for carbon monoxide and impaired 6-min walk test up to 2 years after acute-phase resolution (21). There are limited studies examining long-term pulmonary function in PARDS survivors. One retrospective pediatric study (n=29) reported significantly abnormal spirometry results but normal 6 minute walk test, in children who required mechanical ventilation (MV) for acute respiratory failure, at both 3 and 12 months follow-up (22). Pulmonary dysfunction after survival might be one of the reasons why respiratory domain was the most affected in our cohort at hospital discharge, even though a longer follow-up time is needed to evaluate its long-term clinical significance. The young median age of our cohort also precludes the use of pulmonary function tests post

discharge. Future pediatric PARDS studies can consider utilizing other reported surrogates of pulmonary dysfunction such continued use of home non-invasive ventilation, supplemental oxygen, bronchodilators or steroids (13).

Our study showed that 73% and 38% of our cohort had moderate feeding dysfunction (i.e. oral and tube feeding) at PICU and hospital discharge, respectively. During PICU admission, it is common for children to be kept nil by mouth because of their clinical condition or to facilitate MV (23). However, there is a paucity of evidence describing feeding difficulties persisting after critical illness in the pediatric population. A recent systematic review (n=7 studies) reported prevalence of feeding difficulties in general PICU survivors, ranging from oral aversion to need for long-term NGT feeding even though no risk factors or predictors were identified (24). Possible reasons for feeding difficulties in pediatric ICU survivors might be similar to the adult population: dysphagia caused by prolonged MV, associated malnutrition and muscle weakness (25). Our findings taken together with the overall experience of other PICU patients, should aid the clinical team to anticipate feeding difficulties in PARDS survivors and consider early referral to allied health services for nutritional rehabilitation.

Post-intensive care syndrome (PICS) is increasingly recognized in both adult and pediatric ICU survivors (26, 27). This term encompasses not only impairment in physical functions but also cognitive and mental health that persist beyond acute care hospitalization. Besides physical disabilities, the fore-mentioned follow up study of the RESTORE trial also reported lower health-related quality of life, ranging from domains such as growth and development to emotional and school functioning, in children who survived respiratory failure (12). Moving forward, PARDS studies should also look into other pertinent outcomes such as cognitive impairment and quality of life for both patient and family, as recovery from critical

illness might often be a start of a multitude of problems later in life. Indeed, recently, a group of key stake-holders has advocated for a core outcome set that should be considered in all patients admitted to the PICU (28). Understanding functional deficits in PARDS survivors can also help direct follow up care. A recent report of children who survived respiratory failure (n=155) reported significant variability in follow up post discharge, with only 80% of their patients acquired morbidity being followed up by a primary physician or pulmonologist (29). Taken collectively, clinicians should pay attention to both the respiratory and feeding domains and consider involving relevant specialists and allied health services in the follow up care of PARDS survivors.

The main strength of the study is the complete identification of all patients who fulfilled current definition of PARDS in our center. The list of patients was generated from diagnostic codes as well as via a manual search. This is also the first PARDS study that utilizes FSS as an outcome measure in Asia. Description of functional outcomes in PARDS survivors can help physicians understand the current state of PARDS survivors and encourage a shift of focus from reducing mortality to improving functional outcomes. Our study also identified two main areas that the bedside team should focus rehabilitation efforts on – the respiratory and feeding domains. The main limitation of this study is that it is a single center study with small sample size and thus, our findings may not be generalizable to other institutes with different etiologies of PARDS. In addition, we did not collect data post hospital discharge, precluding us from describing longer term out of hospital outcomes. Future studies are required to validate our findings and to provide valuable data on longer term outcomes in this group of patients.

In conclusion, our study demonstrated that acquired morbidity was common in PARDS survivors. Respiratory and feeding domains were the most affected after both PICU and hospital

discharge. Rehabilitation efforts should focus on these two domains to improve functional outcomes of these children.

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