Review Article

Long-Term Morbidities in Children with Critical Illness: Gaps and Opportunities

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Abstract

Introduction: Improved mortality rates in paediatric critical care may come with the cost of increased morbidity. Goals of modern paediatric intensive care unit (PICU) management should focus on restoring long-term function of paediatric critical illness survivors. This review outlines our current knowledge on trajectories and risk factors of long-term morbidities in PICU survivors. Specifically, we aimed to identify current limitations and gaps in this area so as to identify opportunities for future investigations to reduce the burden of morbidities in these children. Materials and Methods: A review of primary studies published in PubMed, EMBASE, and Cochrane databases in the last decade (2008-2017) describing long-term morbidities in PICU survivors was conducted. Results: Children surviving critical illness continue to experience morbidities after discharge. A set of risk factors modify their long-term trajectories of recovery, with some children achieving their premorbid level of function, while some others deteriorate or die. Limitations in current methodologies of morbidity research impair our understanding on the causes of these morbidities. Opportunities for future endeavours to reduce the burden of these morbidities include identifying patients who are more likely to develop morbidities, evaluating the efficacy of early rehabilitation, identifying patients who might benefit from tight glycaemic control, characterising the optimal nutritional intervention, and improving management of increased intracranial pressure. Conclusion: Survivors of paediatric critical illness experience differing trajectories of recovery from morbidities. Future research is needed to expand our repertoire on management strategies to improve long-term function in these children.

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Key words: Intensive Care, Outcomes assessment (healthcare), Paediatrics

Introduction

Paediatric critical care has evolved in the last 3 decades, largely attributable to advances in medical care and technology. Paediatric intensive care unit (PICU) mortality rates decreased from 15% in 1982 to 2%-5% in the last decade,[1-5] and critical care is now offered to more children who require more complex care.[1,6,7]

Decreased mortality rates come at the cost of increased morbidity rates.[5] A 3-decade analysis reported that the number of PICU survivors with moderate to severe long-term disability had doubled in 2005-2006 compared to 1982.[1] In 1995, 85% of PICU survivors reported good quality of life (QOL) on follow-up, but this number decreased to 66% in 2006.[1] Children surviving critical illnesses are at risk of developing long-term physical, neurocognitive, and psychological morbidities, much like the adult post-intensive care syndrome.[8]

With decreased mortality, the goal of paediatric critical care management has shifted to restore the function of survivors to their preadmission state. This review aimed to summarise the current available literature over the last decade on the long-term morbidities of PICU survivors.

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We first describe the temporal pattern (trajectories) and risk factors of morbidities. We then focus on the gaps in our knowledge about the causes of and strategies to manage long-term morbidities in PICU survivors, to highlight opportunities for further study in this area.

Materials and Methods

In this review, we defined morbidity as any impairment in the patient's functional status, health-related quality of life (HRQOL), health status (e.g., symptoms of uncontrolled asthma), or neurodevelopmental outcomes (including cognition and behaviour). We conducted a literature search of PubMed, EMBASE, and Cochrane databases using a combination of keywords and MESH terms such as "long-term outcome", "functional outcome", and "critical illness" or "paediatric intensive care unit". Primary studies published in 2008-2017 that described long-term morbidities were included. Because of the heterogeneity of outcome measures, follow-up time, and population characteristics, no statistical analysis was performed, and a narrative approach was used to summarise the current evidence.

Results and Discussion

Long-Term Trajectory of Morbidity in PICU Survivors

PICU survivors have persistently poorer health compared to healthy children (*Online Supplementary Table 1).[3,9-11] This includes lower HRQOL, worse visual-motor integration, motor coordination, poorer memory and intelligence quotient (IQ) scores. These children are at greater risk of functional decline with hospital and PICU readmissions.[2,12] There appears to be several recovery trajectories: some PICU survivors deteriorate or die, some return to their baseline status, and some even improve beyond their baseline function. In a longitudinal cohort study of 70 PICU patients, approximately 41% of PICU survivors had worsening of function or death at 3 years, 49% returned to their baseline state, while the remainder 10% showed improvements from baseline.[2] Reported rates of recovery in other studies range from 59%-81%.[1-3] These varying trajectories in PICU survivors suggest that there are certain factors associated with morbidity and recovery. Identifying these factors would be the first step to support long-term recovery of these children.

Risk Factors for Long-Term Morbidities in PICU Survivors

The major groups of risk factors for long-term morbidities in PICU survivors are outlined in this subsection (Table 1).

Admission Diagnoses

Among all admission diagnoses, children with neurological diagnoses had the highest rate of acquired morbidity at hospital discharge and long-term follow-up.[1,5] At 1 year, 48% of children admitted with neurological diagnoses either died or had moderate or severe disability, compared to only 29% of children with other diagnoses.[1] Within the neurological diagnoses group, different aetiologies were associated with different long-term prognoses. After 6 months, survivors of severe traumatic brain injury (TBI) had higher rates of favourable outcomes (Glasgow Outcome Scale [GOS] = 4) compared to children with refractory febrile status epilepticus (90% vs 27%, respectively).[13,14]

Illness Severity

For any group of patients, higher severity of illness on PICU admission was associated with long-term morbidities. Children requiring longer duration of cardiopulmonary resuscitation (CPR) were found to have worse long-term outcomes.[15,16] Specifically, if duration of CPR was more than 30 minutes, outcomes were limited to only death, disabled, or vegetative state.[16]

PICU survivors requiring use of extracorporeal membrane oxygenation (ECMO) had been shown to have poorer quality of life at 1 month with increased time on ECMO.[15] Indeed, the neurological impairments and other morbidities in ECMO survivors are discussed in other excellent reviews.[17-19]

In acute neurological disorders, the occurrence of status epilepticus is a marker of secondary brain injury and was associated with lower functional status, QOL, higher rates of epilepsy, and worse long-term adaptive behaviour.[20,21] In children with moderate to severe TBI, a lower Glasgow Coma Score (GCS), anisocoria, arterial oxygen saturation <90%, and hypothermia were associated with poorer long-term neurological function.[22,23]

Several variables mentioned above (e.g., impaired pupillary reflexes, low GCS, hypothermia) are part of existing illness severity scoring systems in critically ill children (e.g., Paediatric Risk of Mortality [PRISM] or Paediatric Index of Mortality [PIM]).[24,25] It is therefore not surprising that these scores corresponded well with the magnitude of morbidity. Higher PRISM scores correlated with greater deterioration in Paediatric Overall Performance Category (POPC) and Paediatric Cerebral Performance Category (PCPC) scores from baseline to discharge, while higher PIM2 scores was associated with lower QOL 6 months after discharge.[3,26]

Pre-Existing Morbidities

Pre-existing morbidities affect long-term recovery in PICU survivors. Children with worse baseline function were found to have worse adaptive behaviour, functional outcome, and HRQOL at 1 month post-PICU care, higher hospital readmission rates, and persistent acquired morbidities at 6 months and 3 years.[1,2,15,27] Children with pre-existing chronic health conditions (especially neurodevelopmental disability) were at greater risk of persistent functional

*Available online at http://www.annals.edu.sg/pdf/47VolNo8Aug2018/V47N8p291.pdf (pp. 307-37)

Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients

Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
General PICU Patients			
Polic et al, 2013[*]	n = 189 General PICU, with or without pre-existing chronic health condition (CHC) Median (range) age: Without CHC: 15.5 (10,18) years With CHC: 15.3 (10,17.6) years	RAHC MOF	• Pre-existing neurodevelopmental disability • Chronic health conditions • Higher PIM2 scores
Pinto et al, 2017[†]	n = 77 General PICU Median (IQR) age: 8.60 (2.10 – 11.90) years	FSS	• Longer PICU length of stay • Higher number of ventilation days

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

[*]Polic B, Mestrovic J, Markic J, Mestrovic M, Capkun V, Utrobicic I, et al. Long-term quality of life of patients treated in paediatric intensive care unit. Eur J Pediatr 2013;172:85-90.

[†]Pinto NP, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-term function after pediatric critical illness: results from the Survivor Outcomes Study. Pediatr Crit Care Med 2017;18:e122-30.

[‡]van Zellem L, Utens EM, Legerstee JS, Cransberg K, Hulst JM, Tibboel D, et al. Cardiac arrest in children: long-term health status and health-related quality of life. Pediatr Crit Care Med 2015;16:693-702.

[§]Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, et al. Targeted temperature management after pediatric cardiac arrest due to drowning: outcomes and complications. Pediatr Crit Care Med 2016;17:712-20.

[‖]Slomine BS, Nadkarni VM, Christensen JR, Silverstein FS, Telford R, Topjian A, et al. Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children. Resuscitation 2017;115:178-84.

[¶]Wagenman KL, Blake TP, Sanchez SM, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and long-term outcome in critically ill children. Neurology 2014;82:396-404.

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[**]Salorio CF, Slomine BS, Guerguerian AM, Christensen JR, White JR, Natale JE, et al. Intensive care unit variables and outcome after pediatric traumatic brain injury: a retrospective study of survivors. Pediatr Crit Care Med 2008;9:47-53.

[††]Tepas JJ 3rd, Leaphart CL, Pieper P, Beaulieu CL, Spierre LR, Tuten JD, et al. The effect of delay in rehabilitation on outcome of severe traumatic brain injury. J Pediatr Surg 2009;44:368-72.

[‡‡]Kapapa T, König K, Pfister U, Sasse M, Woischneck D, Heissler H, et al. Head trauma in children, part 2: course and discharge with outcome. J Child Neurol 2010;25:274-83.

[§§]Thomale UW, Graetz D, Vajkoczy P, Sarrafzadeh AS. Severe traumatic brain injury in children–a single center experience regarding therapy and long-term outcome. Childs Nerv Syst 2010;26:1563-73.

[‖‖]Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, et al. Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. J Neurosurg Pediatr 2015;16:410-9.

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Table 1. Studies Identifying Risk Factors for Long-Term Morbidities of PICU Patients (Cont'd)

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Cardiac Arrest Patients			
Van Zellem et al, 2015[‡]	n = 57 PICU population who have sustained cardiac arrest Median (range) age at follow-up: 8.7 (2.4 – 18.3) years	PCPC	• Pre-existing health condition related to the cause of cardiac arrest
Moler et al, 2016[§]	n = 68 Out of hospital cardiac arrest (OHCA) patients, and who were admitted to a PICU and remained comatose within 6 hours of return of circulation (ROC), with premorbid VABS-II scores ≥70, mean (SD) age in years: drowning group: 4.6 (4.16); other aetiologies: 5.1 (5.41)	VABS-II	• Duration of CPR >30 minutes
Slomine et al, 2017[‖]	n = 59 Out of hospital cardiac arrest (OHCA) patients who were admitted to a PICU and remained comatose within 6 hours of return of circulation (ROC), with premorbid VABS-II scores ≥70 Mean (SD) age: Drowning group: 4.6 (4.16) years Other aetiologies: 5.1 (5.41) years	VABS-II	• Older age • Higher doses of epinephrine • Aetiologies other than drowning

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Neurological Diagnoses Patients – Non-Traumatic Brain Injury			
Wagenman et al, 2014¶	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median (IQR) age: 3.9 (1.1, 12.7) years	GOS-E, PedsQL	• Electrographic status epilepticus
Abend et al, 2015#	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median age (IQR): 4.1 (2.0, 9.8) years	ABAS-II	• Electrographic seizures • Electrographic status epilepticus

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Neurological Diagnoses Patients – Traumatic Brain Injury			
Salorio et al, 2008[**]	n = 57 Survivors of paediatric moderate and severe TBI (GCS 3 – 12) admitted for rehabilitation Mean age: 10.8 +/- 3.2 years	PIQ: Wechsler Intelligence Scale for Children, DRS	Worse PIQ: • Lower initial GCS score • Hypotension Worse DRS: • Hypertension within the first 24 hours
Tepas et al, 2009[††]	n = 60 Patients with severe blunt TBI (initial GCS score ≤8) that required resuscitation, critical care, and inpatient rehabilitation Mean age: male 11.2 years, females, 10.6 years	FIM, RE: ratio of FIM improvement to length of inpatient rehabilitation	• Delayed inpatient rehab associated with reduced rehabilitation efficiency and reduced improvements in FIM scores
Kapapa et al, 2010[‡‡]	n = 48 Children who sustained head trauma requiring intensive care, receiving cerebral perfusion pressure (CPP)-orientated management Mean age: 5.9 years (range 19 days – 14.5 years)	GOS	• Elevated blood glutamic-oxaloacetic-transaminase • Elevated blood urea and glucose on the first 2 days • ≥1 occurrence of CPP value below recommended standard • Mean arterial pressure below lower limit • Central venous pressure below lower limit
Thomale et al, 2010[§§]	n = 53 Neurosurgically treated patients with diagnosis of severe TBI (GCS <9) undergoing additional decompressive craniectomy or conservative intracranial pressure (ICP) management without craniectomy Median age: craniectomy: 12 years, conservative: 7 years	GOS	• Anisocoria on admission • Arterial oxygen saturation <90% on admission

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Study Reference	Population Characteristics	Outcome Measures Used	Risk Factors for Long-Term Morbidity
Neurological Diagnoses Patients – Traumatic Brain Injury			
Fulkerson et al, 2015[ll]	n = 67 Paediatric head injury patients presented to neurosurgical service at a single centre with: GCS 3 (age 49.8 +/- 51.8 months) or GCS 4 (age 66.9 +/- 58.0 months)	mGOS, mortality	• Impaired pupillary response • Hypothermia • Mechanism of injury (abuse)
Other Specific Populations			
Ebrahim et al, 2013[¶¶]	n = 91; 65 completed 1-month assessment Urgently admitted (<12 hours notice) patients from inpatient ward, or had an ICU cardiac arrest and/or received ECMO treatment irrespective of the urgency of their ICU admission Mean age: 76.4 ± 69.3 months, range 1 month to 18 years	Adaptive behaviour: VABS-II, HRQoL: Peds QL, functional outcome: PCPC, POPC	Worse adaptive behaviour: • Circulatory diagnoses • Worse initial PCPC scores • Worse transcutaneous O_2 saturation • Longer cardiac compression Worse HRQoL: • Worse initial PCPC • Longer ICU stay • Longer duration of ECMO Worse functional outcome: • Same factors as HRQoL • Neurological diagnoses

ABAS-II: Adaptive Behaviour Assessment System-II; CPP: Cerebral perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HRQoL: Health-related quality of life; ICP: Intracranial pressure; IQR: Inter quartile range; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PICU: Paediatric Intensive Care Unit; PIQ: Performance IQ; POPC: Paediatric Overall Performance Category; RAHC MOF: Royal Alexandra Hospital for Children Measure Of Function; RE: Rehabilitation efficiency; TBI: Traumatic brain injury; THAPCA-OHCA: Therapeutic hypothermia after paediatric cardiac arrest-out of hospital cardiac arrest; VABS-II: Vineland Adaptive Behaviour Scale-II

[*]Polic B, Mestrovic J, Markic J, Mestrovic M, Capkun V, Utrobicic I, et al. Long-term quality of life of patients treated in paediatric intensive care unit. Eur J Pediatr 2013;172:85-90.

[†]Pinto NP, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-term function after pediatric critical illness: results from the Survivor Outcomes Study. Pediatr Crit Care Med 2017;18:e122-30.

[‡]van Zellem L, Utens EM, Legerstee JS, Cransberg K, Hulst JM, Tibboel D, et al. Cardiac arrest in children: long-term health status and health-related quality of life. Pediatr Crit Care Med 2015;16:693-702.

[§]Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, et al. Targeted temperature management after pediatric cardiac arrest due to drowning: outcomes and complications. Pediatr Crit Care Med 2016;17:712-20.

[‖]Slomine BS, Nadkarni VM, Christensen JR, Silverstein FS, Telford R, Topjian A, et al. Pediatric cardiac arrest due to drowning and other respiratory etiologies: Neurobehavioral outcomes in initially comatose children. Resuscitation 2017;115:178-84.

[¶]Wagenman KL, Blake TP, Sanchez SM, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and long-term outcome in critically ill children. Neurology 2014;82:396-404.

[#]Abend NS, Wagenman KL, Blake TP, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy Behav 2015;49:238-44.

[**]Salorio CF, Slomine BS, Guerguerian AM, Christensen JR, White JR, Natale JE, et al. Intensive care unit variables and outcome after pediatric traumatic brain injury: a retrospective study of survivors. Pediatr Crit Care Med 2008;9:47-53.

[††]Tepas JJ 3rd, Leaphart CL, Pieper P, Beaulieu CL, Spierre LR, Tuten JD, et al. The effect of delay in rehabilitation on outcome of severe traumatic brain injury. J Pediatr Surg 2009;44:368-72.

[‡‡]Kapapa T, König K, Pfister U, Sasse M, Woischneck D, Heissler H, et al. Head trauma in children, part 2: course and discharge with outcome. J Child Neurol 2010;25:274-83.

[§§]Thomale UW, Graetz D, Vajkoczy P, Sarrafzadeh AS. Severe traumatic brain injury in children–a single center experience regarding therapy and long-term outcome. Childs Nerv Syst 2010;26:1563-73.

[‖‖]Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, et al. Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. J Neurosurg Pediatr 2015;16:410-9.

[¶¶]Ebrahim S, Singh S, Hutchison JS, Kulkarni AV, Sananes R, Bowman KW, et al. Adaptive behavior, functional outcomes, and quality of life outcomes of children requiring urgent ICU admission. Pediatr Crit Care Med 2013;14:10-8.

impairment (decrease in Royal Alexandra Hospital for Children Measure of Function [RAHC MOF] scores from premorbid) compared to children without chronic conditions.[3] Among cardiac arrest survivors, those with pre-existing conditions reported worse general health perception years later.[10]

PICU Length of Stay

Longer length of PICU stay was also identified as a risk factor for long-term acquired morbidities.[2] In a long-stay cohort, among children who had no or mild disability on admission, 20% was found to have long-term moderate to severe disability.[28] In comparison, in the general PICU cohort, only 4% of children ended up with long-term moderate to severe disability.[1] In our own experience of 241 long-stay (>14 days) admissions, we found that long-stayers had high rates of pre-existing comorbidities (55%) and chronic care devices (non-invasive ventilation, tracheostomy, or long-term parenteral nutrition) (49%), consistent with the literature.[4,29,30] Moreover, on PICU discharge, more children were found to require chronic care devices compared to admission.[4]

Initiation of Rehabilitation

Delay in starting rehabilitation influenced the success of subsequent recovery. A study in children with severe blunt TBI found that the duration of delay between PICU discharge and the start of inpatient rehabilitation was inversely correlated with rehabilitation efficiency and improvement in functional independence measurement scores.[31]

Gaps in Knowledge and Opportunities for Future Research

Heterogeneity in Morbidity Measurement Tools and Timing

The number of clinical studies describing long-term morbidities and associated risk factors are increasing. However, our understanding of the causes of morbidities remains inadequate due to several limitations in morbidity research.

Firstly, there is the heterogeneity of outcome measures used to quantify morbidities. This partially stems from a lack of consensus on definitions of outcome measures. For instance, some researchers consider HRQOL as part as functional status, while others consider them as separate entities.[15,32,33] Functional status has been measured using a range of global functional outcome scoring tools (e.g., PCPC), adaptive behaviour functioning scales (e.g., Vineland Adaptive Behaviour Scale-2 [VABS-2]), and QOL rating scales (e.g., RAHC MOF).[3,26,32,34] In addition, some have used unstructured questionnaires to capture long-term sequelae or impairment in functioning (e.g., poorly defined "learning difficulties", "mental impairment", or "behaviour problem").[10,35]

The lack of consensus is a barrier to synthesising and interpreting data across studies.[2,9,32,33,36] Ideally, studies should use a standardised, well defined outcome measure for each type of morbidity and use validated measurement tools to quantify outcomes. This may evolve over time as studies examining morbidities after paediatric critical illness are just recently emerging. Furthermore, we do not fully understand the scope and types of morbidities affecting PICU survivors. The adult population has a well described construct known as the post-intensive care syndrome (PICS)—categorising the acquired morbidities in ICU survivors to 3 domains: physical, neurocognitive, and psychological.[34] It has been suggested that the same construct could be applied to children so as to standardise the description of the landscape of morbidity in PICU survivors.[8]

Secondly, comparison between studies are challenging because of the lack of standardisation in design and quality of the studies, most particularly in terms of long-term follow-up. Duration of follow-up varied greatly across studies, from 1 month[14,15] to greater than 10 years.[12,37] Most long-term follow-up will assess the child's status compared to baseline, however, the time point to establish "baseline" also differed between studies—some defined "baseline" as the pre-acute illness functioning while others considered "baseline" as the 24-hours window after PICU admission.[2,3,5,15] Some studies only reported absolute morbidity, with no comparison with the child's baseline status or appropriately matched controls in the analysis. Not all studies accounted for the children lost to follow-up by ensuring they were comparable to the children remaining in the studies. The quality assessment of the included studies in our review is detailed in [*]Online Supplementary Table 2.

To achieve our goal of restoring PICU survivors to their premorbid function, it is imperative for future studies to standardise the follow-up interval and duration to allow for comparison of data across different centres. Currently, the best timing for follow-up is unknown. The available evidence suggests that recovery from morbidity may reach a plateau between 6 months and 3 years after hospital discharge. In PICU survivors, children who recover at the end of 3 years still had decreased mean Functional Status Scale (FSS) scores at 6 months compared to baseline.[2] In children with severe TBI, the optimum follow-up time may be 1 year. Median GOS improved from 4 to 5 between hospital discharge and 12 months, while scores at 5 and 11 years were the same as those at 1 year.[23,37] Additionally, studies should include baseline measurements of the child's premorbid function, or to include matched controls to serve as a benchmark. It is also important to select appropriate measures to best capture age-specific needs and to evaluate response to intervention over time.

[*]Available online at http://www.annals.edu.sg/pdf/47VolNo8Aug2018/V47N8p291.pdf (pp. 307-37)

Early Identification of Children At Risk of Developing Long-Term Morbidities

An important step in reducing long-term morbidities would be to identify patients who are at greater risk of acquired morbidities so that early interventions to reduce morbidities can be instituted.

Currently, disease severity scoring systems (e.g., PIM, PRISM, and Paediatric Logistic Organ Dysfunction [PELOD]) are used to predict risk of PICU mortality.[38,39] As disease severity is associated with morbidities, recent literature suggests that these tools could also predict acquired morbidities. In a large multicentre cohort study, Pollack et al showed that PRISM III scores could be used to simultaneously predict mortality and acquired morbidity (defined as an increase in FSS = 3 compared to baseline) at hospital discharge.[40] In this prediction model, morbidity risk initially increased with higher PRISM III scores, but then decreased with the highest PRISM III scores, as potential morbidities resulted in mortalities. The final prediction model had a strong predictive ability with volume under the surface of 0.50.

While predicting acquired morbidities at hospital discharge would enable us to intervene early during hospital stay, it could potentially miss patients who develop morbidities after hospital discharge. Indeed, a study involving 77 children demonstrated that the rates of acquired morbidity continued to increase after hospital discharge (4%), reaching 6% and 10% at 6 months and 3 years, respectively.[2]

A tool to predict development of long-term morbidities would identify both groups who develop morbidities by hospital discharge as well as those who do so after hospital discharge. It may also enable us to prevent further deterioration in these children by allocating appropriate resources posthospital discharge, including follow-up sessions for early detection of postdischarge acquired morbidities, or structured rehabilitation programmes to aid functional recovery.[41] This proposed tool could build on existing mortality prediction systems, with incorporation of additional variables associated with morbidities, including pre-existing chronic health condition or baseline functional status.

Some mortality prediction systems, such as PIM3, assign different risks into different admission diagnoses.[25] These would need to be modified, since a low-risk diagnosis for mortality might be associated with a high risk for morbidity. For instance, while PIM3 classifies seizure disorders as low-risk, a patient admitted for any neurological diagnosis should be assigned an increased risk for morbidity compared to other admitting diagnoses, and an even higher risk should be assigned for refractory febrile status epilepticus.[25] Conversely, a high risk for mortality may not apply to morbidity. For instance, a cardiac arrest preceding ICU admission would be assigned as a very high-risk for mortality in PIM3 or PRISM4.[24,25] However, up to 82% of cardiac arrest survivors attain favourable long-term outcomes, as long as the duration of CPR was less than 30 minutes.[16,42] An improvement for a morbidity prediction system would be the incorporation of risk factors for morbidities related to a particular admission diagnosis. For instance, for a patient admitted after a cardiac arrest, a high risk for long-term morbidity should be assigned if CPR exceeds 30 minutes, while in TBI patients, higher risk should be assigned if the mechanism of injury is abuse.[16,37]

The existing mortality prediction systems are based on patient parameters within the first 24 hours of PICU admission.[24,25] However, long-term morbidities could be influenced by events occurring any time during the PICU stay. In patients with altered mental status, occurrences of status epilepticus throughout PICU stay were associated with long-term morbidities.[20,21] In TBI patients, at least 1 occurrence of low cerebral perfusion pressure was associated with worse functional outcomes.[35] While prediction of long-term morbidities might be improved by continuously monitoring physiological parameters, it might be impractical to do so. An alternative might be to reassign a long-term morbidity prediction score at PICU discharge, to include additional high-risk events occurring during PICU stay.

Interventions to Reduce Morbidity Within the PICU

To reduce long-term morbidities, interventions need to target modifiable risk factors. This section will discuss some randomised controlled trials (RCTs) (Table 2) from the past decade as well as current gaps in our knowledge pertaining to this issue.

Early Mobilisation to Improve Long-Term Functional Outcomes

Despite the importance of early mobilisation for long-term recovery of function, it is not commonly practised in the PICU.[31] Only half of children received rehabilitation in the PICU, and of these, up to 70% of the rehabilitation received was non-mobile in nature (e.g., chest physiotherapy), while only less than 10% of children received early mobilisation.[43] Leading reasons for delaying mobility treatments include the lack of practice guidelines and conflicting perceptions regarding clinical thresholds and safety of early mobilisation.[44]

There is a need to evaluate the safety, clinical threshold to initiate, and efficacy of early mobilisation. Two pilot studies have reported the safety and feasibility of acute rehabilitation interventions in the PICU, using in-bed cycling and virtual reality (VR) boxing to promote early mobilisation.[45,46] The in-bed cycling pilot trial achieved its

Table 2. Randomised Controlled Trials (RCTs) Evaluating Interventions to Reduce Long-Term Morbidity in PICU Survivors

Study Reference	Study Design	Population Characteristics	Intervention	Outcome Measures Used	Follow-up Time(s)	Long-Term Outcome
Early Rehabilitation						
Abdulsatar et al, 2013*	Pilot RCT	n = 8 Children 3 – 18 years old with anticipated PICU stay >48 hours, baseline normal to moderate cognitive and functional disability Median (IQR) age: 11 (3, 16) years	Nintendo Wii™ boxing for a minimum of 10 minutes twice a day for 2 days	Safety and feasibility	NA	• No adverse events attributable to the intervention • Upper limb activity during intervention was significantly greater than average daily activity • Grip strength did not change significantly from baseline
Choong et al, 2017†	Pilot RCT	n = 30 Children 3 – 17 years old limited to bed rest with expected PICU stay of ≥48 hours Median (IQR) age: Usual care group 9 (6, 11) years Cycling group 8 (5, 14) years	Early mobilisation using in-bed cycling in addition to physiotherapy alone vs usual care (physiotherapy alone)	Safety and feasibility	NA	• No adverse events occurred in either arm • Early mobilisation was feasible • Main threat to feasibility was the availability of personnel

CBCL: Child Behaviour Checklist; CPP: Cerebral perfusion pressure; EN: Enteral nutrition; GCS: Glasgow Coma Score; HUI: Health Utilities Index; ICP: Intracranial pressure; IQR: Inter quartile range; KOSCHI: The Kings Outcome Scale for Childhood Head Injury; LOS: Length of stay; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PELOD: Paediatric logistic organ dysfunction; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCTP: Randomised controlled trial; RRT: Renal replacement therapy; TBI: Traumatic brain injury; TGC: Tight glycaemic control

*Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. J Pediatr Rehabil Med 2013;6:193-204.

†Choong K, Awladthani S, Khawaji A, Clark H, Borhan A, Cheng J, et al. Early exercise in critically ill youth and children, a preliminary evaluation: the wEECYCLE pilot trial. Pediatr Crit Care Med 2017;18:e546-54.

‡Vlasselaers D, Milants I, Desmet L, Wouters P, Vanhorebeek I, Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.

§Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: A randomized controlled trial. JAMA 2012;308:1641-50.

‖Macrae D, Grieve R, Allen E, Sadique Z, Betts H, Morris K, et al. A clinical and economic evaluation of control of hyperglycaemia in paediatric intensive care (CHiP): a randomised controlled trial. Health Technol Assess 2014;18:1-209.

¶Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.

#Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014;42:1775-87.

Table 2. Randomised Controlled Trials (RCTs) Evaluating Interventions to Reduce Long-Term Morbidity in PICU Survivors (Cont'd)

Study Reference	Study Design	Population Characteristics	Intervention	Outcome Measures Used	Follow-up Time(s)	Long-Term Outcome
Management of Hyperglycaemia						
Vlasselaers et al, 2009‡	RCT	n = 700 (317 infants, 383 aged ≥1 year) General PICU from single centre Median (IQR) age: Conventional group: 1.3 (0.3, 4.6) years Intensive group: 1.4 (0.3, 5.5) years	Intensive group: insulin infusion to target normoglycaemia of 2.8 – 4.4 mmol/L in infants and 3.9 – 5.6 mmol/L in children vs conventional group: insulin infusion only to prevent blood glucose from exceeding 11.9 mmol/L	Mortality, PICU LOS, inflammatory response (c-reactive protein)	PICU discharge	• Hypoglycaemia occurred in more in patients in the intensive group (25%) vs conventional group (1%) • Duration of PICU stay was shorter in the intensively treated group • Inflammatory response was attenuated at day 5 in the intensive group • No mortality difference between 2 arms
Mesotten et al, 2012§	Follow-up from survivors of RCT	n = 569 All PICU patients aged 0 – 16 years Median (IQR) age at follow-up: TGC: 5.3 (4.2 – 9.2) years CM: 5.1 (4.2 – 8.2) years	TGC vs conventional glucose management (CM)	Intelligence quotient (Wechsler IQ scales), neurodevelopmental testing (Beery-Buktenica Developmental Test of Visual-Motor Integration), attention, motor coordination, and executive functions (Amsterdam Neuropsychological Tasks), memory (Children's Memory Scale), behaviour (Child Behaviour Checklist)	Median (IQR) of 3.9 (3.8 – 4.1) years after randomisation	• TGC did not affect IQ scores • TCG did not increase incidence of death or severe disability precluding neurocognitive testing • Tight glucose control improved motor coordination and cognitive flexibility
Macrae et al, 2014‖	RCT	n = 1369 Non-diabetic PICU patients Age 0 – 16 years	TGC vs conventional glucose management (CM)	Short-term: Mortality, duration of ventilation, length of PICU/hospital stay, readmission rates, renal replacement therapy, infection, transfusions, seizures, PELOD score, hypoglycaemia Long-term: Mortality, attention and behaviour in TBI patients (KOSCHI, HUI, CBCL), total duration of PICU and hospital stay		

CBCL: Child Behaviour Checklist; CPP: Cerebral perfusion pressure; EN: Enteral nutrition; GCS: Glasgow Coma Score; HUI: Health Utilities Index; ICP: Intracranial pressure; IQR: Inter quartile range; KOSCHI: The Kings Outcome Scale for Childhood Head Injury; LOS: Length of stay; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PELOD: Paediatric logistic organ dysfunction; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCTP: Randomised controlled trial; RRT: Renal replacement therapy; TBI: Traumatic brain injury; TGC: Tight glycaemic control

*Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. J Pediatr Rehabil Med 2013;6:193-204.

†Choong K, Awladthani S, Khawaji A, Clark H, Borhan A, Cheng J, et al. Early exercise in critically ill youth and children, a preliminary evaluation: the wEECYCLE pilot trial. Pediatr Crit Care Med 2017;18:e546-54.

‡Vlasselaers D, Milants I, Desmet L, Wouters P, Vanhorebeek I, Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.

§Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: A randomized controlled trial. JAMA 2012;308:1641-50.

‖Macrae D, Grieve R, Allen E, Sadique Z, Betts H, Morris K, et al. A clinical and economic evaluation of control of hyperglycaemia in paediatric intensive care (CHiP): a randomised controlled trial. Health Technol Assess 2014;18:1-209.

¶Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.

#Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014;42:1775-87.

Table 2. Randomised Controlled Trials (RCTs) Evaluating Interventions to Reduce Long-Term Morbidity in PICU Survivors (Cont'd)

Study Reference	Study Design	Population Characteristics	Intervention	Outcome Measures Used	Follow-up Time(s)	Long-Term Outcome
Timing of Supplemental Parenteral Nutrition						
Fivez et al, 2016[¶]	RCT	n = 1440 General PICU from 3 centres Median (IQR) age: Early PN 1.4 (0.3 – 6.1) Late PN 1.5 (0.2 – 7.2)	Early PN: PN to supplement caloric intake from EN, initiated within 24 hours after ICU admission Late PN: supplemental PN delayed until day 8 of PICU	PICU mortality, new infection rates, PICU and hospital LOS, duration of mechanical ventilation, proportion of patients receiving renal replacement therapy (RRT), plasma levels of inflammatory markers	First 7 days in PICU, PICU discharge, 90 days after PICU admission	• No mortality difference between 2 arms • Late PN associated with lower infection rate (10.7% vs 18.5%), shorter ICU (6.5 ± 0.4 vs 9.2 ± 0.8 days) and hospital LOS, shorter duration of mechanical ventilation, lower proportion of RRT, and lower plasma inflammatory markers
Management of Increased Intracranial Pressure						
Kumar et al, 2014[#]	RCT	n = 110 PICU patients with acute CNS infection with modified Glasgow Coma Scale score (m-GCS) ≤8, and evidence of raised ICP Mean age in months: 69.2 ± 37 (ICP); 62.6 ± 36.8 (CPP)	CPP vs ICP – targeted approach	Mortality, neuromorbidity (m-GOS), functional neuro-disability (PCPC), presence of hearing deficit	PICU discharge, 90 days after PICU discharge	• Cumulative mortality was significantly higher in the ICP group • Neuro-disability and hearing deficit were lower in CPP group

CBCL: Child Behaviour Checklist; CPP: Cerebral perfusion pressure; EN: Enteral nutrition; GCS: Glasgow Coma Score; HUI: Health Utilities Index; ICP: Intracranial pressure; IQR: Inter quartile range; KOSCHI: The Kings Outcome Scale for Childhood Head Injury; LOS: Length of stay; MGOS: Modified Glasgow Outcome Scale; PCPC: Paediatric Cerebral Performance Category; PELOD: Paediatric logistic organ dysfunction; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCTP: Randomised controlled trial; RRT: Renal replacement therapy; TBI: Traumatic brain injury; TGC: Tight glycaemic control

[*]Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. J Pediatr Rehabil Med 2013;6:193-204.

[†]Choong K, Awladthani S, Khawaji A, Clark H, Borhan A, Cheng J, et al. Early exercise in critically ill youth and children, a preliminary evaluation: the wEECYCLE pilot trial. Pediatr Crit Care Med 2017;18:e546-54.

[‡]Vlasselaers D, Milants I, Desmet L, Wouters P, Vanhorebeek I, Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.

[§]Mesotten D, Gielen M, Sterken C, Claessens K, Hermans G, Vlasselaers D, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: A randomized controlled trial. JAMA 2012;308:1641-50.

[‖]Macrae D, Grieve R, Allen E, Sadique Z, Betts H, Morris K, et al. A clinical and economic evaluation of control of hyperglycaemia in paediatric intensive care (CHiP): a randomised controlled trial. Health Technol Assess 2014;18:1-209.

[¶]Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.

[#]Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014;42:1775-87.

goals of enrolment and 1 month follow-up rates exceeding 75%, and documented no adverse effects.[45] Similarly, the VR pilot trial did not find any adverse effects of early mobilisation and reported significantly improved upper limb activity compared to average daily activity.[46] Despite promising early results, the long-term efficacy of early mobilisation remains to be evaluated.

Management of Raised Intracranial Pressure in Children Admitted for Critical Neurological Diagnoses

Raised intracranial pressure (ICP) contributes to secondary brain injury.[47] Optimal management of increased ICP is essential to prevent mortality and morbidities.[48,49] There remains clinical equipoise on the optimal strategy to manage ICP in the PICU.[47,50] One strategy focuses on reduction of ICP ("ICP-targeted therapy"), using controlled hyperventilation, administration of hyperosmotic solutions and barbiturates.[51] Another strategy focuses on optimising cerebral perfusion pressure ("CPP-targeted therapy"), involving pharmacologically-induced increase in CPP to improve cerebral blood flow.[52]

In children with acute central nervous system (CNS) infection, a recent RCT reported the superiority of CPP- to ICP-targeted therapy for management of increased ICP.[53] The trial randomised 110 children with GCS = 8 to CPP-targeted (maintaining CPP = 60mm Hg, using normal saline bolus and vasoactive therapy) or ICP-targeted (maintaining ICP <20mm Hg using osmotherapy while ensuring normal blood pressure). The CPP-targeted group had lower mortality, as well as lower prevalence of hearing deficit and neuro-disability at 90 days after discharge. Because the study only involved patients with CNS infections, its finding may not be generalisable to other groups of patients with impaired cerebral autoregulation, such as TBI.[49]

Till date, there are no RCTs assessing the superiority of either strategy in paediatric TBI. However, available literature reported that survival with good neurological outcomes could be achieved using either strategy, ranging from 54%-60% to 70%-90% at hospital discharge and long-term, respectively.[13,23,35] Considering the high rates of morbidities of TBI survivors, a RCT comparing the 2 strategies would add valuable evidence on the superior strategy in reducing morbidities in these children.

Decompressive craniotomy (DC) is widely utilised as a treatment option for increased ICP, mainly for children with refractory high ICP or low CPP that are unresponsive to maximal medical management.[13,23,35,54] Children treated with DC were reported to have comparable long-term outcomes with children with conservative management, although initially, they have worse clinical profiles.[13,23] In a group of 48 patients with severe TBI (GCS = 8), children needing DC had worse peak ICP and lower CPP compared to those responsive to ICP-targeted medical management; however, they showed comparable neurological functional outcomes as measured by GOS scores at hospital discharge and 6 months follow-up.[13] In a similar study involving 53 children, patients needing DC had no difference in neurological functioning at 12 months compared to the children treated conservatively, who had twofold better GCS scores on presentation.[23]

Current guidelines consider DC as a controversial procedure due to insufficient data.[54,55] Two adult RCTs have reported discouraging results, with DC increasing survival but increasing long-term morbidities.[56,57] However, head injuries in children are known to be different than that in adults due to more compressible skull and brain, vulnerability to brain swelling, and different pathophysiology of intracranial hypertension.[23] Given the widespread use of this strategy, there is an urgent need for a RCT to assess the efficacy of DC in the paediatric population.

Tight Glycaemic Control

Hyperglycaemia in PICU patients is associated with adverse short-term outcomes such as organ failure and mortality.[58,59] RCTs evaluating the benefit of intensive insulin therapy for management of hyperglycaemia in PICU patients have yielded mixed results.

A Belgian RCT involving 700 children (majority were cardiac surgical patients) showed that tight glucose control (TGC) to age-adjusted normoglycaemia reduced PICU mortality, length of stay (LOS) and improved long-term motor coordination and cognitive flexibility compared to standard care.[11,60] On the other hand, a United Kingdom (UK) trial involving 1369 children showed no overall mortality or LOS benefit.[61]

TGC carries significant risk of hypoglycaemia.[60-62] In children undergoing cardiac surgery, patients with hypoglycaemic episodes had almost 5 times the mortality of patients without hypoglycaemia.[61] While a long-term follow-up study on the survivors from the Belgian RCT reported that TGC did not affect IQ scores at 4 years, symptomatic hypoglycaemia in young children has previously been reported to be associated with various patterns of brain injury and as well as neurodevelopmental impairments at 18 months.[11,63]

These data suggest that while TGC for hyperglycaemia might benefit some PICU patients, it must be carefully weighed against the risks of hypoglycaemia. Further research is needed to identify the subset of patients for whom the benefits of TGC exceed the risks of hypoglycaemia. The long-term analysis of the UK trial reported that in non-cardiac surgery patients, TGC was associated with shorter hospital stay and reduced healthcare costs at 12 months, highlighting a potential group to be investigated.[61]

Nutritional Intervention in the PICU

Nutrition delivery in PICU is generally inadequate, which may adversely impact clinical outcomes.[64-66] The Paediatric Early versus Late Parenteral Nutrition In Critical Illness (PEPaNIC) RCT explored whether early achievement of nutrition goals using parenteral nutrition (PN) would be associated with better outcomes. A total of 1440 critically ill children were randomised to receive early (within the first day) or late (after day 7 of PICU stay) supplemental PN when enteral nutrition (EN) failed to reach the prescribed caloric targets. Late PN was associated with lower rate of new infections, shorter duration of mechanical ventilation, and shorter PICU and hospital LOS.[67] Of note, the long-term developmental and neurocognitive outcomes of these patients are yet to be published.

Although some aspects of this trial have been controversial, this study highlights the gaps in our knowledge regarding nutrition provision in the PICU.[68,69] The impact of different aspects of nutrition provision (e.g., nutrition route, composition and targets) on functional outcomes of critically ill children deserves further study.

Interventions to Enhance Recovery Posthospital Discharge

The post-ICU phase is regarded as an important time period for rehabilitation.[70] However, there is paucity of research evaluating interventions posthospital discharge that might improve long-term outcomes in survivors of paediatric critical illness.

In adult ICU survivors, enrolling patients in structured programmes that provided physical and nutritional rehabilitation posthospital discharge were shown to improve long-term cognitive, psychological, physical, and functional outcomes.[41,71,72] Unfortunately, there is little reported experience on the role of structured rehabilitation programmes, particularly those combining nutrition and physical interventions, in PICU survivors posthospital discharge.

In PICU survivors, removing environmental barriers to increase child's participation at home and modifying family environment improve recovery.[27,73,74] A significant proportion of parents of PICU survivors reported that environmental factors (e.g., physical layout of the home and services available in the home) hindered the child's participation at home (e.g., school preparation, personal care and household chores).[27] This hindrance was more prevalent in children with underlying functional limitation (33%) compared to previously normal children (20%). While intervention to modify home environment is commonly practised to enhance functional independence in adults with acquired morbidities, there is paucity of research on this topic in the paediatric population.[75,76]

Family environment plays a role in long-term psychosocial outcomes of preschool children sustaining TBI. Better family functioning and parent mental health was associated with better behavioural adjustment and social functioning.[73,74] Some parenting styles were also shown to be more conducive for recovery, as authoritative (as opposed to permissive) parenting style predicted better social competence at 18 months post-TBI.[73] Future research should identify effective ways to equip not only the children, but also their caregivers, in order to create favourable family environment for recovery.

Conclusion

With improved PICU mortality rates, an emerging issue is the increasing prevalence of acquired morbidities in the survivors. In this review, we summarised the literature on trajectories and risk factors for long-term morbidity, described the current limitations of morbidity research, and discussed recent advances in improving long-term outcomes of PICU survivors. Most of the known morbidity risk factors are non-modifiable in nature, and hence improvements in our current methodologies of morbidity research are needed to elucidate modifiable risk factors of morbidity. Future research is needed for early identification of patients who are likely to develop long-term morbidities and development of effective strategies to reduce long-term morbidities of PICU survivors.

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Online Supplementary Table 1. Observational Studies in PICU Patients

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Fiser et al, 2000*	n = 11,106 All consecutive admissions to 16 general PICUs Mean age range = 53.8 – 86.9 months	POPC, PCPC, compared to baseline (premorbid) scores	PICU discharge	PCPC/POPC Normal: 58.4%/27.4% Mild disability: 17.2%/34.9% Moderate disability: 11.6%/19.9% Severe disability: 7.2%/12.2% Coma/vegetative: 1%/1% Brain death: 4.6%/4.6%	• Baseline, discharge, and delta POPC and PCPC outcome scores were associated with length of stay in the PICU and with predicted risk of mortality (PRISM score)

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

*Fiser DH, Tilford JM, Roberson PK. Relationship of illness severity and length of stay to functional outcomes in the pediatric intensive care unit: a multi-institutional study. Crit Care Med 2000;28:1173-9.

†Knoester H, Bronner MB, Bos AP, Grootenhuis MA. Quality of life in children three and nine months after discharge from a paediatric intensive care unit: a prospective cohort study. Health Qual Life Outcomes 2008;6:21.

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¶Pollack MM, Holubkov R, Funai T, Berger JT, Clark AE, Meert K, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. Crit Care Med 2015;43:1699-709.

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‡‡‡‡Abu-Kishk I, Polakow-Farkash S, Elizur A. Long-term outcome after pediatric intensive care unit asthma admissions. Allergy Asthma Proc 2016;37:169-75.

§§§§Only children ≥1 month were included for this review, since after 1982, a separate neonatal ICU was established at the hospital.

Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Knoester et al, 2008[†]	n = 81 Previously healthy general PICU admission Age, median (range): 5.8 (1 – 14.9) years	Based on age (years): 1 – 5: TAPQOL-PF 6 – 11: TACQOL-PF 8 – 11: TACQOL-CF for children 12 – 15: TACQOL-CF for adolescents	3 months and 9 months postdischarge	Based on age groups, compared to normative population 1 – 6 years: more lung problems (3 and 9 months), worse problem behaviour (3 months) and worse liveliness (9 months) 6 – 12 years: worse motor functioning (3 months) 12 – 15 years: worse motor functioning (3 months)	NA

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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General PICU Patients					
Namachivayam et al, 2010‡	General PICU over 3 decades§§§§ Year: n; median age 1982: n = 700; 34 months 1995: n = 882; 31 months 2005 – 2006: n = 1733, 36 months	MGOS compared to preadmission scores, quality of life: HSUV	Median (range) in years: 1982: 2.7 (2.5 – 3.0) 1995: 3.5 (2.5 – 6.0) '05-'06: 1.1 (0.5 – 2.9)	Mortality: 1982: 14.3% 1995: 12.0% – 14.5% '05-'06: 5.4% – 13.1% Moderate-severe disability (preadmission, follow-up): 1982: 12%, 8.4% 1995: 13.9%, 9.3% '05-'06: 14.6%, 17.9% Good quality of life (HSUV 1.00 – 0.70) 1995: 84% '05-'06: 66%	NA

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Polic et al, 2013[§]	n = 189 General PICU, with or without pre-existing chronic health condition (CHC) Median (range) age Without CHC: 15.5 (10,18) years With CHC: 15.3 (10,17.6) years	RAHC MOF compared with baseline (preadmission) scores	6 months and 24 months after PICU discharge	RAHC MOF decreased compared to preadmission scores in 26% of PICU survivors at 6 months, 19% in 24 months	• Higher PIM2 score correlated with worsening of RAHC MOF at 6 months, but not 24 months. • Pre-existing neurodevelopmental disability, chronic health conditions correlated with worse RAHC MOF scores

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General PICU Patients					
Pollack et al, 2014[l]	n = 5017 Randomly selected prospective cohort from 8 medical and cardiac PICUs Median (IQR) age 3.7 (0.8, 10.9) years	Mortality FSS: 6 – 7: good, 8 – 9: mildly abnormal, 10 – 15: moderately abnormal, 16 – 21: severely abnormal, >21: very severely abnormal Acquired morbidity: defined as increase of ≥3 in FSS compared with baseline (preadmission) scores	Baseline (preadmission), PICU discharge, hospital discharge	Of the 5017 patients, there were 242 new morbidities (4.8%), 99 PICU deaths (2.0%) and 120 (cumulative) hospital deaths (2.4%) The worst functional status profile was on PICU discharge and improved on hospital discharge	• Admission diagnoses: Highest new morbidity rates were in the neurological diagnoses (7.3%), acquired cardiovascular disease (5.9%), cancer (5.3%) and congenital cardiovascular disease (4.9%) • Operative category: Highest new morbidity in non-operative patients (5.7%) and general surgery patients (5.7%) followed by cardiac surgery (4.5%) • Age: younger age had increased rates of acquired morbidity

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
General PICU Patients					
Pollack et al, 2015¶	n = 10,078 General and cardiac/ cardiovascular PICUs from 7 sites Median (IQR) age 3.7 (0.8 –10.8) years	Mortality, FSS, acquired morbidity: FSS increase of ≥3 compared to baseline (premorbid)	Hospital discharge	Acquired morbidity: 4.6%; mortality: 2.7%	• Dichotomous model: increasing PRISM III scores were associated with increasing acquired morbidity and mortality risks • Trichotomous model: acquired morbidity risk initially increased with higher PRISM III scores, but further decreased among children with the highest risks of mortality
Pinto et al, 2017#	n = 77 (6 months follow-up) n =70 (3 years follow-up) General PICU Median (IQR) age 8.60 (2.10 – 11.90) years	Mortality, acquired morbidity: FSS increase of ≥3 compared to baseline (premorbid)	Baseline (preadmission), hospital discharge, 6 months, 3 years after hospital discharge	6 months: Mortality 7.8% Acquired morbidity 6.5% 3 years: Mortality 10.4% Acquired morbidity 10.4%	• Longer PICU length of stay and number of ventilation days correlated with worsening of FSS over time. All the above and vasoactive medications correlated with acquired morbidity or death

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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PICU Long Stayers					
Namachivayam et al, 2012[**]	n = 233 PICU long-stayers (>28 days) Median age 4.2 (IQR 0.38 – 41.5) months	Mortality, functional status: MGOS, quality of Life: HUI1	Median of 4 years (IQR 1.4 – 7.6) after discharge from PICU	Functional outcome of survivors: 13.3% normal 15.4% mild disability 8.4% moderate disability 13.3% severe disability 49.6% death QoL of survivors aged >2 years: 21% good 8% moderate 6% poor 68% very poor	NA

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
PICU Long Stayers					
Kirk et al, 2017[††]	n = 241 PICU long stayers (≥14 days) Median (IQR) age 1.37 (0.27 – 6.35) years	Mortality	PICU discharge, hospital discharge	General PICU: Overall PICU deaths: 3.9% Long stayers: PICU mortality: 20% Cumulative hospital mortality: 22%	NA

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Cardiac Arrest Patients					
Del Castillo et al, 2014‡‡	n = 250 Multicentre study of in-PICU cardiac arrest (CA) Age 47.9 ± 61.9 months (range: 1 month – 18 years)	Neurological outcome: PCPC, compared with prearrest scores: stratified into: (good: PCPC 1 – 2; poor: PCPC 3 – 6)	Hospital discharge, 1 year	Neurological outcome of survivors: 81.5% good 18.5% poor	NA

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Cardiac Arrest Patients					
van Zellem et al, 2015[§§]	n = 57 PICU population who sustained cardiac arrest Median (range) age at follow-up: 8.7 (2.4 – 18.3) years	Health status: medical interview, physical examination, and HUI3, HUI2; health-related quality of life: (0 – 3 years: CHQ-IT97; 4 –17 years: CHQ-PF50; 12 – 17 years: CHQ-CF87)	Median 5.6 years (range 1.8 – 11.9 years)	Long-term mortality of survivors: 9% Health status: 13% neurologic impairment 19% had 1 symptom suggestive of CKD 30% need rehabilitation 34% reported chronic symptoms (fatigue, headache, abdominal pain) 21% needed professional assistance for behaviour problem HUI2, HUI3 lower than normative data HR-QoL: Parent reported: lower on role functioning, general health perceptions, parental impact, and overall physical summary compared to normative data Self-reported: no difference from normative data	• On the CHQ-PF50, cardiac arrest-related pre-existing condition was associated with worse patients' general health perception

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Cardiac Arrest Patients					
Slomine et al, 2017[ll]	n = 59 Out of hospital cardiac arrest (OHCA) patients, and who were admitted to a PICU and remained comatose within 6 hours of return of circulation (ROC), with premorbid VABS-II scores ≥70, original RCT arms (69) : hypothermia (target temperature - 33°C) vs normothermia (target temperature - 36.8°C) Mean (SD) age: Drowning group: 4.6 (4.16) years Other aetiologies: 5.1 (5.41) years	Neurobehavioural outcomes: VABS-II; cognitive performance measures (Mullen Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence); comparison made between drowning and other aetiologies of cardiac arrest	1 year	VABS-II composite and domain scores declined significantly from premorbid scores in drowning and non-drowning groups, although declines were less pronounced for the drowning group. Decline in composite scores, communication domain and motor functioning is less pronounced in drowning group. 72% of children had well below average cognitive functioning at 1-year	• Younger age, fewer doses of epinephrine, and drowning aetiology were associated with better VABS-II composite scores at 1 year follow-up

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Cardiac Surgery Patients					
Moga et al, 2011[¶]	n = 772 Patients undergoing cardiac surgery with cardiopulmonary bypass in a paediatric cardiac critical unit Median (range) age: No hyperglycaemia: 0.69 (0.02 – 14.5) Hyperglycaemia: 0.69 (0.02 – 14.5)	Composite morbidity-mortality outcome: hospital death, cardiac arrest, renal/ hepatic failure, lactic acidosis, ECMO use, or infection	PCCU discharge	31% reached composite morbidity-mortality endpoint	• There was a dose-response relationship between hyperglycaemia and odds of reaching composite morbidity-mortality endpoint. Neonates (<1 month of age) tolerated longer periods of hyperglycaemia before showing increased odds of reaching the composite morbidity-mortality endpoint. In the setting of important residual cardiac lesions, mild or moderate hyperglycaemia was not as strongly associated with adverse outcomes

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Neurological Diagnosis Patients – Non-Traumatic Brain Injury					
Wagenman et al, 2014[##]	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median (IQR) age: 3.9 (1.1, 12.7) years Subjects assessed in 3 groups: no seizure, electrographic seizure (ES), electrographic status epilepticus (ESE)	GOS-E; PedsQL proxy report and epilepsy questionnaire; GOS-E scores categorised as favourable (upper good recovery to lower moderate disability) or unfavourable (upper severe disability to vegetative state)	Median 2.7 (IQR 1.5, 3.2) years	Overall GOS-E scores: 64% favourable, 36% unfavourable Subjects with: favourable GOS-E: 64% no seizure, 23% ES, 13% ESE unfavourable GOS-E: 43% no seizure, 14% ES, 43% ESE ES: 23% favourable PedsQL, median (IQR) scores: without seizures: 86 (64, 95) ES: 94 (60, 97) ESE: 62 (48, 71)	• ESE but not ES was associated with unfavourable GOS-E, lower PedsQL scores, and higher rates of subsequently diagnosed epilepsy at follow-up

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Neurological Diagnosis Patients – Non-Traumatic Brain Injury					
Abend et al, 2015[***]	n = 60 Previously neurodevelopmentally normal children with an acute neurologic condition and altered mental status who underwent cEEG Median age (IQR): ABAS-2: 4.1 (2.0, 9.8) years CBCL:3.8 (1.3, 8.8) years BRIEF: 10.6 (6.7, 15.4) years Subjects assessed in 3 groups: no seizure, electrographic seizure (ES), electrographic status epilepticus (ESE)	Adaptive behaviour: ABAS-II; behavioural and emotional problems: CBCL; executive function: BRIEF	Median 2.6 years (IQR 1.2 – 3.8)	ABAS: median (IQR) scores - no seizures: 105 (100, 118) - ES: 92 (47, 106) - ESE: 73 (48, 102) CBCL: Median (IQR) scores - no seizures: 43 (37, 54) - ES: 37 (34, 52) - ESE: 61 (34, 65) BRIEF: Median (IQR scores) - no seizures: 54 (42, 63) - ES: 57 (46, 65) - ESE: 73 (59, 79)	• ES and ESE were associated with worse adaptive behavioural global composite scores

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Online Supplementary Table 1. Observational Studies in PICU Patients (Cont'd)

Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Neurological Diagnosis Patients – Non-Traumatic Brain Injury					
Lin et al, 2017[†††]	n = 35 Febrile refractory status epilepticus patients admitted to PICU, with no history of underlying neurological disorders and prior seizures Comparison of therapeutic burst-suppression coma vs continuous administration of intravenous antiepileptic drugs Mean age 9.58 ± 4.05 years	GOS: ≥4: good outcome ≤3: bad outcome Seizure outcomes: 1) intractable epilepsy 2) favourable outcome 3) successful withdrawal from antiepileptic drug treatment	Baseline, 1 month, 6 months	6 months: Cumulative mortality: 40% Neurological functional outcomes good in 27.3% survivors, 2 returned to clinical baseline	

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Neurological Diagnosis – Traumatic Brain Injury					
Grinkevièiûtë et al, 2008[‡‡‡]	n = 48 PICU patients with severe head injury (postresuscitation GCS ≤8) and treated according to intracranial pressure (ICP)-targeted protocol of severe head trauma management Mean age 10.6 ± 5.2 years	GOS 4 – 5: Favourable outcome 1 – 3: Unfavourable outcome	Hospital discharge, 6 months	Hospital discharge GOS: 19/48 unfavourable 29/48 favourable 6 months: Mortality 2.1% GOS: 5/48 unfavourable 43/48 favourable	• The difference in outcomes between patients with and without decompressive craniectomy was not significant, although the former had higher ICP and lower CPP

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Neurological Diagnosis – Traumatic Brain Injury					
Salorio et al, 2008[§§§]	n = 57 Survivors of paediatric moderate and severe TBI (GCS 3 – 12) admitted for rehabilitation Mean age 10.8 +/- 3.2 years	Cognitive outcome: performance IQ (PIQ, Wechsler Intelligence Scale for Children). Overall functional outcome: DRS	1 year postinjury	NA	• Higher initial GCS score was associated with higher PIQ 1 year postinjury. Episodes of hypotension during the first day after injury were associated with worse cognitive outcome at 1 year. Hypertension within the first 24 hours was associated with worse DRS at 1 year

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Neurological Diagnosis – Traumatic Brain Injury					
Tepas et al, 2009[lll]	n = 60 Patients with severe blunt TBI (initial GCS score ≤8) that required resuscitation, critical care, and inpatient rehabilitation Mean age: male 11.2 years, females, 10.6 years	Functional independence measurement (FIM) score Rehabilitation efficiency (RE): ratio of FIM improvement to length of stay for inpatient rehabilitation	Not specified	NA	• Delayed inpatient rehab was associated with reduced rehabilitation efficiency and reduced improvements in FIM scores • Children with higher GCS score (6 – 8) exhibited a stronger negative correlation between RE and delay than children with GCS 3 – 5

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Neurological Diagnosis – Traumatic Brain Injury					
Kapapa et al, 2010¶¶¶	n = 48 Children who sustained head trauma requiring intensive care, who received cerebral perfusion pressure (CPP)-oriented management Mean age 5.9 years (range 19 days – 14.5 years)	Functional outcome: GOS; quality of life: Short Form 36 Health-related Quality of Life survey; health status: Visual Analogue Scale; others (unstructured questionnaire): physical sequelae, impairments in daily life, neuropsychological abilities, psychosocial characteristics, performance in school	Average 2.1 years	PICU discharge: 20.8% died, 8.3% GOS 2, 16.7% GOS 3, 10.4% GOS 4, 43.8% GOS 5 Long-term: 17 patients who were admitted in poor condition, 6 had persistent paresis or plegia, 5 had paresis of the cranial nerves, 2 were incontinent, 4 had sensory disorders, 7 had coordination disorders, and 5 had speech disorders. In 7 children who were admitted in good condition, 3 had hyperesthesia and 1 had a speech disorder Health status improved during the interval between 1 year after the trauma and the time of completing the questionnaire	• Elevated blood levels of glutamic-oxaloacetic-transaminase on the day of admission, elevated blood urea and glucose on the first 2 days, at least single occurrences of cerebral perfusion pressure values below the recommended standard, or mean arterial pressure and central venous pressure below the lower limits correlated with worse functional outcomes

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Thomale et al, 2010[###]	n = 53 Neurosurgically-treated patients with diagnosis of severe TBI (GCS <9), who had either additional decompressive craniectomy or conservative Intracranial pressure (ICP) management without craniectomy Median age: Craniectomy: 12 years Conservative: 7 years	GOS: (GOS 4 – 5: favourable outcome, GOS 1 – 3: unfavourable outcome)	Hospital discharge, 1 year, long-term (mean 5.2 ± 2.4 years)	Hospital mortality: 11% 1 year: 86% favourable outcome in survivors; no difference in the craniectomy vs conservative group Long-term: 73% favourable outcome 7% GOS 3 20% died due to uncontrollable ICP	• Anisocoria on admission, aSO2 <90% on admission correlated with unfavourable GOS outcomes • Though initial GCS was worse in paediatric TBI patients who underwent decompressive craniectomy compared to the conservatively treated patients, long-term outcome was comparable

ABAS-II: Adaptive Behaviour Assessment System-II; BRIEF: Behaviour Rating Inventory of Executive Function; CBCL: Child Behaviour Checklist; cEEG: Continuous electroencephalography; CF: Child Form; CF87: Child Form 87; CHQ: Child Health Questionnaire; CPP: Cerebal perfusion pressure; DRS: Disability Rating Scale; ECMO: Extracorporeal membrane oxygenation; EPCR: Extracorporeal cardiopulmonary resuscitation; FIM: Functional independence measurement; FSS: Functional Status Score; GCS: Glasgow Coma Score; GINA: Global Initiative for Asthma; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (Extended Paediatric Version); HSUV: Health Status Utility Index; HUI: Health Utility Index; ICP: Intracranial pressure; IQR: Inter quartile range; IT97: Infant Toddler 97; MGOS: Modified Glasgow Outcome Scale; PF: Parent Form; PICU: Paediatric intensive care unit; PCCU: Paediatric cardiac critical unit; PCPC: Paediatric Cerebral Performance Category; PedsQL: Paediatric Quality of Life Inventory; PF50: Parent Form 50; PIM: Paediatric Index of Mortality; PIQ: Performance Intelligence Quotient; POPC: Paediatric Overall Performance Category; PRISM: Paediatric risk of mortality; RAHC MOF: Royal Alexandra Hospital for Children Measure of Function; RE: Rehabilitation efficiency; SD: Standard deviation; TAPQOL-TNO-AZL: Preschool Children Quality of Life Questionnaire; TBI: Traumatic brain injury; THAPCA-OH: Therapeutic hypothermia after paediatric cardiac arrest out-of-hospital; VABS-II: Vineland Adaptive Behaviour Scale-II; VAS: Visual Analogue Scale

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Neurological Diagnosis – Traumatic Brain Injury					
Fulkerson et al, 2015[****]	n = 67 Paediatric head injury patients presented to neurosurgical service at a single centre with: GCS 3 (age 49.8 +/- 51.8 months) or GCS 4 (age 66.9 +/- 58.0 months	Mortality, mGOS: (5, good recovery with minor cognitive or neurological problems, 4, disabled neurologically or cognitively 3, severely disabled, possibly requiring institutional care 2, vegetative survival 1, death)	Hospital discharge, 1 year, long-term (mean 11.04 ± 6.1 years)	1 year mGOS: 11.9% normal 3.0% GOS 5 6% GOS 4 10.4% GOS 3 4.5% GOS 2 56.7% GOS1 Long-term: 95.5% had the same GOS score as 1 year	• Impaired pupillary response, hypothermia, and mechanism of injury (abuse) correlated with death or disability

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Study Reference	Population Characteristics	Outcome Measures Used	Follow-up Time(s)	Outcomes	Risk Factors for Morbidities
Other Specific Populations					
Ebrahim et al, 2013††††	n = 91; 65 completed 1 month assessment Urgently admitted (<12 hours notice) patients from inpatient ward, or had an ICU cardiac arrest and/or received extracorporeal membrane oxygenation (ECMO) treatment irrespective of the urgency of their ICU admission Mean age: 76.4 ± 69.3 months, range 1 month to 18 years	Adaptive behaviour: VABS-II; functional outcomes: PCPC and POPC; quality of life: PedsQL and VAS	1 month postadmission 24 hours (baseline), 1 month postadmission 24 hours (baseline), 1 week, 1 month postadmission	VABS-II (1 month), mean (SD) 83.2 (± 24.8) compared to a population mean (SD) of 100 (±15); mean PedsQL (1 month) was 52.8 ± 27.9; from baseline to 1 month, PCPC did not significantly change, while POPC significantly improved VAS significantly worsened from baseline to 1 week, and significantly improved from 1 week to 1 month	• Worse adaptive behaviour was correlated with circulatory diagnosis, worse initial PCPC score, worse transcutaneous oxygen saturation, and longer cardiac compression • Worse HRQoL correlated with worse initial PCPC, longer ICU stay, and longer duration of ECMO • Worse functional outcome correlated with the same factors as HRQoL, plus neurological diagnosis

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Other Specific Populations					
Abu-Kishk et al, 2016‡‡‡‡	n = 47 PICU patients admitted due to acute asthma exacerbation Median (IQR) age 6 (4 –11) years	Questionnaire on subsequent hospitalisations and current asthma treatment and control (GINA guidelines), pulmonary function studies, allergy skin tests	Mean 10 years after PICU admission	Compared with controls admitted to paediatric ward: PICU survivors had more hospitalisation and ICU admissions after their index admission, more recent asthma exacerbations, weekly wheezing, and bronchodilator use. Lung function tests were comparable between the 2 groups	NA

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§§§§Only children ≥1 month were included for this review, since after 1982, a separate neonatal ICU was established at the hospital.

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Author	Population Clearly Defined	Outcome Clearly Defined	Baseline Function Measured or Control Group Included (for Long-Term Outcome)*	Selection Bias Excluded†	Selective Loss to Follow-up Excluded‡
Fiser et al, 2000§	Yes	Yes	Yes	Yes	NA
Grinkevièiûtë et al, 2008ǀ	Yes	Yes	No	Yes	Yes
Knoester et al, 2008¶	Yes	Yes	Yes	No	No
Salorio et al, 2008#	Yes	Yes	No	No	NA

NA: Not applicable

*Study measured baseline status/scores of the children. Alternatively, study included controls in the form of normative population or matched children from non-PICU sources (eg. outpatient clinic).

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Tepas et al, 2009[**]	Yes	Yes	No	Yes	Yes
Vlasselaers et al, 2009[††]	Yes	Yes	NA	Yes	NA
Namachivayam et al, 2010[‡‡]	Yes	Yes	Yes	Yes	Yes
Kapapa et al, 2010[§§]	Yes	No	No	Yes	No

NA: Not applicable

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Moga et al, 2011¶	Yes	Yes	NA	Yes	NA
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Author	Population Clearly Defined	Outcome Clearly Defined	Baseline Function Measured or Control Group Included (for Long-Term Outcome)*	Selection Bias Excluded†	Selective Loss to Follow-up Excluded‡
Abdulsatar et al, 2013†††	Yes	Yes	NA	No	NA
Ebrahim et al, 2013‡‡‡	Yes	Yes	No	No	Yes
Polic et al, 2013§§§	Yes	Yes	Yes	Yes	No
Del Castillo et al 2014‖‖	Yes	Yes	No	No	No

NA: Not applicable

*Study measured baseline status/scores of the children. Alternatively, study included controls in the form of normative population or matched children from non-PICU sources (eg. outpatient clinic).

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Macrae et al, 2014¶¶	Yes	Yes	No	No	No
Kumar et al, 2014###	Yes	Yes	No	Yes	No
Pollack et al, 2014****	Yes	Yes	Yes	Yes	NA
Wagenman et al, 2014††††	Yes	Yes	No	Yes	Yes

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Abend et al, 2015‡‡‡‡	Yes	Yes	No	Yes	Yes
Fulkerson et al, 2015§§§§	Yes	Yes	No	Yes	No
Pollack et al, 2015¶¶¶¶	Yes	Yes	Yes	Yes	NA
van Zellem et al, 2015¶¶¶¶	Yes	Yes	Yes	No	NA

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Abu-Kishk et al, 2016[####]	Yes	Yes	Yes	No	NA
Fivez et al, 2016[*****]	Yes	Yes	NA	n/a	NA
Moler et al, 2016[†††††]	Yes	Yes	No	Yes	No
Choong et al, 2017[‡‡‡‡‡]	Yes	Yes	NA	Yes	NA

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Online Supplementary Table 2. Quality Assessment of the Included Studies (Cont'd)

Author	Population Clearly Defined	Outcome Clearly Defined	Baseline Function Measured or Control Group Included (for Long-Term Outcome)*	Selection Bias Excluded†	Selective Loss to Follow-up Excluded‡
Lin et al, 2017§§§§§	Yes	Yes	No	Yes	No
Kirk et al, 2017ǁǁǁǁ	Yes	Yes	NA	Yes	NA
Pinto et al, 2017¶¶¶¶¶	Yes	Yes	Yes	No	No
Slomine et al, 2017#####	Yes	Yes	Yes	Yes	No

NA: Not applicable

*Study measured baseline status/scores of the children. Alternatively, study included controls in the form of normative population or matched children from non-PICU sources (eg. outpatient clinic).

†Study did not exclude of >10% of studied/eligible population.

‡Study explained the characteristics of patients lost to follow-up compared to those remaining in the study, or did statistical modelling to account for loss to follow-up.

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