Outcomes Following Admission to Paediatric Intensive Care: A Systematic Review

Dr Claire Procter

PRCCLA006

SUBMITTED IN FULFILMENT OF THE

REQUIREMENTS FOR THE DEGREE

Masters of Philosophy - PAEDIATRIC CRITICAL CARE

FACULTY OF HEALTH SCIENCES AT THE UNIVERSITY OF CAPE

TOWN

Submitted on [07/02/2020]

Supervisors: Prof. Andrew Argent; Prof. Brenda Morrow

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Copyright statement

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Acknowledgements:

- The staff and children of the Paediatric Intensive Care Unit, Red Cross Children's Hospital, Cape Town.
- The library staff of the University of Cape Town
- No funding was obtained for this project.

Abbreviations

PICU = Paediatric Intensive Care Unit
RCWMCH = Red Cross War Memorial Children's Hospital
PIM = Paediatric Index of Mortality score
SMR = Standardised Mortality Ratio
USA = United States of America
RR = Risk Ratio
SEM = Standard Error of the Mean
SD = Standard Deviation
OR = Odds Ratio
CI = Confidence Interval
RD = Risk Difference
NNTB = Number Needed to Treat for an additional Beneficial outcome
NNTH = Number Needed to Treat for an additional Harmful outcome
PRISMA = Preferred Reporting Item for Systematic Reviews and Meta-Analyses
PRISM = Paediatric Risk of Mortality score
PELOD = Paediatric Logistic Organ Dysfunction score
NICU = Neonatal Intensive Care Unit
PCPC = Paediatric Cerebral Performance Category
POPC = Paediatric Overall Performance Category
UK = United Kingdom
IQ = Intelligence Quotient
RCT = Randomised Controlled Trial
LOS = Length of Stay
FSS = Functional Status Scale
RRT = Renal Replacement Therapy
CPR = Cardiopulmonary Resuscitation
ECMO = Extracorporeal Membrane Oxygenation
PTSD = Post Traumatic Stress Disorder
TBI = Traumatic Brain Injury
NAI = Non-Accidental Injury
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
IES = Impact of Events Score
TISS = Therapeutic Interventions Scoring System
PSS = Parental Stressor Scale
CANTAB = Cambridge Neuropsychological Test Automated Battery
CAPS-C = Clinician Administered PTSD Scale for Children
QOL = Quality of Life
HUI = Health Utilities Index
VAS = Visual Analogue Scale
ASD = Acute Stress Disorder

Title Page

Title: Outcomes Following Admission to Paediatric Intensive Care: A Systematic Review

Type of Article: Systematic review

Investigators: *Claire Procter*[1], *Brenda Morrow*[2], *Genee Pienaar*[3], *Mary Shelton*[4], *Andrew Argent*[1]

[1]Pediatric Intensive Care, Division of Pediatric Critical Care and Children's Heart Disease, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa

[2] Department of Paediatrics, University of Cape Town, Cape Town, South Africa

[3] Western Cape Department of Health, Cape Town, South Africa

[4] Reference Librarian, University of Cape Town, Cape Town, South Africa

Corresponding author:

Claire Procter, 17 Planet Africa, Kei Apple Road, Cape Town, 8005

South Africa

E-mail: clairemprocter@gmail.com

Phone: +27720717864 or +447788906

Abstract

Introduction

Paediatric Intensive Care has developed rapidly in recent years with a dramatic increase in survival rates. However, there are increasing concerns regarding the impact that admission to a Paediatric Intensive Care Unit (PICU) has on both the child and their family. Following discharge from PICU, children may be living with complex medical problems as well as dealing with the psychosocial impact that their illness has had on them and their family.

Objectives

To describe the long-term health outcomes of children admitted to a paediatric intensive care unit (PICU).

Methods

A full literature search was conducted including the databases; MEDLINE via PubMed, Cochrane Central Register of Controlled Trials, (CENTRAL), Scopus, Web of Science, CINAHL, ERIC, Health Source Nursing/Academic, APA PsycInfo. All studies including children under 18 admitted to a PICU were included. Primary outcome was short- and longer-term mortality. Secondary outcomes were neurodevelopment/cognition/school performance; physical function, psychological function/behaviour impact, quality of life outcomes and social/family implications. Studies focused on Neonatal Intensive Care Admission and articles with no English translation were excluded.

Results

One hundred and five articles were included in the analysis. Mortality in PICU ranged from 1.3% to 50%. Mortality in high income countries reduced over time but the data did not show the same trend for low- and middle-income countries. Higher income countries were found to have lower Standardised Mortality Rates (SMRs) than low- and middle-income countries. Children had an ongoing risk of death for up to 10 years following PICU admission. Children admitted to PICU also have more ongoing morbidity than their healthy counterparts with more cognitive/developmental problems, more functional health issues, poorer quality of life

as well as increased psychological problems. Their parents also have an increased risk of Post Traumatic Stress Disorder (PTSD).

Discussion

Most of the studies identified are from high income countries and only include short-term follow up. More data is needed from low- and middle-income countries and over longer terms. The studies were markedly heterogenous and were all observational. Agreement is needed regarding which outcomes are most important to measure as well as standardised methods of assessing them. Further research is needed to identify the risk factors which cause children to have poorer outcomes as well as to identify predictive and modifiable factors which could be targeted in practice improvement initiatives.

Key Words:

Child, Children, Paediatric, Critical Care, Intensive Care, PICU, Outcomes

Submission-ready manuscript

Author Guidelines

This paper has been formatted for the Journal of Paediatric and Child Health. Author guidelines may be found in Appendix B.

Introduction

Paediatric intensive care has developed dramatically in recent years with substantial reductions in mortality rates. In the United States of America (USA), mortality rates have fallen from more than 10% in the 1980s to approximately 1.4% in 2014[1]. In South Africa, the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town admits approximately 1300-1400 patients per year to the Paediatric Intensive Care Unit (PICU). The mortality during PICU admission was 6.5% in 2017. This has reduced from 13% in 2000 and 11% in 2006. When adjusted for severity of illness using the Paediatric Index of Mortality (PIM) score these outcomes are similar to those seen in higher income countries; Standardised Mortality Ratio (SMR) 1.1 in 2000, 0.9 in 2006 and 1.19 in 2017[2,3]. However, recent literature has suggested that with reduced mortality comes the risk of increased morbidity rates. Instead of dying, children may survive their admission to PICU but with complex chronic, medical problems[4,5]. Children discharged from PICU may have multiple problems in terms of their physical health, quality of life, neurodevelopment or school performance and there may be significant psychosocial effects on them and their families[6]. These problems may be as a result of the illness that required them to be admitted to PICU, due to their underlying chronic condition or a result of the interventions they received in PICU. Increased childhood survival following complex disorders also means that children being admitted to PICU have increasingly complex morbidities prior to admission[6]. At RCWMCH there is currently no routine system for following up children who are discharged from PICU and we do not know what problems they face in the long term as a result of their admission.

A recently introduced concept is "post-hospital syndrome", referring to a period following discharge from hospital when people are particularly vulnerable to increased morbidity and

mortality[7]. Although this term was first used for adults there is evidence that it also applies to children, particularly those from low and middle income countries[8]. Others have referred specifically to a "post intensive care syndrome" where the focus is specifically on long-term outcome after being in intensive care. This may be significantly worse than for those admitted to general wards due to their increased illness severity and increased interventions[9]. Multiple factors including deranged physiology, poor nutrition and medication side effects as well as a background of acute and chronic diseases increase the risk of further mortality and morbidity following an admission to hospital[9]. This is likely to be worse if a child required PICU admission with a high severity of illness. The home and family circumstances must also be considered and ameliorated, as these factors may contribute to, or exacerbate, the presenting illness as well as impacting on post-discharge outcome. The length of this post-admission vulnerable period will be very variable depending on the child and the illness. Very few studies or guidelines cover this period so it is not known what interventions should be implemented in order to reduce morbidity and mortality in this high risk period[8].

Admitting a child to PICU requires substantial resources. In resource limited settings, difficult decisions often need to be made regarding the admission of specific children to PICU. RCWMCH has clearly defined admission criteria, which have been negotiated with clinicians and the provincial health authorities to optimize the use of scarce resources for those who are likely to benefit the most[10]. However, these criteria were based primarily on short-term mortality in PICU. The "outcomes movement" or the "third revolution in medical care" argues that the benefits of increased survival should not come at the expense of significantly impaired quality of life[11]. As we understand the effectiveness of different interventions, we should use this information to make better decisions and develop standards to guide providers in optimizing resource utilization[12]. A review of the long-term outcomes of PICU may help ensure that resources are offered to those who will benefit the most and that we optimise the use of those resources to minimise the long-term risks.

There have been no previous comprehensive reviews of all the outcomes of general PICU admission. In 2009, Rennick et al. conducted a systematic review of the psychological outcomes but excluded studies on functional PICU outcome[13]. Other systematic reviews have focused on a single outcome. It was hypothesised that a systematic review of the current global literature regarding all the outcomes of general PICU admission would allow us to estimate the expected ongoing mortality, morbidity, quality of life and psychosocial impact

of admission to PICU. It was also hypothesised that the review may identify which outcomes have been sufficiently investigated and which areas which require more attention. A systematic review may also reveal factors that could be addressed during PICU admission to reduce the long-term morbidity or ways to use resources most effectively. Currently, most of the literature on this topic comes from higher income countries and outcomes may be very different in low- and middle-income settings. There are currently no studies from Sub-Saharan Africa that the authors are aware of.

Methods

Study Design

This is a systematic review of published literature. A search was performed of the following databases; MEDLINE via PubMed, Cochrane Central Register of Controlled Trials, (CENTRAL), Scopus, Web of Science, CINAHL, ERIC, Health Source Nursing/Academic, APA PsycInfo (the last four databases via the EBSCO host platform). Reference lists of included articles were screened for potentially missed articles. Efforts were made to include the grey literature including a search of ProQuest Theses and Dissertations. The search strategy was designed to include terms that represented the population (children or adolescents), the intervention (paediatric intensive care) such as " Intensive Care Units, Paediatric or Critical Care", and treatment outcomes such as "Critical Care Outcomes, Outcome Assessment, Neurodevelopmental disorders, stress, psychological, quality of life, critical illness/psychology or services" with the exclusion of neonatal intensive care. For the full search strategy see Appendix A.

Types of Studies

All types of study designs were included, both full-text and those published as abstracts only. There were no restrictions as to language, provided an English translation was obtained. There was no restriction of publication date.

Types of participants

All children aged up to 18 years admitted to a PICU were included. Primary neonatal studies and studies investigating the PICU outcomes of specific disease processes or interventions

were excluded. Those studies with mixed populations, including both neonates and older children were included in the review.

Types of Intervention

Admission to a PICU as reported by the study authors. It is acknowledged that the definition of "intensive care" may vary amongst different socio-geographic regions but papers were accepted if the authors identified their unit as an intensive care.

Types of Controls

All types of controls were included, this included non-PICU hospital admission or healthy age-matched controls. Observational studies without control groups were also included.

Types of Outcomes

All health outcomes were included.

a) Primary outcome examined was mortality – both short (<30 days; including PICU mortality specifically) and longer-term (<3 months, <6 months, <1year, <5 years and >5 year).
b) Secondary outcomes were any valid measures of neurodevelopment/cognition/school performance, physical function, psychological function/behaviour impact, quality of life and social/family implications made at any time point after PICU discharge (short or longer-term)

Consent and Ethical Approval

As there are no patients involved in this study, no consent was taken. The study protocol was submitted to the PROSPERO register – ID CRD42018086373 and the Research Ethics Committee of the University of Cape Town, who waived the need for ethical review. The study was done in accordance with the Declaration of Helsinki, 2013.

Data Collection and Analysis

Selection of Studies

The articles identified during the literature search (Appendix A) were downloaded to Endnote (Endnote X9; Clarivate Analytics, USA) and reviewed by the primary author (CP). If the title/abstract appeared relevant, the full text was retrieved for review for possible inclusion.

Any duplicates were identified, and multiple reports of the same study collated so each study was included and not each report. The selection process was recorded in a PRISMA flow diagram. Where any questions were raised regarding inclusion, a second author (BM) was consulted and in cases of disagreement a third author (AA) was consulted.

Data Collection Process

Data were extracted from included studies into a form summarising the study characteristics and main findings. These data were then entered into an Excel spreadsheet. It was noted if outcome data were not reported in a usable way. For any missing data it was planned to contact the authors via email. The data extracted included:

1. Methods: Study design, duration, location, setting and date
2. Participants: Sample size, age, inclusion and exclusion criteria, length of follow up, severity of illness
3. Outcomes: Primary and secondary outcomes, assessment tools and time points reported.
4. Notes: Key issues or limitations of the study, funding, notable conflicts of interest of authors

Assessment of risk of bias in included studies

The authors planned to assess the risk of bias for any randomised controlled trial that met the inclusion criteria using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions[14], considering the following aspects when judging risk of bias:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

Each potential source of bias would be scored as high, low or unclear, and then summarised into an overall risk of bias. For any observational studies the risk of bias tool would be adapted using the GRADE criteria. However, if only the overall outcomes of the entire cohort were included as relevant to this review then randomized controlled studies included in the review would also be treated as observational studies.

Assessment of bias in conducting the systematic review

The review was conducted according to the protocol published on PROSPERO https://www.crd.york.ac.uk/prospero ID CRD42018086373 and any deviations from it reported in the 'Differences between protocol and review' section of the systematic review.

Data Synthesis

Due to the nature and objectives of the review, the different outcomes of groups from randomized controlled trials of specific PICU interventions were not presented separately, and instead overall PICU outcomes of the all trial participants (as a single cohort) were included. It is unlikely to be feasible or ethically permissible to randomize to PICU admission versus no PICU admission, therefore treatment effect cannot be determined. Data synthesis was therefore focused on a descriptive narrative review of the included studies, using "Summary of Findings" tables. Where possible data was extracted from different studies and compared using simple graphs. Countries were categorised as High, Middle or Low income according to the classification from the World Bank in the year the study was performed *https://data.worldbank.org/country*.

Dealing with missing data

The author planned to contact the investigators or study sponsors for any key missing data where possible (e.g. when a study was available as an abstract only). Where this was not possible, or if missing data was thought to introduce serious bias, these studies would be excluded. For some studies only an abstract was found but these were older studies and no author details were found for contact purposes. The studies included were not thought to introduce significant bias to the overall results as they were small and not recent so were unlikely to change the outcomes.

Reaching Conclusions

Conclusions were based only on the findings of the studies included in the review. Areas of priority for future research were identified where possible, and the data described and recommendations for clinical intervention were limited to study results.

Differences between Protocol and Review Process

1. Included studies were all observational (or treated as observational for the purposes of this review) and were therefore all considered low GRADE and at high risk of bias.
2. A characteristics of excluded studies table was not included due to the large number of exclusions. A summary of the main reasons for exclusion is included in the results.
3. Authors were not contacted for missing data.

Results

Over 20,000 titles were identified by the initial search. On review of these titles, 779 articles were thought to be relevant and downloaded to Endnote (Endnote X9; Clarivate Analytics, USA). Duplicates were identified and removed (318 articles) – see Figure 1. Of the 461 articles remaining, 247 were from Medline, 47 from EBSCO, 9 from Google Scholar, 10 from ProQuest, 133 from Scopus, and 15 from Web of Science, 0 from CENTRAL. Fifty-four further articles were found from the reference lists of those articles or other links giving a total of 515. For four papers, the abstracts or text could not be found. Of the 511 remaining, 145 were deemed not relevant on review of the abstracts. Twenty-three of these focused on adults some were editorial/review articles and some studying interventions on children whilst still in the ICU rather than outcomes at or following discharge. Three articles were excluded because no English translations were available. The reported mortality in PICU was the primary outcome assessed but otherwise the focus was on outcomes following PICU discharge. Many of the identified studies examined homogenous groups of PICU admissions e.g. patients with sepsis or the outcomes of a specific intervention e.g. cardiac surgery. The search strategy was not designed to pick up all studies regarding the outcomes of specific diseases or specific interventions so a further 252 were excluded. For details of the excluded studies please see Appendix B. Only studies looking at general admissions to PICU were included, a total of 111.

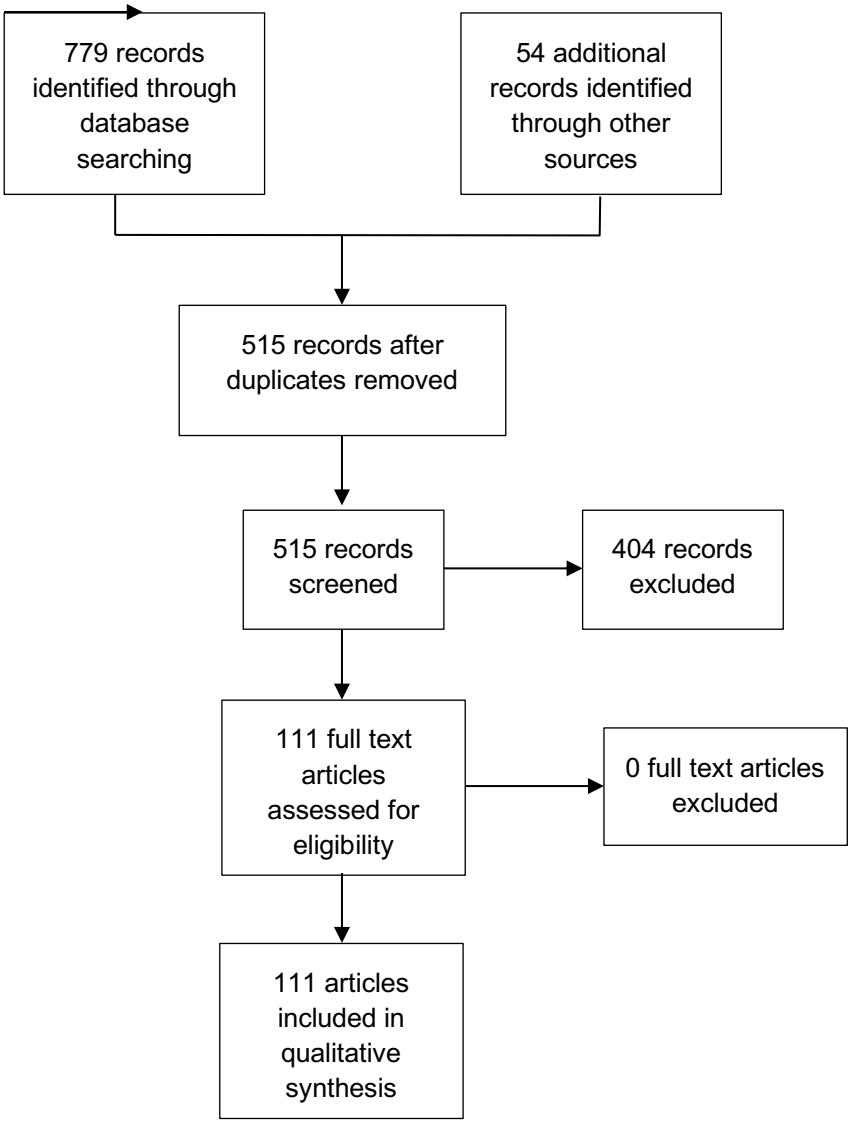

Figure 1: Flow Diagram of identified and excluded records

Mortality

Sixty-one articles were included that examined mortality outcomes of PICU. For two of these articles the full text could not be found, only abstracts were available[15],[16]. Most of the studies included all admissions to PICU, where there were specific inclusions or exclusions these are detailed in the table. Most studies also only reported mortality in the PICU or pre-hospital discharge. For those following up over a longer-term, where reported, the loss to follow up rates have been included. All the included studies were cohort study designs with low GRADE evidence and high risk of bias. The studies are summarized in Table 1.

Table 1: Summary of findings of articles with the primary outcome of mortality (n=62)

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
1	1987	Beaufils[17]	Europe - 8 units	HIC	Cohort	1 month	714	67 lost	12.5%	15%							
2	1987	Pollack[16]	USA	HIC	Cohort	In PICU			3-17.6% (9 units)								
3	1987	Pollack[18]	USA	HIC	Cohort	1 year	647		8%	9.7%							
4	1990	Butt[19]	Australia	HIC	Cohort	36 months	976							20% (3 year)			
5	1992	Fiser[20]	USA	HIC	Cohort	Hospital stay	1469		5.80%								
6	1993	Kapil[21]	India	LIC	Cohort	In PICU	3025		23.5%								
7	1995	Gemke[22]	Netherlands	HIC	Cohort	In PICU	1063		7.1%								0.99
8	1995	Gemke[23]	Netherlands	HIC	Cohort	1 year	468		7.5%	8.3%			10.1 %				

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
9	1997	De Keizer[24]	The Netherlands	HIC	Cohort	1 year	246	Excl <1 year and < 24hour stay					7%				
10	1997	Earle[25]	Mexico and Ecuador	MIC	Cohort	In PICU	1061		8.1% low risk, 28% moderate risk								
11	1998	Tan[26]	Singapore	HIC	Cohort	In PICU	283		4.5%								
12	1998	Tilford[27]	USA	HIC	Cohort	In PICU	10833		4.5%								0.85
13	1999	Jeena[28]	South Africa	MIC	Cohort	In PICU	7580		35.4%								
14	2000	Manzar[29]	Oman	MIC	Cohort	In PICU	131		15%								
15	2001	Singhal[30]	India	LIC	Cohort	In PICU	100		18%								1
16	2002	Morrison[31]	Australia	HIC	Cohort	24 months	909	Excl no PRISM	7%	7.50 %				10% (2 years)		Mean PRISM 5.54	

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
17	2003	El-Nawawy [32]	Egypt	MIC	Cohort	Hospital stay	406		50%								0.95
18	2003	Goh[33]	Malaysia	MIC	Cohort	Hospital stay	346		12.1%								0.88
19	2003	Jayashree[34]	India	LIC	Cohort	1 year	150	Excl <24 hour stay, infants and readmission	12.9%				12.9 %				
20	2003	Taylor[35]	Australia	HIC	Cohort	3.5 years	868		7.9%					16.20%			
21	2004	Khilnani[36]	India	LIC	Cohort	In PICU	948		6.7%							Mean PRISM 18.5	
22	2005	Marcin[37]	USA	HIC	Cohort	In PICU	34880		3.7%							Mean PRISM III 5.8	
23	2006	Jones[38]	UK	HIC	Cohort	6 months	7214		6%			9.7%				Median PIM 2 0.024, PRISM	

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
																III-12 0.018, PRISM III-24 0.016	
24	2006	Lopez[39]	USA	HIC	Cohort	Hospital stay	5749		3.7%								0.88
25	2007	Alievi[40]	Brazil	MIC	Cohort	In PICU	443	Excl <24 hour stay	6.3%							Median PIM2 2.36	
26	2007	Ambuebl[41]	Switzerland	HIC	Cohort	2 years	661		3.9%					7.1% (2 year)			
27	2007	Mestrovic[42]	Croatia	MIC	Cohort	6 - 25 months	372		6.6%					7.5% (2 years)			
28	2007	Odetola[43]	USA	HIC	Cohort	In PICU	8885		4.2%							Mean PRISM 6.4, Median 4	
29	2007	Qureshi[4]	Pakistan	LIC	Cohort	In PICU	139		28.7%								1.47 by PRISM

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
		[4]															, 1.4 by PIM 2, 1.57 by PELOD
30	2008	Gullberg [45]	Sweden	HIC	Cohort	5 years	8063	Excl <1/12	2.1%					5.6%%			
31	2009	Bellad[46]	India	LIC	Cohort	Hospital stay	203	Excl congenital anomalies, LOS <1hr, age <1/12, left against advice	16.7%								
32	2009	Bilan[47]	Pakistan	LIC	Cohort	PICU stay	221		9.05%							Mean PRISM 14	1.005
33	2009	Haque[48]	Pakistan	LIC	Cohort	In PICU	313		14%							Mean PRISM 13	
34	2009	Typpo[49]	USA	HIC	Cohort	In PICU	44693	Excl <1/12	2.8%								

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
35	2010	Nakachi[50]	Peru	MIC	Cohort	30 days	819	Excl <3 years		16.2 %						Mean PRISM 10.8	1.75
36	2010	Namachivayam[4]	Australia	HIC	Cohort	3 years	5250										0.8 in 1995, 0.59 by PIM 1 in 2006, 0.7 by PIM 2
37	2011	Embu[51]	Nigeria	LIC	Cohort	In PICU	302		36.1%								
38	2011	Volakli[52]	Greece	HIC	Cohort	In PICU	300		9.7%							Median PRISM 7	0.87[1]
39	2012	Campos-Mino[53]	Latin America and Europe	MIC	Cohort	In PICU			Mean 12% - 13.3% Latin America, 5%								

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
									Europe								
40	2012	Salamati[54]	Iran	MIC	Cohort	In PICU	240		15%								1.8
41	2012	Volakli[55]	Greece	HIC	Cohort	2 year	300		9.7%	12.7 %	15%	16.7%	19%	19% (2 years)			
42	2013	Cunha[56]	Portugal	HIC	Cohort	6 months	1495		8.50%								
43	2014	Mukhtar[57]	Pakistan	LIC	Cohort	In PICU	605		16.3%								
44	2014	Pollack[58]	USA	HIC	Cohort	Discharge	5017		2%								
45	2014	Solomon[2]	South Africa	MIC	Cohort	In PICU	962 and 1113		13.3% and 11.05%								1.1 and 0.9

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
46	2015	Choong[59]	Canada	HIC	Cohort	6 months	33	12 months to 17 years, Excl <48-hr stay, transferred from NICU.	3%		6%		9%				
47	2015	Haftu[60]	Ethiopia	LIC	Cohort	In PICU	680		8.5%								
48	2015	Haque[61]	Pakistan	LIC	Cohort	In PICU	468		11.9%							Mean PRISM 6.8	
49	2015	Mahajan[62]	India	LIC	Cohort	Hospital stay	42										
50	2015	Pollack[63]	USA	HIC	Cohort	In PICU	10078		2.7%							Median PRISM 2.0	0.98
51	2016	Ballot[64]	South Africa	MIC	Cohort	In PICU	1272	182 records lost	16.2%								
52	2016	Peltoniemi[65]	Finland	HIC	Cohort	In PiCU	4876		1.3%							Mean PIM 23.3	

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
53	2017	Hartman[1]	USA	HIC	Cohort	1 year	109130		1.4%				2%				
54	2017	Johansson[66]	Sweden	HIC	Cohort	90 days	21972		2%		4.4%						0.42
55	2017	Kyosti[67]	Finland	HIC	Case-Control	5 years	2792	Excl <28 days	1.9%	2.3%			3.3%	4.9%			
56	2017	Nyirasafari[68]	Rwanda	LIC	Cohort	In PICU	210		50%								
57	2017	Pereira[69]	Brazil	MIC	Cohort	In PICU	50	Excl <1 month, prem <12months, <24hr stay on vent pre PICU and readmission	12%								
58	2017	Pinto[5]	USA	HIC	Cohort	3 years	77		3.9%			7.8%		10.4% (3 years)			
59	2018	Fraser[70]	England and Wales	HIC	Cohort	10 year	110328		2.8%						11% (10 yr)		

									Mortality at Study endpoint								
No	**Date**	**First Author**	**Study location**	**Country Classification**	**Study Design**	**Follow up duration**	**Sample size (n)**	**Incl/excl criteria, loss to f/up**	**In PICU**	**30 days**	**3 months**	**6 months**	**1 year**	**5 year**	**>5 year**	**PIM or PRISM**	**SMR**
60	2018	Kalzén[71]	Sweden	HIC	Cohort	4 years	3688		2.9%					7.2% (2.6 years)			
61	2018	Valla[72]	France	HIC	Cohort	In PICU	683		5%							Median PELOD 11, PIM 2.0	0.42.[2]

[2] Incl. = Included. Excl. = Excluded. PICU = Paediatric Intensive Care Unit, PIM = Paediatric Index Mortality score, PRISM = Paediatric Risk of Mortality Score, SMR = Standardised Mortality Ratio (Observed – Expected/Expected). UK = United Kingdom, USA = United States America, NICU = Neonatal Intensive Care Unit. PELOD = Paediatric Logistic Organ Dysfunction score, HIC = High Income Country, MIC = Middle Income Country, LIC = Lower Income Country according to Country Income Category (World Bank data at time of study - https://data.worldbank.org/country

As can be seen in the summary of findings Table 1, the in PICU mortality rates in the included studies were highly variable, ranging from 1.3% in the Finnish paper by Peltoniemi et al in 2016[65] to 50% in a Rwandan study by Nyirasafari et al in 2017[68]. One clear trend is that mortality in PICU in high income countries has improved over time (Figure 2). Pollack et al measured ICU and hospital mortality during 1981-1982 and 1984-1985 in the USA. They reported a mortality of 8% in ICU and 9.7% at hospital discharge[18]. The most recent study from the USA by Hartman et al. showed 1.4% mortality in patients admitted between 2006 and 2014[1], and this may have reduced even further in recent years. However, these are studies from different units so cannot be directly compared. Data from low- and middle-income countries have only emerged in more recent years and the trends are harder to determine, with highly variable results amongst different study sites. According to Figure 2, the trend for mortality over time in low- and middle-income countries does not appear to have improved overall, although individual countries or units have reported improvement in mortality over time. In two South African studies mortality improved from 29.9% in 1995[28] to 16.7% in 2015[64] but these were from different units so cannot be directly compared. The trends may also be skewed by a few outlying results e.g. El-Nawawy reported a mortality of 50% in Egypt in 2003[32]. However, their mortality rate was actually lower than expected according to the severity of illness of their patients by PRISM score (which was remarkably high). This highlights the need for measures to compare mortality other than simple mortality rates.

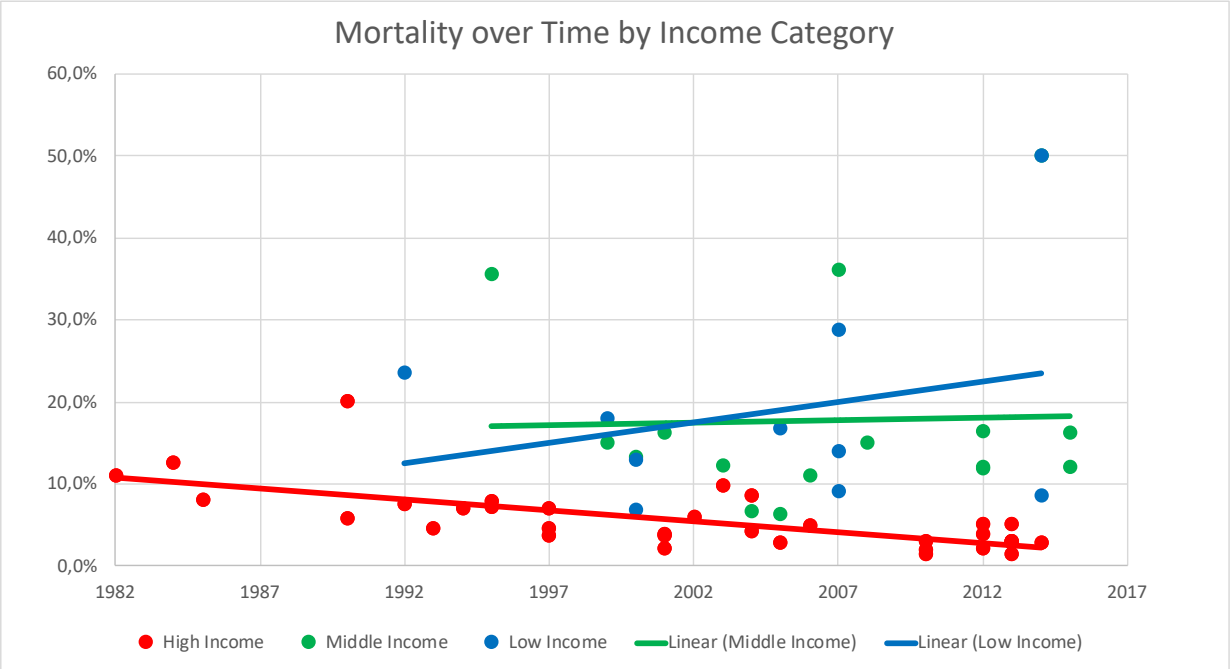

Figure 2 : Mortality In PICU over Time according to Country Income Category (World Bank data at time of study - https://data.worldbank.org/country). Data from Table 1 with best fit lines of correlation: [1,2,4,5,15-72].

Mortality in PICU varied greatly amongst reports from different units. Many studies only included data from one unit but some included multiple units and used various methods to compare these units. These methods can also be used to compare different studies. Although there are multiple factors that affect mortality in a unit, the most important factor to correct for is the severity of illness of the patients admitted. Various scoring systems have been used to do this. These scoring systems have evolved over time so there are now multiple versions of each of them. This continues to make comparisons difficult. Many of the included studies did not use a predicted risk of mortality score at all and only reported actual mortality. Some studies did report expected mortality according to a scoring system and/or a Standardised Mortality Rate (SMR). SMR = Observed Mortality/Expected Mortality. If a SMR was not reported but enough data provided, SMR was calculated (Table 1). Some studies reported that mortality was higher or lower than expected but did not provide numbers to enable SMR calculations. As can be seen in Figure 3, high income countries consistently had SMRs <1 (i.e. Observed mortalities were less than expected according to the severity of illness scoring system used) whilst the results in low- and middle-income countries were more variable and frequently >1 (ie. Higher observed mortality than expected). This may be because the reference populations used in creating mortality risk scores such as PRISM and PIM are from higher income countries and have very different population profiles (e.g. emergency vs

elective admissions, communicable disease vs non-communicable disease), from those in low- and middle-income countries. There may also be other factors that affect mortality but it was not possible to examine these in this study.

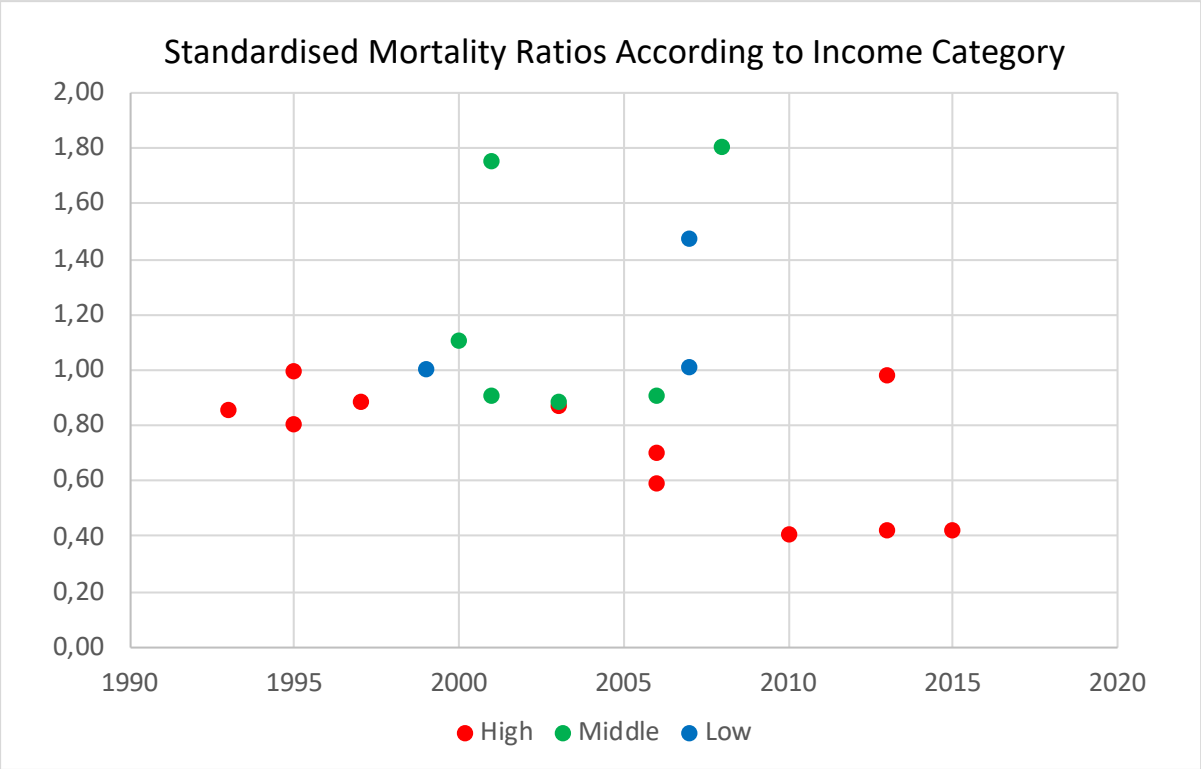

Figure 3 : SMRs of mortality in PICU according to Country Income Category (World Bank data at time of study - https://data.worldbank.org/country). Data from Table 1: [2,4,22,27,32,33,39,44,47,50,52,54,63,66,72].

One of the first studies to compare units whilst adjusting for severity of illness was by Beaufils et al[17]. They studied 714 patients in 8 units across Europe in 1984. Overall the PICU mortality was 12.5%. Across the 8 units included in the study, mortality varied from 4.1% to 20.2% despite similar numbers of severely ill patients (clinical classification score IV). They used the clinical classification score (CCS) to assess severity of illness and also looked for other risk factors for increased mortality. The CCS was a subjective score which may not have differentiated the sickest patients and has since been abandoned in favour of newer scoring systems. Most of the more recent papers report the Paediatric Risk of Mortality Score (PRISM) or the Paediatric Index of Mortality Score (PIM) to enable comparison of different units[2,4,20,22,24-27,30-33,36-40,43,44,46-50,52,54-56,61,63,65,66,68-72].

Another important consideration is mortality after PICU discharge and the long-term outcomes of PICU admission. Children admitted to PICU are at increased risk of death after discharge compared to children not admitted to PICU or the general population[67],[1]. Many of the studies of PICU mortality only report data of children who died during PICU admission. The Beaufils study was one of the first to suggest that mortality after ICU should be considered as they found that 2.5% of children died in the month after discharge from ICU, bringing the mortality up from 12.5% to 15%[17]. A total of 18 studies were identified that followed children up after discharge from ICU and reported mortality rates for up to 10 years[1,5,17,18,23,31,34,35,38,41,42,45,55,66,67,70,71,73]. They are summarized in Figure 4 and almost all of them found an ongoing mortality for years after discharge from PICU. The only one which did not was also the only study from a low- or middle-income country by Jayashree et al in India[34].

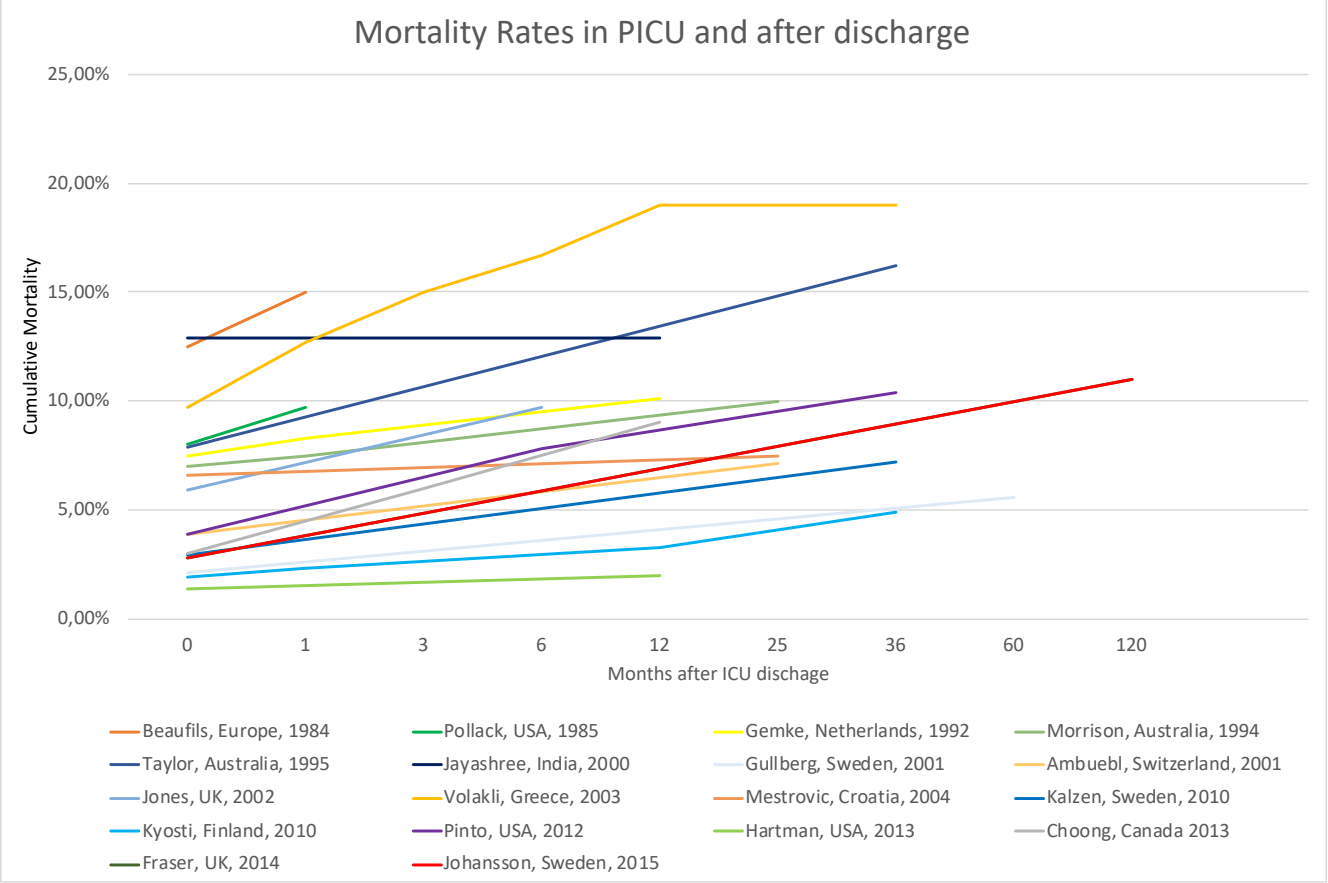

Figure 4: Cumulative Mortality Rate at and following PICU discharge

A few of the studies were able to compare the mortality rates to their national statistics and found that children admitted to PICU had a significantly higher risk of death than the general

population after hospital discharge. At 5 years post PICU discharge, Gullberg et al reported a 2.15 times higher mortality in the PICU group than the general population in Sweden[45] and Hartman et al reported a 2.5 times higher mortality at one year in the USA[1]. Comparing the observed mortality rate of children admitted to PICU to the death rate of one million age matched healthy controls in Finland, Kyosti et al found that children admitted to PICU had a 53.4 times higher rate of death in the 5 years following discharge[67]. Even if children discharged from PICU survived the first year, they still had a 16.7 times greater chance of dying than the healthy population.

Cognitive/Developmental Outcomes

Four studies were included in the cognitive/development outcome category as they looked purely at intellectual functioning and school performance (Table 2). For clarity, articles reporting on outcomes using the Paediatric Cerebral Performance Category (PCPC) and Paediatric Overall Performance Category (POPC) scores are described in the Functional Outcome category, although it is acknowledged that they do include components of cognitive or developmental assessment as well. The studies included one cohort study, two case-control studies and one Randomised Controlled Trial (RCT). These were all treated as observational studies with a low GRADE of evidence and a high risk of bias as only the overall cohort result of the RCT was included.

Table 2: Summary of findings of studies relating to cognitive/developmental outcomes (n=4)

No	Year	First Author	Where	Study Design	Follow up time	Sample size (n) and details	Incl/excl criteria	Indicators used	Results	Risk Factors
1	2013	Als[74]	UK	Case-control	6 months	88 case, 100 control	5-16 years, no prior neuro disorder	Wide Range Intelligence Test, Wechsler Abbreviated Scale of Intelligence, Children's Memory Scale, Cambridge Neuropsychological Test Automated Battery, Questionnaire previously used to assess academic performance	PICU admitted children under perform on neuropsych testing ($p<0.02$) with worse educational performance	Meningoencephalitis and sepsis, younger, lower class, seizures
2	2015	Als[75]	UK	Cohort	12 months	23	5-16 years, no prior neuro disorder	Cambridge Neuropsychological Test Automated Battery, the Children's Memory Scale and the Wechsler Abbreviated Scale of Intelligence of Wide Range Intelligence Test	Significant improvements in measures of memory were seen but with little change in IQ and visual attention over the study period. Educational progress remained below expectation.	

No	Year	First Author	Where	Study Design	Follow up time	Sample size (n) and details	Incl/excl criteria	Indicators used	Results	Risk Factors
3	2008	Elison[76]	UK	Case-control	5 months	16 and 16 controls		CANTAB battery (visual memory) and verbal memory with the Children Memory Scale, Intelligence Quotient was tested using the Wechsler Abbreviated Scale of Intelligence. Emotional and behavioural function was measured with the Strengths and Difficulties Questionnaire and Impact of Event Scales	Poorer performance on tests of spatial memory, sustained attention (rapid visual information) and verbal memory (word pairs learning and delayed recognition) in children admitted to PICU.	Septic illness

No	Year	First Author	Where	Study Design	Follow up time	Sample size (n) and details	Incl/excl criteria	Indicators used	Results	Risk Factors
4	2012	Mesotten[77]	Belgium	RCT	3 years	569 and 216 healthy controls		Wechsler IQ Scale, Beery-Buktenica Developmental Test of Visual Motor Integration, attention, motor co-ordination and executive functions. Amsterdam Neuropsychological Tasks, Children's Memory Scale and Child Behaviour Checklist	Tight glucose control did not result in worse measures of intelligence (compared to usual care). IQ scores were 15 points (p=0.001) lower in post PICU patients than in healthy controls. ,This reduced to 9 points (p=0.001) after matching for baseline risks and biometrics at follow up.	[3]

[3] PICU = Paediatric Intensive Care Unit, UK = United Kingdom, IQ = Intelligence Quotient, CANTAB = Cambridge Neuropsychological Test Automated Battery, RCT = Randomised Controlled Trial

The included studies all used a battery of tests to examine intelligence, memory and executive function (Table 2). All the studies found that scores of cognitive testing worsened after PICU admission. The two studies by Als et al were studies of the same cohort which started with 88 children. The second study was a follow up study to see if outcomes changed at 12 months after ICU compared to 6 months in the first study. At 12 months, the sample size was small with substantial dropouts (n=23). They reported some improvement in memory scores but that children still under performed at school[75]. Elison et al conducted a small study on 16 patients with 16 healthy controls (children of hospital staff or recruited from a local school) using similar tests and also found poorer outcomes in the children admitted to PICU[76]. The largest study, including 569 patients, followed the children up over the longest period (almost 4 years). Although this was an intervention study, it was included in this review because it reported overall outcomes of children admitted to PICU versus healthy controls (siblings of patients and recruited from schools). Mesotten et al. showed a reduction in Intelligence Quotient (IQ) scores, visual-motor integration, Attention Motor Coordination and Memory in children admitted to PICU compared to healthy controls at 4 years following their admission[77].

Functional Outcome

The functional outcome of children was much harder to define than other categories because it can be affected by so many factors. It was decided to include all physical health outcomes as well as studies examining PCPC (which is primarily focused on neurological outcomes) and POPC, as these scoring systems also report on overall function. Although there is a functional component to Quality of Life outcome measurement, studies using scores prioritizing quality of life were included in the "Quality of Life" group. Twenty-four studies were included in the analysis of functional outcome. For one study, only the abstract could be found. A summary of these studies can be found in Table 3. Again, all the studies were observational cohort studies except for one RCT which was treated as a cohort study as it reported the overall outcome of a cohort admitted to PICU. Therefore, all the studies were considered to have a low GRADE of evidence with a high risk of bias.

Table 3: Summary of findings of studies relating to functional outcomes (n=24)

	Year	First Author	Location	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness score	Indicators used	Results	Risk Factors for poor outcome
1	2007	Alievi[40]	Brazil	Cohort	In PICU	443	Excl <24 hr stay	PIM 2	PCPC and POPC	PCPC: 46% cognitive impairment on admission, 60% on discharge. POPC: 66% global impairment on admission, 86% at discharge. Median POPC and PCPC worsened. 4.7% POPC improved.	LOS and PIM 2
2	2014	Bone[78]	USA	Cohort	In PICU	29352			PCPC and POPC	PCPC: 3.4%acquired cognitive disability, POPC: 10.3% acquired global disability.	Trauma, severity of illness, unscheduled admission, oncology and neurology. ventilation, RRT, CPR and ECMO
3	1990	Butt[19]	Australia	Cohort	36 months	976		Clinical Classification Score	Questionnaire to parents	20% died, 5% had a severe handicap, 2% moderate, 12% mild, 17% functional normal but required medical supervision, 42% normal. 80% survived 30 months or more, 91% of survivors would probably lead independent life.	

	Year	First Author	Location	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness score	Indicators used	Results	Risk Factors for poor outcome
4	2015	Choong[59]	Canada	Cohort	6 months	33	12/12-17 years, excl <48 hour stay, from NICU, already mobilizing well or at baseline functional status at time of screening. Language barrier	PIM2 and PELOD	Pediatric Evaluation of Disability Inventory Computer Adaptive Test (includes FSS) and Pediatric Evaluation of Disability Inventory and the Participation and Environment Measure for Children and Youth, POPC and PCPC	POPC: 45% global impairment at admission. PCPC: 39% cognitive impairment at admission. 28% and 42% of cohort recovered to baseline function by 3 and 6 months respectively.	Pre-existing chronic condition/global or cognitive impairment.
5	2018	Choong[73]	Canada	Cohort	6 months	182	12/12-17 years with at least one organ dysfunction, excl patients not expected to survive, NICU transfers and patients unable to do long term follow up		Pediatric Evaluation of Disabilities Inventory Computer Adaptive Test	46.3% had functional limitations at baseline and 81.5% experienced functional deterioration following critical illness. 67.1% demonstrated some recovery by 6/12	Higher baseline function and a neurologic insult at PICU admission were the most sig predictors of functional deterioration. Higher baseline function and increasing age were associated with slower functional recovery

	Year	First Author	Location	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness score	Indicators used	Results	Risk Factors for poor outcome
6	2013	Ebrahim[79]	Canada	Cohort	1 month	65	1/12-18yr, Only urgent admissions		Vineland Adaptive Behaviour Scale 2, PCPC and POPC, Pediatric Quality of Life Inventory 4 and Visual Analogue Scale.	PCPC did not change from baseline to 1 month but POPC improved (p=0.03). Low mean adaptive behaviour and quality of life scores at 1 month post admission.	Resuscitation intensity and illness severity
7	1992	Fiser[20]	USA	Cohort	Hospital discharge	1469		PRISM	POPC and PCPC	POPC and PCPC correlate well with more comprehensive outcome measures	LOS and PRISM
8	2000	Fiser[12]	USA	Cohort	6 months	200	PCPC 5-6 at discharge excluded		POPC and PCPC, Stanford-Binet Intelligence Scale 4th edn, Bayley Scales of Infant Development 2nd edn, Vineland Adaptive Behaviour Scales	Normal children improved from 1 month to 6 months after discharge but POPC category 2 children decreased in function. No statistically sig differences over time for categories 3 and 4.	
9	2000	Fiser[80]	USA	Cohort	In PICU	11106			POPC and PCPC	10% increase in impairment by PCPC, 14% by POPC.	LOS and PIM
10	1995	Gemke[23]	The Netherlands	Cohort	1 year	254	Excl <1 year and <24 hour stay	PRISM	Mutliattribute Health Status Classification	25.7% health status improved, 27.4% deteriorated but most changes minor	No correlation mortality risk and attributes affected

	Year	First Author	Location	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness score	Indicators used	Results	Risk Factors for poor outcome
11	2018	Gupta[81]	USA	Cohort	In PICU	160570			PCPC	1.04% declined by at least 2 categories by PCPC.	higher weight at PICU admission, higher PIM 2, cardiac arrest, stroke, seizures, trauma, ventilation, oscillation, prolonged LOS, prolonged ventilation. Protective - chromosomal anomaly, cardiac surgery and inhaled nitric oxide.
12	2003	Jayashree[34]	India	Cohort	1 year	150	Excl <1 year and <24 hour stay and readmission		Mutliattribute Health Status Classification	75% improved or were equal to their baseline score, 25% deteriorated.	
13	2008	Knoester[82]	The Netherlands	Cohort	3 months	186			POPC and PCPC	69% had physical sequelae. At 3 months PCPC: 5% impairment at admission, 75% at discharge, 23% at 3 months, POPC: 27% impairment at admission, 99% at discharge and 69% at 3 months.	

	Year	First Author	Location	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness score	Indicators used	Results	Risk Factors for poor outcome
14	2010	Namachivayam [4]	Australia	Cohort	3 years	5250		PIM 1 and PIM 2	Modified Glasgow Outcome Score	Proportion with moderate to severe disability at f/up increased from 8.4% in 1982 to 17.9% in 2005-2006. Total dying or surviving with severe disability did not change.	
15	2017	Pereira[69]	Brazil	Cohort	1 day	50	Excl <1 month, prems <12 months , <24 hour stay, on vent pre picu and readmission	PIM2	FSS	18% normal. 6 % severe or very severe impairment at discharge.	Readmission, longer stay, PIM 2
16	2017	Pinto[5]	USA	Cohort	3 years	77			FSS	FSS increased by > 3 from baseline in 5.2% at discharge, 6.5% at 6 months, 10.4% at 3 years. 44% survived without change whilst <10% had functional gains.	Severity illness, invasive therapy
17 and 18	2014	Pollack[58],[83]	USA	Cohort	Hospital discharge	5017			FSS, POPC and PCPC	4.8% new morbidities; improved on hospital discharge. FSS and POPC/PCPC system closely associated.	
19	2015	Pollack[63]	USA	Cohort	In PICU	10078		PRISM III	FSS	4.6% new morbidity	PRISM

	Year	First Author	Location	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness score	Indicators used	Results	Risk Factors for poor outcome
20	2016	Pulham[84]	UK	Cohort	1 year	160			POPC and PCPC, Child behaviour checklist	77% normal at baseline and 71% at discharge but 61% of parents had behavioural concerns at 1 year.	
21	2003	Taylor[35]	Australia	Cohort	3.5 years	727		PRISM	Glasgow Outcome Score (function)	89.7% survivors had favourable outcomes and were likely to lead independent lives.	
22	2009	Typpo[49]	USA	Cohort	In PICU	44693	Excl <1/12	PIM 2, PRISM II and PRISM III	POPC and PCPC	POPC and PCPC scores worsened in PICU.	Day 1 Multi-organ dysfunction score
23	2015	Volakli[85]	Greece	Cohort	2 years	300		PRISM III	POPC and PCPC	PCPC: 33% impairment at admission, 34% at 2 years, ie. no significant difference. POPC: 41% impairment at admission, 53% at 2 years ie. significant worsening in global function (p=0.001)	Best resp and post op
24	2018	Watson[86]	USA	RCT	6 months	949			POPC and PCPC	Functional status worsened in 20%	Baseline impairment[4]

[4] PICU = Paediatric Intensive Care, USA = United States America, PIM = Paediatric Index Mortality, PRISM = Paediatric Risk Mortality Score, LOS = Length of Stay, PCPC = Paediatric Cerebral Performance Category, POPC = Paediatric Overall Performance Category, FSS = Functional Status Scale, RRT = Renal Replacement Therapy, CPR = Cardiopulmonary Resuscitation, ECMO = Extracorporeal Membranous Oxygenation, PELOD = Pediatric Logistic Organ Dysfunction, NICU = Neonatal Intensive Care Unit RCT = Randomised Controlled Trial

Comparing outcomes of the different studies was challenging because of marked heterogeneity in outcomes reporting. Various outcome measures were used: 13 studies used PCPC and POPC as outcome measures; six used the Functional Status Scale (FSS), two used the Glasgow Outcome Scale (GOS), two used the Multi-attribute Health Status Classification (MHSC) and two used the Paediatric Evaluation of Disability Inventory (Table 3). Even studies using the same outcome measure reported results in very different ways, for example change in median vs. percentage with abnormal scores.

Ten out of the 24 studies only reported changes in function between admission and discharge and did not follow the children up thereafter. The longest duration of follow up was 3.5 years with many patients changing over time, either worsening or improving but showing that discharge function was not a reliable measure of long-term outcome[35]. Of the 24 studies, only three were from low- or middle-income countries; two studies from Brazil[69] and one from India[34]. The majority of included studies were conducted in the USA.

The first paper to look at functional PICU outcome was by Butt et al from Australia, who followed a cohort admitted in 1982-1983[19]. They reported that 20% died, 5% had a severe handicap, 2% moderate handicap, 12% mild handicap, 17% were functionally normal but required medical supervision and 42% had normal function. 91% of survivors were assessed as likely to lead an independent life[19]. This was followed by the paper by Namachivayam et al who studied two further Australian cohorts in 1995 and 2005-2006. They reported that although the length of stay and severity of illness of children admitted to PICU had not changed, the mortality was significantly reduced in the second cohort. This reduction was accompanied by an increase in children surviving with moderate to severe disability – from 8.4% in 1982 to 17.4% in the 2005-6 cohort[4].

Data were synthesized from the studies reporting PCPC and POPC, where there was sufficient detail for calculations. The results can be seen in Figures 5 and 6, which show that all the studies reported worsening of function between admission to and discharge from PICU. Some of the studies that followed children up for longer saw a trend to recovery over time with some even returning to baseline function whilst others report ongoing deterioration. More patients had a global impairment as determined by POPC than cognitive impairment as measured by PCPC.

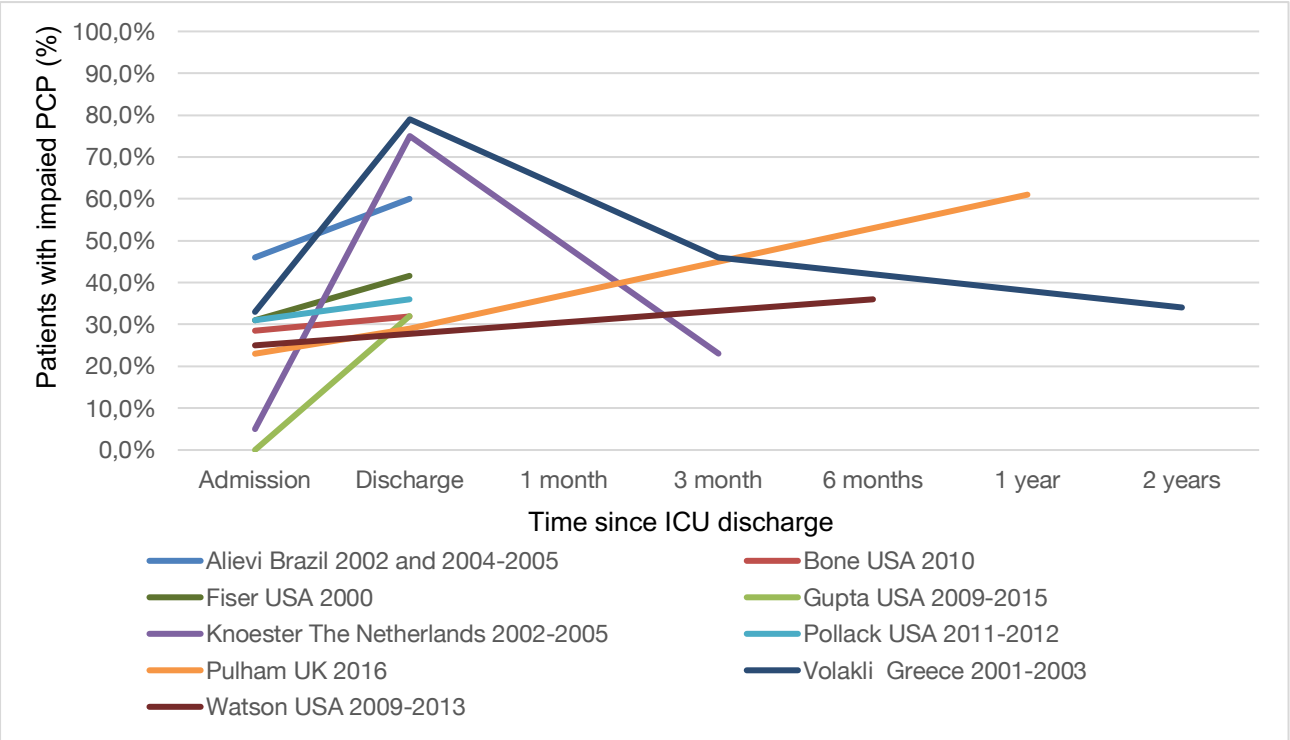

Figure 5: *Proportion of patients* with PCPC >1 (i.e. cerebral impairment) over time

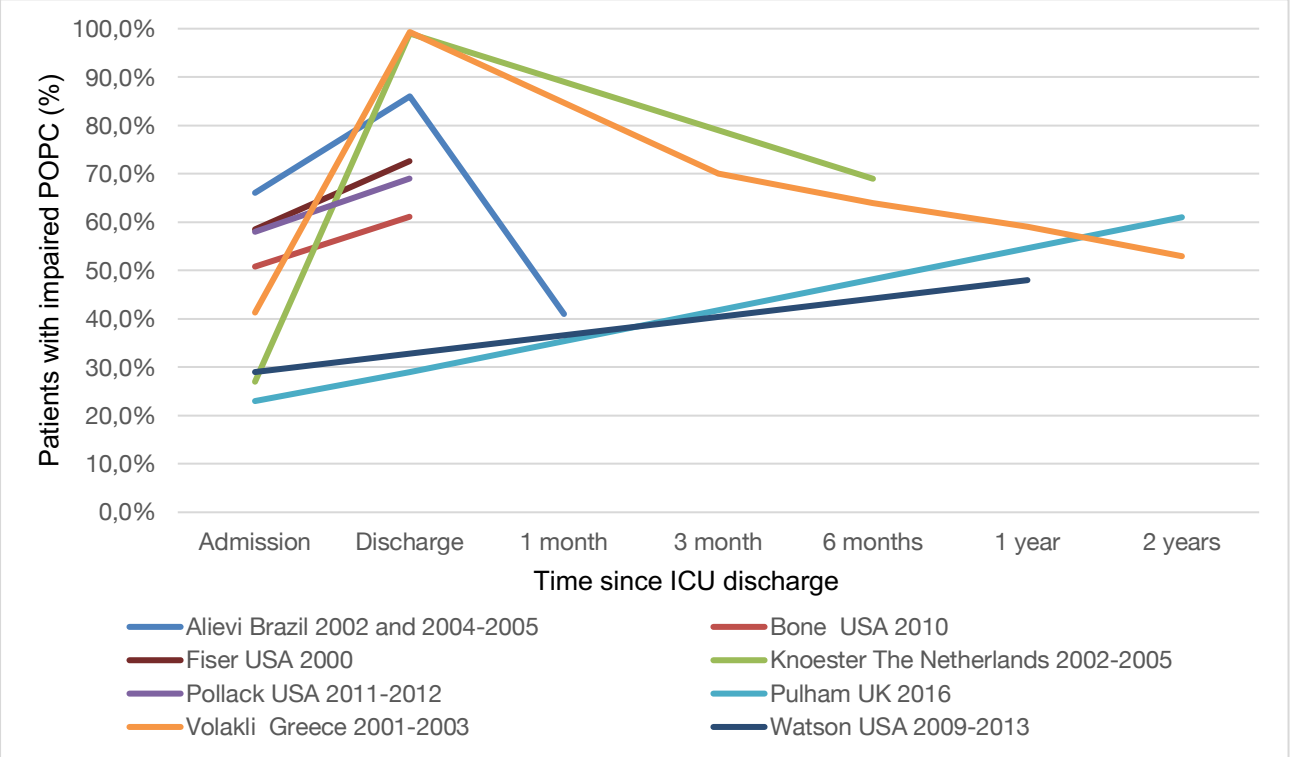

Figure 6: Proportion of patients with POPC>1 (i.e. Overall functional impairment) over time

Psychological/Behaviour Outcomes

Twenty-four studies were included in this category, which used various outcome measures to assess psychological outcomes after PICU admission (Table 4). Two of the studies examining functional outcome were from India[87,88] whilst the remaining studies were all from high-income countries, the majority from the UK. For one study only the abstract could be found. All except one of the studies were cohort studies and the one RCT was again treated as a cohort study therefore all were considered as having a low GRADE of evidence and high risk of bias.

Table 4: Summary of findings studies relating to psychological outcomes (n=24*)*

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
1	2017	Als[89]	UK	2008-2010	Case-control	6 months	33	Excl. prior neuro disorder	PIM 2	Impact of Events Scale (IES)	36.4% at risk for PTSD. Mean IES 13.1	Past health problems and sepsis
2	2015	Als[90]	UK	2007-2010	Cohort	5 months	88 case, 100 control	5-16 years, no prior neuro disorder		IES	20% at risk for psych disorder, 38% high levels of symptoms of PTSD	Sepsis
3	2005	Board[91]	USA		Cohort	24 hours	21	7-12 years, developmentally normal and no previous hospital		Schoolagers Coping Strategies Inventory, Child Drawing; Hospital	Children's memories of the people in ICU were good but they also remembered having bad feelings whilst in PICU. Low levels of coping strategies.	
4	2011	Board[92]	USA		Cohort	3 months	8	Previously normal only	PRISM and TISS	Parent Stressor Scale, State-Trait Anxiety Scale, Child Drawing: Hospital,	Mothers' anxiety increased whilst children's PTSD decreased over time.	

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
										Child Post Traumatic Stress Index		
5	2008	Bronner[93]	The Netherlands	2002-2005	Case-control	9 months	36 plus 355 controls	8-17 only, previously healthy		Dutch Children's Responses to Trauma Inventory	34.5% subclinical PTSD, 13.8% met criteria for PTSD at 3 months increasing to 35.7% and 17.9% at 9 months (not sig diff). Same levels as fire victims	Maternal PTSD
6	2008	Colville[94]	UK	2004-2005	Cohort	3 months	102	7-17 years		ICU Memory Scale and IES	63% had one factual memory, 33% delusional memories. IES median score 9, 28% at risk of PTSD.	TBI worsens factual memory, opiates/benzos increased delusions. PTSD increased if delusions
7	2012	Colville[95]	UK		Cohort	12 months	66	7-17 years. Excl sig learning difficulty and readmission	PIM	Children's Revised-IES, SPAN (Short version Davidson Trauma Scale)	44% either child or parent scored positive for PTSD at 12 months. At 3 months 42% parents and 32%	Higher PIM

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
											children at risk of PTSD, By 12 months,risk reduced to 27% parents, 26% of children.	
8	2013	Colville[96]	UK	2004-2005	Cohort	1 year	97	>7 years with no learning diff		Children's Revised-IES- 8	Higher emotional functioning than a community cohort	Assoc lower QOL, Emergency admission especially TBI
9	2013	Dow[97]	Australia	2008-2011	Cohort	6 months	59	6-16 years, >8 hour stay, excl previous PICU, LOS >28/7, NAI, dev delay	PIM 2	Children's PTSD Inventory	25% scored as having PTSD by DSM-IV, 29% by PTSD-alternative algorithm	
10	2018	Dow[98]	Australia	2008-2011	Cohort	3 weeks	95	6-16 years, >8 hour stay, excl previous PICU, LOS>28/7, amnesia >28/7, NAI, dev delay		Children's Revised-IES	Children’s Revised-IES mean score 18.56, 20% scored as having PTSD	Younger age, admission for traumatic injury and cognitive/affective factors

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
11	2013	Ebrahim[79]	Canada	2008-2010	Cohort	1 month	65	1/12-18yr, Only urgent admissions		Vineland Adaptive Behaviour Scale 2, PCPC and POPC, Pediatric Quality of Life Inventory 4 and Visual Analogue Scale.	Mean score adaptive behaviour 83.2, considered low/moderate behaviour function.	
12	2008	Elison[76]	UK		Case-control	3-7 months	16 cases plus 16 controls	5-16 years	PIM	CANTAB battery, Children Memory Scale, Wechsler Abbreviated Scale of Intelligence, Strengths and Difficulties Questionnaire, IES	Reduced Working Memory (p=0.01), Visual Information Processing (p=0.009) and Verbal Memory (p=0.05) after PICU.	Sepsis
13	2005	Karande[88]	India	2001-2001	Cohort	1-5 days	50	5-12 years, excl <24hr stay and previous PICU		Questionnaire	74% had neutral recollections of PICU stay, 28% positive 24% negative	
14	2017	Manning[99]	UK	2012-2013	Case study	6-20 months	9	6-16 years		Interviews and art-based approaches	Complex stories with numerous challenges	

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
											and adversities were documented.	
15	2004	MeInk[100]	USA		Case-control	1 year	163	2-7 years. Excl stay >21 days, readmission		State Anxiety Index, Profile of Mood states, Parental Stressor Scale, Post Hospital Stress Index, Behavioural Assessment System for Children	25.9% behavioural problems at 1 year. 14.3% externalising behaviour problems at 6 months , increasing to 22.2% at 12 months.	
16	2008	Muranjan[87]	India		Case-Control	1 month	30+30	>5 years, >48 hrs	PRISM, TISS	Temperament Measurement Scale, IES, Birleson Depression Scale, Self-esteem Scale	43% had intrusive thoughts at discharge from PICU vs 6.7% discharged from ward, but scores were the same at 1 month. Mean IES score 1.56	
17	2012	Paulus[101]	USA		Cohort		26 mother child pairs			Stanford and Child Acute Stress Questionnaires, PSS:PICU		Environmental stressors, Parental Stress

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
18	2000	Playfor[102]	UK		Cohort		38	>4 years		Structured interview	15% of recollections were negative	
19	2004	Rees[103]	UK	1998-2000	Cohort	1 year	35 cases and 31 controls	5-18 years		CAPS-C, Impact of Events Scale, Strengths and Difficulties Questionnaire, Birleson Depression Scale, Revised Children's Anxiety Manifest Scale, Child Somatisation Inventory	21% PTSD after PICU, 0% after ward admission	
20	2002	Rennick[104]	Canada		Cohort	6 months	60+60	6-17 years		Child IES	No sig difference between PICU and ward for levels of PTSD, control over health, fears and behaviour changes	Younger, severe illness, invasive procedures - increased fears, lower sense of control and PTSD

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
21	2006	Small[105]	USA	1997-2002	Cohort	6 months	163	2-7 years		State Trait Anxiety Index, Stressful Family Life Events Measure, Visual Analog Scale, Index of Parent Participation, Post Hospitalisation Questionnaire, Behavioural Assessment System for Children	Elevations of externalising and internalising behaviours after PICU compared to baseline - worst at 3 months then improving at 6 months.	Maternal anxiety, Marital status, previous behaviour, age
22	2015	Stowman[106]			Cohort	7 weeks	50	9-17 years		Children's PTSD Inventory, Children's Depression Inventory, Multidimensional Anxiety Scale for Children, Subjective Experience Measure	26% substantial PTSD symptoms	Acute stress disorder

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors for poor outcome
23	2016	Verstraete[107]	Belgium		Cohort	4 years	449 +100 controls			Amsterdam neuropsychological Tasks, Wechsler Intelligence Quotient Scale, Berry-Butenika Development Scale, Children's Memory Scale, Children's Behaviour Checklist	Phthalates were higher in children in PICU and associated with attention deficit and poorer motor coordination	Phthalate levels
24	2016	Vet[108]	Netherlands		RCT	8 weeks	8	> 4 years		Dutch Children's Responses to Trauma Inventory	No PTSD found	[5]

[5] UK = United Kingdom. PIM = Paediatric Index Mortality. PTSD = Post Traumatic Stress Disorder, IES = Impact of Events Scale. LOS = Length of Stay, USA = United States of America, TBI = Traumatic Brain Injury, NAI = Non-Accidental Injury, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, TISS = Therapeutic Interventtions Scoring System, PCPC = Paediatric Cerebral Performance Category, POPC = Paediatric Overall Performance Category, CANTAB = Cambridge Neuropsychological Test Automated Battery, PSS = Parental Stressor Scale. CAPS-C = Clinician Administered PTSD Scale for Children

Most of the included studies concentrated on the risk of Post-Traumatic Stress Disorder (PTSD) but some also examined other mental health or behaviour problems. Outcome measures used included: The Impact of Events Scale (IES) in 10 studies, the State Trait Anxiety Scale in 3 studies and multiple other assessment scales/inventories for childhood behaviour/memory/depression. Due to the complexities of assessing childhood psychology the studies all used different age groups, many only using school aged children and excluding younger children. Most also excluded children with prior psychological or neurological problems. These studies were mostly small studies, with the largest having 449 patients.

Only a few of the studies reporting IES Results could be compared because of the different methods of reporting eg. Medians/means/percentages. Table 5 presents the proportion of children reported to be at risk of PTSD using the IES at different time points after PICU admission. From these findings, approximately one third of children appear to be at risk of PTSD for up to one year post ICU discharge.

Table 5: Children at risk from PTSD according to Impact of Events Scale

	% at risk			
	1 month	3 months	6 months	1 year
Als, UK, 2017			36%	
Als, UK, 2015			34%	
Colville, UK, 2004-2005		28%		
Colville, UK, 2012		32%		26%
Dow, Australia, 2008-2011	20%			

Quality of Life

Nineteen included studies examined quality of life following PICU admission (Table 6). The outcome measures used were mostly the Health Utilities Index (9 studies), the Paediatric Quality of Life Inventory (3 studies) and the Royal Alexandra Hospital Measure of Function (3 studies). Multiple versions of the Health Utilities Index were used so it was not possible to combine the data. Only one RCT was included and was treated as a cohort study, the rest were cohort studies with a low GRADE of evidence and high risk of bias.

Table 6: Summary of findings of studies relating to quality of life outcomes (n=19)

No	Year	Author	Where	When	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
1	2007	Ambuebl[41]	Switzerland	2001	Cohort	2 years	661			Health State Classification Index	Good outcome 77%, moderate 15%, poor 8%. 21% new chronic illness	Respiratory illness - best, worse if cardiac
2	2016	Aspesberro[109]	USA	2012-2013	Cohort	12 weeks	367			Pediatric Quality of Life Index Scores	Mean change in QOL score physical domain 34.8 and in psychosocial domain, 23.1.	Chronic disease
3	2013	Colville[96]	UK	2004-2005	Cohort	1 year	97	>7 years with no learning diff		Paediatric Quality of Life Inventory	At 3 months after PICU lower mean QOL score than community but same by 1 year	PTSD
4	2012	Cunha[110]	Portugal	2002-2004	Cohort	6 months	252	>6 years	PIM and PRISM III	Health Utilities Index (HUI) Mark 3	Median score 0.86 at admission, 0.83 at follow up, 40% improved, 38% declined, 21% no change	Severe disability - improved. Trauma worsened.
5	2013	Cunha[56]	Portugal	2002-2004	Cohort	6 months	320	>6 years	PIM and PRISM III	Health Utilities Index Mark 3	Median score 0.87 at admission, 0.84 at follow up, 38% improved, 41% declined, 21% no change	Improvement predicted by no ventilation, pre-admission pain and lower pre-admission score

No	Year	Author	Where	When	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
6	1997	De Keizer[24]	The Netherlands	1997	Cohort	1 year	209	Excl <1 year and <24 hour stay	PRISM	Health Utility Index	Worse score 1 year after ICU	Cardiac surgery protective.
7	2015	Ebrahim[111]	Canada	2008-2010	Cohort	1 month	52	> 4 years		Health Utilities Index 3 and Visual Analog Scale (VAS)	Mean VAS and HUI-3 utilities were 0.82 and 0.70, respectively, at baseline, and worsened to 0.81 and 0.58 at one month.	
8	2013	Ebrahim[79]	Canada	2008-2010	Cohort	1 month	65	1/12-18yr, Only urgent admissions		Vineland Adaptive Behaviour Scale 2, PCPC and POPC, Paediatric Quality of Life Inventory 4 and VAS	Significant decline in adaptive behaviour functioning. Mean QOL rating of 52.8 = poor QOL at 1 month. .	Resuscitation intensity and illness severity
9	2003	Jayashree[3,4]	India	1999-2000	Cohort	1 year	150	Excl <24 hour stay or readmission		Multiattribute Health Status Classification	75% improved or equal to baseline	Neurological illness
10	2006	Jones[38]	UK	2001-2002	Cohort	6 months	2642	Excl <6 months	PIM2, PRISM III	Health Utility Index	27.3% in full health, 4.4% impaired in all outcome measures	PIM 2 and PRISM III

No	Year	Author	Where	When	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
11	2008	Knoester[112]	The Netherlands	2002-2005	Cohort	9 months	81			TNO-AZL (Preschool) Children's Quality of Life Questionnaire Parents	1-6 years more lung problems, worse liveliness, better appetite and problem solving than normal. 6-15 years worse motor function. All improved at 9 months compared with 3 months post discharge.	
12	2018	Kyosti[113]	Finland	2009-2010	Cohort	6 years	1109			Paediatric Quality of Life Inventory Scores	8.4% poor QOL	Chronic disease, daily medication, increased healthcare services
13	2007	Mestrovic[42]	Croatia	2002-2004	Cohort	25 months	371		PIM 2	Royal Alexandra Hospital Measure of Function	88.8% with no chronic condition and 81.6% with chronic condition excl. neurodevelopment had good QOL. With Neurodevelopmental problems 39.3% poor, 39.3% fair QOL.	Neurodevelopmental disability
14	2002	Morrison[31]	Australia	1992-1994	Cohort	24 months	432	Excl no PRISM	PRISM	Royal Alexandra Hospital Measure of Function	59.3% normal, 32.4% fair, 2% poor QOL.	Comorbidities, LOS, Malignancy

No	Year	Author	Where	When	Study Design	Follow up time	Sample size (n)	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
15	2010	Namachivayam[4]	Australia	1982-2006	Cohort	3 years	5250	>2 years	PIM 1 and PIM 2	Health Status Utility Index	84% good QOL in 1995, 66% good QOL in 2005	
16	2013	Polic[114]	Croatia	2006-2008	Case-control	24 months	189 + 179	10-18 years	PIM 2	Royal Alexandra Hospital Measure of Function	70% good QOL but worse than pre-admission and controls	Chronic condition
17	2012	Rantell[115]	UK	2001-2002	Cohort	6 months	1221	>6 months	PIM, PIM 2, PRISM and PRISM 3	Health Utilities Index Mark 2	66% mod to severe disability,	PIM
18	2003	Taylor[35]	Australia	1995	Cohort	3.5 years	727		PRISM	Health State Utility Index	83.6% favourable QOL	
19	2016	Vet[108]	The Netherlands		RCT	8 weeks	64			Child Health Questionnaire	Below Dutch normative scores for QOL. Behaviour scores higher.	[6]

[6] PIM = Paediatric Index Mortality, PRISM = Paediatric Risk of Mortality, PTSD = Post Traumatic Stress Disorder, QOL = Quality of Life, HUI = Health Utilities Index, VAS = Visual Analogue Scale, PCPC = Paediatric Cerebral Performance Category, POPC = Paediatric Overall Performance Category.

The children were followed up for longer in studies reporting on quality of life outcomes than in some of the other outcome categories, with a maximum of 6 years follow-up in a large Finnish study that showed that 8.4% of children still have poor quality of life 6 years after PICU admission[113]. All the studies showed that some children had impaired quality of life after PICU but the numbers were quite variable. One of the largest studies, by Jones et al from the UK, reported that only 27.3% of children were in full health at 6 months post PICU but also that only 4.4% had impairment in all areas[38]. The Indian study by Jayashree et al showed that 75% had improved or equal quality of life at one year compared to pre-admission, suggesting that PICU was beneficial to their long term health and quality of life[34]. This was the only study from a lower income country, the rest were from highincome countries.

Social/Family Outcomes

Twenty-four studies were identified that examined some aspect of the impact of PICU admission on the family (Table 7). Most of the studies focused on the mental health of the parents and the risk of PTSD. Five studies used the Parent Stressor Scale as an outcome measure. Other studies were qualitative research, describing the parents/family's journey through PICU and beyond. For five papers, only the abstract could be found. The social/family outcomes papers were mostly smaller studies with maximum 223 patients. The maximum follow-up duration was 5 years. One case-control study was included, the rest were all cohort studies and therefore considered to have a low GRADE of evidence with a high risk of bias.

All the studies agreed that admission of a child to PICU is a stressful experience for most parents with high rates of both acute and chronic stress as well as a significant risk of PTSD for parents. A recent study by Rodrigues-Rey et al observed a 23 % rate of PTSD in parents at 6 months post PICU admission[116]. Several papers reported similar results. No papers from lower income countries were found in this category.

Table 7: Summary of findings of studies relating to social and family outcomes (n=24)

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
1	2012	Atkins[117]	UK		Cohort	18 months	9	5-16 years. Excl <24 hours. 1 biological parent			Described family journeys - physical recovery first before psych and social. Families have to find a "new normal".	
2	2004	Balluffi[118]	USA	2000-2001	Cohort	2 months	272	>48 hr stay	PRISM III	ASD Scale, PTSD Checklist	32% of parents ASD, 21% PTSD	ASD symptoms, unexpected admission, parent's degree of worry child might die, another hospital admission or other traumatic event subsequent
3	2011	Board[92]	USA		Cohort	3 months	8	Previously normal only	PRISM, TISS	PSS, State-Trait Anxiety Scale, Child Drawing: Hospital, Child PTSD Index	Mother's anxiety increased whilst child's PTSD decreased over time	

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
4	2002	Board[119]	USA		Case-control	6 months	31/32/32	< 5 years, no abuse or chronic illness, parents co-habiting		PSS: PICU, Symptom Checklist-90, Family Assessment Measure III, Family Inventory of Life Events and Changes	PICU parents had higher stress levels than general ward. Stress related symptoms and difficulties with family functioning were ongoing at 6 months.	
5	2008	Bronner[120]	The Netherlands	2002-2005	Cohort	9 months	144	Previously normal only. Ventilated >24 hours or LOS >7/7 or trauma/RSV/ Meningococc. Not abuse/self-intoxication		Self-Rating Scale for post-traumatic stress disorder	15% mothers and 9.3% fathers had clinical PTSD	
6	2010	Bronner[121]	The Netherlands	2002-2005	Cohort	9 months	190	Unexpected admissions only			30.3% parents had subclinical with 12.6% clinical PTSD at 3 months and didn't	Earlier stressful life events, earlier psychosocial care and PTS at 3/12 predictive

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
											significantly at 9 months.	
7	1999	Carnevale [122]			Cohort	5 years	10				Parents describe striving to recapture their previous life	
8	2009	Colville[123]	UK		Cohort	4 months	50	>12 hours	PIM	Post-traumatic Growth Inventory, IES, The Hospital Anxiety and Depression Scale	88% parents reported a positive change to great degree. This was associated with moderate PTSD more than low or high levels of PTSD.	Ventilated, older
9	2012	Colville[95]	UK		Cohort	12 months	66	7-17 years		Children's Revised-IES – 8, SPAN (Short version Davidson Trauma Scale) and Hospital Anxiety and Depression Scale	In 44% of child-parent pairs, at least one member scored for PTSD with scores increasing over time	Emergency admission, child higher scores

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
10	2006	Colville[124]	UK		Cohort	8 months	34			PSS, General Health Questionnaire, IES	18% mothers scored as having PTSD.	Don't talk about feelings at admission. Reports of feeling stressed retrospectively
11	1985	Eberly[125]			Cohort		223+262			PSS, State-Trait Anxiety Scale	Admission was reported as stressful	Worse if unplanned
12	2015	Hagstrom[126]	USA	2015	Cohort	5 weeks	8	>1 week stay. Excl 2/52 stay in another unit, acute event in last 48 hours, abuse, DNR, Foster care, parent <18		Family Inventory of Life Events and Family System Stressor Strength Inventory.	Describes the sources of stress for parents. These were reported to change in over time but compounded each other.	Separation, not knowing, and the child's illness and distress
15	1999	Mitchell[127]			Cohort	6 months					Resiliency Model can predict outcomes at 1 and 3 months but not 6 months	

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
16	2018	Muscara[128]	Australia	2010-2012	Cohort	18 months	159	Excl another major trauma		ASD Scale, Post-traumatic Stress Checklist-Specific Version	33% had low stress levels whilst 52% had high levels stress that declined. 13% had high stress levels that continued	Mood, anxiety, and emotional response
17	2917	Muscara[129]	Australia	2010-2012	Cohort	4 weeks	171	Excl another major trauma		ASD Scale, Depression-Anxiety Stress Scales - Short Form, Psychosocial Assessment Scale, State Trait Anxiety Inventory	Psychosocial factors significantly explained 36.8% of the variance in parent acute stress responses.	Younger parental age
18	2004	Rees[103]	UK	1998-2000	Cohort	1 year	35 and 31 controls	5-18 years		CAPS-C, IES,, Strengths and Difficulties Questionnaire, Birleson Depression Scale, Revised Children's Anxiety	27% parents from PICU but only 7% parents from the wards screened positive for PTSD	

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
										Manifest Scale, Child Somatisation Inventory		
19	2017	Rodriguez-Rey[130]	Spain		Cohort	6 months	143			Posttraumatic Growth Inventory, Davidson Trauma Scale, Hospital Anxiety and Depression Scale	3.1% parents had PTSD, 21% moderate to severe anxiety, 9.1% moderate to severe depression. 37.1% medium degree of post traumatic growth.	Higher PTSD, depression and anxiety was associated with greater post traumatic growth
20	2018	Rodriguez-Rey[116]	Spain		Cohort	6 months	196				23% parents had symptoms of PTSD, 21% moderate-severe anxiety, 9% moderate-severe depression. Not different at 6 months compared to 3 months	47% of the variance in psychopathology symptoms at 6 months can be predicted at diagnosis. Resilience was a strong negative predictor.
21	2015	Stowman[106]	USA		Cohort	7 weeks	50	9-17 years		Acute Stress Disorder Scale, Beck Depression Inventory, Multi-dimensional	24% parents had significant PTSD	

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
										anxiety Questionnaire, PTSD Checklist-Civilian		
22	2017	Stremler[131]	Canada		Cohort	In ICU	118			State Trait Anxiety Index, Centre for Epidemiological Studies Depression Scale, Decisional Conflict Scale, sleep diaries	24% parents had severe anxiety, 51% depression, 26% decisional conflict	Social support protective. Lack of or changing place of sleep worsened.
23	2017	Terp[132]	Sweden	2012-2013	Cohort	2 years	10	Child -15 years. Excl child died			Parents carried vivid memories and the family continued to be affected by the experience.	
24	1995	Tomlinson[133]			Cohort	9 weeks	20	2 days to 17 years			70% parents had a decrease in mental health scores, 43% reported a change in family behaviour	Chronic disease

No	Year	First Author	Where	When	Study Design	Follow up time	Sample size and details	Incl/excl criteria	Severity of illness	Indicators used	Results	Risk Factors
25	1995	Youngblut [134]	USA		Cohort	3 years	27 + 25	1-5 years	PRISM	Cohesion and Adaptability subscales of the Family Adaptation and Cohesion Scales III and the Feetham Family Functioning Survey	Family functioning not sig different between PICU and general ward cohorts.	PRISM, LOS
26	1993	Youngblut [135]	USA		Cohort	4 weeks	9	<5 years	PRISM	Parental Concern Scale and PSS, Posthospitalization Behavior Questionnaire, Feetham Family Functioning Survey and Family Adaptation and Cohesion Scales	Mothers' family cohesion and satisfaction with family after discharge were negatively related to time the child was intubated.	[7]

[7] UK = United Kingdom, USA = United States of America, ASD = Acute Stress Disorder, PTSD = Post Traumatic Stress Disorder, PRISM = Paediatric Risk Mortality. TISS = Therapeutic Intervention Scale. PICU = Paediatric Intensive Care Unit, PSS = Parental Stressor Scale, LOS = Length of Stay,

Discussion

This review showed that mortality rates in PICU have improved over time in high-income countries. The data extracted here did not confirm the same trend for low- and middle-income countries, but country specific reports suggest that most countries are following the same trend. The SMR was lower in high- income countries than in low- and middle-income countries. It is not within the scope of this study to determine the reasons for these differences, and it is recommended that these be addressed in future studies. More studies from low- and middle-income countries are needed to determine expected mortality in these resource limited settings. Mortality prediction scores should then be adjusted to include this data. Following this review, it is intended that a large, prospective, long-term cohort study of children admitted to PICU in South Africa will be conducted.

It is recommended that future studies use standardized methods of reporting mortality including both actual and predicted mortalities so that a SMR can be used to compare the results of different units. Comparing the outcomes of different units and countries is challenging, as multiple, complex factors may influence mortality and other PICU outcomes. These factors include: when the study was done, the size of the unit, location, characteristics of patients admitted (including admission criteria, pre-existing health conditions, severity of illness, family background and length of stay), staffing levels and facilities/treatments available. It was beyond the scope of this review to identify independent risk factors that may worsen outcomes of PICU.

Critically ill children admitted to PICU are at higher risk of death than the general population and they remain at risk of death for years after PICU discharge[45,67]. This may be related to having a pre-existing chronic disease that precipitated PICU admission; an acute illness requiring PICU admission; or a complication of the PICU admission itself. Further research is required to identify the causes of ongoing mortality as well as to identify predictive and modifiable factors which could be targeted in practice improvement initiatives. It was also noted that loss to follow up is a major concern for studies following children up after discharge and all methods to minimise this should be included in any studies. This may be very variable amongst different communities with different levels of mobility and stability.

Mortality may, however, no longer be the most important outcome of PICU admission[5]. The effects of an admission to PICU are multiple and far reaching, affecting not just the child's

physical and mental health but also the family, community and general population. As more children survive PICU, other outcome measures are needed to ensure the reduction in child mortality does not come with too high a cost to the child, their family or the wider community. If it is possible to predict morbidity, it may be that this should also be considered in deciding if a child should be admitted to PICU. However, whilst this may prove difficult, there is a need to identify interventions and processes in the PICU that are associated with long-term morbidity and improve performance in those areas. It was not possible to identify these risk factors with this study. We also need to consider health care budgets. PICU admission is expensive and may impact on the health of other children e.g. by reducing budgets available for primary health care.

This review highlighted the body of data showing that children admitted to PICU have greater ongoing morbidity than their healthy counterparts with more cognitive/developmental and functional health problems, poorer quality of life and increased psychological problems. Their parents also have an increased risk of PTSD. This has significant implications for the healthcare system if ongoing care is required. From this study it was not possible to determine the root causes of these problems, or what could be done to improve the outcomes for children admitted to PICU.

This review identified 105 studies describing various outcomes of PICU admission. Most of the studies are from high income countries and focused on outcomes during PICU admission or shortly thereafter. Studies that investigated longer term outcomes mostly focused on one outcome, such as quality of life or functional status. Those that examined more than one outcome mostly included mortality data and then focused on one other outcome. However, these are complex outcomes that are a result of an amalgamation of multiple issues. With such complex issues there is a need to define measurable, clearly defined, agreed outcomes of interest to standardise the data and make it comparable. Many studies not included in this review examined outcomes of one condition such as cardiac disease or sepsis. A review of these studies may reveal specific interventions that impact on outcomes or allow comparison of outcomes for different diseases. No studies were found that described all the possible long-term outcomes of general PICU admission.

Other studies not included here examined outcomes of adult intensive care admission. Although these studies may reveal some areas for consideration there are too many differences between children and adults to allow direct comparison. PICUs generally have lower mortality rates than their adult versions and the impact of PICU interventions on a

growing and developing brain may be very different from the impact on an adult brain. Follow up of children will also be longer and may impact that child throughout their lives, including their adult productive lives, which will have ongoing financial implications.

The studies included in this review were markedly heterogenous and were all observational making it very difficult to compare studies, and impossible to accurately pool data or perform meta-analyses. The studies were all a low GRADE level of evidence (observational studies); and furthermore were at risk of substantial bias in all domains. Even those studies that seemed to examine the same outcome did so in very different ways using different outcome measures or ways of reporting those outcomes. Research is needed to determine which outcomes are most important to study, not just to medical professionals but to the patients and their families. There may also need to be consideration of other perspectives and outcomes e.g. medical managers, governments and health care insurers will all have outcomes that they deem important and affect their policies. Agreement is needed in determining what outcomes to assess, how to assess and how to report them. This will be difficult and time consuming but large studies, in different locations, using the same outcome assessment methods, are needed. It may be impossible to perform randomized controlled trials looking at PICU versus no PICU admission, but other control groups may be used such as hospitalized, non-PICU admitted children or healthy children. Randomised controlled studies may also be able to look at particular interventions that have an effect on outcome in children with the same disease or interventions may be compared in different diseases.

If functional outcome can be predicted, then it may be possible to include this assessment in determining admission criteria in the future, but this is unlikely. Current scores such as PIM and PRISM only include the likelihood of short-term mortality but other, holistic, outcomes should also be considered and new scores created to aid in determining the best resource allocation.

Further research is also needed to determine what interventions could be implemented to reduce the ongoing morbidity and mortality seen in children after PICU admission. Does the intervention need to take place in PICU or could follow up clinics/therapy have a significant impact on these children after they are discharged to hospital wards or home? We also need to identify whose responsibility this follow up is. Intensivists usually only manage children during their time in PICU and it is often difficult to identify whose responsibility it is to follow up all the aspects of a child's care. As Hartman et al said in their review paper in 2013

"Having saved them in the ICU, these children remain our responsibility. And what a tremendous accomplishment it will be when a good save means not just being alive but rather living life.[136]" This applies to all children admitted to PICU, not just those with severe sepsis. However, until we know what "living life" means, we cannot properly measure the outcomes of PICU.

Limitations of the Study

This was a systematic review of the current literature. It is hoped that all relevant studies were found through the extensive search process, but some studies may have been missed. If the text could not be found or no English translation was available then studies were not included and this may be a source of bias. To reduce bias, it would be preferable to have the articles reviewed by more than one person but this was not possible for this study. It would also be beneficial to assess each study for risk of bias but there is no agreed upon tool for doing this. The authors are looking at ways to do this in the future.

Conflict of interest declaration

We, the researchers, declare that we have no conflicts of interest.

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Appendix A: Search Strategy

Table A1: PubMed Search strategy, modified as needed for other electronic databases

Intensive Care		
#1	MeSH terms:	Intensive Care Units, Pediatric [MeSH] OR Critical Care [MeSH]
#2	Keyword search in title/abstract fields	intensive care OR PICU OR critical care
#3	#1 OR #2	
Children		
#4	MeSH terms:	Child [MeSH] OR Adolescent [MeSH]
#5	Keyword search in title/abstract fields	child OR children OR adolescent OR teenage OR youths OR paediatric OR pediatric
#6	#4 OR #5	
Outcome:		
#7	MeSH terms:	Critical Care Outcomes [MeSH] OR Outcome Assessment [MeSH] OR Neurodevelopmental Disorders [MeSH] OR Stress, Psychological [MeSH] OR Quality of Life [MeSH] OR Critical Illness/Psychology [MeSH] OR Survivors [MeSH]
#8	Keyword search in title/abstract fields	treatment outcome OR clinical effectiveness OR clinical efficacy OR treatment effectiveness OR patient-relevant outcome OR treatment efficacy OR follow-up OR follow up OR post-hospital syndrome OR post-traumatic stress OR psychosocial OR psychological OR emotional OR cognitive OR post-discharge OR neurodevelopment OR neurodevelopmental OR neurocognitive OR neurologic OR behavioural OR behavioral
#9	#7 OR #8	
#10	#3 AND #6 AND #9	
#11	Keyword search in title/abstract fields	"neonatal intensive care" OR "neonatal critical care" OR "neonatal ICU" OR “NICU”
#12	#10 NOT #11	

Appendix B: Excluded Studies

1. Papers only including children with cardiac disease or interventions:

1. Amigoni, A.P., A.: Biban, P.: Suppiej, A.: Freato, F.: Zaramella, P.: Zacchello, F., *Neurologic outcome in children after extracorporeal membrane oxygenation: prognostic value of diagnostic tests.* Pediatr Neurol, 2005. **32**(3): p. 173-9.
2. Ben-Abraham, R.E., O.: Mishali, D.: Yulia, F.: Vardi, A.: Barzilay, Z.: Paret, G., *Predictors for mortality after prolonged mechanical ventilation after cardiac surgery in children.* J Crit Care, 2002. **17**(4): p. 235-9.
3. Brown, K.L.I., R.: Marino, B. S.: Thiagarajan, R. R., *Outcomes following extracorporeal membrane oxygenation in children with cardiac disease.* Pediatr Crit Care Med, 2013. **14**(5 Suppl 1): p. S73-83.
4. Brunetti, M.A.G., A. C.: McCardle, K.: Mott, A. R.: Ravishankar, C.: Gaynor, J. W., *Unplanned Readmission to the Pediatric Cardiac Intensive Care Unit: Prevalence, Outcomes, and Risk Factors.* World Journal for Pediatric and Congenital Heart Surgery, 2015. **6**(4): p. 597-603.
5. Cashen, K.R., R.: Dalton, H. J.: Berg, R. A.: Shanley, T. P.: Newth, C. J. L.: Pollack, M. M.: Wessel, D.: Carcillo, J.: Harrison, R.: Dean, J. M.: Jenkins, T.: Meert, K. L., *Functional Status of Neonatal and Pediatric Patients After Extracorporeal Membrane Oxygenation.* Pediatr Crit Care Med, 2017. **18**(6): p. 561-570.
6. Chandler, H.K.T., B.: Johnson, K. A.: McCracken, C.: Fortenberry, J. D.: Paden, M. L., *Determining comorbidities and quality of life among pediatric survivors of extracorporeal life support.* J Crit Care, 2015. **30**(5): p. 1085-9.
7. Cheng, Y.L., Z. J.: Yan, X. G.: He, J.: Yan, G. F.: Cai, X. D.: Shen, W. J.: Jin, A. L.: Lu, G. P., *[Follow-up of survived children supported by extracorporeal membrane oxygenation].* Zhonghua Er Ke Za Zhi, 2016. **54**(11): p. 847-850.
8. Connolly, D.M., S.: Hayman, L.: Mahony, L.: Artman, M., *Posttraumatic stress disorder in children after cardiac surgery.* J Pediatr, 2004. **144**(4): p. 480-4.
9. Costello, J.M.O.B., M.: Wypij, D.: Shubert, J.: Salvin, J. W.: Newburger, J. W.: Laussen, P. C.: Arnold, J. H.: Fynn-Thompson, F.: Thiagarajan, R. R., *Quality of life of pediatric cardiac patients who previously required extracorporeal membrane oxygenation.* Pediatr Crit Care Med, 2012. **13**(4): p. 428-34.
10. de Mos, N.v.L., R. R. L.: McCrindle, B.: Bohn, D. J.: Parshuram, C. S., *Pediatric in-intensive-care-unit cardiac arrest: incidence, survival, and predictive factors.* Critical Care Medicine, 2006. **34**(4): p. 1209-1215.
11. Dhandayuthapani, G.C., S.: Ranasinghe, A.: Hunt, L.: Grant, D.: Martin, R. P.: Kenny, D., *Short-term outcome of infants presenting to pediatric intensive care unit with new cardiac diagnoses.* Congenital Heart Disease, 2010. **5**(5): p. 444-449.
12. Egbe, A.C.N., K.: Mittnacht, A. J.: Joashi, U., *Predictors of Intensive Care Unit Morbidity and Midterm Follow-up after Primary Repair of Tetralogy of Fallot.* Korean J Thorac Cardiovasc Surg, 2014. **47**(3): p. 211-9.
13. Eldadah, M.L., S.: Kovach, K.: Ricardo Argueta Morales, I.: Pepe, J.: Fakioglu, H.: Decampli, W., *Influence of a dedicated paediatric cardiac intensive care unit on patient outcomes.* Nurs Crit Care, 2011. **16**(6): p. 281-6.
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15. Franck, L.S.M., A.: Wray, J.: Grocott, M. P.: Goldman, A., *Parent stress levels during children's hospital recovery after congenital heart surgery.* Pediatr Cardiol, 2010. **31**(7): p. 961-8.
16. Gaies, M.G.J., H. E.: Jacobs, J. P.: Laussen, P. C., *Measuring quality and outcomes in pediatric cardiac critical care.* Progress in Pediatric Cardiology, 2012. **33**(1): p. 33-36.
17. Garcia Guerra, G.R., C. M.: Alton, G. Y.: Joffe, A. R.: Moez, E. K.: Dinu, I. A.: Ross, D. B.: Rebeyka, I. M.: Lequier, L., *Health-related quality of life in pediatric cardiac extracorporeal life support survivors.* Pediatr Crit Care Med, 2014. **15**(8): p. 720-7.
18. Garcia Guerra, G.Z., L.: Robertson, C. M.: Alton, G. Y.: Joffe, A. R.: Moez, E. K.: Dinu, I. A.: Ross, D. B.: Rebeyka, I. M.: Lequier, L., *Survival and neurocognitive outcomes in pediatric extracorporeal-cardiopulmonary resuscitation.* Resuscitation, 2015. **96**: p. 208-13.
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25. Limperopoulos, C.M., A.: Shevell, M. I.: Rosenblatt, B.: Rohlicek, C.: Tchervenkov, C.: Darwish, H. Z., *Functional limitations in young children with congenital heart defects after cardiac surgery.* Pediatrics, 2001. **108**(6): p. 1325-1331.
26. Limperopoulos, C.M., A.: Shevell, M. I.: Rohlicek, C.: Rosenblatt, B.: Tchervenkov, C.: Darwish, H. Z., *Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects.* J Pediatr, 2002. **141**(1): p. 51-8.
27. Long, S.H.E., B. J.: Harris, S. R.: Cheung, M. M., *Motor skills of 5-year-old children who underwent early cardiac surgery.* Cardiol Young, 2016. **26**(4): p. 650-7.
28. Long, S.H.H., S. R.: Eldridge, B. J.: Galea, M. P., *Gross motor development is delayed following early cardiac surgery.* Cardiol Young, 2012. **22**(5): p. 574-82.
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35. Namachivayam, S.P.d.U., Y.; Millar, J.; Cheung, M. M.; Butt, W., *Survival status and functional outcome of children who required prolonged intensive care after cardiac surgery.* Journal of Thoracic and Cardiovascular Surgery, 2016. **152**(4): p. 1104-1112.e3.
36. Obas, K.A.L., J. M.: Zegray, M.: Rennick, J. E., *Parental perceptions of transition from intensive care following a child's cardiac surgery.* Nurs Crit Care, 2016. **21**(3): p. e1-9.
37. Pedersen, K.R.H., V. E.: Christensen, S.: Pedersen, J.: Hjortholm, K.: Larsen, S. H.: Povlsen, J. V., *Clinical outcome in children with acute renal failure treated with peritoneal dialysis after surgery for congenital heart disease.* Kidney Int Suppl, 2008(108): p. S81-6.
38. Penk, J.S.L., Y. H.: Waloff, K. R.: Frank, L. H.: Stockwell, D. C.: Spaeder, M. C.: Berger, J. T., *Unplanned admissions to a pediatric cardiac critical care unit: a review of 2 years' experience.* Pediatr Crit Care Med, 2015. **16**(2): p. 155-60.
39. Raissadati, A.N., H.: Jokinen, E.: Sairanen, H., *Progress in late results among pediatric cardiac surgery patients: a population-based 6-decade study with 98% follow-up.* Circulation, 2015. **131**(4): p. 347-53; discussion 353.
40. Raucci, F.J., Jr.: Hoke, T. R.: Gutgesell, H. P., *Predicting economic and medical outcomes based on risk adjustment for congenital heart surgery classification of pediatric cardiovascular surgical admissions.* Am J Cardiol, 2014. **114**(11): p. 1740-4.

41. Shamszad, P.H., M.: Rossano, J. W.: Denfield, S. W.: Knudson, J. D.: Penny, D. J.: Towbin, J. A.: Cabrera, A. G., *Characteristics and outcomes of heart failure-related intensive care unit admissions in children with cardiomyopathy.* Journal of Cardiac Failure, 2013. **19**(10): p. 672-677.
42. Simons, J.S., E. D.: Derby, C. D.: Pizarro, C., *Predictive value of near-infrared spectroscopy on neurodevelopmental outcome after surgery for congenital heart disease in infancy.* J Thorac Cardiovasc Surg, 2012. **143**(1): p. 118-25.
43. Taylor, A.K.C., R.: Butt, W. W., *The long-term outcome of children managed with extracorporeal life support: an institutional experience.* Crit Care Resusc, 2007. **9**(2): p. 172-7.
44. van Zellem, L.U., E. M.: Legerstee, J. S.: Cransberg, K.: Hulst, J. M.: Tibboel, D.: Buysse, C., *Cardiac Arrest in Children: Long-Term Health Status and Health-Related Quality of Life.* Pediatr Crit Care Med, 2015. **16**(8): p. 693-702.
45. von Bahr, V.H., J.: Eksborg, S.: Gerleman, R.: Enstad, O.: Frenckner, B.: Kalzen, H., *Long-Term Survival and Causes of Late Death in Children Treated With Extracorporeal Membrane Oxygenation.* Pediatr Crit Care Med, 2017. **18**(3): p. 272-280.
46. Walsh, M.A.A., K.: Van Arsdell, G. S.: Humpl, T., *Critical care outcomes in pulmonary atresia and intact ventricular septum undergoing single-ventricle palliation.* Cardiol Young, 2010. **20**(3): p. 290-6.
47. Weigand, J.M., C. D.: Bacha, E. A.: Chen, J. M.: Richmond, M. E., *Repair of anomalous left coronary artery from the pulmonary artery in the modern era: preoperative predictors of immediate postoperative outcomes and long term cardiac follow-up.* Pediatr Cardiol, 2015. **36**(3): p. 489-97.

2. Papers only including children with endocrine disease or interventions:

1. Jayashree, M.S., S., *Diabetic ketoacidosis: Predictors of outcome in a pediatric intensive care unit of a developing country.* Pediatric Critical Care Medicine, 2004. **5**(5): p. 427-433.
2. Knoester, H.B., M. B.: Bos, A. P.: Grootenhuis, M. A., *Quality of life in children three and nine months after discharge from a paediatric intensive care unit: A prospective cohort study.* Health and Quality of Life Outcomes, 2008. **6**.
3. Naranje, K.M.P., B.: Bhriguvanshi, A.: Lal, R.: Azim, A.: Singh, R. K.: Gurjar, M.: Baronia, A. K., *Blood glucose variability and outcomes in critically ill children.* Indian Journal of Critical Care Medicine, 2017. **21**(3): p. 122-126.
4. *Cognitive function is unaffected by tight glucose control in paediatric intensive care.* Bmj, 2012. **345**: p. e7065.

3. Papers only including children with gastroenterology disease or interventions:

1. Centeno, M.A.B., D. F.: Sasbon, J. S., *Mortality risk factors of a pediatric population with fulminant hepatic failure undergoing orthotopic liver transplantation in a pediatric intensive care unit.* Pediatr Crit Care Med, 2002. **3**(3): p. 227-233.
2. Krull, K.F., C.: Yurk, H.: Boone, P.: Alonso, E., *Neurocognitive outcome in pediatric liver transplant recipients.* Pediatr Transplant, 2003. **7**(2): p. 111-8.
3. Rowan, C.M.V., R. M.; Speicher, R. H.; Mangus, R. S.; Tector, A. J.; Nitu, M. E., *Post-transplant critical care outcomes for pediatric multivisceral and intestinal transplant patients.* Pediatr Transplant, 2012. **16**(7): p. 788-95.

4. Papers only including children with haematology/oncology disease or interventions:

1. Abraham, R.B.T., A.: Ono, N.: Weinbroum, A. A.: Vardi, A.: Barzilay, Z.: Paret, G., *Predictors of outcome in the pediatric intensive care units of children with malignancies.* Journal of Pediatric Hematology/Oncology, 2002. **24**(1): p. 23-26.
2. Akhtar, N.F., Z.: Panju, S.: Haque, A., *Outcome and prognostic factors seen in pediatric oncology patients admitted in PICU of a developing country.* Indian Journal of Pediatrics, 2011. **78**(8): p. 969-972.
3. Ali, A.M.S., H. A.: Mohammed, M. M., *The Outcome of Critically Ill Pediatric Cancer Patients Admitted to the Pediatric Intensive Care Unit in a Tertiary University Oncology Center in a Developing Country: A 5-Year Experience.* J Pediatr Hematol Oncol, 2016. **38**(5): p. 355-9.
4. Ball, L.M., *Intensive care and outcome in children undergoing haematopoietic stem cell transplantation.* Reports of Practical Oncology and Radiotherapy, 2007. **12**(3): p. 171-174.

5. Bartram, J.L.T., S. L.: Gardner, K.: Egberongbe, Y.: D'Silva, P.: Height, S. E.: Dick, M. C.: O'Driscoll, S.: Rees, D. C., *Outcome of children with sickle cell disease admitted to intensive care - A single institution experience.* British Journal of Haematology, 2010. **150**(5): p. 614-617.
6. Ben Abraham, R.T., A.: Ono, N.: Weinbroum, A. A.: Vardi, A.: Barzilay, Z.: Paret, G., *Predictors of outcome in the pediatric intensive care units of children with malignancies.* J Pediatr Hematol Oncol, 2002. **24**(1): p. 23-6.
7. Chima, R.S.D., R. C.: Kim, M. O.: Li, D.: Wheeler, D. S.: Davies, S. M.: Jodele, S., *Improved outcomes for stem cell transplant recipients requiring pediatric intensive care.* Pediatric Critical Care Medicine, 2012. **13**(6): p. e336-e342.
8. Cole, T.S.J., I. C.: Pearce, M. S.: Fulton, B.: Cant, A. J.: Gennery, A. R.: Slatter, M. A., *Outcome of children requiring intensive care following haematopoietic SCT for primary immunodeficiency and other non-malignant disorders.* Bone Marrow Transplantation, 2012. **47**(1): p. 40-45.
9. Dalton, H.J.S., A. D.: Pollack, M. M., *MultiCenter outcome of pediatric oncology patients requiring intensive care.* Pediatr Hematol Oncol, 2003. **20**(8): p. 643-9.
10. De Oliveira Costa, P.A., E. H.: da Silva, A. R. A., *Predictors of 7- and 30-day mortality in pediatric intensive care unit patients with cancer and hematologic malignancy infected with Gram-negative bacteria.* Brazilian Journal of Infectious Diseases, 2014. **18**(6): p. 591-599.
11. Diaz, M.A.V., M. G.: Prudencio, M.: Rodriguez, F.: Marin, C.: Serrano, A.: Sevilla, J.: Casado, J.: Madero, L., *Predicting factors for admission to an intensive care unit and clinical outcome in pediatric patients receiving hematopoietic stem cell transplantation.* Haematologica, 2002. **87**(3): p. 292-8.
12. Faraci, M.B., F.: Giardino, S.: Conte, M.: Micalizzi, C.: Castagnola, E.: Lampugnani, E.: Moscatelli, A.: Franceschi, A.: Carcillo, J. A.: Haupt, R., *Intensive care unit admission in children with malignant or nonmalignant disease: Incidence, outcome, and prognostic factors: A single-center experience.* Journal of Pediatric Hematology/Oncology, 2014. **36**(7): p. e403-e409.
13. Fernandez-García, M.G.-V., M.: Mastro-Martinez, I.: Serrano, A.: Diaz, M. A., *Intensive care unit admissions among children after hematopoietic stem cell transplantation: Incidence, outcome, and prognostic factors.* Journal of Pediatric Hematology/Oncology, 2015. **37**(7): p. 529-535.
14. Gale, G.B., *Pediatric stem cell transplantation and critical care (an outcome evaluation).* Front Biosci, 2001. **6**: p. G33-7.
15. Gutierrez y Lamelas, R.D.C., B., *Improved outcomes of children with malignancy admitted to a pediatric intensive care [1].* Critical Care Medicine, 2001. **29**(6): p. 1292.
16. Hallahan, A.R.S., P. J.: Rowell, G.: O'Connell, A.: Schell, D.: Gillis, J., *Improved outcomes of children with malignancy admitted to a pediatric intensive care unit.* Crit Care Med, 2000. **28**(11): p. 3718-21.
17. Hayes, C.L., R. J.: Cornish, J. M.: Foot, A. M.: Henderson, J.: Jenkins, I.: Murphy, P.: Oakhill, A.: Pamphilon, D. H.: Steward, C. G.: Weir, P.: Wolf, A.: Marks, D. I., *The outcome of children requiring admission to an intensive care unit following bone marrow transplantation.* British Journal of Haematology, 1998. **102**(3): p. 666-670.
18. Heying, R.S., D. T.: Korholz, D.: Stannigel, H.: Lemburg, P.: Gobel, U., *Efficacy and outcome of intensive care in pediatric oncologic patients.* Crit Care Med, 2001. **29**(12): p. 2276-80.
19. Houdemont, S.P.D.C., E.: Delion, M.: Ringuier, B.: Chapotte, C.: Jeudy, C.: Mercier, P.: Granry, J. C.: Rialland, X., *Short-term neurological outcome of children after surgery for brain tumors: incidence and characteristics in a pediatric intensive care unit.* Childs Nerv Syst, 2011. **27**(6): p. 933-41.
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Appendix C: Journal Author Guidelines

CONTENTS

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting, conference or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at: https://mc.manuscriptcentral.com/jpch

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By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at **https://authorservices.wiley.com/statements/data-protection-policy.html**.

2. AIMS AND SCOPE

Journal of Paediatrics and Child Health is the official journal of the Paediatrics and Child Health Division (The Royal Australasian College of Physicians) in affiliation with the Perinatal Society of Australia and New Zealand, the Paediatric Research Society of Australia and the Australasian Association of Paediatric Surgeons, and publishes original research articles of scientific excellence in paediatrics and child health. Research Articles and Editorial Correspondence are published, together with invited Reviews, Annotations, Editorial Comments and manuscripts of educational interest.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

Viewpoint

Word limit: 2,500 words maximum
Abstract: 250 words maximum; unstructured
References: Referenced only if appropriate (Vancouver style).
Description: Viewpoint is available for papers expressing a personal practice or personal view on medical or non-medical topics that are relevant to the readers. They can be up to 2,500 words long, with an unstructured abstract, and referenced if appropriate.

Annotations

Word limit: 1,500 words maximum (excludes 5 required keywords, abstract & references)
Abstract: 150 words maximum; unstructured

References: Maximum of 12 references (Vancouver style).
Key Points: Summarise the main points raised in the manuscript
Multiple choice questions: 3 multiple choice questions preferably 'A-type' single best of 5 alternatives with brief explanations for each answer) based on the article. Ensure that brief explanations are provided for both correct and incorrect answers.

Ethical Debate

Word limit: 2,500 words maximum
Abstract: 250 words maximum; unstructured
References: Referenced only if appropriate (Vancouver style).
Description: Ethical Debate is available for papers describing an ethical dilemma in clinical practice. They may argue only one perspective or two different viewpoints.

Position Paper

Word limit: 2,500 words maximum
References: Maximum of 50 references (Vancouver style).
Description: Position Papers express the consenses view of an organisation, e.g. about the management of a condition. Any recommendations should be evidence-based and should state the Level of Evidence (using NHMRC criteria).

Review Article

Word limit: 2,500 words maximum
Abstract: 150 words maximum; unstructured or structured using sub heads: Aim, Methods, Results, Conclusions. (Abstract must state: The purpose, basic procedures, main findings and principal conclusions of study.)
References: Maximum of 50 references (Vancouver style).
Key Points: Summarise the main points raised in the manuscript with 3 brief Key Points.

Original Article

Word limit: 2,500 words maximum
Abstract: 250 words maximum; structured using sub heads: Aim, Methods, Results, Conclusions. (Abstract must state: The purpose, basic procedures, main findings and principal conclusions of study.)
References: Maximum of 24 references (Vancouver style).
Brief Points: Authors are to provide up to 3 separate points for each Brief Point: 'What is already known on this topic' and 'What this paper adds'.

Instructive Cases

Word limit: 1,200 words maximum
Abstract: No abstract or key words required
References: Maximum of 8 references (Vancouver style).
Figures/Tables: Maximum combined limit of 3 figures/tables
Learning Points: A Summary listing learning points should be included at the end of the Instructive Case.
Description: Instructive Cases involve a clinical problem or issue of clear educational benefit. There is an initial case report, then a brief discussion with appropriate references.

Journal Club

Word limit: 2,500 words maximum
Abstract: 250 words maximum; structured using sub heads: Aim, Methods, Results, Conclusions. (Abstract must state: The purpose, basic procedures, main findings and principal conclusions of study.)
References: Maximum of 24 references (Vancouver style).
Description: They should reflect what happens at journal clubs where doctors come with a clinical question, search for evidence, critically appraise the best evidence and then apply it to their patient, reflecting how the research could have been conducted better. The paper should be divided into the headings: Scenario, Structured clinical question, Search strategy, Table (of relevant papers found in the search), Critical appraisal of all relevant papers (using standard critical appraisal guidelines), followed by a brief discussion of how to do the research better, how to apply the information to the patient and the clinical bottom line.

Brief Communications

Word limit: 600 words maximum
Description: Brief Communications are used to fill gaps in the *Journal of Paediatrics and Child Health*and will be indexed. They are supposed to be entertaining, humourous, informative, thought-provoking or all of the above. They should be relevant, in a broad sense, to paediatrics and those who work in child health. Examples include humourous or poignant stories or instructive mistakes. Consent will be needed if the subject of the Brief Communication is identifiable.

Image of the Month

Submit a photograph or image, together with a short clinical question and a brief answer. For an example, please follow these links: **Question** and **Answer**. If the photograph is identifiable, please send written permission from a parent and/or child or confirm that verbal approval has been obtained. Privacy is the responsibility of the author(s).

Heads Up

Word limit: 200 words approximately
Description: A Heads Up submission is a summary of a recent paper of interest. This should not be the abstract but a short digest of the results, putting them in context of what the paper adds. Please attach a file with a single graph or histogram (preferably not a table) from the paper to make the most important point visually (not essential). A photograph or illustration (subject to copyright) would also be suitable.

Humorous Article

Word limit: 2,500 words maximum
Abstract: An unstructured and tweetable abstract to be provided.
References: Referenced only if appropriate (Vancouver style).
Description: Open format. Make us laugh.

Letters to the Editor

Word limit: 400 words maximum
References: Maximum of 4 references (Vancouver style).
Figures/Tables: Combined maximum of 1 figure/table
Description: New Case Notes/Reports will now only be considered for publication as a Letter to the Editor. Please format as a Letter to the Editor as outlined above and remember that Clinical Trials must be registered with the appropriate governing body.

4. PREPARING A MANUSCRIPT FOR SUBMISSION

Parts of the Manuscript

The manuscript should be submitted in separate files: Title page; main text file; figures.

Title Page

The title page should contain (i) a short informative title that contains the major key words. The title should not contain abbreviations (ii) the type of manuscript (e.g. Original Article, Instructive Case, Editorial Correspondence: Case Note), (iii) the full names of the authors and (iv) the addresses of the institutions at which the work was carried out together with (v) the full postal and email address, plus telephone numbers, of the author to whom correspondence about the manuscript, proofs and requests for offprints should be sent. The present address of any author, if different from that where the work was carried out, should be supplied in a footnote. (v) Acknowledgements, (vi) Conflicts of interest.

Acknowledgements

The source of financial grants and other funding should be acknowledged, including a frank declaration of the authors' industrial links and affiliations. The contribution of colleagues or institutions should also be acknowledged. Thanks to anonymous reviewers are not allowed. This is to be placed in the title page file only for blinding purposes.

Main Text

As papers are double-blind peer reviewed the main text file should not include any information that might identify the authors. The main text of the manuscript should be presented in the following order: (i) Abstract and key words, (ii) text, (iv) references, (v) tables (each table complete with title and footnotes), (vi) figure legends.

Abstract and Key Words

Please refer to the section **'Manuscript Categories and Requirements'** for details about which article types require abstracts. The abstract should not contain abbreviations or references.

Key words should be taken from those recommended by the US National Library of Medicine's **Medical Subject Headings (MeSH) browser list**.

Text

Authors should use subheadings to divide the sections of their manuscript: Introduction, Materials and Methods, Results, Discussion.

Figures and Supporting Information should be submitted as separate files. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter. Photos that identify individuals where faces are visible, the eyes must be pixelated or have a coloured bar covering them for privacy.

Reference Style

Manuscripts are to follow the Vancouver style, as detailed in the International Committee of Medical Journal Editors' revised 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication', as presented at **http://www.ICMJE.org**.

In the text, references should be cited using superscript Arabic numerals in the order in which they appear. If cited only in tables or figure legends, number them according to the first identification of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text.

Cite the names of all authors when there are six or fewer; when there are seven or more list the first three followed by *et al.*

Names of journals should be abbreviated in the style used in *Index Medicus*.

Reference to unpublished data and personal communications should not appear in the list but should be cited in the text only (e.g. A Smith, unpubl. data, 2000).

Journal Article

Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N. Engl. J. Med.* 1976; **294**: 687–90.

Online Article not yet Published in an Issue

An online article that has not yet been published in an issue (therefore has no volume, issue or page numbers) can be cited by its Digital Object Identifier (DOI). The DOI will remain valid and allow an article to be tracked even after its allocation to an issue.

Hall A, Jones GV. Effect of potential atmospheric warming on temperature-based indices describing Australian winegrape growing conditions. *Aust. J. Grape Wine Res.* 2008; https://doi.org/10.1111/j.1755-0238.2008.00035.x (forthcoming).

Book

Kaufmann HE, Baron BA, McDonald MB, Waltman SR, eds. *The Cornea*. New York: Churchill Livingstone; 1988.

Chapter in a Book

McEwen WK, Goodner IK. Secretion of tears and blinking. In: Davson H, ed. *The Eye*, vol. 3, 2nd edn. New York: Academic Press; 1969; 34–78.

Tables

Tables should be self-contained and complement, but not duplicate, information contained in the text. Tables should be numbered consecutively in Arabic numerals. Tables should be presented at the end of the article file after the references with a comprehensive but concise legend above the table OR they can be placed into one separate file. Tables should be double-spaced and vertical lines should not be used to separate columns. Column headings should be brief, with units of measurement in parentheses; all abbreviations should be defined in footnotes. Footnote symbols: †, ‡, §, ¶ should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings. The table and its legend/footnotes should be understandable without reference to the text.

Preparing Figures

Although we encourage authors to send us the highest-quality figures possible, for peer-review purposes we are happy to accept a wide variety of formats, sizes, and resolutions. Do not provide separate files in a zip file, each figure must be uploaded separately as requested.

Do not provide separate files in a zip file. Each figure must be uploaded as a separate file and must be deidentified if there are human subjects included. Click **here** for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Colour figures

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Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Appendices

Appendices will be published after the references. For submission they should be supplied as a separate file and referred to in the text as 'Supporting Information'.

Supporting Information

Supporting information is information that is not essential to the article but that provides greater depth and background. It is hosted online, and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc. Click here for **Wiley's FAQs on Supporting Information**.

Note, if data, scripts or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

The following points provide general advice on formatting and style.

Formatting: The main text file should be prepared using Microsoft Word, using 1.5 line spacing.

Spelling: The journal uses UK spelling and authors should therefore follow the latest edition of the Concise Oxford Dictionary.

Abbreviations: In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

Units of measurement: Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website for more information about SI units.

Numbers: Numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).

Equations: Equations should be numbered sequentially with Arabic numerals; these should be ranged right in parentheses. All variables should appear in italics. Use the simplest possible form for all mathematical symbols.

Trade Names: Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

Resource Identification Initiative

The journal supports the **Resource Identification Initiative**, which aims to promote research resource identification, discovery, and reuse. This initiative, led by the **Neuroscience Information Framework** and

the **Oregon Health and Science University Library**, provides unique identifiers for antibodies, model organisms, cell lines, and tools including software and databases. These IDs, called Research Resource Identifiers (RRIDs), are machine-readable and can be used to search for all papers where a particular resource was used and to increase access to critical data to help researchers identify suitable reagents and tools.

Authors are asked to use RRIDs to cite the resources used in their research where applicable in the text, similar to a regular citation or Genbank Accession number. For antibodies, authors should include in the citation the vendor, catalogue number, and RRID both in the text upon first mention in the Methods section. For software tools and databases, please provide the name of the resource followed by the resource website, if available, and the RRID. For model organisms, the RRID alone is sufficient.

Additionally, authors must include the RIIDs in the list of key words associated with the manuscript.

To Obtain Research Resource Identifiers

Use the Resource Identification Portal, created by the Resource Identification Initiative Working Group.

Search for the research resource (please see the section titled 'Search Features and Tips' for more information).

Click on the 'Cite This' button to obtain the citation and insert the citation into the manuscript text.

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If any difficulties in obtaining identifiers arise, please contact **rii-help@scicrunch.org** for assistance.

Example Citations:

Antibodies: Wnt3 was localized using a rabbit polyclonal antibody C64F2 against Wnt3 (Cell Signaling Technology, Cat# 2721S, RRID: AB_2215411).
Model Organisms: Experiments were conducted in c. elegans strain SP304 (RRID:CGC_SP304).
Cell lines: Experiments were conducted in PC12 CLS cells (CLS Cat# 500311/p701_PC-12, RRID:CVCL_0481).
Tools, Software and Databases: Image analysis was conducted with CellProfiler Image Analysis Software, V2.0 (http://www.cellprofiler.org, RRID:nif-0000-00280).

Wiley Author Resources

Manuscript Preparation Tips

Wiley has a range of resources for authors preparing manuscripts for submission available **here**. In particular, we encourage authors to consult Wiley's best practice tips on **Writing for Search Engine Optimization**.

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The acceptance criteria for all papers are the quality and originality of the research and its significance to journal readership. Except where otherwise stated, manuscripts are double-blind peer reviewed. Papers will only be sent to review if the Editor-in-Chief determines that the paper meets the appropriate quality and relevance requirements.

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MEDLINE evaluates a journal's ethical policy by checking that journals ask submitting authors to provide three things: a declaration of conflict of interest (CoI), confirmation that informed consent was sought from test subjects, and that animal rights were taken into consideration. The reviewer will then check three things during the review:

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requirements are followed?

Policy is Adequate: Is the policy appropriate for the journal? E.g. a review journal does not need to have a statement on human/animal rights or informed consent.

Policy Consistently Followed: Is there evidence in all the published articles that authors have declared their conflicts of interest and that appropriate procedures were followed when the research was conducted? This will be checked in the final published articles.

It is recommended that all articles include a statement regarding CoI, regardless of whether or not a CoI exists – for example, 'The authors have stated explicitly that there are no conflicts of interest in connection with this article.'

There should be robust journal workflows in place to ensure all three criteria are met. Examples of failures would be: a journal that requires authors to declare that institutional review board (IRB) approval was sought for their research, but this is not communicated to the readers of the final article; journals that do require declarations of informed consent, but don't say so in the author guidelines; or journals that only publish statements when conflicts-of-interest were declared, and assume that all readers know omission means that there aren't any conflicts.

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: **Declaration of Helsinki**; **US Federal Policy for the Protection of Human Subjects**; or **European Medicines Agency Guidelines for Good Clinical Practice**. It should also state clearly in the text that all persons gave their informed consent prior to their inclusion in the study.

Patient anonymity should be preserved. When detailed descriptions, photographs, or videos of faces or identifiable body parts are used that may allow identification, authors should obtain the individual's free prior informed consent. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a **standard patient consent form** available for use. Where photographs are used they need to be cropped sufficiently to prevent human subjects being recognized; black eye bars should not be used as they do not sufficiently protect an individual's identity).

Animal Studies

A statement indicating that the protocol and procedures employed were ethically reviewed and approved, as well as the name of the body giving approval, must be included in the Methods section of the manuscript. Authors are encouraged to adhere to animal research reporting standards, for example the **ARRIVE guidelines** for reporting study design and statistical analysis; experimental procedures; experimental animals and housing and husbandry. Authors should also state whether experiments were performed in accordance with relevant institutional and national guidelines for the care and use of laboratory animals:

US authors should cite compliance with the US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals, and Guide for the Care and Use of Laboratory Animals.

UK authors should conform to UK legislation under the Animals (Scientific Procedures) Act 1986 Amendment Regulations (SI 2012/3039).

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Clinical Trial Registration

The journal requires that clinical trials are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. If the trial is not registered, or was registered retrospectively, the reasons for this should be explained.

Research Reporting Guidelines

Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. Authors are encouraged to adhere to recognised research reporting standards. The EQUATOR Network collects more than 370 reporting guidelines for many study types, including for:

Randomised trials: CONSORT

Observational studies: STROBE

Systematic reviews: PRISMA

Case reports: CARE

Qualitative research: SRQR

Diagnostic/Prognostic studies: STARD

Quality improvement studies: SQUIRE

Economic evaluations: CHEERS

Animal pre-clinical studies: ARRIVE

Study protocols: SPIRIT

Clinical practice guidelines: AGREE

We also encourage authors to refer to and follow guidelines from:

Future of Research Communications and e-Scholarship (FORCE11)

National Research Council's Institute for Laboratory Animal Research guidelines

The Gold Standard Publication Checklist from Hooijmans and colleagues

Minimum Information guidelines from Diverse Bioscience Communities (MIBBI) website

FAIRsharing website

Species Name

Upon its first use in the title, abstract, and text, the common name of a species should be followed by the scientific name (genus, species, and authority) in parentheses. For well-known species, however, scientific names may be omitted from article titles. If no common name exists in English, only the scientific name should be used.

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Sequence variants should be described in the text and tables using both DNA and protein designations whenever appropriate. Sequence variant nomenclature must follow the current HGVS guidelines; see **varnomen.hgvs.org**, where examples of acceptable nomenclature are provided.

Sequence Data

Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL, or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL, and GenBank on a daily basis. The suggested wording for referring to accession-number information is: 'These sequence data have been submitted to the DDBJ/EMBL/GenBank databases under accession number U12345'. Addresses are as follows:

DNA Data Bank of Japan (DDBJ): www.ddbj.nig.ac.jp

EMBL Nucleotide Archive: ebi.ac.uk/ena

GenBank: www.ncbi.nlm.nih.gov/genbank

Proteins sequence data should be submitted to either of the following repositories:

Protein Information Resource (PIR): pir.georgetown.edu

SWISS-PROT: expasy.ch/sprot/sprot-top

Structural Data

For papers describing structural data, atomic coordinates and the associated experimental data should be deposited in the appropriate databank (see below). **Please note that the data in databanks must be released, at the latest, upon publication of the article.** We trust in the cooperation of our authors to ensure that atomic coordinates and experimental data are released on time.

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Inorganic compounds: Fachinformationszentrum Karlsruhe (FIZ; fiz-karlsruhe.de)

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Final approval of the version to be published; AND

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Human Subject Information in Databases

The journal refers to the **World Health Medical Association Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks**.

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155 Cremorne Street
Richmond, Victoria 3121
Australia

Guidelines updated 10 September 2019