Intensive Care Med (2019) 45:1262–1271
https://doi.org/10.1007/s00134-019-05675-1

ORIGINAL

Epidemiology of childhood death in Australian and New Zealand intensive care units

Katie M. Moynihan[1,2,3,4*], Peta M. A. Alexander[1,2], Luregn J. Schlapbach[3,4,5], Johnny Millar[6], Stephen Jacobe[7], Hari Ravindranathan[8], Elizabeth J. Croston[9], Steven J. Staffa[10], Jeffrey P. Burns[2,10], Ben Gelbart[6,11] and For the Australian and New Zealand Intensive Care Society Pediatric Study Group (ANZICS PSG) and the ANZICS Centre for Outcome and Resource Evaluation (ANZICS CORE)

Abstract

Purpose: Data on childhood intensive care unit (ICU) deaths are needed to identify changing patterns of intensive care resource utilization. We sought to determine the epidemiology and mode of pediatric ICU deaths in Australia and New Zealand (ANZ).

Methods: This was a retrospective, descriptive study of multicenter data from pediatric and mixed ICUs reported to the ANZ Pediatric Intensive Care Registry and binational Government census. All patients < 16 years admitted to an ICU between 1 January 2006 and 31 December 2016 were included. Primary outcome was ICU mortality. Subject characteristics and trends over time were evaluated.

Results: Of 103,367 ICU admissions, there were 2672 (2.6%) deaths, with 87.6% of deaths occurring in specialized pediatric ICUs. The proportion of ANZ childhood deaths occurring in ICU was 12%, increasing by 43% over the study period. Unadjusted (0.1% per year, 95% CI 0.096–0.104; $p < 0.001$) and risk-adjusted (0.1%/year, 95% CI 0.07–0.13; $p < 0.001$) ICU mortality rates fell. Across all admission sources and diagnostic groups, mortality declined except following pre-ICU cardiopulmonary arrest where increased mortality was observed. Half of the deaths followed withdrawal of life-sustaining therapy (51%), remaining constant throughout the study. Deaths despite maximal resuscitation declined (0.92%/year, 95% CI 0.89–0.95%; $p < 0.001$) and brain death diagnoses increased (0.72%/year, 95% CI 0.69–0.75%; $p = 0.001$).

Conclusions: Unadjusted and risk-adjusted mortality for children admitted to ANZ ICUs is declining. Half of pediatric ICU deaths follow withdrawal of life-sustaining therapy. Epidemiology and mode of pediatric ICU death are changing. Further investigation at an international level will inform benchmarking, resource allocation and training requirements for pediatric critical care.

Keywords: Intensive care units, Death, Comorbidity, End-of-life care, Pediatric

*Correspondence: Katie.Moynihan@cardio.chboston.org
[1] Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
Full author information is available at the end of the article

Springer

Introduction

Death in childhood is a particularly challenging facet of pediatric critical care [1, 2]. The health care team must balance burdensome and invasive measures to support recovery against recognition and acceptance of unsurvivable illness. Recent medical advances have resulted in decreased mortality for many pediatric diseases previously considered incurable [1, 3, 4]; consequently, increasing numbers of children survive with chronic comorbidities and technological dependence requiring recurrent and sometimes prolonged intensive care unit (ICU) admissions [5–7]. The availability of more sophisticated and invasive resuscitation and life support measures in the ICU have further complicated decision making at the end-of-life [2, 8]. These clinical developments necessitate an understanding of changing patterns of mortality and invite broader examination of the associated ethical, legal and economic issues, along with the goals and values of families and clinicians [2, 8].

Fifteen years ago, the Institute of Medicine called for descriptive data to guide the provision, funding and evaluation of palliative care for children, with little progress detailed in follow-up reports [9]. Observational studies have described considerable geographical and institutional variability [1, 8, 10, 11]. There is a paucity of large-scale, population-based epidemiological data describing patterns and modes of pediatric ICU death. Exploration of this changing landscape and drawing comparisons between countries facilitates benchmarking, quality initiatives, resource allocation, planning of organ donation programs, development of pediatric ICU-based palliative care services and design of interventions to improve end-of-life care [9, 12].

We sought to describe the epidemiology and modes of pediatric ICU deaths in a population-based study in Australia and New Zealand [13].

Materials and methods

We performed a binational, multicenter retrospective study of patients < 16 years old admitted to ICU in Australia and New Zealand (ANZ) between 01/01/2006 and 12/31/2016, using data from the Australian and New Zealand Pediatric Intensive Care Registry (ANZPICR) [14]. Pediatric population data were obtained from the national census of both countries [15, 16]. Primary outcome was ICU death. This study was approved by the Children's Health Queensland Human Research Ethics Committee.

Details, data dictionaries and structure of 32 ICUs reporting to the ANZPICR have been described, with further information in the online data supplement [14, 17–19]. In brief, all paediatric intensive care units (PICUs) in ANZ prospectively collect data for admitted patients and submit to the ANZPICR. Additional data are voluntarily submitted by most mixed ICUs—those that predominantly care for adults, admitting children for stabilization prior to PICU transfer, brief admissions or new acute disease in adolescents. Neonatal intensive care unit (NICU) admissions are not included.

Take-home message

ICU mortality of Australian and New Zealand children is falling. Our binational study demonstrates that half of all pediatric ICU deaths follow withdrawal of life-sustaining therapy.

We examined ICU and population-based mortality over time. Demographic and clinical characteristics of survivors and ICU decedents were compared. Pediatric Index of Mortality (PIM2) was the severity of illness marker [20]. Primary diagnoses and associated diagnoses were identified by ANZPICR coding (see online data supplement) [17]. Associated diagnoses comprise syndromes, congenital anomalies, or diseases either present at ICU admission or identified during admission, including prematurity, congenital heart disease, chronic pulmonary, renal or liver disease, degenerative neurological disorders and immunocompromise (see online data supplement) [18, 19]. Among decedents, we compared the following modes of death: death despite maximal support; brain death; death with treatment limited but not withdrawn; and death following withdrawal of life-sustaining treatment (WLST). Previous ICU admission was defined as prior admission to the same ICU during the study.

Statistical analysis

Categorical data are presented as counts and percentages, and compared using Fisher's exact or Chi-squared test. Continuous data are reported as median with interquartile range (IQR) and compared using the Mann–Whitney *U* test or Kruskal–Wallis test. The relationship between year of admission and population level data per year is described using aggregated counts and relative percentage changes from 2006 to 2016. Relationships between admission year and rates or proportions of individual patient level data are analyzed using logistic regression. Receiver operating characteristic (ROC) curve analysis was used to determine the discriminatory ability of PIM2 for mortality. Changes in median PIM2 levels over time were evaluated by quantile regression on the median. PIM2 was used for risk adjustment in multivariable logistic regression modeling. Logistic regression modeling was used to obtain model-based predicted probabilities for mortality rates per study year. Trends in proportions

and rates are presented with 95% confidence intervals. Slopes were compared in a logistic regression framework by assessing the subgroup by year interaction terms. Statistical analyses were conducted using Stata (version 15.0, StataCorp LLC, College Station, Texas), and GraphPad Prism (version 8, GraphPad Software, La Jolla, California). A two-sided alpha level of 0.05 was used to determine statistical significance.

Results

Pediatric mortality in intensive care units

There were 103,367 pediatric ICU admissions during the study period, 2672 (2.6%) of whom died in ICU. Of these deaths, 2342 (87.6%) occured in a PICU and 330 (12.4%) in mixed ICUs (Fig. 1). Demographics and clinical characteristics of survivors and decedents are compared in Table 1. The area under the receiver operating curve for PIM2 in predicting mortality in our dataset was 0.89 (0.89–0.90). Median PIM2 risk of death decreased by 0.030% per year in the whole cohort (0.27–0.033, $p<0.001$) but not in the cohort of decedents ($p=0.750$). Pediatric ICU admissions increased by 40.3% and absolute numbers of pediatric deaths in ICU remained stable over the study period (Fig. 2a). This represents a decrease in both unadjusted mortality (0.1% per year, 95% CI 0.096–0.104; $p<0.001$) and risk-adjusted mortality (0.1%/year, 95% CI 0.07–0.13%; $p<0.001$, slopes compared $p=0.374$) (Fig. 2b). Against the background mortality rate of 2.6%, this represents a 3.9% per year reduction in expected pediatric ICU deaths. The annual ICU admission rate was 170/100,000 ANZ children, and population-based childhood admissions to an ICU rose by 25.8% during the study (146–183/100,000). Twelve percent of all childhood deaths in ANZ occurred in an ICU. While annual childhood deaths in ANZ declined, the proportion of these deaths occurring in ICU increased by 42.6% from 2006 to 2016.

Over the study period, changes in mortality rates differed by diagnostic category (Fig. 3a and online data supplement). In both unadjusted and risk-adjusted analyses, a decline in mortality was observed in trauma (0.36%/year, 95% CI 0.33–0.39%; $p<0.001$, adjusted $p=0.003$), sepsis (0.54%/year, 95% CI 0.51–0.57%; $p=0.001$, adjusted $p=0.038$), cardiac-surgical diagnoses (0.07%/year, 95% CI 0.06–0.08%; $p=0.004$, adjusted $p=0.004$) and respiratory pathology (0.13%/year, 95% CI 0.12–0.14%; $p<0.001$, adjusted $p=0.011$). Unadjusted mortality rates in patients admitted to ICU post-cardiopulmonary arrest increased by 0.97%/year (95% CI 0.96–0.99; $p=0.004$) and for patients with neurological diseases declined (0.14%/year, 95% CI 0.13–0.15%; $p=0.001$), following adjustment ($p=0.116$ and $p=0.151$, respectively). Mortality rates in patients with cardiac medical disease and other diagnoses were unchanged from 2006 to 2016 in unadjusted and risk-adjusted analyses ($p>0.1$).

Reduction in unadjusted ICU mortality was evident across all admission sources, with the greatest decline in admissions from hospital wards (0.20%, 95% CI 0.19-0.21%; $p<0.001$) (online data supplement). Whilst the fall in mortality amongst operating room admissions was the lowest magnitude amongst admission

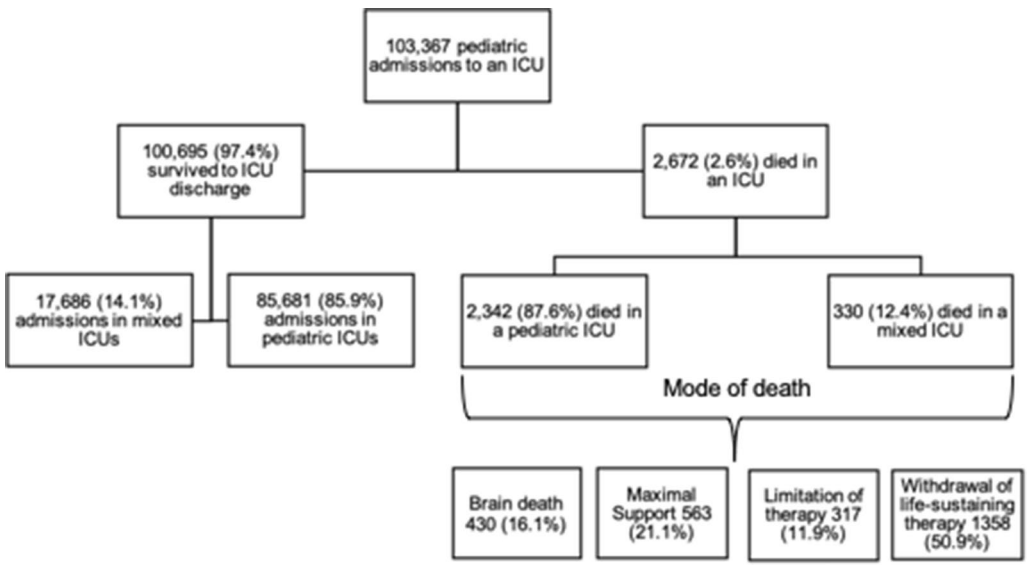

Fig. 1 Study population

Table 1 Comparison of survivors and decedents in pediatric admissions to an intensive care unit

Patient characteristic	Survival to ICU discharge, $n = 100,695$	Death in the ICU, $n = 2672$	*P* value
Male	57,676 (57.3)	1517 (56.8)	0.603
Age (months)	21.6 (4.7, 82.1)	15.0 (2.3, 76.8)	< 0.001
Age group			
Neonate up to 30 days	9601 (9.5)	461 (17.3)	< 0.001
> 30 days to 1 year	29,575 (29.4)	737 (27.6)	0.045
1–5 years	29,181 (29.0)	666 (24.9)	< 0.001
5–12 years	19,798 (19.7)	443 (16.6)	< 0.001
12–16 years	12,540 (12.5)	365 (13.7)	0.063
Pediatric Index of Mortality 2 (risk of death %)	1.0 (0.3, 2.8)	15.8 (4.4, 59.4)	< 0.001
Elective admission	36,846 (36.6)	250 (9.4)	< 0.001
Admission source			
Operating room	39,758 (39.5)	348 (13.0)	< 0.001
Emergency department	21,400 (21.3)	606 (22.7)	0.075
In-patient ward	17,730 (17.6)	667 (25.0)	< 0.001
Inter-hospital transport	21,807 (21.7)	1051 (39.3)	< 0.001
Diagnostic category*			
Cardiac surgical	15,055 (15.0)	133 (5.0)	< 0.001
Cardiac medical	5016 (5.0)	313 (11.7)	< 0.001
Respiratory	29,510 (29.3)	469 (17.6)	< 0.001
Neurological	14,540 (14.4)	365 (13.7)	0.258
Trauma	6192 (6.1)	275 (10.3)	< 0.001
Sepsis	2814 (2.8)	235 (8.8)	< 0.001
Pre-ICU arrest	1255 (1.2)	591 (22.1)	< 0.001
Other	26,313 (26.1)	291 (10.9)	< 0.001
Associated diagnosis*	60,246 (59.8)	1817 (68.0)	< 0.001
Previous ICU admission	39,709 (39.4)	707 (26.5)	< 0.001
Extracorporeal life support	708 (0.7)	317 (11.9)	< 0.001
Renal replacement therapy	2749 (2.7)	478 (17.9)	< 0.001
ICU length of stay			
Number of days	1.5 (0.8, 3.3)	3.4 (1.2, 10.0)	< 0.001
> 7 days	10,276 (10.2)	860 (32.2)	< 0.001
Intubation			
Proportion intubated	43,925 (43.6)	2511 (94.0)	< 0.001
Duration** (hours)	25.6 (10.3, 86.1)	69.6 (22.1, 209.9)	< 0.001

*Diagnostic category is main admission diagnosis, see online data supplement for diagnosis and associated diagnosis definitions. **Intubation duration in those intubated. Data are given as *n* (%) or median (IQR)

sources (0.049% 95% CI 0.046–0.052, $p = 0.001$), it remained significant following risk adjustment ($p < 0.001$) as opposed to ward, inter-hospital transfer and emergency department admission rates ($p = 0.166$, 0.077 and 0.724, respectively). The percentage of decedents with associated diagnoses increased over the study period (0.70%/year, 95% CI 0.69–0.71%; $p = 0.015$). Similarly, the percentage of decedents with previous ICU admissions increased (0.85%/yr, 95% CI 0.84–0.87; $p = 0.002$).

Mode of death

Mode of death was available for 2668 (99.9%) pediatric ICU deaths (Fig. 1 and Table 2). Demographics and admission characteristics differed by mode of death (Table 2). The most common mode of death was withdrawal of life-sustaining therapy (WLST, 51%). For children who died following WLST the median age was 9.9 (IQR 1.6, 56.6) months and median ICU stay was 5.1 (IQR 2.0, 12.9) days, with 42% staying > 7 days. Brain death was present in 16%. These patients were older than

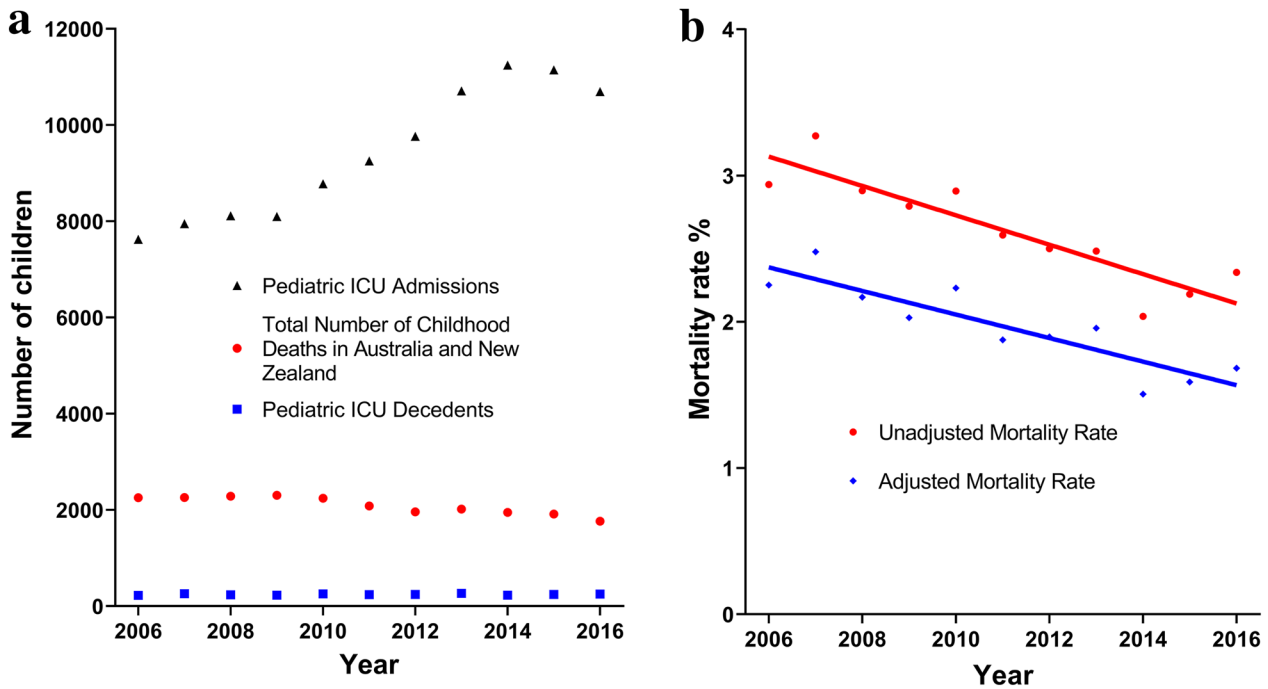

Fig. 2 **a** Australia and New Zealand childhood deaths, pediatric ICU admissions and pediatric ICU deaths over time. Absolute number of Australia and New Zealand childhood deaths (red circle), absolute number of pediatric ICU admissions (black triangle) and pediatric ICU deaths (blue square) over the study period. **b** Unadjusted and adjusted mortality rate over time. Unadjusted mortality rate (pediatric ICU deaths/pediatric ICU admissions (red circle)) and risk-adjusted mortality rate (PIM2) (blue diamond) over the study period. Empirical aggregated year-level data shown as symbols; line represents model-based fitted probabilities of ICU mortality for each study year

other modes (median 58.2 months; IQR 18.6, 135.0), and had shorter ICU stays (median 1.8 days; IQR 1.1, 3.2), with 23% in ICU > 7 days (all $p < 0.001$). Deaths occurred despite maximal support in 21%, and treatment was limited in 12%. Mode of death varied over the study period (Fig. 3b), with an increase in the proportion of brain death (0.72%/year, 95% CI 0.69–0.75%; $p = 0.001$) and a decline in maximal resuscitation at the end-of-life (0.92%/year, 95% CI 0.89–0.95%; $p < 0.001$). The proportion of children dying following treatment limitation or WLST remained stable ($p = 0.662$ and $p = 0.243$, respectively). Organ and/or tissue donation occurred in 7.4% of ICU deaths, representing 33.5% of brain dead patients and 3.5% of those dying following WLST.

Discussion

We report a binational, multicenter study demonstrating a reduction in pediatric ICU deaths. This mortality reduction persists when adjusted for severity of illness. Against the very low overall mortality rate in pediatric ICUs, this reduction holds both statistical and clinical relevance for families and society, as well as intensive care resource allocation, training and benchmarking. A small but increasing proportion of all ANZ childhood deaths occurred in ICUs. Half of all pediatric ICU deaths followed WLST. While the proportions of children dying following treatment limitation and WLST remained stable, rates of brain death increased and children dying despite maximal resuscitation declined.

Pediatric mortality in intensive care units

The unadjusted pediatric ICU mortality in ANZ of 2.6% is amongst the lowest in published literature, and is falling, consistent with United Kingdom (UK) registry reports [1, 4, 7, 21]. Whilst a small decrease in illness severity was observed, decreasing risk-adjusted ICU mortality over this period implies more children with comparable severity of illness are now surviving. Advances in PICU management may underlie this improvement in mortality, rather than lower ICU admission thresholds or decreased illness severity, but differences in subject characteristics and institutional practice variation mean contributing factors are difficult to elucidate [22]. The observed trends in our study may also reflect increasing acceptance of survival with greater disability [2, 8]. An alternative explanation for ICU mortality reduction may be that end-of-life care is being relocated to external locations such as wards, home or hospice. The pediatric ICU admission

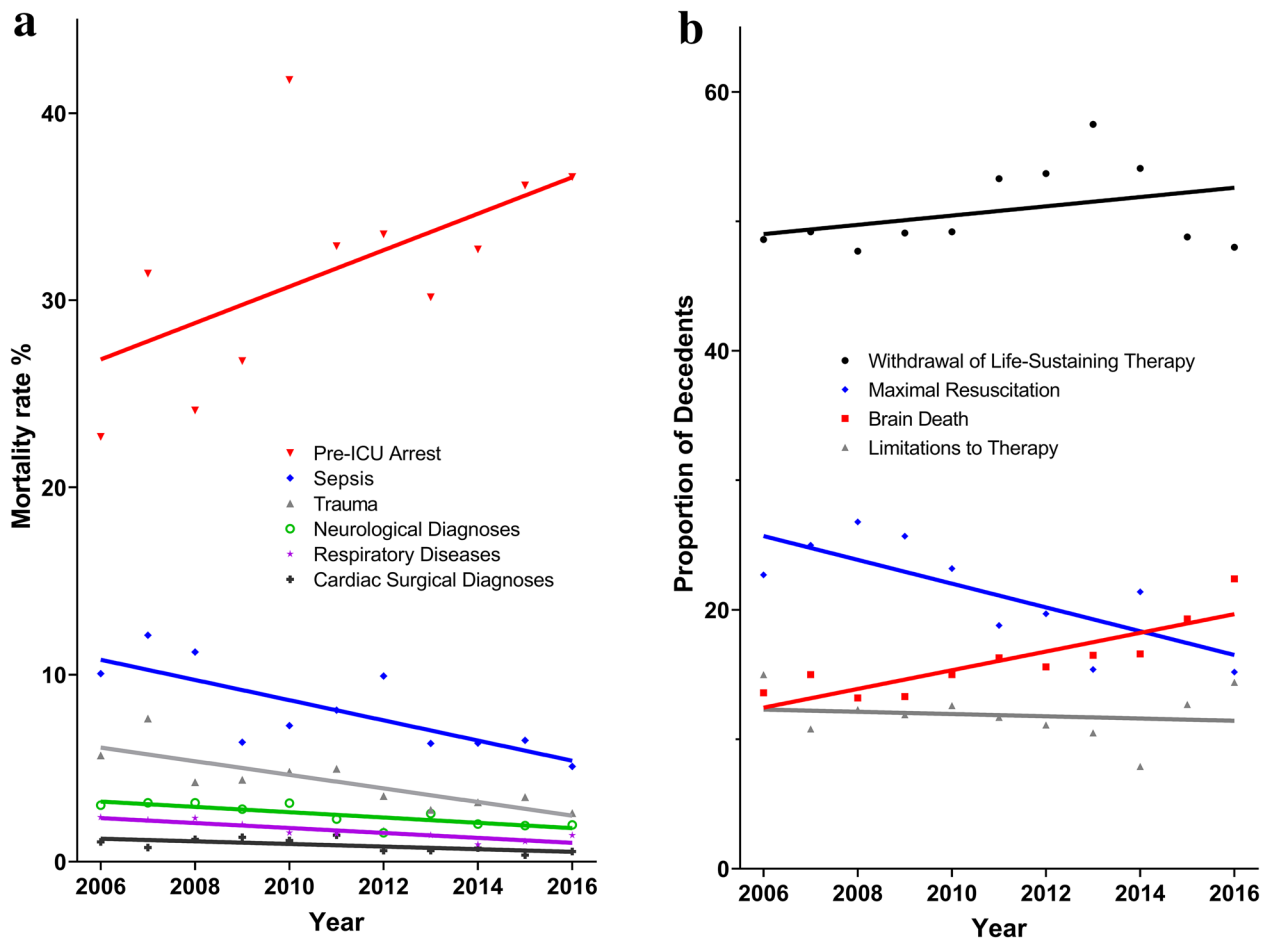

Fig. 3 **a** ICU Mortality Rate Over Time by Diagnostic Category. Mortality rate for pre-ICU arrest (red triangle), sepsis (blue diamond), trauma (gray triangle), neurological diagnoses (green circle), respiratory diseases (purple star) and cardiac surgical diagnoses (black cross). Empirical aggregated year-level data shown as symbols; line represents model-based fitted probabilities of ICU mortality for each study year. **b** Mode of death over time. Proportion of pediatric ICU deaths due to withdrawal of life-sustaining therapy (black circle), treatment limitation (gray triangle), brain death (red square) or despite maximal support (blue diamond) in 2668 children who died in an IUC over the study period. Empirical aggregated year-level data shown as symbols; line represents model-based fitted probabilities of ICU mortality for each study year

rate in ANZ rose more than population increases, similar to UK experience [14, 22]. Whilst we observed an increase in the proportion of ANZ childhood deaths that occur in ICU, the absolute proportion is low, comparable to UK registry reports but less than North American studies [10, 21, 23]. Overall, the location of childhood death seems to be shifting to the community setting [3, 24]. International disparities may reflect differences in hospice availability, numbers of out of hospital or NICU deaths, and regional variation in registry coding.

Unadjusted and risk-adjusted pediatric ICU mortality rates associated with cardiac-surgical, respiratory, sepsis and trauma diagnoses, as well as operating room admissions fell over time. These findings are aligned with trends outside the ICU and are likely attributable to public health safety campaigns, pre-hospital management and perioperative care improvements [18, 19, 25]. Deaths in children admitted from a hospital ward, the emergency department and following retrieval are decreasing; however, trends are non-significant following risk adjustment. Implementation of early warning scores, medical emergency teams, hospital quality initiatives and peripheral hospital care with improved disease severity recognition facilitating earlier ICU admission may be responsible [26, 27]. Our finding of increasing mortality in ICU admissions following pre-ICU cardiopulmonary arrest contrasts with US population outcome data and reported improvements in adult survival [28]. Compared with UK data, we report a higher proportion of ICU admissions following cardiopulmonary arrest, and these

Table 2 Pediatric deaths in intensive care units by mode of death

Patient characteristic	Brain death, *n* = 430 (16.1)	Maximal resuscitation, *n* = 563 (21.1)	Limitation of therapy, *n* = 317 (11.9)	Withdrawal of life-sustaining therapy, *n* = 1358 (50.9)	*P* value
Male	248 (57.7)	312 (55.4)	167 (52.7)	787 (58.0)	0.321
Age (months)	58.2 (18.6, 135.0)	13.8 (1.9, 74.1)	21.6 (3.6, 98.7)	9.9 (1.6, 56.6)	< 0.001
Pediatric Index of Mortality 2 (risk of death %)	69.0 (25.0,92.0)	11.5 (3.5,39.5)	9.6 (3.4,25.4)	13.6 (4.2,45.1)	< 0.001
Elective admission	10 (2.3)	73 (13.0)	26 (8.2)	141 (10.4)	< 0.001
Admission source					
Operating room	45 (10.5)	95 (16.9)	33 (10.4)	175 (12.9)	0.008
Emergency dept	159 (37.0)	115 (20.4)	65 (20.5)	266 (19.6)	< 0.001
In-patient ward	33 (7.7)	182 (32.3)	124 (39.1)	328 (24.2)	< 0.001
Inter-hospital transport	193 (44.8)	171 (30.4)	95 (30.0)	589 (43.4)	< 0.001
Diagnostic category*					< 0.001‡
Cardiac	10 (2.3)	128 (22.7)	53 (16.7)	255 (18.8)	
Respiratory	7 (1.6)	113 (20.1)	97 (30.6)	252 (18.6)	
Neurological	118 (27.4)	26 (4.6)	27 (8.5)	192 (14.1)	
Trauma	106 (24.7)	38 (6.7)	17 (5.4)	112 (8.2)	
Sepsis	16 (3.7)	97 (17.2)	24 (7.6)	98 (7.2)	
Pre-ICU arrest	157 (36.5)	88 (15.6)	50 (15.8)	296 (21.8)	
Associated diagnosis*	172 (40.0)	418 (74.2)	257 (81.1)	969 (71.4)	< 0.001
Previous ICU admission	39 (9.1)	179 (31.8)	130 (41)	359 (24.6)	< 0.001
ICU length of stay					
Days	1.8 (1.1, 3.2)	1.3 (0.4, 7.9)	3.9 (1.2, 15.0)	5.1 (2.0, 12.9)	< 0.001
> 7 days	23 (5.3)	150 (26.6)	116 (36.6)	571 (42.0)	< 0.001
Intubation					
Proportion intubated	430 (100)	540 (95.9)	236 (74.4)	2507 (94.0)	< 0.001
Duration (hours)	41.5 (23.8, 72.2)	14.2 (2.3, 148.6)	38.4 (0, 227.9)	106.7 (34.2, 262.7)	< 0.001
Organ donation**	144 (33.5)	7 (1.3)	0	48 (3.5)	< 0.001

Mode of death data available for 2668 pediatric patients who died in an ICU. Data are given as n (%) or median (IQR). **11 patients missing data on organ donation; organ donation includes tissue donation. ‡$p < 0.001$ for all diagnostic categories

children had a lower subsequent mortality [29]. Although this trend and the observed decrease in unadjusted mortality from neurological diagnoses become non-significant with risk adjustment, PIM2 includes pre-ICU arrest and several neurological conditions as a high-risk diagnosis covariate impacting interpretation. More research is warranted to determine if these results reflect changing pre-hospital practices, post-resuscitation care, changing illness severity or shifting ICU admission thresholds.

We report an increasing proportion of ICU decedents with associated diagnoses, consistent with international reports on children with life-limiting conditions (LLC) or complex chronic conditions (CCC) [5–7, 10, 30–33]. The overall proportion of children in our study with associated diagnoses closely approximates registry data for LLC and CCC in the UK, North America and Europe [5, 7, 30, 32]. Similar to our observations, rising readmission rates have been observed in UK and North American settings, particularly in patients with comorbidities [2, 34]. This growing population of children who experience recurrent PICU admissions and higher mortality rates has implications for ICU resource allocation and increases the need for ICUs to refine palliative care expertise [22].

Mode of death

Half of the pediatric ICU deaths in ANZ follow WLST. There is significant geographical and institutional variation in pediatric ICU mode of death with limited contemporary data on temporal trends [10, 23, 32, 35]. Treatment limitation or WLST occur in 44–84% of deaths in reports from diverse international settings, consistent with our findings of 63% [1, 8, 10, 11, 23, 35–37]. We found that the rate of WLST was unchanged over the 11-year study period, whereas there was a reduction in patients receiving maximal resuscitation at end-of-life. While historically children have been more likely to receive maximal intensive care therapies prior to death, reported rates of WLST are higher in some settings [1, 10, 11, 23, 37]. Declining rates of death despite maximal support may signify improved end-of-life care;

conversely, the lack of a concomitant increase in WLST may imply improved short term acute in-hospital resuscitation outcomes and availability of extracorporeal cardiopulmonary resuscitation. A single center US study reported that subspecialty palliative care involvement was associated with a reduction in deaths following failed resuscitation [23]. This supports the view that pre-emptive consideration of palliative care pathways for children with diminishing chance of survival is vital in the provision of intensive care.

The proportion of children diagnosed with brain death in our study was amongst the highest in contemporary literature from developed and developing nations, and was observed to be increasing [10, 23, 36–38]. Further research is required to determine if this reflects increasing diagnostic awareness and confidence diagnosing brain death in children, changing resuscitation practices or greater focus on identification and support of potential organ donors as a result of government Organ and Tissue Authority initiatives.

Strengths and limitations

The strengths of this study are the 11-year binational population-based analysis utilizing ANZPICR and government census data. The large sample size is a double-edged sword: it allows for a rigorous analysis of population-wide trends in mortality rates in ANZ along with potential generalizability, yet even small differences may reach statistical significance. The ANZPICR is well established, validated and regularly audited; however, as for any registry-based study, there may be variability in coding, and observed trends and associations can only be hypothesis generating. Several additional limitations must be considered when interpreting our results. The number of institutions contributing data to ANZPICR increased during the study, so the increase in reported annual PICU admissions may be partly due to improved capture of children in ICU. Identification of recurrent admissions for individual patients is limited to admissions to the same ICU during the study period, resulting in underestimation in our dataset. Children dying in NICUs are not recorded in ANZPICR, yet premature deaths are included in national census data. A small number of children are admitted to ICUs not reporting to the registry, accounting for < 10% of pediatric ICU admissions [14]. No international consensus definition exists for patients with comorbidities; however, the frequency of reported comorbid conditions is similar across international studies [6, 10, 24, 30, 39]. The associated diagnosis classification in ANZPICR incorporates chronic comorbidities and conditions that may be long standing at admission or congenital, along with complications that develop during intensive care that are serious or life-limiting. Our data cannot distinguish complications arising during the ICU admission from chronic disorders in children that die in ICU [7, 18, 19]. Whilst PIM2 demonstrated high discrimination in predicting death in our cohort, the incorporation of high-risk diagnoses limits interpretation of risk adjustment in diagnostic subgroup analyses. Post-hospital discharge outcome data and functional status are not collected, so it is not possible to ascertain whether increasing rates of ICU survivorship are associated with an increase in significant, life-limiting comorbidities. No cause of death or decision-making information regarding treatment limitation orders is recorded [33].

Implications and future considerations

The observed reduction in childhood ICU mortality in our study is encouraging. The epidemiology and mode of pediatric deaths in ICU appear to be changing over time with notable international variation. Both of these warrant further investigation via large-scale, population-based collaborative research efforts at an international level. Exploration of variation in patient and admission characteristics and outcomes between centers will better identify determinants of ICU mortality, guide performance benchmarking tools and facilitate quality improvement programs. Understanding current epidemiology of pediatric ICU death is essential for studies using mortality as a primary endpoint. Evaluating whether falling ICU mortality is associated with increased disability among pediatric survivors is a key area for future research, necessitating reliable measures of functional recovery and quality of life. This may provide additional evidence to look beyond mortality as a primary outcome measure [2, 8, 33]. The increasing prevalence of decedents with associated diagnoses and previous ICU admission implies that greater efforts should be directed toward addressing the needs of these children and their families, with opportunities for anticipatory palliative care and advanced care planning [7, 31]. A comprehensive understanding of changing modes of pediatric death and the relationship with subspecialty palliative care services has important implications for resource allocation [9, 10, 12, 22, 23]. Increasing incidence of brain death is highly relevant, with contemporary high profile cases and controversy [38, 40]. Our study emphasizes the importance of palliative care expertise in the PICU, as well as prioritizing pediatric and ICU trainee education about end-of-life management, brain death and organ and tissue donation.

Conclusion

Unadjusted and risk-adjusted ICU mortality for Australian and New Zealand children is declining. Most pediatric ICU deaths follow treatment limitation or withdrawal

of life sustaining therapy, with decreasing rates of maximal resuscitation at end-of-life and increasing brain death diagnoses. Further investigation via large-scale population-based collaborative research efforts at an international level are required to better inform pediatric critical care benchmarking, resource allocation and training requirements.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05675-1) contains supplementary material, which is available to authorized users.

Author details
[1] Department of Cardiology, Boston Children's Hospital, Boston, MA, USA. [2] Department of Pediatrics, Harvard Medical School, Boston, MA, USA. [3] Paediatric Critical Care Research Group, Child Health Research Centre, University of Queensland, Brisbane, Australia. [4] Paediatric Intensive Care Unit, Queensland Children's Hospital, Brisbane, Australia. [5] Department of Pediatrics, Inselspital, Bern University Hospital, Bern, Switzerland. [6] Royal Children's Hospital and Murdoch Children's Research Institute, Melbourne, Australia. [7] The Children's Hospital at Westmead, and Sydney Medical School, University of Sydney, Sydney, Australia. [8] Sydney Children's Hospital, Sydney, Australia. [9] Perth Children's Hospital, Perth, Australia. [10] Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, MA, USA. [11] Department of Paediatrics, University of Melbourne, Melbourne, Australia.

Acknowledgements
The authors would like to thank centers that contribute registry data and the individuals at each center who collect and enter the data, along with staff from the Australian and New Zealand Pediatric Intensive Care Registry (ANZPICR) and the ANZICS Centre for Outcome and Resource Evaluation (ANZICS CORE). The Pediatric Study Group (ANZICR PSG) members include: Simon Erickson, Samantha Barr, Perth Children's Hospital, Perth, Australia; Luregn Schlapbach (Chair), Andreas Schibler, Debbie Long, Jan Alexander (ANZPIC registry), Queensland Children's Hospital, Brisbane, Australia; Anusha Ganeshalingam, Claire Sherring, Starship Children's Hospital, Auckland, New Zealand; Gary Williams, Vicky Smith, Sydney Children's Hospital, Randwick, Australia; Johnny Millar (ANZPIC registry lead), Warwick Butt, Carmel Delzoppo, Royal Children's Hospital, Melbourne, Australia; Felix Oberender, Monash Children`s Hospital, Melbourne, Australia; Subodh Ganu, Georgia Letton, Women's and Children's Hospital, Adelaide, Australia; Marino Festa (Past Chair), Jonathan Egan, Gail Harper, Westmead Children's Hospital, Sydney, Australia. Statistical support for this study was funded by the Norva Dhalia grant from the College of Intensive Care Medicine (CICM) and resources (statistical analysis and support) were utilized from Boston Children's Hospital.

Funding
This work was supported by the Norva Dhalia Grant (College of Intensive Care Medicine) to KM. LJS is supported by a Practitioner Fellowship of the National Health and Medical Research Council of Australia and New Zealand, and by the Children`s Hospital Foundation, Brisbane, Australia.

Compliance with ethical standards

Conflicts of interest
The authors have not declared any conflict of interest. This work was supported by the Norva Dhalia Grant (College of Intensive Care Medicine) to KM. LJS is supported by a Practitioner Fellowship of the National Health and Medical Research Council of Australia and New Zealand, and by the Children`s Hospital Foundation, Brisbane, Australia.

Publisher's Note

Received: 3 March 2019 Accepted: 19 June 2019
Published online: 3 July 2019

References

1. Burns JP, Sellers DE, Meyer EC, Lewis-Newby M, Truog RD (2014) Epidemiology of death in the PICU at five U.S. teaching hospitals*. Crit Care Med 42:2101–2108
2. Pearson GA (2018) Intensive care: because we can or because we should? Arch Dis Child 103:527–528
3. Fraser LK, Fleming S, Parslow R (2018) Changing place of death in children who died after discharge from paediatric intensive care units: a national, data linkage study. Palliat Med 32:337–346
4. McShane P, Draper ES, McKinney PA, McFadzean J, Parslow RC, Paediatric Intensive Care Audit N (2013) Effects of out-of-hours and winter admissions and number of patients per unit on mortality in pediatric intensive care. J Pediatr 163(1039–1044):e1035
5. Cremer R, Leclerc F, Lacroix J, Ploin D, Group GRCDiPS (2009) Children with chronic conditions in pediatric intensive care units located in predominantly French-speaking regions: prevalence and implications on rehabilitation care need and utilization. Crit Care Med 37:1456–1462
6. Edwards JD, Houtrow AJ, Vasilevskis EE, Rehm RS, Markovitz BP, Graham RJ, Dudley RA (2012) Chronic conditions among children admitted to U.S. pediatric intensive care units: their prevalence and impact on risk for mortality and prolonged length of stay*. Crit Care Med 40:2196–2203
7. Fraser LK, Parslow R (2018) Children with life-limiting conditions in paediatric intensive care units: a national cohort, data linkage study. Arch Dis Child 103:540–547
8. Laussen PC (2016) Modes and causes of death in pediatric cardiac intensive care: digging deeper. Pediatr Crit Care Med 17:461–462
9. Committee on Approaching Death: Addressing Key End of Life Issues; Institute of Medicine (2015) Dying in America: improving quality and honoring individual preferences near the end of life. Appendix B; progress and significant remaining gaps and appendix F; pediatric end-of-life and palliative care: epidemiology and health service use. Washington (DC): National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK285681/. Accessed 01 Oct 2017
10. Meert KL, Keele L, Morrison W, Berg RA, Dalton H, Newth CJ, Harrison R, Wessel DL, Shanley T, Carcillo J, Clark A, Holubkov R, Jenkins TL, Doctor A, Dean JM, Pollack M, Eunice Kennedy Shriver National Institute of Child H, Human Development Collaborative Pediatric Critical Care Research N (2015) End-of-Life practices among tertiary care PICUs in the United States: a multicenter study. Pediatr Crit Care Med 16:e231–238
11. Launes C, Cambra FJ, Jordan I, Palomeque A (2011) Withholding or withdrawing life-sustaining treatments: an 8-yr retrospective review in a Spanish pediatric intensive care unit. Pediatr Crit Care Med 12:e383–385
12. Hospice Section On, Medicine Palliative, Care Committee On Hospital (2013) Pediatric palliative care and hospice care commitments, guidelines, and recommendations. Pediatrics 132:966–972
13. Moynihan K, Alexander P, Millar J, Schlapbach L, Jacobe S, Ravindranathan H, Croston E, Gelbart B, Burns J (2018) Abstract P-359. Pediatr Crit Care Med 19(6S):156–157. https://doi.org/10.1097/01.pcc.0000537816.30679.b9
14. Australian and New Zealand Paediatric Intensive Care Registry (ANZPICR) (2016) ANZPIC Registry Annual Report. ANZPIC Centre for Outcome and Resource Evaluation (CORE). https://www.anzics.com.au/wp-content/uploads/2018/08/ANZPICR-Annual-Report-2016.pdf Accessed 05 Oct 2018
15. Australian Bureau of Statistics (2016) Australian population by age and sex, 3101.0 Australian Demographic Statistics. http://www.abs.gov.au/Ausstats/abs@.nsf/mf/3101.0. Accessed 01 Oct 2017
16. Statistics New Zealand (2016) Population: age-specific death rates by sex, December years (total population). https://www.stats.govt.nz/topics/population. Accessed 01 Oct 2017
17. Slater A, Shann F, McEniery J, Group AS (2003) The ANZPIC registry diagnostic codes: a system for coding reasons for admitting children to intensive care. Intensive Care Med 29:271–277

18. Schlapbach LJ, Straney L, Alexander J, MacLaren G, Festa M, Schibler A, Slater A, Group APS (2015) Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. Lancet Infect Dis 15:46–54
19. Schlapbach LJ, MacLaren G, Festa M, Alexander J, Erickson S, Beca J, Slater A, Schibler A, Pilcher D, Millar J, Straney L, Australian, New Zealand Intensive Care Society Centre for O, Resource E, Australian, New Zealand Intensive Care Society Paediatric Study G (2017) Prediction of pediatric sepsis mortality within 1 h of intensive care admission. Intensive Care Med 43:1085–1096
20. Slater A, Shann F, Pearson G, Paediatric Index of Mortality Study G (2003) PIM2: a revised version of the paediatric index of mortality. Intensive Care Med 29:278–285
21. Paediatric Intensive Care Audit Network (PICANet) (2018) PICANet 2018 annual report. Leeds: PICANet. www.picanet.org.uk. Accessed 05 Apr 2019
22. Davis P, Stutchfield C, Evans TA, Draper E (2018) Increasing admissions to paediatric intensive care units in England and Wales: more than just rising a birth rate. Arch Dis Child 103:341–345
23. Trowbridge A, Walter JK, McConathey E, Morrison W, Feudtner C (2018) Modes of death within a Children's Hospital. Pediatrics 142:e20174182
24. Feudtner C, Feinstein JA, Satchell M, Zhao H, Kang TI (2007) Shifting place of death among children with complex chronic conditions in the United States, 1989–2003. JAMA 297:2725–2732
25. Workman JK, Ames SG, Reeder RW, Korgenski EK, Masotti SM, Bratton SL, Larsen GY (2016) Treatment of pediatric septic shock with the surviving sepsis campaign guidelines and PICU patient outcomes. Pediatr Crit Care Med 17:e451–e458
26. Mumford V, Greenfield D, Hogden A, Debono D, Gospodarevskaya E, Forde K, Westbrook J, Braithwaite J (2014) Disentangling quality and safety indicator data: a longitudinal, comparative study of hand hygiene compliance and accreditation outcomes in 96 Australian hospitals. BMJ Open 4:e005284
27. Tibballs J, Kinney S (2009) Reduction of hospital mortality and of preventable cardiac arrest and death on introduction of a pediatric medical emergency team. Pediatr Crit Care Med 10:306–312
28. Jayaram N, McNally B, Tang F, Chan PS (2015) Survival after out-of-hospital cardiac arrest in children. J Am Heart Assoc 4:e002122
29. Scholefield BR, Gao F, Duncan HP, Tasker RC, Parslow RC, Draper ES, McShane P, Davies P, Morris KP (2015) Observational study of children admitted to United Kingdom and Republic of Ireland Paediatric Intensive Care Units after out-of-hospital cardiac arrest. Resuscitation 97:122–128
30. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D (2014) Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr 14:199
31. Feudtner C, Kang TI, Hexem KR, Friedrichsdorf SJ, Osenga K, Siden H, Friebert SE, Hays RM, Dussel V, Wolfe J (2011) Pediatric palliative care patients: a prospective multicenter cohort study. Pediatrics 127:1094–1101
32. Forjaz de Lacerda A, Gomes B (2017) Trends in cause and place of death for children in Portugal (a European country with no Paediatric palliative care) during 1987–2011: a population-based study. BMC Pediatr 17:215
33. Namachivayam P, Shann F, Shekerdemian L, Taylor A, van Sloten I, Delzoppo C, Daffey C, Butt W (2010) Three decades of pediatric intensive care: who was admitted, what happened in intensive care, and what happened afterward. Pediatr Crit Care Med 11:549–555
34. Bucholz EM, Toomey SL, Schuster MA (2019) Trends in pediatric hospitalizations and readmissions: 2010–2016. Pediatrics 143:e20181958
35. Zimmermann K, Cignacco E, Engberg S, Ramelet AS, von der Weid N, Eskola K, Bergstraesser E, Consortium P, Ansari M, Aebi C, Baer R, Popovic MB, Bernet V, Brazzola P, Bucher HU, Buder R, Cagnazzo S, Dinten B, Dorsaz A, Elmer F, Enriquez R, Fahrni-Nater P, Finkbeiner G, Frey B, Frey U, Greiner J, Hassink RI, Keller S, Kretschmar O, Kroell J, Laubscher B, Leibundgut K, Malaer R, Meyer A, Stuessi C, Nelle M, Neuhaus T, Niggli F, Perrenoud G, Pfammatter JP, Plecko B, Rupf D, Sennhauser F, Stade C, Steinlin M, Stoffel L, Thomas K, Vonarburg C, von Vigier R, Wagner B, Wieland J, Wernz B (2018) Patterns of paediatric end-of-life care: a chart review across different care settings in Switzerland. BMC Pediatr 18:67
36. Siddiqui NU, Ashraf Z, Jurair H, Haque A (2015) Mortality patterns among critically ill children in a pediatric intensive care unit of a developing country. Indian J Crit Care Med 19:147–150
37. Kipper DJ, Piva JP, Garcia PC, Einloft PR, Bruno F, Lago P, Rocha T, Schein AE, Fontela PS, Gava DH, Guerra L, Chemello K, Bittencourt R, Sudbrack S, Mulinari EF, Morais JF (2005) Evolution of the medical practices and modes of death on pediatric intensive care units in southern Brazil. Pediatr Crit Care Med 6:258–263
38. Kirschen MP, Francoeur C, Murphy M, Traynor D, Zhang B, Mensinger JL, Ichord R, Topjian A, Berg RA, Nishisaki A, Morrison W (2019) Epidemiology of brain death in pediatric intensive care units in the United States. JAMA Pediatr. https://doi.org/10.1001/jamapediatrics.2019.0249
39. Pearson GA, Ward-Platt M, Kelly D (2011) How children die: classifying child deaths. Arch Dis Child 96:922–926
40. Lewis A, Greer D (2017) Current controversies in brain death determination. Nat Rev Neurol 13:505–509