FACTORS INVOLVED IN MORTALITY OF LOW-RISK PEDIATRIC INTENSIVE CARE PATIENTS

CARIN VERLAAT

FACTORS INVOLVED IN MORTALITY OF LOW-RISK PEDIATRIC INTENSIVE CARE PATIENTS

CARIN VERLAAT

The work presented in this thesis was carried out within the Radboud Institute for Health Sciences. Publication of this thesis was financially supported by the by the Radboud University Medical Centre and by the Stichting Spoedeisende hulp bij Kinderen.

Cover and lay out: © evelienjagtman.com
Printing: Ridderprint

ISBN: 978 94 649 1312 5

FACTORS INVOLVED IN MORTALITY OF LOW-RISK PEDIATRIC INTENSIVE CARE PATIENTS

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 21 mei 2024
om 10.30 uur precies

door

Catharina Wilhelmus Maria Verlaat
geboren op 17 juli 1964
te Oosterhout

Promotoren:
Prof. dr. J.G. van der Hoeven
Prof. dr. J.A. Hazelzet (Erasmus Universiteit Rotterdam)

Copromotoren:
Dr. J. Lemson
Dr. H.W.M. Zegers

Manuscriptcommissie:
Prof. dr. G.P. Westert
Prof. dr. M. de Hoog (Erasmus Universiteit Rotterdam)
Dr. J. Fuijkschot

Table of contents

CHAPTER 1

INTRODUCTION AND OUTLINE OF THIS THESIS

Introduction

Children, who are admitted to the Pediatric Intensive Care Unit (PICU) suffer from severe and sometimes life-threatening conditions. They use multiple medicines and need technical support like mechanical ventilation. Most of the children recover, but some children die during their PICU stay.

Over the last decades, PICU mortality in the more economically developed countries has declined substantially from around 9% to approximately 2-4% (1-3). This is due to many factors, including factors that are not healthcare related, such as improvements in road safety, seatbelts, bike-helmets, swimming lessons, less poverty etcetera. Prevention of infectious diseases, faster recognition of severely ill children, higher levels of care in the hospital ward and improvements in PICU care also contributed to the decline in PICU mortality. The last decade, focus on PICU outcomes is no longer restricted to mortality alone. Short and long-term outcome, functional outcome, mental and cognitive outcomes and quality of life are becoming increasingly important (4-6). Nevertheless, PICU-mortality remains an important outcome measure.

When studying (P)ICU outcome, it is important to correct for the severity of illness. This is done by using 'mortality prediction models', also known as 'severity of illness models'. These models have been developed in both the adult intensive care unit (ICU) and PICU to predict outcome, in particular mortality (1, 2, 7-15). They are useful for standardizing results of research and for comparing the quality of patient care between (P)ICUs. The ultimate goal of these scoring systems is to improve quality of care.

The mortality risk of PICU patients, as measured by prediction models, may vary between groups of patients. The majority of the PICU patients has a mortality risk of less than 1% or between 1-5% (1, 11). In a group of patients with a low mortality risk, the number of deaths will be low (but not zero). The model itself only gives a predicted mortality risk, does not perform perfectly, and also does not explain the underlying reason why a patient dies. Low-risk PICU nonsurvivors are potentially an interesting population. If low-risk PICU patients die, death can be considered as 'unexpected'. Mortality, despite low severity of illness score, might be attributed to factors not included in the model or to possibly preventable causes like healthcare related harm. Studying 'unexpected deaths' may be an efficient way to study healthcare related harm, since in a study among hospital deaths, the unexpected deaths had a higher prevalence of problems related to quality of care compared to all hospital deaths (16). Therefore, identifying the reasons why low-risk patients die might reveal opportunities to improve the safety and quality of PICU care (16).

An imaginary example of a patient with a low predicted mortality risk who is exposed to healthcare related harm, is given below.

Boy John, an infant of two months, develops a cough and dyspnea and is admitted to the hospital. The diagnosis of bronchiolitis is made, an infection of the airways caused by a virus. He receives extra oxygen and is admitted to the PICU because of high work of breathing. The next day, the work of breathing worsens, he is intubated and is put on a mechanical ventilator. He gets a central intravenous line to give sedative medications. His parents are overwhelmed at first by the sudden deterioration and the sight of all the machines, tubes, lines and sedatives that he is receiving. The nurses and doctors assure them however that his situation is stable and he will recover in about a week.

After several days, John develops a high fever. He is treated with antibiotics. Despite these interventions, he gets sicker. He develops a severe 'septic shock', with a low blood pressure during many hours. He receives medication to support the circulation. The next day, it is discovered that a mistake has been made in the dosage of the antibiotics. The dosage was ten-fold too low. The dosage is increased. Gradually, John recovers and the sedative medications are stopped. However, he does not wake up. A scan of the brain reveals severe and irreversible damage, probably induced by the ischemia during the period of low blood pressure. It is decided to stop the mechanical ventilation, and John dies, two weeks after being admitted to the pediatric intensive care.

In the imaginary example, a central line infection that was inadequately treated, changed the outcome of the patient. The central line infection itself and the mistake in the dosage of the antibiotics are examples of so called 'adverse events'. Adverse events are unintended injuries, caused by healthcare management rather than by the patient's underlying disease. In this case, the adverse events resulted in a septic shock, hypotension, cerebral ischemia and, finally, death.

There has been extensive research on healthcare related harm (adverse events) and avoidable death among the hospital population, both internationally and in the Netherlands (17-19). There are several studies on healthcare related harm in the general PICU population (20, 21). There is hardly any research however on healthcare related harm in low-risk PICU nonsurvivors.

An important but unanswered question is if death of low-risk PICU patients might be preventable in some cases. Can we discover the reasons why some of these children die? Can we find opportunities for increasing quality of care in the PICU? In the example of boy John, death probably could have been prevented. This thesis tries to unravel the above-mentioned questions.

Aims and outline of this thesis

The aim of this thesis is to study factors involved in mortality of low-risk PICU patients, defined as PICU patients with a low predicted mortality risk (<1%) that died during their PICU stay. Studying these 'unexpected deaths' might reveal opportunities to improve quality of PICU care.

In order to differentiate between low-risk patients and other PICU patients, we also studied patients at the other end of mortality range, the high-risk PICU patients (predicted mortality risk ≥ 30%). Are the same factors involved in the death of high-risk PICU patients?

The main research questions in this thesis are:

1. What factors are associated with death in low-risk PICU patients and in high-risk PICU patients?
2. What is the occurrence of adverse events in low-risk PICU patients and in high-risk PICU patients?
3. What is the contribution of (preventable) adverse events in death of low-risk PICU patients?

In **Chapter 2**, a retrospective cohort study on factors associated with death of low-risk PICU patients is presented. **Chapter 3** is a retrospective cohort study on factors involved in mortality of high-risk PICU patients. **Chapter 4** is an exploratory study on adverse events in low-risk PICU nonsurvivors in two PICUs. **Chapter 5** is a nationwide case control study of adverse events in low-risk PICU nonsurvivors, compared with low-risk survivors, high-risk nonsurvivors and high-risk survivors. In **Chapter 6**, the main findings and conclusions of this thesis are discussed and recommendations for future research are given. In the last two chapters (**Chapter 7 and 8**) a summary and Dutch summary are given.

Reference list

1. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med. 1988;16(11):1110-6.
2. Pollack MM, Holubkov R, Funai T, Dean JM, Berger JT, Wessel DL, et al. The Pediatric Risk of Mortality Score: Update 2015. Pediatr Crit Care Med. 2016;17(1):2-9.
3. Moynihan KM, Alexander PMA, Schlapbach LJ, Millar J, Jacobe S, Ravindranathan H, et al. Epidemiology of childhood death in Australian and New Zealand intensive care units. Intensive Care Med. 2019;45(9):1262-71.
4. Pollack MM, Holubkov R, Glass P, Dean JM, Meert KL, Zimmerman J, et al. Functional Status Scale: new pediatric outcome measure. Pediatrics. 2009;124(1):e18-28.
5. Biagas KV, Hardart GE. The importance of functional outcomes in the PICU. Pediatr Crit Care Med. 2013;14(1):100-1.
6. Ebrahim S, Singh S, Hutchison JS, Kulkarni AV, Sananes R, Bowman KW, et al. Adaptive behavior, functional outcomes, and quality of life outcomes of children requiring urgent ICU admission. Pediatr Crit Care Med. 2013;14(1):10-8.
7. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med. 1981;9(8):591-7.
8. Apolone G, Bertolini G, D'Amico R, Iapichino G, Cattaneo A, De Salvo G, et al. The performance of SAPS II in a cohort of patients admitted to 99 Italian ICUs: results from GiViTI. Gruppo Italiano per la Valutazione degli interventi in Terapia Intensiva. Intensive Care Med. 1996;22(12):1368-78.
9. Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. JAMA. 1993;270(20):2478-86.
10. Zimmerman JE, Kramer AA, McNair DS, Malila FM, Shaffer VL. Intensive care unit length of stay: Benchmarking based on Acute Physiology and Chronic Health Evaluation (APACHE) IV. Crit Care Med. 2006;34(10):2517-29.
11. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med. 1997;23(2):201-7.
12. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996;24(5):743-52.
13. Slater A, Shann F, Group APS. The suitability of the Pediatric Index of Mortality (PIM), PIM2, the Pediatric Risk of Mortality (PRISM), and PRISM III for monitoring the quality of pediatric intensive care in Australia and New Zealand. Pediatr Crit Care Med. 2004;5(5):447-54.
14. Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care*. Pediatr Crit Care Med. 2013;14(7):673-81.
15. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26(11):1793-800.
16. Hannan EL, Bernard HR, O'Donnell JF, Kilburn H, Jr. A methodology for targeting hospital cases for quality of care record reviews. Am J Public Health. 1989;79(4):430-6.

17. Kohn LT, Corrigan J, Donaldson MS, Institute of Medicine (U.S.). Committee on Quality of Health Care in America. To err is human : building a safer health system. Washington, D.C.: National Academy Press; 2000. xxi, 287 p. p.
18. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ. 2004;170(11):1678-86.
19. Zegers M, de Bruijne MC, Wagner C, Hoonhout LH, Waaijman R, Smits M, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. Qual Saf Health Care. 2009;18(4):297-302.
20. Larsen GY, Donaldson AE, Parker HB, Grant MJ. Preventable harm occurring to critically ill children. Pediatr Crit Care Med. 2007;8(4):331-6.
21. Agarwal S, Classen D, Larsen G, Tofil NM, Hayes LW, Sullivan JE, et al. Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med. 2010;11(5):568-78.

CHAPTER 2

FACTORS ASSOCIATED WITH MORTALITY IN LOW-RISK PEDIATRIC CRITICAL CARE PATIENTS IN THE NETHERLANDS

Carin W. Verlaat
Idse H. Visser
Nina Wubben
Jan A. Hazelzet
Joris Lemson
Dick van Waardenburg
Douwe van der Heide
Nicolette A. van Dam
Nicolaas J. Jansen
Marc van Heerde
Cynthia van der Starre
Roelie van Asperen
Martin Kneyber
Job B. van Woensel
Mark van den Boogaard
Johannes van der Hoeven

on behalf of the SKIC (Dutch Collaborative PICU Research Network)

Pediatr Crit Care Med 2017; 18:e155–e161

Abstract

Objective: To determine differences between survivors and nonsurvivors and factors associated with mortality in pediatric intensive care patients with low risk of mortality.

Design: Retrospective cohort study.

Setting: Patients were selected from a national database including all admissions to the PICUs in The Netherlands between 2006 and 2012.

Patients: Patients less than 18 years old admitted to the PICU with a predicted mortality risk lower than 1% according to either the recalibrated Pediatric Risk of Mortality or the Pediatric Index of Mortality 2 were included.

Interventions: None.

Measurements and Main Results: In total, 16,874 low-risk admissions were included of which 86 patients (0.5%) died. Nonsurvivors had more unplanned admissions (74.4% vs 38.5%; $p < 0.001$), had more complex chronic conditions (76.7% vs 58.8%; $p = 0.001$), were more often mechanically ventilated (88.1% vs 34.9%; $p < 0.001$), and had a longer length of stay (median, 11 [interquartile range, 5–32] d vs median, 3 [interquartile range, 2–5] d; $p < 0.001$) when compared with survivors. Factors significantly associated with mortality were complex chronic conditions (odds ratio, 3.29; 95% CI, 1.97–5.50), unplanned admissions (odds ratio, 5.78; 95% CI, 3.40–9.81), and admissions in spring/summer (odds ratio, 1.67; 95% CI, 1.08–2.58).

Conclusions: Nonsurvivors in the PICU with a low predicted mortality risk have recognizable risk factors including complex chronic condition and unplanned admissions.

Introduction

Over the last decades, the mortality rate in the PICU in the more economically developed countries has decreased substantially from around 9% (United States, 1980–1985) to approximately 3% (1–5). The PICU mortality rate in The Netherlands has decreased from 7.1% in 1992 to 2.9% in 2013 (6–9). The PICU care in The Netherlands has been organized in eight tertiary centers. The Pediatric Intensive Care Evaluation (PICE) data registry is evaluating practices and outcomes of all patients admitted to the PICUs in The Netherlands since 2003. To predict the mortality risk for PICU patients, the PICE registry is using both Pediatric Risk of Mortality (PRISM) and Pediatric Index of Mortality 2 (PIM2) (1, 9, 10). Eighty percent of the children admitted to a Dutch PICU between 2006 and 2009 had a predicted mortality risk lower than 10% according to both prediction models (9).

Nonsurvival within the low-risk subpopulation may reflect avoidable mortality and thus substandard quality of care (11). It is unknown whether there are differences between low-risk PICU survivors and nonsurvivors. Identifying these differences may recognize currently unknown risk factors and may lead to improvement of care for this population.

Therefore, the aim of this study is to determine differences between survivors and nonsurvivors of PICU patients with a low risk of mortality and to determine which factors are associated with mortality in the low-risk group.

Materials and methods

Study Population

Patients less than 18 years old with a low predicted mortality risk who were admitted to one of the eight PICUs in The Netherlands between January 1, 2006, and January 1, 2012, were included in this study. A "low mortality risk" was defined as a predicted mortality risk less than 1% according to either the PRISM II (referred to as PRISM) or the PIM2 risk score (9). In this study, both models were recalibrated to predict the overall mortality in the total population in this particular 6-year period without altering the relative weights of risk factors in the models and thus retaining the discriminative power of the original models (9).

Patients who were already dead before PICU admission (e.g., patients admitted for organ transplantation already being brain-dead) or patients admitted for palliative care, patients dying within 2 hours of PICU admission, and patients transferred to another ICU during their PICU treatment were excluded from the study. Data of patients that did not pass quality control during local site audit visits and were excluded from the annual reports were also excluded from the study.

Cases who died in the PICU were defined as nonsurvivors of the PICU, controls as survivors.

The Institutional Review Board waived the need for informed consent.

Design

This was a retrospective cohort study based on prospectively collected data from the Dutch PICE registry.

PICE Registry

The PICE registry was established in 2000 as an independent national nonprofit foundation to develop and maintain a continuous registration of data relating to all children admitted to all pediatric intensive care departments in The Netherlands (12). The database contains anonymized information regarding characteristics of patients and admission, severity of illness and risk of mortality (PRISM and PIM2), treatment, and patient outcome (1, 10, 13). For the primary admission diagnosis, underlying and associated diagnoses, the "Australian and New Zealand Paediatric Intensive Care" (ANZPIC) coding system is being used (14). Data quality is assessed using standard procedures including audit site visits. Mortality is registered as PICU mortality.

Data Collection and Definitions

To determine differences between both groups, variables were included that represented several aspects of the PICU stay as defined in the PICE code book, such as variables describing the circumstances of admission, physiologic state, PRISM and PIM2, and patient outcome.

A "complex chronic condition" (CCC) was defined according to Feudtner et al (15) as "any medical condition that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or one organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center." The PICE registry uses the ANZPIC registry diagnostic code list (14). An admission was classified as having a CCC if either the primary diagnosis, the primary underlying diagnosis, or the first additional diagnosis was a diagnosis defined as a CCC according to a modified list by Feudtner et al (15–17). PICE diagnoses not appearing on these lists were classified before analyzing the data according to expert opinion (C.W.V., J.L.). The list of the PICE database diagnoses grouped as a CCC is described in Appendix (Supplemental Digital Content 1, http://links.lww.com/PCC/A387).

"Admission outside office hours" was defined as admission between 6:00 p.m. and 8:00 a.m. on weekdays, or on a Saturday or Sunday (18). "Specialized transport upon admission" was defined as a transport to the PICU center by a specialized transport team accompanied by a pediatric intensivist, neonatologist, or specialized trauma team. "Readmission" was defined as a readmission within 48 hours after discharge from the PICU.

Statistical Analysis

The data were first checked for nonvalid data. Illogical and impossible values that surpassed physiologic threshold values were excluded if the value likely resulted from a typo or a measurement error. In case of typo/measurement error, the corresponding PIM2 or PRISM value was coded as "invalid." (Examples of typo/measurement errors: diastolic blood pressure > 400 mm Hg, low Pao_2 in combination with cyanotic congenital heart disease which by definition should be excluded from PRISM score.) Depending on their distribution, differences between cases and controls for continuous variables were tested using the Student *t* test or Mann-Whitney *U* test. For dichotomous variables, Fisher exact test or chi-square test was used.

To determine associations between PICU mortality and risk factors, a multivariable logistic regression model was used. For the number of independent variables that can be included in the regression model, the rule of thumb is the number of cases divided by 10, as long as the number of noncases is the same or higher (19). The number of cases let us to include a maximum of eight independent variables in the final analysis. Subsequently, several variables were recoded/dichotomized. Criteria for choosing the variables were significant result of the univariable logistic regression analysis, being present at admission, not being part of the PIM/PRISM score and no relevant interaction with another variable. The only exception on variables not being part of a mortality score was the variable "unplanned admission," which is part of the PIM2 model but not of the PRISM model. "Statistically significant" was defined as *p* value of less than 0.05. Statistical analyses were performed using IBM SPSS Statistics version 22.0 (Chicago, IL). During the process, an independent statistician was involved.

Results

Population Characteristics

In total, there were 30,778 PICU admissions, 29,707 survivors and 1,073 nonsurvivors (3.5%). A total of 1,422 admissions (55 nonsurvivors) were excluded based on nonvalid data (admissions not passing quality control, not included in the annual PICE reports or no known mortality risk). A total of 1,023 admissions (54 nonsurvivors) were excluded based on the exclusion criteria. Those admissions were either admitted with infaust prognosis, died within 2 hours after admission and therefore did not fulfill criteria to obtain PRISM or were greater than 18 years old (Fig. 1). A total of 11,459 admissions with a mortality risk greater than or equal to 1% were excluded. The remaining 16,874 patients (54.8%) had a low mortality risk and were included. Of these patients with a low mortality risk in total, 86 patients (0.5%) died in the PICU. Their median age was 4 years (interquartile range [IQR], 0–11), the median recalibrated PRISM mortality was 0.62% (IQR, 0.46–0.94%), and median PIM2 recalibrated mortality risk was 0.84% (IQR, 0.40–1.36%) (Table 1).

Differences Between Low-Risk Survivors and Nonsurvivors

There were no differences between both groups in age and gender (Table 2). Although the predicted mortality risk was low, there was a small but statistically significant difference in predicted risk between nonsurvivors and survivors in both prediction models.

Nonsurvivors compared to survivors had more unplanned admissions (74.4% vs 38.5%; $p < 0.001$), CCCs (76.7% vs 58.8%; $p = 0.001$) and were more often mechanically ventilated (88.1% vs 34.9%; $p < 0.001$). Nonsurvivors were more often admitted for circulatory problems, more often admitted outside office hours, and more often transported with a specialized transport upon admission (Table 2). Furthermore, nonsurvivors had significantly more ventilator days (median, 9 [IQR, 3–22] vs median, 2 [IQR, 1–3]; $p < 0.001$) and longer length of stay (median, 11 [IQR, 5–32] d vs median, 3 [IQR, 2–5] d; $p < 0.001$) compared to survivors.

Factors Associated With Mortality in Low-Risk Patients

Based on the univariable analysis, review of the literature and expert opinion, the following seven variables age, admission outside office hours, CCCs, unplanned admissions, readmissions, specialized transport, and season of admission were considered as relevant risk factors and were subsequently included in multivariable logistic regression analysis. This showed that CCCs and unplanned admissions

were most significantly associated with mortality (odds ratio [OR], 3.29 [95% CI, 1.97–5.50] and OR, 5.78 [95% CI, 3.40–9.81], respectively) (Table 3). Furthermore, whether a patient was admitted between April and September was associated with increased mortality (OR, 1.67 [95% CI, 1.08–2.58]).

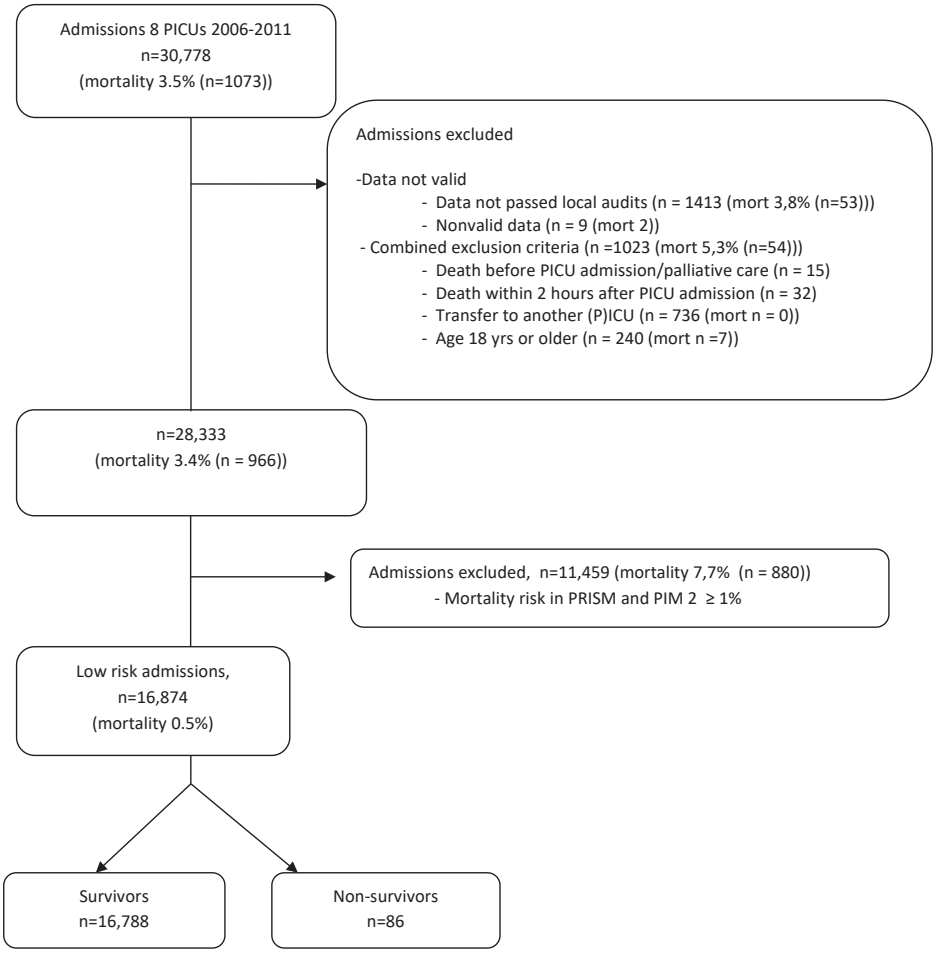


Figure 1. Flowchart of the study population.

PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality.

Table 1. Demographic Characteristics of Low-Risk admissions

Characteristic	**n = 16,874**
Male	9,676 (57.5)
Age (years), median [IQR[a]]	4.0 [0-11]
Unplanned admission	6,522 (38.7)
PRISM recalibrated mortality risk, median [IQR] (%)	0.62 [0.46-0.94]
PIM2 recalibrated mortality risk, median [IQR] (%)	0.84 [0.40-1.36]
Chronic complex condition	9,945 (58.9)
Mechanically ventilated during PICU stay	5,674 (33.6)
Number of days mechanically ventilated, median [IQR]	2.0 [1 - 3]
Length of stay (days), median [IQR]	3.0 [2 - 6]
Number of nonsurvivors with low risk according to	86 (0.5)
PRISM < 1%	52 (60.5)
PIM2 < 1%	28 (32.5)
PIM2 and PRISM < 1%	6 (7.0)

IQR = interquartile range, PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality.

[a] Interquartile range (25th to 75th percentile).

Data are presented as n (%) unless mentioned otherwise.

Table 2. Differences between low-risk survivors and nonsurvivors

Characteristic
Demographic characteristics
Male
Age, median [IQR[a]]
Diagnosis characteristics
Diagnosis subgroups
Trauma
Circulatory
Neurological
Respiratory
Renal
Gastrointestinal
Post procedure diagnosis
Miscellaneous
Complex chronic condition
Admission characteristics
PRISM recalibrated mortality risk, median (%) [IQR]
PIM2 recalibrated mortality risk, median (%) [IQR]
Unplanned admission
Admission outside office hours
Readmission within 48 hours
Recovery as primary reason for admission
Specialized transport upon admission
Admission between April and September
Mechanically ventilated
Physiological parameters[b]
Minimal systolic blood pressure (mmHg), mean [SD]
Abnormal heart rate
Maximal respiratory rate, median [IQR]
Minimal Glasgow Coma Score, median [IQR]
Maximal glucose level (mmol/L) , median [IQR]
Outcome characteristics
Number of days mechanically ventilated, median [IQR]
Length of stay, median [IQR]

IQR = interquartile range,

[a] *Interquartile range (25th to 75th percentile).*

	Survivors (n=16,788)	Nonsurvivors (n=86)	Differences
	9628 (57.5)	48 (55.8)	0.747
	4 [0-11]	3.5 [0-13]	0.993
	801 (4.8)	0 (0.0)	0.036
	475 (2.8)	16 (18.6)	0.000
	794 (4.7)	4 (4.7)	1.000
	1,579 (9.4)	8 (9.3)	1.000
	64 (0.4)	0 (0.0)	1.000
	300 (1.8)	2 (2.3)	0.668
	9,020 (53.7)	24 (27.9)	<0.001
	2,732 (16.3)	12 (14.0)	0.561
	9,879 (58.8)	66 (76.7)	0.001
	0.62 [0.46-0.94]	0.76 [0.59-1.21]	0.001
	0.83 [0.40-1.35]	1.50 [0.94-5.13]	<0.001
	6,458 (38.5)	64 (74.4)	<0.001
	4,512 (26.9)	32 (37.2)	0.031
	161 (1.0)	3 (3.5)	0.017
	5,969 (35.6)	8 (9.3)	<0.001
	989 (5.9)	11 (12.8)	0.007
	8,304 (49.5)	53 (61.6)	0.024
	5,600 (34.9)	74 (88.1)	<0.001
	87 [17]	84[20]	0.278
	8,098 (52.7)	37 (47.4)	0.356
	32 [25-44]	42 [32-55]	<0.001
	15 [15-15]	15 [15-15]	0.007
	7.5 [6.2-9.2]	8.3 [6.8-11.2]	0.017
	2 [1-3]	9 [3-22.25]	<0.001
	3 [2-5]	11 [5-32]	<0.001

[b] *The physiologic parameters are the most abnormal values collected in the first 24 hr. after admission. Data are presented as n (%), unless mentioned otherwise.*

Table 3. Variables associated with nonsurvival in the low-risk group

Factor	Odds ratio	95% CI
Age (years)	1.02	0.98 – 1.06
Complex chronic condition	3.29	1.97 – 5.50
Admission out of office hours	0.80	0.50 – 1.28
Unplanned admission	5.78	3.40 – 9.81
Specialized transport upon admission	1.79	0.92 – 3.48
Admission between April and September	1.67	1.08 – 2.58
Indication: readmission within 48 hours	2.24	0.69 – 7.30

OR = odds ratio

Discussion

In this large cohort study of PICU patients with a low predicted mortality risk in The Netherlands, several differences were found between survivors and nonsurvivors. CCCs and unplanned admissions were more prevalent among nonsurvivors when compared with survivors, and in addition, they were strongly associated with mortality.

The hospitalization rates of children with multiple CCCs have been increasing over the last decades (20). The association between CCCs and mortality in our study is in accordance with the current literature. The association of CCCs with PICU mortality was established in the overall PICU population admitted to 54 units in the United States (16). This study shows that CCCs are common not only in the PICU population in general but also in patients with low severity of illness as scored by PRISM and PIM2. Although some CCCs are incorporated in the PIM2, neither the PIM2 nor PRISM model scores CCCs completely. The declining mortality rate in PICUs combined with the increasing prevalence of patients with CCCs suggests that PICU outcome studies should shift their focus from mortality to morbidity (21).

Also, an association was found between unplanned admissions and mortality. It is likely that unplanned low-risk admissions form a different, more seriously ill, group than planned low-risk admissions, despite relative normal physiology and laboratory results at admission. No association was found between off-hours admissions and mortality. Other studies on this subject in adult and pediatric ICUs show inconsistent results (18, 22–27). Results of these studies might be influenced by structural factors like nursing and medical staffing during off-hours. No association was found between PICU readmissions within 48 hours and mortality, which is in contrast with a North American study (28). This might be due to the low number of readmissions in the low-risk survivor and the nonsurvivor group in our study. The increased OR for death associated with admission between April and September compared with winter months is counterintuitive (26, 29–31). We can only speculate on this.

One of the main differences between survivors and nonsurvivors is the larger number of ventilator days and increased length of PICU stay in nonsurvivors. It appears that most of the low-risk nonsurvivors probably deteriorated after admission and after the recording of the values used to calculate the mortality prediction scores, resulting in residual confounding. This is in accordance with

the literature on this subject showing a decrease of the predictive capability of the models in patients with a longer length of stay and in patients with a higher predicted mortality risk and a long length of stay (9, 32). The increased length of PICU stay is also associated with the number of adverse events (33, 34). This could possibly have influenced the length of stay and outcome in this group.

Our study has several limitations. First, we considered an admission as low-risk when either the PRISM- or the PIM2- predicted risk of mortality was less than 1%. This choice was arbitrary, since there is no consensus about a cut-off point for low-risk of mortality (4). On the other hand, both the PICE and ANZPIC report a risk of less than or equal to 1% as the lowest level of mortality risk in their tables meaning this cut-off point is generally accepted in the field. Second, the PIM2 and PRISM prediction models are not intended for individual patients, but for groups of patients and for individual patients these models misrepresent their actual risk of mortality. For example, patients with congenital heart disorders sometimes are admitted preoperatively to the PICU, prior to their critical issues and not detected by risk scores. New PRISM methods deal with this issue and might reflect mortality risk better in this type of patients in the future (5). Similarly, there is often a difference between the two scores, which in the majority of our cases resulted in a patient being considered low-risk by one prediction model and not by the other. To a certain degree, a difference between scores is expected: the prediction models include data on different predictors and in different time windows. We only found gradual differences between the two models. The aim of the study was not to choose the best model for predicting the low-risk patient but to determine factors influencing outcome in this population.

Finally, nonsurvival was defined based on PICU mortality and not on long-term follow-up, possibly introducing bias. Data on hospital mortality or long-term follow-up unfortunately were not available in the registry. However, the prediction models are based on PICU mortality as well and not on hospital mortality.

Our results indicate that future research is necessary to determine whether adding complex chronic conditions to the currently used mortality prediction models would result in improvement of the performance of these models, especially for the low-risk category PICU patients. It seems that there are more factors involved in nonsurvival in the low-risk PICU population. Besides deteriorations of patients' condition over time and socioeconomic status that has been linked to health and mortality (35), it would be of interest to determine adverse events emerging during a prolonged PICU stay. Studies in adult ICU patients show that adverse events are associated with increased mortality (36–38). A retrospective study showed a substantial amount of preventable

deaths in hospitals in The Netherlands (39), but prevalence has not been determined in the low-risk PICU population. From the perspective of quality improvement, limiting adverse events could be a modifiable factor in the death of these patients.

Although the number of low-risk admissions is high in the PICU, the total number of nonsurvivors is—as expected by risk models—low. The absolute number of nonsurvivors in the high-risk population is much higher. It would be interesting to investigate that whether in the high-risk population the same or other risk factors influence mortality.

Conclusion

Children dying in the PICU with a low predicted mortality have recognizable risk factors including complex chronic conditions and/or emergency admissions.

Reference list

1. Pollack MM, Ruttimann UE, Getson PR: Pediatric Risk of Mortality (PRISM) score. Crit Care Med 1988; 16:1110–1116
2. PICANET: Paediatric Intensive Care Audit Network: PICANET: Annual Report March 2003-February 2004. 2004. Available at: http://www.picanet.org.uk/Audit/Annual Reporting/Annual-Report-Archive/PICANet_National_Report_2004.pdf. Accessed February 1, 2017
3. PICANET: Paediatric Intensive Care Audit Network: PICANET 2013 Annual Report. 2013. Available at: http://www.picanet.org.uk/Audit/Annual-Reporting/Annual-Report-Archive/PICANet_Annual_Report_2013_Summary.pdf. Accessed February 1, 2017
4. ANZPIC: Report of the Australian and New Zealand Paediatric Intensive Care Registry 2013. 2013. Available at: http://www.anzics.com.au/Pages/CORE/CORE-Reports.aspx. Accessed February 1, 2017
5. Pollack MM, Holubkov R, Funai T, et al: The Pediatric Risk of Mortality Score: Update 2015. Pediatr Crit Care Med 2016; 17:2–9
6. Gemke RJ, Bonsel GJ: Comparative assessment of pediatric intensive care: A national multicenter study. Pediatric Intensive Care Assessment of Outcome (PICASSO) Study Group. Crit Care Med 1995; 23:238–245
7. Visser IHE: Dutch Pediatric Intensive Care Evaluation. PICE Report 2003–2005. 2008. Available at: http://www.pice.nl/documenten/reports/9789078022039/reportPICE2003-2005.pdf. Accessed February 1, 2017
8. Visser IHE; Nederlandse PICE werkgroep: Pediatrische Intensive Care Evaluatie, Jaarrapport 2012–2013. Rotterdam, Stichting PICE, 2014. Available at: http://www.pice.nl/eng/index-eng.htm. Accessed February 1, 2017
9. Visser IH, Hazelzet JA, Albers MJ, et al: Mortality prediction models for pediatric intensive care: Comparison of overall and subgroup specific performance. Intensive Care Med 2013; 39:942–950
10. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group: PIM2: A revised version of the Paediatric Index of Mortality. Intensive Care Med 2003; 29:278–285
11. Hannan EL, Bernard HR, O'Donnell JF, et al: A methodology for targeting hospital cases for quality of care record reviews. Am J Public Health 1989; 79:430–436
12. PICE: PICE Registry. Available at: http://www.pice.nl/eng/index-eng. htm. Accessed December 15, 2016
13. Shann F, Pearson G, Slater A, et al: Paediatric Index of Mortality (PIM): A mortality prediction model for children in intensive care. Intensive Care Med 1997; 23:201–207
14. Slater A, Shann F, McEniery J; ANICS Study Group: The ANZPIC registry diagnostic codes: A system for coding reasons for admitting children to intensive care. Intensive Care Med 2003; 29:271–277
15. Feudtner C, Christakis DA, Connell FA: Pediatric deaths attributable to complex chronic conditions: A population-based study of Washington State, 1980-1997. Pediatrics 2000; 106:205–209

Additional Files Chapter 2

Appendix 1
List of diagnoses classified as complex chronic conditions

Appendix 2
Mode of death in low-risk non-survivors

Appendix 1. List of diagnoses classified as complex chronic conditions

Complex chronic conditions	
Subgroup	Diagnoses from the PICE database
Cardiovascular	Absent pulmonary valve syndrome*
	Anomaly of the coronary artery
	Arterial switch*
	Atrioventricular septal defect
	Cardiomyopathy
	Cavo pulmonary shunt*
	Cor triatriatum
	Double outlet right ventricle
	Ebstein's anomaly
	Fontan procedure*
	Hypoplastic left heart syndrome
	Hypoplastic left ventricle*
	Hypoplastic or interrupted aortic arch*
	Hypoplastic right ventricle*
	Levo transposition of the great arteries
	Mitral valve stenosis
	Monoventricle
	Norwood procedure – step 1*
	Pacemaker insertion/revision*
	Portal hypertension*
	Pulmonary atresia or stenosis
	Pulmonary artery banding*
	Reconstruction of aortic arch*
	Reconstruction of left ventricular outflow*
	Reconstruction of right ventricular outflow*
	Restoration of atrioventricular septumdefect*
	Repair of plastic pulmonary artery*
	Repair or replacement of conduit*
	Repair of tetralogy of Fallot*
	Right ventricular outflow tract obstruction*
	Senning procedure*
	Supraventricular arrhythmia
	Surgery of pulmonary collateral arteries*
	Systemic to pulmonary shunt procedure*
	Tetralogy of Fallot
	Total abnormal pulmonary venous return
	Transplantation of heart
	Transplantation of heart and lung
	Transplantation of heart and lung – state after procedure
	Transposition of the great arteries
	Tricuspid atresia or stenosis

Appendix 1. Continued

Complex chronic conditions	
Cardiovascular (Continued)	Truncus arteriosus Vasculitis* Ventricular arrhythmia
Respiratory	Bronchiectasis Central apnea* Choanal atresia or stenosis* Chronic lung disease* Congenital lung disease Cystic fibrosis Infant respiratory distress syndrome* Laryngomalacia Malacia trachea or bronchus Massa mediastinum* Pulmonary edema Pulmonary hypoplasia Pulmonary insufficiency* Reconstuction of larynx* Subglottic stenosis Tracheostomy* Trachea or bronchus stenosis Transplantation of lung Transplantation of lung – state after procedure Vocal cord paralysis*
Hematological	Coagulation defects Hematologic disease*
Endocrinological	Congenital metabolism disorder Diabetes (comorbidity)* Diabetes insipidus Diabetes mellitus with ketoacidosis Diabetes mellitus without ketoacidosis Endocrine disorder Kasai procedure*

Appendix 1. Continued

Complex chronic conditions	
Gastrointestinal	Biliary atresia
	Colitis
	Congenital diaphragmatic hernia
	Gastroschisis or exomphalos
	Hirschsprung's disease*
	Liver disease – other*
	Esophageal atresia
	Repair of esophageal atresia*
	Repair of esophageal fistula*
	Repair of total anomalous pulmonary venous return*
	Short bowel syndrome*
	Transplantation of kidney
	Transplantation of liver
	Transplantation of liver – state after procedure
	Transplantation of small intestine
	Varices of esophagus or stomach*
Immunological	Congenital immunodeficiency
	Graft versus host disease
	Neutropenia*
	Pancytopenia*
	Pheochromocytoma*

Appendix 1. Continued

Complex chronic conditions	
Neuromuscular	Acute disseminated encephalomyelitis*
	Arnold-Chiari malformation
	Brain arteriovenous malformation*
	Brain tumor
	Central nervous system shunt dysfunction or infection*
	Cerebral aneurism
	Cerebral cyst
	Cerebral infarction*
	Chronic traumatic encephalopathy
	Congenital brain disease*
	Convulsions*
	Craniotomy – fossa anterior*
	Epilepsy (comorbidity)
	Hydrocephalus
	Insertion of revision of central nervous system shunt*
	Lobectomy or hemispherectomy*
	Meningomyelocele or spina bifida
	Muscular dystrophy
	Myasthenia gravis
	Myelum – impairment*
	Myopathy
	Repair of myelomeningocele*
	Static encephalopathy
Oncological	Cystic hygroma
	Leukemia or lymphoma
	Malignant solid organ neoplasm
	Transplantation of bone marrow
	Transplantation of bone marrow – state after procedure
Renal	Chronic kidney failure
	Hydronephrosis*
	Nephrotic or nephritic syndrome*
	Transplantation of kidney – state after procedure
Endocrinal	Syndrome of inappropriate antidiuretic hormone secretion*
Genetic	Chromosome abnormality
	Craniosynostosis*
	DiGeorge syndrome
	Down syndrome
	Pierre Robin syndrome*
Urological	Repair of extrophia vesicae*
Miscellaneous	Syndrome or malformation*

** Diagnoses that were not on the original list (as CCC)*

Appendix 2. Mode of death in low-risk non-survivors

	Number of patients
Brain death	2
Maximal treatment including cardiopulmonary resuscitation (CPR)	4
Maximal treatment without CPR	7
Limiting treatment / withdrawal of treatment	14
Data missing*	59
Total	86

* *Registration of 'mode of death' was started in 2010 and therefore not available for most of the patients in the database*

CHAPTER 3

RETROSPECTIVE COHORT STUDY ON FACTORS ASSOCIATED WITH MORTALITY IN HIGH-RISK PEDIATRIC CRITICAL CARE PATIENTS IN THE NETHERLANDS

Carin W. Verlaat
Nina Wubben
Idse H. Visser
Jan A. Hazelzet
SKIC (Dutch collaborative PICU research network)
Johannes van der Hoeven
Joris Lemson
Mark van den Boogaard

BMC Pediatrics (2019): 19: 274

Abstract

Background: High-risk patients in the pediatric intensive care unit (PICU) contribute substantially to PICU-mortality. Complex chronic conditions (CCCs) are associated with death. However, it is unknown whether CCCs also increase mortality in the high-risk PICU-patient. The objective of this study is to determine if CCCs or other factors are associated with mortality in this group.

Methods: Retrospective cohort study from a national PICU-database (2006–2012, n = 30,778). High-risk PICU patients, defined as patients < 18 years with a predicted mortality risk > 30% according to either the recalibrated Pediatric Risk of Mortality-II (PRISM) or the Paediatric Index of Mortality 2 (PIM2), were included. Patients with a cardiac arrest before PICU-admission were excluded.

Results: In total, 492 high-risk PICU patients with mean predicted risk of 24.8% (SD 22.8%) according to recalibrated PIM2 and 40.0% (SD 23.8%) according to recalibrated PRISM were included of which 39.6% died. No association was found between CCCs and nonsurvival (odds ratio 0.99; 95% CI 0.62–1.59). Higher Glasgow coma scale at PICU admission was associated with lower mortality (odds ratio 0.91; 95% CI 0.87–0.96).

Conclusions: Complex chronic conditions are not associated with mortality in high-risk PICU patients.

Background

Patients with a high predicted mortality risk in the pediatric intensive care unit (PICU) are a challenge to the clinical team. The relatively small subset of these patients contributes substantially to the number of nonsurvivors and to PICU-resources. Around 1% of the PICU-admissions in the Australian and New Zealand Paediatric Intensive Care Registries (ANZPIC) has a predicted mortality risk between 30 and 100%, but this small cohort contributes to one third of all deaths (1–3).

Complex chronic conditions (CCCs) are associated with prolonged length of stay in PICU patients, unplanned readmissions and death (4, 5). A CCC is defined as *'any medical condition that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or 1 organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center'* (6). There are many CCCs in several organ systems. Examples are spinal cord malformations, cystic fibrosis, hypoplastic left heart syndrome, extreme immaturity, metabolic disorders, etc. (7). Besides CCCs there are so called 'noncomplex chronic conditions' (NCCCs), diagnoses that could be expected to last > 12 months but not meeting the additional CCC criteria. Examples of NCCCs are asthma, atrial septal defect, obesity, etc. (4). The prevalence of CCCs among hospitalized patients and among PICU patients is increasing (4). Only few CCCs are incorporated in severity-of illness models like Paediatric Index of Mortality (PIM (2,3)) and Pediatric Risk of Mortality (PRISM (II, III, IV) (4, 8–12). In low-risk PICU-patients (patients with predicted mortality risk < 1%) CCCs and unplanned admissions are associated with death (OR 3.29, 95% CI 1.97–5.50) (13, 14). It is unknown whether CCCs increase mortality in the high-risk PICU patient as well.

Therefore, the aim of the present study is to determine if CCCs or other identifiable factors are associated with death in high-risk PICU-patients.

Methods

Study population

Patients were derived from a national PICU database containing data from all pediatric intensive care departments in the Netherlands (2006–2012, n = 30,778); the 'PICE-registry' (13, 15). The same cohort was used in a previous study on low-risk PICU-patients (13). Patients < 18 years old with a high predicted mortality risk were included in the study. High-risk was defined as a predicted mortality risk > 30% according to either the PRISM II (referred to as PRISM) or the PIM2 risk score (9, 10). In this study, as described before, both models were recalibrated to predict the overall mortality in the total population in this particular 6-year period without altering the relative weights of risk factors in the models and thus retaining the discriminative power of the original models (13, 15).

Patients who were already dead before PICU admission (e.g., patients admitted for organ transplantation already being brain-dead) or patients admitted for palliative care, patients dying within 2 h of PICU admission, and patients transferred to another ICU during their PICU treatment were excluded from the study. Data of patients that did not pass quality control during local site audit visits and were excluded from the annual reports were also excluded from the study (13). Patients with a cardiac arrest prior to PICU admission were excluded due to possible bias of the results (16, 17).

Design

Retrospective cohort study based on data prospectively collected in a national registry.

Risk variables and data-handling

Variables that were analyzed represented many aspects of the PICU stay, including admission characteristics, physiological state, diagnoses and outcome. Nonsurvivors were defined as patients who died in the PICU. The ANZPIC diagnostic code list was used in the PICE-registry (18). Patients were classified as patients with a CCC if either the primary diagnosis, underlying diagnosis or first additional diagnosis was a CCC (6, 7). Patients were classified as having a NCCC if the primary diagnosis, underlying diagnosis or first additional diagnosis was a diagnosis defined as a NCCC. A modified Feudtner's list was used to classify diagnoses into CCC or NCCC (4, 6, 7, 18). ANZPIC diagnoses not appearing on these lists were classified according to expert opinion (C.V. and J.L.). The list of CCC-diagnoses was recently published (13). Definitions of 'Admission outside office hours', 'readmission' and 'specialized transport' were published previously (13). The data were checked for non-valid data. Illogical and

impossible values that surpassed physiologic threshold values were excluded if the value likely resulted from a typo or measurement error, as described before. (Examples of typo/ measurement errors: diastolic blood pressure > 400 mmHg, low paO2 in combination with cyanotic congenital heart disease which by definition should be excluded from PRISM score.) (13).

Statistical analysis

Depending on distribution, continuous variables were tested using an independent T test or Mann-Whitney U test. For dichotomous variables, chi-square test or, in case of small expected frequencies, Fisher's exact test was used. To adjust for multiple testing, Bonferroni correction was performed and differences were considered statistically significant if p-value was < 0.001.

For the multivariable logistic regression analysis, only risk factors that were present at the time of admission were included in the regression analysis. Because the selection of the study population was based on PIM2 and PRISM scores, predictors from these scores were not included in the multivariable logistic regression analysis, except for the Glasgow Coma Scale (GCS) at admission.

Statistical analyses were carried out using IBM SPSS Statistics Version 22.1.

Results

Population characteristics

In total, there were 30,778 admissions of which 738 patients were high-risk patients (Fig.1). After excluding patients with cardiac arrest before PICU admission, a total of 492 high-risk patients was included with a mortality rate of 39.6%. The mean predicted mortality risk of these 492 patients was 24.8% (SD: 22.8%) according to the recalibrated PIM2 and 40.0% (SD: 23.8%) according to the recalibrated PRISM. The majority of the high-risk patients had an unplanned admission for medical reasons.

Analysis of differences

Baseline characteristics are shown in Table 1. The median GCS at time of admission was significantly higher in survivors compared to nonsurvivors (median 15 vs. median 12, respectively; $p < 0.001$). Both PRISM and PIM2 mortality risks were significantly lower in survivors compared to nonsurvivors. Ventilator-days and length of stay were longer in survivors compared to nonsurvivors. No other significant differences were found.

Factors associated with survival

Higher GCS at admission was associated with lower mortality (OR 0.91; 95% CI 0.87–0.96) (Table 2). No association was found between CCCs and nonsurvival (OR 0.99; 95% CI 0.62–1.59). No other factors were associated with mortality. Results from the unadjusted ORs are shown in (Additional file 1: Table S3).

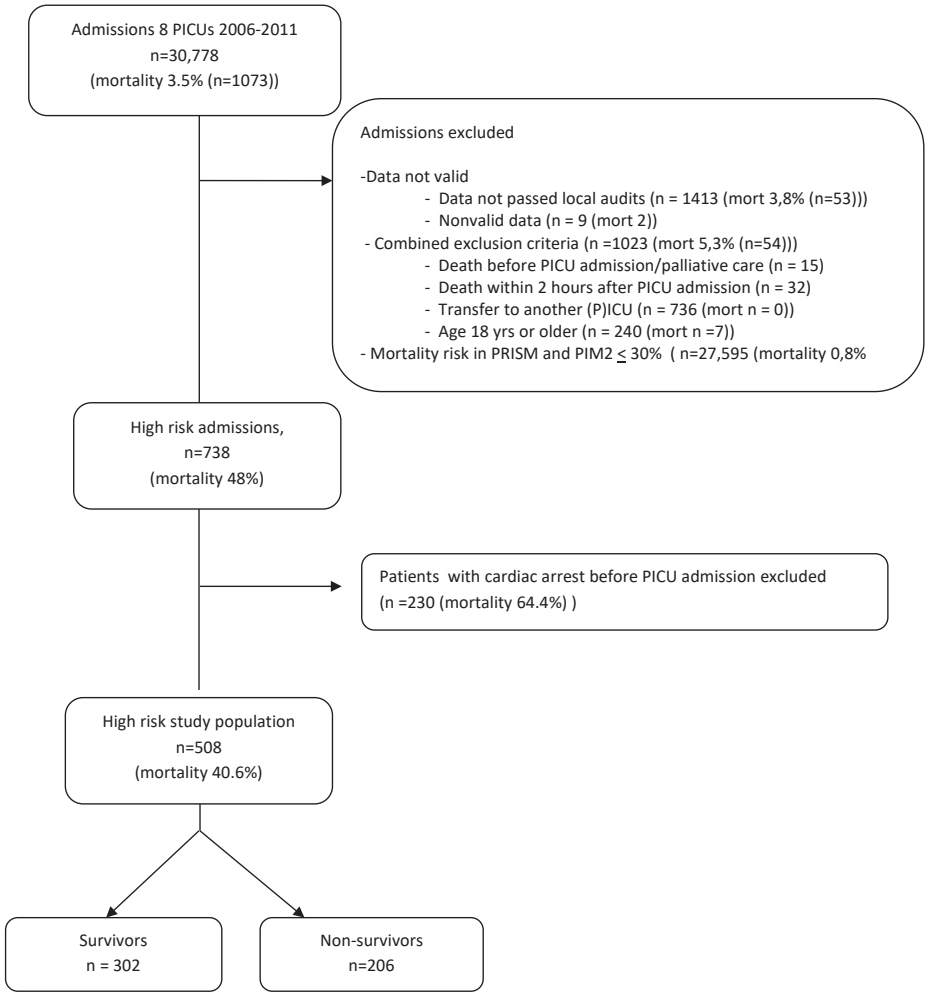


Figure 1. Flowchart of the population

Table 1. Population characteristics and differences between high-risk survivors and nonsurvivors

Characteristic
Male
Age < 12 months
Unplanned admission
Medical admission
Readmission < 48 hours
Admission outside office hours
Mode of transport upon admission
None
Non-specialized transport
Specialized transport
Season of admission
Winter
Spring
Summer
Autumn
Recovery as reason for PICU admission
PRISM recalibrated mortality risk, median [IQR]
PIM2 recalibrated mortality risk, median [IQR]
Patients with
PRISM > 30% (and PIM ≤ 30%)
PIM2 > 30% (and PRISM ≤ 30%)
PRISM and PIM2 > 30%
Chronic conditions
No chronic condition
NCCC
CCC
Diagnose groups
Trauma
Cardiovascular
Neurological
Respiratory
Renal
Gastrointestinal
Post procedure diagnosis
Miscellaneous
Glasgow Coma Scale at admission

Survivors n= 297	Nonsurvivors n=195	p value
179 (60.3)	105 (53.8)	0.16
161 (54.2)	90 (46.2)	0.08
275 (92.6)	182 (93.3)	0.76
227 (76.4)	146 (74.9)	0.69
4 (1.3)	3 (1.5)	0.86
151 (50.8)	96 (49.2)	0.73
159 (53.5)	104 (53.3)	0.97
52 (17.5)	20 (10.3)	0.03
107 (36.0)	84 (43.1)	0.12
74 (24.9	46 (23.6)	0.74
64 (21.5)	51 (26.1)	0.24
59 (19.8)	50 (25.6)	0.13
100 (33.7)	48 (24.6)	0.03
22 (7.4)	15 (7.7)	0.91
0.36 [0.15-0.48]	0.44 [0.31-0.66]	< 0.001
0.14 [0.05-0.34]	0.21 [0.09-0.46]	< 0.001
190 (64.0)	115 (59.0)	0.26
89 (30.0)	43 (22.1)	0.05
18 (6.1)	37 (19.1)	< 0.001
82 (27.6)	68 (34.9)	0.09
19 (6.4)	7 (3.6)	0.17
196 (66.0)	120 (61.5)	0.31
9 (3.0)	16 (8.2)	0.01
30 (10.1)	22 (11.3)	0.68
30 (10.1)	31 (15.9)	0.06
79 (26.6)	29 (14.9)	0.002
2 (0.7)	1 (0.5)	0.82
14 (4.7)	12 (6.2)	0.49
45 (15.2)	32 (16.4)	0.71
88 (29.6)	52 (26.7)	0.48
15 [9-15]	12 [3-15]	< 0.001

Table 1. Continued

Characteristic
Mechanically ventilated (n=660)
Outcome
Number of days mechanically ventilated, median [IQR]
Length of stay PICU, median [IQR]

Data are presented as n (%), unless mentioned otherwise.
[IQR] is defined as interquartile range: [25th percentile – 75th percentile].

Survivors n= 297	Nonsurvivors n=195	p value
260 (91.5)	178 (97.8)	0.01
7 [4-13]	3 [2-7]	< 0.001
12 [7-21]	3 [2-7]	< 0.001

NCCC: non-complex chronic condition, CCC: complex chronic condition.
The physiological parameters are the most abnormal values collected in the first 24 hours after admission.

Table 2. Variables associated with nonsurvival in the high-risk group

Factor	OR	95% CI
Male	0.75	0.51-1.12
Age < 1 yr	0.84	0.56-1.27
Specialized transport	1.24	0.82-1.88
Admission outside office hours	0.79	0.53-1.17
Season		
Winter	Ref	
Spring	1.29	0.74-2.25
Summer	1.53	0.87-2.70
Autumn	0.84	0.49-1.43
Chronic conditions		
No chronic condition	Ref	
CCC	0.99	0.62-1.59
NCCC	0.53	0.19-1.45
Diagnose subgroups		
Trauma	Ref	
Cardiovascular	0.91	0.30-2.77
Neurological	1.06	0.48-2.33
Respiratory	0.85	0.39-1.87
Renal	0.70	0.36-1.36
Gastrointestinal	0.61	0.05-7.79
Post procedure	0.77	0.42-1.44
Miscellaneous	1.38	0.54-3.52
Glasgow coma scale at admission	0.91	0.87-0.96

NCCC: non-complex chronic condition, CCC:= complex chronic condition.
Results from the unadjusted ORs are shown in Additional file 1: Table S3.

Discussion

In this large retrospective cohort study in high-risk PICU patients, complex chronic conditions were not associated with mortality.

This is different compared to our previous study looking into low-risk admissions, where CCCs were associated with increased mortality (13). In a general PICU-population, without risk stratification, a similar association was found (4). Although some CCCs (for example: leukemia, hypoplastic left heart syndrome) are incorporated in the PIM2, the majority of CCCs is not part of the risk models. Having a chronic disease is often not reflected in physiological values and therefore not shown as a higher mortality risk. CCCs can be very heterogeneous. Some CCCs might be associated with death in the PICU (e.g. a patient with a complex heart disorder) while other CCCs are not lethal but may have impact on other outcome parameters like functional outcome. Furthermore, it's possible that some patients with CCCs may be refused PICU admission and thus do not contribute to the overall PICU mortality. We did not investigate this and therefore this statement is conjecture. In true high-risk patients other factors like the GCS have a clearer influence on mortality for patients with CCCs.

Our study has several limitations. First, an arbitrary choice was made for the definition of high-risk patients, using a combination of PIM2 and PRISM scores with a certain cut-off point. Both models use different predictors and different time windows to calculate their scores and do not give the same result. Because in the Dutch PICE registry both models are used and no model is superior to another, we used a combination of both models. Using only one model instead of a combination might underestimate a cohort of high-risk patients. Only a minority had a mortality risk of > 30% in both models. Mean predicted mortality was higher according to PRISM compared to PIM2. However, if only PRISM model had been used to detect high-risk patients, roughly a third of the high-risk cohort would not have been detected.

Third, an older version of the PRISM was used, dating from 1988 (10). If the original PRISM model would have been used without recalibration, the predicted mortality would have been overestimated. However, because the PRISM was recalibrated to fit, it is a good predictor of mortality (15).

Fourth, no factors which are part of the PIM2/PRISM models were used for the multivariable logistic regression analysis, with the exception of the GCS at admission. The GCS at admission is not incorporated in the PIM2 model but is indirectly part of

the PRISM score as a dichotomous variable. If the GCS within the first 24 h is less than 8, the PRISM score increases. However, a mild decrease in GCS such as GCS between 8 and 10 does not increase PRISM score, although there might be a serious neurological condition. We found a significant and clinically important lower GCS in nonsurvivors. This difference could not be explained by cardiac arrest patients. Therefore we decided to add the GCS as a continuous variable in the analysis.

Conclusions

Complex chronic conditions are not associated with mortality in PICU patients with a high predicted mortality-risk, in contrast to low-risk PICU patients. We recommend to explore the role of CCCs in (PICU) patients with different risk profiles further. Higher Glasgow coma scale at PICU admission was associated with lower mortality.

Ethics approval and consent to participate

The Institutional Review Board approved the study and waived the need for informed consent (Commissie Mensgebonden Onderzoek Radboudumc; 2017–3848).

Reference list

1. ANZPIC-registry: Report of the Australian and New Zealand Paediatric intensive care registry 2013. In: https://www.anzics.com.au/annual-reports/. 2013.
2. ANZPIC-registry: ANZPICR Annual Report 2014. In. https://www.anzics.com. au/annual-reports/. 2014.
3. ANZPIC-registry: ANZPICR Annual Report 2015. In. https://www.anzics.com. au/annual-reports/. 2015.
4. Edwards JD, Houtrow AJ, Vasilevskis EE, Rehm RS, Markovitz BP, Graham RJ, Dudley RA. 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. 2012; 40(7):2196–203.
5. Edwards JD, Lucas AR, Boscardin WJ, Dudley RA. Repeated critical illness and unplanned readmissions within 1 year to PICUs. Crit Care Med. 2017; 45(8):1276–84.
6. Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington state, 1980-1997. Pediatrics. 2000; 106:205–9.
7. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr. 2014; 14:199.
8. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med. 1997; 23(2):201–7.
9. Slater A, Shann F, Pearson G. Paediatric index of mortality study G: PIM2: a revised version of the Paediatric index of mortality. Intensive Care Med. 2003; 29(2):278–85.
10. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med. 1988; 16(11):1110–6.
11. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. Crit Care Med. 1996; 24(5):743–52.
12. Pollack MM, Holubkov R, Funai T, Dean JM, Berger JT, Wessel DL, Meert K, Berg RA, Newth CJ, Harrison RE, et al. The pediatric risk of mortality score: update 2015. Pediatr Crit Care Med. 2016; 17(1):2–9.
13. Verlaat CW, Visser IH, Wubben N, Hazelzet JA, Lemson J, van Waardenburg D, van der Heide D, van Dam NA, Jansen NJ, van Heerde M, et al. Factors associated with mortality in low-risk pediatric critical care patients in the Netherlands. Pediatr Crit Care Med. 2017; 18(4):e155–61.
14. Eulmesekian PG. Low-risk pediatric critical care patients, are they really a different population? Pediatr Crit Care Med. 2017; 18(4):390–1.
15. Visser IH, Hazelzet JA, Albers MJ, Verlaat CW, Hogenbirk K, van Woensel JB, van Heerde M, van Waardenburg DA, Jansen NJ, Steyerberg EW. Mortality prediction models for pediatric intensive care: comparison of overall and subgroup specific performance. Intensive Care Med. 2013; 39(5):942–50.
16. Atkins DL, Everson-Stewart S, Sears GK, Daya M, Osmond MH, Warden CR, Berg RA. Resuscitation outcomes consortium I: epidemiology and outcomes from out-of-hospital cardiac arrest in children: the resuscitation outcomes consortium Epistry-cardiac arrest. Circulation. 2009; 119(11):1484–91.
17. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Browning B, Pemberton VL, Page K, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med. 2017; 376(4):318–29.
18. Slater A, Shann F, McEniery J, Group AS. The ANZPIC registry diagnostic codes: a system for coding reasons for admitting children to intensive care. Intensive Care Med. 2003; 29(2):271–7.

Additional File Chapter 3

Table S3. Variables associated with mortality survival in the high-risk group

Factor	Crude OR	95% CI	Adjusted OR	95% CI
Male	0.77	0.53-1.11	0.75	0.51-1.12
Age < 1 yr.	0.72	0.50-1.04	0.84	0.56-1.27
Specialized transport	1.34	0.93-1.94	1.24	0.82-1.88
Admission outside office hours	0.94	0.65-1.35	0.79	0.53-1.17
Season				
Winter	Ref		Ref	
Spring	1.28	0.76-2.16	1.29	0.74-2.25
Summer	1.36	0.81-2.31	1.53	0.87-2.70
Autumn	0.77	0.47-1.28	0.84	0.49-1.43
Chronic conditions				
No chronic condition	Ref		Ref	
CCC	0.74	0.50-1.09	0.99	0.62-1.59
NCCC	0.44	0.18-1.12	0.53	0.19-1.45
Diagnose subgroups				
Trauma	Ref		Ref	
Cardiovascular	0.41	0.15-1.10	0.91	0.30-2.77
Neurological	0.58	0.22-1.52	1.06	0.48-2.33
Respiratory	0.21	0.08-0.52	0.85	0.39-1.87
Renal	0.28	0.02-3.55	0.70	0.36-1.36
Gastrointestinal	0.48	0.16-1.48	0.61	0.05-7.79
Post procedure	0.40	0.16-1.02	0.77	0.42-1.40
Miscellaneous	0.33	0.14-0.81	1.38	0.54-3.52
Glasgow coma scale at admission	0.91	0.87-0.94	0.91	0.87-0.96

OR = odds ratio, NCCC = non-complex chronic condition, CCC= complex chronic condition

CHAPTER 4

THE OCCURRENCE OF ADVERSE EVENTS IN LOW-RISK NONSURVIVORS IN PEDIATRIC INTENSIVE CARE PATIENTS: AN EXPLORATORY STUDY

Carin W. Verlaat
Cynthia van der Starre
Jan A. Hazelzet
Dick Tibboel
Johannes van der Hoeven
Joris Lemson
Marieke Zegers

European Journal of Pediatrics 2018; 177:1351-8

Abstract

We studied the occurrence of adverse events (AEs) in low-risk nonsurvivors (LN), compared to low-risk survivors (LS), high-risk nonsurvivors (HN), and high-risk survivors (HS) in two pediatric intensive care units (PICUs).

The study was performed as a retrospective patient record review study, using a PICU-trigger tool. A random sample of 48 PICU patients (0–18 years) was chosen, stratified into four subgroups of 12 patients: LN, LS, HN and HS. Primary outcome was the occurrence of AEs. The severity, preventability, and nature of the identified AEs were determined.

In total, 45 AEs were found in 20 patients. The occurrence of AEs in the LN group was significantly higher compared to that in the LS group and HN group (AE occurrence: LN 10/12 patients; LS 1/12 patients; HN 2/12 patients; HS 7/12 patients; LN-LS difference, $p < 0.001$; LN-HN difference, $p < 0.01$). The AE rate in the LN group was significantly higher compared to that in the LS and HN groups (median [IQR]: LN 0.12 [0.07–0.29], LS 0 [0–0], HN 0 [0–0], and HS 0.03 [0.0–0.17] AE/PICU day; LN-LS difference, $p < 0.001$; LN-HN difference, $p < 0.01$). The distribution of the AEs among the four groups was as follows: 25 AEs (LN), 2 AEs (LS), 8 AEs (HN), and 10 AEs (HS). Fifteen of forty-five AEs were preventable. In 2/12 LN patients, death occurred after a preventable AE.

Conclusion:
The occurrence of AEs in LN was higher compared to that in LS and HN. Some AEs were severe and preventable and contributed to mortality.

Introducton

The mortality rate in the pediatric intensive care unit (PICU) in economically developed countries has decreased in the last decades to approximately 3% (26). Moreover, a substantial part of the PICU population (55% in a recent study) has a mortality risk of <1% (35). Although these are low-risk patients, some of these patients die on the PICU. Patient factors like complex chronic conditions (CCCs) do not explain all deceased patients in this patient group (6,35). For quality purposes, it is interesting to analyze whether adverse events (AEs) or even medical errors play a role in the death of low-risk PICU patients (3, 16). An AE is an unintended injury that results in temporary or permanent disability, death, or prolonged hospital stay and that is caused by healthcare management rather than by the patient's underlying disease process (38). A national project on preventable deaths in Dutch hospitals showed that preventable AEs contributed to 4.1% of hospital deaths (38,39). In most international AE studies, (young) children were excluded or the number of included PICU admissions was not specified or very low, so data about PICU patients are scarce (2-4, 18, 38).

Because of their vulnerability, intensive care patients are more prone to iatrogenic events (10, 12, 13). The incidence of AEs in the PICU population depends on the method used to detect AEs (1, 17, 19, 22, 28, 31, 33, 36). Studies using a trigger tool method show that 59–76% of all PICU patients encounter at least one AE during their stay (1, 17, 36).

Although one could speculate that AE incidence is higher in the more complex and sicker patients needing extensive support (high-risk patients), AEs also occur in the less severely ill PICU patients (1, 17, 22). To our knowledge, no studies have focused on the occurrence of AEs in low-risk PICU patients. The incidence of AEs among low-risk patients might be underestimated when only the general PICU population is examined. Analyzing medical records from nonsurvivors with a low risk of dying is an efficient tool to discover problems in the quality of care (14). If low-risk PICU patients deteriorate or die because of preventable AEs, there is a potential for improving their outcome.

The aim of this exploratory study was to study the occurrence of AEs in the low-risk nonsurvivors (LN), compared to low-risk survivors (LS), high-risk nonsurvivors (HN), and high-risk survivors (HS) in two PICUs. Of all AEs, we studied the severity, preventability, and nature. The study was designed as a retrospective exploratory study that used chart review to examine the feasibility of detecting AEs in this patient group.

Methods

Study design and setting

This is a retrospective patient record study to measure the occurrence of AEs in low-risk nonsurvivors and to compare the results with patients with a different risk profile and different outcomes, using a random stratified sample of 48 records. The study was performed in two PICUs. Data collection was performed in 2015.

Admission selection

Admissions in each PICU between 1 January 2006 and 1 January 2012 were stratified into four groups with different risk profiles and different outcomes. The study group consisted of LN. Three control groups were chosen: LS, HN and HS. Low-risk admissions were defined as admissions with a mortality risk in the simply recalibrated Pediatric Index of Mortality (PIM) 2 score and/or recalibrated Pediatric Risk of Mortality II score (further referred as "PRISM") of <1% (24, 25, 27, 29, 35). High-risk admissions were defined as admissions with a mortality risk in the simply recalibrated PIM2 and/or PRISM of ≥30% (35).

Other inclusion criteria were the following: age <18 years and PICU length of stay of at least 2 h. Exclusion criteria were the following: patients already deceased before admission (*for example, brain dead patients, admitted for organ donation*), corrected age <36 weeks (gestational age), invalid or impossible PIM2/PRISM score, and no clinical data available.

The mortality risk scores and PICU outcome data were provided by the national PICU registry (Pediatric Intensive Care Evaluation (PICE) registry) (23). The PICE registry is a national database containing anonymized information of admission characteristics, severity of illness, and patient outcome. Data quality is assessed using standard procedures including audit site visits. Of all patients, both PIM2 and PRISM scores are collected. The models were recalibrated for the study period to predict the overall mortality in the total population in this period without altering the relative weights of risk factors in the models and thus retaining the discriminative power of the models (35, 37). A local copy from the PICE registry was sent to the local PICUs including all admissions between 2006 and 2012. The database of these two PICUs (total of 11,216 admissions: PICU-1, 8438 admissions; PICU-2, 2778 admissions) contained 39 LN.

Since the study was designed as an exploratory study, a selection of roughly one third of the LN was used for the study. Twelve LN were selected for the study. Because the number of patients between the two participating centers was unequal, nine

admissions from PICU-1 and three admissions from PICU-2 were selected for each study group, using a computer-based research randomizer (34). To avoid different population characteristics, the patients in the control groups (LS (n = 12), HN (n = 12), HS (n = 12)) were stratified based on PICU center, gender, and age category. After stratification, the patients were randomly chosen using the computer-based research randomizer.

To verify if the risk profile of patients was correct, the PIM2 and PRISM scores were checked using available physiologic and laboratory data. If a discrepancy was discovered, e.g., the corrected mortality risk turned out to be >2% in LN and LS or <30% in HN and HS, the patient was excluded from the study. The next from the list of available patients (with the same risk group/outcome/PICU center/gender/age category) was selected until, in each group, 12 patients were included.

Data collection

An established set of triggers was modified to local characteristics of the PICU population and was used in a retrospective chart review to discover AEs (Table 4, online only) (1). In the first stage, patient charts were manually reviewed for the presence of 19 triggers. In the second stage, each positive trigger was followed by an in-depth investigation for the presence of associated AEs. Both stages were performed by a pediatric intensivist (CV) with more than 15 years of PICU experience who was trained in the use of the trigger tool method.

Primary outcomes were the occurrence of AEs and AE rate (AE/PICU day). For the AE rate, only AEs occurring during the PICU admission were included. AEs that occurred shortly before PICU admission and were beyond doubt related to the PICU admission were scored as "AE pre PICU." The severity of AEs was rated using the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) Index for Categorizing Errors (Table 5, online only) (20). Preventability of AEs was scored on a 6-point scale (Table 6, online only) (3). AEs with a preventability score of 4–6 were defined as preventable. A preventable AE results from an error in management due to failure to follow accepted practice at an individual or system level. Accepted practice was taken to be "the current level of expected performance for the average practitioner or system that manages the condition in question" (38). AEs were grouped into eight categories, based on the classification made by Hogan et al. (Table 7, online only) (15). If problems were encountered in AE determination and categorizing AEs, a decision was taken after discussion within the research group.

The ANZPIC registry diagnostic code list was used for diagnosis classification (30). An admission was classified as having a CCC or a non-complex chronic condition (NCCC) if either the primary diagnosis, the primary underlying diagnosis, or the first additional diagnosis was a diagnosis defined as a CCC or NCCC according to a modified Feudtner's list (5, 7, 8). PICE diagnoses not appearing on these lists were classified before analyzing the data according to expert opinion (CV, JL) (35). The list of the PICE database diagnoses grouped as a CCC and NCCC is described in Table 8 and Table 9 (online only).

Socio-economic status of the family was obtained by coupling the four digits of the postal code to the socio-economic status of the neighborhood in 2006 (The Netherlands Institute for Social Research) and grouped into three categories (32).

Data analysis

Normal distribution of continuous variables was tested using sampling distributions and skewness and kurtosis tests. Not normally distributed data were reported by median and inter-quartile range (IQR). Non-parametric tests (Mann-Whitney *U*) were used for the analyses of not normally distributed data. For categorical variables, Fisher's exact test or the chi-square test was used (software: IBM SPSS Statistics 22).

Reliability study

To assess the reliability of the record review process, a random sample of nine records (20%) was reviewed by a second investigator.

Results

Respondent characteristics

A total of 48 patients were randomly selected. Nine admissions were excluded, and therefore, nine new admissions were chosen as described (Fig. 1, flowchart).

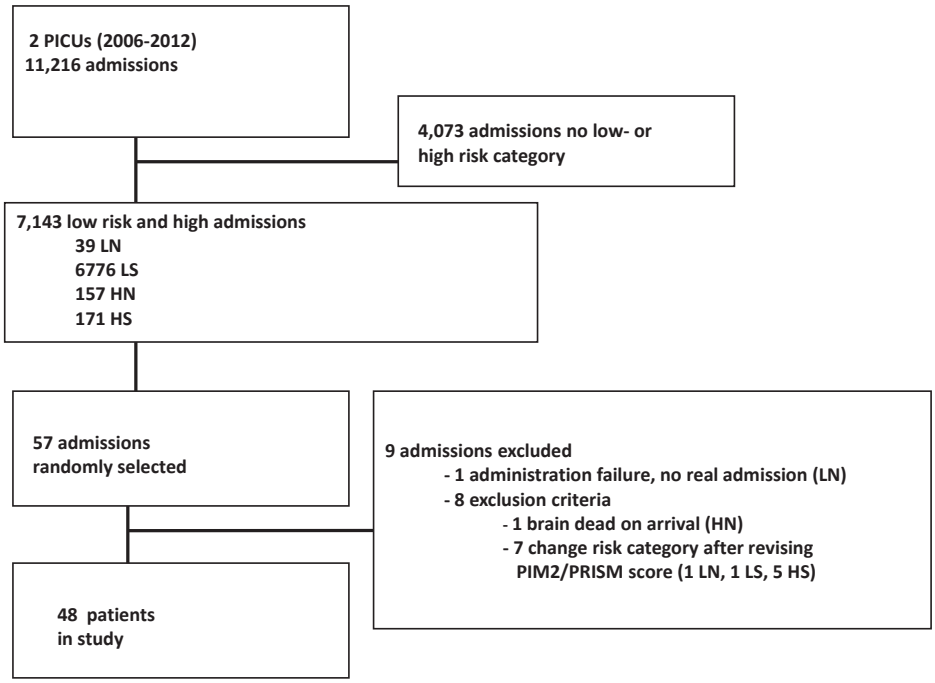


Figure 1. Flowchart of the study population

LN = low-risk nonsurvivor, LS = low-risk survivor, HN = high-risk nonsurvivor, HS = high-risk survivor, PIM2 = Pediatric Index of Mortality score, PRISM = Pediatric Risk of Mortality.

Patient characteristics are listed in Table 1. The four groups were different on admission characteristics, mortality risk scores, presence of CCCs, and outcome characteristics like length of stay. The LN group had more medical admissions and higher PRISM mortality risk compared to the LS group. The PIM2 mortality risks between LN and LS were comparable. LN patients were more often mechanically ventilated; had more ventilator days, more central venous catheters, and more central venous catheter days; and had a longer length of stay compared to LS patients.

Table 1. Patient characteristics

Characteristic
Patients in each subgroup
Gender: male
Age group
1–28 days
29–365 days
1–4 years
5–17 years
Age: median [IQR] (years)
Weight: median [IQR] (kg)
Socio-economic status
Low
Intermediate
High
Unknown
Non-elective admission
Medical admission
CPR or brain herniation as the cause for PICU admission
Off-hours admission
Chronic condition
CCC
NCCC
None
Recalibrated PRISM mortality risk, median [IQR] (%)
Recalibrated PIM2 mortality risk, median [IQR] (%)
Mechanical ventilation
Ventilator days, median [IQR]
Central venous catheter
Central venous catheter days, median [IQR]
Extracorporeal life support
Length of stay, median [IQR] (days)
Mode of death ($n = 24$)
Brain death
Maximal treatment including CPR
Maximal treatment without CPR
Limiting or withdrawal of therapy

All numbers are expressed as the number of patients unless specified otherwise.
LN = low-risk nonsurvivors, LS = low-risk survivors, HN = high-risk nonsurvivors, HS = high-risk survivors.
[1]Two patients in LN with extracorporeal life support (ECLS): one patient, a neonate with a very complex congenital cardiac disorder including pulmonary atresia and total abnormal pulmonary venous return, was admitted preoperatively for cardiac surgery and needed ECLS after surgery but did not survive. he mortality risk in this patient was—according to the PIM2/PRISM criteria—measured before surgery and was low. Another patient, admitted with severe asthma, was resuscitated during PICU stay (day 2) and supported by ECLS after resuscitation but died of cerebral post-anoxic complications.

LN	LS	HN	HS
12	12	12	12
6	6	6	6
1	1	1	1
4	4	4	4
0	0	0	0
7	7	7	7
9.5 [0-12.8]	7.5 [0-13.0]	5.0 [0-13.3]	5.5 [0-11.3]
32.5 [3.9-53.5]	14.9 [3.1-44.8]	20.0 [7.0-50.0]	22.0 [5.5-37.0]
3	3	2	3
5	8	8	8
3	1	1	1
1	0	1	0
10	7[d,f]	12	12
12[aa,c]	6	8	10
0	0	9[b]	3
6	4	6	7
9[cc]	7	3[b]	6
2	1	0	3
1	4	9	3
0.9 [0.7-1.4][a,ccc,eee]	0.6 [0.5-0.8][ddd,fff]	77.0 [21.4-87.4]	43.6 [35.3-60.5]
1.3 [0.8-6.1][ccc,e]	1.3 [1.0-2.2][d,fff]	56.1 [21.8-83.4][b]	14 [14-46]
11[aa]	4[dd,ff]	12	12
6.5 [2.5-30.8][aaa]	0 [0-1.8][ddd,ff]	2.5 [1.0-9.3]	6.5 [4.3-11.5]
10[a]	5[ff]	11	9
4.5 [1.3-14.3][aa]	0 [0-2][dd,ff]	2.5 [1-17.5]	6.5 [1-11.8]
2[1]	0	1	3
16 [5.5-32.8][aa,c,e]	2 [2-2.8][dd]	2.5 [1-9.3][b]	11 [6.3-13]
	Not applicable		Not applicable
0[c]		6	
1		0	
2		1	
9		5	

[a]p < 0.05, [aa]p < 0.01, and [aaa]p < 0.001, LN compared with LS; [b]p < 0.05, HN compared with HS; [c]p < 0.05, [cc]p < 0.01, and [ccc]p < 0.001, LN compared with HN; [d]p < 0.05, [dd]p < 0.01, and [ddd]p < 0.001, LS compared with group HS; [e]p < 0.05, and [eee]p < 0.001, LN compared with group HS; [f]p < 0.05, [ff]p < 0.01, and [fff]p < 0.001, LS compared with group HN.

In the LN group, most patients had a CCC (not resulting in a higher PIM2 or PRISM score) in contrast to the HN, where CCCs occurred in a minority of patients. In the HN, cardiopulmonary resuscitation was a frequent reason for admission, often resulting in brain death as the cause of death. In the majority of the LN, patients died after limiting therapeutic options. The length of stay in the LN was much longer compared to the HN and also longer compared to the HS.

Adverse events

The occurrence of AEs in the LN group was significantly higher compared to that in the LS and HN groups (Table 2). Eighty-three percent of the LN patients suffered from at least one AE. Twenty-five AEs occurred in the LN group. The AE rate (AE per PICU day) in the LN group was significantly higher compared to that in the LS and HN groups (median 0.12 AE/PICU day).

Table 2. Adverse events

Outcome measure	LN	LS	HN	HS
Patients with ≥1 AE(/*n*)	10/12[aaa,cc]	1/12[dd]	2/12[b]	7/12
AE PICU/PICU day, median [IQR]	0.12 [0.07–0.29][aaa,cc]	0 [0–0][dd]	0 [0–0][b]	0.03 [0.0–0.17]
Number of AEs, total	25	2	8	10
Number of AEs/patient, median [IQR]	2 [1–3.8]	0 [0–0]	0 [0–0]	1 [0–1]

Only the primary outcome (patients with greater than or equal to one AE) and AE rate were tested. LN = low-risk nonsurvivors, LS = low-risk survivors, HN = high-risk nonsurvivors, HS = high-risk survivors, AE = adverse event, PICU = pediatric intensive care unit, AE PICU/PICU day = the number of AEs per patient day.

[aaa]p < 0.001, LN compared with LS; [b]p < 0.05, HN compared with HS; [cc]p < 0.01, LN compared with HN; [dd]p < 0.01, LS compared with group HS.

In Table 3, preventability, severity, and classification of all identified AEs are shown. In the LN group, eight preventable AEs occurred. In five of these preventable AEs, the severity was high (grade G-I). Two patients, in both the LN groups, died after a preventable AE. Looking at all 15 preventable AEs found among all subgroups in this study, most preventable AEs were related to problems in clinical monitoring (*n* = 5), infection control (*n* = 5), and diagnosis (*n* = 2). Detailed information about all patients with AEs including description, timing, severity, and preventability of the AEs is shown in Table 10 (online only). The day on which the AE occurred varied from day 0 (preceding the PICU admission) to the last days of the PICU stay.

Table 3. Preventability, severity, and classification of adverse events

Group	No AEs	Preventability	Severity	Classification
LN	25	8 preventable AEs	I = 2	Infection control = 1
				Clinical monitoring = 1
			G–H = 3	Drug or fluid related = 1
				Diagnosis = 2
			E–F = 3	Infection control = 2
				Clinical monitoring = 1
		17 non-preventable AEs	I = 4	Other = 3
				Drug or fluid related = 1
			G–H = 5	Other = 4
				Drug or fluid related = 1
			E–F = 8	Infection control = 4
				Other = 3
				Technical = 1
LS	2	2 preventable AEs	H = 2	Infection control = 1
				Drug or fluid related = 1
HN	8	2 preventable AEs	G–H = 1	Clinical monitoring = 1
			E–F = 1	Infection control = 1
		6 non-preventable AEs	I = 1	ECLS = 1
			G–H = 1	ECLS = 1
			E–F = 4	ECLS = 1
				Other = 3
HS	10	3 preventable AEs	G–H = 1	ECLS = 1
			E–F = 2	ECLS = 1
				Clinical monitoring = 1
		7 non-preventable AEs	G–H = 5	Clinical monitoring = 1
				ECLS = 1
				Other = 3
			E–F = 2	ECLS = 1
				Technical = 1

Table 3. Continued

Group	No AEs	Preventability	Severity	Classification
Total	45	15 preventable		Clinical monitoring = 4
		30 unpreventable		Diagnosis = 2
				Drug or fluid related = 2
				ECLS = 2
				Infection control = 5
				Clinical monitoring = 1
				Drug or fluid related = 2
				Technical = 2
				ECLS = 5
				Infection control = 4
				Other = 16

Severity categories: E = contributed to or resulted in temporary harm to the patient and required intervention, F = contributed to or resulted in temporary harm to the patients and required initial or prolonged hospitalization, G = contributed to or resulted in permanent patient harm, H = required intervention to sustain life, I = contributed to or resulted in the patient's death.
LN = low-risk nonsurvivors, LS = low-risk survivors, HN = high-risk nonsurvivors, HS = high-risk survivors, AE = adverse event, ECLS = extracorporeal life support.

Interobserver agreement

Nine patient records were reviewed by the second investigator. Interobserver agreement was 8/9 (89%).

Discussion

Major findings

In this exploratory study, AEs occurred in 83% of the LN. The occurrence of AEs and AE rate in these LN patients were significantly higher compared to those in LS patients and also higher compared to those in HN patients. A substantial part of the AEs in the LN group was preventable and had severe consequences, including two LN patients who died after a preventable AE. Screening patients with a low mortality risk is a valuable tool to discover problems in the quality of care and might reduce preventable death by implementing targeted quality improvement measures.

A possible explanation for the higher occurrence of AEs in the LN group might be that "low-risk" as defined by a calculated low mortality risk does not always reflect a true low risk of dying. Mortality risk scores such as PIM2 or PRISM scores perform reasonably well for the PICU population in general with an AUC between 0.83 and 0.90 but not for each individual (37). Many patients in the LN group are sicker than they appear based on the PIM2 or PRISM score. Misclassifications do occur. For example, seven LN patients were admitted to the PICU with major comorbidity such as hemato-oncology patients and patients with complex congenital heart disorders. These low-risk patients with a CCC are often at high risk for AEs (35). Patients with congenital heart disorders are sometimes admitted preoperatively to the PICU. Mortality risk scores can be obtained before surgery and do not measure true postoperative risk. New PRISM methods like PRISM IV might reflect mortality risk better in these patients because the risk score is measured after surgery (26). However, severe and preventable AEs did occur in patients with and without a CCC, so to our opinion, this is not the only explanation.

Comparing the AE rate from this study with other studies is difficult because in this exploratory study, we did not include the general PICU population but focused on the low- and high-risk groups. A single PICU study on patient safety factors in 47 PICU nonsurvivors found that 36% of nonsurvivors suffered at least one AE of category I and 60% suffered a "critical incident" (19). These results cannot be compared with our study not only because of different population characteristics but also due to different outcome measures. The "critical incidents" used in the study of Monroe could either be AEs or medical errors not causing harm (categories B–D), a category which is too wide in our opinion (21).

From the viewpoint of quality improvement, preventable AEs are the most interesting. Looking at the nature of the 15 preventable AEs found in this study, problems in clinical monitoring ($n = 5$), infection control ($n = 5$), and diagnosis ($n = 2$) were most prevalent.

For example, a pediatric early warning system might lead to timely recognition of deterioration and thus lead to lower mortality (11). During the study period, pediatric early warning systems and sepsis bundles were implemented in the participating hospitals, but the effectiveness could not be systematically examined yet.

The length of stay in the LN group was significantly longer compared to that in all other groups. A longer duration of stay may be the consequence of the AEs or might have contributed to an increased chance for AEs, and this cannot be estimated from this retrospective study.

Limitations

Our study has several limitations. First, children in the age group of 1–4 years were not present in the randomly chosen LN group and therefore not in the other groups, possibly giving rise to bias. Second, a relatively high number of admissions were excluded from the study. The decision to exclude patients was made on predefined criteria. Remarkably, in seven patients, the PIM2/PRISM score turned out to be false after verifying with the data from the medical record. This should encourage better surveillance of the database. Third, poor quality of the information in patient records might lead to underestimation of the number of AEs. The assessment of AEs with a trigger tool method depends on the presence of data in the medical record. However, in a patient record review study in Dutch hospitals, poor quality of the information present in the medical record was associated with higher rates of AEs (40). Another weakness of all retrospective studies is hindsight bias (9, 39). Knowledge of the final outcome may have influenced judgment on severity and preventability. This could lead to an overestimation of preventable severe AEs as judged by the investigators. Finally, the mortality prediction models do not perform perfectly. However, we found that both in real LN and in LN with a CCC, severe AEs and AEs contributing to death occur.

Conclusion

This exploratory study shows that AEs do occur in PICU low-risk nonsurvivors. The occurrence of AEs in low-risk nonsurvivors was higher compared to that in low-risk survivors and high-risk nonsurvivors. Some AEs were severe and preventable and contributed to morbidity and mortality. The exact scale and nature of this safety problem should be analyzed in a larger multi-center study.

Informed consent and ethics

The study protocol has been presented to the Medical Ethical Committee of the Radboud University Medical Center in Nijmegen (registration number: 2016-2829). The committee judged that ethical approval was not required under Dutch national law. Data were anonymized and handled according to the principles of good clinical practice. No informed consent was obtained.

Reference list

1. Agarwal S, Classen D, Larsen G, Tofil NM, Hayes LW, Sullivan JE, Storgion SA, Coopes BJ, Craig V, Jaderlund C, Bisarya H, Parast L, Sharek P (2010) Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med 11(5):568–578
2. Baines RJ, Langelaan M, de Bruijne MC, Asscheman H, Spreeuwenberg P, van de Steeg L, Siemerink KM, van Rosse F, Broekens M, Wagner C (2013) Changes in adverse event rates in hospitals over time: a longitudinal retrospective patient record review study. BMJ Qual Saf 22(4):290–298
3. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, Etchells E, Ghali WA, Hébert P, Majumdar SR, O'Beirne M, Palacios-Derflingher L, Reid RJ, Sheps S, Tamblyn R (2004) The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ 170(11):1678-1686
4. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, Newhouse JP, Weiler PC, Hiatt HH (1991) Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med 324(6):370–376
5. 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(7):2196–2203
6. Eulmesekian PG (2017) Low-risk pediatric critical care patients, are they really a different population? Pediatr Crit Care Med 18(4):390–391
7. Feudtner C, Christakis DA, Connell FA (2000) Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington state, 1980-1997. Pediatrics 106(1 Pt 2):205–209
8. 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
9. Fischhoff B (1975) Hindsight not equal to foresight—effect of outcome knowledge on judgment under uncertainty. J Exp Psychol Hum Percept Perform 1(3):288–299
10. Forster AJ, Kyeremanteng K, Hooper J, Shojania KG, van Walraven C (2008) The impact of adverse events in the intensive care unit on hospital mortality and length of stay. BMC Health Serv Res 8:259
11. Fuijkschot J, Vernhout B, Lemson J, Draaisma JMT, Loeffen JLCM (2015) Validation of a Paediatric Early Warning Score: first results and implications of usage. Eur J Pediatr 174(1):15–21
12. Garrouste Orgeas M et al (2008) Impact of adverse events on outcomes in intensive care unit patients. Crit Care Med 36(7):2041–2047
13. Garrouste-Orgeas M, Timsit JF, Vesin A, Schwebel C, Arnodo P, Lefrant JY, Souweine B, Tabah A, Charpentier J, Gontier O, Fieux F, Mourvillier B, Troché G, Reignier J, Dumay MF, Azoulay E, Reignier B, Carlet J, Soufir L, OUTCOMEREA Study Group (2010) Selected medical errors in the intensive care unit: results of the IATROREF study: parts I and II. Am J Respir Crit Care Med 181(2):134-142
14. Hannan EL, Bernard HR, O'Donnell JF, Kilburn H Jr (1989) A methodology for targeting hospital cases for quality of care record reviews. Am J Public Health 79(4):430–436

15. Hogan H, Healey F, Neale G, Thomson R, Vincent C, Black N (2012) Preventable deaths due to problems in care in English acute hospitals: a retrospective case record review study. BMJ Qual Saf 21(9):737–745
16. Kohn LT et al (2000) To err is human: building a safer health system, vol xxi. National Academy, Washington, D.C., p 287
17. Larsen GY, Donaldson AE, Parker HB, Grant MJ (2007) Preventable harm occurring to critically ill children. Pediatr Crit Care Med 8(4):331–336
18. Mendes W, Martins M, Rozenfeld S, Travassos C (2009) The assessment of adverse events in hospitals in Brazil. Int J Qual Health Care 21(4):279–284
19. Monroe K, Wang D, Vincent C, Woloshynowych M, Neale G, Inwald DP (2011) Patient safety factors in children dying in a paediatric intensive care unit (PICU): a case notes review study. BMJ Qual Saf 20(10):863–868
20. NCC-MERP (2001) February 20; National Coordinating Council for Medication Error Reporting and Prevention. Available from: http://www.nccmerp.org/types-medication-errors
21. Neale G, Chapman EJ, Hoare J, Olsen S (2006) Recognising adverse events and critical incidents in medical practice in a district general hospital. Clin Med (Lond) 6(2):157–162
22. Niesse OW, Sennhauser FH, Frey B (2011) Critical incidents in paediatric critical care: who is at risk? Eur J Pediatr 170(2):193–198
23. PICE. PICE registry (2016) 2016, December 15; Available from: http://www.pice.nl/eng/index-eng.htm
24. Pollack MM, Ruttimann UE, Getson PR (1988) Pediatric Risk of Mortality (PRISM) score. Crit Care Med 16(11):1110–1116
25. Pollack MM, Patel KM, Ruttimann UE (1996) PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 24(5):743–752
26. Pollack MM, Holubkov R, Funai T, Dean JM, Berger JT, Wessel DL, Meert K, Berg RA, Newth CJ, Harrison RE, Carcillo J, Dalton H, Shanley T, Jenkins TL, Tamburro R, Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (2016) The Pediatric Risk of Mortality score: update 2015. Pediatr Crit Care Med 17(1):2–9
27. Shann F, Pearson G, Slater A, Wilkinson K (1997) Paediatric Index of Mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med 23(2):201–207
28. Silas R, Tibballs J (2010) Adverse events and comparison of systematic and voluntary reporting from a paediatric intensive care unit. Qual Saf Health Care 19(6):568–571
29. Slater A et al (2003) PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 29(2):278–285
30. Slater A et al (2003) The ANZPIC registry diagnostic codes: a system for coding reasons for admitting children to intensive care. Intensive Care Med 29(2):271–277
31. Stambouly JJ, McLaughlin LL, Mandel FS, Boxer RA (1996) Complications of care in a pediatric intensive care unit: a prospective study. Intensive Care Med 22(10):1098–1104
32. The Netherlands Institute for Social Research Socio economic status of neighborhood in the Netherlands. Available from: http://www.scp.nl/english/
33. Tibby SM, Correa-West J, Durward A, Ferguson L, Murdoch IA (2004) Adverse events in a paediatric intensive care unit: relationship to workload, skill mix and staff supervision. Intensive Care Med 30(6):1160–1166
34. Urbaniak GC, Plous S Research randomizer. 2013; Available from: https://www.randomizer.org/

35. Verlaat CW et al (2017) Factors associated with mortality in low-risk pediatric critical care patients in the Netherlands. Pediatr Crit Care Med 18(4):e155-e161
36. Vermeulen JM, van Dijk M, van der Starre C, Wösten-van Asperen RM, Argent AC (2014) Patient safety in South Africa: PICU adverse event registration*. Pediatr Crit Care Med 15(5):464–470
37. Visser IH et al (2013) Mortality prediction models for pediatric intensive care: comparison of overall and subgroup specific performance. Intensive Care Med 39(5):942–950
38. Zegers M, de Bruijne MC, Wagner C, Groenewegen PP, Waaijman R, van der Wal G (2007) Design of a retrospective patient record study on the occurrence of adverse events among patients in Dutch hospitals. BMC Health Serv Res 7:27
39. Zegers M, de Bruijne MC, Wagner C, Hoonhout LHF, Waaijman R, Smits M, Hout FAG, Zwaan L, Christiaans-Dingelhoff I, Timmermans DRM, Groenewegen PP, van der Wal G (2009) Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. Qual Saf Health Care 18(4):297–302
40. Zegers M, de Bruijne MC, Spreeuwenberg P, Wagner C, Groenewegen PP, van der Wal G (2011) Quality of patient record keeping: an indicator of the quality of care? BMJ Qual Saf 20(4):314–318

Additional Files Chapter 4

Table 4
Triggers used to identify adverse events

Table 5
Harm classification using the NCC MERP criteria

Table 6
Preventability of adverse events

Table 7
Classification of adverse events

Table 8
List of diagnoses classified as complex chronic conditions

Table 9
List of diagnoses classified as non-complex chronic conditions

Table 10
Detailed description of patients with adverse events

Table 4. Triggers used to identify adverse events (modification of triggertool used by Agarwal (1)).

No	Trigger	Examples / Potential AEs
1	Cardiac or respiratory arrest	Resuscitation, defibrillation, cardioversion, emergency intubation, administration of epinephrine
2	Accidental extubation	
3	Pulmonary	Pneumothorax, chylothorax , aspiration pneumonia
4	Neurology	CNS bleed, CNS ischemia/infarction
5	Infectious disease	Infection of any kind occurring ≥ 3 days after admission
6	Subcutaneous infusion	Need for hyaluronidase infusion
7	Decubitus ulcer (pressure sores)	
8	Readmission < 48 hours	
9	Central catheter	Central catheter clot, inadvertent catheter removal, bleeding from central catheter, change of ECLS system
10	Trachea	Post extubation stridor, racemic epinephrine administration
11	Dislocation endotracheal tube	Order to pull back or push ETT or chest X ray with tube > 0.5 cm to (un)deep, not direct after intubation/ ETT mal-positioning requiring reposition
12	Oversedation	COMFORT-B score < 11 during 24 hours
13	Allergy	Allergic reaction, treatment with clemastine, allergic rash
14	Pain,undersedation	Uncontrolled pain, undersedation (two times COMFORT-B score ≥ 17 and/or NRS ≥ 4 within one hour)
15	Hypo-/ hyperglycaemia	Insulin treatment, glucose <4 or > 8 mmol/l in children, glucose <2.7 or >8 mmol/l in neonates
16	Withdrawal symptoms	Notification of withdrawal symptoms in medical record, use of medications (like methadon, lorazepam, clonidine orally), SOS score > 4 twice.
17	Delirium	Notification of delirium in medical record, use of medications like haloperidol, risperidon, combinations of different scores (CAP-D score, pCAM-ICU score, SOS-PD score)
18	Thrombosis	Deep vein thrombosis
19	Other	Other incidents: unplanned return to surgery, problems with foley catheter, problems with epidural catheter, falling incidents, diagnostic delay

CNS = central nervous system, ECLS = extra corporal life support, ETT = endotracheal tube, COMFORT-B score= COMFORT behavioral score (sedation score), NRS =Numerical Rating Scale (pain score), SOS-score = Sophia Observation withdrawal Score, CAP-D score = Cornell Assessment of the Pediatric Delirium, pCAM-ICU = pediatric Confusion Assessment Method for the Intensive Care Unit, SOS-PD score = Sophia Observation withdrawal Score – Pediatric Delirium.

Table 5. Harm classification using the NCC MERP criteria (2)

Category	Definition	Error? Harm?
A	Circumstances or events that have the capacity to cause error	No error
B	An error occurred but the error did not reach the patient	Error, no harm
C	An error occurred that reached the patient but did not cause patient harm	Error, no harm
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm	Error, no harm
E	Contributed to or resulted in temporary harm to the patient and required intervention	Harm
F	Contributed to or resulted in temporary harm to the patients and required initial or prolonged hospitalization	Harm
G	Contributed to or resulted in permanent patient harm	Harm
H	Required intervention to sustain life	Harm
I	Contributed to or resulted in the patient's death	Death

NCC MERP = National Coordination Council for Medication Error Reporting and Prevention
Categories E-I = Adverse event.

Table 6. Preventability of adverse events (3)

Category	Definition
1	(Virtually) no evidence for preventability
2	Slight to modest evidence of preventability
3	Preventability not quite likely (less than 50/50, but 'close call')
4	Preventability more than likely (more than 50/50, but 'close call')
5	Strong evidence of preventability
6	(Virtually) certain evidence of preventability

AE = adverse event
AEs with a preventability score of 4 to 6 were defined as preventable AEs.

Table 7. Classification of adverse events (Modification of classification made by Hogan (4))

Type of problem	Definition
Clinical monitoring	Failure to act upon results of tests or clinical findings, set up monitoring systems or respond to such systems or increase intensity of care when required
Diagnosis	Missed, delayed or inappropriate diagnosis as a result of failure to perform an adequate assessment of patient's overall condition including appropriate tests or lack of focused assessment when required
Drug or fluid related	Side effects, inappropriate use, failure to give prophylactic care, anaphylaxis, etc.
Technical problems	Related to a device, an operation or procedure whether on ward, in a diagnostic situation or in theatre and including inappropriate or unnecessary procedures (*other than technical problems related to ECLS)*
ECLS	Problems related to ECLS including technical problems, hemorrhage
Infection related	Healthcare associated infections including infections from indwelling device
Resuscitation	Problems in resuscitation including cardiopulmonary resuscitation such as delay in beginning resuscitation, problems related to resuscitation technique, resuscitation medication/fluids, resuscitation equipment
Other	Any other problem not fitting categories above

ECLS = extracorporeal life support.

Table 8. List of diagnoses classified as complex chronic conditions (CCC) (Modification of Feudtner's list (5-8))

Complex chronic conditions	
Subgroup	Diagnoses from the PICE database
Cardiovascular	Absent pulmonary valve syndrome*
	Anomaly of the coronary artery
	Arterial switch*
	Atrioventricular septal defect
	Cardiomyopathy
	Cavopulmonary shunt*
	Cor triatriatum
	Double outlet right ventricle
	Ebstein's anomaly
	Fontan procedure*
	Hypoplastic left heart syndrome
	Hypoplastic left ventricle*
	Hypoplastic or interrupted aortic arch*
	Hypoplastic right ventricle*
	Levo transposition of the great arteries
	Mitral valve stenosis
	Monoventricle
	Norwood procedure – step 1*
	Pacemaker insertion/revision*
	Portal hypertension*
	Pulmonary atresia or stenosis
	Pulmonary artery banding*
	Reconstruction of aortic arch*
	Reconstruction of left ventricular outflow*
	Reconstruction of right ventricular outflow*
	Restoration of atrioventricular septumdefect*
	Repair of plastic pulmonary artery*
	Repair or replacement of conduit*
	Repair of tetralogy of Fallot*
	Right ventricular outflow tract obstruction*
	Senning procedure*
	Supraventricular arrhythmia
	Surgery of pulmonary collateral arteries*
	Systemic to pulmonary shunt procedure*
	Tetralogy of Fallot
	Total abnormal pulmonary venous return
	Transplantation of heart
	Transplantation of heart and lung
	Transplantation of heart and lung – state after procedure
	Transposition of the great arteries

Table 8. Continued

Complex chronic conditions	
Cardiovascular (Continued)	Tricuspid atresia or stenosis
	Truncus arteriosus
	Vasculitis*
	Ventricular arrhythmia
Respiratory	Bronchiectasis
	Central apnea*
	Choanal atresia or stenosis*
	Chronic lung disease*
	Congenital lung disease
	Cystic fibrosis
	Infant respiratory distress syndrome*
	Laryngomalacia
	Malacia trachea or bronchus
	Massa mediastinum*
	Pulmonary edema
	Pulmonary hypoplasia
	Pulmonary insufficiency*
	Reconstuction of larynx*
	Subglottic stenosis
	Tracheostomy*
	Trachea or bronchus stenosis
	Transplantation of lung
	Transplantation of lung – state after procedure
	Vocal cord paralysis*
Hematological	Coagulation defects
	Hematologic disease*
Endocrinological	Congenital metabolism disorder
	Diabetes (comorbidity)*
	Diabetes inspididus
	Diabetes mellitus with ketoacidosis
	Diabetes mellitus without ketoacidosis
	Endocrine disorder
	Kasaï procedure*

Table 8. Continued

Complex chronic conditions	
Gastrointestinal	Biliary atresia
	Colitis
	Congenital diaphragmatic hernia
	Gastroschisis or exomphalus
	Hirschsprung's disease*
	Liver disease – other*
	Oesophageal atresia
	Repair of esophageal atresia*
	Repair of esophageal fistel*
	Repair of total anomalous pulmonary venous return*
	Short bowel syndrome*
	Transplantation of kidney
	Transplantation of liver
	Transplanation of liver – state after procedure
	Transplantation of small intestine
	Varices of oesophagus or stomach*
Immunological	Congenital immunodeficiency
	Graft versus host disease
	Neutropenia*
	Pancytopenia*
	Pheochromocytoma*

Table 8. Continued

Complex chronic conditions	
Neuromuscular	Acute disseminated encephalomyelitis*
	Arnold-Chairi malformation
	Brain arteriovenous malformation*
	Brain tumour
	Central nervous system shunt dysfunction or infection*
	Cerebral aneurism
	Cerebral cyst
	Cerebral infarction*
	Chronic traumatic encephalopathy
	Congenital brain disease*
	Convulsions*
	Craniotomy – fossa anterior*
	Epilepsy (comorbidity)
	Hydrocephalus
	Insertion of revision of central nervous system shunt*
	Lobectomy or hemispherectomy*
	Meningomyelocele or spina bifida
	Muscular dystrophy
	Myastenia gravis
	Myelum – impairment*
	Myopathy
	Repair of myelomeningocele*
	Static encephalopathy
Oncological	Cystic hygroma
	Leukemia or lymphoma
	Malignant solid organ neoplasm
	Transplantation of bone marrow
	Transplantation of bone marrow – state after procedure
Renal	Chronic kidney failure
	Hydronephrosis*
	Nephrotic or nephritic syndrome*
	Transplantation of kidney – state after procedure
Endocrinal	Syndrome of inappropriate antidiuretic hormone secretion*
Genetic	Chromosome abnormality
	Craniosynotosis*
	DiGeorge syndrome
	Down syndrome
	Pierre Robin syndrome*
Urological	Repair of exstrophia vesicae*
Miscellaneous	Syndrome or malformation*

** Diagnoses that were not on the original Feudtner's list (as CCC).*

Table 9. List of diagnoses classified as non-complex chronic conditions (NCCC) (modification of Feudtner's list (5-7))

Non-complex chronic conditions	
Subgroup	Diagnoses from the PICE database
Cardiovascular	Aorta insufficiency
	Aorta stenosis
	Atrial septal defect
	Aortopulmonary window*
	Arteriovenous malformation*
	Acquired cardiovascular disorder – other*
	Coartectomy*
	Coarctatio aortae
	Closed valvotomy*
	Closed heart surgery – other*
	Congenital cardiovascular disorder- other
	Ductus arteriosus
	Left ventricle outflow tract obstruction*
	Mitral insufficiency
	Myocardal infarction or ischemia*
	Open valvotomy*
	Open heart surgery – other*
	Pulmonary hypertension*
	Past heart surgery*
	Repair of atrial septal defect*
	Repair of ventricular septal defect*
	Repair of coronary artery*
	Repair of ductus arteriosus*
	Repair or replacement of valve*
	Systemic hypertension
	Tricuspidal insufficiency
	Ventricular septal defect
Respiratory	Asthma
	Chylous effusion*
	Obstructive sleep apnoea syndrome
	Pneumectomy or lobectomy*
Gastrointestinal	Repair of gastroschisis or exomphalos*
Neuromuscular	Guillain Barré syndrome*
	Neuropathy
	Neurosurgery - other*

Table 9. Continued

Non-complex chronic conditions	
Oncological	Cardiac tumour*
	Non-malignant solid organ neoplasm
	Resection of abdominal tumour*
	Resection of cardiac tumour *
	Resection of thoracic tumour*
	Subglottic hemangioma
Genetic	Repair of cheiloschisis*
	Repair of palatoschisis*
Miscellaneous	Scoliosis

NCCC = non complex chronic condition

** Diagnoses that were not mentioned on the original Feudtner's list (as NCCC).*

Table 10. Detailed description of patients with adverse events (AEs). AEs occurred in 20/48 patients

Group/ patient	Age (yr)	Diagnosis	CCC	No. AE	LOS	Timing AE (day)
LN						
1	10	Acute myeloid leukemia, neutropenic enterocolitis	CCC	1	7	6
2	12	Acute myeloid leukemia, hyperleuco-cytosis	CCC	1	3	2
3	9	Trauma, pelvic fracture	no CCC	3	1	0 0 1
4	13	Morbus Steinert, pneumonia	NCCC	3	32	23 26 30
5	15	Epilepsy, status epilepticus	CCC	4	36	3 21 22 33
6	0	Premature, short bowel after necrotising enterocolitis, cholestasis	CCC	1	16	16
7	0	Giant omphalocele, pulmonary hypertension	CCC	1	10	5
8	17	Juvenile chronic arthritis, hemophago-cytic lympho-histiocytosis	CCC	4	16	0 1 11 14
9	11	Status asthmaticus	NCCC	3	5	2 2 3
10	0	Hypoplastic right ventricle, total abnormal venous return	CCC	4	33	20 20 26 28
LS						
11	12	Marfan syndrome, Bental procedure, hematothorax	CCC	2	2	0 0

Location AE (pre PICU /PICU)	Description of AE	Severity	Preventability (x/6)
PICU	Abdominal compartment syndrome	Cat H	1
PICU	Fluid overload	Cat H	4
2 pre PICU	Missed diagnosis gut perforation	Cat H	4
	Fat embolism	Cat I	3
1 PICU	Tension pneumothorax (found post mortem)	Cat I	1
PICU	Sudden resuscitation	Cat G	1
	Urinary tract infection	Cat E	2
	Post anoxic encephalopathy	Cat I	2
PICU	CLABSI	Cat E	5
	CLABSI	Cat E	5
	Urinary tract infection	Cat E	2
	Deep vein thrombosis (despite prophylaxis)	Cat E	1
PICU	CLABSI	Cat I	4
PICU	Extravasation injury	Cat E	4
1 pre PICU	Gastric perforation during steroids (despite	Cat H	1
3 PICU	prophylaxis)	Cat H	4
	Delay in diagnosis of gastric perforation	Cat E	1
	Pneumothorax	Cat I	2
	Cerebral Hemorrhage		
PICU	Resuscitation during spontaneous ventilation	Cat I	4
	in PICU	Cat E	1
	Hypoglycaemia	Cat E	1
	Pneumothorax (on ECLS)		
PICU	Resuscitation - SVT	Cat H	1
	Resuscitation	Cat H	1
	CLABSI (on ECLS)	Cat E	2
	CLABSI	Cat E	2
2 pre PICU	Infected pericardial effusion	Cat H	4
	Hematothorax, no antagonising coumarines	Cat H	5
	before inserting central venous line		

Table 10. Continued

Group/ patient	Age (yr)	Diagnosis	CCC	No. AE	LOS	Timing AE (day)
HN						
12	11	Trauma, cardiac arrest at trauma site	no CCC	1	1	0
13	14	Necrotizing pneumonia (influenza, staphylococcus aureus), transfer from another PICU for ECLS	no CCC	7	21	5 9 9 11 15 18 21
HS						
14	9	Cerebral herniation, hydrocephalus, neurofibromatosis	CCC	1	24	13
15	0	Meconium aspiration syndrome, transfer for ECLS	no CCC	3	12	1 3 5
16	0	Urgent laparotomy, bleeding from large abdominal tumor	CCC	1	13	1
17	0	Trisomie 21, meningo-encephalitis, septic shock	CCC	2	8	1 1
18	12	Out of hospital resuscitation, aspiration, ARDS, transfer from another PICU for ECLS	no CCC	1	5	2
19	12	Status asthmaticus	NCCC	1	11	3
20	5	Juvenile myelomono-cytic leukemia, bone marrow transplant, graft versus host, short bowel, seizures	CCC	1	41	21

LN = low-risk nonsurvivors, LS = low-risk survivors, HN = high-risk nonsurvivors, HS = high-risk survivors, CCC= complex chronic condition, NCCC = non-complex chronic condition, no CCC= no (non-) complex chronic condition, AE = adverse event, No.AE = number of AEs in this patient, LOS = length of stay (days),

Location AE (pre PICU /PICU)	Description of AE	Severity	Preventability (x/6)
pre PICU	Hypoxia and hypotension during transport to PICU	Cat H	4
PICU	Small cerebral hemorrhage (on ECLS)	Cat E	2
	Pneumothorax	Cat E	1
	Hematothorax after drainage of	Cat H	2
	pneumothorax on ECLS	Cat E	1
	Pneumothorax	Cat E	1
	Pneumothorax	Cat E	4
	CLABSI	Cat I	2
	Cerebral hemorrhage (on ECLS)		
PICU	Decubitus	Cat E	4
PICU	Resuscitation before ECLS was started	Cat H	1
	Replacement ECLS canule (wrong canule	Cat E	6
	placed)	Cat G	2
	Cerebral hemorrhage on ECLS		
PICU	Abdominal compartment syndrome / resuscitation	Cat H	2
PICU	Subdural empyema and cerebral hemorrhage	Cat G	1
	Necrosis of digits	Cat G	1
PICU	Hemorrhage around ECLS canula in left groin	Cat E	1
PICU	Ischaemia leg, on veno-arterial ECLS	Cat G	4
PICU	Obstruction of CVL	Cat E	1

PICU = pediatric intensive care unit, CLABSI = central line-associated blood stream infection, ECLS = extracorporal life support, CVL = central venous line.
Timing AE (day) = day op PICU admission when AE occurred, if an AE was preceding the PICU admission, it was scored as day 0.

Reference list Additional files Chapter 4

1. Agarwal, S., et al., Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med, 2010. 11(5): p. 568-78.
2. NCC MERP Index for Categorizing Medication Errors. National Coordinating Council for Medication Error Reporting and Prevention]. Available from: http://www.nccmerp.org/types-medication-errors.
3. Baker, G.R., et al., The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ, 2004. 170(11): p. 1678-86.
4. Hogan, H., et al., Preventable deaths due to problems in care in English acute hospitals: a retrospective case record review study. BMJ Qual Saf, 2012. 21(9): p. 737-45.
5. Feudtner, C., D.A. Christakis, and F.A. Connell, Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980-1997. Pediatrics, 2000. 106(1 Pt 2): p. 205-9.
6. Feudtner, C., et al., Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr, 2014. 14: p. 199.
7. Edwards, J.D., et al., 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, 2012. 40(7): p. 2196-203.
8. Verlaat, C.W., et al., Factors Associated With Mortality in Low-Risk Pediatric Critical Care Patients in The Netherlands. Pediatr Crit Care Med, 2017. 18(4): p. e155-e161.

CHAPTER 5

ADVERSE EVENTS IN PEDIATRIC CRITICAL CARE NONSURVIVORS WITH A LOW PREDICTED MORTALITY RISK: A MULTICENTER CASE CONTROL STUDY

Carin W. Verlaat
Marieke Zegers
Richard Klein
Dick van Waardenburg
Jan Willem Kuiper
Maaike Riedijk
Martin Kneyber
Brigitte Timmers
Marc van Heerde
Jan A. Hazelzet
Johannes van der Hoeven
Joris Lemson

Pediatr Crit Care Med 2023; 24(1): 4-16

Abstract

Objectives: Some patients with a low predicted mortality risk in the PICU die. The contribution of adverse events to mortality in this group is unknown. The aim of this study was to estimate the occurrence of adverse events in low-risk nonsurvivors (LN), compared with low-risk survivors (LS) and high-risk PICU survivors and nonsurvivors, and the contribution of adverse events to mortality.

Design: Case control study. Admissions were selected from the national Dutch PICU registry, containing 53,789 PICU admissions between 2006 and 2017, in seven PICUs. PICU admissions were stratified into four groups, based on mortality risk (low/high) and outcome (death/survival). Random samples were selected from the four groups. Cases were "LN." Control groups were as follows: "LS," "high-risk nonsurvivors" (HN), and "high-risk survivors" (HS). Adverse events were identified using the validated trigger tool method.

Setting: Patient chart review study.

Patients: Children admitted to the PICU with either a low predicted mortality risk (< 1%) or high predicted mortality risk (≥ 30%).

Interventions: None.

Measurements and main results: In total, 419 patients were included (102 LN, 107 LS, 104 HN, and 106 HS). LN had more complex chronic conditions (93.1%) than LS (72.9%; $p < 0.01$), HN (49.0%; $p < 0.001$), and HS (48.1%; $p < 0.001$). The occurrence of adverse events in LN (76.5%) was higher than in LS (13.1%) and HN (47.1%) ($p < 0.001$). The most frequent adverse events in LN were hospital-acquired infections and drug/fluid-related adverse events. LN suffered from more severe adverse events compared with LS and HS ($p < 0.001$). In 30.4% of LN, an adverse event contributed to death. In 8.8%, this adverse event was considered preventable.

Conclusions: Significant and preventable adverse events were found in low-risk PICU nonsurvivors. 76.5% of LN had one or more adverse events. In 30.4% of LN, an adverse event contributed to mortality.

Introduction

Despite the introduction of several safety programs, adverse events (AEs) remain a great threat to modern healthcare, leading to patient harm, morbidity, increased healthcare costs, and even death. AEs occur in 22–76% of admissions in the PICU (1–5). Ninety percent of AEs in the PICU do not cause permanent harm (4). PICU mortality in affluent countries has decreased over the last decades to 2–4%, but PICU patients often have underlying complex chronic conditions, receive multiple drugs, need invasive supportive technologies, depend on many clinical decisions being made, and are at risk for iatrogenic harm (6).

Validated mortality prediction models like the "Pediatric Index of Mortality" (PIM) and "Pediatric Risk of Mortality" (PRISM) and their updates are used in the PICU for benchmarking and for research purposes (7–10). A significant portion of PICU patients has a low predicted mortality risk, as measured by these prediction models. Nevertheless, some of the "low-risk" patients die in the PICU. Unplanned admissions and underlying complex chronic conditions are known risk factors associated with mortality in this group (11–13). These factors increase the risk for mortality significantly, but it seems that more factors are involved in the death of the "low-risk" PICU population. Specifically, the contribution of AEs in these "unexpected deaths" is unknown but of great interest. Although one may expect that AEs mainly occur in the most complex, critically ill PICU patients, two small studies showed that low-risk PICU patients who die have a high occurrence of AEs (14, 15). In order to gain more insight into the occurrence and relevance of AEs in low-risk PICU nonsurvivors, we performed a nation-wide study in The Netherlands. More knowledge about the role of AEs might reveal opportunities to increase safety in the PICU.

The primary aim was to study the occurrence of AEs in PICU nonsurvivors with a low predicted mortality risk (low-risk nonsurvivors (LN)), compared to low-risk survivors (LS), high-risk nonsurvivors (HN) and high-risk survivors (HS). Secondary aims were to compare the severity, preventability and nature of AEs between LN and LS and high-risk patients and to establish the contribution of AEs to mortality.

Materials and methods

Study design and setting

We conducted a case control study, in which admissions were selected from the national PICU registry containing anonymized information of all seven PICUs in The Netherlands ("Pediatric Intensive Care Evaluation" ("PICE-registry") (https://pice.nl/). The PIM2 and PRISM-II (further referred as "PRISM") scores of all PICU admissions were collected, and the models were recalibrated to predict overall mortality in the 11-year cohort without altering the relative weights of the risk factors (12, 14, 16). Mortality in the database was registered as mortality during PICU admission (12).

Study population

PICU admissions between January 1, 2006, and January 1, 2017, were stratified into four groups based on risk profile and outcome, comparable with previous studies (12, 14, 17). The study group consisted of LN, defined as "admissions with a mortality risk in the simply recalibrated PIM2 and/or recalibrated PRISM of < 1% and PICU-nonsurvivor). The three control groups consisted of "LS" (mortality risk < 1% and survivor), "HN" (mortality risk > 30% and nonsurvivor), and "HS" (mortality risk > 30% and survivor). Nonsurvivors were defined as patients who died during PICU admission. After stratification, a random sample of the four groups was selected by a computer-based randomizer (18).

The methodology was equal compared with a pilot study which was performed in two PICUs. Based on the results of a pilot study, with an anticipated occurrence of patients with greater than one AE of 80% in the LN group and 60% in the HS group, with alpha of 0.0167, beta of 0.2, and power 80%, 420 patients were needed (14). Anticipating 15% exclusions, a total of 4 × 125 (500) admissions were selected. To obtain sufficient patients in the LN group (n = 125), patients were selected from a large time frame. Inclusion criteria were children less than 18 years with PIM2 and PRISM scores. Exclusion criteria were patients who were admitted for palliative reason or who were brain dead at admission, premature patients, patients in whom the medical record was unavailable, or patients who did not fulfill criteria for being high- or low-risk after the PIM2 and PRISM scores were checked for errors. Details are shown in the additional file, Table S1 (http://links.lww.com/PCC/C245).

Data collection

Data were collected using a validated two-staged record review method (4, 14).

The first stage of the analysis was performed by a team of three trained medical students and the primary investigator. The primary investigator is a pediatric intensivist with over 20 years of clinical experience. PIM2 and PRISM scores were checked for errors based on physiologic and laboratory data. Patient characteristics were extracted from the registry and from the medical record (Table S2, http://links.lww.com/PCC/C245). All medical records and nursing records were manually screened for potential AEs using a PICU trigger tool method which was adapted from Agarwal et al (4) and used in the exploratory study (Table S3, http://links.lww.com/PCC/C245) (14).

During the second stage, performed by the primary investigator, patient records were reviewed for diagnoses, health status at PICU admission, mode of death (if applicable), and AEs. For diagnosis classification, the diagnostic code list of the Australian New Zealand Pediatric Intensive Care society was used (19).

Health status of the patient at PICU admission was based on the presence of an underlying complex chronic condition (CCC) or non-CCC, according to a modified Feudtner's list (Table S4, http://links.lww. com/PCC/C245) (11, 12, 14, 20). Because the presence of CCCs does not always differentiate between children with a short life expectancy and children who are able to survive for many more years, a tool to categorize life expectancy before PICU admission was developed. Life expectancy was based on patient history including CCCs and using professional judgment from the primary investigator (13, 21, 22). An expert panel of (pediatric) intensivists (J.A.H., J.v.d.H., J.L.) was available if problems were encountered in judgment of AEs.

Outcome measures

Definitions and outcome measures are shown in Table 1. Primary outcome was the occurrence of AEs. An AE was defined as unintended injury that results in prolonged hospital stay, temporary or permanent disability, or death, caused by healthcare management rather than by the patient's underlying disease process (23). Secondary outcomes were severity, preventability, nature and timing of AEs, and contribution of AEs to mortality.

The severity of AEs was rated according to the criteria of the National Coordinating Council for Medication Error Reporting and Prevention (24). Regarding grade I AEs ("contributed to or resulted in the patient's death"), three subcategories were developed: I-1: "AE partially contributed to death," I-2: "AE substantially contributed to death," or I-3: "death completely caused by AE". All AEs contributing to mortality were discussed within in the expert panel.

A preventable AE was defined as "an AE resulting from mismanagement due to failure to follow accepted practice at an individual or system level" (23). Accepted practice was taken to be "the current level of expected performance for the average practitioner or system that manages the condition in question," using guidelines and protocols that were valid at that time/ period (25). Preventability of AEs was scored using a six-point Likert scale. AEs with a preventability score of 4–6 were considered as preventable (21, 23).

AEs were grouped into nine categories, based on the classification made by Hogan et al (22), for example "clinical monitoring," "drug or fluid related," "infection related," or "technical problems." A category was added for extracorporeal membrane oxygenation and procedures taking place outside the PICU ("surgical procedure") (Table 1). AEs that occurred before PICU admission and were related to the PICU admission, were included in the total number of AEs as "AE before PICU admission," modified from the Canadian AE Study (23). As they occurred before and not during PICU admission, they were not incorporated in the AE rate (number of AEs/PICU day). Data that could not be retrieved were categorized as "missing."

Data analysis

Normal distribution of continuous variables was tested using sampling distributions and skewness and kurtosis tests. Skewed distributed data were reported by median and interquartile range (IQR) and were tested by nonparametric tests (Mann-Whitney U). For categorical variables, chi-square test was used (software: IBM statistics 22).

LN patients were compared with LS, HN, and HS patients. Because of multiple testing, a Bonferroni correction was applied, and therefore an alpha of 0.0167 was considered significant.

Reliability study

To assess the reliability of the review process, a sample of 24 medical records was independently reviewed by a panel of three pediatric intensivists, for the presence and preventability of AE(s). The panel was not part of the core team and was blinded for the study results. A k-value between 0.00 and 0.20 was classified as "slight," between 0.21 and 0.40 as "fair," between 0.41 and 0.60 as "moderate," between 0.61 and 0.80 as "substantial," and between 0.81 and 1.00 as "almost perfect" (26).

Table 1. Definitions and Outcome Measures

Adverse Event (AE)

An unintended injury that results in temporary or permanent disability, death or prolonged hospital stay and that is caused by healthcare management rather than by the patient's underlying disease process

Timing of AE

1 AEs that occurred during the index PICU admission.

2 AEs that occurred shortly before PICU admission and were related to the PICU admission, were scored as "AE before PICU."

"AEs before PICU admission were not incorporated in the AE rate."

AE rate

Number of AEs occurring during PICU admission divided by PICU length of stay

Severity of AEs according to National Coordinating Council for Medication Error Reporting and Prevention categories (24)

E contributed to or resulted in temporary harm to the patient and required intervention

F contributed to or resulted in temporary harm to the patients and required initial or prolonged hospitalization

G contributed to or resulted in permanent patient harm

H required intervention to sustain life

I contributed to or resulted in the patient's death

For category I, subcategories were developed[a]:

I-1 Partially contributed to death

I-2 Substantially contributed to death

I-3 Death was completely caused by AE

Preventability

The degree of preventability of AEs was measured on a six-point Likert scale

1 (Virtually) no evidence for preventability

2 Slight to modest evidence of preventability

3 Preventability not quite likely (less than 50/50, but "close call")

4 Preventability more than likely (more than 50/50, but "close call")

5 Strong evidence of preventability

6 (Virtually) certain evidence of preventability

AEs with a preventability score of 4 to 6 were defined as preventable AEs.

Table 1. Continued

Classification Based on the classification made by Hogan (22)	
Clinical monitoring	Failure to act upon results of tests or clinical findings, set up monitoring systems or respond to such systems or increase intensity of care when required
Diagnosis	Missed, delayed or inappropriate diagnosis as a result of failure to perform an adequate assessment of patient's overall condition including appropriate tests or lack of focused assessment when required
Drug or fluid related	Side effects, inappropriate use, failure to give prophylactic care, anaphylaxis, etc.
Technical problems	Related to a device, an operation or procedure whether on ward, in a diagnostic situation or in theatre and including inappropriate or unnecessary procedures (other than technical problems related to extracorporeal life support[b])
ECMO[b]	Problems related to ECMO including technical problems, haemorrhage
Infection related	Healthcare-associated infections including infections from indwelling device
Resuscitation	Problems in resuscitation including cardiopulmonary resuscitation such as delay in beginning resuscitation, problems related to resuscitation technique, resuscitation medication/fluids, resuscitation equipment
Surgical procedure[b]	Problems related to a procedure taking place during PICU admission but outside the PICU, e.g. an operation or heart catheterization (other than standard procedures performed in the ICU like intubations, insertion of central catheters, insertion of pneumothorax, ECMO cannulations etc.)
Other	Any other problem not fitting categories above or a combination of categories above

AE = adverse event, ECMO = extracorporeal membrane oxygenation.

[a] *Modification from original National Coordinating Council for Medication Error Reporting and Prevention criteria.*

[b] *Modification from original classification by Hogan et al (22).*

Ethical approval

The study protocol was approved by the Research Ethics Committee of the Radboud University Medical Center in Nijmegen (File number: 2017-3526). The committee waived the need for informed consent. Data were anonymized and handled according to the principles of good clinical practice. The collection of data started in 2018 and ended in 2021.

Results

Patient characteristics

The entire cohort contained 53,789 PICU admissions (mortality 3.0%), including 33,961 low-risk admissions (mortality 0.5% [n = 180]) and 1,250 high-risk admissions (mortality 48.2% [n = 603]) (Fig. 1, flowchart). In total, 419 and 81 unique patients were included and excluded, respectively. Five LN patients and one HN patient were also part of the pilot study (14).

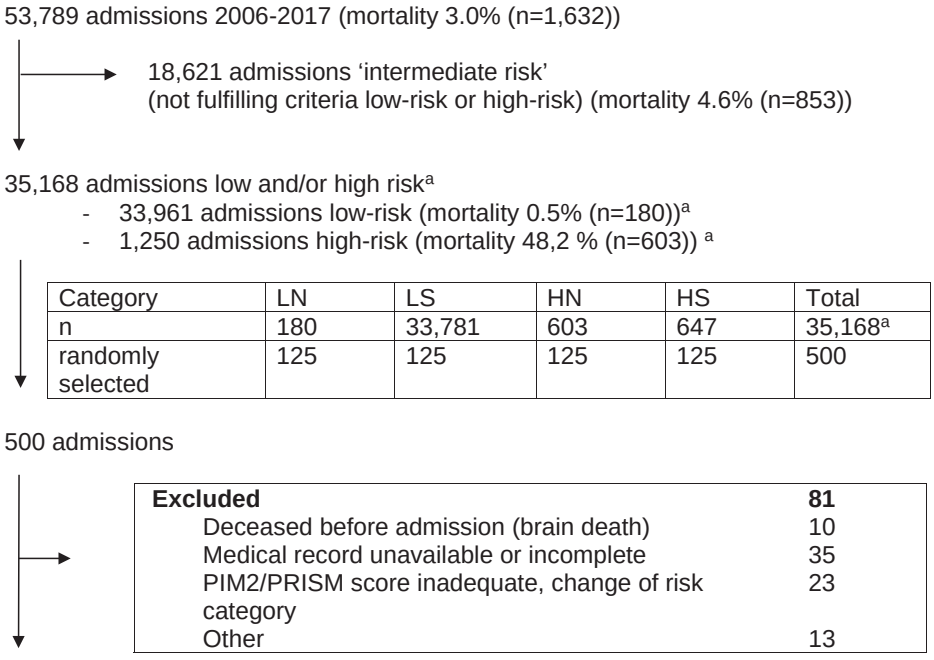


Figure 1. Flowchart of the study

Figure legend: [a]In total, 43 of 35,168 admissions had discrepancies between the mortality prediction models: they were low-risk in one model and high-risk in the second model, therefore fulfilling criteria for both low-risk and high-risk (e.g. "low-risk according to PIM2 and simultaneously high-risk according to PRISM"). Four admissions both LN and HN. Thirty-nine admissions both LS and HS.

HN = high-risk nonsurvivors, HS = high-risk survivors, LN = low-risk nonsurvivors, LS = low-risk survivors, PIM2 = Pediatric Index of Mortality 2, PRISM = Pediatric Risk of Mortality.

LN had more unplanned admissions (71.6%) than LS (35.5%) but less than HN (94.2%) and HS (91.5%) (Table 2). LN were more often admitted outside office hours and were more often medical (nonsurgical) admissions compared with LS. The prevalence of complex chronic conditions was higher in LN (93.1%) than LS (72.9%), HN (49.0%), and HS (48.1%). A majority of LN (88.2%) had a shorter life expectancy before PICU admission. Many HN (43/104 [41%]) were admitted after cardiac arrest preceding PICU admission. Mortality risk at admission of LN was slightly but significantly higher than LS and (by definition) lower than HN and HS. LN had a longer length of stay (LOS) (median [IQR], 10 d [5–27 d]) compared with LS (2 d [2–3 d]) and HN (3 d [2–6 d]) ($p < 0.001$). The mode of death between LN and HN was different. In HN, 39.4% of patients died because they were brain death. In 71.6% of LN, patients died after treatment was limited or withdrawn.

Adverse Events

In total, 196 AEs were found in 78 of 102 LN patients (76.5%) (Table 3). The occurrence of AE in LN was higher compared with LS (13.1%) and HN (47.1%) ($p < 0.001$) and not significantly different from HS (67.0%). The AE rate of LN (median [IQR], 10.00 [0.00–19.05] AEs/100 d) was higher compared with LS (0.00 [0.00– 0.00]) in LS and not significantly different from HN (0.00 [0.00–16.15]) and HS (5.90 [0.00–14.29]). Of all AEs in LN, 31.1% was preventable. No significant difference in preventability was found between the groups.

LN suffered from more severe AEs compared with LS and HS, including 41 of 196 AEs grade H (20.9%) (intervention needed to sustain life) and 32 of 196 AEs (16.3%) contributing to death (grade I).

Details of the AEs that contributed to death in LN are presented in Table 4. In 31 of 102 LN patients (30.4%), an AE contributed to death, including 8.8% having a preventable AE. In three LN patients, death was completely caused by an AE. In one of these patients, the AE was considered preventable. In 18 LN, an AE substantially contributed to death (of which five were preventable), and in nine LN, an AE partially contributed to death (three preventable).

Most prevalent AEs in LN were infection-related AEs (33.2%) and drug/fluid-related AEs (16.8%). Details on severity, preventability, and classification of all AEs are shown in Tables S5 and S6 (http://links.lww. com/PCC/C245). Most preventable AEs both in LN and other groups were related to "infections," "drugs/ fluids," and "clinical monitoring." The number of AEs during the years remained stable (Supplementary Figs. 1 and 2, http://links.lww.com/PCC/C245).

Interobserver variability study

The interobserver agreement of the determination of AEs was almost perfect (κ = 0.83), and agreement on preventability of AEs was moderate (κ = 0.60). Results are shown in Table S7 (http://links.lww.com/PCC/C245).

Table 2. Patient Characteristics

Characteristics, n
Gender: male
Age group:
1-28 d
29-365 d
1-4 yrs
5-17 yrs
Age: median [IQR] (yr)
Weight: median [IQR] (kg)
Socio economic status: low
Unplanned admission
Cardiac arrest before PICU admission
Medical admission
Admission outside office hours
Readmission within 48 hr
Chronic condition
Complex chronic condition
Noncomplex chronic condition
No chronic condition
Health status before PICU admission
Healthy
Chronic condition, normal life expectancy
Chronic condition, shorter life expectancy
Unknown
Recalibrated PIM2 mortality risk, median [IQR] (%)
Recalibrated PRISM mortality risk, median [IQR] (%)
Mechanical ventilation
Ventilator days, median [IQR]
Length of stay, median [IQR] (d)
Mode of death
Brain death
Maximal treatment including CPR
Maximal treatment without CPR
Limiting or withdrawal of therapy

PIM2 = Pediatric Index of Mortality 2, PRISM = Pediatric Risk of Mortality, CPR = cardiopulmonary resuscitation, IQR = interquartile range

All numbers are expressed as the number of patients (% column) unless specified otherwise.

Low-Risk Nonsurvivors, N = 102	Low-Risk Survivors, N = 107	High-Risk Nonsurvivors, N = 104	High-Risk Survivors, N = 106
55 (53.9)	61 (57.0)	65 (62.5)	67 (63.2)
7 (6.9)	6 (5.6)	15 (14.4)	32 (30.2)[b]
33 (32.4)	21 (19.6)	29 (27.9)	28 (26.4)
14 (13.7)	30 (28.0)	25 (24.0)	26 (24.5)
48 (47.1)	50 (46.7)	35 (33.7)	20 (18.9)
3.5 [0.3-13]	4.0 [0.8-10]	2.0 [0.25-8]	0.7 [0.0-2.0][b]
15 [5-42]	17 [9-35]	13 [6-29]	8 [3-15][b]
18 (17.6)	21 (19.6)	19 (18.3)	20 (18.9)
73 (71.6)	38 (35.5)[b]	98 (94.2)[b]	97 (91.5)[b]
0 (0)	0 (0)	43 (41.3)[b]	17 (16.0)[b]
80 (78.4)	44 (41.1)[b]	84 (80.8)	75 (70.8)
50 (49.0)	31 (29.0)[a]	66 (63.5)	64 (60.4)
4 (3.9)	1 (0.9)	0 (0.0)	1 (1.0)
95 (93.1)	78 (72.9)[a]	51 (49.0)[b]	51 (48.1)[b]
3 (2.9)	15 (14.0)	5 (4.8)	6 (5.7)
4 (3.9)	14 (13.1)	48 (46.2)	49 (46.2)
4 (3.9)	15 (14.0)[b]	47 (45.2)[b]	48 (45.3)[b]
6 (5.9)	51 (47.7)	12 (11.5)	16 (15.1)
90 (88.2)	41 (38.3)	42 (40.2)	40 (37.3)
2 (1.9)	0 (0.0)	3 (2.9)	2 (1.9)
1.1 [0.9-4.3]	0.9 [0.4-1.7][b]	41 [16-71]b	21 [7-39][b]
0.8 [0.6-2.4]	0.6 [0.4-0.9][b]	45 [29-65][b]	37 [12-51][b]
94 (92.1)	52 (48.6)[b]	102 (98.1)	100 (94.3)
7 [3-20]	0 [0-1][b]	3 [2-6][b]	6 [3-12]
10 [5-27]	2 [2-3][b]	3 [2-6][b]	8 [5-19]
10 (9.8)		41 (39.4)[b]	
9 (8.8)		10 (9.6)	
10 (9.8)		11 (10.6)	
73 (71.6)		42 (40.4)	

[a] *p < 0.01 compared with low-risk nonsurvivor (LN).*

[b] *p < 0.001 compared with LN.*

Table 3. Outcome – Adverse Events

Outcome measure
Patients
Patients, *n*
Patients with ≥ 1 AE, *n* (%)
Number of AE / patient, median [IQR]
AE rate (no/100 d) median [IQR]
Patients with ≥ 1 AE contributing to death
Patients with ≥ 1 preventable AE contributing to death
AEs
Total number of AEs, *n*
Timing of AEs, *n* (%)
Before PICU admission
During PICU admission
AE severity, *n* (%)
Grade E (temporary harm)
Grade F (prolonged hospitalization)
Grade G (permanent harm)
Grade H (intervention to sustain life)
Grade I (contributing to death)
I-partially
I-substantially
I-completely
AE preventability, *n* (%)
Not preventable
Preventable
Unknown
AE classification, *n* (%)
Clinical monitoring
Diagnosis
Drug/fluid related
Technical problems
Extracorporeal membrane oxygenation
Surgical procedure
Infection related
Resuscitation
Other

AE = adverse event, IQR = interquartile range.

All numbers are expressed as the number of AEs (% column) unless specified otherwise.

Low-Risk Nonsurvivors	Low-Risk Survivors	High-Risk Nonsurvivors	High-Risk Survivors
102	107	104	106
78 (76.5)	14 (13.1)[b]	49 (47.1)[b]	71 (67.0)
1 [1-3]	0 [0-0][b]	0 [0-1][b]	1 [0-2]
10.00 [0.00-19.05]	0.00 [0.00-0.00][b]	0.00 [0.00-16.15]	5.90 [0.00-14.29]
31 (30.4)		27 (26.0)	
9 (8.8)		10 (9.6)	
196	21[b]	86[b]	161
7 (3.6)	6 (28.6)[b]	20 (23.5)[b]	19 (11.8)[a]
189 (96.4)	15 (71.4)	65 (76.5)	142 (88.2)
117 (59.7)	14 (66.7)[b]	40 (46.5)	109 (67.7)[b]
4 (2.0)	4 (19.0)	1 (1.2)	7 (4.3)
2 (1.0)	1 (4.8)	1 (1.2)	8 (5.0)
41 (20.9)	2 (9.5)	17 (19.8)	37 (23.0)
32 (16.3)	0 (0.0)	27 (31.4)	0 (0.0)
10 (5.1)		7 (8.2)	
19 (9.7)		20 (23.5)	
3 (1.5)		0 (0.0)	
131 (66.8)	10 (47.6)	43 (50.0)	103 (64.0)
61 (31.1)	11 (52.4)	36 (41.9)	56 (34.8)
4 (2.0)	0 (0.0)	7 (8.1)	2 (1.2)
10 (5.1)	3 (14.3)[a]	16 (19.3)[a]	13 (8.1)
4 (2.0)	1 (4.8)	3 (3.6)	5 (3.1)
33 (16.8)	7 (33.3)	13 (15.7)	33 (20.6)
15 (7.7)	2 (9.5)	10 (12.0)	17 (10.6)
11 (5.6)	0 (0.0)	7 (8.4)	9 (5.6)
11 (5.6)	3 (14.3)	7 (8.4)	17 (10.6)
65 (33.2)	4 (19.0)	15 (18.1)	39 (24.4)
2 (1.0)	0 (0.0)	1 (1.2)	2 (1.3)
45 (23.0)	1 (4.8)	11 (13.3)	25 (15.5)

[a] *p < 0.01 compared with low-risk nonsurvivor (LN).*

[b] *p < 0.001 compared with LN.*

Table 4. Adverse Events (*n*=32) Contributing to Death in Low-Risk Nonsurvivors (*N* = 31)[a]

ID	Severity	Prev	Class	Description of the adverse event	CCC	Description CCC
1	I-3	Y	surg	Severe hypotension during elective cardiac catheterization leading to intestinal necrosis	CCC	cong heart dis
2	I-3	Unk	surg	Massive hemorrhage after tear in atrium after atrial septal defect repair	nCCC	cong heart dis[b]
3	I-3	N	other	Occlusion of pulmonary arteries after cavo pulmonary shunt and repair of pulmonary artery	CCC	cong heart dis
4	I-2	Y	mon	Resuscitation during MRI in patient on high flow oxygen with respiratory insufficiency	CCC	hem dis
5	I-2	Y	mon	Cardiac arrest in patient with asthma during PICU admission	nCCC	asthma
6	I-2	Unk	mon	Sudden circulatory collapse with electrocardiogram abnormalities, leading to death	CCC	leukemia
7	I-2	Y	diagn	Missed diagnosis of pulmonary mycosis	CCC	hemat dis
8	I-2	Y	ECMO	Suction of heparin in ECMO system	CCC	cong heart dis
9	I-2	N	ECMO	Asystole after replacement of artificial kidney on ECMO	CCC	cong heart dis
10	I-2	Y	inf	CLABSI in patient with short bowel	CCC	short bowel
11	I-2	N	inf	Hospital acquired pneumonia after spinal surgery, underlying severe psychomotor retardation	CCC	chrom abn
12	I-2	N	inf	Ventilator acquired pneumonia	CCC	cong heart dis
13	I-2	N	inf	Septic shock acquired during PICU admission	CCC	epilepsy
14	I-2	N	inf	Septic shock acquired during PICU admission	CCC	chrom abn
15	I-2	N	inf	Septic shock acquired during PICU admission	CCC	cong brain dis
16	I-2	N	inf	Sepsis, pulmonary hypertension in patient with high output stoma and multiple abdominal adhesions	CCC	syndrome or malformation
17	I-2	N	inf	Aspergillus infection	CCC	neoplasm

Table 4. Continued

ID	Severity	Prev	Class	Description of the adverse event	CCC	Description CCC
18	I-2	N	surg	Thrombosis left ventricular assist device, resuscitation followed by multi-organ failure and cerebral infarction	CCC	cardiomyopathy
19	I-2	N	surg	Thrombi in Fontan circuit ultimately leading to death	CCC	cong heart dis
20	I-2	N	other	Resuscitation during intubation in patient with underlying cong heart dis	CCC	cong heart dis
21	I-2	N	other	Abdominal compartment syndrome in patient with typhlitis	CCC	leukemia
22	I-1	Y	mon	Delay of intervention in dysfunction of intraventricular drain	CCC	brain tumor
23	I-1	N	drug	Possible allergic reaction, leading to deterioration of fragile respiratory balance	CCC	hem dis
24	I-1	N	drug	Pulmonary veno-occlusive disease after chemotherapy	CCC	neoplasm
25[a]	I-1	N	drug	Liver insufficiency, possibly iatrogenic (medication) or septic	CCC	chrom abn
25	I-1	N	inf	CLABSI in patient with infected intravascular thrombi	CCC	chrom abn
26	I-1	N	inf	Resuscitation in patient with pulmonary mycosis	CCC	leukemia
27	I-1	N	inf	Possible CLABSI on ECMO leading to forced decannulation	CCC	cong lung dis
28	I-1	Y	inf	Systemic fungal infection in patient with neutropenia, no prophylaxis given	CCC	neoplasm
29	I-1	Y	other	Cerebral herniation partly due to osmotic changes with continuous veno-venous hemofiltration and compression of jugular vein by central venous catheter	CCC	cdh
30	I-1	N	other	Lung bleeding, partially caused by artificial ventilation with large tidal volumes (20 mL/kg)	CCC	cong lung dis
31	I-1	N	other	Cerebral ischemia due to several episodes of hypotension	CCC	chrom abn

Table 4. Continued

CCC = complex chronic condition, cdh = congenital diaphragmatic hernia, chrom abn = chromosomal abnormality, CLABSI = central catheter-associated blood stream infection, cong brain dis = congenital brain disease, cong heart dis = congenital heart disease, cong lung dis = congenital lung disease, ECMO = extracorporeal membrane oxygenation, hemat dis = hematologic disease, nCCC = non-complex chronic condition, neoplasm = malignant solid organ neoplasm.

[a]One patient (patient ID 25) had two adverse events partially contributing to death.

[b]Many complex congenital heart diseases are CCC, some simple congenital heart diseases are nCCC.

Severity of adverse event: I-3: death was completely caused by adverse event; I-2: substantially contributing to death; I-1: partially contributing to death.

Prev: Preventability of adverse event: Y: preventable; N: not preventable; Unk: preventability unknown.

Class: Classification of adverse event: mon: clinical monitoring; diagn: diagnosis; drug: drug or fluid related; ECMO: extracorporeal membrane oxygenation; inf: infection related; surg: surgical procedure; other: other.

Discussion

In this multicenter study, a significant number of AEs was found in a PICU subpopulation of LN. In total, 76.5% of LN suffered from an AE, of which one third was preventable. The occurrence of AEs in the LN group was higher compared with the LS and HN groups and not different from AEs in the HS group. Most AEs were infections or drug/fluid-related AEs. In 30.4% of LN, an AE contributed to death, and in 8.8% of LN, a preventable AE partially contributed to death.

This is a large study determining the contribution of AEs to unexpected deaths among PICU patients. The study population was derived from a large cohort representing all Dutch PICU admissions. The trigger-tool is a validated and commonly used method to detect AEs. Interobserver variability on the presence and preventability of AEs was relatively high compared with other studies (22, 27, 28). However, our study does also have limitations.

First, there is no gold-standard for low-risk for mortality (12, 15). A combination of low PIM2 and/ or low PRISM mortality risk was used to classify low-risk patients. The overall performance of the prediction models in our large PICU cohort was reasonably well. The mortality rate among the cohort of low-risk patients was 0.5%. LN consist of a small subgroup from all low-risk patients and have different characteristics compared with LS. Some factors might influence mortality risk prediction in certain subgroups (16). In long-stay patients, such as many LN and HS, mortality prediction models perform less well, since the used variables in the prediction models are measured early after initial admission (16). Dynamic changes occurring after the first 24 hours are by definition not incorporated in the prediction models. Perhaps more importantly, the majority of LN had an underlying CCC, not being reflected in the mortality prediction models. Over the last decades, an increasing number of CCC patients, with a higher mortality rate and longer LOS, is being admitted to the PICU (11, 29). We modified the original list of CCCs based on a study performed in 2012 (11, 20). There has been a 2014 update from the list of CCCs that we did not incorporate in our study (30). However, our list of CCCs reflects many diagnoses incorporated in the updated list. Even though the real mortality risk for LN was higher than presumed, we think that it is worthwhile to develop methods to discover a cohort of "unexpected deaths" and subsequently evaluate quality of care in these patients. Awareness of the possible role of AEs in outcome of children with a low predicted mortality risk but with a CCC is the first step in quality improvement.

Second, there were large differences in patient characteristics between the groups. This may, in part, explain the difference in AE occurrence. As mentioned before, both LN and HS had a long LOS. It is difficult to determine in retrospect whether AEs caused a longer LOS or the longer LOS led to more AEs. Not many AEs resulting in prolonged hospitalization (grade F) were found, but in retrospect it is difficult to estimate if an AE was the cause of a longer LOS. The difference in LOS does not explain the complete difference in occurrence of AEs. If we correct the number of AEs for LOS by using the AE rate, it was higher in LN compared with LS and not significantly different from HN and HS. There were significant differences in the mode of death between LN and HN. The majority of LN died after therapy was restricted or withdrawn. This decision was often made after a long PICU stay. The patients were not admitted with do-not-resuscitate orders at the time of PICU admission. In some cases, the decision was influenced by injuries caused by AEs.

Third, a general weakness of retrospective studies is hindsight bias (31). The primary investigator, who performed both the categorization of life expectancy and determined the presence of AEs, was not blinded to the study group. Knowledge of the outcome of the patient might influence judgment of severity and preventability of AEs. By using clear definitions and a predefined, validated trigger tool, using a panel of intensivists for questions and judgment of preventability and an interobserver reliability study, we tried to avoid the effects of hindsight bias.

Fourth, during the study period, safety programs were developed and implemented. Theoretically it is possible that during the study period, the prevalence of AEs declined. The study was not powered to analyze the occurrence of AEs during different time frames. We did not see a decline on the number of AEs during the years. It is likely that the prevalence of AEs has not changed.

The severity of AEs found in our study contrasts with several studies in the general PICU-population who mainly found low grade AEs (2, 4). In a cross-sectional multicenter study, 62% of all PICU patients had at least one AE, and 10% of the found AEs were classified as severe (contributing to permanent harm or worse) (4). In our study, the percentage of severe AEs was higher among LN (38%), HN (52%), and HS (28%). The higher occurrence of AEs and the more severe AEs in our study can be explained by differences in case-mix. In order to get an effective study sample, we did not randomly select patients from the total cohort but stratified patient categories and selected a relatively high proportion of LN, HN, and HS patients. The proportion of LS patients (with few AEs) was low, and the "intermediate" risk group was not represented at all in our study. Therefore, our results cannot be generalized to the total PICU-population.

Only a few small studies focused on LN. The results of the present study are consistent with our previous study and with another single-center study on LN (14, 15). In the study by Ruegger (15), LN had four times more AEs than LS, although the cut off point for "low-risk" (PIM2 mortality risk < 10%) was different compared with our study. LN seem to be associated with serious AEs, including preventable AEs. Evaluating deaths and especially "unexpected deaths" is an efficient way to obtain valuable information on iatrogenic harm (32, 33).

What this study adds is more insight into the occurrence of AEs in low-risk PICU nonsurvivors and their contribution to mortality. PICU deaths are often multifactorial. AEs contribute to death almost a third of LN, but the degree of the contribution to death may vary. Are deaths of LN preventable? In one patient death could be considered avoidable, since a preventable AE was completely responsible for death. In five and three LN, respectively, a preventable AE substantially or partially contributed to death, so death might be possibly preventable. Underlying complex chronic conditions seem to play a role in death of LN. Patients with chronic conditions may be "sicker" than predicted by the standard PICU severity of illness models. But, this cannot explain fully why LN die. Although CCCs are present in more than 90% of LN, they are also present in more than 70% of LS and therefore cannot explain the huge difference in AE occurrence between these groups.

Despite safety programs that have been developed over the last decades, our results show that there is still a large potential for improvement. One third of the AEs was considered preventable, which is comparable with other studies (2, 4, 23). So far, safety programs have succeeded to a certain extent. Although quality improvement programs have been implemented extensively in The Netherlands over the last decades, preventable AEs were still encountered (34).

Future research might focus on the interaction between CCCs and AEs. We have seen examples of patients where a CCC makes a patient more prone for AEs, for example patients with immune disorders who are more prone to hospital-acquired infections. It would be interesting to study further the interaction between CCCs and AEs.

Increasing patient safety remains an urgent but complex task. The focus of patient safety shifts more and more from what goes wrong ("Safety-I") to why things go right ("Safety-II") (35). A key to a safer PICU might be the development of resilient teams, capable of acting in a complex setting.

Conclusions

Significant and preventable AEs were found in low-risk PICU nonsurvivors. 76.5% of LN had one or more AEs. In 30.4% of LN an AE contributed to mortality.

Acknowledgements

This work would not have been possible without collaboration between seven PICUs in The Netherlands, the SKIC (“Stichting Kinder Intensive Care”, Dutch Collaborative PICU Research Network) and Pediatric Intensive Care Evaluation (PICE) working group. We would like to thank Idse Visser, data scientist of the PICE-registry for his contribution on the stratification and randomization process, Cynthia van der Starre for her contribution to the PICU trigger tool and prof. Dr. J. Legemaate and prof. Dr. B. Bos, for their contribution as “confidential committee.”

Reference list

1. Tibby SM, Correa-West J, Durward A, et al: Adverse events in a paediatric intensive care unit: Relationship to workload, skill mix and staff supervision. Intensive Care Med 2004; 30:1160–1166
2. Larsen GY, Donaldson AE, Parker HB, et al: Preventable harm occurring to critically ill children. Pediatr Crit Care Med 2007; 8:331–336
3. Silas R, Tibballs J: Adverse events and comparison of systematic and voluntary reporting from a paediatric intensive care unit. Qual Saf Health Care 2010; 19:568–571
4. Agarwal S, Classen D, Larsen G, et al: Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med 2010; 11:568–578
5. Vermeulen JM, van Dijk M, van der Starre C, et al: Patient safety in South Africa: PICU adverse event registration*. Pediatr Crit Care Med 2014; 15:464–470
6. Pollack MM, Holubkov R, Funai T, et al: Pediatric intensive care outcomes: Development of new morbidities during pediatric critical care. Pediatr Crit Care Med 2014; 15:821–827
7. Pollack MM, Ruttimann UE, Getson PR: Pediatric risk of mortality (PRISM) score. Crit Care Med 1988; 16:1110–1116
8. Pollack MM, Holubkov R, Funai T, et al: The pediatric risk of mortality score: Update 2015. Pediatr Crit Care Med 2016; 17:2–9
9. Shann F, Pearson G, Slater A, et al: Paediatric index of mortality (PIM): A mortality prediction model for children in intensive care. Intensive Care Med 1997; 23:201–207
10. Slater A, Shann F, Pearson G, et al: PIM2: A revised version of the paediatric index of mortality. Intensive Care Med 2003; 29:278–285
11. Edwards JD, Houtrow AJ, Vasilevskis EE, et al: 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 2012; 40:2196–2203
12. Verlaat CW, Visser IH, Wubben N, et al: Factors associated with mortality in low-risk pediatric critical care patients in The Netherlands. Pediatr Crit Care Med 2017; 18:e155–e161
13. Fraser LK, Parslow R: Children with life-limiting conditions in paediatric intensive care units: A national cohort, data linkage study. Arch Dis Child 2018; 103:540–547
14. Verlaat CW, van der Starre C, Hazelzet JA, et al: The occurrence of adverse events in low-risk non-survivors in pediatric intensive care patients: An exploratory study. Eur J Pediatr 2018; 177:1351–1358
15. Ruegger CM, Frey B: The pediatric index of mortality as a trigger tool for the detection of serious errors and adverse events. Pediatr Crit Care Med 2018; 19:869–874
16. Visser IH, Hazelzet JA, Albers MJ, et al: Mortality prediction models for pediatric intensive care: Comparison of overall and subgroup specific performance. Intensive Care Med 2013; 39:942–950
17. Verlaat CW, Wubben N, Visser IH, et al: Retrospective cohort study on factors associated with mortality in high-risk pediatric critical care patients in the Netherlands. BMC Pediatr 2019; 19:274
18. Urbaniak GC, Plous S: Research Randomizer (Version 4.0) [computer software]. 2013. Available at: http://www.randomizer.org/. Accessed June 22, 2013
19. Slater A, Shann F, McEniery J, et al: The ANZPIC registry diagnostic codes: A system for coding reasons for admitting children to intensive care. Intensive Care Med 2003; 29:271–277
20. Feudtner C, Christakis DA, Connell FA: Pediatric deaths attributable to complex chronic conditions: A population-based study of Washington State, 1980-1997. Pediatrics 2000; 106:205–209

21. Zegers M, de Bruijne MC, Wagner C, et al: Adverse events and potentially preventable deaths in Dutch hospitals: Results of a retrospective patient record review study. Qual Saf Health Care 2009; 18:297–302
22. Hogan H, Healey F, Neale G, et al: Preventable deaths due to problems in care in English acute hospitals: A retrospective case record review study. BMJ Qual Saf 2012; 21:737–745
23. Baker GR, Norton PG, Flintoft V, et al: The Canadian adverse events study: The incidence of adverse events among hospital patients in Canada. CMAJ 2004; 170:1678–1686
24. Hartwig SC, Denger SD, Schneider PJ: Severity-indexed, incident report-based medication error-reporting program. Am J Hosp Pharm 1991; 48:2611–2616
25. Zegers M, de Bruijne MC, Wagner C, et al: Design of a retrospective patient record study on the occurrence of adverse events among patients in Dutch hospitals. BMC Health Serv Res 2007; 7:27
26. Landis JR, Koch GG: The measurement of observer agreement for categorical data. Biometrics 1977; 33:159–174
27. Klein DO, Rennenberg R, Koopmans RP, et al: Adverse event detection by medical record review is reproducible, but the assessment of their preventability is not. PLoS One 2018; 13:e0208087
28. Zegers M, de Bruijne MC, Wagner C, et al: The inter-rater agreement of retrospective assessments of adverse events does not improve with two reviewers per patient record. J Clin Epidemiol 2010; 63:94–102
29. Edwards JD, Lucas AR, Boscardin WJ, et al: Repeated critical illness and unplanned readmissions within 1 year to PICUs. Crit Care Med 2017; 45:1276–1284
30. Feudtner C, Feinstein JA, Zhong W, et al: Pediatric complex chronic conditions classification system version 2: Updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr 2014; 14:199
31. Henriksen K, Kaplan H: Hindsight bias, outcome knowledge and adaptive learning. Qual Saf Health Care 2003; 12 (Suppl 2):ii46–ii50
32. Monroe K, Wang D, Vincent C, et al: Patient safety factors in children dying in a paediatric intensive care unit (PICU): A case notes review study. BMJ Qual Saf 2011; 20:863–868
33. Nilsson L, Pihl A, Tagsjo M, et al: Adverse events are common on the intensive care unit: Results from a structured record review. Acta Anaesthesiol Scand 2012; 56:959–965
34. Baines R, Langelaan M, de Bruijne M, et al: How effective are patient safety initiatives? A retrospective patient record review study of changes to patient safety over time. BMJ Qual Saf 2015; 24:561–571
35. Hollnagel E, Wears RL, Braithwaite J: From Safety-I to Safety-II: A White Paper. The Resilient Health Care Net. Published simultaneously by the University of Southern Denmark, University of Florida, USA, and Macquarie University, Australia, 2015

Additional Files Chapter 5

Table S1
Inclusion and exclusion criteria

Table S2
Patient and admission characteristics

Table S3
PICU trigger tool

Table S4
Complex chronic conditions and non-complex chronic conditions

Table S5
Summary of all adverse events

Table S6
Adverse events classified as 'other'

Supplementary Figures 1 and 2
Adverse events by year of admission

Table S7
Interobserver variability study

Refererence list
of supplemental files

Table S1. Inclusion and exclusion criteria

Inclusion criteria
Age < 18 years
Length of stay at least 2 hours
PIM2 and PRISM scores available in the PICE
Exclusion criteria
Patients already deceased before admission *(for example brain dead patients, admitted for organ donation)*
Corrected age < 36 weeks (gestational age)
Invalid/impossible PIM2/PRISM score
No clinical data available (*medical record unavailable*)
Revised predicted mortality score (PIM2 or PRISM) changed from <1% to ≥ 2% (low-risk admissions) or from >30% to < 20% (high-risk admissions) after revision of PIM/PRISM score

PIM2 = Paediatric Index of Mortality 2, PRISM = Pediatric Risk of Mortality.

Table S2. Patient and admission characteristics

Socio-economic status was obtained by coupling the four digits of the postal code to the socio-economic status of the neighborhood.	
A low socio-economic status was defined as a status score < -1	
Planned admission	an admission is considered elective (planned) if it was planned or foreseeable
Unplanned admission	unexpected and/or emergency admission
Admission out of office hours	admission between 6.00 PM and 8.00 AM on weekdays, or on a Saturday or Sunday
Medical admission	admission for medical reason(s)
Surgical admission	admission for surgical reasons(s)
Mode of death was grouped into	
1. Brain dead (clinically brain dead)	
2. Maximal treatment including cardiopulmonary resuscitation	
3. Maximal treatment without cardiopulmonary resuscitation	
4. Limiting or withholding therapeutic options	

Table S3. PICU trigger tool (4,5)

No	Trigger	Examples / Potential AEs
1	Cardiac or respiratory arrest	Resuscitation, defibrillation, cardioversion, emergency intubation, administration of epinephrine
2	Accidental extubation	
3	Pulmonary	Pneumothorax, chylothorax, aspiration pneumonia
4	Neurology	CNS bleed, CNS ischemia/infarction
5	Infectious disease	Infection of any kind occurring ≥ 3 days after admission
6	Subcutaneous infusion	Need for hyaluronidase infusion
7	Decubitus ulcer (pressure sores)	
8	Readmission < 48 hours	
9	Central catheter	Central catheter clot, inadvertent catheter removal, bleeding from central catheter, change of ECMO system
10	Trachea	Post extubation stridor, racemic epinephrine administration
11	Dislocation endotracheal tube	Order to pull back or push ETT or chest X ray with tube > 0.5 cm to (un)deep, not direct after intubation/ ETT mal-positioning requiring reposition
12	Over sedation	Comfort-B score < 11 during 24 hours
13	Allergy	Allergic reaction, treatment with clemastine, allergic rash
14	Pain, undersedation	Uncontrolled pain, undersedation (two times Comfort-B ≥ 17 and/or NRS ≥ 4 within one hour)
15	Hypo-/ hyperglycemia	Insulin treatment, glucose <3.5 or > 8 mmol/l in children, glucose <2.7 or >8 in neonates
16	Withdrawal symptoms	
17	Delirium	
18	Thrombosis	Deep vein thrombosis
19	Other	Other incidents: unplanned return to surgery, problems with foley catheter, problems with epidural catheter, falling incidents, diagnostic delay

AE = adverse event, CNS = central nervous system, ECMO = extracorporeal membrane oxygenation, ETT = endotracheal tube, Comfort-B score= score to measure comfort of child, NRS = numeric pain scale.

Table S4. Complex chronic conditions and non-complex chronic conditions

Complex chronic condition (CCC): Any medical condition that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or one organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center (6,7).
Non-complex chronic condition (nCCC): a medical condition that that can be reasonably expected to last at least 12 months but does not meet additional CCC criteria (5,8).
Health status: A tool was developed to categorize patients considering the health status of the patient at PICU-admission as described in the patient records, based on (n)CCCs and based on the reason for PICU-admission, using professional judgment. If several conditions exist simultaneously, the most severe condition is chosen. 1. Previously healthy 2. Chronic illness with normal life expectancy 3. Chronic illness with shorter life expectancy 4. Health status unknown

Table S4a. List of diagnoses classified as complex chronic conditions

Complex chronic conditions (CCCs)	
Subgroup	Diagnoses from the PICE database (ANZPIC diagnose list)
Cardiovascular	Absent pulmonary valve syndrome*
	Anomaly of the coronary artery
	Arterial switch*
	Atrioventricular septal defect
	Cardiomyopathy
	Cavo pulmonary shunt*
	Cor triatriatum
	Double outlet right ventricle
	Ebstein's anomaly
	Fontan procedure*
	Hypoplastic left heart syndrome
	Hypoplastic left ventricle*
	Hypoplastic or interrupted aortic arch*
	Hypoplastic right ventricle*
	Levo transposition of the great arteries
	Mitral valve stenosis
	Monoventricle
	Norwood procedure – step 1*
	Pacemaker insertion/revision*
	Portal hypertension*
	Pulmonary atresia or stenosis
	Pulmonary artery banding*
	Reconstruction of aortic arch*
	Reconstruction of left ventricular outflow*

Table S4a. Continued

Complex chronic conditions (CCCs)	
Cardiovascular (Continued)	Reconstruction of right ventricular outflow*
	Restoration of atrioventricular septal defect*
	Repair of plastic pulmonary artery*
	Repair or replacement of conduit*
	Repair of tetralogy of Fallot*
	Right ventricular outflow tract obstruction*
	Senning procedure*
	Supraventricular arrhythmia
	Surgery of pulmonary collateral arteries*
	Systemic to pulmonary shunt procedure*
	Tetralogy of Fallot
	Total abnormal pulmonary venous return
	Transplantation of heart
	Transplantation of heart and lung
	Transplantation of heart and lung – state after procedure
	Transposition of the great arteries
	Tricuspid atresia or stenosis
	Truncus arteriosus
	Vasculitis*
	Ventricular arrhythmia
Respiratory	Bronchiectasis
	Central apnea*
	Choanal atresia or stenosis*
	Chronic lung disease*
	Congenital lung disease
	Cystic fibrosis
	Infant respiratory distress syndrome*
	Laryngomalacia
	Malacia trachea or bronchus
	Mediastinal mass*
	Pulmonary edema
	Pulmonary hypoplasia
	Pulmonary insufficiency*
	Reconstruction of larynx*
	Subglottic stenosis
	Tracheostomy*
	Trachea or bronchus stenosis
	Transplantation of lung
	Transplantation of lung – state after procedure
	Vocal cord paralysis*
Hematological	Coagulation defects
	Hematologic disease*

Table S4a. Continued

Complex chronic conditions (CCCs)	
Endocrinological	Congenital metabolism disorder
	Diabetes (comorbidity)*
	Diabetes insipidus
	Diabetes mellitus with ketoacidosis
	Diabetes mellitus without ketoacidosis
	Endocrine disorder
	Kasaï procedure*
Gastrointestinal	Biliary atresia
	Colitis
	Congenital diaphragmatic hernia
	Gastroschisis or exomphalos
	Hirschsprung's disease*
	Liver disease – other*
	Esophageal atresia
	Repair of esophageal atresia*
	Repair of esophageal fistula*
	Repair of total anomalous pulmonary venous return*
	Short bowel syndrome*
	Transplantation of kidney
	Transplantation of liver
	Transplantation of liver – state after procedure
	Transplantation of small intestine
	Varices of esophagus or stomach*
Immunological	Congenital immunodeficiency
	Graft versus host disease
	Neutropenia*
	Pancytopenia*
	Pheochromocytoma*

Table S4a. Continued

Complex chronic conditions (CCCs)	
Neuromuscular	Acute disseminated encephalomyelitis*
	Arnold-Chiari malformation
	Brain arteriovenous malformation*
	Brain tumor
	Central nervous system shunt dysfunction or infection*
	Cerebral aneurysm
	Cerebral cyst
	Cerebral infarction*
	Chronic traumatic encephalopathy
	Congenital brain disease*
	Convulsions*
	Craniotomy – fossa anterior*
	Epilepsy (comorbidity)
	Hydrocephalus
	Insertion of revision of central nervous system shunt*
	Lobectomy or hemispherectomy*
	Meningomyelocele or spina bifida
	Muscular dystrophy
	Myasthenia gravis
	Myelum – impairment*
	Myopathy
	Repair of myelomeningocele*
	Static encephalopathy
Oncological	Cystic hygroma
	Leukemia or lymphoma
	Malignant solid organ neoplasm
	Transplantation of bone marrow
	Transplantation of bone marrow – state after procedure
Renal	Chronic kidney failure
	Hydronephrosis*
	Nephrotic or nephritic syndrome*
	Transplantation of kidney – state after procedure
Endocrinal	Syndrome of inappropriate antidiuretic hormone secretion*
Genetic	Chromosomal abnormality
	Craniosynostosis*
	DiGeorge syndrome
	Down syndrome
	Pierre Robin syndrome*
Urological	Repair of exstrophia vesicae*
Miscellaneous	Syndrome or malformation*

** Diagnoses that were not on the original list (as CCC) (5,8).*

Table S4b. List of diagnoses classified as non-complex chronic conditions

Non-complex chronic conditions	
Subgroup	Diagnoses from the PICE database
Cardiovascular	Aortic insufficiency
	Aortic stenosis
	Atrial septal defect
	Aortopulmonary window*
	Arteriovenous malformation*
	Acquired cardiovascular disorder – other*
	Coarctectomy*
	Coarctatio aortae
	Closed valvotomy*
	Closed heart surgery – other*
	Congenital cardiovascular disorder- other
	Ductus arteriosus
	Left ventricular outflow tract obstruction*
	Mitral insufficiency
	Myocardial infarction or ischemia*
	Open valvotomy*
	Open heart surgery – other*
	Pulmonary hypertension*
	Previous heart surgery*
	Repair of atrial septal defect*
	Repair of ventricular septal defect*
	Repair of coronary artery*
	Repair of ductus arteriosus*
	Repair or replacement of valve*
	Systemic hypertension
	Tricuspid insufficiency
	Ventricular septal defect
Respiratory	Asthma
	Chylous effusion*
	Obstructive sleep apnea syndrome
	Pneumectomy or lobectomy*
Gastrointestinal	Repair of gastroschisis or exomphalos*
Neuromuscular	Guillain Barré syndrome*
	Neuropathy
	Neurosurgery – other*
Oncological	Cardiac tumor*
	Non-malignant solid organ neoplasm
	Resection of abdominal tumor*
	Resection of cardiac tumor *
	Resection of thoracic tumor*
	Subglottic hemangioma
Genetic	Repair of cheiloschisis*
	Repair of palatoschisis*

** Diagnoses that were not mentioned on the original Feudtner's list (as nCCC) (5,8).*

Table S5. Summary of all adverse events

Group	Severity	Classification	Preventable			Total
			yes	no	unknown	
LN	E	Clinical monitoring	4	1		5
		Diagnosis		1		1
		Drug or fluid related	7	17		24
		Technical problems	2	9	1	12
		ECMO		2		2
		Surgical procedure		1		1
		Infection related	16	30		46
		Other	8	17	1	26
	F	ECMO		1		1
		Infection related		1		1
		Other		2		2
	G	Other		2		2
	H	Clinical monitoring	1			1
		Diagnosis	2			2
		Drug or fluid related	4	2		6
		Technical problems	2	1		3
		ECMO	2	4		6
		Surgical procedure	1	4		5
		Infection related		6		6
		Resuscitation	1	1		2
		Other	2	8		10
	I	Clinical monitoring	3		1	4
		Diagnosis	1			1
		Drug or fluid related		3		3
		ECMO	1	1		2
		Surgical procedure	1	2	1	4
		Infection related	2	10		12
		Other	1	5		6
	Total LN		61	131	4	196
LS	E	Clinical monitoring	1	1		2
		Diagnosis	1			1
		Drug or fluid related	4	2		6
		Technical problems	1	1		2
		Infection related	1	2		3
	F	Surgical procedure		2		2

Table S5. Continued

Group	Severity	Classification	Preventable			Total
			yes	no	unknown	
		Infection related	1			1
		Other	1			1
	G	Clinical monitoring	1			1
	H	Drug or fluid related	1			1
		Surgical procedure	1			1
	Total LS		13	8	0	21
HN	E	Clinical monitoring	3	1		4
		Drug or fluid related	4	6		10
		Technical problems	4	2		6
		ECMO		1		1
		Infection related	7	6		13
		Resuscitation	1			1
		Other	1	3	1	5
	F	Surgical procedure		1		1
	G	Technical problems		1		1
	H	Clinical monitoring	4	1		5
		Diagnosis	1			1
		Drug or fluid related		1		1
		Technical problems	2	1		3
		ECMO		3		3
		Other		4		4
	I	Clinical monitoring	6		1	7
		Diagnosis	1	1		2
		Drug or fluid related		1	1	2
		ECMO		3		3
		Surgical procedure	2	2	2	6
		Infection related	1	1		2
		Other		3	2	5
	Total HN		37	42	7	86
HS	E	Clinical monitoring	4	6		10
		Drug or fluid related	13	14		27
		Technical problems	1	11		12
		ECMO		3		3
		Surgical procedure		6		6
		Infection related	15	20		35

Table S5. Continued

Group	Severity	Classification	Preventable			Total
			yes	no	unknown	
		Resuscitation	1			1
		Other	4	10	1	15
	F	ECMO		1		1
		Infection related		3		3
		Other	1	2		3
	G	Clinical monitoring	1			1
		Drug or fluid related	1			1
		Technical problems		1		1
		ECMO		3		3
		Surgical procedure	1	1		2
		Other				0
	H	Clinical monitoring	2			2
		Diagnosis	2	3		5
		Drug or fluid related	2	3		5
		Technical problems	1	3		4
		ECMO	2			2
		Surgical procedure	2	6		8
		Infection related	1			1
		Resuscitation	1			1
		Other	1	7	1	9
	Total HS		56	103	2	161
Total AEs from all groups			Preventable			Total
			yes	no	unknown	
			167	284	13	464

LN = low-risk nonsurvivor, LS = low-risk survivor, HN = high-risk nonsurvivor, HS = high-risk survivor, ECMO = extracorporeal membrane opxygenation, AEs = adverse events.

Table S6. Adverse events classified as 'other'

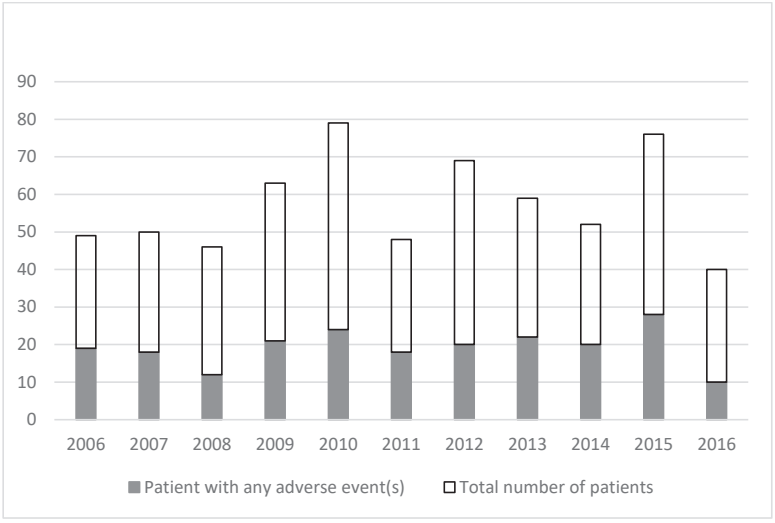
	AE	Examples	No. of AEs	
			Multiple factors Involved[a]	Cause of AE unknown[b]
Airway	Accidental extubation		3	7
	Other type AEs related to airway	Unrecognized airway tampon	1	
Breathing	Lung problems	Pneumothorax, lung bleeding	12	3
	Accidental removal pleural drain		1	1
Circulation	Resuscitation	Resuscitation during PICU admission	13	
	Thrombi	Thrombo-embolic events,	4	
	Bleeding	Bleeding events		1
	Hypotensive episode related to treatment		1	
Disability	Cerebral AEs	Cerebral ischemia, cerebral edema	4	
	Delirium		3	
	Critical illness polyneuropathy		2	
Exposure	Akute kidney injury		4	
	AEs of gut/liver	Intestinal ischemia, necrosis, ileus, abdominal compartment syndrome	4	1
	Pressure ulcer		4	
	Hypoglycemia		2	
	AEs due to logistic problems	Necessary care postponed by logistic or health insurance problems	2	
	Other type AEs related to 'exposure'	Fall out of bed, extravasation injury, hemolytic anemia	3	
Total			68	14

AE = adverse event(s).

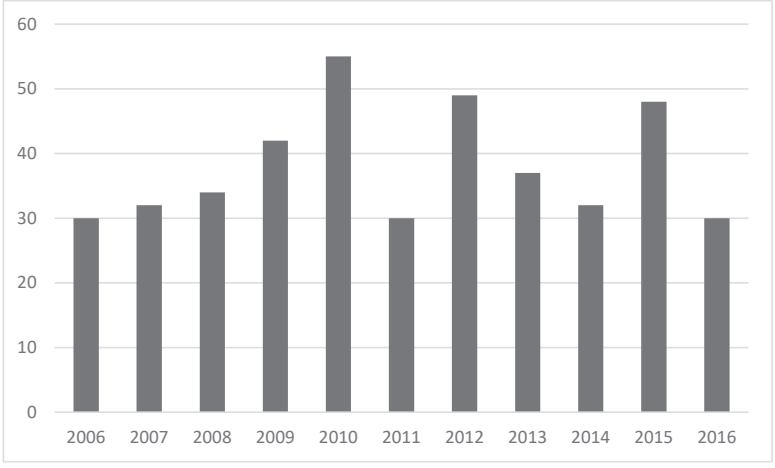
[a]*Multiple factors: Combination of factors; Example: a patient suffered from extravasation injury by combination of accidental luxation of a port-a-cath needle which was unrecognized for several hours and caused extravasation of parenteral feeding. It could be categorized as a combination of 'technical' (port-a-cath) and 'diagnosis' (luxation of the needle was missed) and 'drug or fluid related' (parenteral feeding), therefore was categorized as 'other'.*

[b]*Cause of AE unknown: not enough data available from medical chart to make a judgement.*

Supplementary Figures 1 and 2. Adverse events by year of admission



Supplementary Figure 1. Patients with any adverse event by year of admission, all groups



Supplementary Figure 2. Total number of adverse events by year of admission, all groups

Table S7. Interobserver variability study

Interobserver variability on presence or absence of adverse events				
		Panel		Total
		present	absent	
Primary investigator	present	10	2	12
	absent	2	10	12
Total		12	12	24
Kappa = 0.83 (9)				
Interobserver variability of preventability of adverse events				
		Panel		Total
		potentially preventable	not preventable	
Primary investigator	potentially preventable	4	4	7
	not preventable	1	2	3
Total		5	5	10
Kappa = 0.60				

Reference list – Supplemental files Chapter 5

1. Slater, A., et al., PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med, 2003. 29(2): p. 278-85.
2. Pollack, M.M., U.E. Ruttimann, and P.R. Getson, Pediatric risk of mortality (PRISM) score. Crit Care Med, 1988. 16(11): p. 1110-6.
3. PICE registry. 2020; Available from: https://pice.nl/#.
4. Agarwal, S., et al., Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med, 2010. 11(5): p. 568-78.
5. Verlaat, C.W., et al., The occurrence of adverse events in low-risk non-survivors in pediatric intensive care patients: an exploratory study. Eur J Pediatr, 2018. 177(9): p. 1351-1358.
6. Feudtner, C., D.A. Christakis, and F.A. Connell, Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980-1997. Pediatrics, 2000. 106(1 Pt 2): p. 205-9.
7. Feudtner, C., et al., Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr, 2014. 14: p. 199.
8. Edwards, J.D., et al., 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, 2012. 40(7): p. 2196-203.
9. Landis, J.R. and G.G. Koch, The measurement of observer agreement for categorical data. Biometrics, 1977. 33(1): p. 159-74.

CHAPTER 6

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Introduction

The general objective of this thesis was to study factors involved in mortality of low-risk PICU patients. We studied PICU patients with a low predicted mortality risk (<1%) that died during their PICU stay. Mortality, despite low severity of illness score, might be attributed to possibly preventable causes like adverse events. Therefore exploring the reasons why a low-risk patient dies might reveal opportunities to improve the quality of PICU-care.

In order to differentiate between low-risk patients and other PICU patients, we also studied patients at the other end of mortality range, the high-risk PICU patients, with a predicted mortality risk ≥ 30%. We wondered if the same factors were involved in the death of high-risk PICU patients.

The main research questions in this thesis were:

1. Which factors are associated with death in low-risk PICU patients and in high-risk PICU patients?
2. What is the occurrence of adverse events in low-risk PICU patients and in high-risk PICU patients?
3. What is the contribution of (preventable) adverse events in death of low-risk PICU patients?

In this chapter, we will review the results and discuss them in a broader perspective. Furthermore, the clinical relevance of our results and recommendations for future research will be addressed.

Main findings

Factors involved in death of low-risk PICU patients

We performed a retrospective cohort study including low-risk PICU patients admitted between 2006 and 2012 in the Netherlands derived from the Dutch 'PICE registry' (Pediatrische Intensive Care Evaluatie) (Chapter 2). The mortality rate in this cohort was 0.5%. Evaluating the factors that were associated with mortality, we found that low-risk nonsurvivors were more often admitted unplanned, had more complex chronic conditions and had a longer length of stay (LOS) compared to low-risk survivors. In a multivariable logistic regression analysis, complex chronic conditions (CCCs) and unplanned admissions were significantly associated with mortality.

Factors involved in death of high-risk PICU patients

In Chapter 3, we described a retrospective cohort study including high-risk PICU patients, derived from the same Dutch cohort of PICU admissions between 2006 and 2012. The mortality rate in this cohort was 40.5%. Contrary to the low-risk nonsurvivors, 'Unplanned admission' was not associated with mortality. While more than 90% of the admissions within the high-risk cohort was unplanned, this was not different between survivors and nonsurvivors. A lower Glasgow Coma Scale at the time of PICU admission was significantly associated with mortality. In contrast to the low-risk nonsurvivors, no association was found between CCCs and mortality.

Adverse events in low-risk and high-risk PICU patients

The factors that were derived from the PICE registry and were associated with death were: CCCs, unplanned admissions and Glasgow coma scale at time of admission. Although awareness of these factors is important and might contribute to better recognition of patients at risk, the factors themselves are not modifiable. In order to look further for opportunities for improvement of outcome, we performed two patient record review studies, described in Chapter 4 and 5. The occurrence of adverse events among low-risk PICU nonsurvivors was compared with low-risk survivors, high-risk nonsurvivors and high-risk survivors. In Chapter 4 an exploratory study was performed in two PICUs. This study suggested that the occurrence of adverse events in low-risk nonsurvivors was high. These findings were confirmed in the case-control study on a national level, described in Chapter 5. In 76.5% of low-risk PICU nonsurvivors one or more adverse events occurred. This was significantly higher compared to low-risk survivors (13.1%). In 30.4% of low-risk nonsurvivors, an adverse event contributed to death. In 8.8%, a preventable adverse event contributed to death. Some examples of preventable adverse events contributing to death are medication errors, hospital acquired infections, delay in diagnosis, all occurring in patients with an underlying CCC.

The occurrence of adverse events in low-risk nonsurvivors (76.5%) was significantly higher compared to high-risk nonsurvivors (47.1%). Death in high-risk nonsurvivors was often caused by out-of-hospital cardiac arrest, leading to brain death (39.4%) (Chapter 5, Table 2). Although high-risk nonsurvivors had fewer adverse events compared to low-risk nonsurvivors, the adverse events that did occur were often severe. In 26% of high-risk nonsurvivors, an adverse event contributed to death, including 9.6% patients with a preventable adverse event. The occurrence of adverse events in high-risk survivors (67.0%) was not significantly different from low-risk nonsurvivors; most (67.7%) of these adverse events caused temporary harm.

Critical review

Mortality prediction models in the PICU

In the adult ICU and in the PICU, mortality prediction models are used as instruments for determining the mortality risk adjusted for severity of illness and case mix. These models should only be used in patient groups and should never be used to predict mortality or to guide the management in individual patients (1-4). Table 1, developed by Wetzel, illustrates several possible purposes of data registries and prediction models (5).

Table 1. Purposes of data registries and prediction models

1	Define the natural history of diseases
2	Define and monitor care delivery processes
3	Determine efficiency and efficacy of care
4	Monitor quality and safety
5	Identification of clinical needs
6	Research: hypothesis generation, cohort discovery

With the use of prediction models, the standardized mortality ratio (SMR) can be calculated. The SMR is calculated by dividing the number of observed deaths in a certain population by the number of expected deaths, based on the prediction model (1). A SMR less than 1.00 means that less patients die than expected and a SMR greater than 1.00 means that more patients die than expected. The latter may be an indicator for suboptimal quality of care. Thus, the SMR is an important tool for monitoring safety and efficacy of care.

In this thesis, low-risk PICU patients were defined as patients with a predicted mortality risk of <1% in the recalibrated 'Pediatric Risk of Mortality Score' (PRISM) and/or 'Paediatric Index of Mortality' (PIM2) prediction model. High-risk PICU patients had a predicted mortality risk of ≥ 30% in PRISM and/or PIM2. PRISM and PIM and their successors (PRISM III, PRISM IV, PIM2, PIM3) are validated models used in the PICU for mortality prediction (6-11). Mortality risk intervals of <1% and ≥ 30% respectively are presented as the lowest and highest risk intervals in the original PRISM model and in several (inter)national PICU registries (6, 12).

Length of stay

Length of stay (LOS) is one of the often used indicators of PICU care. In the studies in this thesis, large differences were found in LOS between survivors and nonsurvivors in low-risk and high-risk PICU patients. Low-risk nonsurvivors do not die immediately

after PICU admission, but do so after a prolonged LOS (median 11 days, IQR [5-32]). They have a longer LOS compared to low-risk survivors (median 3 days, IQR [2-5] ($p < 0.001$) (Chapter 2). Considering the mode of death, more than 70% of patients die because PICU treatment is limited or withdrawn (Chapter 5). This implies that in low-risk PICU nonsurvivors, a complex process during admission leads to prolonged LOS and ultimately death.

In high-risk patients, the opposite occurs. High-risk non-survivors die after a short LOS (median 3 days, IQR [2-7]), significantly shorter compared to high-risk survivors (median ≥ 12 days, IQR [7-21]) ($p < 0.001$)) (Chapter 3). More than 40% of high-risk nonsurvivors are admitted after a cardiac arrest. Mode of death is mainly by established brain death (30.4%) or treatment withdrawal or limitation (40.4%) (Chapter 5).

Considering mode of death, treatment limitation or withdrawal of life-sustaining therapy occurs in 44-84% of PICU deaths, as reported from international studies (13-16). In these studies, no differences are made between low-risk or high-risk nonsurvivors. In a Spanish study, among PICU nonsurvivors with an underlying chronic disease, life-sustaining treatment limitations were more frequent compared to other modes of death (59.4% vs 27.4%, $p < 0.001$) (16). Nonsurvivors that died after treatment limitations had a longer LOS compared to nonsurvivors that died with other modes of death (median 7.5 vs 2 days, $p < 0.01$).

The PIM and PRISM models depend on data collected within the first hour (PIM) or first 24 hours (PRISM) after PICU admission. It is known that these models become unreliable when predicting mortality in long-stay patients (17). Physiological data obtained within the first 24 hours after admission do not predict what will happen after several days of admission. There are several explanations for a longer LOS in general. The LOS may be longer due to the severity of illness, for example in children with septic shock who have a longer LOS compared to children admitted after elective surgery. The LOS might be longer in children with CCCs who depend on PICU facilities and cannot be transferred to a lower level of care. Organizational aspects and capacity of healthcare may influence LOS. Another possibility is the occurrence of adverse events that increases the LOS (2, 18).

As a method to correct LOS for case mix, PRISM and PIM have been used to predict PICU LOS and to measure the standardized length of stay ratio (SLOSR) (5).The SLOSR is the average LOS, corrected for severity of illness. An interesting combination of outcome measurements is the use of the standardized mortality ratio (SMR), as a measurement of efficacy, against the SLOSR, as proposed by Wetzel and shown in

Figure 1 (5). If a PICU has a high SMR and a high SLOSR (quadrant IV), this could be considered as a potential marker for reduced quality. The relationship between quality of care and SLOSR/SMR however, is often not straight forward. For example, a PICU treating many complex oncologic patients might perform in quadrant IV, since mortality is often higher than predicted by PRISM or PIM and LOS may be longer because of the complexity of these patients (19). So performance of a PICU in quadrant IV might be considered as a warning sign and should be explored further.

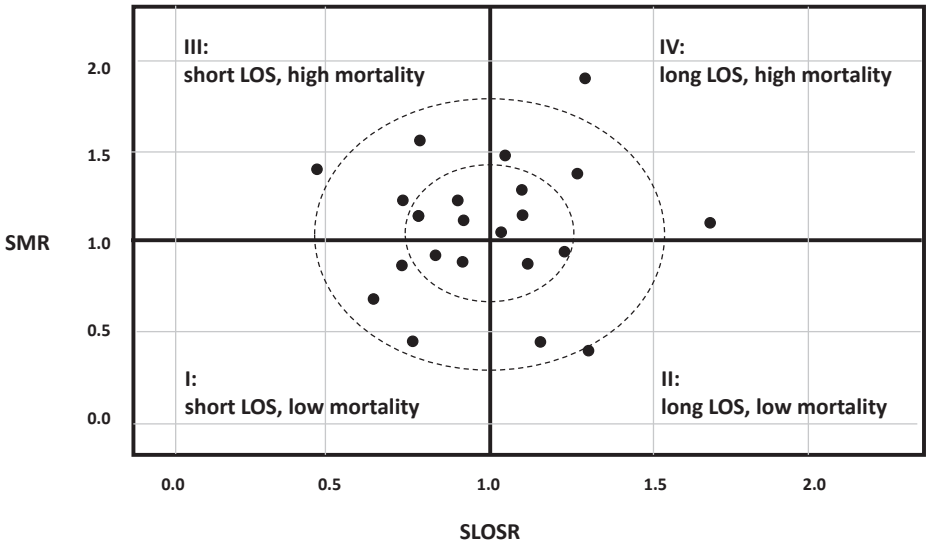


Figure 1 Standardized mortality ratio against standardized length of stay

Legend: SMR = standardized mortality ratio, SLOSR = standardized length of stay, LOS = length of stay. This figure is copied from Wetzel 2016 (5).

Complex chronic conditions

CCCs increase mortality in patients with a low predicted mortality risk (Chapter 2), however not in patients with a high predicted mortality risk (Chapter 3). There are many synonyms for children with chronic illness, like 'children with medical complexity', 'chronic critical illness', 'severe chronic illness', 'life-limiting conditions' and 'technology-dependent children', but they all share common features, like dependence on medical technologies and functional limitations (20-22). Feudtner introduced the definition of 'complex chronic conditions' (CCCs) in the year 2000, defined as '*any medical condition that can be reasonably expect to last at least 12 months (unless death intervenes) and to involve either several different organ systems or 1 organ system severely enough to require specialty pediatric*

care and probably some period of hospitalization in a tertiary care center' (23). These children are susceptible to many health risks and are a growing portion of hospitalized patients and PICU patients. Despite the fact that only a small fraction of the childhood population has a CCC, they comprise more than half of all PICU admissions (22, 24, 25). In general, these patients have a longer LOS and may have multiple PICU-admissions (20, 26). Sometimes they are called 'frequent flyers' (27). They may consume more than 75% of PICU days and financial resources (24). Unfortunately, except for a few diagnoses like hypoplastic left heart syndrome, CCCs are not incorporated in the current mortality prediction models (28, 29).

In the general PICU population, the mortality of PICU patients with a CCC is higher than predicted, but only limited data were available for the influence of CCCs on mortality in low-risk PICU patients (28). A Dutch multicenter study from 1995 showed that in a sub-population of low-risk patients, observed mortality was higher than predicted (30). As a probable explanation, the large number of low-risk tertiary care patients suffering from severe, incurable chronic disease was suggested. In our Dutch cohort of low-risk PICU patients, prevalence of CCCs was high (Chapter 2). In low-risk nonsurvivors, 76.7% of patients had a CCC. In low-risk survivors, 58.8% had a CCC. We found that having a CCC increases the mortality risk in the low-risk PICU patient. This implies that mortality risk in low-risk CCC patients is underestimated.

The presence of CCCs may not always be recorded within the PICE data registry. In Chapter 5, the presence of CCCs was derived from the medical record and not only from the PICE registry, leading to a higher prevalence rate of CCCs compared to Chapter 2 (93.1% versus 72.9% in low-risk survivors respectively).

Adverse events, definitions and severity

The first studies on adverse events in hospitals were published more than three decades ago (31, 32). In the year 2000, an important report was published, called *'To Err Is Human: Building a safer health system'*, estimating that In the USA, 98,000 people died yearly because of medical errors (33). In this report, an adverse event was defined as *'an unintended injury that results in temporary or permanent disability, death, or prolonged hospital stay and that is caused by healthcare management rather than by the patient's underlying disease process'*.

Not all, but a sizeable proportion of adverse events are the results of errors, the so called 'preventable' adverse events. A preventable adverse event is defined as '*an adverse event resulting from an error in management due to failure to follow*

accepted practice at an individual or system level'. Accepted practice was taken to be *'the current level of expected performance for the average practitioner or system that manages the condition in question'*.

A grading system, developed for medication errors by the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP), is shown in Table 2 (34). Although this grading system was meant originally for medication errors, it is also used to categorize the severity of adverse events (Grade E-I).

Table 2. Severity of medical errors according to the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP)

Category	Description	Adverse event
A	Circumstances or events that have the capacity to cause error	no
B	An error occurred but the error did not reach the patient	no
C	An error occurred that reached the patient but did not cause harm	no
D	An error occurred, reached the patient, required monitoring but resulted in no harm and / or required intervention to preclude harm	no
E	Contributed to or resulted in temporary harm to the patient and required intervention	yes
F	Contributed to or resulted in temporary harm to the patients and required initial or prolonged hospitalization	yes
G	Contributed to or resulted in permanent patient harm	yes
H	Required intervention to sustain life	yes
I	Contributed to or resulted in the patient's death	yes

In this paragraph, we will focus on the literature of adverse events among the general PICU population, PICU nonsurvivors and on low-risk PICU patients. To our knowledge, no studies are available on adverse events among PICU patients with a high predicted mortality.

Adverse events in the general PICU population

Studies on the occurrence of adverse events in the general PICU population show a large variability in the percentage of PICU patients with one or more adverse events (8-76%) (18, 35-39). An important explanation for the variation in occurrence of adverse events in the PICU is the method used to detect adverse events. Structured retrospective record review is considered to be superior compared to incident reporting systems and reporting from administrative data (38, 40, 41). Examples of structured retrospective record review are the Harvard Medical Practice Study Method and Trigger Tool methods (31, 42-45).

Recently, a systematic review was published on adverse events in the pediatric hospital and PICU/NICU population (40). Among ten PICU and NICU studies, using a trigger tool method, the pooled estimate of the percentage of patients with at least one adverse event, was 47.3% (95% confidence interval 31.9-63.2%). The difference in occurrence between the studies may be partly explained by differences in the definition of adverse events. Six out of ten studies used a definition of adverse events that was wider compared to the definition according to the Institute for Healthcare Improvement, therefore also including medical errors that did not lead to patient harm (grade B-I according to NCC-MERP criteria). Another possible explanation may be differences among health systems, since five out of ten studies were performed in low/middle income countries. Table 3 summarizes explanations for the differences in the occurrence of adverse events in the pediatric population.

The largest PICU multicenter study was published by Agarwal (18). In this study, using the trigger tool method, 62% of patients had one or more adverse events. The results of Chapter 4 and 5 however cannot be compared with Agarwal directly, due to the focus on low-risk nonsurvivors in Chapter 4 and 5. In the study by Agarwal, PICU survivors had fewer adverse events compared to nonsurvivors (Odds ratio of survivors compared to nonsurvivors survivors 0.51, $p < 0.001$). This is in accordance with the results in low-risk nonsurvivors in Chapter 4 and 5, but seems not to be the case among high-risk patients. We did not test for differences between high-risk nonsurvivors and high-risk survivors, but high-risk nonsurvivors seem to have less often an adverse event (47.1%) compared to high-risk survivors (67.0%), also when corrected for LOS. However, if high-risk nonsurvivors do have an adverse event, it is often severe. In 19.8% of the high-risk nonsurvivors, a life-saving intervention was needed and in 31.4%, an adverse effect contributed to death (Chapter 5, Table 3).

Adverse events in PICU nonsurvivors

A few single center studies focus on the occurrence of adverse events among PICU nonsurvivors.

Table 3. Reasons for heterogeneity between studies on adverse events (AEs) in children

Differences between studies	Examples	
Population	Hospital population Pediatric general care population PICU population NICU population Deceased patients Autopsy studies	
Context	High income countries versus low/middle income countries Type hospital (general, tertiary, quaternary) Year of admission	
Inclusion/exclusion criteria	Different thresholds for length of stay, age, different patient categories, patients with multiple admissions etc.	
Method used to detect AE	Voluntary reporting Administrative data Prospective observation Structured retrospective chart review (HPMS, GTT, TT)	
Definition of AE	a. HPMS like	*Requiring temporary or permanent disability, prolonged hospitalization or death.* *Grade F-I according to NCC-MERP criteria.*
	b. IHI like	*Includes a. + incidents requiring additional monitoring.* *Grade E-I according to NCC-MERP criteria.*
	c. Wider than IHI	*Includes b. + 'medical errors' or 'critical incidents' not leading to patient harm.* *Grade B-I according to NCC-MERP criteria.*
Time frame of AE detection	Before index admission During index admission After index admission	
Focus on specific AEs	Adverse drug events Diagnostic adverse events Serious AEs	
Outcome measure	Number (or %) of patients (or admissions) with $\geq$ 1 AE Number of AEs per (100) admission(s) or patient(s) Number of AE/ (100, 1000) patient day(s) Number of preventable AEs Patients (or admissions) with preventable AEs	

Legend: AE: adverse event, PICU: pediatric intensive care unit, NICU: neonatal intensive care unit HPMS: Harvard Medical Practice Study Method, GTT: global trigger tool, TT: trigger tool, IHI: Institute for Healthcare Improvement, NCC-MERP: National Coordinating Council for Medication Error Reporting and Prevention.

A study from the United Kingdom by Monroe, looked for adverse events contributing to death (grade I) among PICU nonsurvivors (46). A standardized medical record review tool was used. The PICU nonsurvivors had a high median predicted mortality (39% according to the PIM2 score, with an IQR [7-69%]), comparable to the high-risk nonsurvivors in Chapter 5 (median predicted mortality according to the recalibrated PIM2 score 41%, IQR [17-71%]). An adverse event contributing to death occurred in 17/47 (36%) of the nonsurvivors, compared to 26% in high-risk nonsurvivors in Chapter 5. A major difference between the two studies was the timing of the adverse events. In the study by Monroe, all adverse events contributing to death (n=22) occurred in the pre-PICU hospital care or in the pre-hospital environment, mainly due to problems in diagnosis and management. This is different from the results from Chapter 5, where the majority of adverse events occurred during PICU admission. Possible explanations for this difference may be that Monroe focused on adverse events that contributed to death instead on all adverse events. Furthermore, Monroe studied a relatively small number of patients and there are differences in healthcare organization between the United Kingdom and the Netherlands. Monroe also described what was called 'critical incidents', defined as errors not reaching the patient and adverse events that did not contribute to death (NCC MERP category B-H (34). In 28/47 (60%) of PICU nonsurvivors, a 'critical incident' occurred, not only in pre-PICU care but also during PICU admission.

Another single center study on 92 PICU nonsurvivors by Abbas looked for potentially preventable mortality (47). In this study, 4.3% of the deaths would be considered preventable according to the definitions used in Chapter 5. This number is roughly half of what was found in Chapter 5 among low- and high-risk nonsurvivors (8.8% and 9.6% respectively). The difference can be explained not only by differences in the study population but also by methodological differences. The study by Abbas was performed in all nonsurvivors from a general PICU in Pakistan. The patients were more severely ill, as can be derived from the relatively high median PRISM III score and the high mortality (13%). The review of the medical records was done by two pediatricians with half-a-day training in record review. This method might be less sensitive to detect adverse events compared to the trigger tool method that was used in Chapter 5.

In a systematic review concerning autopsy studies, looking for diagnostic errors in pediatric critical care, a 10-23% rate of missed major diagnoses was found (48). Autopsy rates were 20-47%. In the Netherlands, autopsy is used in a minority of PICU nonsurvivors and therefore results from autopsy studies may be prone for bias. In Chapter 4 and 5, findings from autopsy were not measured as a separate item.

Adverse events in low-risk nonsurvivors in the hospital, ICU and PICU

The first study looking into death of low-risk patients as a potential marker for the quality of care was published in 1989 (49). In a sample of more than 8000 in hospital deaths, patients who died with a predicted risk of death of <0.5%, were 5.2 times more likely to have quality of care problems compared to other patients that died. Evaluating deaths and perhaps especially 'unexpected deaths' may be an efficient way to obtain information about iatrogenic harm, but literature on this topic in the ICU and PICU population is scarce. In a single center study on causes of death in adult ICU patients with a low APACHE II score ('Acute Physiology And Chronic Health Evaluation II' score, a severity of disease classification system used in the adult ICU), death related to iatrogenic injury was rare and occurred in less than 1:1000 ICU patients with a low APACHE II score (50).

One Swiss single-center study by Ruegger looked at the occurrence of adverse events in low-risk PICU nonsurvivors (51). In the Swiss study, the number of adverse events per low-risk nonsurvivor (0.46) was significantly higher compared to low-risk survivors (0.11) ($p < 0.001$). There were differences in definitions and outcome measures between this study and the studies from Chapter 4 and 5. The definition of 'low-risk' by Ruegger was a PIM2 mortality risk <10%, compared to < 1% in the studies from Chapter 4 and 5. Outcome of the study by Ruegger was measured on the level of the *number of* (serious) *adverse events*, while in Chapter 4 and 5 main outcome was measured on the level of *patients* with an adverse event. Despite these differences in methods, the results confirmed that low-risk nonsurvivors have more (serious) adverse events compared to low-risk survivors.

Safety measures in hospitals and in the PICU

The report *'To Err is Human'* increased awareness of safety issues in healthcare worldwide. In the Netherlands, after the first study on healthcare related harm in hospitals, a nationwide campaign was released to increase patient safety in the hospitals between 2008 and 2012 *('Veiligheidsmanagement systeem (VMS)' , also named as 'Prevent Harm, Work Safely')* (52, 53). This program was also implemented in Dutch PICUs. The studies in this thesis were not powered to show differences over time, but adverse events were found in all admissions between 2006 and 2017 (Chapter 5, supplementary Figure 1 and 2).

A follow up study by Baines on healthcare related harm in Dutch hospitals, published in 2015, showed a decrease in crude preventable adverse events rates during that period. However, after correction for the hospital level and for differences in patient mix, the decrease was not statistically significant ($p = 0.10$) (53). In the study, no data from PICU patients were available.

Although safety programs may have a positive impact, health related patient harm is a persistent problem and is difficult to manage. Zero health related harm is an utopian objective. Causes of AEs are multifactorial, including technical factors, organizational factors, and human factors. Most adverse events that were described in Chapter 5 in low-risk nonsurvivors were infection related and drug/fluid related, but the nature of the adverse events was very diverse.

Relationship between adverse events and complex chronic conditions

In our case-control study, 93% of low-risk nonsurvivors had a CCC (Chapter 5). This number is high, but the prevalence of CCCs among low-risk survivors was also high (73%).

Children with CCCs are more vulnerable for developing adverse events (54). There are several hypothetic explanations for this phenomenon. These children often depend on multiple medications, technical support, parental support and have repeated surgical procedures, exposing them to higher iatrogenic risks. They may be 'harder to read' and their symptoms are often difficult to interpret which makes them prone for diagnostic errors or problems in interpreting clinical deterioration. They may have a longer PICU stay, which is associated with a higher risk for adverse events. Adverse events themselves can lead to increased LOS, and therefore indirectly increasing the risk for more/multiple adverse events.

Due to the retrospective nature of our studies, a causal relationship cannot be established, but in our study population we observed the combination of children with CCCs, adverse events, long LOS and death. Therefore, we developed a hypothetical relationship between those factors as shown in Figure 2. The underlying CCC cannot be influenced, but by reducing the number of adverse events, possibly the LOS and mortality might be reduced.

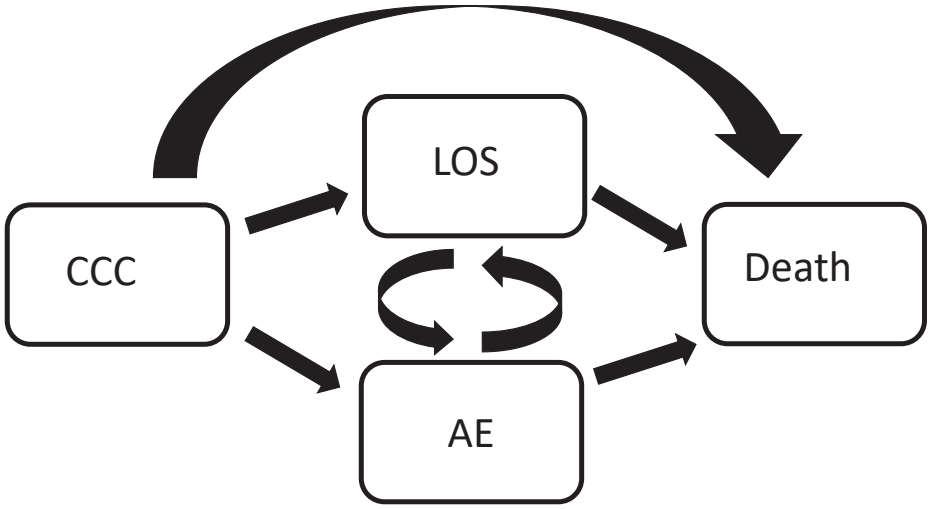


Figure 2. Possible relationship between complex chronic conditions, length of stay, adverse events and death

Figure legend: CCC = complex chronic condition, LOS = length of stay, AE = adverse event.

Potentially avoidable death among low-risk nonsurvivors and high-risk nonsurvivors in the Netherlands

Based on the study described in Chapter 5, in this paragraph we try to estimate the contribution of preventable adverse events leading to death among low-risk nonsurvivors and high-risk nonsurvivors. This could be considered as 'potentially avoidable death'.

First, if we speak about 'potentially avoidable death', it does not mean that death was completely caused by a preventable adverse event. Often there is a combination of complex underlying chronic diseases and adverse events. A patient with, for example, a lethal underlying condition, would have died anyway, but death might have been accelerated due to an adverse event. After performing the exploratory study (Chapter 4), we decided to develop three subcategories of adverse events that contributed to or resulted in death (= grade I according to NCC-MERP criteria). The three subcategories were: I-1 (adverse event is *partially* contributing to death), I-2 (adverse event is *substantially* contributing to death) and I-3 (death was *completely caused* by the adverse event). In most cases, the adverse event partially or substantially contributed to death (Chapter 5, Table 4).

Second, it seems that 'preventability' is either present or not present, but in reality, preventability is measured on a 6 point scale, varying from no evidence for preventability (=1) until certain evidence for preventability (=6). Scores from 1-3 were defined as not preventable, and scores from 4-6 were defined as preventable, such as in other large studies on adverse events (52, 55). Preventability is hard to estimate and the judgment of preventability may vary during the years, as medical standards improve. Hindsight bias may also influence judgement of preventability (56). We used several measures to optimize judgment of adverse events and of preventability. Guidelines and protocols of the period in which the admission took place, were used if available. We discussed adverse events and preventability within an expert panel and we measured the interobserver relability, which was moderate (for preventability estimation) to almost perfect (for adverse events estimation).

Extrapolated to a national level, the occurrence of potentially avoidable death among patients with a low predicted mortality risk is 1.4 (95% CI 0.67-2.63) patients per year (Table 4).

In high-risk patients, the occurrence of potentially avoidable death is 5.3 (95% CI 2.58-9.30) patients per year. The number of preventable death among high-risk nonsurvivors is larger compared to the low-risk nonsurvivors, due to the larger number of high-risk nonsurvivors in the total population (Table 4).

The total number of PICU deaths in the 11-year cohort described in Chapter 5 was 1,632, meaning that around 148 children in the Netherlands die each year in the PICU. In Chapter 5, we excluded patients with an intermediate mortality risk. This group is a large part of the PICU population and is responsible for 853/1,632 nonsurvivors. Due to the focus on low-risk and high-risk patients in this thesis, we cannot make any estimation of the total number of 'avoidable death' among the whole PICU population in the Netherlands. The numbers of avoidable death among low-risk and high-risk nonsurvivors have to be used carefully, due to the reasons mentioned before. But, based on this thesis, we can conclude there is potentially avoidable death among PICU patients in the Netherlands.

Table 4. Estimation of 'potentially avoidable death' in low-risk and high-risk nonsurvivors in the Netherlands

	Low-risk non-survivors	**High risk non-survivors**
Total in 11 year cohort (n)	180	603
Number of deaths per year	16.4 (180/11)	54.8 (603/11)
Randomly selected in study (n)	125	125
Included in the study (n)	102	104
Patients with preventable adverse event contributing to death (n) and % (95% CI)	9/102 8.8% (4.1%-16.1%)	10/104 9.6% (4.7% - 16.1%)
Prevalence of patients with preventable adverse events contributing to death per year (n) (95% CI)	1.4 (0.67-2.63)	5.3 (2.6-9.3)

Legend: Numbers are based on study described in Chapter 5. Patients were selected from an 11 year cohort containing all Dutch PICU admissions (2006-2017). The cohort contained 53,789 PICU admissions with a mortality of 1,632 (3.0%). In the cohort, there were 180 low-risk nonsurvivors and 603 high-risk nonsurvivors (Chapter 5, Figure 1). From both groups, 125 patients were selected but some patients were excluded. In total, 102 low-risk nonsurvivors and 104 high-risk nonsurvivors were included. Based on the number of patients with preventable adverse events contributing to death, the exact (Pearson-Clopper) 95% confidence interval (CI) was measured (57). Under the assumption that the reasons for exclusion are unrelated to outcome, we took the 180 and 603 nonsurvivors as basis for the extrapolation. The number of low-risk nonsurvivors is 180/11 = 16.4 per year and the number of high-risk nonsurvivors is 603/11 = 54.8 per year. If we applicate the % of patients with preventable adverse events contributing to death on this number, we estimate the numbers of avoidable death among low-risk nonsurvivors and high-risk nonsurvivors.

Considerations for future research and implications for practice on prediction models and patient safety in the PICU

PICU prediction models and data registries

So, how would the ideal (PICU) database and prediction model look like and how can we process the increasing amounts of data in a good an efficient way? (2, 5). Besides obvious general requirements, including a clear data dictionary, extracting data directly from the electronic health record and securing the data carefully, we have some suggestions for the future.

The PICU has changed since the development of the first prediction model, nearly 40 years ago. Mortality is declining and may no longer be the sufficient to evaluate PICU care (6, 8, 13, 58). New morbidities can develop in children during their PICU stay and can have consequences after their PICU stay (59, 60). Based on the literature of the last decades, we advise to use functional and long-term outcomes and to involve patients and their families in the assessment of outcome measurements, including patient reported outcomes (58, 59, 61-63).

There is an increasing number of children with CCCs in the PICU (20, 28). The performance of PICU models might be improved by adding CCCs into these models. This should be developed and tested using the whole PICU population, preferentially in several large international registries. In our studies, we focused on the low- and high-risk patients and did not incorporate patients with an intermediate mortality risk. There are codes available that connect diagnoses from the International Classification of Disease (ICD-9 and ICD-10) to CCCs (23, 64). We developed a list connecting the codes used in the ANZPIC diagnostic system with CCCs, which might facilitate incorporating CCCs within prediction models (Chapter 2) (65). A medical vocabulary has been developed for electronic health records, the 'Systematized Nomenclature of Medicine Clinical Terms' (SNOMED CT) (66). ICD-10 diagnoses are linked to SNOMED CT (67). Using a structured problem list, including diagnoses and underlying chronic diagnoses in an unequivocal way in the electronic health record is extremely important. More and more, data are extracted directly from electronic health records into data registries. This will probably facilitate incorporating CCCs into prediction models.

It might be important to incorporate adverse events into the problem list of electronic health records. This will increase awareness of adverse events, give better understanding of causes and consequences of adverse events and will possibly allow adverse events to be part of (PICU) prediction models.

(International) collaboration, such as has been shown during the Covid-19 pandemic can lead to steps forward (68, 69). A new development is the collaboration of national registries from different domains, which is taking place in the United Kingdom and in the Netherlands (70, 71). Improving data registries is not an easy road but it is possible. The ultimate goal of data registries is to improve quality of care. 'Quality of care' means a healthcare system that is safe, effective, patient-centered, timely, efficient and equitable (72). Data registries can organize feedback to healthcare providers on several aspects of quality and therefore can facilitate a quality improvement process.

Data registries themselves should be lean and efficient. There is a balance between gathering more and more information that is potentially useful and gathering the minimum information required for feedback to healthcare providers. Keeping this balance requires an ongoing discussion between healthcare providers, data registries and patients and their families.

Adverse events

So far, most strategies on healthcare safety have focused on investigating what went wrong ('Safety I'). A new approach ('Safety II') focuses on learning from situations that usually go well (73). In the Safety II approach, it is important to recognize that healthcare is a complex system, mandating resilience and flexibility within systems and individuals to avoid errors (74, 75). Methods from Crew Resource Management might be useful for the complex environment such as the PICU.

Wolfe and Mack stress the role of leadership in patient safety in the PICU (76). Crucial is building a robust 'culture of safety', the 'secret sauce' leading to succes. It is about 'how we do things when no one is looking'. Hospitals should use a framework and collaborate in networks. A leader should verbalize and demonstrate that safety is top priority. In the beginning of a safety improvement process, healthcare related harm that was previously undetected, is getting noticed. Therefore the apparent harm seems to increase, but this should not discourage the team. Improving patient safety is a long and slow process. Elements of this safety process, as mentioned by Wolfe and Mack, are:

- Identifying specific domains for improvement strategies *(examples: healthcare acquired infections, handoffs, cardiopulmonary resuscitation, etcetera)*
- Measuring quality indicators
- Display data to the team in a meaningful way
- Using patients and families in the safety process
- Using Plan-Do-Study-Act cycles

- Event reporting with feedback to the reporters, without retaliation
- Using 'bundles' (small set of evidence-based interventions for a defined population and care setting that, when implemented together, will result in significantly better outcomes than when implemented individually) (77)

An example of a successful intervention, using a combination of interventions was recently published by Dewan (78). In a large quaternary care PICU, a clinical decision support tool to identify PICU patients at high risk for clinical deterioration was developed (79). Twice a day, safety huddles were held by clinicians and nurses among patients identified by this 'PICU Warning Tool' and among patients manually identified as high risk, for example patients with a high-risk intubation or at-risk for extracorporeal membrane oxygenation. For these patients, an individual mitigation plan was made and communicated to the team and family. The number of cardiopulmonary resuscitation events within the PICU was reduced (by half) during the intervention. This study shows that even in large, high tech PICUs there are opportunities for decreasing the number of adverse events by increasing Situational Awareness, one of the tools from Crew Resource Management.

In our studies, most common types of adverse events were infection related and drug/fluid related adverse events. If comparisons of the prevalence of these adverse events between PICUs would be available in data registries, discussing these differences and learning from best practices might reveal opportunities for improvement.

Based on our studies, it would be interesting to study the relationship between CCCs, adverse events, LOS and outcome. Possibly for children with CCCs, a warning tool might be developed, using knowledge of the parents on their children. Parents are an underused source of data about errors and preventable adverse events (80). Family centered care processes may improve quality of care (81). Perhaps an individual mitigation plan for children with CCCs at risk for deterioration can reduce the number of adverse events and therefore improve outcome.

Conclusions

In low-risk PICU patients, complex chronic conditions are associated with increased mortality. Low-risk PICU nonsurvivors have a longer length of stay compared to low-risk survivors. They have a high occurrence of adverse events, including preventable adverse events that contribute to death. The occurrence of adverse events among low-risk nonsurvivors is higher compared to low-risk survivors and high-risk nonsurvivors.

Due to the increasing prevalence of children with complex chronic conditions, incorporating underlying chronic diseases might improve the PICU prediction model(s). This should be evaluated in the total PICU population, preferentially on an international basis.

The underlying complex chronic condition cannot be influenced, but by reducing the number of adverse events, possibly the length of stay and mortality could be reduced. There is potential to reduce PICU mortality in low-risk nonsurvivors but also in high-risk nonsurvivors. The role of the 'Safety II' approach and family participation should be evaluated further in reducing the number of (preventable) adverse events.

Reference list

1. Shann F. Are we doing a good job: PRISM, PIM and all that. Intensive Care Med. 2002;28(2):105-7.
2. Pittman E, Bernier M, Fackler J. Data, Anomalies; a Call to Cease and Desist. Pediatr Crit Care Med. 2023;24(1):72-4.
3. Le Gall JR. The use of severity scores in the intensive care unit. Intensive Care Med. 2005;31(12):1618-23.
4. Abulebda K, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, et al. Post-ICU admission fluid balance and pediatric septic shock outcomes: a risk-stratified analysis. Crit Care Med. 2014;42(2):397-403.
5. Wetzel RC. Pediatric Intensive Care Databases for Quality Improvement. J Pediatr Intensive Care. 2016;5(3):81-8.
6. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med. 1988;16(11):1110-6.
7. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996;24(5):743-52.
8. Pollack MM, Holubkov R, Funai T, Dean JM, Berger JT, Wessel DL, et al. The Pediatric Risk of Mortality Score: Update 2015. Pediatr Crit Care Med. 2016;17(1):2-9.
9. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med. 1997;23(2):201-7.
10. Slater A, Shann F, Pearson G, Paediatric Index of Mortality Study G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med. 2003;29(2):278-85.
11. Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care*. Pediatr Crit Care Med. 2013;14(7):673-81.
12. ANZPIC-registry. ANZPICR Annual Report 2015. https://www.anzics.com.au/annual-reports/: ANZPIC registry; 2015. Available from: https://www.anzics.com.au/wp-content/uploads/2018/08/ANZPICR-Annual-Report-2015.pdf.
13. Moynihan KM, Alexander PMA, Schlapbach LJ, Millar J, Jacobe S, Ravindranathan H, et al. Epidemiology of childhood death in Australian and New Zealand intensive care units. Intensive Care Med. 2019;45(9):1262-71.
14. Meert KL, Banks R, Holubkov R, Pollack MM, and the Eunice Kennedy Shriver National Institute of Child H, Human Development Collaborative Pediatric Critical Care Research N. Morbidity and Mortality in Critically Ill Children. II. A Qualitative Patient-Level Analysis of Pathophysiologies and Potential Therapeutic Solutions. Crit Care Med. 2020.
15. Zimmermann K, Cignacco E, Engberg S, Ramelet AS, von der Weid N, Eskola K, et al. Patterns of paediatric end-of-life care: a chart review across different care settings in Switzerland. BMC Pediatr. 2018;18(1):67.
16. Agra-Tunas C, Rodriguez-Ruiz E, Rodriguez Merino E, Care MOdMeUP-sgotSSoPI. How Do Children Die in PICUs Nowadays? A Multicenter Study From Spain. Pediatr Crit Care Med. 2020;21(9):e610-e6.
17. Visser IH, Hazelzet JA, Albers MJ, Verlaat CW, Hogenbirk K, van Woensel JB, et al. Mortality prediction models for pediatric intensive care: comparison of overall and subgroup specific performance. Intensive Care Med. 2013;39(5):942-50.

18. Agarwal S, Classen D, Larsen G, Tofil NM, Hayes LW, Sullivan JE, et al. Prevalence of adverse events in pediatric intensive care units in the United States. Pediatr Crit Care Med. 2010;11(5):568-78.
19. Wosten-van Asperen RM, van Gestel JPJ, van Grotel M, Tschiedel E, Dohna-Schwake C, Valla FV, et al. PICU mortality of children with cancer admitted to pediatric intensive care unit a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2019;142:153-63.
20. Edwards JD, Goodman DM. The Child With Severe Chronic Illness in the ICU: A Concise Review. Crit Care Med. 2022;50(5):848-59.
21. Cohen E, Kuo DZ, Agrawal R, Berry JG, Bhagat SK, Simon TD, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics. 2011;127(3):529-38.
22. Fraser LK, Parslow R. Children with life-limiting conditions in paediatric intensive care units: a national cohort, data linkage study. Arch Dis Child. 2018;103(6):540-7.
23. Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980-1997. Pediatrics. 2000;106(1 Pt 2):205-9.
24. Chan T, Rodean J, Richardson T, Farris RWD, Bratton SL, Di Gennaro JL, et al. Pediatric Critical Care Resource Use by Children with Medical Complexity. J Pediatr. 2016;177:197-203 e1.
25. Arias Lopez MDP, Fernandez AL, Fiquepron K, Meregalli C, Ratto ME, Siaba Serrate A, et al. Prevalence of Children With Complex Chronic Conditions in PICUs of Argentina: A Prospective Multicenter Study. Pediatr Crit Care Med. 2020;21(3):e143-e51.
26. Edwards JD, Lucas AR, Boscardin WJ, Dudley RA. Repeated Critical Illness and Unplanned Readmissions Within 1 Year to PICUs. Crit Care Med. 2017;45(8):1276-84.
27. Piva J, Garros D. PICU Frequent Flyers: An Opportunity for Reconciling Humanism and Science! Pediatr Crit Care Med. 2020;21(9):846-7.
28. Edwards JD, Houtrow AJ, Vasilevskis EE, Rehm RS, Markovitz BP, Graham RJ, et al. 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. 2012;40(7):2196-203.
29. Typpo KV, Petersen NJ, Petersen LA, Mariscalco MM. Children with chronic illness return to their baseline functional status after organ dysfunction on the first day of admission in the pediatric intensive care unit. J Pediatr. 2010;157(1):108-13 e1.
30. Gemke RJ, Bonsel GJ. Comparative assessment of pediatric intensive care: a national multicenter study. Pediatric Intensive Care Assessment of Outcome (PICASSO) Study Group. Crit Care Med. 1995;23(2):238-45.
31. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med. 1991;324(6):370-6.
32. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991;324(6):377-84.
33. Kohn LT, Corrigan J, Donaldson MS, Institute of Medicine (U.S.). Committee on Quality of Health Care in America. To err is human : building a safer health system. Washington, D.C.: National Academy Press; 2000. xxi, 287 p. p.
34. NCC MERP Index for Categorizing Medication Errors [Accessed 7 March 2022]. National Coordinating Council for Medication Error Reporting and Prevention]. Available from: http://www.nccmerp.org/types-medication-errors.

35. Stambouly JJ, McLaughlin LL, Mandel FS, Boxer RA. Complications of care in a pediatric intensive care unit: a prospective study. Intensive Care Med. 1996;22(10):1098-104.
36. Tibby SM, Correa-West J, Durward A, Ferguson L, Murdoch IA. Adverse events in a paediatric intensive care unit: relationship to workload, skill mix and staff supervision. Intensive Care Med. 2004;30(6):1160-6.
37. Larsen GY, Donaldson AE, Parker HB, Grant MJ. Preventable harm occurring to critically ill children. Pediatr Crit Care Med. 2007;8(4):331-6.
38. Vermeulen JM, van Dijk M, van der Starre C, Wosten-van Asperen RM, Argent AC. Patient Safety in South Africa: PICU Adverse Event Registration*. Pediatr Crit Care Med. 2014;15(5):464-70.
39. Cifra CL, Ten Eyck P, Dawson JD, Reisinger HS, Singh H, Herwaldt LA. Factors Associated With Diagnostic Error on Admission to a PICU: A Pilot Study. Pediatr Crit Care Med. 2020.
40. Dillner P, Eggenschwiler LC, Rutjes AWS, Berg L, Musy SN, Simon M, et al. Incidence and characteristics of adverse events in paediatric inpatient care: a systematic review and meta-analysis. BMJ Qual Saf. 2023;32(3):133-49.
41. Hooper AJ, Tibballs J. Comparison of a Trigger Tool and voluntary reporting to identify adverse events in a paediatric intensive care unit. Anaesth Intensive Care. 2014;42(2):199-206.
42. Resar RK, Rozich JD, Classen D. Methodology and rationale for the measurement of harm with trigger tools. Qual Saf Health Care. 2003;12 Suppl 2(Suppl 2):ii39-45.
43. Classen DC, Resar R, Griffin F, Federico F, Frankel T, Kimmel N, et al. 'Global trigger tool' shows that adverse events in hospitals may be ten times greater than previously measured. Health Aff (Millwood). 2011;30(4):581-9.
44. Matlow A, Flintoft V, Orrbine E, Brady-Fryer B, Cronin CM, Nijssen-Jordan C, et al. The development of the Canadian paediatric trigger tool for identifying potential adverse events. Healthc Q. 2005;8 Spec No:90-3.
45. Stockwell DC, Bisarya H, Classen DC, Kirkendall ES, Landrigan CP, Lemon V, et al. A trigger tool to detect harm in pediatric inpatient settings. Pediatrics. 2015;135(6):1036-42.
46. Monroe K, Wang D, Vincent C, Woloshynowych M, Neale G, Inwald DP. Patient safety factors in children dying in a paediatric intensive care unit (PICU): a case notes review study. BMJ Qual Saf. 2011;20(10):863-8.
47. Abbas Q, Memon F, Laghari P, Saleem A, Haque A. Potentially Preventable Mortality in the Pediatric Intensive Care Unit: Findings from a Retrospective Mortality Analysis. Cureus. 2020;12(3):e7358.
48. Cifra CL, Custer JW, Singh H, Fackler JC. Diagnostic Errors in Pediatric Critical Care: A Systematic Review. Pediatr Crit Care Med. 2021.
49. Hannan EL, Bernard HR, O'Donnell JF, Kilburn H, Jr. A methodology for targeting hospital cases for quality of care record reviews. Am J Public Health. 1989;79(4):430-6.
50. van Berkel A, van Lieshout J, Hellegering J, van der Hoeven JG, Pickkers P. Causes of death in intensive care patients with a low APACHE II score. Neth J Med. 2012;70(10):455-9.
51. Ruegger CM, Frey B. The Pediatric Index of Mortality as a Trigger Tool for the Detection of Serious Errors and Adverse Events. Pediatr Crit Care Med. 2018;19(9):869-74.
52. Zegers M, de Bruijne MC, Wagner C, Hoonhout LH, Waaijman R, Smits M, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. Qual Saf Health Care. 2009;18(4):297-302.
53. Baines R, Langelaan M, de Bruijne M, Spreeuwenberg P, Wagner C. How effective are patient safety initiatives? A retrospective patient record review study of changes to patient safety over time. BMJ Qual Saf. 2015;24(9):561-71.

54. Matlow AG, Baker GR, Flintoft V, Cochrane D, Coffey M, Cohen E, et al. Adverse events among children in Canadian hospitals: the Canadian Paediatric Adverse Events Study. CMAJ. 2012;184(13):E709-18.
55. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ. 2004;170(11):1678-86.
56. Henriksen K, Kaplan H. Hindsight bias, outcome knowledge and adaptive learning. Qual Saf Health Care. 2003;12 Suppl 2:ii46-50.
57. C.Pezzullo J. Exact Binomial and Poisson Confidence Intervals (Pearson, Clopper). 2009.
58. Namachivayam P, Shann F, Shekerdemian L, Taylor A, van Sloten I, Delzoppo C, et al. Three decades of pediatric intensive care: Who was admitted, what happened in intensive care, and what happened afterward. Pediatr Crit Care Med. 2010;11(5):549-55.
59. Pollack MM, Holubkov R, Glass P, Dean JM, Meert KL, Zimmerman J, et al. Functional Status Scale: new pediatric outcome measure. Pediatrics. 2009;124(1):e18-28.
60. Pollack MM, Holubkov R, Funai T, Berger JT, Clark AE, Meert K, et al. Simultaneous Prediction of New Morbidity, Mortality, and Survival Without New Morbidity From Pediatric Intensive Care: A New Paradigm for Outcomes Assessment. Crit Care Med. 2015;43(8):1699-709.
61. Pinto NP, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-Term Function After Pediatric Critical Illness: Results From the Survivor Outcomes Study. Pediatr Crit Care Med. 2017.
62. Pearson GA. Intensive care: because we can or because we should? Arch Dis Child. 2018.
63. Graham RJ, Pemstein DM, Curley MA. Experiencing the pediatric intensive care unit: perspective from parents of children with severe antecedent disabilities. Crit Care Med. 2009;37(6):2064-70.
64. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr. 2014;14:199.
65. Slater A, Shann F, McEniery J, Group AS. The ANZPIC registry diagnostic codes: a system for coding reasons for admitting children to intensive care. Intensive Care Med. 2003;29(2):271-7.
66. Vuokko R, Vakkuri A, Palojoki S. Systematized Nomenclature of Medicine-Clinical Terminology (SNOMED CT) Clinical Use Cases in the Context of Electronic Health Record Systems: Systematic Literature Review. JMIR Med Inform. 2023;11:e43750.
67. Vikstrom A, Skaner Y, Strender LE, Nilsson GH. Mapping the categories of the Swedish primary health care version of ICD-10 to SNOMED CT concepts: rule development and intercoder reliability in a mapping trial. BMC Med Inform Decis Mak. 2007;7:9.
68. Haendel MA, Chute CG, Bennett TD, Eichmann DA, Guinney J, Kibbe WA, et al. The National COVID Cohort Collaborative (N3C): Rationale, design, infrastructure, and deployment. J Am Med Inform Assoc. 2021;28(3):427-43.
69. Jacobs DB, Schreiber M, Seshamani M, Tsai D, Fowler E, Fleisher LA. Aligning Quality Measures across CMS - The Universal Foundation. N Engl J Med. 2023.
70. Healthcare Quality Improvement Partnership [Available from: https://www.hqip.org.uk/about-us/#.Y-Y1xP6ZOUI.
71. Samenwerkende kwaliteitsregistraties [Available from: https://skr-zorg.nl/.
72. Committee on Quality of Health Care in America IoM. Crossing the Quality Chasm: A New Health System for the 21st Century. National Academies Press (NAP); 2001. Report No.: 0-309-51193-3.
73. Hollnagel E, Wears, R., Breaithwaite, J. From Safety-I to Safety-II: A White Paper. The Resilient Health Care Net.: Published simultaneously by the University of Southern Denmark, University of Florida, USA, and Macquarie University, Australia. ; 2015.

74. Merandi J, Vannatta K, Davis JT, McClead RE, Jr., Brilli R, Bartman T. Safety II Behavior in a Pediatric Intensive Care Unit. Pediatrics. 2018;141(6).
75. Verhagen MJ, de Vos MS, Sujan M, Hamming JF. The problem with making Safety-II work in healthcare. BMJ Qual Saf. 2022;31(5):402-8.
76. Wolfe HA, Mack EH. Making care better in the pediatric intensive care unit. Transl Pediatr. 2018;7(4):267-74.
77. Resar R. Using Care Bundles to Improve Health Care Quality2012. Available from: https://www.ihi.org/resources/white-papers/using-care-bundles-improve-health-care-quality
78. Dewan M, Soberano B, Sosa T, Zackoff M, Hagedorn P, Brady PW, et al. Assessment of a Situation Awareness Quality Improvement Intervention to Reduce Cardiac Arrests in the PICU. Pediatr Crit Care Med. 2022;23(1):4-12.
79. Dewan M, Muthu N, Shelov E, Bonafide CP, Brady P, Davis D, et al. Performance of a Clinical Decision Support Tool to Identify PICU Patients at High Risk for Clinical Deterioration. Pediatr Crit Care Med. 2020;21(2):129-35.
80. Khan A, Furtak SL, Melvin P, Rogers JE, Schuster MA, Landrigan CP. Parent-Reported Errors and Adverse Events in Hospitalized Children. JAMA Pediatr. 2016;170(4):e154608.
81. Khan A, Spector ND, Baird JD, Ashland M, Starmer AJ, Rosenbluth G, et al. Patient safety after implementation of a coproduced family centered communication programme: multicenter before and after intervention study. BMJ. 2018;363:k4764.

CHAPTER 7

SUMMARY

Summary

PICU (Pediatric Intensive Care Unit) mortality in the economically developed countries has declined over the last decades to 2-4%. Mortality prediction models are important in studying PICU outcome and in evaluating PICU quality of care. A substantial part of the PICU population has a predicted mortality risk of <1%. If these 'low-risk' PICU patients die, death can be considered as 'unexpected'. Studying 'unexpected deaths' may be an efficient way to discover problems in safety of PICU care and therefore may reveal opportunities to improve quality of PICU care. The goal of this thesis is to get insight in factors associated with death of low-risk PICU nonsurvivors. We were interested in the role of healthcare related harm (adverse events) in this group. An *adverse event* is an unintended injury that results in prolonged hospital stay, temporary or permanent disability, or death, and is caused by healthcare management rather than by the patient's underlying disease process. A *preventable adverse event* is the result of healthcare management below the professional standards or by healthcare system failures.

As a comparison, these factors were also studied among high-risk PICU patients.

Chapter 2 describes a retrospective cohort study among PICU admissions between 2006 and 2012 in the Netherlands. Data were extracted from the Dutch PICU data registry ('Pediatrische Intensive Care Evaluatie'(PICE)). PICU admissions with a predicted mortality risk of less than 1% according to the recalibrated 'Pediatric Risk of Mortality' (PRISM) or the 'Paediatric Index of Mortality 2' (PIM2) were defined as low-risk PICU patients. Low-risk PICU nonsurvivors had significantly more unplanned admissions (74.4% vs 38.5%), more complex chronic conditions (76.7% vs 58.8%) and a longer PICU length of stay (median 11 days vs median 3 days) compared to low-risk survivors (all $p \leq 0.001$). In a multivariable regression model, factors associated with death were complex chronic conditions (Odds ratio 3.29; 95% CI 1.97-5.50), unplanned admissions (Odds ratio 5.78; 95% CI 3.40-9.81) and admissions during spring/summer (Odds ratio 1.67; 95% CI 1.08-2.58).

Chapter 3 focuses on high-risk PICU patients, again with data obtained from the PICE registry 2006-2012. High-risk patients had a predicted mortality risk of ≥ 30%. In contrast to the findings among low-risk nonsurvivors, 'unplanned admissions' were not associated with mortality. While more than 90% of the admissions within the high-risk cohort was unplanned, this was not different between survivors and nonsurvivors. Glasgow Coma Scale at the time of PICU admission was significantly associated with lower mortality risk (Odds ratio 0.91; 95% CI 0.87-0.96). No association was found between complex chronic conditions and mortality in high-risk PICU patients, again, in contrast to the findings among low-risk patients.

In **Chapter 4**, a retrospective patient record review study on healthcare related harm, performed in two PICUs, is described. Patient records from 12 low-risk nonsurvivors, 12 low-risk survivors, 12 high-risk nonsurvivors and 12 high-risk survivors were randomly selected. The 'trigger tool method' was used to detect adverse events. In the first stage, the patient records were screened for 19 'triggers', indicating a potential for adverse events. In the second stage, patient records were reviewed for the presence of healthcare related harm. In 10 out of 12 low-risk PICU nonsurvivors healthcare related harm occurred, significantly higher compared to low-risk PICU survivors (1/12, $p < 0.001$) and to high-risk nonsurvivors (2/12, $p < 0.01$), and not statistically different from high-risk survivors (7/12).

Chapter 5 consists of a case-control study, performed on a national level, including PICU admissions from 2006 until 2017. In total, 419 patient records were studied of low-risk survivors ('cases', n = 102), and three control groups: low-risk survivors (n = 107), high-risk nonsurvivors (n = 104) and high-risk survivors (n = 106). Outcome measures were the occurrence, severity, preventability and nature of adverse events, and its contribution to mortality. In 76.5% of PICU low-risk nonsurvivors, one or more adverse events occurred. This was significantly higher compared to low-risk survivors (13.1%, $p < 0.001$) and high-risk nonsurvivors (47.1%, $p < 0.001$) and not significantly different from high-risk survivors (67%). Almost one third (31.1%) of the adverse events among low-risk nonsurvivors was preventable. Considering the nature of the adverse events, most prevalent were healthcare-associated infections and drug/fluid related harm. Moreover, in 30.4% of low-risk nonsurvivors an adverse event contributed to death and in 8.8% death was potentially avoidable. Although high-risk nonsurvivors had less frequent adverse events compared to low-risk nonsurvivors, they were exposed to severe adverse events too. In 26.0% of high-risk nonsurvivors an adverse event contributed to death and in 9.6% death was considered potentially avoidable.

In the general discussion (**Chapter 6**) of this thesis, the main findings and methodological considerations of this thesis are summarized and discussed. In low-risk PICU patients, complex chronic conditions are associated with mortality. Incorporating complex chronic conditions in PICU mortality prediction models might improve these prediction models, but this should be tested among the total PICU population and not in subgroups. Other developments for data registries in the future are standardization of data, for example by using internationally validated diagnose-lists, and the direct import of (standardized) data from electronic patient records.

Low-risk PICU nonsurvivors often have adverse events. They also suffer from chronic conditons and have a long length-of-stay. Therefore, there seems to be an interaction between complex chronic conditions, length-of-stay and adverse events.

In both low- and in high-risk nonsurvivors, (preventable) adverse events contribute to death in some cases.

In conclusion, this thesis shows that in the Netherlands there is a potential for reducing mortality in PICU patients. Possible strategies to reduce healthcare related harm might use elements from the 'Safety II' approach, with emphasis on learning from what goes well instead of what goes wrong, and by using family centered care. Involving parents in PICU care may be helpful as they may quickly notice vital changes in their children and thereby play a role in reducing healthcare related harm.

CHAPTER 8

NEDERLANDSE SAMENVATTING

Nederlandse samenvatting

De sterfte bij kinderen opgenomen op de kinder-intensive care ('Pediatrische Intensive Care Unit' (PICU)) in de economisch welvarende landen is de laatste decennia gedaald van ongeveer 9% naar ca. 2-4%. Het kunnen voorspellen van overlijden kan behulpzaam zijn bij de inschatting of de sterfte van een bepaalde PICU onder- of bovengemiddeld is. Een dergelijke voorspelling is mogelijk met zogenaamde mortaliteitspredictie modellen. In combinatie met geobserveerde sterfte maken deze het mogelijk een uitspraak te doen over de kwaliteit van zorg op de kinder-intensive care.

Een aanzienlijk deel van de PICU populatie heeft een voorspelde overlijdenskans van <1%. Als deze 'laag-risico' PICU patiënten overlijden, kan dat worden bestempeld als 'onverwachte sterfte'. Het bestuderen van 'onverwachte sterfte' kan een manier zijn om problemen in de patiëntveiligheid te vinden en zo mogelijkheden te ontdekken voor het verbeteren van de kwaliteit van de zorg op de PICU. Het doel van dit proefschrift was om inzicht te krijgen in factoren die een rol spelen bij het overlijden van laag-risico PICU patiënten. In het bijzonder waren wij geïnteresseerd in de rol van onbedoelde zorggerelateerde schade in deze groep. *Onbedoelde zorggerelateerde schade* is gedefinieerd als een onbedoelde uitkomst voor de patiënt, veroorzaakt door de zorg of het zorgsysteem in plaats van door de onderliggende ziekte en resulterend in een langere opnameduur, tijdelijke of permanente schade, of overlijden. *Vermijdbare schade* is onbedoelde schade die is ontstaan door het onvoldoende handelen volgens de professionele standaard en/of door tekortkomingen van het zorgsysteem.

Ter vergelijking hebben we deze factoren ook bestudeerd bij hoog-risico PICU patiënten.

Hoofdstuk 2 beschrijft een retrospectieve cohort studie onder Nederlandse PICU opnames tussen 2006 en 2012. De data werden verkregen uit de Nederlandse PICU dataregistratie ('Pediatrische Intensive Care Evaluatie' (PICE)). PICU patiënten met een voorspelde overlijdenskans van minder dan 1% volgens de gerecalibreerde 'Pediatric Risk of Mortality' (PRISM) of de 'Paediatric Index of Mortality 2' (PIM2) werden gedefinieerd als laag-risico patiënten. Laag-risico sterfgevallen hadden significant vaker ongeplande opnames (74,4% versus 38,5%), meer complexe chronische aandoeningen (76,7% versus 58,8%) en een langere PICU opnameduur (mediaan 11 dagen versus 3 dagen) in vergelijking met laag-risico overlevers (allen $p \leq 0{,}001$). In een multivariabel regressiemodel waren de volgende factoren geassocieerd met een verhoogde sterftekans: complexe chronische aandoeningen (Odds ratio 3,29; 95% CI 1,97-5,50), ongeplande opnames (Odds ratio 5,78; 95% CI 3,40-9,81) en opnames tijdens de lente of zomer (Odds ratio 1,67; 95% CI 1,08-2,58).

Hoofdstuk 3 richt zich op hoog-risico PICU patiënten, opnieuw met data vanuit de PICE registratie uit de periode 2006-2012. Hoog-risico patiënten hadden een voorspelde overlijdenskans van ≥ 30%. In tegenstelling tot de bevindingen onder laag-risico patiënten, waren 'ongeplande opnames' niet geassocieerd met sterfte. Meer dan 90% van alle hoog-risico patiënten had een ongeplande PICU opname, echter dit was niet verschillend tussen de overlevers en de sterfgevallen. Een hogere Glasgow Coma Scale ten tijde van de PICU opname was significant geassocieerd met lagere sterfte (Odds ratio 0,91; 95% CI 0,87-0,96). Er werd geen verband gevonden tussen complexe chronische aandoeningen en sterfte onder de hoog-risico patiënten, in tegenstelling tot de bevindingen onder de laag-risico patiënten.

In **Hoofdstuk 4** wordt een retrospectief dossieronderzoek beschreven naar onbedoelde schade, uitgevoerd op twee PICUs. Medische dossiers van 12 laag-risico sterfgevallen, 12 laag-risico overlevers, 12 hoog-risico sterfgevallen en 12 hoog-risico overlevers werden geselecteerd door middel van loting. Om onbedoelde schade op te sporen, werd gebruik gemaakt van de 'trigger tool methode'. Hierbij werden de medische dossiers eerst gescreend op 19 aanwijzingen (triggers), die kunnen wijzen op mogelijke onbedoelde zorggerelateerde schade. In tweede instantie werden de dossiers beoordeeld op de aan- of afwezigheid van onbedoelde zorggerelateerde schade. Bij 10 van de 12 laag-risico sterfgevallen was er sprake van onbedoelde zorggerelateerde schade, significant vaker dan bij laag-risico overlevers (1 van de 12, $p < 0,001$) en hoog-risico sterfgevallen (2 van de 12, $p < 0,01$) en niet statistisch significant verschillend van hoog-risico overlevers (7 van de 12).

Hoofdstuk 5 omschrijft een case-control onderzoek op nationaal niveau, met PICU opnames van 2006 tot 2017. In totaal werden 419 medische dossiers onderzocht van laag-risico sterfgevallen ('cases', n = 102) en drie controle groepen: laag-risico overlevers (n = 107), hoog-risico sterfgevallen (n = 104) en hoog-risico overlevers (n = 106). Uitkomstmaten waren de aanwezigheid, ernst, vermijdbaarheid en aard van de onbedoelde zorggerelateerde schade en de bijdrage hiervan aan het overlijden. In 76,5% van de laag-risico sterfgevallen was er sprake van onbedoelde zorggerelateerde schade. Dit was significant vaker dan bij laag-risico overlevers (13,1%, $p < 0,001$) en hoog-risico sterfgevallen (47,1%, $p < 0,001$) en niet significant verschillend van hoog-risico overlevers (67%). In bijna een derde (31,1%) van de onbedoelde schade bij laag-risico sterfgevallen was de schade vermijdbaar. De meest voorkomende soorten schade waren ziekenhuisinfecties en schade gerelateerd aan medicatie of toegediende vloeistoffen. Bij 30,4% van de laag-risico sterfgevallen droeg onbedoelde zorggerelateerde schade bij aan het overlijden van deze patiënten en in 8,8% droeg potentieel vermijdbare schade mogelijk bij aan het overlijden.

Hoewel hoog-risico sterfgevallen minder vaak onbedoelde zorggerelateerde schade ondervonden, was er bij deze categorie toch ook sprake van ernstige onbedoelde schade. Bij 26% van de hoog-risico sterfgevallen droeg onbedoelde zorggerelateerde schade bij aan het overlijden en in 9,6% droeg potentieel vermijdbare schade mogelijk bij aan het overlijden.

In de algemene discussie (**Hoofdstuk 6**) van dit proefschrift worden de belangrijkste bevindingen en methodologische overwegingen samengevat en besproken. Bij laag-risico PICU patiënten, zijn complexe chronische aandoeningen (onderliggende ziektebeelden die ernstig zijn en langdurig) geassocieerd met sterfte. Het meenemen van complexe chronische aandoeningen in de PICU mortaliteitspredictiemodellen zou deze modellen mogelijk kunnen verbeteren. Dit moet echter worden getest in de totale PICU populatie en niet alleen in subgroepen. Andere ontwikkelingen voor dataregistraties in de toekomst zijn het standaardiseren van data, bijvoorbeeld door middel van het gebruik van internationale diagnoselijsten, en het direct importeren van (gestandaardiseerde) data vanuit electronische patiëntendossiers.

Bij laag-risico sterfgevallen is er vaak sprake van onbedoelde zorggerelateerde schade. Laag-risico sterfgevallen hebben meestal een onderliggende complexe chronische aandoening en een lange opnameduur. Er lijkt dan ook een relatie te zijn tussen complexe chronische aandoeningen, opnameduur en onbedoelde schade.

Bij een deel van de laag-risico en ook bij hoog-risico PICU sterfgevallen, lijken onbedoelde zorggerelateerde schade en potentieel vermijdbare schade een bijdrage te leveren aan het overlijden.

Concluderend toont dit proefschrift dat er nog steeds mogelijkheden zijn om de sterfte van PICU patiënten in Nederland verder te verlagen. Mogelijke oplossingen om onbedoelde zorggerelateerde schade in de toekomst te verminderen zijn het gebruik van elementen vanuit de 'Safety II' benadering, waarbij de nadruk ligt op leren van wat goed gaat in plaats van wat fout gaat, en door het nog meer betrekken van de familie bij de zorg van de patiënten. Ouders kennen hun kinderen door en door, kunnen ook zien wanneer er veranderingen optreden en kunnen een rol spelen bij het verminderen van onbedoelde zorggerelateerde schade.

APPENDIX

LIST OF ABBREVIATIONS

List of abbreviations

AE	Adverse event
ANZPIC	Australian and New Zealand paediatric intensive care society
CCC	Complex chronic condition
CI	Confidence interval
ECLS	Extracorporeal life support
GTT	Global trigger tool
HN	High-risk nonsurvivor
HS	High-risk survivor
ICU	Intensive care unit
IQR	Inter-quartile range
LN	Low-risk nonsurvivor
LOS	Length of stay
LS	Low-risk survivor
NCCC	Non-complex chronic condition
NCC-MERP	National coordinating council for medication error reporting and prevention
NICU	Neonatal intensive care unit
OR	Odds ratio
PICE	Pediatrische intensive Care evaluatie
PICU	Pediatric intensive care unit
PIM	Paediatric index of mortality
PRISM	Pediatric risk of mortality
SMR	Standardized mortality ratio
TT	Trigger tool

APPENDIX

RESEARCH DATA MANAGEMENT

Research data management

This thesis is based on the result of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands, has given approval to conduct these studies.

All data presented in this project were stored on the secured H-drive of the department of intensive care of the Radboudumc (H:\IC Staf\PICE onderzoek CV). The paper data were stored in a locked closet in a locked room within the staff department.

All data will be saved for 15 years after publication of the results. The dataset analysis during these studies are available from the author (Carin Verlaat) on reasonable request.

APPENDIX

LIST OF PUBLICATIONS

This thesis

Verlaat CW, Visser IH, Wubben N, Hazelzet JA, Lemson J, van Waardenburg D, van der Heide D, van Dam NA, Jansen NJ, van Heerde M, van der Starre C, van Asperen R, Kneyber M, van Woensel JB, van den Boogaard M, van der Hoeven J; SKIC (Dutch Collaborative PICU Research Network). Factors Associated With Mortality in Low-Risk Pediatric Critical Care Patients in The Netherlands
Pediatr Crit Care Med 2017 Vol. 18 Issue 4 Pages e155-e161

Verlaat CW, Wubben N, Visser IH, Hazelzet JA; SKIC (Dutch collaborative PICU research network); van der Hoeven J, Lemson J, van den Boogaard M. Retrospective cohort study on factors associated with mortality in high-risk pediatric critical care patients in the Netherlands. BMC Pediatr 2019 Vol. 19 Issue 1 Pages 274

Verlaat CW, van der Starre C, Hazelzet JA, Tibboel D, van der Hoeven J, Lemson J, Zegers M. The occurrence of adverse events in low-risk non-survivors in pediatric intensive care patients: an exploratory study. Eur J Pediatr. 2018 Sep;177(9):1351-1358. Epub 2018 Jun 26.

Verlaat CW, Zegers M, Klein R, van Waardenburg D, Kuiper JW, Riedijk M, Kneyber M, Timmers B, van Heerde M, Hazelzet JA, van der Hoeven J, Lemson J. Adverse Events in Pediatric Critical Care Nonsurvivors With a Low Predicted Mortality Risk: A Multicenter Case Control Study. Pediatr Crit Care Med. 2023 Jan 1;24(1):4-16. Epub 2022 Nov 17

Publications outside of this thesis

Teheux L, **Verlaat CW**, Lemson J, Draaisma JMT, Fuijkschot J. Risk stratification to improve Pediatric Early Warning Systems: it is all about the context. Eur J Pediatr. 2019 Oct;178(10):1589-1596.

Löwensteyn YN, Jansen NJG, van Heerde M, Klein RH, Kneyber MCJ, Kuiper JW, Riedijk MA, **Verlaat CWM**, Visser IHE, van Waardenburg DA, van Hasselt PM. Increasing the dose of oral vitamin K prophylaxis and its effect on bleeding risk. Eur J Pediatr. 2019 Jul;178(7):1033-1042.

Vet NJ, de Wildt SN, **Verlaat CW**, Mooij MG, Tibboel D, de Hoog M, Buysse CM. Short-Term Health-Related Quality of Life of Critically Ill Children Following Daily Sedation Interruption. Pediatr Crit Care Med. 2016 Nov;17(11):e513-e520.

Vet NJ, Brussee JM, de Hoog M, Mooij MG, **Verlaat CW**, Jerchel IS, van Schaik RH, Koch BC, Tibboel D, Knibbe CA, de Wildt SN. Inflammation and Organ Failure Severely Affect Midazolam Clearance in Critically Ill Children. Am J Respir Crit Care Med. 2016 Jul 1;194(1):58-66.

Vet NJ, de Wildt SN, **Verlaat CW**, Knibbe CA, Mooij MG, van Woensel JB, van Rosmalen J, Tibboel D, de Hoog M. A randomized controlled trial of daily sedation interruption in critically ill children. Intensive Care Med. 2016 Feb;42(2):233-44.

Vet NJ, de Wildt SN, **Verlaat CW**, Knibbe CA, Mooij MG, Hop WC, van Rosmalen J, Tibboel D, de Hoog M. Daily interruption of sedation in critically ill children: study protocol for a randomized controlled trial. Trials. 2014 Feb 13;15:55.

Verlaat CW, Heesen GP, Vet NJ, de Hoog M, van der Hoeven JG, Kox M, Pickkers P. Randomized controlled trial of daily interruption of sedatives in critically ill children. Paediatr Anaesth. 2014 Feb;24(2):151-6.

Visser IH, Hazelzet JA, Albers MJ, **Verlaat CW**, Hogenbirk K, van Woensel JB, van Heerde M, van Waardenburg DA, Jansen NJ, Steyerberg EW. Mortality prediction models for pediatric intensive care: comparison of overall and subgroup specific performance. Intensive Care Med. 2013 May;39(5):942-50.

Vet NJ, **Verlaat CW**, de Wildt SN, Tibboel D, de Hoog M. Daily interruption of sedation in critically ill children. Pediatr Crit Care Med. 2012 Jan;13(1):122; author reply 122-3.

Latour JM, van Goudoever JB, Duivenvoorden HJ, Albers MJ, van Dam NA, Dullaart E, van Heerde M, de Neef M, **Verlaat CW**, van Vught EM, Hazelzet JA. Differences in the perceptions of parents and healthcare professionals on pediatric intensive care practices. Pediatr Crit Care Med. 2011 Sep;12(5):e211-5.

Martin-Loeches I, Lisboa T, et.al. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med. 2011 Feb;37(2):272-83.

Latour JM, van Goudoever JB, Schuurman BE, Albers MJ, van Dam NA, Dullaart E, van Heerde M, **Verlaat CW**, van Vught EM, Hazelzet JA. A qualitative study exploring the experiences of parents of children admitted to seven Dutch pediatric intensive care units. Intensive Care Med. 2011 Feb;37(2):319-25.

Latour JM, van Goudoever JB, Duivenvoorden HJ, Albers MJ, van Dam NA, Dullaart E, van Heerde M, de Neef M, **Verlaat CW**, van Vught EM, Hazelzet JA. Construction and psychometric testing of the EMPATHIC questionnaire measuring parent satisfaction in the pediatric intensive care unit. Intensive Care Med. 2011 Feb;37(2):310-8.

van de Glind GJ, Gidding CE, **Verlaat CM**, Duthoi K, Backx AP, Verweij PE, Warris A. Acute Cardiac Failure due to Intra-Atrial Mass Caused by Zygomycetes in an Immunocompromised Paediatric Patient. Case Rep Med. 2010;2010:241791.

Latour JM, van Goudoever JB, Duivenvoorden HJ, van Dam NA, Dullaart E, Albers MJ, **Verlaat CW**, van Vught EM, van Heerde M, Hazelzet JA. Perceptions of parents on satisfaction with care in the pediatric intensive care unit: the EMPATHIC study. Intensive Care Med. 2009 Jun;35(6):1082-9.

Holla M, Ijland MM, van der Vliet AM, Edwards M, **Verlaat CW**. [Death of an infant following 'craniosacral' manipulation of the neck and spine]. Ned Tijdschr Geneeskd. 2009 Apr 25;153(17):828-31.

van der Meer W, Stephen Scott C, **Verlaat C**, Gunnewiek JK, Warris A. Measurement of neutrophil membrane CD64 and HLA-Dr in a patient with abdominal sepsis. J Infect. 2006 Jul;53(1):e43-6.

Verlaat CW, Peters HM, Semmekrot BA, Wiersma-van Tilburg JM. Congenital pulmonary lymphangiectasis presenting as a unilateral hyperlucent lung. Eur J Pediatr. 1994 Mar;153(3):202-5.

Other

Podcast Society of Critical Care Medicine: Pod-470: Adverse events and mortality in the PICU. 2/22/23.

https://sccm.org/pod470

APPENDIX

PHD PORTFOLIO

PhD portfolio

Department: **Intensive Care**
PhD period: **12/09/2013 – 01/12/2023**
PhD Supervisor(s): **Prof. dr. J.G. van der Hoeven, Prof. dr. J.A. Hazelzet**
PhD Co-supervisor(s): **Dr J. Lemson, Dr. H.W.M. Zegers**

Training activities	**Hours**
Courses	
- Crew Resource Management: Refreshertraining (2014)	6.00
- Communicatie rond donatie (2014)	6.00
- Quality assurance and quality control in clinical research (2015)	2.00
- Simulatioeworkshop geavanceerde hemodynamische bewaking (2015)	6.00
- RIHS - Introduction course for PhD candidates (2015)	15.00
- Herregistratie BROK (2015)	1.00
- Principes van epidemiologische data analyse (V20) (2015)	30.00
- Advanced Paediatric Life Support (2018)	18.00
- Crew Resource Management: Refreshertraining (2018)	6.00
- Radboudumc - Scientific integrity (2019)	20.00
- Herregistratie BROK (2019)	3.00
- Basic Life Support and Pediatric Basic Life Support (2022)	1.00
- Herregistratie van BROK (2023)	3.00
- NVIC cursus Luchtwegmanagement op de IC (2023)	9.00
Seminars	
- Toekomst academische kindzorg in Nijmegen - Innovation or hype? (2014)	3.00
- Periodieke Conferentie Kindergeneeskunde (2014)	4.00
- Periodieke Conferentie Kindergeneeskunde (2015)	4.00
- Acute Zorgregio Oost scholing: 'Huiselijk geweld en kindermishandeling' (2015)	2.00
- Acute Zorgregio Oost scholing: 'Nieuwe reanimatierichtlijnen' (2016)	2.00
- Congres KNMG: 'Niet alles wat kan, hoeft' (2016)	6.00
- Periodieke Conferentie Kindergeneeskunde (2016)	4.00
- SICK symposium: Hemodynamics in Extremes (2016)	6.00
- Docentprofessionalisering Kindergeneeskunde (2016)	1.00

Training activities	**Hours**
- Regionale refereeravond intensive care (2016)	2.00
- Periodieke Conferentie Kindergeneeskunde (2016)	4.00
- 10th neuroradiology conference section neuroradiology (2016)	6.00
- Zorg voor lucht (nascholing kindergeneeskunde) (2017)	5.00
- Docentprofessionalisering Kindergeneeskunde (2017)	1.00
- Periodieke Conferentie Kindergeneeskunde (2017)	4.00
- 4th Netherlands International Sepsis Symposium (2017)	6.00
- Scholing Acute Zorgregio Oost: Brandwondenzorg (2017)	2.00
- The critically ill child; From translational research to reflection (Farewell symposium prof.dr. D.Tibboel) (2018)	6.00
- Docentprofessionalisering Kindergeneeskunde (2018)	1.00
- Scholing Acute Zorgregio Oost: De Traumatische Luchtweg (2018)	2.00
- Docentprofessionalisering Kindergeneeskunde (2018)	1.00
- Periodieke Conferentie Kindergeneeskunde (2019)	4.00
- Docentprofessionalisering Kindergeneeskunde (2019)	4.00
- Periodieke Conferentie Kindergeneeskunde (2019)	4.00
- Hemodynamisch beleid bij kinderen met ernstige brandwonden (2019)	2.00
- Hempurificatie bij kritisch zieke patiënten (2020)	6.00
- Kindergeneeskundige zorg in de tweede golf (2020)	1.00
- Duin en Kruidberg Voedingsavond (2020)	2.00
- 7th Netherlands International Sepsis Symposium (2020)	6.00
- Scholing Acute Zorgregio Oost: CO intoxicatie	2.00
- Docentprofessionalisering Kindergeneeskunde (2021)	1.00
- Periodieke Conferentie Kindergeneeskunde (2021)	3.00
- NVK Webinar MIS-C en COVID-19 (2021)	2.00
- Refereeravond Covid-19 (NIV Intensive Care) (2021)	2.00
- Valkhof Lecture (2022)	1.00
- Docentprofessionalisering Kindergeneeskunde (2022)	1.00
- Docentprofessionalisering Kindergeneeskunde (2022)	1.00
- De kinder IC: klaar voor de toekomst! Jubileumsymposium 25 jaar intensive care kinderen in het Radboudumc Amalia (2022)	6.00
- Periodieke Conferentie Kindergeneeskunde (2023)	4.00

Training activities	**Hours**
Conferences	
- Society Critical Care Medicine annual congress 2014 (2013)	18.00
- Intensivistendagen 2015 (2015)	6.00
- Meeting Point 2015 Using Physiology to Personalize Mechanical Ventilation (2015)	12.00
- 28th Annual congress European Society of Intensive Care Medicine (2015)	27.00
- NVIC Intensivistendagen (poster presentation) (2016)	11.00
- 8th World Congress of the World Federation of Pediatric Intensive and Critical Care Societies (poster presentation) (2016)	23.00
- Conferentie IQ healthcare: Onderweg naar betaalbare persoonsgerichte zorg (2016)	5.00
- International Symposium on Intensive Care and Emergy Medicine (2017)	24.00
- Congres Nederlandse Vereniging voor Kindergeneeskunde (2017)	17.00
- Conference European Society Pediatric Neonatal Intensive Care / EAPS / ESPR (oral presentation) (2018)	24.00
- Conference Society Critical Care Medicine (2019)	22.00
- Conference European Society Intensive Care Medicine (2020)	18.00
- Congres Nederlandse Vereniging voor Kindergeneeskunde (2020)	6.00
- European Society Pediatric Neonatal Intensive Care - conference (poster presentation) (2021)	27.00
- NVIC Intensivistendagen (2022)	12.00
- Conference Society Critical Care Medicine (2022)	9.00
- Conference European Society Pediatric Neonatal Intensive Care / EAPS (2022)	24.00
- Conference Society Critical Care Medicine (2023)	24.00
- Docentprofessionalisering Kindergeneeskunde (2023)	1.00

Training activities	**Hours**
Other	
- Wetenschappelijke vergadering SICK (2014)	3.00
- Researchbespreking Amalia (oral presentation) (2017)	1.00
- Wetenschappelijke vergadering Sectie Intensive Care Kinderen (2018)	1.00
- Wetenschappelijke vergadering Sectie Intensive Care Kinderen (2019)	3.00
- Researchbespreking Amalia (oral presentation) (2021)	1.00
- Wetenschappelijke vergadering Sectie Intensive Care Kinderen (oral presentation) (2021)	2.00
- Wetenschappelijke vergadering Sectie Intensive Care Kinderen (2022)	1.00
- Wetenschappelijke vergadering Sectie Intensive Care Kinderen (2022)	2.00
- Adverse Events and Mortality in the PICU (podcast SCCM) (2023)	2.00
Teaching activities	
Lecturing	
- Kinderartsenweek: Kindermishandeling; The golden (blue, red, pink, black) hour (2021)	2.00
- Onderwijs arts assistenten kindergeneeskunde 2013-2023	40.00
Supervision of internships / other	
- Training PICE registratie module (instructor) (2013)	4.00
- Acute Pediatric Burn Course (instructor) (2018)	7.00
- Generic instructor course SHK (2019)	12.00
- Acute Pediatric Burn Course (instructor) (2019)	6.00
- Acute Pediatric Burn Course (instructor) (2020)	7.00
- Advanced Paediatric Life Support (instructor) (2021)	18.00
- Advanced Paediatric Life Support (instructor) (2021)	18.00
- Recertification course APLS (instructor) (2021)	6.00
- Kindertrauma en Brandwonden (instructor) (2021)	2.00
- Advanced Paediatric Life Support (instructor) (2021)	18.00
- Recertification course APLS (instructor) (2021)	6.00
- Advanced Paediatric Life Support (instructor) (2022)	18.00
- Advanced Paediatric Life Support (instructor) (2022)	18.00
- Instructeursdag Stichting Spoedeisende Hulp bij Kinderen 2022 (2022)	5.00
- Advanced Paediatric Life Suport (instructor) (2023)	18.00
Total	**781.00**

APPENDIX

CURRICULUM VITAE

Curriculum Vitae

Carin Verlaat werd geboren op 17 juli 1964 te Oosterhout (NB). Na het behalen van haar athenaeum-diploma aan het Dominicuscollege te Nijmegen in 1976, begon ze aan de studie geneeskunde aan de Katholieke Universiteit (tegenwoordig Radbouduniversiteit) te Nijmegen. Als student was ze aktief in het (sub-)factulteitsbestuur en liep ze een co-schap sociale geneeskunde in Nicaragua.

Ze begon als ANIOS op de neonatale intensive care unit te Nijmegen, waarna ze van 1991-1996 de opleiding kindergeneeskunde deed in het Sint Elisabethziekenhuis te Tilburg en het Wilhelmina Kinderziekenhuis Utrecht (opleiders: dr. Johan Rammeloo, prof.dr. Leo Van den Brande, prof.dr. Jan Stoop). Ze werkte tijdelijk als algemeen kinderarts in het Wilhelmina Kinderziekenhuis.

In 1997 begon ze haar fellowship kinder-intensive care in het Sint Radboudziekenhuis te Nijmegen, tegenwoordig bekend als Radboudumc (supervisie: dr. Chris Neeleman). Sinds 1999 is ze als kinderarts-intensivist werkzaam op de afdeling intensive care (leiding: respectievelijk drs. Eric van Leeuwen, prof. dr. Hans van der Hoeven en prof. dr. Leo Heunks; leiding kinder-intensive care: dr. Joris Lemson). Ze is instructeur bij de Advanced Paediatric Life Support cursus van de Stichting Spoedeisende Hulp bij Kinderen.

Ze houdt zich onder andere bezig met kwaliteit en veiligheid en is sinds 2002 aktief in de stichting Pediatrische Intensive Care Evaluatie (PICE). Vanuit dit aandachtsgebied is zij gestart met dit proefschrift onder supervisie van prof. dr. Hans van der Hoeven, prof. dr. Jan Hazelzet, dr. Joris Lemson en dr. Marieke Zegers.

Carin woont in Nijmegen met haar echtgenoot Marc ten Dam. Samen hebben ze drie kinderen, Casper, Koen en Saskia.

APPENDIX

DANKWOORD

Dankwoord

Na 10 jaar is dan eindelijk mijn proefschrift klaar! Ik voelde me altijd meer dokter dan wetenschapper, maar het onderzoek heeft me veel gebracht! Zonder onderstaande personen zou het nooit gelukt zijn.

Alle **patiëntjes** van de kinder intensive care en hun ouders. Jullie zijn de drijfveer achter dit onderzoek. Dankzij jullie (geanonimiseerde) data in de landelijke PICE registratie kunnen we de zorg op de kinder intensive care verbeteren.

Beste **prof. dr. Hans van der Hoeven**. Jij gaf mij de kans om tussen mijn werkzaamheden door dit onderzoek op te pakken en door te zetten. Jouw kritische maar constructieve oordeel was altijd verfrissend. Als hoofd van de intensive care, ben je 20 jaar lang een leider geweest die, in woord en daad, veiligheid en kwaliteit van zorg uitstraalt. Je mag nu genieten van je welverdiende emeritaat. Ik voel me vereerd dat ik nog bij jou mag promoveren.

Beste **prof. dr. Jan Hazelzet**. Toen ik in 2002 gevraagd werd om in het PICE bestuur te gaan, onder jouw voorzitterschap, kon ik nog niet vermoeden dat we dit traject zouden ingaan. Je bent altijd bezig om te kijken hoe data kunnen worden ingezet voor het verbeteren van de zorg. Je legt daarbij de horizon steeds weer een beetje verder. Dank voor jouw brede visie en je begeleiding!

Beste **dr. Joris Lemson**. Ruim 10 jaar geleden vroeg je me of ik niet wat meer wetenschappelijks wilde gaan doen met de PICE data. Wat heb ik veel geleerd de afgelopen jaren. Ik ben ontzettend blij met jouw altijd stimulerende rol. Het combineren van klinische taken met onderzoek was niet altijd eenvoudig, maar je had altijd geduld als het niet zo snel liep als gepland.

Beste **dr. Marieke Zegers**. Wat was ik blij toen jij als copromotor werd aangesteld. Jouw eigen promotie onderzoek is baanbrekend geweest op dit gebied. Jouw ervaring maar vooral ook je enthousiasme hebben me enorm geholpen.

De leden van de manuscriptcommissie. **Prof. dr. Gert Westert, prof.dr. Matthijs de Hoog en dr. Joris Fuijkschot**, wil ik hartelijk danken voor het beoordelen van mijn proefschrift.

Beste **prof. Mark van den Boogaart**. In het eerste deel van mijn proefschrift kon ik terugvallen op jouw epidemiologische kennis. Toen was je misschien nog een jonge hond op onderzoeksgebied, intussen ben je zelf hoogleraar geworden, en terecht!

(Ex-) leden van de **PICE werkgroep**. Sinds 2002 mag ik deel uitmaken van deze groep en heb ik de kans gekregen om vanuit de PICE registratie dit onderzoek te doen. Ik wil een aantal 'oudgedienden' in het bijzonder noemen: **Douwe, Koos, Marcel, Job, Marc** en **Nicolette**. De huidige ploeg (**Richard, Jan Willem, Maaike, Dick, Casper** en **Jeroen**) zet jullie pionierswerk voort. Er zijn ook een paar voormalige medewerkers van PICE die ik wil noemen: **Leo Bakker**, in memoriam, die zich onder andere bezighield met de audits. **Idse Visser**, je bent van onschatbare waarde geweest voor het verzamelen van de PICE gegevens. Je bewaakte de kwaliteit ervan als een leeuw. Na 20 jaar ben je onlangs vertrokken naar een nieuwe functie, maar voor mij ben je onlosmakelijk verbonden met de PICE registratie.

Alle **hoofden van de PICUs** in Nederland (naast Joris): **Brigitte, Job, Martin, Dick, PP, Matthijs.** Dank voor het mogelijk maken van het landelijk onderzoek naar zorggerelateerde schade. Wat is het uniek dat ik in ieders keuken mocht kijken. Wat mooi dat we als kinder intensive care afdelingen zo samenwerken. Dank ook aan alle secretaressen in den lande en aan **Sandra Dijkstra** voor het faciliteren van mijn onderzoek.

Roel Geilleit en **Nina Wubben** wil ik hartelijk danken voor het opschonen en analyseren van de brei aan PICE data. Nina, je hebt me intussen ingehaald, jouw proefschrift was in 2022 al klaar....

Arthur Lemson, Jorian Leerling en **Dominiek Rutten**. Heel veel dank voor jullie onmisbare bijdrage aan dit proefschrift. Het gezamenlijk doorspitten van al die medische dossiers, het herberekenen van de mortaliteitsrisicos en het zoeken van 'triggers'. Ik heb goede herinneringen aan gezamenlijke reisjes het hele land door, inclusief wachten in de vrieskou op een klein stationnetje op weg naar Groningen, het opsnorren van medische dossiers in een stoffig archief en het leren kraken van alle typen electronische patientendossiers. Jullie zijn talentvolle jonge mensen, op weg naar een mooie toekomst!

Dr. Cynthia van der Starre. Het was fijn om van jou de kneepjes van de triggertool methode te leren. Je bent een inspirerende collega. Veiligheid in de zorg is onderdeel van jouw DNA. **Prof. dr. Dick Tibboel**. Dank voor jouw steun voor dit project en je gastvrijheid om de pilotstudie samen met Rotterdam te doen.

Prof. dr. Bert Bos en **prof.dr. Johan Legemaate**. Hartelijk dank dat jullie in de vertrouwenscommissie deelnamen voor het landelijke dossieronderzoek. Gelukkig hebben we deze commissie niet hoeven te gebruiken...

Bestuur en medewerkers van de **Stichting Spoedeisende Hulp bij Kinderen**, hartelijk dank voor jullie financiële ondersteuning van de drukkosten van dit proefschrift. Dankzij jullie zijn de kennis en vaardigheden bij de opvang van vitaal bedreigde kinderen enorm toegenomen. Het is altijd leerzaam maar ook beregezellig om de APLS cursus te geven.

(Ex-) collega's van het **Amalia kinderziekenhuis** en van de **kinder intensive care, verpleegkundigen** en andere **medewerkers**. Beste **Louis, Chris, Ruud, Anique, Anneliese, Twiggy, Ronald, Marloes, Annelies, Gerald** en **Saskia.** Ik ben jullie dankbaar voor de jarenlange fijne samenwerking, ook als er eens iets tegenzit. Het maakt dat ik, na meer dan 25 jaar, nog elke dag met plezier naar mijn werk ga. Ook de collega's van **IC research**, waaronder **Matthijs** en **Peter**, dank voor tips and tricks en jullie enthousiasme om promovendi op te leiden.

Lieve **vrienden**. Jullie zorgen voor de luchtige noot, de gezellige avond, het onverwachte bezoekje, de mooie wandeling, de leuke weekendjes, de oliebollen bij oud en nieuw. **Astrid** en **Irene**, we delen al meer dan 40 jaar lief en soms ook leed met elkaar, laten we nog heel veel jaren lekker blijven doorkletsen....

Lieve **(schoon-) familie**, Etiënne, Jan-Willem, Sandra, Caroline, Cor, Marcel, Karin, neven en nichtjes. Al jaren vragen jullie met belangstelling naar dat boekje. Misschien waren jullie ook wel een beetje bezorgd en dachten jullie ook wel eens: gaat het lukken? Nou, het is eindelijk af!

Lieve schoonpapa **Gerard**. Helaas ben jij er ook niet bij vandaag. Ik had je graag ingehuurd om met je accordeon en gezellige praatjes iedereen vrolijk te maken. Gelukkig is mijn lieve schoonmama **Truusje** erbij vandaag. Je bent een eeuwige optimist en dat inspireert iedereen om je heen.

Lieve **Ma**, jij hebt helaas niets meegemaakt van dit hele project. Maar je hebt mij wel doorzettingsvermogen doorgegeven, daar ben ik je dankbaar voor.

Lieve **Pa**. Je vroeg bij ieder bezoekje altijd weer: 'En, hoe is het nu met je onderzoek?'. En dan zei ik weer dat het langzaam ging, maar wel vooruit. Helaas mag je de afronding van dit proefschrift niet meer meemaken, maar ik denk dat je er toch op een of andere manier bij zal zijn. **Els** is aanwezig vandaag en dat maakt me blij.

Lieve kinderen. **Casper, Koen** en **Saskia**. Jullie zijn allemaal verschillend maar zo bijzonder. Volwassen intussen. Volgen jullie eigen pad. Wat ben ik er trots op om jullie moeder te zijn. Welkom ook **Millie** in onze familie.

Lieve **Marc**, dank voor jouw steun, je gezonde verstand en je liefde. Je bent de liefste en knapste (...) man die ik me kan wensen, ook als je een paar grijze haren krijgt. Als jij nou eens wat rustiger aan gaat doen en ik ook, gaan we er veel weekendjes erop uit met ons busje.

Radboudumc
university medical center
IN DEI NOMINE FELICITER
Radboud University