Factors Associated With Mortality in Low-Risk Pediatric Critical Care Patients in The Netherlands*

Carin W. Verlaat, MD[1]; Idse H. Visser, MSc, MA[2]; Nina Wubben[3]; Jan A. Hazelzet, MD, PhD[4]; Joris Lemson, MD, PhD[1]; Dick van Waardenburg, MD, PhD[5]; Douwe van der Heide, RN[6]; Nicolette A. van Dam, MD[7]; Nicolaas J. Jansen, MD, PhD[8]; Mark van Heerde, MD, PhD[9]; Cynthia van der Starre, MD, PhD[10]; Roelie van Asperen, MD, PhD[8]; Martin Kneyber, MD, PhD, FCCM[11]; Job B. van Woensel, MD, PhD[12]; Mark van den Boogaard, RN, PhD[1]; Johannes van der Hoeven, MD, PhD[1] on behalf of the SKIC (Dutch Collaborative PICU Research Network)

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. (*Pediatr Crit Care Med* 2017; 18:e155–e161)

Key Words: child; chronic complex condition(s); mortality; outcome assessment (healthcare); pediatric intensive care

***See also p. 390.**

[1]Department of Intensive Care, Radboud University Medical Center, Nijmegen, The Netherlands.

[2]Dutch Pediatric Intensive Care Evaluation, Department of Pediatric Intensive Care, Erasmus Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands.

[3]Radboud University, Nijmegen, The Netherlands.

[4]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.

[5]Department of Pediatric Intensive Care, Academic Hospital Maastricht, The Netherlands

[6]Faculty Board Member, PICE Registry, the Netherlands.

[7]Department of Pediatric Intensive Care, Leiden University Medical Center, Leiden, The Netherlands.

[8]Department of Pediatric Intensive Care, University Medical Center Utrecht, Utrecht, The Netherlands.

[9]Department of Pediatric Intensive Care, VU University Medical Center, Amsterdam, The Netherlands.

[10]Department of Neonatal and Pediatric Intensive Care, Erasmus University Medical Center–Sophia Children's Hospital, Rotterdam, the Netherlands.

[11]Department of Pediatric Intensive Care, University Medical Center Groningen, Groningen, The Netherlands.

[12]Department of Pediatric Intensive Care, Academic Medical Center, Amsterdam, The Netherlands. This work was performed at the Department of Pediatric Intensive Care, Radboud University Medical Center, Nijmegen, The Netherlands.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: carin.verlaat@radboudumc.nl

DOI: 10.1097/PCC.0000000000001086

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 PM and 8:00 AM 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 Pa_{O_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 a 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.

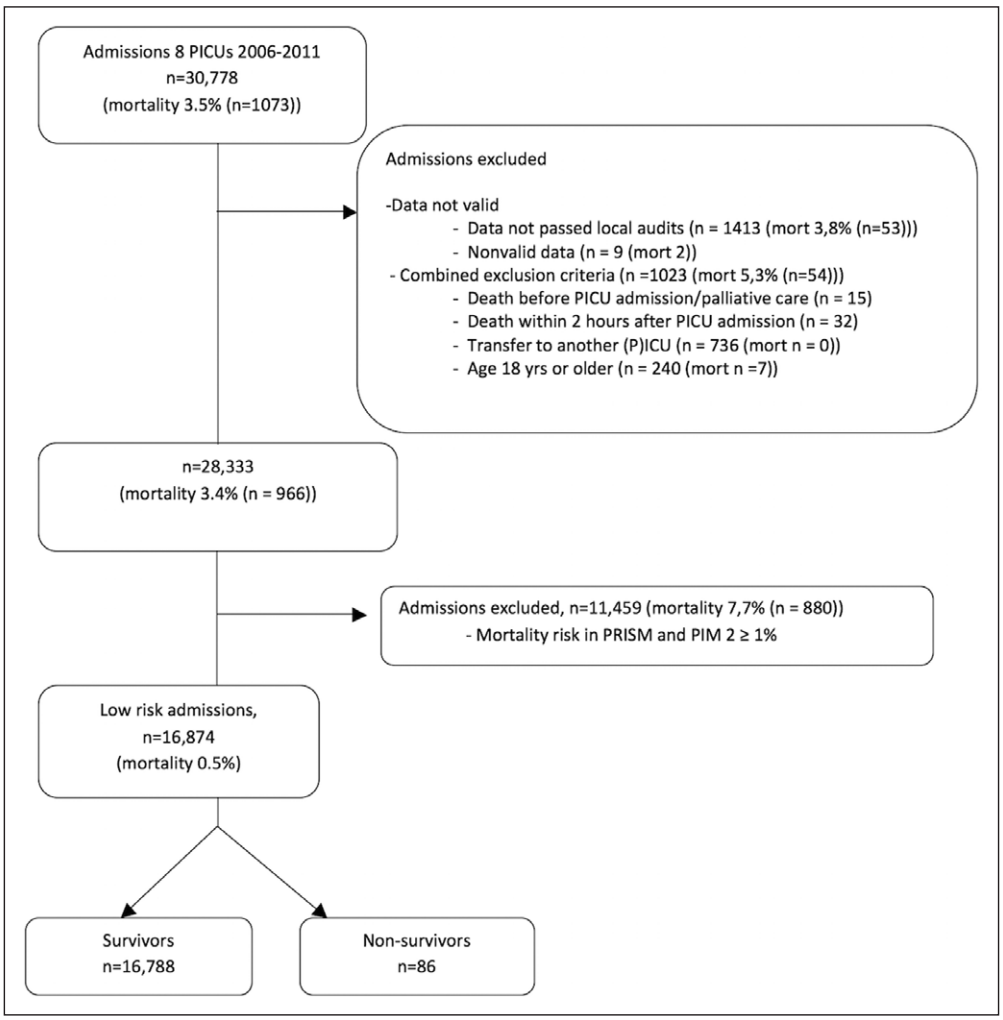

Figure 1. Flowchart of the study population. PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality.

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

TABLE 1. Demographic Characteristics of Low-Risk Admissions

Characteristic	*n* = 16,874
Male	9,676 (57.5)
Age (yr), 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)
No. of days mechanically ventilated, median (IQR)	2.0 (1–3)
Length of stay (d), 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.

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]).

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 subject in adult and PICUs 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

TABLE 2. Differences Between Low-Risk Survivors and Nonsurvivors

Characteristic	Survivors ($n = 16,788$)	Nonsurvivors ($n = 86$)	Differences
Demographic characteristics			
Male	9,628 (57.5)	48 (55.8)	0.747
Age (yr), median (IQR[a])	4 (0–11)	3.5 (0–13)	0.993
Diagnosis characteristics			
Diagnosis subgroups			
Trauma	801 (4.8)	0 (0.0)	0.036
Circulatory	475 (2.8)	16 (18.6)	0.000
Neurologic	794 (4.7)	4 (4.7)	1.000
Respiratory	1,579 (9.4)	8 (9.3)	1.000
Renal	64 (0.4)	0 (0.0)	1.000
Gastrointestinal	300 (1.8)	2 (2.3)	0.668
Postprocedure diagnosis	9,020 (53.7)	24 (27.9)	< 0.001
Miscellaneous	2,732 (16.3)	12 (14.0)	0.561
Complex chronic condition	9,879 (58.8)	66 (76.7)	0.001
Admission characteristics			
Pediatric Risk of Mortality recalibrated mortality risk, median (IQR) (%)	0.62 (0.46–0.94)	0.76 (0.59–1.21)	0.001
Pediatric Index of Mortality 2 recalibrated mortality risk, median (IQR) (%)	0.83 (0.40–1.35)	1.50 (0.94–5.13)	< 0.001
Unplanned admission	6,458 (38.5)	64 (74.4)	< 0.001
Admission outside office hours	4,512 (26.9)	32 (37.2)	0.031
Readmission within 48 hr	161 (1.0)	3 (3.5)	0.017
Recovery as primary reason for admission	5,969 (35.6)	8 (9.3)	< 0.001
Specialized transport upon admission	989 (5.9)	11 (12.8)	0.007
Admission between April and September	8,304 (49.5)	53 (61.6)	0.024
Mechanically ventilated	5,600 (34.9)	74 (88.1)	< 0.001
Physiologic parameters[b]			
Minimal systolic blood pressure (mm Hg),mean (SD)	87 (17)	84 (20)	0.278
Abnormal heart rate	8,098 (52.7)	37 (47.4)	0.356
Maximal respiratory rate, median (IQR)	32 (25–44)	42 (32–55)	< 0.001
Minimal Glasgow Coma Score, median (IQR)	15 (15–15)	15 (15–15)	0.007
Maximal glucose level (mmol/L), median (IQR)	7.5 (6.2–9.2)	8.3 (6.8–11.2)	0.017
Outcome characteristics			
No. of days mechanically ventilated, median (IQR)	2 (1–3)	9 (3–22.25)	< 0.001
Length of stay, median (IQR)	3 (2–5)	11 (5–32)	< 0.001

IQR = interquartile range,
[a]Interquartile range (25th to 75th percentile).
[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.

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

TABLE 3. Variables Associated With Nonsurvival in the Low-Risk Group

Factor	OR	95% CI
Age (yr)	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 hr	2.24	0.69–7.30

OR = odds ratio.

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.

ACKNOWLEDGMENTS

Members of SKIC (Dutch collaborative PICU Research Network) were as follows: Dick van Waardenburg, MD, PhD (Department of Pediatric Intensive Care, Academic Hospital Maastricht, Maastricht, The Netherlands); Douwe van der Heide, RN (Faculty Board Member, PICE Registry, The Netherlands); Nicolette A. van Dam, MD (Department of Pediatric Intensive Care, Leiden University Medical Center, Leiden, The Netherlands); Nicolaas J. Jansen, MD, PhD (Department of Pediatric Intensive Care, University Medical Center Utrecht, Utrecht, The Netherlands); Mark van Heerde, MD, PhD (Department of Pediatric Intensive Care, VU University Medical Center, Amsterdam, The Netherlands); Cynthia van der Starre, MD, PhD (Department of Neonatal and Pediatric Intensive Care, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands); Roelie van Asperen, MD, PhD (Department of Pediatric Intensive Care, University Medical Center Utrecht, Utrecht, The Netherlands); Martin Kneyber, MD, PhD, FCCM (Department of Pediatric Intensive Care, University Medical Center Groningen, Groningen, The Netherlands); and Job B. van Woensel, MD, PhD (Department of Pediatric Intensive Care, Academic Medical Center, Amsterdam, The Netherlands).

REFERENCES

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

16. 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
17. 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
18. Peeters B, Jansen NJ, Bollen CW, et al: Off-hours admission and mortality in two pediatric intensive care units without 24-h in-house senior staff attendance. *Intensive Care Med* 2010; 36:1923–1927
19. Peduzzi P, Concato J, Kemper E, et al: A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; 49:1373–1379
20. Burns KH, Casey PH, Lyle RE, et al: Increasing prevalence of medically complex children in US hospitals. *Pediatrics* 2010; 126:638–646
21. Pollack MM, Holubkov R, Funai T, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: A new paradigm for outcomes assessment. *Crit Care Med* 2015; 43:1699–1709
22. Kuijsten HA, Brinkman S, Meynaar IA, et al: Hospital mortality is associated with ICU admission time. *Intensive Care Med* 2010; 36:1765–1771
23. Wunsch H, Mapstone J, Brady T, et al: Hospital mortality associated with day and time of admission to intensive care units. *Intensive Care Med* 2004; 30:895–901
24. Hixson ED, Davis S, Morris S, et al: Do weekends or evenings matter in a pediatric intensive care unit? *Pediatr Crit Care Med* 2005; 6:523–530
25. Numa A, Williams G, Awad J, et al: After-hours admissions are not associated with increased risk-adjusted mortality in pediatric intensive care. *Intensive Care Med* 2008; 34:148–151
26. McShane P, Draper ES, McKinney PA, et al; Paediatric Intensive Care Audit Network (PICANet): Effects of out-of-hours and winter admissions and number of patients per unit on mortality in pediatric intensive care. *J Pediatr* 2013; 163:1039–1044.e5
27. Arias Y, Taylor DS, Marcin JP: Association between evening admissions and higher mortality rates in the pediatric intensive care unit. *Pediatrics* 2004; 113:e530–e534
28. Edwards JD, Lucas AR, Stone PW, et al: Frequency, risk factors, and outcomes of early unplanned readmissions to PICUs. *Crit Care Med* 2013; 41:2773–2783
29. Harrison DA, Lertsithichai P, Brady AR, et al: Winter excess mortality in intensive care in the UK: An analysis of outcome adjusted for patient case mix and unit workload. *Intensive Care Med* 2004; 30:1900–1907
30. Reinikainen M, Uusaro A, Ruokonen E, et al: Excess mortality in winter in Finnish intensive care. *Acta Anaesthesiol Scand* 2006; 50:706–711
31. Boyle J, Zeitz K, Hoffman R, et al: Probability of severe adverse events as a function of hospital occupancy. *IEEE J Biomed Health Inform* 2014; 18:15–20
32. Naghib S, van der Starre C, Gischler SJ, et al: Mortality in very long-stay pediatric intensive care unit patients and incidence of withdrawal of treatment. *Intensive Care Med* 2010; 36:131–136
33. Larsen GY, Donaldson AE, Parker HB, et al: Preventable harm occurring to critically ill children. *Pediatr Crit Care Med* 2007; 8:331–336
34. 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
35. Epstein D, Reibel M, Unger JB, et al: The effect of neighborhood and individual characteristics on pediatric critical illness. *J Community Health* 2014; 39:753–759
36. Forster AJ, Kyeremanteng K, Hooper J, et al: The impact of adverse events in the intensive care unit on hospital mortality and length of stay. *BMC Health Serv Res* 2008; 8:259
37. 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
38. 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
39. 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