Identifying the critically ill pediatric oncology patient

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Content

1

General introduction

Cancer is a leading cause of death by disease among children.[1] In the Netherlands, approximately 600 children are diagnosed with cancer annually, of which 45% suffer from a hemato-oncological malignancy, 30-35% from a solid tumor and 20-25% from a neuro-oncological tumor.[2] Over the past decades, significant medical progress has been achieved by intensified and new treatment protocols, advancements in molecular diagnostics, and vigilant supportive care. As a result, the overall 5-year survival for pediatric oncology patients has greatly improved from 50% in the late 1970s to over 80% nowadays.[3-7] Unfortunately, the intensification of treatment has also led to life threatening side-effects, that may require admission to the pediatric intensive care unit (PICU).

Critically ill pediatric oncology patients

Pediatric oncology patients who require PICU admission represent a unique and heterogeneous population, with specific critical care needs considering their underlying malignancies and treatment-related toxicities. Recent studies show that between 4 - 28% of pediatric oncology patients require at least one PICU admission during their treatment.[8-12] Approximately two-thirds of PICU admissions are for planned post-operative care[13], mostly following tumor resections in neuro-oncological or solid tumor patients. The other one-third comprises unplanned admissions, with respiratory failure, sepsis and neurological deterioration as main PICU admission reasons.[14-16] Patients with hematological malignancies are particularly at risk for unplanned PICU transfer, as the prolonged myelosuppression caused by their treatment increases the susceptibility to severe infections, which may rapidly result in hemodynamic and respiratory failure.[14 17] Moreover, an allogeneic hematological stem cell transplantation (HSCT) carries a substantial risk of severe complications, including sepsis and graft-versus-host-disease (GVHD), for which a patient may require PICU transfer.[8 18 19]

Critically ill pediatric oncology patients have a worse prognosis compared to their non-cancer peers. Specifically, they are three times less likely to survive in-hospital cardiopulmonary resuscitation (CPR) compared to general pediatric patients.[20] Moreover, the mortality rate at the PICU for pediatric oncology patients is considerably high; ranging from 7 to 39%, depending on patient categories, and far exceeds that of general pediatric patients (2%).[8 14 15 21-23] Particularly unplanned PICU admissions have a high PICU mortality, that has remained high over the past decades.[24]

Multi-organ dysfunction (MOD), which is characterized by the concomitant failure of two or more organ systems, is a major cause of death in children admitted to the PICU.[25 26] Pediatric oncology patients are particularly susceptible to organ dysfunction due to cancer-related organ infiltration and impaired immune function, as well as the treatment

that may lead to systemic toxic side-effects and prolonged immunodeficiency. Studies have shown that for both general pediatric and pediatric oncology patients, the risk of dying in the PICU increases with each additional failing organ system.[15 26 27] As such, the need for organ support, including mechanical ventilation, inotropic medication, or continuous renal replacement therapy, is significantly associated with higher PICU mortality.[8 14 24 28-31] Other factors that increase the risk of PICU mortality among pediatric oncology patients include a hemato-oncological diagnosis, specifically acute myeloid leukemia (AML), a history of HSCT, a fungal infection, severe GVHD, and sepsis.[14 19 30 32-36]

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Risk factors for developing multi-organ dysfunction

Previous studies on pediatric oncology patients admitted to the PICU have primarily focused on mortality. As a result, risk factors for PICU mortality are widely recognized, with MOD being the dominant factor. Nevertheless, the factors that contribute to the emergence of MOD in pediatric oncology patients remain unidentified, and the research described in this thesis aims to bridge this knowledge gap. Organ dysfunction may be modifiable through timely identification and prompt intervention.[37-40] Accordingly, it is essential to instantly and accurately identify patients who develop organ dysfunction, allowing for early intervention to prevent progression to irreversible organ failure and death. Insight into factors at PICU admission that increase the risk of MOD during PICU admission may facilitate enhanced monitoring and timely interventions, ultimately aimed at improving patient outcomes.

Timely recognition of clinical deterioration

Patients who require to be transferred from the ward to the PICU often already have some extent of (multi) organ dysfunction at PICU admission. Consequently, to initiate early interventions for organ dysfunction, it is important to consider the period preceding the PICU admission. In adult oncology patients, studies showed that transfer to the intensive care unit shortly after onset of critical illness at the inpatient was associated with better short- and long-term outcomes.[37 38 41 42] In pediatric HSCT patients, it was shown that a delay before PICU admission was a risk factor for PICU mortality.[18] Similarly, it has been suggested that early interventions and early PICU transfer in clinically deteriorating pediatric oncology patients may be important steps in reducing morbidity and mortality.[11 15 39 43] Failure to recognize early signs of deterioration may indicate a missed opportunity for intervention and may lead to adverse events, including cardiac arrest and death.[44] However, recognizing a deteriorating patient may be challenging in daily practice, as early signs are often overlooked.[44]

Pediatric Early Warning System Scores

Various pediatric early warning scores have been developed to aid in the timely recognition of clinically deteriorating patients. These scores are often implemented in a system, with both response and implementation components (e.g., a rapid response team), a so-called pediatric early warning system (PEWS). Within a PEWS score, numerals are assigned to reflect the deviance from the normal range of vital signs or clinical observations, and then all numerals are combined into a numerical score. The PEWS score is typically assessed at regular intervals and accompanied by an escalation of care algorithm, which indicates the action to be taken by health care professionals at each score. These actions may include an altered frequency of monitoring, or evaluation by a physician to ensure more appropriate treatment or management.

Early warning scores for deteriorating patients were first described in the late 1990s in adult patients, but it was not until 2005 that the first pediatric early warning score was published, based on experiences from adult care.[45] This was followed by a national review of child mortality in the United Kingdom, which described that one in five and potentially one in two children who died unexpectedly in a hospital had identifiable features that, if recognized and addressed earlier, could have prevented their death.[44] To reduce these missed opportunities, hospitals were advised to implement a standard monitoring system with an embedded PEWS score. This recommendation was a key driver in the worldwide adoption of PEWS.[46]

Since then, various PEWS scores have been developed, often tailored to individual settings based on previously published PEWS scores or expert opinions.[47 48] The choice of PEWS score is important, as there is considerable variation in the predictive performance between different PEWS scores.[49] The BedsidePEWS is one of the most extensively evaluated PEWS, and the only one that has been assessed in a randomized controlled trial in hospitalized children.[50 51] This trial showed a reduction in late admission to the PICU, but no reduction in all-cause mortality.[51] When implemented as a care package that includes rapid response teams and education, a PEWS may reduce the incidence of cardiorespiratory arrests.[47 48 52] Moreover, PEWS implementation may improve multidisciplinary teamwork, communication, and situational awareness.[48]

PEWS in hospitalized pediatric oncology patients

Despite the widespread implementation of PEWS, also in pediatric oncology patients, only some studies have validated a PEWS in this patient population.[21 53-58] These studies are primarily small retrospective cohort studies[55-57] or used the maximum PEWS score in the 24 hours prior to PICU admission, combined with a matched case-control design, which could lead to a biased estimation of the predictive performance of a PEWS score.[21 53] Consequently, there are still gaps in knowledge in this area. First, there is a lack of

systematic evaluation of the predictive performance or impact of PEWS scores in pediatric oncology patients. Second, no study has yet prospectively assessed the predictive performance of a PEWS score, incorporating all PEWS scores of all patients potentially at risk for clinical deterioration during a hospital admission. This thesis aims to address both knowledge gaps.

A research agenda to further advance pediatric onco-critical care

In addition to the knowledge gaps in identifying deteriorating patients, the area of pediatric onco-critical care faces further challenges. Overarching, the optimal standard of critical care delivery to pediatric oncology patients has yet to be rigorously studied. Given the significantly high mortality rates in the PICU, more studies are needed to put forward a standard of care for the management of critically ill pediatric oncology patients and to improve their outcomes. However, there is currently no research agenda in place to guide such studies, making it difficult to prioritize research efforts. A prioritizing framework is necessary to facilitate harmonization of studies, advance our ability to appropriately use life-saving therapies, and define new therapeutic approaches that may increase the survival and quality of life in critically ill pediatric oncology patients.[59]

Objectives and outline of this thesis

The research presented in this thesis ultimately aims to improve outcomes in pediatric oncology patients who require critical care. The focus will be on the timely recognition of a clinically deteriorating patient.

In **Chapter 2**, we describe a modified Delphi process among European pediatric intensivists and oncologists to identify and prioritize areas of research in critically ill pediatric oncology patients. We hereby present the top 5 research priorities for the next decade. In **Chapter 3**, we systematically appraise the existing evidence on predictive performance and impact of pediatric early warning systems in hospitalized pediatric oncology patients. **Chapter 4** outlines the study design of the first prospective observational cohort study that aims to validate a modified BedsidePEWS in hospitalized pediatric oncology patients. This study design enables the inclusion of all PEWS scores during the full trajectory of a hospital ward admission, in all patients potentially at risk for deterioration. **Chapter 5** presents the results of this validation study. In **Chapter 6**, we describe risk factors for new or progressive multi-organ failure in pediatric oncology patients admitted to the PICU. **Chapter 7** provides an overview of the key points of this thesis, alongside future perspectives proposing directions for further research.

References

1. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014;64(2):83-103. doi: 10.3322/caac.21219
2. Dutch Childhood Oncology Group. Annual report 2019. Available at: https://www.skion.nl/workspace/uploads/Skion-Jaarverslag-2019.pdf
3. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 2004;364(9451):2097-105. doi: 10.1016/S0140-6736(04)17550-8
4. Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene* 2004;23(38):6429-44. doi: 10.1038/sj.onc.1207717
5. Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, et al. Cancer in children and adolescents in Europe: developments over 20 years and future challenges. *Eur J Cancer* 2006;42(13):2183-90. doi: 10.1016/j.ejca.2006.06.006
6. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol* 2014;15(1):35-47. doi: 10.1016/S1470-2045(13)70548-5
7. Erdmann F, Frederiksen LE, Bonaventure A, et al. Childhood cancer: Survival, treatment modalities, late effects and improvements over time. *Cancer Epidemiol* 2021;71(Pt B):101733. doi: 10.1016/j.canep.2020.101733
8. Faraci M, Bagnasco F, Giardino S, et al. Intensive care unit admission in children with malignant or nonmalignant disease: incidence, outcome, and prognostic factors: a single-center experience. *J Pediatr Hematol Oncol* 2014;36(7):e403-9. doi: 10.1097/MPH.0000000000000048
9. Zaidman I, Mohamad H, Shalom L, et al. Survival of pediatric patients requiring admission in the intensive care unit post hematopoietic stem cell transplantation: Prognostic factors associated with mortality. *Pediatric blood & cancer* 2022;69(3):e29549. doi: 10.1002/pbc.29549
10. Ranta S, Broman LM, Abrahamsson J, et al. ICU Admission in Children With Acute Lymphoblastic Leukemia in Sweden: Prevalence, Outcome, and Risk Factors. *Ped Crit Care Med* 2021;22(12):1050-60. doi: 10.1097/PCC.0000000000002787
11. Pillon M, Amigoni A, Contin A, et al. Risk Factors and Outcomes Related to Pediatric Intensive Care Unit Admission after Hematopoietic Stem Cell Transplantation: A Single-Center Experience. *Biol Blood Marrow Transplant* 2017;23(8):1335-41. doi: 10.1016/j.bbmt.2017.04.016
12. Caballero M, Faura A, Margarit A, et al. Outcomes for paediatric acute leukaemia patients admitted to the paediatric intensive care unit. *Eur J Pediatr* 2022;181(3):1037-45. doi: 10.1007/s00431-021-04292-9
13. Dalton HJ, Slonim AD, Pollack MM. MultiCenter outcome of pediatric oncology patients requiring intensive care. *Pediatr Hematol Oncol* 2003;20(8):643-9. doi: 10.1080/08880010390243095
14. Zinter MS, DuBois SG, Spicer A, et al. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014;40(10):1536-44. doi: 10.1007/s00134-014-3389-2
15. Barking CTMM, Masjosthusmann K, Rellensmann G, et al. Treatment of Children With Cancer and/or Hematopoietic Stem Cell Transplantation in the Intensive Care Unit: Experience at a Large European Pediatric Cancer Center. *J Pediatr Hematol Oncol* 2020;42(7):e583-e88. doi: 10.1097/MPH.0000000000001718
16. Demaret P, Pettersen G, Hubert P, et al. The critically-ill pediatric hemato-oncology patient: epidemiology, management, and strategy of transfer to the pediatric intensive care unit. *Ann Intensive Care* 2012;2(1):14. doi: 10.1186/2110-5820-2-14
17. Loeffen EAH, Knops RRG, Boerhof J, et al. Treatment-related mortality in children with cancer: Prevalence and risk factors. *Eur J Cancer* 2019;121:113-22. doi: 10.1016/j.ejca.2019.08.008
18. Cheuk DK, Ha SY, Lee SL, et al. Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplant. *Hematol Oncol* 2004;22(1):1-9. doi: 10.1002/hon.724
19. Zinter MS, Logan BR, Fretham C, et al. Comprehensive Prognostication in Critically Ill Pediatric Hematopoietic Cell Transplant Patients: Results from Merging the Center for International

Blood and Marrow Transplant Research (CIBMTR) and Virtual Pediatric Systems (VPS) Registries. *Biol Blood Marrow Transplant* 2020;26(2):333-42. doi: 10.1016/j.bbmt.2019.09.027

20. López-Herce J, Del Castillo J, Matamoros M, et al. Factors associated with mortality in pediatric in-hospital cardiac arrest: a prospective multicenter multinational observational study. *Intensive Care Med* 2013;39(2):309-18. doi: 10.1007/s00134-012-2709-7
21. Agulnik A, Forbes PW, Stenquist N, et al. Validation of a Pediatric Early Warning Score in Hospitalized Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients. *Pediatr Crit Care Med* 2016;17(4):e146-53. doi: 10.1097/pcc.0000000000000662
22. Maude SL, Fitzgerald JC, Fisher BT, et al. Outcome of pediatric acute myeloid leukemia patients receiving intensive care in the United States. *Pediatr Crit Care Med* 2014;15(2):112-20. doi: 10.1097/PCC.0000000000000042
23. Heneghan JA, Pollack MM. Morbidity: Changing the Outcome Paradigm for Pediatric Critical Care. *Pediatr Clin North Am* 2017;64(5):1147-65. doi: 10.1016/j.pcl.2017.06.011
24. Wösten-van Asperen RM, van Gestel JPJ, van Grotel M, 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. doi: 10.1016/j.critrevonc.2019.07.014
25. Watson RS, Crow SS, Hartman ME, et al. Epidemiology and Outcomes of Pediatric Multiple Organ Dysfunction Syndrome. *Pediatr Crit Care Med* 2017;18(3_suppl Suppl 1):S4-S16. doi: 10.1097/PCC.0000000000001047
26. Leclerc F, Leteurtre S, Duhamel A, et al. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. *Am J Respir Crit Care Med* 2005;171(4):348-53. doi: 10.1164/rccm.200405-630OC
27. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med* 2013;41(7):1761-73. doi: 10.1097/CCM.0b013e31828a2bbd
28. Heying R, Schneider DT, Korholz D, et al. Efficacy and outcome of intensive care in pediatric oncologic patients. *Crit Care Med* 2001;29(12):2276-80. doi: 10.1097/00003246-200112000-00007
29. Haase R, Mathony U, Lieser U, et al. [Oncology patients in a pediatric intensive care unit--a 7-year experience]. *Klin Padiatr* 2003;215(4):234-40. doi: 10.1055/s-2003-41399
30. Dursun O, Hazar V, Karasu GT, et al. Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit. *J Pediatr Hematol Oncol* 2009;31(7):481-4. doi: 10.1097/MPH.0b013e3181a330ef
31. Raymakers-Janssen P, Lilien MR, Tibboel D, et al. Epidemiology and Outcome of Critically Ill Pediatric Cancer and Hematopoietic Stem Cell Transplant Patients Requiring Continuous Renal Replacement Therapy: A Retrospective Nationwide Cohort Study. *Crit Care Med* 2019;47(11):e893-e901. doi: 10.1097/CCM.0000000000003973
32. Vogiatzi L, Ilia S, Sideri G, et al. Invasive candidiasis in pediatric intensive care in Greece: a nationwide study. *Intensive Care Med* 2013;39(12):2188-95. doi: 10.1007/s00134-013-3057-y
33. Pound CM, Johnston DL, Armstrong R, et al. The morbidity and mortality of pediatric oncology patients presenting to the intensive care unit with septic shock. *Pediatr Blood Cancer* 2008;51(5):584-8. doi: 10.1002/pbc.21670
34. Bonig H, Schneider DT, Sprock I, et al. 'Sepsis' and multi-organ failure: predictors of poor outcome after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 2000;25 Suppl 2:S32-4. doi: 10.1038/sj.bmt.1702350
35. Owens C, Mannion D, O'Marcaigh A, et al. Indications for admission, treatment and improved outcome of paediatric haematology/oncology patients admitted to a tertiary paediatric ICU. *Ir J Med Sci* 2011;180(1):85-9. doi: 10.1007/s11845-010-0634-8
36. Ben Abraham R, Toren A, Ono N, et al. Predictors of outcome in the pediatric intensive care units of children with malignancies. *J Pediatr Hematol Oncol* 2002;24(1):23-6. doi: 10.1097/00043426-200201000-00007
37. Lee DS, Suh GY, Ryu JA, et al. Effect of Early Intervention on Long-Term Outcomes of Critically Ill Cancer Patients Admitted to ICUs. *Crit Care Med* 2015;43(7):1439-48. doi: 10.1097/CCM.0000000000000989
38. Song JU, Suh GY, Park HY, et al. Early intervention on the outcomes in critically ill cancer patients

admitted to intensive care units. *Intensive Care Med* 2012;38(9):1505-13. doi: 10.1007/s00134-012-2594-0

39. Fausser JL, Tavenard A, Rialland F, et al. Should We Pay Attention to the Delay Before Admission to a Pediatric Intensive Care Unit for Children With Cancer? Impact on 1-Month Mortality. A Report From the French Children's Oncology Study Group, GOCE. *J Pediatr Hematol Oncol* 2017;39(5):e244-e48. doi: 10.1097/MPH.0000000000000816
40. Inwald DP, Tasker RC, Peters MJ, et al. Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit. *Arch Dis Child* 2009;94(5):348-53. doi: 10.1136/adc.2008.153064
41. van der Zee EN, Benoit DD, Hazenbroek M, et al. Outcome of cancer patients considered for intensive care unit admission in two university hospitals in the Netherlands: the danger of delayed ICU admissions and off-hour triage decisions. *Ann Intensive Care* 2021;11(1):125. doi: 10.1186/s13613-021-00898-2
42. Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en reanimation onco-hematologique study. *J Clin Oncol* 2013;31(22):2810-8. doi: 10.1200/JCO.2012.47.2365
43. Piastra M, Fognani G, Franceschi A, et al. Pediatric Intensive Care Unit admission criteria for haemato-oncological patients: a basis for clinical guidelines implementation. *Pediatr Rep* 2011;3(2):e13. doi: 10.4081/pr.2011.e13
44. Pearson GA, Ward-Platt M, Harnden A, et al. Why children die: avoidable factors associated with child deaths. *Arch Dis Child* 2011;96(10):927-31. doi: 10.1136/adc.2009.177071
45. Monaghan A. Detecting and managing deterioration in children. *Paediatric nursing* 2005;17(1):32-5. doi: 10.7748/paed2005.02.17.1.32.c964
46. Chapman SM, Maconochie IK. Early warning scores in paediatrics: an overview. *Arch Dis Child* 2019;104 doi: 10.1136/archdischild-2018-314807
47. Chapman SM, Wray J, Oulton K, et al. Systematic review of paediatric track and trigger systems for hospitalised children. *Resuscitation* 2016;109:87-109. doi: 10.1016/j.resuscitation.2016.07.230
48. Lambert V, Matthews A, MacDonell R, et al. Paediatric early warning systems for detecting and responding to clinical deterioration in children: a systematic review. *BMJ open* 2017;7(3):e014497. doi: 10.1136/bmjopen-2016-014497
49. Chapman SM, Wray J, Oulton K, et al. 'The Score Matters': wide variations in predictive performance of 18 paediatric track and trigger systems. *Arch Dis Child* 2017;102(6):487-95. doi: 10.1136/archdischild-2016-311088
50. Parshuram CS, Bayliss A, Reimer J, et al. Implementing the Bedside Paediatric Early Warning System in a community hospital: A prospective observational study. *Paediatrics & Child Health* 2011;16(3):e18-e22. doi: 10.1093/pch/16.3.e18
51. Parshuram CS, Dryden-Palmer K, Farrell C, et al. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. *Jama* 2018;319(10):1002-12. doi: 10.1001/jama.2018.0948
52. Trubey R, Huang C, Lugg-Widger FV, et al. Validity and effectiveness of paediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalised children: a systematic review. *BMJ Open* 2019;9(5):e022105. doi: 10.1136/bmjopen-2018-022105
53. Agulnik A, Méndez Aceituno A, Mora Robles LN, et al. Validation of a pediatric early warning system for hospitalized pediatric oncology patients in a resource-limited setting. *Cancer* 2017;123(24):4903-13. doi: 10.1002/cncr.30951
54. Agulnik A, Nadkarni A, Mora Robles LN, et al. Pediatric Early Warning Systems aid in triage to intermediate versus intensive care for pediatric oncology patients in resource-limited hospitals. *Pediatr Blood Cancer* 2018;65(8):e27076. doi: 10.1002/pbc.27076
55. Cater DT, Tori AJ, Moser EAS, et al. Modification and Assessment of the Bedside Pediatric Early Warning Score in the Pediatric Allogeneic Hematopoietic Cell Transplant Population. *Pediatr Crit Care Med* 2018;19(5):483-88. doi: 10.1097/pcc.0000000000001521
56. Dean NP, Fenix JB, Spaeder M, et al. Evaluation of a Pediatric Early Warning Score Across

Different Subspecialty Patients. *Pediatr Crit Care Med* 2017;18(7):655-60. doi: 10.1097/pcc.0000000000001176

57. Fuijkschot J, Vernhout B, Lemson J, et al. Validation of a Paediatric Early Warning Score: first results and implications of usage. *Eur J Pediatr* 2015;174(1):15-21. doi: 10.1007/s00431-014-2357-8
58. Gawronski O, Ciofi Degli Atti ML, Di Ciommo V, et al. Accuracy of Bedside Paediatric Early Warning System (BedsidePEWS) in a Pediatric Stem Cell Transplant Unit. *J Pediatr Oncol Nurs* 2016;33(4):249-56. doi: 10.1177/1043454215600154
59. Azoulay E, Schellongowski P, Darmon M, et al. The Intensive Care Medicine research agenda on critically ill oncology and hematology patients. *Intensive Care Med* 2017;43(9):1366-82. doi: 10.1007/s00134-017-4884-z

2

Research priorities in pediatric onco-critical care: an international Delphi consensus study

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Introduction

Up to 40% of pediatric oncology patients require admission to the pediatric intensive care unit (PICU) during the course of their disease, with acute respiratory failure and sepsis as the main admission reasons.[1-3] Further intensification, as well as development of novel strategies including immunotherapy, may potentially increase the need for intensive care admission and support. A recent review on current standard of care for critical care delivery to adult oncology patients and major recent advances in this field, has shown the importance of new clinical perspectives such as time-limitation in PICU treatment trials, the value of using surveillance strategies for earlier admission to ICU, and the value of starting chemotherapy in high risk patients while providing advanced supportive care on the ICU.[4] However, scarce data are available on the optimal standard of critical care delivered to the pediatric oncology patient group, nor are systematic multi-center outcome data available.

Recognizing the need for international collaboration on this issue, the European Society for Paediatric and Neonatal Intensive Care (ESPNIC) established, in collaboration with pediatric oncologists, the PICU Oncology Kids in Europe Research group (POKER), with the aim to design international optimal common harmonized care, in order to ultimately improve outcomes in pediatric oncology patients admitted to the PICU. As a first step, this study aims to provide a research agenda for the next decade.

Methods

We conducted a three-round modified Delphi consensus process from October 2018 to April 2019 among pediatric intensivists and pediatric oncologists in Europe, aiming to identify and prioritize areas of research on pediatric oncology patients admitted to the PICU.[5] The Delphi process is well recognized as a method to develop consensus among experts or stakeholders.[6] Key aspects of the Delphi process include the ability to provide anonymity, iteration (i.e., multiple stages), controlled acquisition of feedback, and analytic aggregation of responses. A particular benefit of this approach is that it can sample the opinion of a group of experts without being overwhelmed by unduly influential persons and that it can be controlled by appropriate feedback and modification to drive findings toward a group consensus.[6]

Selection of participants

Expert participants were pediatric intensivists and pediatric oncologists in Europe. As commonly adopted in Delphi studies, we employed a purposive strategy. In our recruitment method, organizations and members of the POKER group invited respondents to participate in the study to increase the likelihood that invited individuals

will respond and to allow for a selection of individuals who are considered to have the most relevant expertise.[6 7] An invitation to participate was distributed among pediatric intensivists through ESPNIC. Pediatric oncologists were invited by disseminating the survey through established relationships of the members of the POKER group or through existing collaborations within the framework of international pediatric oncology society working groups. Due to this 'snowballing' approach to recruitment, we were unable to identify a denominator of total people who received the survey, in order to calculate a response rate.

Consensus methodology

The Delphi process consisted of three rounds (Figure 1). Agreement regarding participant selection, consensus threshold, question structure and survey format, as well as analysis processes, was reached according to proposed quality indicators for a Delphi study.[5] Ten preliminary research topics were defined based on review of the literature and expert opinion of the members of the POKER group. An anonymous questionnaire was distributed online via SurveyMonkey (see Supplement – Questionnaire Delphi round 1). Demographic information for participants was collected in round 1. In the same round, participants were asked to rank each proposed research domain on a four-point scale as (1) very important, urgent priority; (2) moderately important, intermediate priority; (3) somewhat important, low priority; or (4) not important, not a priority. In addition, the survey allowed participants to add research domains that they believed were of particular importance to the field. Consensus on priority was determined based on percentage of respondents who ranked the item as "very important" or "moderately important". The standard of consensus was a more than 80% frequency of priority selection.[8] Items were excluded if more than 80% of the respondents provided a negative result ("not important, not a priority"). In addition, in round 2 of the modified Delphi procedure, the topics were ranked based on the mean of each item's ranking by POKER members (see Supplement – Questionnaire Delphi round 2).

Ethical approval

The study was approved by the Institutional Ethical Review Board of the University Medical Center Utrecht (METC reference number 19-223/C). Consent of participants was implied when they responded to the survey via the survey portal and checked a box on the survey instrument indicating consent to participate.

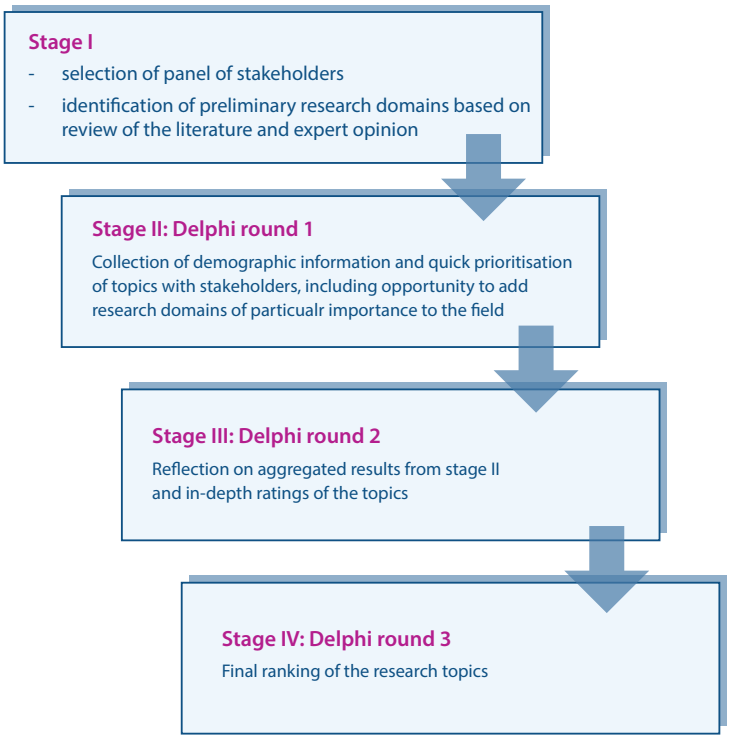

Figure 1. Stages of the proposed Research Priority Setting process

Results

One hundred seventy-two (59% intensivists and 34% oncologists) and 157 physicians (53% intensivists and 38% oncologists) from 13 different countries participated in rounds 1 and 2, respectively (Supplementary Table S1). The results of the first round of rating the preliminary research topics are displayed in Supplementary Table S2. The possibility to suggest additional research topics in round 1 resulted in a total of 15 topics for round 2. The additional research topics and the questionnaire for Delphi round 2 can be found in the Supplement. Round 2 yielded consensus on high priority topics (Supplementary Table S3). In round 3, a final top five was established (see Table 1).

The following research topics were identified as top priorities: (1) Optimal timing of the use of life-sustaining therapies; (2) Development of specific oncological early warning scores; (3) Role of non-invasive ventilation in acute respiratory insufficiency; (4) End-of-life care and ethical issues; and (5) Sepsis.

Table 1. Consensus research priorities in pediatric onco-critical care.

Top 5 research priorities ranked in order	Suggestions for future studies	Suggested future endpoints
Determine the optimal timing of the use of life-sustaining therapies (mechanical ventilation, use of vasopressors, CRRT, and ECMO) and identify agreements and controversies between the different clinicians (intensivists, oncologists) and parents at the PICU on the futility or non-futility of these therapies in critically ill pediatric cancer patients.	Prospective, observational studies in order to stratify life-sustaining therapies by days of PICU treatment and outcome in order to determine the optimal time for a time-limited "PICU-Trial" of therapy.	PICU mortality Degree of organ dysfunction (e.g., measured by daily Pediatric Logistic Organ Dysfunction (PELOD) score) Length of PICU stay
Development of specific early warning scores to timely recognize critically ill pediatric cancer patients on the non-ICU ward requiring intensive care support	Prospective, multi-center study to develop specific oncological pediatric early warning score consisting of the clinical signs most predictive for critical deterioration requiring PICU admission and treatment.	Transfer to PICU Use of life-sustaining therapies such as mechanical ventilation, vasopressors, renal replacement therapy, and ECMO PICU- and hospital mortality Length of PICU stay
Determine the role of non-invasive ventilation in acute respiratory insufficiency in critically ill pediatric cancer patients	A multicenter randomized controlled trial of the (early) use of non-invasive ventilation or high-flow nasal cannula versus standard care in acute hypoxemic respiratory failure.	Need for invasive mechanical ventilation PICU mortality
Exploring end-of-life care and ethical issues for children with cancer at the PICU, i.e., change to end-of-life care, ethical considerations regarding decision making, communication with patients and parents, 'suffering' in pediatric cancer patients and their families on PICU, young people decision making in oncology	Qualitative studies to examine the quality of collaborative decision making from the perspective of physicians, nurses, and families.	Qualitative measurement of parents, oncologist and PICU physicians' feelings and acceptance of the discussion and eventual decision (e.g., moral distress in PICU teams); Formalization of time limited trials of therapy and innovative and experimental therapy use in PICU End-of-life choices in PICU (parent and child)
Sepsis in critically ill pediatric cancer patients at the PICU: management, outcomes, and costs	Multicenter, clinical trials with prospectively collected data in order to delineate those factors that predispose pediatric cancer patients to sepsis, and to identify factors that stratify their outcome.	PICU admission PICU- and hospital mortality Factors predicting sepsis development Requirement of life sustaining therapies (MV, vasopressors, CRRT) Length of PICU stay

CRRT continuous renal replacement therapy; *ECMO* extracorporeal membrane oxygenation; *MV* mechanical ventilation; *PICU* pediatric intensive care unit.

Discussion

Rationale, current knowledge and existing areas of uncertainty of the research priorities in pediatric onco-critical care are discussed below.

Research topic 1: Optimal timing of the use of life-sustaining therapies

There may be "golden hours or days" of PICU treatment associated with improved outcomes for the management of critically ill cancer patients at the PICU. During this period, aggressive, life-sustaining therapy is indicated to try to improve the child's outcome. However, once this time has passed, the continuation or introduction of life-sustaining therapies may not be beneficial. Observational studies are needed to determine the optimal time for such a time-limited "PICU-Trial" of therapy, i.e., stratification of interventions by days of PICU treatment and outcome. ICU-trials, the so-called time-limited trials of therapy, have been one of the major changes in treating critically ill adult cancer patients.[9] The ICU-trial consists of unlimited, aggressive ICU management with full resuscitation status for a specific limited period. One large French/Belgian study, that assessed time-limited trials in critically ill patients with cancer, showed that patients with hematologic malignancies or less severe illness benefited most from longer duration of trials (at least 2 weeks of intensive care); whereas for patients with poor-prognostic solid tumors, shorter trial durations of 1 to 4 days were enough to provide a comparable survival to unlimited aggressive care.[10] In addition, it was demonstrated that ICU-admission shortly after the start of the critical care illness was associated with better survival rates.[10] Whether time-limited trials would also improve PICU survival and reduce costs associated with PICU stay in pediatric oncology patients needs to be determined.

Research topic 2: Development of early warning scores

The Bedside Pediatric Early Warning System (BedsidePEWS) has shown promise. A large multi-center prospective study in hospitalized children showed that implementation of this score compared with usual care did significantly decrease clinical deterioration events, yet did not significantly decrease all-cause mortality.[11 12] Agulnik and co-workers demonstrated in a retrospective, single-center study that the Children's Hospital Early Warning Score was highly correlated with the need for unplanned PICU transfer in hospitalized oncology and hematopoietic stem cell transplant patients.[13] However, this score has not been validated in a large prospective study. Hence, international efforts to improve early detection of clinical deterioration at the inpatient ward are warranted.

Research topic 3: The role of non-invasive ventilation (NIV) in cancer patients

The role of non-invasive ventilation (NIV) in cancer patients has received a lot of interest in adult oncology patients. The use of invasive mechanical ventilation is a key factor for poor

prognosis in immunocompromised adult patients, and so avoiding invasive mechanical ventilation has become a major treatment goal. However, one multicenter randomized clinical trial showed no survival benefit of NIV compared with standard oxygen therapy.[14] NIV was either neutral or even harmful in oncology patients.[14 15] Studies in pediatric oncology patients on the role of NIV are scarce. A recent prospective study in which 42 children with impaired immunity and acute respiratory failure were randomly assigned to early PICU admission for continuous positive airways pressure (CPAP) or to standard care showed that early admission and CPAP did not provide benefit, and was in fact associated with higher intubation and 90-day mortality.[16] However, this study was significantly underpowered and larger, multi-center studies are needed to show whether (early) NIV is beneficial for these patients.

Research topic 4: Exploring end-of-life care and ethical issues for children with cancer at the PICU

Recent technological advances have led to the development of treatments that can sustain life in circumstances where this was previously impossible. But some treatments may neither restore health nor confer overall benefits to the child. Some of the most challenging and emotionally complex decisions arise in relation to withholding, withdrawing or otherwise limiting treatment that has the potential to sustain life, yet imposes burdens or has serious impact on quality of life.[17] Clear and effective communication between children with cancer, their families and healthcare providers is essential for informed decision-making, particularly when those children require intensive care.[18] Pediatric intensivists are often responsible for discussing end-of-life options with families, including the option of limitation or withdrawal of life support (LWLS). Keele and coworkers showed that a primary diagnosis of cancer was independently associated with greater likelihood of LWLS discussions.[19] This may reflect the more terminal nature of some cancer diagnoses, especially when complicated by serious illness requiring PICU admission. Few studies describe the communication challenges faced by both pediatric oncologists and intensivists or how the pediatric oncologist-intensivist relationship impacts communication and initiation of goals of care discussions.[20 21] Limited adult data demonstrate significant cultural differences in how oncologists and intensivists approach critically ill oncologic patients, however there can be significant challenges dealing with expectations that may be unrealistic due to these issues.[22 23] Qualitative studies to examine the quality of collaborative decision making from the perspective of physicians, nurses, and families are needed.

Research topic 5: Sepsis

Sepsis is one of the main indications for PICU admission in the pediatric cancer population.[1 2] Data from retrospective cohorts have demonstrated increased morbidity and mortality in

subsets of septic patients with malignancy.[24 25] Pediatric oncology patients are particular at risk for organ dysfunction, likely due to their primary disease, which can lead to organ infiltration and immunodeficiency, and their treatment regimes, with therapy-related systemic toxicity. Considering the high sepsis-related mortality among pediatric oncology patients, there may be several explanations, including the impaired immune function, in addition to the presence of multiple active medical problems that may lead to the delayed recognition and initiation of sepsis therapies.[26] As sepsis is one of the main PICU admission reasons, research in this field must extend beyond retrospective, epidemiologic studies and expand into multicenter trials with prospectively collected data in order to delineate those factors that predispose pediatric oncology patients to sepsis, and to identify factors that stratify their outcome.

Conclusion

The results of this Delphi study indicate a broad consensus among providers from different subspecialties across Europe on the research priorities for pediatric onco-critical care. In the context of limited published evidence, these results create a framework for the top research priorities in the field of pediatric oncology patients at the PICU for the next 10 years.

References

1. Tamburro RF, Barfield RC, Shaffer ML, et al. Changes in outcomes (1996-2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. *Pediatr Crit Care Med* 2008;9(3):270-7. doi: 10.1097/PCC.0b013e31816c7260
2. Hallahan AR, Shaw PJ, Rowell G, et al. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. *Crit Care Med* 2000;28(11):3718-21. doi: 10.1097/00003246-200011000-00030
3. Rosenman MB, Vik T, Hui SL, et al. Hospital resource utilization in childhood cancer. *J Pediatr Hematol Oncol* 2005;27(6):295-300. doi: 10.1097/01.mph.0000168724.19025.a4
4. Azoulay E, Schellongowski P, Darmon M, et al. The Intensive Care Medicine research agenda on critically ill oncology and hematology patients. *Intensive Care Med* 2017;43(9):1366-82. doi: 10.1007/s00134-017-4884-z
5. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol* 2014;67(4):401-9. doi: 10.1016/j.jclinepi.2013.12.002
6. Hsu CC, Sandford, B.A. . The Delphi Technique: Making Sense of Consensus. *Pract Assess Res Eval* 2007;12(10) doi: 10.7275/pdz9-th90
7. Hoekstra D, Mutsch M, Kien C, et al. Identifying and prioritising systematic review topics with public health stakeholders: A protocol for a modified Delphi study in Switzerland to inform future research agendas. *BMJ Open* 2017;7(8):e015500. doi: 10.1136/bmjopen-2016-015500
8. Vernon W. The Delphi Technique: A Review. *Int J Ther Rehabil* 2009;16:69-76. doi: 10.12968/ijtr.2009.16.2.38892
9. Shrime MG, Ferket BS, Scott DJ, et al. Time-Limited Trials of Intensive Care for Critically Ill Patients With Cancer: How Long Is Long Enough? *JAMA Oncol* 2016;2(1):76-83. doi: 10.1001/*JAMA*oncol.2015.3336
10. Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en reanimation onco-hematologique study. *J Clin Oncol* 2013;31(22):2810-8. doi: 10.1200/JCO.2012.47.2365
11. Parshuram CS, Dryden-Palmer K, Farrell C, et al. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. *JAMA* 2018;319(10):1002-12. doi: 10.1001/*JAMA*.2018.0948
12. Parshuram CS, Duncan HP, Joffe AR, et al. Multicentre validation of the bedside paediatric early warning system score: a severity of illness score to detect evolving critical illness in hospitalised children. *Crit Care* 2011;15(4):R184. doi: 10.1186/cc10337
13. Agulnik A, Forbes PW, Stenquist N, et al. Validation of a Pediatric Early Warning Score in Hospitalized Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients. *Pediatr Crit Care Med* 2016;17(4):e146-53. doi: 10.1097/pcc.0000000000000662
14. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2015;314(16):1711-9. doi: 10.1001/*JAMA*.2015.12402
15. Frat JP, Ragot S, Girault C, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *Lancet Respir Med* 2016;4(8):646-52. doi: 10.1016/S2213-2600(16)30093-5
16. Peters MJ, Agbeko R, Davis P, et al. Randomized Study of Early Continuous Positive Airways Pressure in Acute Respiratory Failure in Children With Impaired Immunity (SCARF) ISRCTN82853500. *Pediatr Crit Care Med* 2018;19(10):939-48. doi: 10.1097/PCC.0000000000001683
17. Larcher V, Craig F, Bhogal K, et al. Making decisions to limit treatment in life-limiting and life-threatening conditions in children: a framework for practice. *Arch Dis Child* 2015;100 Suppl 2:s3-23. doi: 10.1136/

archdischild-2014-306666
18. Davidson JE, Powers K, Hedayat KM, et al. Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force 2004-2005. *Crit Care Med* 2007;35(2):605-22. doi: 10.1097/01.CCM.0000254067.14607.EB
19. Keele L, Meert KL, Berg RA, et al. Limiting and Withdrawing Life Support in the PICU: For Whom Are These Options Discussed? *Pediatr Crit Care Med* 2016;17(2):110-20. doi: 10.1097/PCC.0000000000000614
20. Davies B, Sehring SA, Partridge JC, et al. Barriers to palliative care for children: perceptions of pediatric health care providers. *Pediatrics* 2008;121(2):282-8. doi: 10.1542/peds.2006-3153
21. Durall A, Zurakowski D, Wolfe J. Barriers to conducting advance care discussions for children with life-threatening conditions. *Pediatrics* 2012;129(4):e975-82. doi: 10.1542/peds.2011-2695
22. du Pre P, Brierley J. Challenges in managing parental expectations in paediatric care. *Br J Haematol* 2018;183(1):15-22. doi: 10.1111/bjh.15554
23. Youngner SJ, Allen M, Montenegro H, et al. Resolving problems at the intensive care unit/oncology unit interface. *Perspect Biol Med* 1988;31(2):299-308. doi: 10.1353/pbm.1988.0060
24. Fiser RT, West NK, Bush AJ, et al. Outcome of severe sepsis in pediatric oncology patients. *Pediatr Crit Care Med* 2005;6(5):531-6. doi: 10.1097/01.pcc.0000165560.90814.59
25. Zinter MS, DuBois SG, Spicer A, et al. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014;40(10):1536-44. doi: 10.1007/s00134-014-3389-2
26. Lindell RB, Gertz SJ, Rowan CM, et al. High Levels of Morbidity and Mortality Among Pediatric Hematopoietic Cell Transplant Recipients With Severe Sepsis: Insights From the Sepsis PRevalence, OUtcomes, and Therapies International Point Prevalence Study. *Pediatr Crit Care Med* 2017;18(12):1114-25. doi: 10.1097/PCC.0000000000001338

Supplement – Tables

Supplementary Table S1. Responder characteristics in the first and second Delphi survey rounds.

Characteristics	Round 1 (n = 172)	Round 2 (n = 157)
Position in organization (n; %)		
Pediatric intensivist	93 (54.1)	77 (49.0)
Pediatric anesthesiologist	9 (5.2)	6 (3.8)
Pediatric oncologist	59 (34.3)	60 (38.2)
Other	10 (5.8)	14 (8.9)
Unknown	1 (0.6)	0
Country (n; %)		
Belgium	7 (4.1)	8 (5.1)
Denmark	10 (5.8)	9 (5.8)
France	48 (27.9)	41 (26.3)
Germany	46 (26.7)	35 (22.4)
Italy	0	5 (3.2)
Norway	1 (0.6)	1 (0.6)
Spain	0	1 (0.6)
Sweden	0	1 (0.6)
Switzerland	2 (1.2)	2 (1.2)
The Netherlands	31 (18.0)	32 (20.5)
United Kingdom	23 (13.4)	19 (12.2)
Other	2 (1.2)	2 (1.3)
Unknown	2 (1.2)	1 (0.6)
Type of PICU		
Medical	24 (14.0)	6 (3.8)
Medical/surgical	138 (80.2)	98 (62.4)
Unknown	10 (5.8)	53 (33.8)
Number of PICU beds		
0-5	8 (4.7)	1 (0.6)
6-10	47 (27.3)	18 (11.5)
11-15	56 (32.6)	32 (20.4)
15-20	37 (21.5)	45 (28.7)
>20	18 (10.5)	8 (5.1)
Unknown	4 (2.3)	53 (33.8)
Number cancer patients admitted to PICU/ year		
0-10	31 (18.0)	4 (2.5)
10-25	66 (38.4)	31 (19.7)
25-50	35 (20.3)	33 (21.0)
50-100	24 (14.0)	4 (2.5)
>100	11 (6.4)	32 (20.4)
Unknown	3 (1.7)	53 (33.8)

Supplementary Table S1. Responder characteristics in the first and second Delphi survey rounds - *continued*.

Characteristics	Round 1 (n = 172)	Round 2 (n = 157)
New oncological cases/year		
0-100	62 (36.0)	21 (13.4)
100-200	40 (23.2)	26 (16.7)
200-300	10 (5.8)	8 (5.1)
300-400	6 (3.5)	9 (5.7)
> 500	29 (16.9)	35 (22.3)
Unknown	8 (4.7)	58 (36.9)
Allogeneic SCT		
Yes	122 (70.9)	94 (59.9)
No	49 (28.5)	10 (6.4)
Unknown	1 (0.6)	53 (33.8)
CRRT		
Yes	157 (91.3)	103 (65.6)
No	9 (5.2)	0
Unknown	4 (2.3)	54 (34.4)
ECMO		
Yes	71 (41.3)	64 (40.8)
No	73 (42.4)	40 (25.4)
Unknown	2 (1.2)	53 (33.8)

PICU pediatric intensive care unit*; SCT* stem cell transplantation*; CRRT* continuous renal replacement therapy*; ECMO* extracorporeal membrane oxygenation.

Supplementary Table S2. Results of Delphi round 1.

Research topic	% 1 or 2a
1. Optimal timing of life-sustaining therapies (PICU trial)	94.7
2. Sepsis	91.2
3. The role of NIV in acute respiratory insufficiency	89.4
4. Anti-infective strategies	88.3
5. Development of early warning scores	84.7
6. End-of-life care	83.6
7. Impact of PICU admission on long-term outcomes	83.0
8. Nutritional aspects	82.9
9. Epidemiology	79.4
10. Transfusion policies	76.5

[a] Denotes percentage of respondents who ranked research topic as moderate or very important (scale 2 or 1, respectively). *NIV* non-invasive ventilation; *PICU* pediatric intensive care; *SD* standard deviation.

Additional research topics suggested by the participants in Delphi round 1

- Ethical issues around multiple relapse patients and parental expectations
- Electrolyte imbalance
- Ethical point of view and end of life
- Management and treatment of neutropenic enterocolitis
- Tumor lysis syndrome, CAR-T-cells
- Advantage of isolation from other patients
- Determination of an efficient and effective handover between the wards
- Measuring/intervention medical traumatic stress
- Neuropsychological follow-up
- Effect of admission to PICU in relation to event free survival for oncological disease - e.g., how much is your event free survival affected by PICU admission. Also some sort of score indicating when administration of chemotherapy is applicable to a cancer patient in the PICU
- Pulmonary hypertension, dehydration
- Specific interest post-operative neuro-oncology including hypothalamic – pituitary – prolactin (HPP) axis
- 'I think that as researchers we need to understand which oncology patients are being admitted to PICU and when (e.g., hematological vs. solid tumors; bone marrow transplantation (BMT); elective vs. emergency), before we can launch in major interventional studies. There is also a difference in the presentations seen (e.g., the child with mediastinal mass at presentation, the child who develops tumor lysis, the child with respiratory insufficiency, the child with sepsis). From my own experience in epidemiology, and my involvement in studies of transfusion practice, and non-invasive ventilation, including in oncology patients, there is a need to differentiate groups and really understand the numbers involved before progressing with future research projects in a particular proportion of PICU patients, who actually constitute a relatively small number in a given center, and may also prove difficult to recruit to randomized controlled trials.'
- Differences between views on outcomes between oncology/hematology team and PICU team in shaping the views and wishes of the families of a critically ill child with hemato-oncological conditions on PICU/pre PICU admission.
- Collegiate consensus development between the Oncologist and Intensivists about the limitations of care. Often an area of debate.
- The role of microvesicles in sepsis, thrombo-micro angiopathy, and other complications leading to PICU treatment in pediatric cancer patients
- Develop guidelines for the use of catecholamines in critically ill patients
- Cognitive outcome of septic patients
- 'Suffering' in pediatric cancer patients and their families on PICU

- Role of respiratory viral infections
- If parents' and physicians' view on treatment options are different: How to find a consensus agreement on futile or non-futile therapeutic options?
- Which patients should not be put through invasive therapies without a reasonable chance of survival.
- Oncology encephalopathy - an outcome study
- Neuroprotection
- Role of PICU for critically ill children at newly diagnosis of cancer: e.g., patients with lymphomas and mediastinal tumor or acute renal failure, hyperleukocytosis and standardization of blood exchange
- Drug related toxicity like posterior reversible encephalopathy syndrome (PRES), interstitial pneumonitis
- Pharmacokinetics, efficacy and safety of pharmacotherapy: these patients have extensive co-morbidity and polypharmacy impacting on drug concentrations, efficacy and safety.
- Associated risk factors in patients with poor outcome (death of disease, death of complication) should be identified in retrospect and analyzed in order to either improve prognosis by earlier and more aggressive treatment (e.g., earlier start of mechanical ventilation or e.g., renal replacement therapy) or by reduction of treatment toxicity, or to change to a palliative setting.
- A prospective documentation and survey of quality of life aspects in the involved families prior, during and after PICU treatment might help to improve psychosocial support aspects for patients and their families.
- Renal insufficiency in pediatric oncology patients, risk factors, prevention, treatment, optimal timing of renal replacement therapies
- Delirium in pediatric oncology patients in PICU: prevalence, prevention, treatment
- Side effects of special bone marrow transplant therapy
- Outcome study supporting strategy to optimize PICU therapy and/or to stop PICU therapy
- Pulmonary damage, nosology and treatment

Supplementary Table S3. Results of Delphi round 2.

Research topic	% 1 or 2[a]	Mean (SD)[b]
1. Optimal timing of life-sustaining therapies (PICU trial)	95.5	1.26 (0.56)
2. Development early warning scores	92.3	1.44 (0.67)
3. The role of NIV in acute respiratory insufficiency	92.3	1.52 (0.64)
4. End-of-life care and ethical issues	91.7	1.66 (0.67)
5. Sepsis	89.1	1.68 (0.68)
6. Anti-infective strategies	84.6	1.73 (0.73)
7. Impact of PICU admission on long-term outcomes	83.4	1.85 (0.70)
8. Nutritional aspects	80.1	1.99 (0.68)
9. Acute kidney injury	75.5	2.00 (0.74)
10 Pharmacokinetics and pharmacotherapy	71.1	2.02 (0.80)
11. CAR-T cell therapy	69.9	2.06 (0.90)
12. Specific oncological cerebral disorders	66.7	2.10 (0.78)
13. Electrolyte imbalances	59.6	2.25 (0.81)
14. PTSS and QOL after PICU admission	56.4	2.36 (0.72)
15. Delirium	53.2	2.39 (0.82)

[a] Denotes percentage of respondents who ranked research topic as moderate or very important (scale 2 or 1, respectively). [b] Denotes mean (±SD) of each item's ranking. *NIV* non-invasive ventilation; *PICU* pediatric intensive care unit; *PTSS* post-traumatic stress syndrome; *QOL* quality of life; *SD* standard deviation.

Supplement – Questionnaires

Questionnaire research topics Delphi round 1:

Research topic 1: Development of specific early warning scores to timely recognize critically ill pediatric oncology patients on the non-ICU ward requiring intensive care support.

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 2: Epidemiology of pediatric oncology patients admitted to the PICU: prevalence and outcome.

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 3: Determine the role of non-invasive ventilation in acute respiratory insufficiency in critically ill pediatric oncology patients.

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 4: Determine the optimal timing of the use of life-sustaining therapies (mechanical ventilation, use of vasopressors, CRRT, and ECMO) in critically ill pediatric oncology patients.

There may be "golden hours or days" of resuscitation associated with improved outcome, for the management of critically ill oncology patients at the PICU. During this time, everything should be done. Subsequently, the continuation or introduction of life-sustaining therapies in patients whose conditions are worsening may not be beneficial. Observational studies are needed to determine the optimal time for the "PICU Trial", i.e., stratification of interventions by days of PICU treatment and outcome.

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 5: Exploring end-of-life care for children with cancer at the PICU, i.e., change to end-of-life care: medical consequences, communication with patients and parents.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 6: Sepsis in critically ill pediatric oncology patients at the PICU: management, outcomes, and costs.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 7: Determine the impact of critical illness and PICU admission on long-term outcomes.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 8: Develop international standards for transfusion policies (red blood cells and/or platelets) in critically ill pediatric oncology patients.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 9: Anti-infective strategies in pediatric oncology patients at the PICU (e.g., empiric antibiotic therapy, surveillance and treatment of invasive fungal diseases).
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 10: Nutritional aspects of oncology patients supportive care in PICU: Graft-versus-host disease, severe mucositis: enteral versus parenteral nutrition.
1. very important, urgent priority
2. moderately important, intermediate priority

3. somewhat important, low priority
4. not important, not a priority

Question: Please suggest any research topics that you think should be addressed in the field of pediatric oncology patients admitted to the PICU.
[free text field]

Questionnaire research topics round 2:

Research topic 1: Development of specific early warning scores to timely recognize critically ill pediatric oncology patients on the non-ICU ward requiring intensive care support (84.62% in round 1).
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 2: Determine the role of non-invasive ventilation in acute respiratory insufficiency in critically ill pediatric oncology patients (89.35% in round 1).
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 3: Determine the optimal timing of the use of life-sustaining therapies (mechanical ventilation, use of vasopressors, CRRT. and ECMO) and identifying agreements and controversies between the different clinicians (intensivists, oncologists) and parents at the PICU on the futility or non-futility of these therapies in critically ill pediatric oncology patients (94.67% in round 1; topic expanded as a result of comments of the participants).
There may be "golden hours or days" of resuscitation associated with improved outcome, for the management of critically ill oncology patients at the PICU. During this time, everything should be done. Subsequently, the continuation or introduction of life-sustaining therapies in patients whose conditions are worsening may not be beneficial. Observational studies are needed to determine the optimal time for the "PICU Trial", i.e., stratification of interventions by days of PICU treatment and outcome.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 4: Exploring end-of-life care and ethical issues for children with cancer at the PICU, i.e., change to end-of-life care, ethical considerations regarding decision making, communication with patients and parents, 'suffering' in pediatric oncology patients and their families on PICU, young people decision making in oncology (83.53% in round 1; topic expanded as a result of comments of the participants).

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 5: Sepsis in critically ill pediatric oncology patients at the PICU: management, outcomes, and costs (91.12% in round 1).

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 6: Determine the impact of critical illness and PICU admission on long-term outcomes: event free survival, somatic long-term complications, neuropsychological follow-up (83.44% in round 1; topic expanded as a result of comments of the participants).

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 7: Anti-infective strategies in pediatric oncology patients at the PICU (e.g., empiric antibiotic therapy, surveillance and treatment of invasive fungal diseases) (88.17% in round 1).

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 8: Nutritional aspects of oncology patients supportive care in PICU: Graft-versus-host disease, neutropenic enterocolitis, severe mucositis: enteral versus parenteral nutrition (82.74% in round 1; topic expanded as a result of comments of the participants).

1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority

4. not important, not a priority

Research topic 9 (new): Electrolyte imbalances in pediatric oncology patients at the PICU (tumor lysis syndrome, disturbances of the hypothalamic–pituitary–adrenal axis after brain surgery): epidemiology, treatment, and outcome.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 10 (new): A prospective documentation and survey of post-traumatic stress and QOL aspects in the involved patients and families prior, during and after PICU treatment.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 11 (new): Acute kidney injury in pediatric oncology patients: prevalence, risk factors, prevention, treatment, and optimal timing of renal replacement therapy.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 12 (new): Delirium in pediatric oncology patients in PICU: prevalence, prevention, and treatment.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 13 (new): Specific oncological cerebral disorders (PRES, oncological encephalopathy): prevalence, treatment, and outcome.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 14 (new): CART-cell therapy: prevalence and outcome of complications

requiring PICU admission.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority

Research topic 15 (new): Pharmacokinetics, efficacy and safety of pharmacotherapy of critically ill pediatric oncology patients.
1. very important, urgent priority
2. moderately important, intermediate priority
3. somewhat important, low priority
4. not important, not a priority


3

The predictive performance and impact of pediatric early warning systems in hospitalized pediatric oncology patients: A systematic review

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Abstract

Pediatric early warning systems (PEWS) are widely used to identify clinically deteriorating patients. Hospitalized pediatric oncology patients are particularly prone to clinical deterioration. We assessed the PEWS performance to predict early clinical deterioration and the effect of PEWS implementation on patient outcomes in pediatric oncology patients. PubMed, EMBASE and CINAHL databases were systematically searched from inception up to March 2020. Quality assessment was performed using the Prediction model study Risk of Bias Assessment Tool (PROBAST) and the Cochrane Risk of Bias tool. Nine studies were included. Due to heterogeneity of study designs, outcome measures, and diversity of PEWS, it was not possible to conduct a meta-analysis. Although the studies reported high sensitivity, specificity and AUROC of PEWS detecting inpatient deterioration, overall risk of bias of the studies was high. This review highlights limited evidence on the predictive performance of PEWS for clinical deterioration and the effect of PEWS implementation.

Introduction

The prompt identification of pediatric oncology patients who clinically deteriorate forms an important component of patient safety, but may be challenging in daily clinical practice. Pediatric oncology patients are prone to clinical deterioration given their severity of illness and intensity of treatment. Despite advances in supportive care, up to one third of patients require admission to a pediatric intensive care unit (PICU) during their disease course with sepsis and respiratory failure as the main admission reasons.[1] Moreover, PICU mortality has remained high (between 25 – 35%) and pediatric oncology patients have worse outcomes after cardiopulmonary arrest compared to other pediatric patients.[2 3] Early detection of deterioration coupled to effective interventions may therefore improve outcome of these patients.

Pediatric early warning scores are used to aid in the timely detection of clinical deterioration. Various clinical observations and vital signs are combined into a numerical score, and escalation of care is triggered when the score exceeds a prespecified threshold. The scores are often embedded in a system with response and implementation components (e.g., a rapid response team), the so-called pediatric early warning systems (PEWS). Currently, a broad range of PEWS are used, with variable predictive performance for identifying clinical deterioration.[4-8] In hospitalized pediatric oncology patients, various PEWS have been implemented as well.[9-11] While several systematic reviews report the predictive performance of PEWS and their effects on patient outcome in the general pediatric population[8 12 13], systematic evaluation of the performance of PEWS in pediatric oncology patients is lacking. This review aimed to summarize and critically appraise the evidence on the performance of PEWS in pediatric oncology patients. We will focus on 1) the ability of PEWS to predict inpatient deterioration and 2) the effect of implementation of PEWS on patient outcomes.

Methods

Data sources and search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[14] (Supplementary Table S1). A systematic comprehensive search of the databases PubMed, EMBASE and CINAHL was conducted from inception up to March 2020. Search terms included keywords and medical subject headings (MeSH) terms related to pediatrics, cancer and pediatric early warning system or score. A complete description of the search is provided in Supplementary Table S2. Ultimately, the online database Scopus was used for snowballing references from our included papers. Only peer-reviewed articles were included to warrant validity and enable full text assessment.

Study eligibility criteria

All studies reporting original data on development, validation, or effects on patient outcome (impact study) of PEWS in pediatric oncology or hematological stem cell transplantation (HSCT) patients aged 0 to 21 years were eligible for inclusion. The outcomes were unplanned PICU transfer, cardiopulmonary arrest, and mortality. Studies that focused solely on the implementation process itself were excluded. In addition, studies in general pediatric patients without subgroup analysis for oncology patients, published in abstract form only or without full text in English were excluded.

Screening and selection process

After removal of duplicates, titles and abstracts of records were independently screened by two reviewers (MS and CL). Subsequently, the full texts of 37 papers were reviewed (MS and CL). Any discrepancies were resolved through discussion with a third reviewer (RW-vA).

Quality appraisal

Risk of bias and applicability concerns for validation studies were assessed by two reviewers (MS and TK) using PROBAST (Prediction model study Risk Of Bias Assessment Tool).[15] PROBAST consists of 20 signaling questions within four domains, including participant selection, predictors, outcome, and analysis. Within each domain, studies were classified as low, high, or unclear risk of bias, guided by the signaling questions (Supplementary Table S3). If all domains were at low risk of bias, a study was classified as having low risk of bias.[16] Applicability of a study was assessed for domains of participant selection, predictors and outcome and classified as low, high, or unclear concerns. If all domains were judged to have low concerns for applicability, the study was classified as having good applicability.[16] Risk of bias for impact studies was assessed by two reviewers (MS and WT) using Cochrane Risk of Bias assessment for selection bias, attrition bias, detection bias, reporting bias, confounding bias, or other bias.[17]

Data extraction and synthesis

For each included study, information on the aim, design, setting, patient population, type of PEWS score used, and outcomes was extracted. All data were narratively synthesized as it was not possible to conduct a meta-analysis due to heterogeneity of the study designs, and the diversity of PEWS.

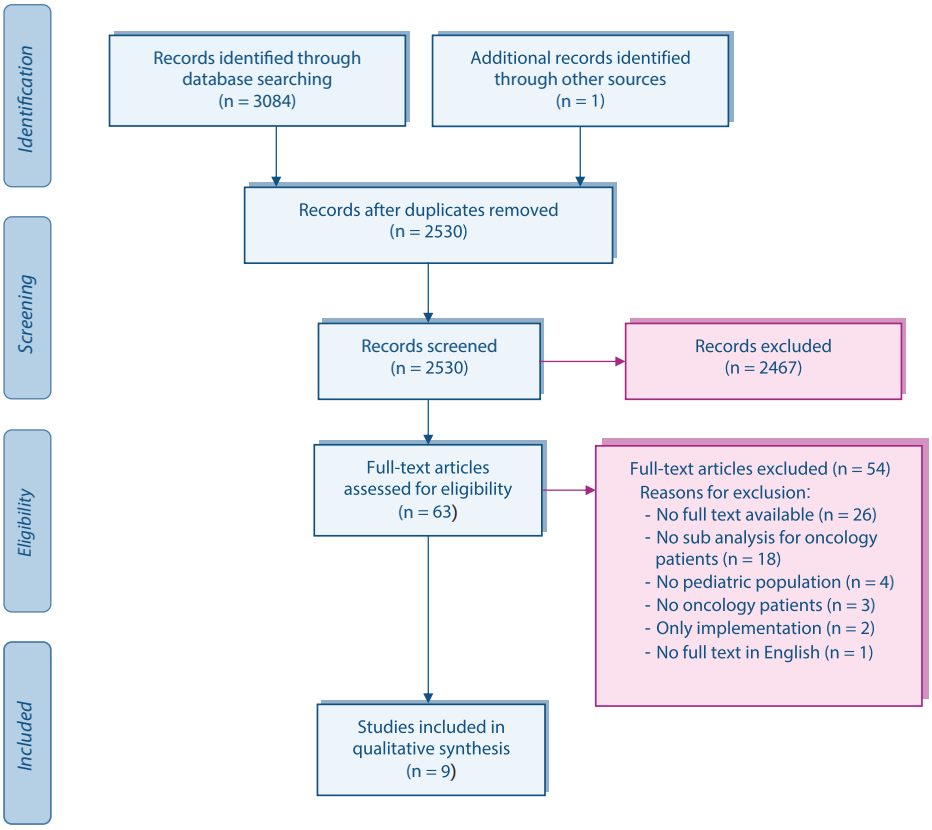

Figure 1. PRISMA flowchart of search and selection of eligible studies.

Results

Nine studies were included in our review. A PRISMA flowchart displays the search and selection process (Figure 1). Seven studies were external validation studies[9 11 18-22] and two studies were impact studies assessing the effect of implementation of a PEWS on clinical outcomes.[10 23] These nine studies together assessed seven different PEWS.[9-11 18 20-23]

Characteristics of pediatric early warning systems

Of the seven PEWS, four PEWS were slight modifications or a translation of previously published PEWS.[10 11 19 21] The different parameters of the PEWS are displayed in Supplementary Table S4. Parameters used in all PEWS include heart rate, capillary refill time, respiratory rate, respiratory effort, and oxygen therapy. Three PEWS used composite parameters, i.e., one single parameter of the score is represented by a composite score of multiple different parameters.

Results of validation studies

Performance of PEWS in predicting clinical deterioration requiring PICU admission

Six of the seven external validation studies assessed the performance of PEWS to predict unplanned PICU transfer.[9 11 18 20-22] One study validated PEWS to triage between intermediate care or intensive care unit.[19] Characteristics and the most important findings of the validation studies are shown in Table 1. For unplanned PICU transfer, the reported sensitivity and specificity ranged from 74% to over 94% and 88% to 99%, respectively. The area under the receiver operating characteristics curve (AUROC) was overall reported to be higher than 0.80, depending on cut-off value of the PEWS. In most of the studies, this AUROC was based on the maximum value of the PEWS in 24 hours prior to the outcome event.[9 11 18 20] To identify 'sick' patients, a positive predictive value of 0.73 at a BedsidePEWS cut-off score ≥ 8 was reported.[21]

Table 1. Overview of study characteristics of the external validation studies.

Paper, Country	Study design	Study inclusion criteria	Study population	System
Agulnik et al. (9), USA	Retrospective case-control	Patients aged 0-18 years admitted to oncology and HSCT ward	110 cases, 220 controls	CHEWS
Agulnik et al. (17), Guatemala	Retrospective case-control	Patients aged 0 – 18 years admitted to oncology ward	129 cases, 129 controls	EVAT
Cater et al. (19), USA	Retrospective cohort	Patients admitted to HSCT ward, aged 0-21 years old	102 patients (29 events)	Bedside PEWS
Dean et al., (11), USA	Retrospective cohort	Patients admitted to hemato-oncology/HSCT ward	5558 patient days (43 events)	Modified Brighton PEWS
Fuijkschot et al. (20), The Netherlands	Retrospective case-cohort	Patients admitted to pediatric oncology ward	1 case, 118 controls	Modified PEWS
Gawronski et al. (21), Italy	Prospective nested case-control	Patients aged 0-18 years, admitted to HSCT ward	19 cases, 29 controls	Bedside PEWS
Agulnik et al. (18), Guatemala	Retrospective chart review	Patients admitted to pediatric oncology ward	5 cases, 34 controls	EVAT

Risk of bias assessment for external validation studies was performed using PROBAST.
Major potential sources of bias: [a] unnested case-control design; [b] limited number of participants with the outcome, [c] not all relevant performance parameters were measured appropriately. The 95% confidence interval in italics was calculated manually with data provided.
HSCT hematopoietic stem cell transplantation; *CHEWS* Children's Hospital Early Warning Score; *PICU* pediatric intensive care unit; *EVAT* Escala de Valoración de Alerta Temprana; *PEWS* pediatric early warning system; *LOS* time from start hospital admission to PICU transfer; *IMCU* intermediate care unit; *NA* not assessed; *WG* ≥7% weight gain.

One study assessed the additional value of a new parameter to the PEWS.[20] In this study, an AUROC of 0.83 for BedsidePEWS cut-off 8 and 0.88 for BedsidePEWS cut-off 8 plus ≥ 7% weight gain in hematological stem cell transplantation (HSCT) patients was reported, unfortunately without 95% confidence intervals of the AUROCs and a model update was not performed. For the triage between intermediate or intensive care unit, no measures of predictive performance of the PEWS were reported.[19]

Performance of PEWS in predicting cardiopulmonary arrest or mortality

Three of the seven validation studies used the outcome measures cardiopulmonary arrest and mortality.[20-22] However, the predictive performance of the PEWS for these outcomes could not be extracted from these studies as no cardiopulmonary arrests occurred during the study period[21], no analysis for the predictive value of the PEWS for cardiopulmonary arrest was provided[22], or only the mortality rate of patients admitted to the PICU was reported.[20]

Primary outcome	Score cut-off	Most important findings			Overall Risk of Bias
		Sensitivity (%)	Specificity (%)	AUROC (95% CI)	
Unplanned PICU transfer	≥3	94	88	0,96 (0,93-0,98)	High[a, c]
	≥4	86	95	-	
Unplanned PICU transfer	≥3	93	85	0,94 (0,91-0,97)	High[a, c]
	≥4	88	97	-	
PICU admission	≥8	76	90	0,83 (0,77-0,89)	High[b, c]
	≥8 + WG	28	99	0,88 (0,82-0.94)	
Unplanned PICU transfer	≥3	88	90	0,93 (0,88-0,98)	High[b, c]
	≥4	79	96	-	
Unplanned PICU transfer	≥8	100	88	-	High[b, c]
Unplanned PICU transfer or urgent call to rapid response team	≥6	79	97	0,93 (0.88-0.97)	High[b, c]
	≥7	79	99	-	
	≥8	74	99	-	
Early PICU transfer (within 24 hours of IMCU transfer)	NA	PEWS prior to IMCU transfer was significantly higher in patients requiring subsequent PICU transfer (within 24 hours) compared to patients remaining in the IMCU (PEWS 5.6 vs. 3.1, p = 0.03)			High[b,c]

Risk of bias assessment validation studies

Overall risk of bias was high in all seven validation studies (Figure 2).[9 11 18 20-22] The complete risk of bias assessment can be found in Supplementary Table S5. The domain participant selection was at low risk of bias in three (43%) validation studies and at high risk of bias in four (57%) studies. The most common source of bias was the use of an unnested case-control design, in which cases and controls were sampled from a source population of unknown size.[9 18 19] Consequently, baseline risks and absolute outcome probabilities cannot be estimated. One study selected control patients based on PEWS score[21], this may have resulted in a biased estimate of the predictive performance of the PEWS score. The domain predictors was at low risk of bias in all studies. The domain outcome was at low risk of bias in six studies (86%) and unclear in one study (14%). Last, the domain of analysis was at high risk of bias in all studies, with several potential sources for bias. First, four (57%) studies assessed the maximum PEWS score in a 24 hour-period prior to the event.[9 11 18 20] Second, none of the studies assessed all measures of predictive performance, such as calibration and discrimination. Last, five (71%) studies had limited number of outcome events (range 1 to 43 events).[11 19-22] It was recommended for external validation studies to include at least 100 participants with the outcome, otherwise the risk for biased estimates of model performance becomes more likely.[16] All external validation studies had good applicability (Supplementary Table S5 and Figure 2).

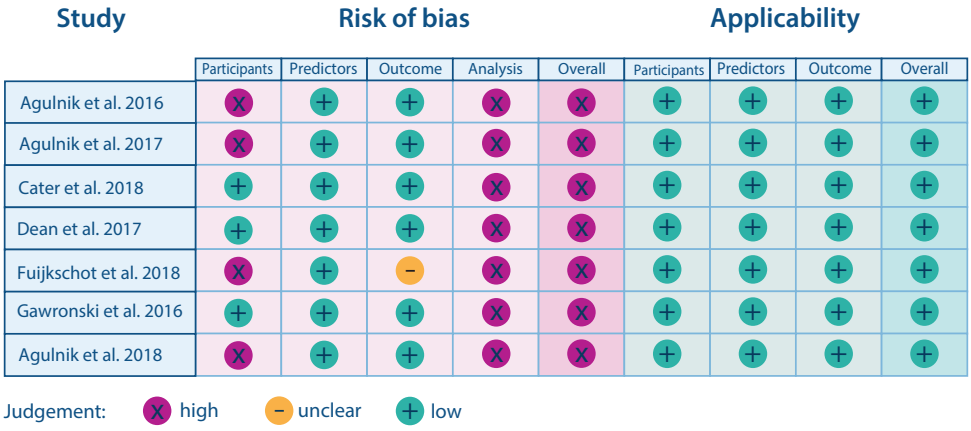

Figure 2. Risk of bias and applicability of the external validation studies as assessed by Prediction model study Risk Of Bias Assessment Tool (PROBAST).

Results of impact studies

Impact of PEWS implementation on patient outcomes

We included two impact studies.[10 23] The first study, a retrospective before-and-after study in a resource-limited setting, reported a significant reduction in unplanned PICU transfers, decreased PICU length of stay, and decreased severe sepsis or septic shock on PICU transfer after PEWS implementation (Table 2).[10] Although the authors report a decrease in organ dysfunction within 24h of PICU admission after PEWS implementation, we found contradicting evidence in their results with no statistical difference for organ dysfunction within 24h of PICU admission. There was no reduction in use of invasive mechanical ventilation or vaso-active medication, PICU length-of-stay nor mortality after PEWS implementation. The second study, a retrospective before-and-after study at the hemato/oncology ward of a tertiary hospital, reported a 3-fold increased number of days between cardiopulmonary arrests on the unit after PEWS implementation.[23] However, this study focused mainly on the implementation process itself and no patient characteristics or statistical analysis were reported. PEWS implementation had enhanced multidisciplinary team communication and aided in removing barriers that prevented timely identification and referral of clinically deteriorating children.

Risk of bias assessment impact studies

The risk of bias assessment of impact studies is displayed in Supplementary Table S6. Our main concern for the first impact study was the use of an uncontrolled before-and-after design, including only cases that experienced an unplanned PICU transfer, and the conclusion that implementation of PEWS resulted in fewer inpatient clinical deterioration events and decreased PICU utilization, without demonstration of a clear causal relationship.[10] The study by Demmel et al. was at high risk of bias for selection bias, attrition bias, and reporting bias as no patient or respondent characteristics, number of included subjects, no (handling of) missing data or details of statistical analysis were reported.[23]

Table 2. Overview of impact studies and risk of bias assessment.

Paper, Country	Study design	Study population
Agulnik et al., 2018, Guatemala	Retrospective before-and-after study	All pediatric oncology patients with unplanned PICU transfers; n = 157 unplanned PICU transfers before PEWS implementation (2013) and n = 130 unplanned PICU transfers after PEWS implementation (2015)
Demmel et al., 2010, USA	Retrospective before-and-after study	Implementation of PEWS and development of action algorithm at pediatric hemato/oncology ward at academic children's hospital. Study population not described

Quality assessment with Cochrane Risk of Bias tool, [a] risk of bias: no reporting of or adjustment for confounding factors. [b] uncontrolled retrospective before-and-after study design with only cases (unplanned PICU transfer) included. [c] sources of risk of bias: no information on included number or characteristics of study subjects, handling of missing data or statistical analyses was provided. *PICU* pediatric intensive care unit; *EVAT* Escala de Valoración de Alerta Temprana.

Discussion

This systematic review aimed to critically appraise the evidence on the ability of a PEWS to predict clinical deterioration and the impact of PEWS implementation on patient outcomes in pediatric oncology patients. We identified limited evidence for both research questions. Although the reported predictive performances of the PEWS scores to detect clinical deterioration requiring unplanned PICU transfer were good in terms of sensitivity (range 74-94%), specificity (range 88 – 99%), and AUROC (higher than 0.80), the overall risk of bias of the included studies was high. Most important risks of bias involved the use of an unnested case control design - which hampers the calculation of baseline and absolute risk, and the limited number primary outcome events which increases the risk for biased estimates of model performance. Concerning the impact of PEWS implementation, a reduction of inpatient clinical deterioration events and PICU patient-days but no effect on use of PICU resources and mortality was reported.[10] Unfortunately, the exact elements that were improved by implementation could not be pinpointed due to the uncontrolled retrospective before-and-after design, and the resource limited setting may limit generalizability.

System	Most important findings	Risk of bias a. Selection bias b. Attrition bias c. Detection bias d. Reporting bias e. Confounding bias f. Other bias
Modified EVAT	After PEWS implementation: - Fewer unplanned PICU transfers after PEWS implementation (9.3 vs 6.5 per 1,000 patient days, p = 0.003); - less PICU utilization for unplanned PICU transfer (1376 vs 1088 total PICU patient days, p < 0.0001); - decreased severe sepsis or septic shock on PICU transfer (3,9 vs 2,7 per 1000 patient days, p = 0.044). - No difference in mortality or PICU length of stay.	a. Low b. Low c. Low d. Unclear e. Unclear[a] f. High[b]
PEWS Monaghan 2005 with development of action algorithm	Three-fold increase in days between cardiopulmonary arrests on the unit, enhanced multidisciplinary communication and removal of barriers that prevented the timely referral of children who are clinically deteriorating.	a. High[c] b. High[c] c. Low d. High[c] e. Unclear[a]

The methodological concerns we identified in the external validation studies are similar to what was found in a recent review of early warning scores (EWS) in adult hospitalized patients.[24] In this latter review, high risks of bias were detected, including inadequate handling of statistical issues and lack of assessing essential aspects of model performance. The performance of a newly developed prediction model is likely to be overoptimistic, especially when applied to new patients. For validation, assessment of the two key aspects to characterize the performance, i.e., discrimination and calibration, are required.[16 25 26]

Calibration reflects the accuracy of risk estimates, relating to the agreement between the estimated and observed number of events, and is often not appropriately evaluated in validation studies of risk prediction models.[27] Likewise, none of our included studies assessed calibration. Hence, in pediatric oncology patients, information on the reliability of the risk estimates of PEWS for unplanned PICU transfer or mortality is lacking. Poorly calibrated predictive algorithms can be misleading due to over- or underestimation of the risk, which may result in incorrect clinical decision making.[27] Discrimination was

most often assessed by an AUROC using the maximum PEWS score in the 24-hour period prior to PICU admission. The assessment of a 24-hour period prior to the event, often matched with a 24-hour period in patients not experiencing the event, excludes other time intervals in which a PEWS score could be high but no event occurred, and may lead to an overestimation of the predictive ability of a PEWS. The use of the area under the precision-recall curve to verify false-alarm rates with varying sensitivity may be more appropriate to assess.

Pediatric oncology patients are at high risk for rapid deterioration given their severity of illness, toxicity of treatment and immunosuppression. Moreover, they may have specific underlying causes for PICU admission. Using a general pediatric PEWS in pediatric oncology patients may risk missing clinical deterioration or suboptimal timing of escalation of care. It is therefore important to have valid, reliable risk estimates for clinical deterioration in this vulnerable population.

Despite the widespread use of PEWS, also in pediatric oncology patients, their effect on patients' outcome has not been clearly determined. In general pediatric patients, systematic reviews underline the limited evidence for early warning system as a single intervention for reducing cardiopulmonary arrests or mortality.[8 12 13] When implemented as part of an intervention package (e.g., with a rapid response team), there is moderate evidence that PEWS implementation may reduce mortality and cardiorespiratory arrest.[12] Secondary benefits of implementation may include improvements in communication, teamwork, and situation awareness[13], also at the pediatric oncology ward.[23] Recently, research priorities to optimize the care for deteriorating pediatric patients have been suggested that are also important to the pediatric oncology population. Besides the optimization of recognition of clinical deterioration, these priorities include evaluation of decision-making and response, quality improvement of implementation, and an overarching domain of evaluation of the effect of implementation with robust, valid, and clinically meaningful outcome parameters.[28] Mortality may not be the most appropriate outcome to asses PEWS efficacy due to its relatively rare occurrence and accordingly required large study sample size.[29] Significant clinical deterioration events – e.g., the need for endotracheal intubation, fluid boluses > 60 ml/kg, vasoactive medication or cardiopulmonary resuscitation, may propose an alternative.[29 30] However, some of these events, such as cardiopulmonary resuscitation, may indicate a lost opportunity for preventative action. Minor clinical deterioration events – i.e., a composite of the use of high flow oxygen or fluid boluses – reflect early escalation of care and may also serve as clinically useful outcome measures.

Of all PEWS included in our systematic review, the BedsidePEWS had significant prior validation in hospitalized children. In addition, it is the only PEWS that has been evaluated in a randomized controlled trial, showing a reduction in significant clinical deterioration

events but no reduction in all-cause mortality.[30 31] Moreover, it was one of the best performing PEWS in a study that compared 18 different track-and-trigger systems in general pediatric patients.[32] Our review identified two studies validating the BedsidePEWS in HSCT patients, reporting AUROCs of 0.93.[20 22] This may indicate that the BedsidePEWS may also be clinically useful in pediatric oncology patients, albeit more prospective cohort studies are needed.

Our systematic review has several limitations. The total number of included studies was small. In addition, we could not pool the results of the included studies due to heterogeneity of the study designs and the diversity of PEWS. Other limitations may be the exclusion of non-English papers and inclusion of only published validation studies of a PEWS, resulting in a potential risk of publication bias. Finally, we included studies from both high- and low-income settings, which may affect the generalizability of our findings.

Conclusion

Gaps of knowledge remain in both predictive performance and impact of PEWS in the high-risk population of pediatric oncology patients. A valid estimation of the predictive performance of PEWS should ideally be performed in a large prospective cohort including all underlying malignancies, and in line with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) recommendations.[26] The widespread implementation of electronic health records and possibilities for continuous monitoring combined with “big data” analytics offer potential to improve prediction and personalize risk assessment.[33-35] Ultimately this may aid in decision support for adequate escalation of care without unnecessary administrative burden.

References

1. Hallahan AR, Shaw PJ, Rowell G, et al. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. *Crit Care Med* 2000;28(11):3718-21. doi: 10.1097/00003246-200011000-00030
2. Wösten-van Asperen RM, van Gestel JPJ, van Grotel M, 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. doi: 10.1016/j.critrevonc.2019.07.014
3. López-Herce J, Del Castillo J, Matamoros M, et al. Factors associated with mortality in pediatric in-hospital cardiac arrest: a prospective multicenter multinational observational study. *Intensive Care Med* 2013;39(2):309-18. doi: 10.1007/s00134-012-2709-7
4. Duncan H, Hutchison J, Parshuram CS. The Pediatric Early Warning System score: a severity of illness score to predict urgent medical need in hospitalized children. *J Crit Care* 2006;21(3):271-8. doi: 10.1016/j.jcrc.2006.06.007
5. Haines C, Perrott M, Weir P. Promoting care for acutely ill children-development and evaluation of a paediatric early warning tool. *Intensive Crit Care Nurs* 2006;22(2):73-81. doi: 10.1016/j.iccn.2005.09.003
6. Parshuram CS, Hutchison J, Middaugh K. Development and initial validation of the Bedside Paediatric Early Warning System score. *Crit Care* 2009;13(4):R135. doi: 10.1186/cc7998
7. Edwards ED, Powell CV, Mason BW, et al. Prospective cohort study to test the predictability of the Cardiff and Vale paediatric early warning system. *Arch Dis Child* 2009;94(8):602-6. doi: 10.1136/adc.2008.142026
8. Trubey R, Huang C, Lugg-Widger FV, et al. Validity and effectiveness of paediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalised children: a systematic review. *BMJ Open* 2019;9(5):e022105. doi: 10.1136/bmjopen-2018-022105
9. Agulnik A, Forbes PW, Stenquist N, et al. Validation of a Pediatric Early Warning Score in Hospitalized Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients. *Pediatr Crit Care Med* 2016;17(4):e146-53. doi: 10.1097/pcc.0000000000000662
10. Agulnik A, Mora Robles LN, Forbes PW, et al. Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. *Cancer* 2017;123(15):2965-74. doi: 10.1002/cncr.30664
11. Dean NP, Fenix JB, Spaeder M, et al. Evaluation of a Pediatric Early Warning Score Across Different Subspecialty Patients. *Pediatr Crit Care Med* 2017;18(7):655-60. doi: 10.1097/pcc.0000000000001176
12. Chapman SM, Wray J, Oulton K, et al. Systematic review of paediatric track and trigger systems for hospitalised children. *Resuscitation* 2016;109:87-109. doi: 10.1016/j.resuscitation.2016.07.230
13. Lambert V, Matthews A, MacDonell R, et al. Paediatric early warning systems for detecting and responding to clinical deterioration in children: a systematic review. *BMJ Open* 2017;7(3):e014497. doi: 10.1136/bmjopen-2016-014497
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535. doi: 10.1136/bmj.b2535
15. Wolff RF, Moons KGM, Riley RD, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann Intern Med* 2019;170(1):51-58. doi: 10.7326/M18-1376
16. Moons KGM, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. *Ann Intern Med* 2019;170(1):W1-W33. doi: 10.7326/M18-1377
17. Reeves BC DJ, Higgings JPT,Wells GA. *Cochrane handbook for systematic reviews of interventions*. Version 5.0.1 ed: The Cochrane Collaboration 2011.
18. Agulnik A, Méndez Aceituno A, Mora Robles LN, et al. Validation of a pediatric early warning system for hospitalized pediatric oncology patients in a resource-limited setting. *Cancer* 2017;123(24):4903-13. doi: 10.1002/cncr.30951
19. Agulnik A, Nadkarni A, Mora Robles LN, et al. Pediatric Early Warning Systems aid in triage to intermediate versus intensive care for pediatric

oncology patients in resource-limited hospitals. *Pediatr Blood Cancer* 2018;65(8):e27076. doi: 10.1002/pbc.27076
20. Cater DT, Tori AJ, Moser EAS, et al. Modification and Assessment of the Bedside Pediatric Early Warning Score in the Pediatric Allogeneic Hematopoietic Cell Transplant Population. *Pediatr Crit Care Med* 2018;19(5):483-88. doi: 10.1097/pcc.0000000000001521
21. Fuijkschot J, Vernhout B, Lemson J, et al. Validation of a Paediatric Early Warning Score: first results and implications of usage. *Eur J Pediatr* 2015;174(1):15-21. doi: 10.1007/s00431-014-2357-8
22. Gawronski O, Ciofi Degli Atti ML, Di Ciommo V, et al. Accuracy of Bedside Paediatric Early Warning System (BedsidePEWS) in a Pediatric Stem Cell Transplant Unit. *J Pediatr Oncol Nurs* 2016;33(4):249-56. doi: 10.1177/1043454215600154
23. DemmelKM,WilliamsL,FleschL.Implementation of the pediatric early warning scoring system on a pediatric hematology/oncology unit. *J Pediatr Oncol Nurs* 2010;27(4):229-40. doi: 10.1177/1043454209358410
24. Gerry S, Bonnici T, Birks J, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. *BMJ* 2020;369:m1501. doi: 10.1136/bmj.m1501
25. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart* 2012;98(9):691-8. doi: 10.1136/heartjnl-2011-301247
26. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162(1):W1-73. doi: 10.7326/M14-0698
27. Van Calster B, McLernon DJ, van Smeden M, et al. Calibration: the Achilles heel of predictive analytics. *BMC Med* 2019;17(1):230. doi: 10.1186/s12916-019-1466-7
28. Chapman SM, Maconochie IK. Early warning scores in paediatrics: an overview. *Arch Dis Child* 2019;104 doi: 10.1136/archdischild-2018-314807
29. Chapman SM, Wray J, Oulton K, et al. 'Death is not the answer': the challenge of measuring the impact of early warning systems. *Arch Dis Child* 2019;104(3):210-11. doi: 10.1136/archdischild-2018-315392
30. Parshuram CS, Dryden-Palmer K, Farrell C, et al. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. *JAMA* 2018;319(10):1002-12. doi: 10.1001/*JAMA*.2018.0948
31. Parshuram CS, Duncan HP, Joffe AR, et al. Multicentre validation of the bedside paediatric early warning system score: a severity of illness score to detect evolving critical illness in hospitalised children. *Crit Care* 2011;15(4):R184. doi: 10.1186/cc10337
32. Chapman SM, Wray J, Oulton K, et al. 'The Score Matters': wide variations in predictive performance of 18 paediatric track and trigger systems. *Arch Dis Child* 2017;102(6):487-95. doi: 10.1136/archdischild-2016-311088
33. Zhai H, Brady P, Li Q, et al. Developing and evaluating a machine learning based algorithm to predict the need of pediatric intensive care unit transfer for newly hospitalized children. *Resuscitation* 2014;85(8):1065-71. doi: 10.1016/j.resuscitation.2014.04.009
34. Churpek MM, Yuen TC, Park SY, et al. Using electronic health record data to develop and validate a prediction model for adverse outcomes in the wards*. *Crit Care Med* 2014;42(4):841-8. doi: 10.1097/ccm.0000000000000038
35. Rothman MJ, Tepas JJ, Nowalk AJ. Development and validation of a continuously age-adjusted measure of patient condition for hospitalized children using the electronic medical record. *J Biomed Inform* 2017;66 doi: 10.1016/j.jbi.2016.12.013

Appendix

Supplementary Table S1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist 2009.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	39
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	40
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	41
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	41
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	42
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	41, 42
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	42
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	42, 43

Supplementary Table S1. *PRISMA Checklist 2009 - continued.*

Section/topic	#	Checklist item	Reported on page #
METHODS (2)			
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	42
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	42
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	43, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	43-45, 48, 49
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	46
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	44, 45
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	44, 45
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA

Supplementary Table S1. *PRISMA Checklist 2009 - continued.*

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	48, 49
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	50
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	51
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	colofon

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

Supplementary Table S2. Search strategy.

Database: Pubmed

Data searched: March 5, 2020

Records retrieved: 1057

adolescent[MeSH] OR child[MeSH] OR "Infant"[Mesh] OR infan*[Title/Abstract] OR newborn*[Title/Abstract] OR new-born*[Title/Abstract] OR perinat*[Title/Abstract] OR neonat*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract] OR toddler*[Title/Abstract] OR minor[Title/Abstract] OR minors*[Title/Abstract] OR boy[Title/Abstract] OR boys[Title/Abstract] OR boyfriend[Title/Abstract] OR boyhood[Title/Abstract] OR girl*[Title/Abstract] OR kid[Title/Abstract] OR kids[Title/Abstract] OR child[Title/Abstract] OR children[Title/Abstract] OR childhood[Title/Abstract] OR schoolchild*[Title/Abstract] OR school child*[Title/Abstract] OR adolescen*[Title/Abstract] OR juvenil*[Title/Abstract] OR youth*[Title/Abstract] OR teen*[Title/Abstract] OR underage*[Title/Abstract] OR pubescen*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric*[Title/Abstract] OR peadiatric*[Title/Abstract] OR prematur*[Title/Abstract] OR preterm*[Title/Abstract]

AND

leukemi*[Title/Abstract] OR leukaemi*[Title/Abstract] OR ALL[Title/Abstract] OR AML[Title/Abstract] OR lymphom*[Title/Abstract] OR hodgkin*[Title/Abstract] OR non-hodgkin*[Title/Abstract] OR T-cell[Title/Abstract] OR B-cell[Title/Abstract] OR sarcom*[Title/Abstract] OR sarcoma ewings[Title/Abstract] OR ewing*[Title/Abstract] OR osteosarcom*[Title/Abstract] OR wilms[Title/Abstract] OR nephroblastom*[Title/Abstract] OR neuroblastom*[Title/Abstract] OR rhabdomyosarcom*[Title/Abstract] OR teratom*[Title/Abstract] OR hepatom*[Title/Abstract] OR hepatoblastom*[Title/Abstract] OR PNET[Title/Abstract] OR medulloblastom*[Title/Abstract] OR metasta*[Title/Abstract] OR neuroectodermal tumor*[Title/Abstract] OR retinoblastom*[Title/Abstract] OR meningiom*[Title/Abstract] OR gliom*[Title/Abstract] OR paraneoplastic[Title/Abstract] OR cancer*[Title/Abstract] OR oncolog*[Title/Abstract] OR oncogen*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinom*[Title/Abstract] OR tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour*[Title/Abstract] OR malignan*[Title/Abstract] OR hematooncologic*[Title/Abstract] OR hemato oncologic*[Title/Abstract] OR neoplasm*[Title/Abstract] OR hematolo*[Title/Abstract] OR hematopoietic*[Title/Abstract] OR stem cell[Title/Abstract] OR transplant[Title/Abstract] OR neoplasms[Mesh]

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early warning alert*[Title/Abstract] OR early warning criteria*[Title/Abstract] OR early warning detection[Title/Abstract] OR early warning device*[Title/Abstract] OR early warning index[Title/Abstract] OR early warning indicator*[Title/Abstract] OR early warning method*[Title/Abstract] OR early warning model*[Title/Abstract] OR early warning monitoring[Title/Abstract] OR early warning parameter*[Title/Abstract] OR early warning response[Title/Abstract] OR early warning scor*[Title/Abstract] OR early warning sign*[Title/Abstract] OR early warning surveillance[Title/Abstract] OR early warning system*[Title/Abstract] OR early warning tool*[Title/Abstract] OR early warning trigger*[Title/Abstract] OR PEWS[Title/Abstract] OR MPEWS[Title/Abstract] OR advanced warning score[Title/Abstract] OR PAWS[Title/Abstract] OR alert criteria[Title/Abstract] OR PAC[Title/Abstract] OR sepsis six[Title/Abstract] OR track trigger system*[Title/Abstract] OR track trigger tool*[Title/Abstract] OR TTS[Title/Abstract] OR TTT[Title/Abstract] OR instrument validity[Title/Abstract] OR instrument reliability[Title/Abstract] OR instrument evaluation[Title/Abstract] OR calling criteri*[Title/Abstract] OR rapid response*[Title/Abstract] OR escalation protocol*[Title/Abstract] OR communication tool*[Title/Abstract] OR situation awareness*[Title/Abstract] OR activation criteri*[Title/Abstract] OR MAC[Title/Abstract] OR trigger scor*[Title/Abstract] OR NTS[Title/Abstract] OR observation priority scor*[Title/Abstract] OR POPS[Title/Abstract] OR NEW system[Title/Abstract] OR CHEWS[Title/Abstract] OR C-CHEWS[Title/Abstract] OR ManCHEWS[Title/Abstract] OR PAT-POPS[Title/Abstract]

Supplementary Table S2. Search strategy - *continued*.

Database: EMBASE

Data searched: March 5, 2020

Records retrieved: 1162

adolescent/exp OR child/exp OR "Infant"/exp OR infan*:ti,ab,kw OR newborn*:ti,ab,kw OR new-born*:ti,ab,kw OR perinat*:ti,ab,kw OR neonat*:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw OR toddler*:ti,ab,kw OR minor:ti,ab,kw OR minors*:ti,ab,kw OR boy:ti,ab,kw OR boys:ti,ab,kw OR boyfriend:ti,ab,kw OR boyhood:ti,ab,kw OR girl*:ti,ab,kw OR kid:ti,ab,kw OR kids:ti,ab,kw OR child:ti,ab,kw OR children:ti,ab,kw OR childhood:ti,ab,kw OR schoolchild*:ti,ab,kw OR school child*:ti,ab,kw OR adolescen*:ti,ab,kw OR juvenil*:ti,ab,kw OR youth*:ti,ab,kw OR teen*:ti,ab,kw OR underage*:ti,ab,kw OR pubescen*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR peadiatric*:ti,ab,kw OR prematur*:ti,ab,kw OR preterm*:ti,ab,kw

AND

leukemi*:ti,ab,kw OR leukaemi*:ti,ab,kw OR ALL:ti,ab,kw OR AML:ti,ab,kw OR lymphom*:ti,ab,kw OR hodgkin*:ti,ab,kw OR non-hodgkin*:ti,ab,kw OR T-cell:ti,ab,kw OR B-cell:ti,ab,kw OR sarcom*:ti,ab,kw OR sarcoma ewings:ti,ab,kw OR ewing*:ti,ab,kw OR osteosarcom*:ti,ab,kw OR wilms:ti,ab,kw OR nephroblastom*:ti,ab,kw OR neuroblastom*:ti,ab,kw OR rhabdomyosarcom*:ti,ab,kw OR teratom*:ti,ab,kw OR hepatom*:ti,ab,kw OR hepatoblastom*:ti,ab,kw OR PNET:ti,ab,kw OR medulloblastom*:ti,ab,kw OR metasta*:ti,ab,kw OR neuroectodermal tumor*:ti,ab,kw OR retinoblastom*:ti,ab,kw OR meningiom*:ti,ab,kw OR gliom*:ti,ab,kw OR paraneoplastic:ti,ab,kw OR cancer*:ti,ab,kw OR oncolog*:ti,ab,kw OR oncogen* :ti,ab,kw OR neoplasm*:ti,ab,kw OR carcinom*:ti,ab,kw OR tumor:ti,ab,kw OR tumors:ti,ab,kw OR tumour*:ti,ab,kw OR malignan*:ti,ab,kw OR hematooncologic*:ti,ab,kw OR hemato oncologic*:ti,ab,kw OR neoplasm*:ti,ab,kw OR hematolo*:ti,ab,kw OR hematopoietic*:ti,ab,kw OR stem cell:ti,ab,kw OR transplant:ti,ab,kw OR neoplasms/exp

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early warning alert*:ti,ab,kw OR early warning criteria*:ti,ab,kw OR early warning detection:ti,ab,kw OR early warning device*:ti,ab,kw OR early warning index:ti,ab,kw OR early warning indicator*:ti,ab,kw OR early warning method*:ti,ab,kw OR early warning model*:ti,ab,kw OR early warning monitoring:ti,ab,kw OR early warning parameter*:ti,ab,kw OR early warning response:ti,ab,kw OR early warning scor*:ti,ab,kw OR early warning sign*:ti,ab,kw OR early warning surveillance:ti,ab,kw OR early warning system*:ti,ab,kw OR early warning tool*:ti,ab,kw OR early warning trigger*:ti,ab,kw OR PEWS:ti,ab,kw OR MPEWS:ti,ab,kw OR advanced warning score:ti,ab,kw OR PAWS:ti,ab,kw OR alert criteria:ti,ab,kw OR PAC:ti,ab,kw OR sepsis six:ti,ab,kw OR track trigger system*:ti,ab,kw OR track trigger tool*:ti,ab,kw OR TTS:ti,ab,kw OR TTT:ti,ab,kw OR instrument validity:ti,ab,kw OR instrument reliability:ti,ab,kw OR instrument evaluation:ti,ab,kw OR calling criteri*:ti,ab,kw OR rapid response*:ti,ab,kw OR escalation protocol*:ti,ab,kw OR communication tool*:ti,ab,kw OR situation awareness*:ti,ab,kw OR activation criteri*:ti,ab,kw OR MAC:ti,ab,kw OR trigger scor*:ti,ab,kw OR NTS:ti,ab,kw OR observation priority scor*:ti,ab,kw OR POPS:ti,ab,kw OR NEW system:ti,ab,kw OR CHEWS:ti,ab,kw OR C-CHEWS:ti,ab,kw OR ManCHEWS:ti,ab,kw OR PAT-POPS:ti,ab,kw

Supplementary Table S2. Search strategy - *continued*.

Database: CINAHL

Data searched: March 5, 2020

Records retrieved: 865

MH "adolescent" OR MH "child" OR MH "Infant" OR TI (infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR babies OR toddler* OR minor OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR children OR childhood OR schoolchild* OR school child* OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*) OR AB (infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR babies OR toddler* OR minor OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR children OR childhood OR schoolchild* OR school child* OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*)

AND

TI (leukemi* OR leukaemi* OR ALL OR AML OR lymphom* OR hodgkin* OR non-hodgkin* OR T-cell OR B-cell OR sarcom* OR sarcoma ewings OR ewing* OR osteosarcom* OR wilms OR nephroblastom* OR neuroblastom* OR rhabdomyosarcom* OR teratom* OR hepatom* OR hepatoblastom* OR PNET OR medulloblastom* OR metasta* OR neuroectodermal tumor* OR retinoblastom* OR meningiom* OR gliom* OR paraneoplastic OR cancer* OR oncolog* OR oncogen* OR neoplasm* OR carcinom* OR tumor OR tumors OR tumour* OR malignan* OR hematooncologic* OR hemato oncologic* OR neoplasm* OR hematolo* OR hematopoietic* OR *(Supplementary Table S2. Search strategy - continued)*
stem cell OR transplant) OR MH "neoplasms"

OR

AB (leukemi* OR leukaemi* OR ALL OR AML OR lymphom* OR hodgkin* OR non-hodgkin* OR T-cell OR B-cell OR sarcom* OR sarcoma ewings OR ewing* OR osteosarcom* OR wilms OR nephroblastom* OR neuroblastom* OR rhabdomyosarcom* OR teratom* OR hepatom* OR hepatoblastom* OR PNET OR medulloblastom* OR metasta* OR neuroectodermal tumor* OR retinoblastom* OR meningiom* OR gliom* OR paraneoplastic OR cancer* OR oncolog* OR oncogen* OR neoplasm* OR carcinom* OR tumor OR tumors OR tumour* OR malignan* OR hematooncologic* OR hemato oncologic* OR neoplasm* OR hematolo* OR hematopoietic* OR stem cell OR transplant)

AND

TI (early warning alert* OR early warning criteria* OR early warning detection OR early warning device* OR early warning index OR early warning indicator* OR early warning method* OR early warning model* OR early warning monitoring OR early warning parameter* OR early warning response OR early warning scor* OR early warning sign* OR early warning surveillance OR early warning system* OR early warning tool* OR early warning trigger* OR PEWS OR MPEWS OR advanced warning score OR PAWS OR alert criteria OR PAC OR sepsis six OR track trigger system* OR track trigger tool* OR TTS OR TTT OR instrument validity OR instrument reliability OR instrument evaluation OR calling criteri* OR rapid response* OR escalation protocol* OR communication tool* OR situation awareness* OR activation criteri* OR MAC OR trigger scor* OR NTS OR observation priority scor* OR POPS OR NEW system OR CHEWS OR C-CHEWS OR ManCHEWS OR PAT-POPS) OR AB (early warning alert* OR early warning criteria* OR early warning detection OR early warning device* OR early warning index OR early warning indicator* OR early warning method* OR early warning model* OR early warning monitoring OR early warning parameter* OR early warning response OR early warning scor* OR early warning sign* OR early warning surveillance OR early warning system* OR early warning tool* OR early warning trigger* OR PEWS OR MPEWS OR advanced warning score OR PAWS OR alert criteria OR PAC OR sepsis six OR track trigger system* OR track trigger tool* OR TTS OR TTT OR instrument validity OR instrument reliability OR instrument evaluation OR calling criteri* OR rapid response* OR escalation protocol* OR communication tool* OR situation awareness* OR activation criteri* OR MAC OR trigger scor* OR NTS OR observation priority scor* OR POPS OR NEW system OR CHEWS OR C-CHEWS OR ManCHEWS OR PAT-POPS)

Supplementary Table S3. Signalling questions for risk of bias (RoB) and applicability of the Prediction model study Risk of Bias Assessment Tool (PROBAST).

Risk of Bias	
Domain	**Risk of Bias Signaling Questions**
1. Participants	1.1 Were appropriate data sources used, e.g., cohort, RCT or nested case-control study data?
	1.2 Were all inclusions and exclusions of participants appropriate?
2. Predictors	2.1 Were predictors defined and assessed in a similar way for all participants?
	2.2 Were predictor assessments made without knowledge of outcome data?
	2.3 Are all predictors available at the time the model is intended to be used?
3. Outcome	3.1 Was the outcome determined appropriately?
	3.2 Was a prespecified or standard outcome definition used?
	3.3 Were predictors excluded from the outcome definition?
	3.4 Was the outcome defined and determined in a similar way for all participants?
	3.5 Was the outcome determined without knowlevdge of predictor information?
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?
4. Analysis	4.1 Were there a reasonable number of participants with the outcome?
	4.2 Were continuous and categorical predictors handled appropriately?
	4.3 Were all enrolled participants included in the analysis?
	4.4 Were participants with missing data handled appropriately?
	4.5 Was selection of predictors based on univariable analysis avoided?
	4.6 Were complexities in the data (e.g. censoring, competing risk, sampling of control participants) accounted for appropriately?
	4.7 Were relevant model performance measures evaluated appropriately?
	4.8 Were model overfitting, underfitting and optimism in model performance accounted for?
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?
Applicability	
Domain	**Applicability Questions / Concerns**
1. Participants	Concern that the included participants and setting do not match the review question
2. Predictors	Concern that the definition, assessment or timing of predictors in the model that do not match the review question
3. Outcome	Concern that the outcome, its definition, timing or determination do not match the review question

From: Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019 Jan 1;170(1):W1-W33. doi: 10.7326/M18-1377. PMID: 3059687

Supplementary Table S4. Overview of the characteristics of the different PEWS used in validation or impact studies.

Pediatric Early Warning System	Bedside PEWS [20, 22]	CHEWS [9]	Modified Brighton PEWS [11]	Modified Bedside PEWS [21]	EVAT [10, 18]	Monaghan PEWS [23]
Validation (V) or impact (I) study	V	V	V	V	V[18] I[10]	I
Score range	0 - 26	0 - 11	0 - 13	0 - 28	0 - 11	0 - 9
Number of age categories	4	4	-	8	4	8
Number of individual parameters required for a complete score	7	16	10	8	16	8
Parameters						
Respiratory		✓[a]	✓[a]		✓[a]	✓[a]
Cardiovascular		✓[b]	✓[b]		✓[b]	✓[b]
Behavior/neurologic		✓[c]	✓[c]		✓[c]	✓[c]
Staff concern		✓			✓	
Family concern		✓			✓	✓
Respiratory rate	✓	✓[a]	✓[a]	✓	✓[a]	✓[a]
Respiratory effort	✓	✓[a]	✓[a]	✓	✓[a]	✓[a]
Oxygen saturation	✓	✓[a]		✓	✓[a]	
Oxygen therapy	✓	✓[a]	✓[a]	✓	✓[a]	✓[a]
Apnea		✓[a]			✓[a]	
Nebulization		✓[a]			✓[a]	
Heart rate	✓	✓[b]	✓[b]	✓	✓[b]	✓[b]
Systolic blood pressure	✓			✓		
Skin tone		✓[b]	✓[b]		✓[b]	✓[b]
Capillary refill time	✓	✓[b]	✓[b]	✓	✓[b]	✓[b]
Heart rhythm		✓[b]			✓[b]	
Alertness		✓[c]	✓[c]		✓[c]	✓[c]
Response to stimuli		✓[c]	✓[c]		✓[c]	
Seizures		✓[c]			✓[c]	
Pupils		✓[c]			✓[c]	
Presence of tracheostomy			✓			
Persistent vomiting after surgery			✓			
Temperature				✓		

[a, b, c] bold parameters represent composite parameters and the grey parameters with corresponding superscripts are the required parameters to score the composite parameter. *V* validation; *I* impact; *PEWS* pediatric early warning system; *CHEWS* Children's Hospital Early Warning Score; *EVAT* Escala de Valoración de Alerta Temprana.

Supplementary Table S5. Risk of bias assessment of external validation studies with Prediction model study Risk of Bias Assessment Tool.

Study	Domain 1: Participants		Comments	RoB of domain 1	Domain 2: Predictors			RoB of domain 2	Domain 3: Outcome						Comments	RoB of domain 3
	1.1	1.2			2.1	2.2	2.3		3.1	3.2	3.3	3.4	3.5	3.6		
Agulnik et al. 2016	N	PY	Ad 1.1 Unnested case-control (CC) study	High	PY	Y	Y	Low	Y	Y	Y	Y	PN	Y	Ad 3.5 For all studies: the outcome unplanned PICU transfer is a decision made by physicians. In this decision, PEWS may be taken into account, but several other factors as well and it is unlikely that PEWS alone determined the outcome.	Low
Agulnik et al. 2017	N	PY	Ad 1.1 Unnested CC study	High	Y	Y	Y	Low	Y	Y	Y	Y	PN	Y		Low
Cater et al. 2018	PY	PY		Low	Y	Y	Y	Low	Y	Y	Y	Y	PN	PY		Low
Dean et al. 2017	PY	PY		Low	PY	Y	Y	Low	Y	Y	Y	Y	PN	PY		Low
Fuijkschot et al. 2015	PY	N	Ad 1.2 Selection of controls with PEWS <= 4, not all patients at risk of developing the outcome are included.	High	PY	Y	Y	Low	Y	Y	Y	Y	PN	NA	Ad 3.6 time interval of PEWS prior to event not clearly reported	Unclear
Gawronski et al. 2016	Y	Y		Low	Y	PY	Y	Low	Y	Y	Y	Y	PN	Y		Low
Agulnik et al. 2018	N	Y		High	PY	PY	Y	Low	Y	Y	Y	Y	PN	PY	Ad 3.6 The three most recent PEWS prior to transfer were used. Although a time interval was not specified, it was stated that the PEWS scores were documented at least every 4 hours.	Low

Supplemental Table S5. *Risk of bias assessment - continued.*

Study	Domain 4 Analysis									Comments	RoB of domain 4	Overall RoB
	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9			
Agulnik et al. 2016	Y	Y	PN	PN	NA	PN	N	NA	NA	Ad 4.3, 4.4 complete case analysis with exclusion of patients with missing PEWS data prior to outcome event. Only maximum value of PEWS in 24 hours prior to outcome was assessed. Ad 4.6 No time-to-event analysis performed. Ad 4.7 No calibration or discrimination reported, only AUROC calculated using maximum value of PEWS in 24h prior to outcome event. Ad 4.8 Overfitting and underfitting not reported.	High	High
Agulnik et al. 2017	Y	Y	PN	PN	NA	PN	N	NA	NA	Ad 4.3, 4.4 complete case analysis with exclusion of patients with absence of PEWS in 6 hours prior to outcome event. Only maximum value of PEWS in 24 hours prior to outcome was assessed. Ad 4.6 No time-to-event analysis performed. Ad 4.7 No calibration or discrimination reported, only AUROC calculated using maximum value of PEWS in 24h prior to outcome event. Ad 4.8 Overfitting and underfitting not reported.	High	High
Cater et al. 2018	N	PN	N	PN	Y	N	N	NA	NA	Ad 4.1 n= 29 patients with unplanned PICU transfer Ad 4.2 Only prespecified and widely accepted cut points in PEWS. However weight gain was dichotomized based on the data at hand. Ad 4.3, 4.4 complete case analysis with exclusion of patients with missing PEWS data prior to outcome event. Ad 4.7 No calibration or discrimination reported, only AUROC calculated using maximum value of PEWS in 24h prior to outcome event. Ad 4.8 Overfitting and underfitting not reported.	High	High
Dean et al. 2017	N	PY	NA	NA	NA	N	N	NA	NA	Ad 4.1 n = 43 unplanned PICU transfers in hemato-onco patients Ad 4.3, 4.4 No information on (handling of) missing data Ad 4.6 No time-to-event analysis or equivalent performed. Ad 4.7 No discrimination / calibration reported Ad 4.8 Overfitting and underfitting not reported.	High	High

Supplemental Table S5. *Risk of bias assessment - continued.*

Study	Domain 4 Analysis									Comments	RoB of domain 4	Overall RoB
	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9			
Fuijkschot et al. 2015	N	Y	N	N	NA	N	N	NA	NA	Ad 4.1 n = 1 outcome event Ad 4.3 Participants with missing data excluded, 59% of the admissions had sufficient data to be included in the study Ad 4.4 Complete case analysis, exclusion of patients with missing data. Ad 4.7 No discrimination / calibration reported Ad 4.8 Overfitting and underfitting not reported.	High	High
Gawronski et al. 2016	N	PY	NA	PN	NA	PY	N	NA	NA	Ad 4.1 n = 19 outcome events Ad 4.3 No information on missing data Ad 4.4 At study enrollment, research nurses reviewed the 7 clinical indicators of the PEWS and assigned the PEWS score. Conflicting or missing observations were resolved by interviews with the SCT team, risk of recall bias. Ad 4.6 Analysis using fixed intervals (4 hours) in 24 hours prior to outcome event Ad 4.7 No discrimination / calibration reported Ad 4.8 Overfitting and underfitting not reported.	High	High
Agulnik et al. 2018	N	PY	N	PN	NA	N	N	NA	NA	Ad 4.1 n = 39 outcome events, of which 37 analyzed Ad 4.3, 4.4 Exclusion of patients with missing data Ad 4.7 No predictive performance of PEWS analysed, only t-test and Fisher exact test to compare maximum PEWS prior to transfer to IMCU for patients who stayed in IMCU and patients who had a subsequent PICU transfer within 24hours of IMCU admission.	High	High

The included articles were assessed guided by the signaling questions (see Supplementary Table 3) and classified as low, high, or unclear risk of bias for each domain. A study was classified as having an overall low risk of bias only if it was at low risk of bias within each domain.

RoB risk of bias*; N* no; *PN* probably no; *Y* yes; *PY* probably yes; *NA* not reported in study; *AUROC* area under receiver operating characteristics curve; *SCT* stem cell transplantation; *IMCU* intermediate care unit.

Supplementary Table S6. Risk of bias assessment of impact studies.

	Impact study 1: Agulnik et al. 2017				Impact study 2: Demmel et al. 2010			
Domain f bias	RoB Question	RoB assessment	Comments	RoB per domain	RoB assessment	Comments	RoB per domain
Selection bias	Is the study group representative?	Low	Only cases selected, no control group, comparison of cases before and after intervention.	Low	Low	No patient or survey respondent characteristics were reported	High
	Were cases and controls selected based on comparable patient characteristics?	Low	Significant difference in respiratory distress and fever and neutropenia in after group		High		
Attrition bias	Is complete outcome data for all the participants available in this study?	Low		Low	High	No report on number of included patients or participants, no report on missing outcome data	High
	Is the follow up adequate?	Low	Before and after implementation 1 year data collection, no information about lost-to-follow up		Low	Follow-up 2 years assessing sustainability of PEWS intervention	
Detection bias	Are the outcome assessors blinded for important determinants related to the outcome?	Low	Not mentioned, retrospective before-and-after design and robust outcome parameter, PEWS measured before occurence of outcome, so absence of blinding is unlikely to have effect on outcome measurement	Low	Low	No information on blinding of outcome assessment Absence of blinding is unlikely to have effect on outcome measurement	Low
Reporting bias	Is the report complete? Are the outcomes that were planned to be measured also reported?	Unclear	No study protocol available	Unclear	High	No study protocol available Mismatch between anticipated and reported outcome	High
Confounding bias	Are the analyses adjusted for important confounding factors?	Unclear	No adjustments for confounders, but we doubt whether this would be applicable	Unclear	Unclear	No details on statistical analysis provided	Unclear
Other bias	Other potential sources of bias in a clinical study?	NA		NA	NA		NA

RoB risk of bias; *PEWS* pediatric early warning system. *NA* not applicable.

The risk of bias for each impact studies was assessed by two reviewers (MS and WT) using Cochrane Risk of Bias assessment for selection bias, attrition bias, detection bias, reporting bias, confounding bias or other bias.

4

A study protocol for a prospective observational cohort study for validation of a modified Bedside Pediatric Early Warning System score in hospitalized pediatric oncology patients

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Abstract

Introduction

Hospitalized pediatric oncology patients are at risk to develop acute complications. Early identification of clinical deterioration enabling adequate escalation of care remains challenging. Various pediatric early warning systems (PEWSs) have been evaluated, also in pediatric oncology patients but mostly in retrospective or case control study designs. This study protocol encompasses the first prospective cohort with the aim of evaluating the predictive performance of a modified BedsidePEWS score for non-elective PICU admission or cardiopulmonary resuscitation in hospitalized pediatric oncology patients.

Methods and analysis

A prospective cohort study will be conducted at the 80-bed Dutch pediatric oncology hospital, where all national pediatric oncology care has been centralized, directly connected to a shared 22-bed pediatric intensive care unit (PICU). All patients between 1st of February 2019 until the 1st of February 2021 admitted to the inpatient nursing wards, aged 0-18 years, with an ICD-O diagnosis of pediatric malignancy will be eligible. A Cox proportional hazard regression model will be used to estimate the association between the modified BedsidePEWS and time to non-elective PICU transfer or cardiopulmonary arrest. Predictive performance (discrimination and calibration) will be assessed internally by using resampling validation. To account for multiple occurrences of the event of interest within each patient, the unit of study is a single uninterrupted ward admission (a clinical episode).

Ethics and dissemination

The study protocol has been approved by the institutional Ethical Review Board of our hospital (MEC protocol number 16-572/C). We adapted our enrolment procedure to General Data Protection Regulation (GDPR) compliance. Results will be disseminated at scientific conferences, regional educational sessions and publication in peer-reviewed journals.

Trial registration number: Netherlands Trial Register NL8957

Introduction

Hospitalized pediatric oncology patients are prone to develop acute complications. Although the intensification of treatment over the past decades has improved outcome with a 5-year survival rate of up to 80%, treatment-related complications have increased.[1] [2] These complications can be life threatening and may require intensive care treatment.[1] [2] Previous studies have shown that up to 38% of all pediatric oncology patients require admission to the pediatric intensive care unit (PICU) during their disease course, with sepsis and respiratory failure as the main admission reasons.[3] [4] The PICU mortality of these patients is high (25-35%) compared to the mortality of the general pediatric PICU population (5%), despite advances in supportive and critical care.[5]

Timely identification of clinical deterioration is crucial for prompt escalation of care, thereby preventing further decline and reducing the risk of cardiopulmonary resuscitation.[6] [7] Pediatric early warning system (PEWS) scores are often used as a prediction tool for detecting clinical deterioration.[8] PEWS scores typically consist of sequential monitoring of physiological parameters, generating a numerical score associated with clinical deterioration and trigger thresholds that are used for escalation of care. A broad range of PEWS scores are currently in use with variable predictive performance for identifying early clinical deterioration.[8] Among all PEWS scores studied, the most studied one is the BedsidePEWS by Parshuram et al, which was validated in the general pediatric patient population.[9-11] A multicenter cluster randomized trial, comparing implementation of BedsidePEWS interventions vs usual care, showed no statistically significant reduction in mortality after PEWS implementation but did show a significant reduction in late PICU admission (significant clinical deterioration events).[9] In pediatric oncology patients, few studies have assessed the performance of a PEWS.[12-15] The majority of these studies were retrospective or case-control studies, and were conducted only in oncological subgroups, e.g., stem cell transplant patients or hemato-oncology patients. Moreover, in most studies the maximum PEWS score in the 24 hours prior to unplanned PICU admission was used to predict adverse outcomes without considering the time from that score to the event, which may have resulted in overestimating the predictive values of these scores.

In this project, we aim to validate a modified BedsidePEWS score for its predictive performance for unplanned PICU transfer or cardiopulmonary resuscitation (CPR) in hospitalized pediatric oncology patients. This paper outlines the design and rationale for this study. The study design may be of interest to other research in the field of clinical prediction models for serious adverse events. The results of this study may add to the scientific basis for the use of the modified BedsidePEWS in this specific population. This may facilitate early recognition of a deteriorating patient and can be useful in clinical decision making, ultimately aimed at improving the outcome of this vulnerable patient population.

Methods and analysis

Study design and setting

The prospective cohort study is conducted between the 1st of February 2019 and the 1st of February 2021 at the Princess Máxima Center, an 80-bed hospital for pediatric oncology in the Netherlands that diagnoses approximately 550 new cases per year. This center provides a unique setting as in this center pediatric oncology care has been centralized for all patients in the Netherlands. All inpatient wards offer the possibility for continuous monitoring of vital parameters. The PICU of the adjacent Wilhelmina Children's hospital is directly connected to, and shared with, the Princess Máxima Center. This PICU consists of a 22-bed tertiary mixed medical-surgical unit. In case of any emergency, a rapid response team is available consisting of a pediatric intensivist, a pediatric anesthetist and two critical care nurses.

Eligibility criteria

All patients with ICD-O diagnosis of pediatric malignancy (ICD-O morphology code 1, 2 or 3) aged 0 to 18 years admitted to the inpatient wards, including a hematological stem cell transplantation (HSCT) ward, of the Princess Máxima Center will be eligible. In our center, from age 0 to 18 years, the BedsidePEWS is used, and from 18 years onwards the adult Early Warning System is used at the wards. Patients admitted as outpatients for routine diagnostic and therapeutic procedures will be excluded. Patients with restrictions in care (palliative care only, do not resuscitate orders, no PICU admission) will be excluded from the moment restriction in care is registered as they can no longer experience the primary outcome event.

Outcome measures

The primary outcome will be the combined end point of a non-elective PICU admission or CPR. A non-elective PICU admission is defined as an unplanned admission to the PICU originating from the ward or operating room that the PICU was not expecting and/or is considered an emergency admission and could not have been postponed for more than 6 hours without adverse effect. Study definitions are elaborated in Table 1.

Table 1. Study definitions.

Study concept	Definition
Non-elective PICU admission	An unplanned admission to the PICU originating from the ward or operating room (OR) that the PICU was not expecting and/or is considered an emergency admission and could not have been postponed for more than 6 hours without adverse effect. PICU admissions initiated in the OR or PICU admissions following a non-elective procedure in the OR are also regarded as non-elective PICU admissions. Elective PICU admission following elective surgery do not constitute a non-elective PICU and are thus censored.
Eligible inpatient ward	Areas where care is provided to pediatric oncology patients who are admitted to the hospital, other than the PICU, NICU, emergency department, outpatient department, OR, and other designated areas where anesthetist-supervised procedures are performed.
Clinical episode	An uninterrupted clinical admission at one of the eligible inpatient wards. This episode can be closed 1) by the primary outcome (non-elective PICU admission or cardiopulmonary resuscitation), 2) by discharge from the hospital (either to home or another facility), 3) through restriction in care (e.g., palliative care, do not resuscitate order or no PICU admission) from the moment the restriction in care is registered in the electronic health care system, 4) when the patient turns 18 years of age. A new clinical episode starts at (re-)admission to the inpatient ward.

PICU pediatric intensive care unit; *OR* operating room; *NICU* neonatal intensive care unit.

Secondary outcomes and their definitions are shown in Table 2. As non-elective PICU admission or CPR may be regarded as a late intervention in the course of clinical deterioration, we will also assess clinical deterioration requiring escalation of care but not resulting in a PICU admission (non-significant clinical deterioration), including the need for high flow nasal cannula oxygen therapy or non-rebreathing mask, fluid resuscitation, or urgent PICU consultation.

Cohort dynamics and unit of study

This study consists of a dynamic cohort, since patients can enter or leave the study at variable times. A single patient may experience multiple admissions to the PICU during the study period, either within one single hospital admission or over multiple hospital admissions. Thus, a patient can be at risk of – or even experience – multiple primary outcome events. Therefore, the unit of study is not a single patient, but a single uninterrupted admission to the inpatient ward, referred to as a clinical episode. See Table 1 for an elaboration of the definition of a clinical episode.

Table 2. Secondary outcome parameters.

Clinical - ward	Definition
Non-significant clinical deterioration event*	The use of high-flow nasal cannula oxygen therapy or non-rebreathing mask but no positive pressure ventilation (bag mask or endotracheal); fluid resuscitation but no intravenous or intraosseous inotrope or vasoactive medications; and/or urgent PICU consultation. If these interventions are given at < 24-hour-interval, the interventions are clustered into one episode of non-significant clinical deterioration, with the start of the episode being the start of the first clinical deterioration event and the end of the episode being 24 hours after the start of the last clinical deterioration event.
Significant clinical eterioration event*	
Invasive respiratory support	Intubated and/or receiving endotracheal ventilation at the time of transfer or intubated within 1 hour of PICU admission.
Circulatory	>60 ml/kg intravenous or intraosseous fluid resuscitation given in the 12h before transfer, and/or administration of any intravenous or intraosseous inotrope or vasopressor at the time of transfer or at any stage in the 12h preceding transfer.
Late transfer	Respiratory (2) and circulatory (3) support before transfer
Hospital mortality	Mortality of an eligible patient at the eligible patient ward
Hospital length of stay	Will be assessed as the duration (days) of the stay of the patient at an eligible inpatient ward
Process of care	
Resuscitation team calls	Immediate medical assistance of the resuscitation team and equipment
Urgent PICU consultations	A total number of new PICU consultations will be counted. Patients who have been previously consulted will be regarded as having a new consult if an urgent call is made that results in a non-elective or earlier than planned review. Planned review involves visits by the ICU during their daily round.
Documentation and compliance to the BedsidePEWS scoring algorithm	The frequency of documenting the 'vital signs' (HR, RR, SBP, capillary refill, work of breathing, oxygen-saturation, additional oxygen therapy, and temperature) and PEWS scores in 24 hours will be recorded during the study period. Moreover, the number of 'stat' calls to a physician, e.g., request for immediate specific physician attendance to provide patient care to a patient admitted to an inpatient ward with a modified BedsidePEWS score ≥ 8, will be documented.

PICU pediatric intensive care unit; *PEWS* pediatric early warning system; *HR* heart rate; *RR* respiratory rate; *SBP* systolic blood pressure.
*Adapted from the Children's Resuscitation Intensity Scale.

Data collection and management

Modified BedsidePEWS score assessment and registration

The modified BedsidePEWS has been used since the early start of the Princess Máxima Center, in 2014.[16] There are two minor modifications compared to the original BedsidePEWS score. First, temperature is added (addition of maximum 2 points to the total score of a patient) as data from adult early warning systems show the importance of temperature as a key physiological parameter in predicting clinical deterioration in adult oncology patients.[17] Second, the oxygen therapy is divided into room air (0 points), <2 L/min (2 points) or the use of high-flow nasal cannula oxygen therapy or non-rebreathing mask (4 points) (Table 3). This results in an eight-parameter-based modified BedsidePEWS with a possible scoring range of 0–28 points.

Modified BedsidePEWS score results are assessed and documented in patients' electronic health record (EHR) by nursing staff as part of routine care on all inpatient wards. All patients admitted to the pediatric oncology wards are routinely scored once every 8-hour shift unless their clinical condition deteriorates. In this case, the frequency of scoring is routinely intensified: at a score of 4–6 points, the scoring frequency is increased to every 4 hours, and at a score of 6-7 points, the scoring frequency is increased to every hour (Figure 1).

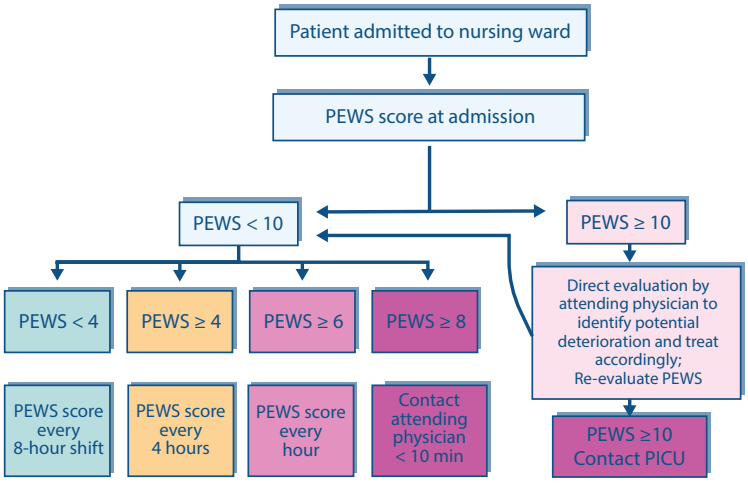

Figure 1. Flowchart of the scoring of the modified BedsidePEWS score as implemented in daily clinical practice in our study setting.

If the score exceeds 8, the nursing staff has to contact the attending physician within 10 minutes, enabling prompt evaluation of the patient. In addition, an urgent PICU evaluation is recommended if the modified BedsidePEWS score exceeds 10. Bedside computers are available on all inpatient wards, and nurses manually enter the vital signs. When the nurses want to calculate a modified BedsidePEWS score, the score is automatically

generated from the entered vital signs and shown with the corresponding clinical action. The adherence to the scoring algorithm will be calculated by the percentage of scoring of all items, and the time intervals between subsequent scores.

Table 3. The modified Bedside Pediatric Early Warning Score items.

Item	Age group	Item sub score			
		0	1	2	4
Respiratory rate (breaths/minute)	0 to < 3 months	30-60	≥ 61 or ≤ 29	≥ 81 or ≤ 19	≥ 91 or ≤ 15
	3 to < 12 months	25-50	≥ 51 or ≤ 24	≥ 71 or ≤ 19	≥ 81 or ≤ 15
	1 to 4 years	20-40	≥ 41 or ≤ 19	≥ 61 or ≤ 15	≥ 71 or ≤ 12
	> 4 – 12 years	20-30	≥ 31 or ≤ 19	≥ 41 or ≤ 14	≥ 51 or ≤ 10
	> 12 years	10-16	≥ 17 or ≤ 11	≥ 23 or ≤ 10	≥ 30 or ≤ 9
Respiratory effort		Normal	Mild increase	Moderate increase	Severe increase/ any apnoea
Oxygen saturation (%)		> 94	91-94	≤ 90	
Oxygen therapy		Room air		Oxygen 2L/min	High flow nasal cannula or non-rebreathing mask
Heart rate (bpm)	0 to < 3 months	110-150	≥ 150 or ≤ 110	≥ 180 or ≤ 90	≥ 190 or ≤ 80
	3 to < 12 months	100-150	≥ 150 or ≤ 100	≥ 170 or ≤ 80	≥ 180 or ≤ 70
	1 to 4 years	90-120	≥ 120 or ≤ 90	≥ 150 or ≤ 70	≥ 170 or ≤ 60
	> 4 – 12 years	70-110	≥ 110 or ≤ 70	≥ 130 or ≤ 60	≥ 150 or ≤ 50
	> 12 years	60-100	≥ 100 or ≤ 60	≥ 120 or ≤ 50	≥ 140 or ≤ 40
Systolic blood pressure (mmHg)	0 to < 3 months	60-80	≥ 80 or ≤ 60	≥ 100 or ≤ 50	≥ 130 or ≤ 45
	3 to < 12 months	80-100	≥ 100 or ≤ 80	≥ 120 or ≤ 70	≥ 150 or ≤ 60
	1 to 4 years	90-110	≥ 110 or ≤ 90	≥ 125 or ≤ 75	≥ 160 or ≤ 65
	> 4 – 12 years	90-120	≥ 120 or ≤ 90	≥ 140 or ≤ 80	≥ 170 or ≤ 70
	> 12 years	100-130	≥ 130 or ≤ 100	≥ 150 or ≤ 85	≥ 190 or ≤ 75
Capillary refill time		< 3 seconds			≥ 3 seconds
Temperature (°C)		36.5 – 37.5	≤36.4 or ≥37.6	<36.0 or >38.5	

Clinical data – validation of modified BedsidePEWS

The modified BedsidePEWS score and its items will be collected from the EHR. Patient data that will be collected include demographics (age, weight, sex), reason for hospital admission, underlying cancer diagnosis and therapy, disease status (e.g., initial diagnosis, during oncological treatment, end of treatment, relapse, refractory disease, progression, and palliative phase), hematopoietic or autologous stem cell transplantation, and CAR-T (chimeric antigen receptor thymocyte) cell therapy or other immunotherapy modalities. Outcome data including non-elective PICU admission, CPR and clinical deterioration events will be collected from the EHR. One of the challenges in data collection is that not all data are stored in a structured data field. For example, the escalation of care for a clinically

deteriorating patient can be documented in the daily reports of nurses and physicians. Therefore, these data are retrieved in a systematic way from the non-structured text fields of the daily nurses' and physicians' reports, using standardized search terms. These search terms are listed in the Supplement, see Supplementary Table S1. First, we manually retrieve these data, and subsequently, we will automate (a large part) of this data collection, using the manually collected data to validate this automation. Admission reason for non-elective PICU admission will be manually classified into respiratory, cardiovascular, sepsis, neurologic deterioration, gastro-intestinal, renal failure, or non-elective post-operative care. For all patients admitted to the PICU, severity of illness scores will be calculated, such as the Pediatric Index of Mortality 3 score [18] and the Pediatric Logistic Organ Dysfunction (PELOD)-2 score.[19] This PELOD-2 score is a valid outcome measure to assess the severity of multiple organ dysfunction syndrome throughout the PICU stay. In addition, the following data will be collected for further research on the evolvement of pediatric oncology patients at the PICU: PICU length of stay, use of PICU resources, e.g., mechanical ventilation, need for vasopressors and/or inotropes, continuous renal replacement therapy (CRRT), nitric oxide (NO) and extra corporeal life support (ECLS).

Statistical analysis

Continuous variables will be reported as means along with their standard deviations if they follow a normal distribution, or as medians with interquartile ranges in case of a skewed distribution. Visual inspection of the data by using Q-Q probability plots together with D'Agostino test [20] for normality will be performed to assess departures from normality for each variable. Discrete variables will be expressed as numbers with percentages. A two-sided alpha of 0.05 will be considered to be statistically significant. The modified BedsidePEWS score is repeatedly measured in individual patients and may vary over time during hospital admissions. To study the association between modified BedsidePEWS and time to non-elective PICU transfer or cardiopulmonary resuscitation – from the first documented PEWS score -, a Cox proportional hazard regression model will be estimated. To deal with the multiple hospital admissions, clusters of episodes will be incorporated into the Cox regression as they may contribute in the variation that needs to be accounted for when investigating the effect of the modified BedsidePEWS on the outcome event. As this study will validate an existing score in an applied setting, the modified BedsidePEWS and its items as measured and documented in daily practice will be used, including incomplete scores. The range of the modified BedsidePEWS is 0 – 28. A low score represents a good clinical condition. We will check the 5% highest range of modified BedsidePEWS to ensure these scores actually represent the patients' clinical condition. Other missing data will be multiple imputed using a regression approach.

The predictive performance of the model will be assessed internally by using resampling validation. [21] Calibration and discrimination of the model will be investigated.[22] Calibration

refers to how similar predicted probabilities and observed probabilities are. Well-known practices are to group patients from "good" to "poor" prognosis - a model is well calibrated if true and predicted group probabilities are very similar- or to calculate a calibration slope and intercept using bootstrapping to investigate possible overfitting. Discrimination refers to the ability of the model to provide higher predicted risk to patients who experience the event earlier compared to those experiencing the event later or not at all. To evaluate the discriminative ability of the model the C-index will be computed.[23] A C-index equal to 1 means that the model has perfect discrimination while a C-index equal to 0.5 means that the model predicts just as well as flipping a coin.

The expected number of events for a study period of two years were calculated. A retrospective analysis was performed between November 2014 and May 2016 in hospitalized pediatric oncology patients admitted to the two inpatient wards of the Princess Máxima Center. In this study period, 39 primary outcome events were observed, which would be 50 events in two years. Before start of the study, the expected number of primary outcome events were estimated based on the information of the retrospective study. In 2017 and 2018, the Princess Máxima Center has gradually grown an approximate 350% as a result of national centralization of pediatric oncology care and the accompanying opening of a new hospital in June 2018. Since patients in the retrospective analysis may have already been more complicated cases, on average 300% more patients instead of 350% were expected to experience the primary outcome event. This would result in an anticipated number of 150 primary outcome events for the study period of two years.

The results of this study will be reported according to the TRIPOD statement (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis).[24] Also, for this study protocol, relevant items are filled out in the TRIPOD statement checklist, see Supplementary Table S2.

Patient and Public involvement

The Dutch Association for Parents, Patients & Cancer (VOKK) fully supports the design, conduct, and analysis of this project.

Ethics and dissemination

The study protocol has been approved by the institutional Ethical Review Board of our hospital (MEC protocol number 16-572/C). Need for informed consent for this observational study, was waived based on the non-interventional, non-burdening nature of the study. In addition, we adapted our enrolment procedure to General Data Protection Regulation (GDPR) compliance. Data collection started February 1, 2019 and will last until February 1, 2021. The results from this study will be submitted for publication in a peer-reviewed journal, regardless of the results. Moreover, results will be presented at scientific conferences and disseminated to the healthcare staff and public via summaries and newsletters.

Discussion

This paper describes the background, rationale and design of the first prospective cohort study that aims to externally validate a modified BedsidePEWS score in an applied setting of hospitalized pediatric oncology patients. These patients are at risk to develop acute complications. A clinical prediction tool for the reliable detection of early deterioration in this high-risk population is needed. Recently, priorities for PEWS development and research in general pediatric patients have been suggested.[22] Among these priorities were the determination of the predictive characteristics of PEWS in different patient populations and the exploration of the role of technology in identification of deterioration and escalation of care.[25] With this prognostic study, we will provide an accurate and valid estimation of the modified BedsidePEWS' ability to predict non-elective PICU transfer or cardiopulmonary resuscitation at any time point during an uninterrupted inpatient ward admission in hospitalized pediatric oncology patients. In addition, we will also assess the predictive performance of the modified BedsidePEWS for non-significant clinical deterioration events requiring escalation of care (such as the need for high flow oxygen therapy or fluid resuscitation). An overall key aspect in this external validation is the discrimination of the modified BedsidePEWS - i.e., can this PEWS adequately discriminate between patients that will develop/experience the event and those experiencing the event not at all? [26]

Our study design has several strengths that may be interesting to other researchers in the field of clinical prediction models for critical decline. First, our prospective cohort study design enables to collect relevant routine clinical data in all patients that may potentially experience the primary outcome event. To date, validation studies of the PEWS in pediatric oncology patients most often employed a case-control design or retrospective cohort design, which may be susceptible to bias. In a case-control design, sampling based on the occurrence of the outcome event results in a study sample with a (much) higher prevalence of the outcome event that is no longer representative of the population. Therefore, risk prediction may not be straightforward, traditional risk modelling approaches (i.e., traditional logistic regression) may not be effective, and may yield incorrect estimates of risk prediction.[27 28] Prospective data collection may minimize missing data or difficulties in abstracting certain PEWS components, that is a common source of bias in retrospective studies validating a PEWS.[8] Second, we include all subgroups of pediatric oncology patients (e.g., patients with hemato-oncological malignancies including HSCT patients, solid tumours including immunotherapy patients, brain or central nervous system tumours), possibly improving generalizability as several studies validating a PEWS only included a subgroup of pediatric oncology patients. A third strength is the use of a single clinical episode as a study unit as opposed to a single patient. This enables us to account for re-occurrence of the outcome event and possible

predictors. The longitudinal time-dependent nature of the predictors has not yet been used in validation studies of PEWSs for identifying clinical deterioration.[8]

Along with its strengths, our study design has limitations. First, our primary outcome event, non-elective PICU admission may be a rather subjective outcome measure. The decision to admit a patient to the PICU is complex, reflecting patient factors, resource availability, and the decision-making of individual physicians.[29] In our setting, such decisions are made in a multidisciplinary approach by treating oncologists and intensivists. The modified BedsidePEWS could stimulate an increased situation awareness about children requiring intensive care therapy and may support, not replace, clinical judgement. The use of a hard outcome measure, such as mortality, may be limited in studies conducted in critically ill pediatric patients due to its relatively low occurrence. [30 31] This is illustrated by the first multicenter, randomized controlled trial of BedsidePEWS, which showed that implementation of this score compared with usual care did not significantly decrease all-cause mortality among hospitalized children.[9] Despite the evaluation of 144 539 patient discharges, that study may have been underpowered as the overall mortality rate was significantly lower than anticipated.[32] Second, our study design involves an observational prospective cohort study, to validate a clinical prediction model in an applied setting. Consequently, we are not able to identify the underlying cause of clinical deterioration, since this would require a comparative study design. Third, in this study we will validate a modified BedsidePEWS. There are many different PEWS implemented, also in pediatric oncology patients.[12-16 33] Therefore, the results of our study may not be generalizable to other PEWS scores. Last, the setting of a single pediatric oncology hospital with direct access to a PICU and availability of a rapid response team may also limit the generalizability of our findings to other settings.

The results of this study will contribute to the evidence of the performance of the modified BedsidePEWS in predicting non-elective PICU admission or CPR as well as escalation of care during hospitalization in pediatric oncology patients. A good predictive performance is required for the modified BedsidePEWS to meet its clinical goal: timely detection of clinical deterioration that will prompt appropriate escalation of care. For that purpose, we would expect that the modified BedsidePEWS errs on the side of caution, implying that a high modified BedsidePEWS (score ≥ 8) should have a low threshold of signaling a possible clinical deterioration. Still, it should not result in an unreasonable number of false positives. On the other hand, a low modified BedsidePEWS (score < 8) should indicate that no deterioration will occur, i.e., a very low number of false negatives. We, therefore, consider the predictive performance of the modified BedsidePEWS optimal when at most 80 out of 100 patients with a score ≥ 8 are false positive (a positive predictive value ≥ 20%). In contrast, there should be at most 2 out of 100 patients with a score < 8 that are false negative (a negative predictive value ≥ 98%). The modified BedsidePEWS is considered suboptimal when either of the predictive values does not meet its prespecified target.

We will prospectively collect all relevant clinically available data to enable optimisation in future studies.

Conclusion

This study is the first prospective observational cohort study to evaluate the predictive performance of the BedsidePEWS score as a clinical prediction model to identify hospitalized pediatric oncology patients with evolving critical illness. The outcome of this study may strengthen the evidence for the use of the modified BedsidePEWS for detection of clinical deterioration in hospitalized pediatric oncology patients, or may indicate that the modified BedsidePEWS may need optimization in this population.

References

1. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol* 2014;15(1):35-47. doi: 10.1016/S1470-2045(13)70548-5
2. Fausser JL, Tavenard A, Rialland F, et al. Should We Pay Attention to the Delay Before Admission to a Pediatric Intensive Care Unit for Children With Cancer? Impact on 1-Month Mortality. A Report From the French Children's Oncology Study Group, GOCE. *J Pediatr Hematol Oncol* 2017;39(5):e244-e48. doi: 10.1097/MPH.0000000000000816
3. Hallahan AR, Shaw PJ, Rowell G, et al. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. *Crit Care Med* 2000;28(11):3718-21. doi: 10.1097/00003246-200011000-00030
4. Tamburro RF, Barfield RC, Shaffer ML, et al. Changes in outcomes (1996-2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. *Pediatr Crit Care Med* 2008;9(3):270-7. doi: 10.1097/PCC.0b013e31816c7260
5. Wosten-van Asperen RM, van Gestel JPJ, van Grotel M, 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. doi: 10.1016/j.critrevonc.2019.07.014
6. Brilli RJ, Gibson R, Luria JW, et al. Implementation of a medical emergency team in a large pediatric teaching hospital prevents respiratory and cardiopulmonary arrests outside the intensive care unit. *Pediatr Crit Care Med* 2007;8(3):236-46; quiz 47. doi: 10.1097/01.Pcc.0000262947.72442.Ea [published Online First: 2007/04/10]
7. Bonafide CP, Localio AR, Roberts KE, et al. Impact of rapid response system implementation on critical deterioration events in children. *JAMA Pediatr* 2014;168(1):25-33. doi: 10.1001/*JAMA*pediatrics.2013.3266 [published Online First: 2013/11/13]
8. Trubey R, Huang C, Lugg-Widger FV, et al. Validity and effectiveness of paediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalised children: a systematic review. *BMJ Open* 2019;9(5):e022105. doi: 10.1136/bmjopen-2018-022105
9. Parshuram CS, Dryden-Palmer K, Farrell C, et al. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. *JAMA* 2018;319(10):1002-12. doi: 10.1001/*JAMA*.2018.0948 [published Online First: 2018/02/28]
10. Parshuram CS, Duncan HP, Joffe AR, et al. Multicentre validation of the bedside paediatric early warning system score: a severity of illness score to detect evolving critical illness in hospitalised children. *Crit Care* 2011;15(4):R184. doi: 10.1186/cc10337 [published Online First: 2011/08/05]
11. Parshuram CS, Hutchison J, Middaugh K. Development and initial validation of the Bedside Paediatric Early Warning System score. *Crit Care* 2009;13(4):R135. doi: 10.1186/cc7998 [published Online First: 2009/08/15]
12. Agulnik A, Forbes PW, Stenquist N, et al. Validation of a Pediatric Early Warning Score in Hospitalized Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients. *Pediatr Crit Care Med* 2016;17(4):e146-53. doi: 10.1097/pcc.0000000000000662 [published Online First: 2016/02/26]
13. Cater DT, Tori AJ, Moser EAS, et al. Modification and Assessment of the Bedside Pediatric Early Warning Score in the Pediatric Allogeneic Hematopoietic Cell Transplant Population. *Pediatr Crit Care Med* 2018;19(5):483-88. doi: 10.1097/pcc.0000000000001521 [published Online First: 2018/03/10]
14. Dean NP, Fenix JB, Spaeder M, et al. Evaluation of a Pediatric Early Warning Score Across Different Subspecialty Patients. *Pediatr Crit Care Med* 2017;18(7):655-60. doi: 10.1097/pcc.0000000000001176 [published Online First: 2017/04/27]
15. Gawronski O, Ciofi Degli Atti ML, Di Ciommo V, et al. Accuracy of Bedside Paediatric Early Warning System (BedsidePEWS) in a Pediatric Stem Cell Transplant Unit. *J*

Pediatr Oncol Nurs 2016;33(4):249-56. doi: 10.1177/1043454215600154 [published Online First: 2015/10/27]
16. Fuijkschot J, Vernhout B, Lemson J, et al. Validation of a Paediatric Early Warning Score: first results and implications of usage. *Eur J Pediatr* 2015;174(1):15-21. doi: 10.1007/s00431-014-2357-8 [published Online First: 2014/06/20]
17. Cooksley T, Kitlowski E, Haji-Michael P. Effectiveness of Modified Early Warning Score in predicting outcomes in oncology patients. *QJM* 2012;105(11):1083-8. doi: 10.1093/qjmed/hcs138 [published Online First: 2012/08/03]
18. Straney L, Clements A, Parslow RC, 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. doi: 10.1097/PCC.0b013e31829760cf [published Online First: 2013/07/19]
19. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med* 2013;41(7):1761-73. doi: 10.1097/CCM.0b013e31828a2bbd [published Online First: 2013/05/21]
20. d'Agostino RB. Belanger A. d'Agostino RB Jr. A Suggestion for Using Powerful and Informative Tests of Normality. *Am Stat* 1990;44(4):316 - 21.
21. Frank E. Harrell J. *Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*: Springer, Cham 2015.
22. van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* 2000;19(24):3401-15. doi: 10.1002/1097-0258(20001230)19:24<3401::aid-sim554>3.0.co;2-2
23. Harrell FEL, Kerry L. Mark, Daniel B. . Tutorials in Biostatistics - Multivariable prognostic models: issues in developing models, eveluatiing assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.
24. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162(1):W1-73. doi: 10.7326/M14-0698
25. Chapman SM, Maconochie IK. Early warning scores in paediatrics: an overview. *Arch Dis Child* 2019;104(4):395-99. doi: 10.1136/archdischild-2018-314807
26. Moons KG, Royston P, Vergouwe Y, et al. Prognosis and prognostic research: what, why, and how? *BMJ* 2009;338:b375. doi: 10.1136/bmj.b375
27. Rose SVdL, M. J. A Note on Risk Prediction for Case-Control Studies. *UC Berkeley Division of Biostatistics Working Paper Series* 2008 (Paper 241)
28. Steyerberg EW. *Clinical Prediction Models A Practical Approach to Development, Validation, and Updating*: Springer Science+Business Media, LLC, 2009.
29. Hsu BS, Hill V, Simone S. Executive Summary: Criteria for Critical Care of Infants and Children: PICU Admission, Discharge, and Triage Practice Statement and Levels of Care Guidance. 2019 doi: 10.1542/peds.2019-2433
30. Menon K, McNally JD, Zimmerman JJ, et al. Primary Outcome Measures in Pediatric Septic Shock Trials: A Systematic Review. *Pediatr Crit Care Med* 2017;18(3):e146-e54. doi: 10.1097/pcc.0000000000001078
31. Ospina-Tascón GA, Büchele GL, Vincent JL. Multicenter, randomized, controlled trials evaluating mortality in intensive care: doomed to fail? *Crit Care Med* 2008;36(4):1311-22. doi: 10.1097/CCM.0b013e318168ea3e
32. Halpern NA. Early Warning Systems for Hospitalized Pediatric Patients. *JAMA* 2018;319(10):981-82. doi: 10.1001/*JAMA*.2018.1524
33. Agulnik A, Méndez Aceituno A, Mora Robles LN, et al. Validation of a pediatric early warning system for hospitalized pediatric oncology patients in a resource-limited setting. *Cancer* 2017;123(24):4903-13. doi: 10.1002/cncr.30951

Supplement

Supplementary Table S1. The standardized search terms that will be used for data extraction of data that are in a non-structured text field (i.e., the daily report of the nurses and physicians of the nursing wards).

Purpose of data extraction	Search terms
To identify clinical deterioration events or interventions associated with clinical deterioration events and to enable classification of reason of PICU admission.	Resuscitation ICU ICU admission ICU physician Intubation* Bag | mask, M+B Fluid[s] Adrenalin Clinical deterioration Circulatory deterioration Respiratory deterioration
To identify start of palliative care	Palliative

*these words were searched as regular expressions, thus part of the word, to not miss any alternative search hits, for example: intub~ for intubation or intubated. The search terms that will be used are in Dutch and have been translated for the purpose of this study protocol.

Supplementary Table S2. The TRIPOD checklist (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) considering the study protocol.

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	67
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	68 (if applicable)
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	69
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	69

Supplementary Table S2. The TRIPOD checklist- *continued*.

Section/Topic	Item	Checklist Item	Page
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	70
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	70
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	70
	5b	Describe eligibility criteria for participants.	70
	5c	Give details of treatments received, if relevant.	73
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	70-72
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	74, 75
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	76
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	75
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	75, 76
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	75, 76
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	71-76
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	NA
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	NA
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA

Supplementary Table S2. The TRIPOD checklist- *continued*.

Section/Topic	Item	Checklist Item	Page
Discussion			
Model performance	16	Report performance measures (with CIs) for the prediction model.	NA
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Limitations	18	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data).	78
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	NA
Implications	20	Discuss the potential clinical use of the model and implications for future research.	78
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	colofon

5

Validation of a Modified Bedside Pediatric Early Warning System score for detection of clinical deterioration in hospitalized pediatric oncology patients: A prospective cohort study

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Abstract

Background: Hospitalized pediatric oncology patients are at risk of severe clinical deterioration. Yet pediatric early warning system (PEWS) scores have not been prospectively validated in these patients. We aimed to determine the predictive performance of the modified BedsidePEWS score for unplanned pediatric intensive care unit (PICU) admission and cardiopulmonary resuscitation (CPR) in this patient population.

Methods: We performed a prospective cohort study in an 80-bed pediatric oncology hospital in the Netherlands, where care has been nationally centralized. All hospitalized pediatric oncology patients aged 0 to 18 years were eligible for inclusion. A Cox proportional hazard model was estimated to study the association between the modified BedsidePEWS score and unplanned PICU admissions or CPR. The predictive performance of the model was internally validated by bootstrapping.

Results: A total of 1137 patients were included. During the study, 103 patients experienced 127 unplanned PICU admissions and 3 CPRs. The hazard ratio for unplanned PICU admission or CPR was 1.65 (95% confidence interval (CI) 1.59 -1.72) for each point increase in the modified BedsidePEWS score. The discriminative ability was moderate (D-index close to zero and a C-index of 0.83 (95% CI 0.79 - 0.90)). Positive and negative predictive value of modified BedsidePEWS score at the widely used cut-off of 8 at which escalation of care is required, was 1.4% and 99.9%, respectively.

Conclusion: The modified BedsidePEWS score is significantly associated with requirement of PICU transfer or CPR. In pediatric oncology patients, this PEWS score may aid in clinical decision making for timing of PICU transfer.

Introduction

Unrecognized clinical deterioration in hospitalized pediatric patients may lead to adverse outcomes, such as cardiac arrest or death. Pediatric oncology patients are especially at risk for rapid deterioration, given their severity of illness, toxicity of treatment and associated immunosuppression. Up to 38% of patients require admission to the pediatric intensive care unit (PICU) during their disease course, with sepsis and respiratory failure as main reasons for unplanned PICU admission.[1 2] Mortality rates of pediatric oncology patients requiring PICU admission exceed that of the general PICU population, ranging from 7 to 15%, versus 2-5%.[3-5] Unplanned PICU admissions, often preceded by clinical deterioration, have the highest PICU mortality.[6] In addition, pediatric oncology patients are approximately three times less likely to survive cardiopulmonary arrest than general pediatric patients.[7] Early detection of clinical deterioration resulting in timely escalation of care may therefore ultimately improve patients' outcomes.

A broad range of Pediatric Early Warning System (PEWS) scores are currently used for detection of clinical deterioration in hospitalized children. One of the most used scores, the BedsidePEWS, has been developed for routine use in clinical care for general pediatric patients, showing an excellent performance to identify children at risk for cardiopulmonary arrest.[8 9] In addition, it was one of the best performing PEWS scores in predicting clinical deterioration.[8 9] A multicenter cluster randomized trial showed a significant reduction in late PICU admission after implementation of the BedsidePEWS score.[10 11] This score has also been implemented in our pediatric oncology center, yet has not been validated in this patient population. It has been shown that early warning scores may need different interpretation in specific patient populations. For instance, the Early Warning Score was found to have poor discriminatory value in identifying deteriorating adult cancer patients requiring critical care.[12] Despite the widespread implementation of PEWSs, few studies have assessed the performance of a PEWS in pediatric oncology patients.[4 13-16] The majority of these studies were retrospective studies.[4 13-15] In addition, some of these studies were conducted in oncological subgroups, e.g., stem cell transplant patients, or patients in resource-limited settings, thereby limiting generalizability.[13 14 16] Moreover, most studies used matched case-control designs or the maximum PEWS score in the 24 hours prior to unplanned PICU admission[4 13-15], which may have resulted in overestimating the predictive performance of these scores.

In this prospective cohort study, we aimed to determine the predictive performance of a modified BedsidePEWS score for unplanned PICU admission or cardiopulmonary resuscitation (CPR) in hospitalized pediatric oncology patients.

Methods

Study design and setting

A detailed description of the study rationale and design was previously described.[17] We performed a prospective cohort study between February 1, 2019 and February 1, 2021 at the Princess Máxima Center, an 80-bed national referral center for pediatric oncology in the Netherlands. The study was approved by the ethical review board of our hospital (IRB protocol number 16-572/C). All hospitalized patients with International Classification of Diseases in Oncology (ICD-O) diagnosis of pediatric malignancy (morphology code 1, 2 or 3), aged 0 to 18 years were eligible for inclusion. Patients admitted as outpatients for routine diagnostic and therapeutic procedures were excluded. In addition, patients with restrictions in care (palliative care only, do-not-resuscitate orders, no PICU admission) were excluded from the moment restriction in care was registered.

We evaluated the BedsidePEWS as used in our hospital. At implementation in our hospital in 2014, the score had been slightly modified by adding temperature and categorization of oxygen therapy (Supplementary Table S1). Modified BedsidePEWS scores were assessed and documented in patients' electronic health record (EHR) by nursing staff as part of routine care on all inpatient wards. Nurses could manually enter either the sub items of the score, followed by automated calculation of the score, or the sum score directly into the EHR. In both cases, the required corresponding clinical action was shown. To optimize the adherence to the scoring algorithm, several efforts were made with focus on education, communication and workflow. These included multiple refresher courses, procedures to train newly hired staff, identifying barriers and facilitators, and encouragement to review modified BedsidePEWS scores at rounds and change of shifts. In addition, quality monitoring on modified BedsidePEWS scoring was aided by a weekly dashboard showing the nurses' performance of scoring in the different shifts at the wards.

Data collection

Data on patient characteristics, hospital admissions, outcome measures, vital signs and modified BedsidePEWS scores were extracted from the electronic health records (EHR; HiX, Chipsoft, Amsterdam, the Netherlands). Detailed information about data collection and preparation is provided in Supporting Information.

Primary and secondary outcomes

The primary outcome was the composite of an unplanned PICU admission or CPR. A single patient could experience the primary outcome event multiple times during a hospital stay. Therefore, the unit of study was an uninterrupted inpatient ward admission. This admission was ended when 1) the outcome event occurred 2) the patient was discharged

from the ward, 3) a restriction in care was registered, or 4) the patient turned 18 years. A new uninterrupted ward admission was started when the patient was discharged from the PICU to the ward or was readmitted to the hospital.

Secondary outcomes included minor clinical deterioration events requiring escalation of care (i.e., the initiation of high-flow oxygen therapy or non-rebreathing mask, fluid bolus, epinephrine intramuscular, or an urgent PICU consultation) not resulting in a PICU transfer or CPR, and any clinical deteriorations (i.e., the combination of significant clinical deterioration requiring PICU transfer or CPR and minor clinical deterioration events), see Supporting Information.

Statistical analysis

The modified BedsidePEWS score is a severity of illness score reflecting the clinical condition of the patient. This clinical condition may vary per patient and during a hospital stay. Therefore, we analyzed the modified BedsidePEWS as a time-varying covariate by estimating a Cox proportional hazard model[18] (see detailed description in Supporting Information). Time to event was the time between a current PEWS and the subsequent PEWS or a clinical deterioration event, whichever comes first. In this way, we incorporated all documented modified BedsidePEWS scores of all patients, accounting for the time-varying nature of the PEWS score and reoccurrence of the event within one single patient. Cancer diagnosis groups (solid tumors, hemato-oncology, and neuro-oncology) were also included as prognostic factors in the model. Finally, the same model was used to estimate the association between modified BedsidePEWS and secondary outcomes (see detailed description in Supporting Information). Internal validation of the model was performed by using Efron's bootstrap.[19]

Several threshold-based prediction measures were estimated for the score cut-off of 8 - the threshold at which escalation of care is required– and additionally for cut-offs 5 through 11, using the last modified BedsidePEWS score prior to event. These measures included sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and number needed to evaluate (calculated as 1 / PPV) [20], see Supporting Information.

Finally, we performed a post-hoc qualitative analysis of the modified BedsidePEWS in the 24-hour-period prior to the primary outcome events. All statistical analyses were performed using R-statistical software, version 3.6.2 (2019-12-12), and associated packages (see Supplement - Supporting Information).[21] Reporting of this validation study was performed using the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines (Supplementary Table S2).[21]

Results

A total of 5628 ward admissions of 1137 unique patients, and 119.813 modified BedsidePEWS scores were included. Table 1 reports the clinical characteristics of the included patients. The median (interquartile range [IQR]) age of the included patients was 8 [4 – 14] years and 43.3% was female. There were 127 unplanned PICU admissions and three CPRs among 103 patients. Following CPR and during the PICU admissions, 14 patients died (10.8%).

Compliance to the scoring algorithm

Compliance to the scoring algorithm is shown in Supplementary Table S3. For modified BedsidePEWS score categories 0-3 and 4-5, the median time intervals were below the intended time limit of the scoring algorithm, whereas for modified BedsidePEWS score category 6-7 the median time interval was higher than the intended time limit. In 85% of all modified BedsidePEWS score ≥ 8, a physician was called to evaluate the patient.

Performance of the modified BedsidePEWS – unplanned PICU admission or CPR

The modified BedsidePEWS was significantly associated with time to unplanned PICU admission or CPR with a hazard ratio (HR) of 1.65 (95% CI 1.59 – 1.72) for each point increase in the modified BedsidePEWS score (Table 2). The HRs (95% CI) per diagnosis groups were 1.16 (0.78 – 1.75) for hemato-oncology diagnosis and 1.09 (0.49 – 2.43) for neuro-oncology diagnosis, with solid tumors as reference category.

Internal validation of the model has been performed by using bootstrap. For the discriminative ability of the modified BedsidePEWS score, the C-index (95% CI) was 0.83 (0.79 – 0.90) and the discrimination index D (95% CI) was 0.20 (0.16 – 0.26). The model was well calibrated with an index corrected slope of 0.99 (Table 2).

Table 3 shows the distribution of the modified BedsidePEWS score related to occurrence of the primary outcome event. A cut-off of 8, at which escalation of care is required, yielded a negative predictive value of 99.9%, a positive predictive value of 1.5%, a sensitivity of 33,8%, specificity of 97,7%, and a number needed to evaluate of 67. Results corresponding to different thresholds of the modified BedsidePEWS are shown in Supplementary Table S4. Lowering the cut-off threshold resulted in an increased sensitivity, a decreased specificity, a decreased positive predictive value and a higher number needed to evaluate. On the contrary, raising the cut-off threshold results in a decreased sensitivity, accompanied by an increased specificity, and a higher positive predictive value with lower number needed to evaluate.

Table 1. Demographic and clinical characteristics of included patients.

Characteristic	Total patients (n = 1137)	Patients without primary outcome event (n =1034)	Patients with primary outcome event (n = 103)
Age (years), median [IQR]	8.4 [3.7 – 13.6]	8.4 [3.8 – 13.7]	7.6 [2.9 – 13.2]
Female sex, n (%)	495 (43.5)	446 (43.1)	49 (47.6)
Oncological diagnosis, n (%)			
Hemato-oncological	482 (42.4)	422 (40.8)	60 (58.3)
Solid tumor	412 (36.2)	375 (36.53)	37 (35.9)
Brain / central nervous system tumor	243 (21.4)	237 (22.9)	6 (5.8)
HSCT recipient, n (%)	125 (11.0)	100 (9.7)	25 (24.3)
Allogeneic	58 (5.1)	45 (4.4)	13 (12.6)
Autologous	67 (5.9)	55 (5.3)	12 (11.7)
CAR-T cell therapy recipient, n (%)	20 (1.8)	16 (1.5)	4 (3.9)
Number of primary outcome events per patient, n (%)			
0	1037 (91.2)	1034 (100)	0 (0)
1	82 (7.2)	0	82 (79.6)
2	16 (1.4)	0	16 (15.5)
3	4 (0.4)	0	4 (3.9)
4	1 (0.2)	0	1 (1.0)

CAR-T chimeric antigen receptor t-cell; *CPR* cardiopulmonary resuscitation; *HSCT* hematopoietic stem cell transplantation; *IQR* interquartile range; *NA* not applicable; *PICU* pediatric intensive care unit.

Table 2. Overview of the performance of modified BedsidePEWS score.

Outcome measure	Cox proportional hazard model		Internal validation after bootstrapping (n=500)		
			Discrimination		Calibration
	HR (95% CI)	p-value	C-index (95% CI)	D (95% CI)	Slope
Unplanned PICU admission or CPR	1.65 (1.59 -1.72)	< 0.01	0.83 (0.79 – 0.90)	0.20 (0.16 – 0.26)	0.99
Minor clinical deterioration events*	1.77 (1.71-1.83)	< 0.01	0.86 (0.83 – 0.88)	0.17 (0.15 – 0.19)	0.99
All clinical deterioration events**	1.75 (1.70-1.81)	< 0.01	0.84 (0.82 – 0.87)	0.16 (0.15 – 0.18)	0.99

95% CI 95% confidence interval; *C-index* concordance-index; *D* discrimination index; *HR* hazard ratio.

* Clinical deterioration events: i.e., the initiation of high-flow oxygen therapy or non-rebreathing mask, fluid bolus, epinephrine intramuscular, or an urgent PICU consultation not resulting in a PICU transfer or CPR.

**Unplanned PICU admissions, CPR and minor clinical deterioration events < 24 hours were combined.

Performance of the modified BedsidePEWS – minor and any clinical deterioration events

Of the 1137 included patients, 234 patients experienced a total of 463 minor clinical deteriorations, and 276 patients experienced 583 clinical deterioration events (i.e., combined unplanned PICU admission, CPR and minor clinical deterioration events). The modified BedsidePEWS was significantly associated with time to minor clinical deterioration as well as any clinical deterioration event; HR (95% CI) 1.77 (1.71-1.83) and 1.75 (1.70 – 1.81) respectively (Table 2). The discrimination index D, C-index and calibration were similar to those of the primary outcome event, as is shown in Table 2.

The distribution of the modified BedsidePEWS scores and occurrence of a minor clinical deterioration event is shown in Supplementary Table S5 and for all clinical deterioration events in Supplementary Table S6. Like the primary outcome, the negative predictive value for minor deterioration events as well as all clinical deterioration events was high (99,6% for both outcomes). The positive predictive value at the cut-off of 8 was 8,3% for minor clinical deterioration and 9,6% for any clinical deterioration.

Table 3. Distribution of modified BedsidePEWS score and occurrence of unplanned PICU admission or CPR.

Modified BedsidePEWS score	No event occurred (frequency)	Event occurred (frequency)	No event occurred (%)	Event occurred (%)
0	34653	6	100	0
1	34526	14	100	0.1
2	21763	13	99.9	0.1
3	11197	10	99.9	0.1
4	6290	8	99.9	0.1
5	3658	7	99.8	0.2
6	2878	13	99.6	0.5
7	1893	15	99.2	1.3
8	1035	11	98.9	1.2
9	721	8	98.9	1.1
10	461	6	98.7	2.2
11	281	7	97.6	3.6
12	148	3	98.0	3.2
13	70	2	97.2	9.1
14	42	4	91.3	12.5
15	32	1	97.0	3.0
16	14	2	87.5	12.5
17	1	0	100	0

The modified BedsidePEWS scores were arranged within a single clinical episode from one PEWS score to the next one (time interval between scores), with at the end of each time-interval the patients' status whether or not an event occurred.

Modified BedsidePEWS scores in the 24 hours prior to non-elective PICU admission or CPR

The characteristics of the 127 unplanned PICU admissions and 3 CPRs are shown in Table 4. The three most common reasons for PICU admission were respiratory failure (35%), sepsis (16%) and cardiovascular failure (15%). The median (IQR) PICU length of stay was 2 (1-6) days, with a range of 0 to 79 days. Visual inspection of the modified BedsidePEWS scores clustered into 1-hour-periods prior to unplanned PICU admissions or CPR showed an increasing modified BedsidePEWS score in the 24 hours prior to the event, however there is still large variation from low to high values (Figure 1).

In the 24 hours prior to the event, 67 of the 130 primary outcome events (52%) had a maximum modified BedsidePEWS < 8, whereas 63 / 130 events (48%) had a maximum BedsidePEWS of ≥ 8 (Table 4). A majority of the unplanned PICU admissions with a maximum BedsidePEWS <8 included patients requiring a PICU transfer because of an upper airway problem (e.g., acute vocal cord paralysis or mediastinal mass, n = 14), malignant hypertension (n = 5), neurologic deterioration (n = 7), or unplanned post-operative care (n = 16).

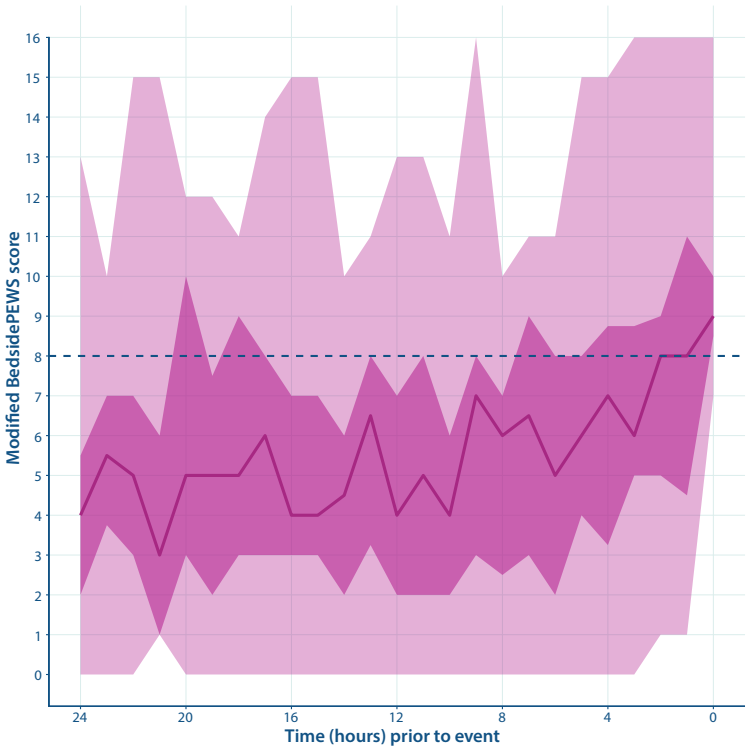

Figure 1. The median modified BedsidePEWS score, clustered per hour, with the interquartile range and range (minimum and maximum), in the 24 hours prior to unplanned PICU admission. A score cut-off of 8, at which escalation of care is required, is marked by a dashed line. The primary outcome events occur at t = 0, which is at the right of the plot.

Table 4. The maximum modified BedsidePEWS score in the 24 hours prior to primary outcome events (unplanned PICU admission or CPR) related to the PICU admission reason.

	Number of events n = 130	Maximum PEWS score < 8 n = 67	Maximum PEWS score ≥ 8 n = 63
Unplanned PICU admission, n (%)	127 (98)	66 (99)	61 (97)
PICU admission reason:			
Respiratory failure, n (%)	45 (35)	15 (22)	30 (48)
Upper airway problems	14	10	4
Pulmonary problems	31	5	26
Sepsis, n (%)	21 (16)	8 (12)	13 (21)
Cardiovascular failure, n (%)	20 (15)	11 (16)	9 (14)
Hypotension / shock	15	8	7
Malignant hypertension	5	3	2
Unplanned post-operative, n (%)	17 (13)	16 (24)	1 (2)
Neurological deterioration, n (%)	9 (7)	7 (10)	2 (3)
Renal failure, n (%)	3 (2)	1 (1)	2 (3)
Hepatic failure, n (%)	1 (1)	0 (0)	1 (2)
After cardiopulmonary resuscitation, n (%)	2 (2)	1 (1)	1 (2)
Other, n (%)	9 (7)	7 (10)	2 (3)
CPR (not followed by PICU admission), n (%)	3 (2)	1 (1)	2 (3)

CPR cardiopulmonary resuscitation; *PEWS* Pediatric Early Warning system; *PICU* Pediatric Intensive Care Unit.

Discussion

We prospectively investigated the performance of a modified BedsidePEWS score to predict clinical deterioration in hospitalized pediatric oncology patients. This score is significantly associated with unplanned PICU admission or cardiopulmonary resuscitation, as well with minor clinical deterioration and any clinical deterioration. We found a high negative predictive value (99,9%) for the widely used cut-off score of 8, indicating that the BedsidePEWS is highly accurate in hospitalized pediatric oncology patients.

However, the results of the predictive performance reveal several nuances to the use of the modified BedsidePEWS score as a prediction tool to timely detect clinical deterioration. First, we found a moderate discriminative ability of the modified BedsidePEWS, as reflected by a C-index of 0.8 and a D-index close to zero. This could be explained by the low incidence rate of the primary outcome. A second nuance is that, despite the high negative predictive value of 99,9%, 67 of the 130 unplanned PICU admissions and CPRs were preceded by a maximum modified BedsidePEWS of < 8 in the 24 hours prior to these events. There may be several explanations for this observation. Some types of critical decline are not

captured by the modified BedsidePEWS (e.g., upper airway problems or neurological deterioration). In addition, unplanned post-operative patients often require PICU transfer as a result of an acute perioperative complication. Low modified BedsidePEWS scores preceding the operating room may represent a good clinical preoperative condition. Since we used the scores as documented by nurses in daily practice, there may be missing items in the score possibly resulting in a lower score. This is a common problem described in previous PEWS validation studies.[10 22] A third nuance to the use of the modified BedsidePEWS as a prediction tool involves the low positive predictive value of 1.5% when using a modified BedsidePEWS cut-off score of 8. The number needed to evaluate of 67 at this cut-off indicates that of the 67 times any patient is evaluated for a modified BedsidePEWS score ≥ 8, 1 time the patient truly requires to be transferred to the PICU. This may lead to alarm fatigue.[23] On the other hand, given the trade-off between positive and negative predictive value, one may accept this false alarm rate in order to not miss any patient. We showed that lowering the modified BedsidePEWS threshold resulted in higher sensitivity. However, this was accompanied with lower positive predictive values and higher numbers needed to evaluate. This risks even more alarm fatigue or suboptimal adherence to the scoring algorithm.[24] Therefore, lowering the threshold at which patient evaluation is required may not necessarily have the desired effect of improving detection of clinical deterioration. Raising the threshold further decreases the sensitivity, which may risk missing patients. Taking these considerations into account, we feel that the threshold of 8 is the optimal score cut-off.

Our study shows that the modified BedsidePEWS score is a strong prognostic factor for time to PICU transfer or detecting clinical deterioration. This supports its use in clinical decision making for timing of PICU transfer or escalation of care. Our results are in line with other studies validating a PEWS score in pediatric oncology patients. These studies reported a good predictive performance of PEWS scores for unplanned PICU transfer [4 13-16], or the early detection of critically ill patients.[25] They all found a high area under the receiver operating characteristic (AUROC) for a PEWS score for the outcome of unplanned PICU transfer, ranging from 0.83 to 0.96.[4 13-16] In addition, it was demonstrated that PEWS may aid in triage of transfer to the PICU.[26]

In contrast to these previous studies, we employed a prospective cohort design including all subgroups of pediatric oncology patients, such as HSCT patients. In addition, we included all modified BedsidePEWS scores as documented in the EHR. This is the first study validating a PEWS in pediatric oncology patients using the time-to-event data. The use of an uninterrupted inpatient ward admission as a study unit as opposed to a single patient allowed us to account for re-occurrence of the outcome event within the same hospitalization period. Taking these points into consideration, we believe that this study yields a valid estimation of the predictive performance of the modified BedsidePEWS in pediatric oncology patients.

Our study has several limitations. First, we used clinical data as documented in the EHRs in a real-life setting. Inherently, this means that modified BedsidePEWS scores may not have been completely scored or adherence to the scoring algorithm was not perfect. Considering the outcome events, there could be documentation errors, mainly of the secondary outcome events as these events were extracted from the physicians' and nurses' daily reports. Missing items in the PEWS score often lead to a lower score and may lead to an undervaluation of the severity of illness.[22] Completing all items of a PEWS score or a sustainable adherence to the scoring algorithm remains challenging in daily practice, as was demonstrated by other studies validating a PEWS score.[22 27] To address these problems, multiple refresher courses and feedback on the scoring were provided throughout the study period. Yet, there were also barriers impeding PEWS implementation, e.g., the manual entry of the vital signs in the computer, which we were unable to fully resolve during the study period. Currently, we are working towards an automatized process of registration of the vital signs and simultaneous calculation of a PEWS score in the EHR. Second, prevention of clinical deterioration is also dependent on the initiation of timely and appropriate interventions. Two before-and-after studies showed a reduction in the rate and the severity of clinical deterioration events following PEWS implementation, implicating improved recognition and timely treatment of clinical deteriorating patients.[28 29] This timely identification followed by the appropriate intervention may influence the need for PICU transfer. Due to the observational design of the study, we are unable to identify the underlying cause of the clinical deterioration (e.g., failure of PEWS, inappropriate interventions, delay in treatment). This is a fundamental limitation that is inherently part of all studies validating a PEWS in a real-life setting. We addressed this problem by analyzing the minor clinical deterioration events in our study as these reflect the care interventions for a clinically deteriorating patient. The hazard ratio for these outcome measures as well as the discriminative ability are comparable to the primary outcome measure. Last, the validation of one modified BedsidePEWS score in a setting of a single pediatric oncology hospital may limit the generalizability of our findings to other settings.

The results of our study contribute to the evidence-based use of a PEWS to support clinical decision making of timing of escalation of care or PICU transfer in pediatric oncology patients. For future research, we see several opportunities to improve the timely recognition of clinical deterioration in pediatric oncology patients. Currently, the modified BedsidePEWS score leverages only a small fraction of the EHR content, since this score was originally designed to be tabulated by hand by nurses.[8] The widespread implementation of EHRs facilitates the development of more sophisticated systems incorporating additional routinely collected patient data, oncology specific factors or contextual factors such as parents' or clinicians' 'gut feeling', which may improve the predictive performance of a model to detect clinical deterioration in pediatric oncology patients.[30] The combination

with the possibility for continuous monitoring and big data analytics may further improve prediction, situation awareness and personalized risk assessment.[31-33] Embedding this score in the digital workflow is important to improve adherence to the scoring algorithm and reduce administrative burden.[34]

After this study was performed, we have implemented the DutchPEWS in our center, a national PEWS score. As this score incorporates caregivers' gut feeling and neurological deterioration, this might at least partially address the missing of patients with specific types of critical deterioration, e.g., neurological deterioration, though the predictive performance of this DutchPEWS has yet to be assessed. Additionally, we have improved the digital workflow, with automated calculation of all PEWS scores, and are working towards automated registration of vital signs in the EHR.

Of note, to prevent delay in escalation of care and to ultimately improve patient outcome, a monitoring tool that timely detects deterioration is not enough. A robust implementation of a PEWS is essential for its validity and impact on patients' outcome. A PEWS is a complex socio-technological intervention that requires consideration at the levels of the individual health care provider, multidisciplinary team, hospital and policy. Several barriers and enablers for successful implementation have been identified.[35] Agulnik et al. demonstrated how barriers could be turned into enablers using targeted strategies such as early engagement of all stakeholders, and a time-limited pilot followed by adaptation.[36] It is necessary to embed a PEWS within a system, which stimulates situational awareness, with available resources and continuous quality monitoring and improvement.[37] Besides the optimization of recognition of clinical deterioration, research should focus on evaluation of decision-making and response, quality improvement of implementation, and the effect of implementation with robust, valid, and clinically meaningful outcome parameters.[38]

Conclusion

This prospective study shows that increasing modified BedsidePEWS scores are significantly associated with requirement of PICU transfer or CPR in hospitalized pediatric oncology patients. Although it does not capture some specific clinical deterioration conditions, the modified BedsidePEWS is a valuable adjunct to clinical decision making in the timing of escalation of care in this high-risk patient population.

References

1. Hallahan AR, Shaw PJ, Rowell G, et al. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. *Crit Care Med* 2000;28(11):3718-21. doi: 10.1097/00003246-200011000-00030
2. Rosenman MB, Vik T, Hui SL, et al. Hospital resource utilization in childhood cancer. *J Pediatr Hematol Oncol* 2005;27(6):295-300. doi: 10.1097/01.mph.0000168724.19025.a4
3. Zinter MS, DuBois SG, Spicer A, et al. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014;40(10):1536-44. doi: 10.1007/s00134-014-3389-2
4. Agulnik A, Forbes PW, Stenquist N, et al. Validation of a Pediatric Early Warning Score in Hospitalized Pediatric Oncology and Hematopoietic Stem Cell Transplant Patients. *Pediatr Crit Care Med* 2016;17(4):e146-53. doi: 10.1097/pcc.0000000000000662
5. Heneghan JA, Pollack MM. Morbidity: Changing the Outcome Paradigm for Pediatric Critical Care. *Pediatr Clin N Am* 2017;64(5):1147-65. doi: 10.1016/j.pcl.2017.06.011
6. Wösten-van Asperen RM, van Gestel JPJ, van Grotel M, 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. doi: 10.1016/j.critrevonc.2019.07.014
7. López-Herce J, Del Castillo J, Matamoros M, et al. Factors associated with mortality in pediatric in-hospital cardiac arrest: a prospective multicenter multinational observational study. *Intensive Care Med* 2013;39(2):309-18. doi: 10.1007/s00134-012-2709-7
8. Parshuram CS, Hutchison J, Middaugh K. Development and initial validation of the Bedside Paediatric Early Warning System score. *Crit Care* 2009;13(4):R135. doi: 10.1186/cc7998
9. Parshuram CS, Duncan HP, Joffe AR, et al. Multicentre validation of the bedside paediatric early warning system score: a severity of illness score to detect evolving critical illness in hospitalised children. *Crit Care* 2011;15(4):R184. doi: 10.1186/cc10337
10. Parshuram CS, Dryden-Palmer K, Farrell C, et al. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. *JAMA* 2018;319(10):1002-12. doi: 10.1001/*JAMA*.2018.0948
11. Chapman SM, Wray J, Oulton K, et al. 'The Score Matters': wide variations in predictive performance of 18 paediatric track and trigger systems. *Arch Dis Child* 2017;102(6):487-95. doi: 10.1136/archdischild-2016-311088
12. Cooksley T, Kitlowski E, Haji-Michael P. Effectiveness of Modified Early Warning Score in predicting outcomes in oncology patients. *QJM* 2012;105(11):1083-8. doi: 10.1093/qjmed/hcs138
13. Agulnik A, Méndez Aceituno A, Mora Robles LN, et al. Validation of a pediatric early warning system for hospitalized pediatric oncology patients in a resource-limited setting. *Cancer* 2017;123(24):4903-13. doi: 10.1002/cncr.30951
14. Cater DT, Tori AJ, Moser EAS, et al. Modification and Assessment of the Bedside Pediatric Early Warning Score in the Pediatric Allogeneic Hematopoietic Cell Transplant Population. *Pediatr Crit Care Med* 2018;19(5):483-88. doi: 10.1097/pcc.0000000000001521
15. Dean NP, Fenix JB, Spaeder M, et al. Evaluation of a Pediatric Early Warning Score Across Different Subspecialty Patients. *Pediatr Crit Care Med* 2017;18(7):655-60. doi: 10.1097/pcc.0000000000001176
16. Gawronski O, Ciofi Degli Atti ML, Di Ciommo V, et al. Accuracy of Bedside Paediatric Early Warning System (BedsidePEWS) in a Pediatric Stem Cell Transplant Unit. *J Pediatr Oncol Nurs* 2016;33(4):249-56. doi: 10.1177/1043454215600154
17. Soeteman M, Kappen TH, van Engelen M, et al. Identifying the critically ill paediatric oncology patient: a study protocol for a prospective observational cohort study for validation of a modified Bedside Paediatric Early Warning System score in hospitalised paediatric oncology patients. *BMJ Open* 2021;11(5):e046360. doi: 10.1136/bmjopen-2020-046360
18. Therneau T, Crowson C, Atkinson E. Using Time Dependent Covariates and Time Dependent Coeficients in the Cox Model. 2019
19. DiCiccio TJ, Efron B. Bootstrap confidence intervals. *Statistical Science* 1996;11(3):189-228, 40.

20. Romero-Brufau S, Huddleston JM, Escobar GJ, et al. Why the C-statistic is not informative to evaluate early warning scores and what metrics to use. *Crit Care* 2015;19:285. doi: 10.1186/s13054-015-0999-1
21. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162(1):W1-73. doi: 10.7326/M14-0698
22. Chapman SM, Oulton K, Peters MJ, et al. Missed opportunities: incomplete and inaccurate recording of paediatric early warning scores. *Arch Dis Child* 2019;104(12):1208-13. doi: 10.1136/archdischild-2018-316248
23. Bedoya AD, Clement ME, Phelan M, et al. Minimal Impact of Implemented Early Warning Score and Best Practice Alert for Patient Deterioration. *Crit Care Med* 2019;47(1):49-55. doi: 10.1097/CCM.0000000000003439
24. Cassidy CE, MacEachern L, Best S, et al. Barriers and Enablers to Implementing the Children's Hospital Early Warning Score: A Pre- and Post-Implementation Qualitative Descriptive Study. *J Pediatr Nurs* 2019;46:39-47. doi: 10.1016/j.pedn.2019.02.008
25. Fuijkschot J, Vernhout B, Lemson J, et al. Validation of a Paediatric Early Warning Score: first results and implications of usage. *Eur J Pediatr* 2015;174(1):15-21. doi: 10.1007/s00431-014-2357-8
26. Agulnik A, Nadkarni A, Mora Robles LN, et al. Pediatric Early Warning Systems aid in triage to intermediate versus intensive care for pediatric oncology patients in resource-limited hospitals. *Pediatr Blood Cancer* 2018;65(8):e27076. doi: 10.1002/pbc.27076
27. de Groot JF, Damen N, de Loos E, et al. Implementing paediatric early warning scores systems in the Netherlands: future implications. *BMC pediatrics* 2018;18(1):128. doi: 10.1186/s12887-018-1099-6
28. Sefton G, McGrath C, Tume L, et al. What impact did a Paediatric Early Warning system have on emergency admissions to the paediatric intensive care unit? An observational cohort study. *Intensive Crit Care Nurs* 2015;31(2):91-9. doi: 10.1016/j.iccn.2014.01.001
29. Agulnik A, Mora Robles LN, Forbes PW, et al. Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. *Cancer* 2017;123(15):2965-74. doi: 10.1002/cncr.30664
30. Brady PW, Muething S, Kotagal U, et al. Improving situation awareness to reduce unrecognized clinical deterioration and serious safety events. *Pediatrics* 2013;131(1):e298-308. doi: 10.1542/peds.2012-1364
31. Churpek MM, Yuen TC, Park SY, et al. Using electronic health record data to develop and validate a prediction model for adverse outcomes in the wards*. *Crit Care Med* 2014;42(4):841-8. doi: 10.1097/ccm.0000000000000038
32. Zhai H, Brady P, Li Q, et al. Developing and evaluating a machine learning based algorithm to predict the need of pediatric intensive care unit transfer for newly hospitalized children. *Resuscitation* 2014;85(8):1065-71. doi: 10.1016/j.resuscitation.2014.04.009
33. Pimentel MA, Redfern OC, Malycha J, et al. Detecting Deteriorating Patients in Hospital: Development and Validation of a Novel Scoring System. *Am J Respir Crit Care Med* 2021 doi: 10.1164/rccm.202007-2700OC
34. Tomasi JN, Hamilton MV, Fan M, et al. Assessing the electronic Bedside Paediatric Early Warning System: A simulation study on decision-making and usability. *Int J Med Inform* 2020;133:103969. doi: 10.1016/j.ijmedinf.2019.103969
35. Connolly F, Byrne D, Lydon S, et al. Barriers and facilitators related to the implementation of a physiological track and trigger system: A systematic review of the qualitative evidence. *Int J Qual Health Care* 2017;29(8):973-80. doi: 10.1093/intqhc/mzx148
36. Agulnik A, Ferrara G, Puerto-Torres M, et al. Assessment of Barriers and Enablers to Implementation of a Pediatric Early Warning System in Resource-Limited Settings. *JAMA Netw Open* 2022;5(3):e221547. doi: 10.1001/*JAMA*networkopen.2022.1547
37. Jacob N, Moriarty Y, Lloyd A, et al. Optimising paediatric afferent component early warning systems: a hermeneutic systematic literature review and model development. *BMJ Open* 2019;9(11):e028796. doi: 10.1136/bmjopen-2018-028796
38. Chapman SM, Maconochie IK. Early warning scores in paediatrics: an overview. *Arch Dis Child* 2019;104 doi: 10.1136/archdischild-2018-314807

Supplementary Methods

Detailed description of the data collection

Modified BedsidePEWS score assessment and registration

The modified BedsidePEWS has been used since the early start of the Princess Máxima Center, in 2014.[1] At implementation of this score in our hospital, prior to the start of this study, there were two minor modifications compared to the original BedsidePEWS score. First, temperature was added (addition of maximum 2 points to the total score of a patient) as data from adult early warning systems show the importance of temperature as a key physiological parameter in predicting clinical deterioration in adult oncology patients.[2] Second, the oxygen therapy was divided into room air (0 points), <2 L/min (2 points) or the use of high-flow nasal cannula oxygen therapy or non-rebreathing mask (4 points). This resulted in an eight-parameter-based modified BedsidePEWS with a possible scoring range of 0–28 points.

According to the clinical protocol of the Modified BedsidePEWS, all patients admitted to the pediatric oncology wards were routinely scored once every 8-hour shift unless their clinical condition deteriorates. In this case, the frequency of scoring was routinely intensified: at a score of 4–6 points, the scoring frequency was increased to every 4 hours, and at a score of 6-7 points, the scoring frequency was increased to every hour. If the score exceeded 8, the nursing staff was instructed to contact the attending physician within 10 minutes, enabling prompt evaluation of the patient. In addition, an urgent PICU evaluation was recommended if BedsidePEWS exceeds 10. See also Chapter 4, Figure 1.

Clinical data collection

The modified BedsidePEWS score and its items were collected from the electronic health record (EHR). Patient data that were collected include demographics (age, sex), reason for hospital admission, underlying cancer diagnosis and therapy, disease status (e.g., initial diagnosis, during oncological treatment, end of treatment, relapse, refractory disease, progression, and palliative phase), hematopoietic or autologous stem cell transplantation, and CAR-T (chimeric antigen receptor t-cell) therapy or other immunotherapy modalities. Outcome data including unplanned PICU admission, CPR and clinical deterioration events were collected from the EHR. All data were stored in a research data warehouse, that was designed and expanded in close collaboration between physicians and data scientists.

One of the challenges in data collection was that not all data were stored in a structured data field. For example, the escalation of care for a clinically deteriorating patient (the secondary outcome) can be documented in the daily reports of nurses and physicians. Therefore, these data were retrieved in a systematic way from the non-structured text

fields of the daily nurses' and physicians' reports, using standardized search terms. For details on the standardized search terms, see Chapter 4, Supplementary Table S1.

First, we manually retrieved these data, and subsequently, we automated this data collection to a large extend, using the manually collected data to validate this automation. Admission reason for unplanned PICU admission were manually classified into respiratory, cardiovascular, sepsis, neurologic deterioration, gastro-intestinal, renal failure, or non-elective post-operative care. For the post-qualitative analysis, the respiratory and cardiovascular unplanned PICU admissions were manually subclassified into airway or breathing problem for respiratory PICU admission reason and hypotension, shock or (malignant) hypertension for cardiovascular PICU admission reason. After retrieving and classifying, these data were stored in Castor Electronic Data Capture (https://castoredc.com) with audit trail.

Detailed description of the secondary outcomes

Secondary outcomes included clinical deterioration events requiring escalation of care (i.e., the initiation of high-flow oxygen therapy or non-rebreathing mask, fluid bolus, epinephrine intramuscular, or an urgent PICU consultation) not resulting in a PICU transfer or CPR. The start of such a minor clinical deterioration was defined as the time point of the first intervention, as recorded in the EHR. We analyzed the association with and the predictive performance for 1) only minor clinical deterioration events and 2) a combination of significant clinical deterioration events (unplanned PICU or CPR) and minor clinical deterioration events.

Clinical deterioration events that occurred within 24 hours of each other were clustered into one episode of clinical deterioration, as they represented a series of clinical interventions. The clinical deterioration event was considered to have ended when no interventions were recorded in the EHR for 24 hours. After those 24 hours, a clinical deterioration event was considered a new initiation of clinical deterioration.

Detailed description of the statistical analyses

Continuous variables were reported as means along with their standard deviations if they follow a normal distribution, or as medians with interquartile ranges in case of a skewed distribution. Visual inspection of the data by using Q-Q probability plots together with D'Agostino test for normality was performed to assess departures from normality for each variable. Discrete variables were expressed as numbers with percentages. A two-sided alpha of 0.05 was considered to be statistically significant.

To study the association between the modified BedsidePEWS scores and unplanned PICU admission or CPR, a Cox proportional hazard model was estimated.[3] Time to event was the time between a current PEWS and the subsequent PEWS or a clinical deterioration event, whichever comes first after the current PEWS score, whichever came first after the current PEWS score. In this way, we were able to use of all of the documented modified

BedsidePEWS scores of all patients potentially at risk of developing the event, accounting for the time-varying nature of the PEWS score and reoccurrence of the event within one single patient. The same model was used to estimate the association between modified BedsidePEWS and secondary outcomes.

Internal validation of the model was performed by using bootstrap. To assess the predictive performance of the model, discrimination and calibration were investigated. Discrimination was assessed by using the concordance (C) and the discrimination (D) index. Efron's bootstrapping was used to obtain the bias-corrected 95% confidence intervals of the C- and D-index.[4] Both the C- and D-index indicate the ability of the model to provide higher predicted risk to patients who experience the event earlier compared to those experiencing the event later or not at all. The C-index should be near 1 and the D-index close to -1 or 1 for a good discriminative ability. Calibration was evaluated using a calibration slope. The calibration slope indicates the degree to which predictions are systematically too low or too high and should be near 1 in a well-calibrated model.

To deal with the multiple hospital admissions, clusters of episodes were incorporated into the Cox regression as they may contribute in the variation that needs to be accounted for when investigating the effect of the modified BedsidePEWS on the outcome event. As this study validated an existing score in an applied setting, the modified BedsidePEWS and its items as measured and documented in daily practice were used. Missing items of the BedsidePEWS were not imputed.

We calculated several threshold-based prediction measures for the current score cut-off of 8 and across different score cut-off points to gain more insight in the challenge of balancing sensitivity and specificity and a possible optimum cut-off point. We therefore estimated sensitivity, specificity, negative and positive predictive value and number needed to evaluate for cut-off 5 through 11. Sensitivity and specificity represent characteristics of the test, or in this case score, and are less affected by the prevalence of the outcome. On the contrary, negative and positive predictive value are influenced by the prevalence of the outcome in the population that is being tested, yet are useful metrics for interpretation of our findings to daily clinical use.[5] In addition, we calculated the "number needed to evaluate" (1/positive predictive value). This number needed to evaluate (NNE) has been proposed as a metric to evaluate early warning scores and refers to the number of patients with an alert that is necessary to further evaluate (or workup) to detect one outcome (true positive).[5]

All statistical analyses were performed using R–statistical software, version 3.6.2 (2019-12-12).[6] We used the following R packages: dplyr (version 1.0.2), tidyverse (version 1.3.0), stringr (version 1.4.0), openxlsx (version 4.1.4), castoRedc (version 1.0.3), lubridate (version 1.7.4), sqldf (version 0.4-11), survival (version 3.2 - 7), survminer (version 0.4.8), rms (version 6.1 - 0), table1 (version 1.2.1), and Hmisc (version 4.4-2).

Supplementary Tables

Supplementary Table S1. The items and related sub scores of the modified Bedside Pediatric Early Warning System score.

Modified BedsidePEWS score item	Sub score ranges	Sub scores
Respiratory rate (breaths / minute)	Deviation from normal ranges (0: normal value to 4: major deviation) by age group (0-3 months, 3-12 months, 1-4 years, 4-12 years, >12 years)	0 1 2 4
Respiratory effort	Deviation from normal respiratory effort (0: normal to 4: severe increase/any apnea)	0 1 2 4
Oxygen saturation	Deviation from expected values (0: >94%; 2: ≤90%)	0 1 2
Oxygen therapy	0: room air; 2: extra oxygen (< 2L/min); 4: High flow nasal cannula or non-rebreathing mask	0 2 4
Heart rate (beats/minute)	Deviation from normal ranges (0: normal value to 4: major deviation) by age group (0-3 months, 3-12 months, 1-4 years, 4-12 years, >12 years)	0 1 2 4
Capillary refill time	0: <3 seconds or 4: ≥3 seconds	0 4
Systolic blood pressure	Deviation from normal ranges (0: normal value to 4: major deviation) by age group (0-3 months, 3-12 months, 1-4 years, 4-12 years, >12 years)	0 1 2 4
Temperature	Deviation from normal ranges (0: 36.5 °C – 37.5 °C to 2: < 36.0 °C or > 38,5 °C	0 1 2

Adapted from Parshuram, et al. Development and initial validation of the Bedside Paediatric Early Warning System score. Crit Care. 2009;13(4):R135.

Supplementary Table S2. The TRIPOD checklist (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) of the validation study.

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	87
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	88 (if applicable)
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	89
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	89
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	90
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	90
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	90
	5b	Describe eligibility criteria for participants.	90
	5c	Give details of treatments received, if relevant.	90
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	90, 91
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	76
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	see Ch 4 - 76
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	91

Supplementary Table S2. The TRIPOD checklist - *continued*.

Section/Topic	Item	Checklist Item	Page
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	91, 103, 104
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	104
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	90
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	92
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	93
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model performance	16	Report performance measures (with CIs) for the prediction model.	93
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion			
Limitations	18	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data).	98
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	96 - 99
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	96 - 99
Implications	20	Discuss the potential clinical use of the model and implications for future research.	98
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	102 - 104
Funding	22	Give the source of funding and the role of the funders for the present study.	colofon

NA not applicable.

Supplementary Table S3. Time difference (hours) between two consecutive modified BedsidePEWS scores, categorized according to the scoring algorithm.

PEWS score category	PEWS score frequency	Number of PEWS scores	Median	IQR	Min	Max	% of PEWS scores ≥ 8 where physician was called
0 – 3	Every 8 hours	96775	5.7	2.0 – 10.8	0.1	48.0	
4 – 5	Every 4 hours	9858	3.0	1.2 – 6.1	0.1	47.2	
6 – 7	Every hour	4752	1.9	0.9 – 4.1	0.1	47.2	
≥ 8	Contacting physician	2800	1.6	0.7 – 3.3	0.1	24.3	85

IQR interquartile range; *Min* minimum; *Max* maximum

Supplementary Table S4. Threshold-based prediction measures calculated at different thresholds of the modified BedsidePEWS.

	Number of PEWS scores resulting in an event*	Number of PEWS scores not resulting in an event*	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)	Number needed to evaluate
PEWS score >= 5	79	11234	60,8	90,6	100	0,7	143
PEWS score < 5	51	108449					
PEWS score >= 6	72	7576	55,4	93,7	99,9	0,9	111
PEWS score < 6	58	112107					
PEWS score >= 7	59	4698	45,4	96,1	99,9	1,2	83
PEWS score < 7	71	114985					
PEWS score >= 8	44	2805	33,8	97,7	99,9	1,5	67
PEWS score < 8	86	116878					
PEWS score >= 9	33	1770	25,4	98,5	99,9	1,8	56
PEWS score < 9	97	117913					
PEWS score >= 10	25	1049	19,2	99,1	99,9	2,3	43
PEWS score < 10	105	118634					
PEWS score >= 11	19	588	14,6	99,5	99,9	3,1	32
PEWS score < 11	111	119095					

*this concerns the last PEWS score prior to the outcome event of unplanned PICU admission or cardiopulmonary resuscitation vs. the other PEWS scores not resulting in an event.

Supplementary Table S5. Distribution of modified BedsidePEWS score and occurrence of minor clinical deterioration event.

Modified BedsidePEWS score	No event occurred (frequency)	Event occurred (frequency)	No event occurred (%)	Event occurred (%)
0	33569	26	99.9	0.1
1	32995	46	99.9	0.1
2	20159	67	99.7	0.3
3	9767	50	99.5	0.5
4	4991	46	99.1	0.9
5	2310	47	98.0	2.0
6	1576	55	96.6	3.4
7	879	37	96.0	4.0
8	425	33	92.8	7.2
9	240	20	92.3	7.7
10	168	18	90.3	9.7
11	80	12	87.0	13.0
12	27	3	90.0	10.0
13	16	2	88.9	11.1
14	7	0	100	0
15	3	0	100	0
16	2	0	100	0

The modified BedsidePEWS scores are displayed as documented in daily clinical practice, arranged within a single clinical episode from one PEWS score to the next one (time interval between scores), with at the end of each time-interval whether or not an event occurred.

Supplementary Table S6. Distribution of modified BedsidePEWS score and occurrence of any clinical deterioration event (significant and minor clinical deterioration events combined).

Modified BedsidePEWS score	No event occurred (frequency)	Event occurred (frequency)	No event occurred (%)	Event occurred (%)
0	34069	34	99.9	0.1
1	33585	65	99.8	0.2
2	20811	82	99.6	0.4
3	10284	60	99.4	0.6
4	5269	55	99.0	1.0
5	2502	59	97.7	2.3
6	1691	66	96.2	3.8
7	952	46	95.4	4.6
8	473	44	91.5	8.5
9	269	27	90.9	9.1
10	189	20	90.4	9.6
11	83	17	83.0	17.0
12	34	4	89.5	10.5
13	16	3	84.2	15.8
14	7	0	100	0.0
15	6	0	100	0.0
16	2	0	100	0.0

The modified BedsidePEWS scores are displayed as documented in daily clinical practice, arranged within a single clinical episode from one PEWS score to the next one (time interval between scores), with at the end of each time-interval whether or not an event occurred.

Supplement - References

1. Fuijkschot J, Vernhout B, Lemson J, Draaisma JM, Loeffen JL. Validation of a Paediatric Early Warning Score: first results and implications of usage. Eur J Pediatr 2015;174:15-21.
2. Cooksley T, Kitlowski E, Haji-Michael P. Effectiveness of Modified Early Warning Score in predicting outcomes in oncology patients. QJM. 2012;105:1083-1088.
3. Therneau T, Crowson C, Atkinson E. Using Time Dependent Covariates and Time Dependent Coeficients in the Cox Model. 2019.
4. DiCiccio TJ, Efron B. Bootstrap confidence intervals. Statistical Science 1996; 11:189-228, 140.
5. Romero-Brufau S, Huddleston JM, Escobar GJ, Liebow M. Why the C-statistic is not informative to evaluate early warning scores and what metrics to use. Crit Care 2015;19:285.
6. Team RC. R: A language and environment for statistical computing. In: R Foundation for Statistical Computing, Vienna, Austria; 2019.

6

Prognostic factors for multi-organ dysfunction in pediatric oncology patients admitted to the pediatric intensive care unit

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Abstract

Background: Pediatric oncology patients who require admission to the pediatric intensive care unit (PICU) have worse outcomes compared to their non-cancer peers. Although multi-organ dysfunction (MOD) plays a pivotal role in PICU mortality and morbidity, risk factors for MOD have not yet been identified. We aimed to identify risk factors at PICU admission for new or progressive MOD (NPMOD) during the first week of PICU stay.

Methods: This retrospective cohort study included all pediatric oncology patients aged 0 to 18 years admitted to the PICU between June 2018 and June 2021. We used the recently published PODIUM criteria for defining multi-organ dysfunction and estimated the association between covariates at PICU baseline and the outcome NPMOD using a multivariable logistic regression model, with PICU admission as unit of study. To study the predictive performance the model was internally validated by using bootstrap.

Results: A total of 761 PICU admissions of 571 patients were included. NPMOD was present in 154 PICU admissions (20%). Patients with NPMOD had a high mortality compared to patients without NPMOD, 14% and 1.0% respectively. Hemato-oncological diagnosis, number of failing organs and unplanned admission were independent risk factors for NPMOD. The prognostic model had an overall good discrimination and calibration.

Conclusion: The risk factors at PICU admission for NPMOD may help to identify patients who may benefit from closer monitoring and early interventions. When applying the PODIUM criteria, we found some opportunities for fine-tuning these criteria for pediatric oncology patients that need to be validated in future studies.

Introduction

The simultaneous dysfunction of multiple organ systems plays a pivotal role in the mortality of children admitted to the pediatric intensive care unit (PICU).[1] Multiple organ dysfunction (MOD) is defined as two or more concurrent organ dysfunctions.[1-3] While the term multiple organ dysfunction syndrome (MODS) has traditionally been used, it was recently posited that this term should be selectively applied to patients with a shared underlying mechanism that affects multiple organ systems simultaneously.[4] MOD can be categorized in new MOD, defined as MOD in patients who have single or no organ dysfunction on PICU admission, and progressive MOD, defined as additional dysfunctional organ systems in patients who already meet MOD criteria at admission.[5]

In children, the risk factors for developing MOD include sepsis, major trauma, severe hypoxemia, and young age (e.g., infancy).[6 7] The number of dysfunctional organ systems is associated with mortality, with each additional failing organ system increasing the risk of death.[7-10] Pediatric oncology patients are particular at high risk for MOD due to the aggressive cancer pathophysiology and intensive treatment regimens, that may lead to organ infiltration, systemic toxicity, and immunosuppression.[11] Similarly to general pediatric patients, MOD plays a significant role in the high morbidity and mortality of these patients.[12] Early recognition and intervention in organ dysfunction may provide the potential to modify its course and prevent further deterioration.[13-16] In adult oncology patients, it was shown that early interventions in deteriorating patients improved both short- and long-term outcomes.[14 15] Therefore, identifying risk factors for MOD at start of the PICU admission could provide opportunities for intensified monitoring and early interventions, which may ultimately reduce morbidity and mortality in critically ill pediatric oncology patients.[12 16 17] Despite the important role of MOD in PICU morbidity and mortality, risk factors for MOD in pediatric oncology patients have not yet been identified.

In this study, we aimed to identify risk factors at PICU admission for MOD during the first week of PICU stay in pediatric oncology patients. Recently, the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) evidence-based pediatric organ dysfunction criteria were published.[18] This is the first study in pediatric oncology patients using these criteria. In addition, fine-tuning of these criteria for pediatric oncology patients may be needed, as they frequently experience organ dysfunction as a result of their oncological treatment. This dysfunction may not necessarily indicate MOD. Therefore, the second objective of this study was to assess whether adjusting the PODIUM criteria for pediatric oncology patients would reveal different risk factors for MOD.

Methods

We performed a retrospective cohort study between June 1, 2018 and June 1, 2021, at an 18-bed PICU of the Wilhelmina Children's Hospital, that is shared with the adjacent Princess Máxima Center, an 80-bed national referral center for pediatric oncology. All pediatric oncology patients with International Classification of Diseases in Oncology (ICD-O) diagnosis of pediatric malignancy (morphology code 1, 2 or 3) aged 0 to 18 years admitted to the PICU were eligible for inclusion. Patients without consent for the use of clinical data were excluded. The study was approved by the ethical review board of our hospital (IRB protocol number 16-572/C).

Assessment of organ dysfunction

We classified organ dysfunction based on the PODIUM criteria[18] (Table 1 and Supplementary Table S1). Clinical data were extracted from the electronic health records and comprised patient characteristics, organ dysfunction in the 24 hours preceding PICU admission, and clinical time series with a frequency of 1 measurement per minute (vital signs and mechanical ventilator data), laboratory results, observations (e.g., Glasgow Coma scores), vasoactive medication, and fluid balance data. Additional data for organ dysfunction, e.g., cardiopulmonary resuscitation, encephalopathy and gastro-intestinal perforation, were acquired from free text fields in clinical or imaging reports through text-mining. In applying the PODIUM criteria, we made assumptions based on clinical expertise to get from a high frequency dataset to the classification of (concurrent) organ dysfunction, including handling measurement errors and missing data. Detailed information on the assessment of the PODIUM criteria is provided in the Supplementary Material. Single organ dysfunction was classified based on the PODIUM criteria within 1-hour windows, and the number of concurrent organ dysfunctions was classified within each 24-hour window.

We assessed presence of organ dysfunction at PICU admission (baseline) by evaluating all relevant laboratory values and free text data in the 24 hours prior to and the first three hours of PICU admission. Missing data were classified as no organ dysfunction at PICU baseline. For further details on assessment of the organ dysfunction criteria, see Supplementary Table S2.

Adjustments in PODIUM criteria for pediatric oncology patients (PONC-PODIUM)

Although some specific criteria for oncology patients are included in the PODIUM criteria, we proposed additional considerations for these patients since some laboratory variables may reflect side-effects of the cancer treatment instead of organ dysfunction in the context of MOD. We therefore adjusted some criteria for this specific patient population: the pediatric oncology (PONC) PODIUM criteria (Table 1).

Table 1. Assessment of the PODIUM and PONC-PODIUM criteria.

Organ system*	PODIUM criteria	PONC-PODIUM criteria adjustments
Neurologic	Glasgow Coma Scale (GCS) ≤ 8 Cornell Assessment of Pediatric Delirium (CAPD) score ≥ 9	
Respiratory	In patients on respiratory support but not invasively ventilated, i.e., on either high flow nasal cannula (HFNC), non-rebreathing mask (NRM) or non-invasive ventilation): • PaO_2/FiO_2 ratio ≤ 300 • SpO_2/FiO_2 ratio ≤ 264 • Non-invasive ventilation for ventilatory failure In invasively ventilated patients: • Oxygenation index (OI) ≥ 4 to ≤ 16 • OI >= 16 • Oxygen saturation index (OSI) ≥ 5 to < 12.3 • OSI ≥ 12.3	Only **severe** respiratory dysfunction; • Invasive ventilation with OI ≥ 16 and/or OSI ≥ 12.3
Cardiovascular	Cardiac arrest HR > 2 SD above normal for age • 0–7 d: HR > 180 beats/min • > 1 wk to 1 m: HR > 180 beats/min • > 1 m to < 1 y: HR > 180 beats/min • 6 y to < 13 y: HR > 150 beats/min • 13 y to < 18 y: HR > 130 SBP > 2 SD above normal for age • 0–7 d: SBP <50 mm Hg • > 1 wk to 1 m: SBP < 70 mm Hg • > 1 m to < 1 y: SBP < 75 mm Hg • 1 y to < 6 y: SBP < 75 mm Hg • 6 y to < 13 y: SBP < 80 mm Hg • 13 y to < 18 y: SBP < 80 mm Hg	Only **severe** cardiovascular dysfunction in case it was graded; • Resuscitation; or • At least 2 out of 5 of the following criteria present at the same time: HR > 2 SD above normal for age; SBP > 2 SD above normal for age, vasoactive-inotropic score ≥ 5, serum lactate ≥ 5 mmol/L, echo cardiographic estimation of LVEF < 30%;

Table 1. Assessment of the PODIUM and PONC-PODIUM criteria - *continued.*

Organ system*	PODIUM criteria	PONC-PODIUM criteria adjustments
Cardiovascular *continued*	Vasoactive-inotropic score ≥ 5 Serum lactate ≥ 3 mmol/L Echo cardiographic estimation of left ventricular ejection fraction (LVEF) < 50%	
Renal	• Urine output < 0.5 mL/kg/h for ≥ 6 hours and < 12 hours with concomitant serum creatinine increase 1.5 – 1.9 times baseline or ≥ 26.5 µmol/L increase. • Urine output < 0.5 mL/kg/h for ≥ 12 hours • Serum creatinine increase ≥ 2 times baseline • eGFR < 35 mL/min/1.73 m2 (and not age < 30 days) • Fluid overload ≥ 20% -- starting 48 hours after start PICU admission • Initiation of continuous renal replacement therapy (CRRT)	• Oliguria for < 0.5 mL/kg/h for ≥ 6 hours **or** concomitant serum creatinine increase 1.5 – 1.9 times baseline **or** ≥ 26.5 µmol/L increase; or • Serum creatinine increase ≥ 2 times baseline; or • Fluid overload of **10%** from PICU admission onwards; or • eGFR < 35 mL/min/1.73; or initiation of renal replacement therapy
Gastrointestinal	Bowel perforation or pneumatosis intestinalis on plain abdominal film, CT or MRI	
Hepatic	• Biochemical evidence of acute liver injury (defined as aspartate aminotransferase > 100 IU/L, alanine aminotransferase > 100 IU/L, gamma-glutamyl transferase > 100 IU/L, total bilirubin > 85.5 µmol/L, or direct bilirubin > 34.2 µmol/L) with prothrombin time (PT) > 15 secs or international normalize ratio (INR) > 1.5 and hepatic encephalopathy • Biochemical evidence of acute liver injury with PT ≥ 20 secs or INR ≥ 2.0	
Hematology	Platelet count < 30 10E9/L or 50% decrease from baseline Hemoglobin < 4.3 mmol/L Leucocytes < 3.0 10E9/L	Only **new dysfunction** throughout PICU stay was included, defined as: • Platelet count < 30 10E9/L (30 000 cells/µL) or 50% decrease from baseline; **or** • Hemoglobin < 4.3 mmol/L

Table 1. Assessment of the PODIUM and PONC-PODIUM criteria - *continued*.

Organ system*	PODIUM criteria	PONC-PODIUM criteria adjustments
Coagulation	In the absence of liver dysfunction, a combination of ≥ 2 of the following criteria: • Platelet count < 30 10E9/L • INR > 1.5 • Fibrinogen 1.5 g/L • D-dimer > 5 µg/mL (= upper limit of normal)	Platelet count < **30** 10E9/L (<30 000 cells/µL), and other coagulation criteria were classified according to the original PODIUM criteria.
Endocrine	Blood glucose ≥ 8.3 mmol/L or < 2.8 mmol/L	
Immunology	Peripheral absolute neutrophil count < 0.5 10E9/L	Only **new dysfunction** throughout PICU stay was included, defined as: Peripheral absolute neutrophil count < 0.5 10E9/L (< 500 cells/µL) or if missing: leucocyte count < 1.0 10E9/L (< 1000 cells/µL)

The main adjustments compared to the original PODIUM criteria are depicted in bold.

*In case an organ system is not displayed, it is classified according to the original PODIUM criteria, see Supplementary Table S2.

PONC-PODIUM pediatric oncology Pediatric Organ Dysfunction Information Update Mandate; *NPMOD* new or progressive organ dysfunction; *OI* oxygenation index; *OSI* oxygenation saturation index; *HR* heart rate; *SBP* systolic blood pressure; *SD* standard deviation; *LVEF* left ventricular ejection fraction; *eGFR* estimated glomerular filtration rate.

Invasive ventilation and the use of vasoactive medication are associated with increased PICU mortality in pediatric oncology patients.[19] Therefore, we used the thresholds of severe respiratory dysfunction, i.e., invasive ventilation and an oxygenation index of ≥ 16 or an oxygenation saturation index of ≥ 12.3. For cardiovascular dysfunction, we used the severe threshold for lactate and left ventricular ejection fraction (LVEF).

Considering the renal criteria, it was shown that patients with a fluid overload greater than 10% were 6 times more likely to die during PICU admission than those with less than or equal to 10% fluid overload.[20] Moreover, oliguria is often not present in pediatric oncology patients with acute kidney injury (AKI).[20] We therefore adjusted the criteria for renal dysfunction: oliguria was not required and a fluid overload > 10%, instead of 20%, was used directly from the start of PICU admission onwards (as opposed to starting 48 hours after admission).

Since hematological and immunological dysfunction at baseline are less relevant due to the idiopathic nature of these in oncology patients and likely does not represent dysfunction due to critical illness**,** we excluded the leukocyte criterion from hematological dysfunction and only included hematological or immunological dysfunction that was newly developed during PICU stay for the classification of NPMOD. In classifying coagulation dysfunction, we used the platelet count threshold for pediatric oncology patients (i.e., < 30 10E9/L or < 30 000 cells/μL).

Primary outcome: new or progressive multi-organ dysfunction

The primary outcome was new or progressive MOD (NPMOD). New MOD was defined as no MOD at baseline and the concurrent dysfunction of at least 2 organs. Progressive MOD was defined as MOD (i.e., concurrent dysfunction of at least 2 organ systems) at baseline, and the development of one or more additional concurrent organ dysfunction(s).

Statistical Analysis

A multivariable logistic regression model was used to estimate the association between covariates and the outcome. Covariates at baseline of PICU admission were selected based on literature and expert opinion. The included covariates encompassed diagnosis category (i.e., hemato-oncological, solid tumor or neuro-oncological); hematopoietic stem cell transplantation; neutropenia at baseline; a composite covariate of sepsis and/or infection (bacterial or fungal [21]); high-flow oxygen therapy preceding PICU admission; the number of organ dysfunctions at baseline (categorized into 0, 1 or ≥ 2), unplanned PICU admission, and previous relevant PICU admission (i.e., a previous PICU admission that was either unplanned or had a protracted course). See Supplementary Material for a detailed description of the covariates.

We analyzed the first week of PICU admission, or up to discharge within seven days, whichever event first occurred. We assessed the outcome NPMOD based on both the original and our PONC-PODIUM criteria, to determine whether adjustments of the organ dysfunction criteria for pediatric oncology population yielded different significant risk factors. In addition, we performed a subgroup analysis of only unplanned PICU admissions to identify possible different significant risk factors for NPMOD. A multivariable logistic regression model was used to estimate the association between covariates and the outcome, which included the same covariates as before except for unplanned PICU admission. The outcome NPMOD within one week based on both original PODIUM criteria and PONC-PODIUM criteria was assessed.

To study the predictive performance of the model, internal validation was performed by using Efron's bootstrap (i.e., resampling the dataset 500 times).[22] Statistical analyses were performed using R-statistical software [23], version 4.2.1. (2022-06-23), see Supplementary Material for associated packages.

Results

A total of 761 PICU admissions of 571 patients were included. Table 2 reports the clinical characteristics of the PICU admissions. The median age [interquartile range] at PICU admission was 6.0 [2.7 – 12.8] years. The cohort included 25% hemato-oncological patients, 35% solid tumor patients, 40% neuro-oncology patients, and 2% had a hematopoietic stem cell transplantation (HSCT) in the year preceding PICU admission. Among the 761 PICU admissions, 288 (37.8%) were unplanned admissions. Neuro-oncology and solid tumor patients most often had planned postoperative PICU admissions (89.4% and 67.1% respectively), whereas hemato-oncology patients largely required unplanned PICU admissions (93%). Data of at least 2 organ systems were available at baseline in 744 of 761 PICU admissions (98%) for the classification of MOD at baseline.

Table 2. Clinical and demographic characteristics of PICU admissions overall and by occurrence of NPMOD (defined according to PODIUM criteria).

Characteristic	Total PICU admissions (n = 761)	PICU admissions without NPMOD (n = 607)	PICU admissions with NPMOD (n = 154)
General characteristics per PICU admission			
Age at admission (years), median [IQR]	6.0 [2.7 – 12.8]	6.5 [3.0 – 13.1]	4.0 [1.5 – 11.0]
Female sex, n (%)	351 (46)	265 (44)	86 (56)
PICU admission reason, n (%)			
Planned post-operative care	473 (62.2)	444 (73.1)	29 (18.8)
Respiratory failure	106 (13.9)	49 (8.1)	57 (37.0)
Sepsis	40 (5.3)	25 (4.1)	15 (9.7)
Neurological deterioration	36 (4.7)	27 (4.4)	9 (5.8)
Cardiovascular failure	33 (4.3)	20 (3.3)	13 (8.4)
Renal failure	7 (0.9)	1 (0.2)	6 (3.9)
Liver failure	2 (0.3)	1 (0.2)	1 (0.6)
Unplanned post-operative care	24 (3.2)	16 (2.6)	8 (5.2)
Other	40 (5.3)	24 (4.0)	16 (10.4)
Covariates			
Oncological diagnosis groups			
Hemato-oncological	190 (25.0)	101 (16.6)	89 (57.8)
Solid tumor	268 (35.2)	225 (37.1)	43 (27.9)
Brain / CNS tumor	303 (39.8)	281 (46.3)	22 (14.3)
HSCT, n (%)	16 (2.1)	5 (0.8)	11 (7.1)
Infection or sepsis at baseline, n (%)	100 (13.1)	52 (8.6)	48 (31.2)
Neutropenia at baseline, n (%)	82 (10.8)	47 (7.7)	35 (22.7)
HFNC preceding admission, n (%)	86 (11.3)	46 (7.6)	40 (26.0)
Previous relevant PICU admission, n (%)	104 (13.7)	67 (11.0)	37 (24.0)
Unplanned PICU admission, n (%)	288 (37.8)	163 (26.9)	125 (81.2)
Number of failing organs at baseline, n (%)			
0	471 (61.9)	416 (68.5)	49 (31.8)
1	159 (20.9)	117 (19.3)	45 (29.2)
>= 2	131 (17.2)	74 (12.2)	60 (39.0)
Outcome			
Maximum number of concomitantly failing organs during first week of PICU stay			
0	346 (45.5)	346 (57.3)	0 (0)
1	209 (27.5)	209 (34.6)	0 (0)
2	78 (10.2)	28 (4.6)	50 (32.5)
3	56 (7.4)	16 (2.6)	40 (26.0)
4	34 (4.5)	5 (0.8)	29 (18.8)
>= 5	38 (4.9)	3 (0.5)	35 (22.3)
PICU length of stay (days), median [IQR]	0.9 [0.8 – 2.5]	0.9 [0.7 – 1.4]	5.0 [2.1 – 10.0]
PICU mortality, n (%)	28 (3.7)	6 (1.0)	22 (14.3)

IQR interquartile range; *CNS* central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy; *NPMOD* new or progressive multi-organ dysfunction; *PICU* pediatric intensive care unit.

NPMOD classified according to original PODIUM criteria

NPMOD was present in 154 PICU admissions (20%). The PICU mortality was 4% in all PICU admissions, 1% in the group without NPMOD, and 14% in the group with NPMOD. In the PICU admissions where patients developed NPMOD, the three most frequently failing organ systems at PICU baseline included hematological (41%), immunological (23%) and respiratory (20%) dysfunction (see Figure 1A).

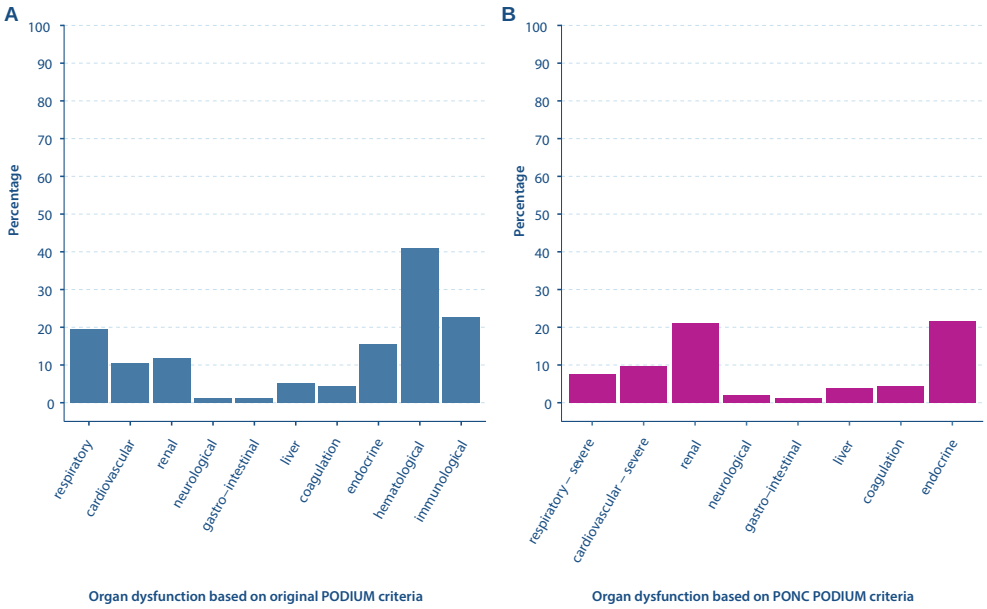

Figure 1. Organ dysfunction at PICU baseline in all PICU admissions with new or progressive multi-organ dysfunction, per organ system with percentage of failing organ system. The left panel (A) considers organ dysfunction classified based on the original PODIUM criteria, whereas the right panel (B) considers organ dysfunction classified based on the PONC-PODIUM criteria, thus adjusted for pediatric oncology patients.

The results of the univariate and multivariable model are displayed in Table 3. Hemato-oncological diagnosis, number of failing organs at baseline and unplanned PICU admissions were significantly associated with NPMOD in the multivariable model. Internal validation of the model yielded a c-index of 0.81, indicating a reasonable discriminative ability. The calibration plot showed an overall good calibration, with an index-corrected slope of 0.93.

NPMOD classified according to PONC-PODIUM criteria

Using the PONC-PODIUM criteria, NPMOD was present in 157 PICU admissions (21%), see Supplementary Table S3. Applying these adjusted criteria revealed a different top three of frequently failing organ systems at PICU baseline, namely endocrine (22%), renal (21%), and

severe cardiovascular dysfunction (10%) (Figure 1B). In the multivariable model, we found the same significant risk factors for NPMOD including hemato-oncological diagnosis, number of failing organs at baseline and unplanned PICU admission (Supplementary Table S4).

Table 3. Considering all PICU admissions - Results of the univariate and multivariable logistic regression model, with estimated odds ratio (OR) along with the 95% confidence interval (CI), for outcome of new or progressive multi organ dysfunction (NPMOD) - defined according to the PODIUM criteria.

Covariate	Univariate OR (95% CI)	Multivariable OR (95% CI)
Oncological diagnosis groups		
Hemato-oncological	11.19 [6.71 – 18.67]	**2.23 [1.14 – 4.36]**
Solid tumor	2.33 [1.36 – 3.98]	1.29 [0.70 – 2.37]
Brain / CNS tumor	*reference*	*reference*
HSCT, n (%)	9.26 [3.17 – 27.07]	1.66 [0.52 – 5.22]
Infection or sepsis at baseline, n (%)	4.83 [3.10 – 7.53]	1.63 [0.93 – 2.88]
Neutropenia at baseline	3.50 [2.16 – 5.66]	0.46 [0.21 – 1.02]
HFNC preceding admission	4.27 [2.67 – 6.84]	1.17 [0.67 – 2.03]
Previous relevant PICU admission	2.54 [1.63 – 3.99]	1.07 [0.63 – 1.83]
Unplanned PICU admission	11.74 [7.55 – 18.27]	**5.82 [3.37 – 10.07]**
Number of failing organs at baseline		
0	*reference*	*reference*
1	3.26 [2.07 – 5.14]	**2.18 [1.30 – 3.67]**
>= 2	6.88 [4.38 – 10.81]	**2.39 [1.18 – 4.83]**

CNS central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy. Significant covariates in the model are in bold.

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Unplanned PICU admissions

We performed a subgroup analysis including only the unplanned admissions (Table 4). NPMOD according to the original PODIUM criteria was present in 125 unplanned PICU admissions (43%). Respiratory failure, sepsis and neurological deterioration were the three major PICU admission reasons for unplanned PICU admission. PICU mortality rate was slightly higher compared to the total cohort, 4% in the patients without NPMOD and 17% in patients with NPMOD. The most frequently failing organ systems at admissions were similar to what was found in the total cohort, including hematological dysfunction (47%), immunological dysfunction (27%), and respiratory dysfunction (23%) (Figure 2A). In the multivariable logistic regression model, the number of failing organs at PICU baseline was significantly associated with NPMOD (Table 5).

Using our PONC-PODIUM criteria in the cohort of unplanned admissions, NPMOD was present in 123 unplanned PICU admissions (43%) (Supplementary Table S5). In the unplanned admissions with NPMOD, the most frequent failing organ systems at admission included renal dysfunction (22%), endocrine dysfunction (20%), and severe cardiovascular dysfunction (12%) (Figure 2B). Consistent with the application of the original PODIUM criteria, the multivariable model showed that the number of failing organs was a significant risk factor associated with the occurrence of NPMOD (Supplementary Table S6).

Table 4. Clinical and demographic characteristics of only unplanned PICU admissions, by occurrence of new or progressive multi organ dysfunction (defined according to PODIUM criteria).

Characteristic	Unplanned PICU admissions (n = 288)	Unplanned PICU admissions without NPMOD (n = 163)	Unplanned PICU admissions with NPMOD (n = 125)
General characteristics per PICU admission			
Age at admission (years), median [IQR]	5.8 [2.3 – 13.1]	7.2 [2.6– 13.5]	4.1 [1.9 – 11.4]
Female sex, n (%)	143 (49.7)	70 (42.9)	73 (58.4)
PICU admission reason, n (%)			
Respiratory failure	106 (36.8)	49 (30.1)	57 (45.6)
Sepsis	40 (13.9)	25 (15.3)	15 (12.0)
Neurological deterioration	36 (12.5)	27 (16.6)	9 (7.2)
Cardiovascular failure	33 (11.5)	20 (12.2)	13 (10.4)
Renal failure	7 (2.4)	1 (0.6)	6 (4.8)
Liver failure	2 (0.7)	1 (0.6)	1 (0.8)
Unplanned post-operative care	24 (8.3)	16 (9.8)	8 (6.4)
Other	40 (13.9)	24 (14.7)	16 (12.8)
Covariates			
Oncological diagnosis groups			
Hemato-oncological	168 (58.3)	84 (51.5)	84 (67.2)
Solid tumor	88 (30.6)	56 (34.4)	32 (25.6)
Brain / CNS tumor	32 (11.1)	23 (14.1)	9 (7.2)
HSCT, n (%)	16 (5.6)	5 (3.1)	11 (8.8)
Infection or sepsis at baseline, n (%)	86 (29.9)	40 (24.5)	46 (36.8)
Neutropenia at baseline, n (%)	75 (26.0)	41 (25.2)	34 (27.2)
HFNC preceding admission, n (%)	79 (27.4)	40 (24.5)	39 (31.2)
Previous relevant PICU admission, n (%)	71 (24.7)	38 (23.3)	33 (26.4)
Number of failing organs at baseline, n (%)			
0	107 (37.2)	75 (46.0)	32 (25.6)
1	65 (22.6)	30 (18.4)	35 (28.0)
>= 2	116 (40.3)	58 (35.6)	58 (46.4)
Outcome			
Maximum number of concomitantly failing organs during first week of PICU stay			
0	59 (45.5)	59 (36.2)	0 (0)
1	58 (27.5)	58 (35.6)	0 (0)
2	53 (10.2)	23 (14.1)	30 (24.0)
3	48 (7.4)	15 (9.2)	33 (26.4)
4	33 (4.5)	5 (3.1)	28 (22.4)
>= 5	37 (12.8)	3 (1.8)	34 (27.2)
PICU length of stay (days), median [IQR]	2.2 [1.0 – 6.0]	1.4 [0.7 – 2.8]	5.6 [2.2 – 10.9]
PICU mortality, n (%)	27 (9.4)	6 (3.7)	21 (16.8)

IQR interquartile range; *CNS* central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy; *NPMOD* new or progressive multi-organ dysfunction; *PICU* pediatric intensive care unit

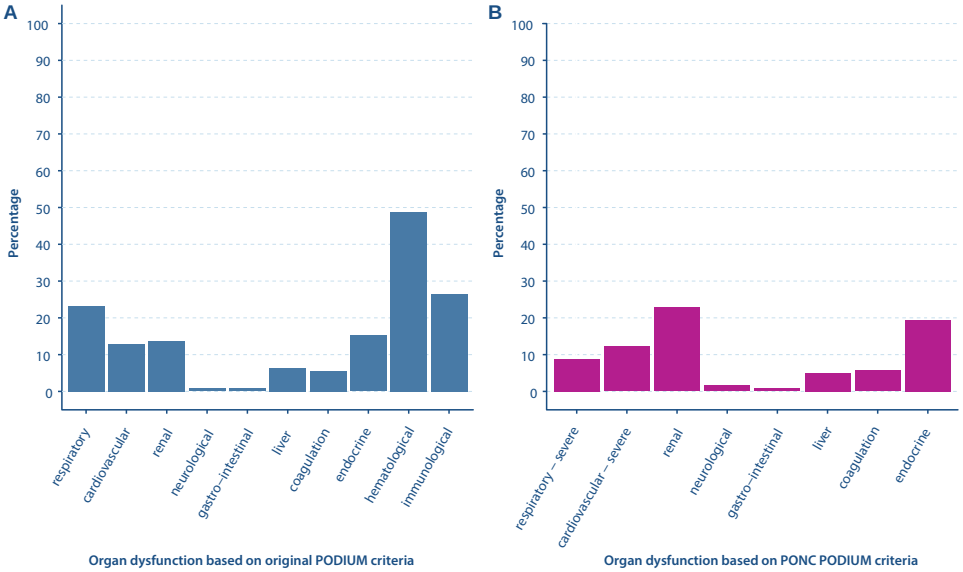

Figure 2. Considering only unplanned PICU admissions – organ dysfunction at PICU baseline in unplanned PICU admissions with new or progressive multi-organ dysfunction. The left panel (A) considers organ dysfunction based on the original PODIUM criteria, whereas the right panel (B) considers organ dysfunction classified based on the PONC-PODIUM criteria.

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Table 5. Considering unplanned PICU admissions - Results of the univariate and multivariable logistic regression model, with estimated odds ratio (OR) along with the 95% confidence interval (CI), for outcome of new or progressive multi organ dysfunction (defined according to the PODIUM criteria).

Covariate	Univariate OR (95% CI)	Multivariable OR (95% CI)
Oncological diagnosis groups		
Hemato-oncological	2.56 [1.12 – 5.85]	1.89 [0.78 – 4.58]
Solid tumor	1.46 [0.60 – 3.54]	1.24 [0.49 – 3.12]
Brain / CNS tumor	*reference*	*reference*
HSCT, n (%)	3.05 [1.03 – 9.01]	1.76 [0.55 – 5.57]
Infection or sepsis at baseline, n (%)	1.79 [1.08 – 2.98]	1.66 [0.90 – 3.03]
Neutropenia at baseline	1.11 [0.65 – 1.89]	0.45 [0.20 – 1.02]
HFNC preceding admission	1.39 [0.83 – 2.34]	1.21 [0.69 – 2.14]
Previous relevant PICU admission	1.18 [0.69 – 2.02]	0.97 [0.54 – 1.74]
Number of failing organs at baseline		
0	*reference*	*reference*
1	2.73 [1.44 – 5.18]	**2.19 [1.13 – 4.28]**
>= 2	2.34 [1.35 – 4.07]	**2.55 [1.17 – 5.66]**

CNS central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy. Significant covariates in the model are in bold.

Discussion

This is the first study using the recently published PODIUM criteria for organ dysfunction[18] in pediatric oncology patients to identify risk factors for new or progressive multi-organ failure during the first week of PICU admission. Considering all PICU admissions, we found that hemato-oncological diagnosis, unplanned PICU admission and number of failing organs at PICU baseline were independent risk factors. In the subgroup of the unplanned PICU admissions, we found that the number of failing organs at PICU baseline was independently associated with NPMOD.

Our finding that hemato-oncological diagnosis is a significant risk factor for developing NPMOD is in line with other studies showing that hemato-oncological patients have greater illness severity at PICU admission, experience multi-organ failure more often, require more PICU resources and have a higher PICU mortality compared to solid tumor patients.[11 12 24 25] The high risk for organ dysfunction may be attributed to the combination of generally more dose-intense chemotherapy and glucocorticoids, that may result in increased toxic side-effects and profound and prolonged myelosuppression.[11 12 26] Yet, upon analysis in only unplanned PICU admissions, we found that although a hemato-oncological diagnosis was associated with NPMOD in the univariate analysis, it was not a significant risk factor for NPMOD in the multivariable analysis.

Surprisingly, neutropenia was not a significant risk factor both in the total cohort and cohort of unplanned admissions. Some other studies in adult and pediatric oncology patients also failed to demonstrate an association of neutropenia with worse outcomes, in a multivariable analysis.[27-29] Advances in the diagnosis and treatment of infections, the prescription of prophylactic antibiotics and antifungals, and antibiotic stewardship may have limited the role of neutropenia in worse outcome in critically ill oncology patients. A recent study including only pediatric hemato-oncology patients with unplanned PICU admissions showed that neutropenia was an independent risk factor for PICU mortality.[30] Our study differs in that we also included patients with a solid or a brain or central nervous system tumor.

The degree of multi-organ dysfunction during PICU admission is a significant prognostic factor for PICU mortality in pediatric oncology patients.[12] We found that the presence of MOD already at PICU admission is an independent risk factor for progressive MOD, in both the total cohort as in the subgroup including only unplanned PICU admissions. These findings are in line with a study in general pediatric patients, showing that the presence of MOD on day 1 of PICU admission was associated with death or poor neurologic outcome.[8] Our finding that PICU mortality in patients with NPMOD in the unplanned admissions was only slightly higher compared to the total cohort including also planned post-operative patients, emphasizes the pivotal role of MOD in the outcome of these patients. Early

recognition of deteriorating organ functions before PICU admission followed by early initiation of appropriate treatment may be important to reduce morbidity and mortality in critically ill pediatric oncology patients.[12 16 31 32]

In the present study, we tailored the PODIUM criteria to pediatric oncology patients. The adjustments in renal criteria can be valuable to prevent missing AKI, as it was shown that AKI, even stage 1, is significantly associated with short- and long-term complications in critically ill children.[33] Second, according to PODIUM, neutropenia is a classifier for dysfunction of two different organ systems (hematologic and immunologic), where we included dysfunction that is more likely to be part of a shared underlying pathway for MOD (e.g., in sepsis) instead of chemotherapeutic treatment. Furthermore, we found a high percentage of endocrine dysfunction. The threshold for glucose ≥ 8.3 mmol/L (150 mg/dL) might be a threshold at which particularly hemato-oncology patients are easily flagged, due to steroid-induced adrenal insufficiency or hyperglycemia.[34] This threshold could be considered to be fine-tuned and validated in future studies.

Using our PONC-PODIUM criteria, we found different organ systems that frequently failed at PICU admissions. Endocrine, renal and severe cardiovascular dysfunction emerged as the most frequently failing organ systems in patients who develop NPMOD. This finding may merely have implications for early surveillance at the inpatient ward, prior to PICU admission. Particularly renal and cardiovascular dysfunction can be recognized in an early phase, and timely, appropriate interventions may potentially halt progression to irreversible organ damage. For example, the development of acute kidney injury (AKI) can be monitored at the ward, and substitution or adjustments of nephrotoxic medication and prevention of fluid overload can be easily implemented.[35] This may lead to decreased AKI rates and better outcomes.[33 35] In addition, closely monitoring the fluid balance and prevention of fluid overload in patients with cardiovascular failure could provide an opportunity to prevent further deterioration.

Our study revealed several challenges in applying predefined criteria for organ dysfunction to a dataset with continuous data at a frequency of 1 minute and interval data. We accounted for measurement errors and missing data. We thereupon defined age-based limits for artefacts in vital signs, carried last observations forward for a limited time defined per variable and classified organ dysfunction within 1-hour timeframes, to minimize that a single value could immediately flag organ dysfunction. Last observation carried forward to deal with missing data was similarly used in a retrospective study on the early prediction of organ dysfunction in children.[36] We used the 24 hours preceding PICU admission to classify organ dysfunction at PICU admission. As PODIUM criteria did not incorporate a specific time period required to fulfil the criteria for organ dysfunction, we classified the concurrent number of failing organ systems within 24-hour windows. Yet, for future studies, a validated time period required to fulfil the criteria especially for

respiratory and cardiovascular dysfunction may further optimize defining (concurrent) organ dysfunction.

This is the first study including all organ systems of the PODIUM criteria, as we extracted free text field data using an automatized process of text mining with standardized search terms to, for example, identify gastro-intestinal dysfunction. In addition, our study evaluated a PICU cohort that encompasses all subgroups of pediatric oncology patients, including HSCT patients, from a national referral center where oncology care has been nationally centralized.

Our study has several limitations. First, the data retrieved from patients' medical records were primarily captured for clinical care. Consequently, selective measurements, such as laboratory values only assessed upon clinical suspicion of organ dysfunction, may bias the timing of onset of (multiple) organ dysfunction. Therefore, we summarized to NPMOD within 24-hour-time frames. Second, our study is a single-center study. Consequently, our findings may not be generalizable due to international differences in PICU policies regarding admission and care. Third, we did not have data on morbidity following prior PICU admissions. We therefore defined a relevant prior PICU admission as any prior unplanned admission, or a prior planned admission with a protracted course. For future studies, to assess the effect of a prior PICU admission on the risk of developing NPMOD in a current PICU admission, it would be beneficial to include data on relevant comorbidity following a prior admission. Last, in this retrospective study, we could not differentiate between underlying mechanisms of organ dysfunction and could thus not define MOD syndrome (MODS). The identification of a common underlying pathobiology, such as in MODS, may be helpful to evolve from isolated organ specific to more holistic strategies that target a common pathobiology.[4]

Conclusion

This study shows that hemato-oncological diagnosis, number of failing organs and an unplanned admission are significant risk factors at PICU admission for the development of NPMOD in pediatric oncology patients. For future perspectives, we see opportunities to further refine the PODIUM criteria for pediatric oncology patients. Currently, the PODIUM criteria have been validated in general pediatric patients [37], and are yet to be validated in pediatric oncology patients. We provided a first step towards further refinement of these criteria for pediatric oncology patients. Yet, the criteria introduced in this study need to be validated, preferably in a large multi-center cohort incorporating all subgroups of pediatric oncology patients. The results of the present study may help to guide both intensivists and oncologists in risk stratification for critically ill pediatric oncology patients and to identify patients who may benefit from closer monitoring and early interventions at the ward prior to PICU admission.

References

1. Proulx F, Joyal JS, Mariscalco MM, et al. The pediatric multiple organ dysfunction syndrome. *Pediatr Crit Care Med* 2009;10(1):12-22. doi: 10.1097/PCC.0b013e31819370a9
2. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6(1):2-8. doi: 10.1097/01.PCC.0000149131.72248.E6
3. Wilkinson JD, Pollack MM, Ruttimann UE, et al. Outcome of pediatric patients with multiple organ system failure. *Crit Care Med* 1986;14(4):271-4. doi: 10.1097/00003246-198604000-00002
4. Weiss SL, Carcillo JA, Leclerc F, et al. Refining the Pediatric Multiple Organ Dysfunction Syndrome. *Pediatrics* 2022;149(1 Suppl 1):S13-S22. doi: 10.1542/peds.2021-052888C
5. Lacroix J, Hebert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med* 2007;356(16):1609-19. doi: 10.1056/NEJMoa066240
6. Upperman JS, Lacroix J, Curley MA, et al. Specific Etiologies Associated With the Multiple Organ Dysfunction Syndrome in Children: Part 1. *Pediatr Crit Care Med* 2017;18(3_suppl Suppl 1):S50-S57. doi: 10.1097/PCC.0000000000001048
7. Leclerc F, Leteurtre S, Duhamel A, et al. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. *Am J Respir Crit Care Med* 2005;171(4):348-53. doi: 10.1164/rccm.200405-630OC
8. Typpo K, Watson RS, Bennett TD, et al. Outcomes of Day 1 Multiple Organ Dysfunction Syndrome in the PICU. *Pediatr Crit Care Med* 2019;20(10):914-22. doi: 10.1097/PCC.0000000000002044
9. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med* 2013;41(7):1761-73. doi: 10.1097/CCM.0b013e31828a2bbd
10. Leteurtre S, Martinot A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. *Lancet*2003;362(9379):192-7. doi: 10.1016/S0140-6736(03)13908-6
11. Zinter MS, DuBois SG, Spicer A, et al. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014;40(10):1536-44. doi: 10.1007/s00134-014-3389-2
12. Barking CTMM, Masjosthusmann K, Rellensmann G, et al. Treatment of Children With Cancer and/or Hematopoietic Stem Cell Transplantation in the Intensive Care Unit: Experience at a Large European Pediatric Cancer Center. *J Pediatr Hematol Oncol* 2020;42(7):e583-e88. doi: 10.1097/MPH.0000000000001718
13. Inwald DP, Tasker RC, Peters MJ, et al. Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit. *Arch Dis Child* 2009;94(5):348-53. doi: 10.1136/adc.2008.153064
14. Lee DS, Suh GY, Ryu JA, et al. Effect of Early Intervention on Long-Term Outcomes of Critically Ill Cancer Patients Admitted to ICUs. *Crit Care Med* 2015;43(7):1439-48. doi: 10.1097/CCM.0000000000000989
15. Song JU, Suh GY, Park HY, et al. Early intervention on the outcomes in critically ill cancer patients admitted to intensive care units. *Intensive Care Med* 2012;38(9):1505-13. doi: 10.1007/s00134-012-2594-0
16. Fausser JL, Tavenard A, Rialland F, et al. Should We Pay Attention to the Delay Before Admission to a Pediatric Intensive Care Unit for Children With Cancer? Impact on 1-Month Mortality. A Report From the French Children's Oncology Study Group, GOCE. *J Pediatr Hematol Oncol* 2017;39(5):e244-e48. doi: 10.1097/MPH.0000000000000816
17. Pillon M, Amigoni A, Contin A, et al. Risk Factors and Outcomes Related to Pediatric Intensive Care Unit Admission after Hematopoietic Stem Cell Transplantation: A Single-Center Experience. *Biol Blood Marrow Transplant* 2017;23(8):1335-41. doi: 10.1016/j.bbmt.2017.04.016
18. Bembea MM, Agus M, Akcan-Arikan A, et al. Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Contemporary Organ Dysfunction Criteria: Executive Summary. *Pediatrics* 2022;149(1 Suppl 1):S1-S12. doi: 10.1542/peds.2021-052888B
19. Wösten-van Asperen RM, van Gestel JPJ, van Grotel M, 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. doi: 10.1016/j.critrevonc.2019.07.014

20. Raymakers-Janssen P, Lilien MR, Tibboel D, et al. Epidemiology and Outcome of Critically Ill Pediatric Cancer and Hematopoietic Stem Cell Transplant Patients Requiring Continuous Renal Replacement Therapy: A Retrospective Nationwide Cohort Study. *Crit Care Med* 2019;47(11):e893-e901. doi: 10.1097/CCM.0000000000003973
21. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020;71(6):1367-76. doi: 10.1093/cid/ciz1008
22. DiCiccio TJ, Efron B. Bootstrap confidence intervals. *Statistical Science* 1996;11(3):189-228, 40.
23. Team RC. R: A language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria, 2019.
24. Heying R, Schneider DT, Korholz D, et al. Efficacy and outcome of intensive care in pediatric oncologic patients. *Crit Care Med* 2001;29(12):2276-80. doi: 10.1097/00003246-200112000-00007
25. Owens C, Mannion D, O'Marcaigh A, et al. Indications for admission, treatment and improved outcome of paediatric haematology/oncology patients admitted to a tertiary paediatric ICU. *Ir J Med Sci* 2011;180(1):85-9. doi: 10.1007/s11845-010-0634-8
26. Loeffen EAH, Knops RRG, Boerhof J, et al. Treatment-related mortality in children with cancer: Prevalence and risk factors. *Eur J Cancer* 2019;121:113-22. doi: 10.1016/j.ejca.2019.08.008
27. Bouteloup M, Perinel S, Bourmaud A, et al. Outcomes in adult critically ill cancer patients with and without neutropenia: a systematic review and meta-analysis of the Groupe de Recherche en Reanimation Respiratoire du patient d'Onco-Hematologie (GRRR-OH). *Oncotarget* 2017;8(1):1860-70. doi: 10.18632/oncotarget.12165
28. Dursun O, Hazar V, Karasu GT, et al. Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit. *J Pediatr Hematol Oncol* 2009;31(7):481-4. doi: 10.1097/MPH.0b013e3181a330ef
29. Zaidman I, Mohamad H, Shalom L, et al. Survival of pediatric patients requiring admission in the intensive care unit post hematopoietic stem cell transplantation: Prognostic factors associated with mortality. *Pediatr Blood Cancer* 2022;69(3):e29549. doi: 10.1002/pbc.29549
30. Pechlaner A, Kropshofer G, Crazzolara R, et al. Mortality of Hemato-Oncologic Patients Admitted to a Pediatric Intensive Care Unit: A Single-Center Experience. *Front Pediatr* 2022;10:795158. doi: 10.3389/fped.2022.795158
31. Piastra M, Fognani G, Franceschi A, et al. Pediatric Intensive Care Unit admission criteria for haemato-oncological patients: a basis for clinical guidelines implementation. *Pediatr Rep* 2011;3(2):e13. doi: 10.4081/pr.2011.e13
32. Lindell RB, Gertz SJ, Rowan CM, et al. High Levels of Morbidity and Mortality Among Pediatric Hematopoietic Cell Transplant Recipients With Severe Sepsis: Insights From the Sepsis PRevalence, OUtcomes, and Therapies International Point Prevalence Study. *Pediatr Crit Care Med* 2017;18(12):1114-25. doi: 10.1097/PCC.0000000000001338
33. Sanchez-Pinto LN, Goldstein SL, Schneider JB, et al. Association Between Progression and Improvement of Acute Kidney Injury and Mortality in Critically Ill Children. *Pediatr Crit Care Med* 2015;16(8):703-10. doi: 10.1097/PCC.0000000000000461
34. Lowas SR, Marks D, Malempati S. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2009;52(7):814-8. doi: 10.1002/pbc.21980
35. Goldstein SL, Dahale D, Kirkendall ES, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. *Kidney Int* 2020;97(3):580-88. doi: 10.1016/j.kint.2019.10.015
36. Bose SN, Greenstein JL, Fackler JC, et al. Early Prediction of Multiple Organ Dysfunction in the Pediatric Intensive Care Unit. *Front Pediatr* 2021;9:711104. doi: 10.3389/fped.2021.711104
37. Sanchez-Pinto LN, Bembea MM, Farris RW, et al. Patterns of Organ Dysfunction in Critically Ill Children Based on PODIUM Criteria. *Pediatrics* 2022;149(1 Suppl 1):S103-S10. doi: 10.1542/peds.2021-052888P

Supplementary Methods

1. Data collection and data cleaning

1.1 Extraction of clinical data

Clinical data pertaining to the period prior to PICU admission were extracted from the electronic health records (EHR; HiX, Chipsoft, Amsterdam, the Netherlands). The extracted datasets include: demographic data - oncological diagnosis, and patient biometrics; previous PICU admissions; bacterial culture results; laboratory values; all free text fields of daily reports of clinicians and radiology reports for defining covariates (e.g., fungal infection) or organ dysfunction (e.g., gastro-intestinal perforation or reduced left ventricular ejection fraction).

Clinical data pertaining to the period of PICU admission were extracted from MetaVision Patient Data Management System (PDMS;iMDsoft,Tel Aviv, Israel). These data include vital signs, ventilator settings, laboratory values, data on procedures (tube, catheter, arterial line), continuous medication, observations (e.g., Glasgow Coma Scale or Cornell Assessment of Pediatric Delirium (CAP-D) score, and fluid balance. An additional dataset on free text field items, such as resuscitation during PICU stay or hepatic encephalopathy was extracted using text mining using standard search terms on the daily clinicians' reports at the PICU. More details on definition and data extraction of the covariates is provided in Supplementary Table S1.

Patients without consent for the use of their clinical data were excluded from our study. Data cleaning and analyses were performed in R, version 4.2.1., running under MacOS Big Sur, and the following packages were used: castoRedc 1.0.5, rms 6.3-0, table1 1.4.2, lubridate 1.9.0, magrittr 2.0.3, tidyverse 1.3.2, ggplot2 3.4.0, sqldf 0.4-11, readxl 1.4.1, tidyr 1.2.1 , stringr 1.4.1, dplyr 1.0.10, xts 0.12.2, zoo 1.8-11, hablar 0.3.0, pacman 0.5.1, quanteda 3.2.4.

1.2 Assessment and classification of the PODIUM organ dysfunction criteria in the EHR datasets

The dataset from the PICU is a clinical time series dataset with a frequency of 1 measurement per minute. It includes vital signs, mechanical ventilator data, laboratory results, observations (e.g., Glasgow Coma scores), inotropic medication, and fluid balance data. In order to populate infrequently measured physiologic data for continuous organ dysfunction labelling, we used carry-forward interpolation, whereby we defined a time period for each variable. As such, ventilator settings were carried forward for 6 hours, lactate and non-invasive systolic blood pressure were carried forward for 1 hour, and all lab values were carried forward for 6 hours, except for blood glucose and creatinine measures that were carried forward for 1 hour and 24 hours, respectively. As some time points were missing in the time series data, for example when the patient was on MRI transport, we

accounted for these missing periods by making the dataset a regular 1-minute time series prior to carrying the last observation forward for the predefined amount of hours.

To identify most commonly occurring patterns of artefacts, the vital signs (mainly heart rate and blood pressure) were checked by visual inspection in MetaVision PDMS electronic health care records (by the first author MS and cases of doubt were resolved by a second reviewer TK). We hereby identified thresholds for artefacts in heart rate and blood pressure, erring on the side of caution, and the values defined as artefacts were transformed into missing values. We did not use the p5 or p95 cut-off values as this more likely could eliminate vital signs that are actually real values.

We summarized the time series with a frequency of 1 measurement per minute to 1-hour windows. Lab values and other relevant data from the period preceding PICU admission were joined to the 1-hour dataset, to enable classification of organ dysfunction at PICU baseline. Moreover, additional datasets with the free text field variables for organ dysfunction criteria were joined. We then defined organ dysfunction according to PODIUM criteria in this 1-hour dataset, see Supplementary Table S2.

The 1-hour dataset with organ dysfunction classification per hour was summarized into 24-hour windows, and new or progressive multi-organ dysfunction was classified based on those 24-hour windows. We defined PICU baseline as the period of 24 hours preceding PICU admission, or the first 3 hours of PICU admission – as it may take a short time from start of PICU admission to start supportive therapy for organ dysfunction, for example intubation and mechanical ventilation. After baseline, any additional organ dysfunction was taken into account for defining NPMOD.

Supplementary Tables

Supplementary Table S1. Assessment and classification of the PODIUM organ dysfunction criteria in the EHR datasets.

Organ system	Criteria that were considered	Additional information
Neurologic	Glasgow Coma Scale (GCS) <= 8	GCS where no sedative medications were given, and the patient was not intubated. Post-operative patients without a tube with a GCS <=8 during the first 3 hours of PICU admission were excluded as this was regarded as a post-sedation effect and not a reflection of neurologic dysfunction. The electroencephalography (EEG) results were not available in a structured format in either the EHR, and therefore were not included as criteria.
	Cornell Assessment of Pediatric Delirium (CAPD) score ≥ 9	
Respiratory	In patients on respiratory support but not invasively ventilated, i.e., on either high flow nasal cannula (HFNC), non-rebreathing mask (NRM) or non-invasive ventilation): • PaO_2/FiO_2 ratio ≤ 300 • SpO_2/FiO_2 ratio ≤ 264 • Non-invasive ventilation for ventilatory failure	As our center does not provide extracorporeal membrane oxygenation (ECMO) for respiratory failure, this was not included as a criterion. However, we have classified these patients with (severe) respiratory failure prior to transfer for ECMO. For the proposed SpO_2-based measures, according to PODIUM criteria only oxygen saturation values between 80% and 97% were considered. PaO_2/FiO_2, SpO_2/FiO_2, OI and OSI were calculated every minute in order to obtain exact ratios, and respiratory dysfunction was classified using the mean value of these ratios / indices per hour.
	In invasively ventilated patients: • Oxygenation index (OI) ≥ 4 to ≤ 16 • OI >= 16 • Oxygen saturation index (OSI) ≥5 to < 12.3 • OSI ≥ 12.3	
Cardiovascular	Cardiac arrest*	Data were obtained through automatized text-mining of free text fields of clinicians' and nurses' notes of MetaVision PDMS, through the Dutch search terms and regular expressions for "resuscitation", "CPR", "thorax compressions", "heart massage".
	Heart rate*	First, artefacts were defined per age category, if a 1-minute value was defined as artefact, we made it a missing (NA). We then summarized this to 1-hour windows, if a window had more than 40 out of 60 observations missing, this window was deemed unsuitable for organ dysfunction classification and we made this 1-hour window missing. We then used the mean value per hour for classification of organ dysfunction per hour.

Supplementary Table S1. Assessment and classification of the PODIUM organ dysfunction criteria in the EHR datasets - *continued*.

Organ system	Criteria that were considered	Additional information
	Systolic blood pressure*	First, artefacts were defined per age category, and artefacts were made missing. Non-invasive systolic blood pressure was interpolated for 1 hour using last observation carried forward. After cleaning of artefacts, invasive and non-invasive blood pressure were combined into one variable, where invasive blood pressure was leading. Organ dysfunction was then classified based on mean value for every 1 hour.
	Vaso-active inotropic score (VIS)*	VIS was calculated every 1 hour, using the maximum value per inotropic medication for that hour.
	Serum lactate >= 3 and < 5 mmol/L* or serum lactate >= 5 mmol/L*	
	Echocardiographic estimation of left ventricular ejection fraction (LVEF) < 50%*	Automatized text-mining with the Dutch search terms and regular expressions for "LVH", "left ventricle", "ejection" with exclusion of patterns with ("good*|normal*|improving*") was used to extract data on LVEF < 50% or LVEF described as 'moderate' or 'poor' from pediatric cardiologists' notes and ultrasound reports.
		Central venous oxygenation and serum troponin were not taken into account as these data were not routinely available. *Cardiovascular dysfunction was classified based on ≥ 2 of the measurements marked with an asterix (*) at the same hour.
Renal	Urine output < 0.5 mL/kg/h for ≥ 6 hours and < 12 hours **with** concomitant serum creatinine increase 1.5 – 1.9 times baseline or ≥ 26.5 µmol/L increase	Only urine output in patients with a catheter was taken into account. Baseline creatinine was the lowest creatinine in 7 days prior to PICU admission, or, if missing, the lowest creatinine in 30 days prior to PICU admission, or, if missing, the lowest creatinine in 90 days prior to PICU admission. To define renal dysfunction at baseline, the last creatinine values in the 36 hours preceding PICU admission were used (relative to their baseline creatinine values). If a prior serum creatinine was unavailable, the age-and gender-based baseline creatinine levels proposed by the PODIUM renal dysfunction group[1] were used. Height and weight measurements were obtained from HiX EPD in the 60 days before (and for height 30 days after) PICU admission.
	Urine output < 0.5 mL/kg/h for ≥ 12 hours	
	Serum creatinine increase ≥ 2 times baseline	
	eGFR < 35 mL/min/1.73 m2 (and not age < 30 days)	
	Initiation of continuous renal replacement therapy (CRRT)	The start date and time of CRRT was used to define initiation of CRRT.
	Fluid overload ≥ 20% -- starting 48 hours after start PICU admission	Fluid overload was calculated based on input/output, as data on weight during PICU admission was not routinely available.

Supplementary Table S1. Assessment and classification of the PODIUM organ dysfunction criteria in the EHR datasets - *continued*.

Organ system	Criteria that were considered	Additional information
Gastro-intestinal	Bowel perforation or pneumatosis intestinalis on plain abdominal film, CT or MRI	Data were extracted using the Dutch search terms and regular expressions for "gastro-intestinal perforation", "gut perforation", "gut ischemia", "pneumatosis intestinalis" or "free abdominal air" on free text fields of radiology reports of the EHR and free text fields of physicians' and nurses' notes during PICU admission from MetaVision PDMS. Sloughing of gut was not taken into account as data were not available in structured format or text fields of the EHR.
Hepatic	• Biochemical evidence of acute liver injury (defined as aspartate aminotransferase > 100 IU/L, alanine aminotransferase > 100 IU/L, gamma-glutamyl transferase > 100 IU/L, total bilirubin > 85.5 µmol/L, or direct bilirubin > 34.2 µmol/L) **with** prothrombin time (PT) > 15 secs or international normalize ratio (INR) > 1.5 **and** hepatic encephalopathy • Biochemical evidence of acute liver injury **with** PT ≥ 20 secs or INR ≥ 2.0	Hepatic encephalopathy was extracted using the search terms or regular expressions for "encephalopathy" in HiX EHR to identify patients with hepatic encephalopathy preceding PICU admission and in MetaVision PDMS for hepatic encephalopathy during PICU stay. This rendered 1 PICU admission, in which the patient already had a PT > 20 or INR > 2.0, and was therefore already classified as having hepatic dysfunction. Lab values in 24 hours preceding PICU admission were used for classification of hepatic dysfunction at PICU baseline.
Hematology	Platelet count < 30 10E9/L or 50% decrease from baseline Hemoglobin < 4.3 mmol/L Leucocytes < 3.0 10E9/L	Baseline thrombocytopenia was defined as lowest value where platelet count < 100 10E9/L in the 24 hours preceding PICU admission. We used the lowest value in the 24 hours preceding PICU admission for defining hematological dysfunction at PICU baseline.
Coagulation	In the absence of liver dysfunction, a combination of ≥ 2 of the following criteria: • Platelet count < **30** 10E9/L • INR > 1.5 • Fibrinogen 1.5 g/L • D-dimer > 5 µg/mL (= upper limit of normal)	As we included only pediatric oncology patients, we adjusted for thrombocytopenia by using a platelet count threshold < 30 10E9/L or 50% decrease from thrombocyte baseline, i.e., we used the same criteria as defined in hematological dysfunction by PODIUM.
Endocrine	Blood glucose ≥ 8.3 mmol/L or < 2.8 mmol/L	Glucose measurements in the 12 hours preceding PICU admission were used to define endocrine dysfunction at baseline.
Immune	Peripheral absolute neutrophil count < 0.5 10E9/L	If neutrophil count was missing, we used leucocyte count < 1.0 10E9/L as a substitute or neutropenia. Lymphocyte count, $CD4^+$ T lymphocyte measurements, monocyte HLA-DR expression and ex vivo LPS-induced TNF-α were not taken into account as these data were not routinely available.

Supplementary Table S2. Detailed description of the covariates, including data extraction and data cleaning.

Covariate	Definition
Oncological diagnosis group	Hemato-oncological, solid tumor or brain / central nervous system tumor. Diagnoses were manually classified into one of the three diagnosis groups.
Hematopoietic stem cell transplantation (HSCT)	A HSCT in the year prior to PICU admission.
Sepsis or infection	Sepsis: PICU admission reason was classified as sepsis, based on criteria of the 2005 Pediatric Sepsis Consensus Conference.[2] Fungal infection: probable or proven Aspergillus, Mucor mycosis, or invasive Candida infection, according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.[3] Bacterial infection: positive bacterial culture with treatment consequences, i.e., no bacterial colonization. All bacterial cultures were cross checked through text mining in the electronic health records.
Neutropenia at baseline	Neutropenia (i.e., neutrophil granulocytes < 0.5 10E9/L or if missing leukocytes < 1.0 10E9/L) in the 24 hours preceding PICU admission or the first 3 hours of PICU admission.
Previous relevant PICU admission	Per patient, a prior PICU admission that was either unplanned or had a protracted course, i.e., longer than the anticipated PICU stay; for solid tumor resections the anticipated stay was 1 day, for neuro-oncology patients this was manually defined, ranging from 1 to 3 days based on the risk for developing central diabetes insipidus.
Unplanned PICU admission	All other PICU admission reasons other than planned post-operative care or a planned admission after a procedure.
Number of failing organs at baseline	Organ dysfunction was defined according to PODIUM criteria.[4] The concomitant number of failing organs per 24-hour window was then categorized into: 0 = no failing organs at baseline 1 = 1 failing organ at baseline 2 = 2 or more failing organs at baseline. Baseline = 24 hours prior to PICU admission and up to first 3 hours of PICU admission.

Supplementary Table S3. Clinical and demographic characteristics of PICU admissions, with NPMOD defined by PONC-PODIUM criteria**.**

Characteristic	Total PICU admissions (n = 761)	PICU admissions without NPMOD (n = 605)	PICU admissions with NPMOD (n = 157)
General characteristics per PICU admission			
Age at admission (years), median [IQR]	6.0 [2.7 – 12.8]	6.6 [3.0 – 13.1]	4.1 [1.5 – 10.8]
Female sex, n (%)	351 (46)	269 (44.5)	82 (52.6)
PICU admission reason, n (%)			
Planned post-operative care	473 (62.2)	439 (72.7)	34 (21.7)
Respiratory failure	106 (13.9)	53 (8.8)	53 (33.8)
Sepsis	40 (5.3)	21 (3.5)	19 (12.1)
Neurological deterioration	36 (4.7)	28 (4.6)	8 (5.1)
Cardiovascular failure	33 (4.3)	18 (3.0)	16 (10.2)
Renal failure	7 (0.9)	2 (0.3)	5 (3.2)
Liver failure	2 (0.3)	1 (0.2)	1 (0.6)
Unplanned post-operative care	24 (3.2)	19 (3.1)	5 (3.2)
Other	40 (5.3)	24 (4.0)	16 (10.2)
Covariates			
Oncological diagnosis groups			
Haemato-oncological	190 (25.0)	100 (16.6)	90 (57.3)
Solid tumor	268 (35.2)	222 (36.8)	46 (29.3)
Brain / CNS tumor	303 (39.8)	282 (46.7)	21 (13.4)
HSCT, n (%)	16 (2.1)	4 (0.7)	12 (7.6)
Infection or sepsis at baseline, n (%)	100 (13.1)	49 (8.1)	51 (32.5)
Neutropenia at baseline, n (%)	82 (10.8)	39 (6.5)	43 (27.4)
HFNC preceding admission, n (%)	86 (11.3)	43 (7.1)	43 (27.4)
Previous relevant PICU admission, n (%)	104 (13.7)	63 (10.4)	41 (26.1)
Unplanned PICU admission, n (%)	288 (37.8)	165 (27.3)	123 (78.8)
Number of failing organs at baseline, n (%)			
0	552 (72.5)	481 (79.6)	71 (45.2)
1	169 (22.2)	105 (17.4)	64 (40.8)
≥ 2	40 (5.3)	18 (3.0)	22 (14.0)
Outcome			
Maximum number of concomitantly failing organs during first week of PICU admission			
0	358 (47.0)	358 (59.3)	0 (0)
1	234 (30.7)	234 (38.7)	0 (0)
2	82 (10.8)	10 (1.7)	72 (45.9)
3	47 (6.2)	0 (0.0)	47 (29.9)
4	30 (3.9)	2 (0.3)	28 (17.8)
≥ 5	9 (1.2)	0 (0)	10 (6.4)
PICU length of stay (days), median [IQR]	0.9 [0.8 – 2.5]	0.9 [0.7 – 1.4]	4.5 [2.0 – 10.3]
PICU mortality, n (%)	28 (3.7)	7 (1.2)	21 (13.4)

PONC-PODIUM pediatric oncology - Pediatric Organ Dysfunction Information Update Mandate; *IQR* interquartile range; *NPMOD* new or progressive multi-organ dysfunction; *OR* odds ratio; *95% CI* 95% confidence interval; *CNS* central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy; *PICU* pediatric intensive care unit.

Supplementary Table S4. Considering all PICU admissions – Results of univariate and multivariable logistic regression model, with estimated odds ratio (OR) along with the 95% confidence interval (CI) for the outcome of new or progressive multi organ dysfunction (defined according to the PONC-PODIUM criteria).

Covariate	Univariate OR (95% CI)	Multivariable OR (95% CI)
Oncological diagnosis groups		
Hemato-oncological	12.09 [7.13 – 20.47]	**2.64 [1.33 – 5.26]**
Solid tumor	2.78 [1.61 – 4.80]	1.63 [0.89 – 2.98]
Brain / CNS tumor	*reference*	*reference*
HSCT, n (%)	12.41 [3.95 – 39.05]	2.65 [0.76 – 9.23]
Infection or sepsis at baseline, n (%)	5.45 [3.50 – 8.49]	1.46 [0.82 – 2.60]
Neutropenia at baseline	5.46 [3.39 – 8.81]	1.09 [0.58 – 2.04]
HFNC preceding admission	4.92 [3.08 – 7.86]	1.40 [0.79 – 2.49]
Previous relevant PICU admission	3.03 [1.95 – 4.72]	1.42 [0.83 – 2.44]
Unplanned PICU admission	9.62 [6.32 – 14.64]	**3.92 [2.27 – 6.76]**
Number of failing organs at baseline		
0	*reference*	*reference*
1	4.13 [2.77 – 6.15]	**3.61 [2.27 – 5.73]**
>= 2	8.28 [4.23 – 16.20]	**3.00 [1.44 – 6.25]**

PONC-PODIUM pediatric oncology - Pediatric Organ Dysfunction Information Update Mandate; *NPMOD* new or progressive multi-organ dysfunction; *CNS* central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy; *PICU* pediatric intensive care unit.

Supplementary Table S5. Clinical and demographic characteristics of only unplanned PICU admissions, by occurrence of NPMOD (defined according to PONC-PODIUM criteria).

Characteristic	Unplanned PICU admissions (n = 288)	Unplanned PICU admissions without NPMOD (n = 165)	Unplanned PICU admissions with NPMOD (n = 123)
General characteristics per PICU admission			
Age at admission (years), median [IQR]	5.8 [2.3 – 13.1]	7.6 [2.4– 13.5]	4.5 [2.1 – 11.3]
Female sex, n (%)	143 (49.7)	73 (44.2)	70 (56.9)
PICU admission reason, n (%)			
Respiratory failure	106 (36.8)	53 (32.1)	53 (43.1)
Sepsis	40 (13.9)	21 (12.7)	19 (15.4)
Neurological deterioration	36 (12.5)	28 (17.0)	8 (6.5)
Cardiovascular failure	33 (11.5)	17 (10.3)	16 (13.0)
Renal failure	7 (2.4)	1 (0.6)	5 (4.1)
Liver failure	2 (0.7)	1 (0.6)	1 (0.8)
Unplanned post-operative care	24 (8.3)	16 (9.8)	5 (4.1)
Other	40 (13.9)	24 (14.5)	16 (13.0)
Covariates			
Oncological diagnosis groups			
Hemato-oncological	168 (58.3)	80 (48.5)	88 (71.5)
Solid tumor	88 (30.6)	61 (37.0)	27 (22.0)
Brain / CNS tumor	32 (11.1)	24 (14.5)	8 (6.5)
HSCT, n (%)	16 (5.6)	4 (2.4)	12 (9.8)
Infection or sepsis at baseline, n (%)	86 (29.9)	37 (22.4)	49 (39.8)

Supplementary Table S5. Clinical and demographic characteristics of only unplanned PICU admissions, by occurrence of NPMOD (defined according to PONC-PODIUM criteria) - *continued*.

Characteristic	Unplanned PICU admissions (n = 288)	Unplanned PICU admissions without NPMOD (n = 165)	Unplanned PICU admissions with NPMOD (n = 123)
Neutropenia at baseline, n (%)	75 (26.0)	32 (19.4)	43 (35.0)
HFNC preceding admission, n (%)	79 (27.4)	37 (22.4)	42 (34.1)
Previous relevant PICU admission, n (%)	71 (24.7)	35 (21.2)	36 (29.3)
Number of failing organs at baseline, n (%)			
0	174 (60.4)	120 (72.7)	54 (43.9)
1	78 (27.1)	31 (18.8)	47 (38.2)
>= 2	36 (12.5)	14 (8.5)	22 (17.9)
Outcome			
Maximum number of concomitantly failing organs during first week of PICU stay			
0	82 (45.5)	59 (36.2)	0 (0)
1	73 (27.5)	58 (35.6)	0 (0)
2	53 (10.2)	23 (14.1)	30 (24.0)
3	42 (7.4)	15 (9.2)	33 (26.4)
4	29 (4.5)	5 (3.1)	28 (22.4)
>= 5	(12.8)	3 (1.8)	38 (30.8)
PICU length of stay (days), median [IQR]	2.2 [1.0 – 6.0]	1.4 [0.7 – 2.8]	5.8 [2.4 – 12.7]
PICU mortality, n (%)	27 (9.4)	7 (4.2)	20 (16.3)

IQR interquartile range; *CNS* central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy; *NPMOD* new or progressive multi-organ dysfunction; *PICU* pediatric intensive care unit

Supplementary Table S6. Considering unplanned PICU admissions - Results of the univariate and multivariable logistic regression model, with estimated odds ratio (OR) along with the 95% confidence interval (CI), for outcome of new or progressive multi organ dysfunction (defined according to the PONC-PODIUM criteria).

Covariate	Univariate OR (95% CI)	Multivariable OR (95% CI)
Oncological diagnosis groups		
Hemato-oncological		1.97 [0.78 - 4.93]
Solid tumor		0.96 [0.67 – 2.56]
Brain / CNS tumor	*reference*	*reference*
HSCT, n (%)	4.35 [1.36 – 13.8]	2.59 [0.75 – 8.98]
Infection or sepsis at baseline, n (%)	2.29 [1.37 – 3.83]	1.55 [0.84 – 2.87]
Neutropenia at baseline	2.23 [1.31 – 3.81]	1.19 [0.62 – 2.29]
HFNC preceding admission	1.79 [1.06 – 3.02]	1.56 [0.86 – 2.83]
Previous relevant PICU admission	1.54 [0.90 – 2.64]	1.23 [0.67 – 2.25]
Number of failing organs at baseline		
0	*reference*	*reference*
1	3.37 [1.93 – 5.87]	**2.80 [1.56 – 5.03]**
>= 2	3.49 [1.66 – 7.34]	**2.94 [1.34 – 6.40]**

CNS central nervous system; *HSCT* hematopoietic stem cell transplantation; *HFNC* high flow nasal cannula oxygen therapy. Significant covariates in the model are in bold.

Supplement - References

1. Fitzgerald JC, Basu RK, Fuhrman DY, Gorga SM, Hassinger AB, Sanchez-Pinto LN, et al. Renal Dysfunction Criteria in Critically Ill Children: The PODIUM Consensus Conference. *Pediatrics* (2022)149(1 Suppl 1):S66-S73.
2. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care* (2005);6(1):2-8.
3. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* (2020);71(6):1367-76.
4. Bembea MM, Agus M, Akcan-Arikan A, Alexander P, Basu R, Bennett TD, et al. Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Contemporary Organ Dysfunction Criteria: Executive Summary. *Pediatrics* (2022);149(1 Suppl 1):S1-S12.

7

General discussion and Future perspectives

Critically ill pediatric oncology patients generally have a worse prognosis compared to their non-cancer peers. With the increasing survival rates for pediatric oncology patients, it is essential to target the high mortality rate among patients admitted to the pediatric intensive care unit (PICU).

This thesis ultimately aims to improve the outcome of critically ill pediatric oncology patients. To address the scarce data on the optimal standard of care for these patients, we identified five research priorities for the next decade, based on a broad consensus among pediatric oncologists and intensivists across Europe (**Chapter 2**). One of these priorities was to improve the detection of clinically deteriorating patients at the ward.

Subsequently, in this thesis we primarily focused on timely identification of clinically deteriorating pediatric oncology patients, both at the ward and the PICU. We conducted a comprehensive review and critical appraisal of existing evidence on the performance and impact of currently used Pediatric Early Warning Systems (PEWS) (**Chapter 3**). Additionally, we prospectively evaluated the predictive performance of a modified BedsidePEWS score for clinical deterioration in an applied setting of hospitalized pediatric oncology patients (**Chapters 4 and 5**). Furthermore, we identified risk factors at the start of PICU admission for the development of new or progressive multi-organ failure during the first week of admission (**Chapter 6**).

In this chapter, the main findings of this thesis will be discussed. Moreover, future perspectives on how our findings can be used to improve risk prediction of clinical deterioration and decision support in the timely escalation of care for critically ill pediatric oncology patients will be provided.

Main findings of this thesis - identifying the clinically deteriorating patient

The use(fulness) of a PEWS score for escalation of care at the inpatient ward

Hospitalized pediatric oncology patients are at risk for rapid clinical deterioration, and PEWS scores are widely used to aid the timely recognition of clinically deteriorating patients. The scores reflect the clinical condition of a patient by enumerating the deviation from normal vital signs and clinical observations, and are accompanied by an escalation of care algorithm. PEWS scores are often embedded within a system (a pediatric early warning system – PEWS), including a response component, such as a rapid response team. Despite the widespread implementation of PEWS, there has been limited research on their effectiveness, specifically in pediatric oncology patients. **Chapter 3** of this thesis, a critical appraisal of existing evidence on the performance of PEWS in pediatric oncology patients, revealed gaps in knowledge regarding both the predictive performance and impact of PEWS in this high-risk population. Although the validation studies reported

good performance of a PEWS score to detect clinical deterioration requiring transfer to the PICU, further assessment revealed that these studies were all at high risk of bias.

Therefore, we conducted a prospective evaluation of the modified BedsidePEWS score in hospitalized pediatric oncology patients, which addressed several methodological issues previously raised (**Chapters 4 and 5**).[1-4] We found that the modified BedsidePEWS score was significantly associated with time to unplanned PICU admission or cardiopulmonary resuscitation (CPR), as well as minor clinical deterioration events. A Cox proportional hazard regression model was used to estimate the association between the modified BedsidePEWS score and the outcome. The estimated hazard ratio (HR) for the primary outcome of unplanned PICU admission or CPR was equal to 1.7 (95% CI [1.6-1.7]), indicating that for each 1-point increase in the BedsidePEWS score, a patient will go, on average, 1.7 times faster to the PICU or require CPR. An 8-point increase in the modified BedsidePEWS multiplies the hazard by exp(0.5 x 8) = 55. This implied that a patient with a score of 8 will go, on average, 55 times faster to the PICU or require CPR compared to a patient with a BedsidePEWS score of 0. We obtained similar results for the secondary outcomes of minor clinical deterioration events (i.e., the start of high flow oxygen, fluid boluses or urgent PICU consultation) and any clinical deterioration event (i.e., PICU/CPR with or without minor event). Our study provides evidence to support the use of a modified BedsidePEWS score as a valuable adjunct in clinical decision-making of timely escalation of care in pediatric oncology patients.

On the other hand, we found a moderate discriminative ability of the PEWS score, and a low positive predictive value for requiring unplanned PICU admission or CPR at the threshold of 8 or higher – the threshold at which the physician is alerted. Considering clinical interpretation of these results, this discrepancy may be explained by the low incidence rate of the outcome event. In our study, we included almost 120.000 PEWS scores and 130 outcome events, yielding an incidence rate of 0,1% for unplanned PICU admission or CPR. This indicates a low probability of requiring such events. Consequently, the threshold of 8 or higher is more likely to produce false positive alerts than true positive alerts, unless the PEWS score would have an outstanding discriminative ability. For the secondary outcome of any clinical deterioration event, the positive predictive value was higher, as the incidence rate of these events was also higher. Ultimately, the decision which false alarm rate may be acceptable in order not to miss any deterioration is a clinical matter, in which costs and benefits of using a PEWS score are balanced, as will be argued later in this chapter.

We also found that the modified BedsidePEWS score was unable to identify all types of clinical deterioration that led to PICU admission or CPR. Specifically, PICU admissions for upper airway problems, neurological deterioration, and unplanned post-operative care were preceded by PEWS scores below the threshold at which the physician is alerted.

This is not surprising since this PEWS score does not include items for these types of deteriorations and is not intended for use within the theatre. However, missing neurological deterioration may pose a particular problem in neuro-oncological conditions and should therefore be included in a score that aims to timely detect clinical deterioration. The Dutch PEWS score, a new PEWS score that was implemented after our validation study, contains an item for neurological decline and gut feeling of caregivers. This may at least partially address missing certain types of clinical deterioration. Albeit to a lesser extent, we also found that the modified BedsidePEWS score did not always capture sepsis, respiratory failure, and cardiovascular dysfunction in the 24 hours preceding PICU admission.

Like previous studies, we encountered the challenge of sustaining adherence and completing all items when using PEWS scores on a daily basis.[5,6] Upon the implementation of the Dutch PEWS score, we applied the insights we gained from our study to enhance the documentation and use of this PEWS score. For example, we have 1) automatized the calculation of the PEWS score; 2) reduced the possibility for missing items by streamlining documentation of PEWS scores and mandatory data entry for all required items, and 3) improved the digital workflow within the electronic healthcare records. However, manual data entry is still required for all items of the Dutch PEWS score. This is a labor-intensive, error prone process, which may add up to the already high administrative burden perceived by health care providers. Automatized integration of clinical data and optimal embedding of an early warning system in the electronic health records (EHR) could alleviate the administrative burden.

In summary, we may improve the quality of care by more accurate risk prediction, and we can increase efficiency by automatized integration of clinical data in the EHR[7-9], as will be explored later in this chapter.

Risk factors for development of multi organ dysfunction during PICU admission

Besides considering clinical deterioration at the inpatient ward, we assessed pediatric oncology patients admitted to the PICU who may further deteriorate by developing new or progressive multi-organ dysfunction (NPMOD) (**Chapter 6**). Our multivariate prognostic model at PICU admission identified hemato-oncological diagnosis, unplanned PICU admission, and the number of failing organs at PICU admission as significant risk factors for the development of NPMOD.

Our study revealed an interesting result: upon refining the existing organ dysfunction criteria for pediatric oncology patients, renal failure and severe cardiovascular failure emerged as one of the most frequently failing organs at PICU admission in patients who develop NPMOD. This finding merely has its implications for early surveillance at the inpatient ward, to prevent progressive organ dysfunction. For example, the development of acute kidney injury (AKI) can be monitored at the ward, and substitution or adjustments

of nephrotoxic medication as well as prevention of fluid overload can be implemented. This may lead to decreased AKI rates and better outcomes.[10 11] Also, closely monitoring the fluid balance in patients with cardiovascular failure may prevent further deterioration.

Future perspectives

Optimizing risk prediction of clinical deterioration in pediatric oncology patients

When treating critically ill patients, clinicians often face important and urgent decisions about when and which treatment should be initiated. Risk prediction models may support clinical decision-making, by leveraging clinical data and providing accurate prognostic information that can ease the uncertainty surrounding these life-and-death decisions.[12]

In working towards a robust risk prediction model for clinical deterioration, the goal is to accurately and timely predict clinical deterioration at all times during hospitalization while keeping the burden of screening as low as possible. However, achieving a perfect model that ensures no unexpected deterioration events and no false alarm rates is merely hypothetical. Certain events, like anaphylactic shock, can be challenging to predict at the inpatient ward. Thus, the priority is to find a balance between optimal detection of clinical deterioration events and the costs of screening, including a high false alarm rate and burden of screening for patients and caregivers.

The accuracy of risk prediction for clinical deterioration can be enhanced in several ways. One strategy is to incorporate additional variables into the model and to account for temporal changes in clinical parameters. Moreover, in studies developing a risk prediction model, a higher number of outcome events is needed to encompass all clinical subtleties and facilitate a more precise prediction.

When incorporating additional variables into the risk prediction model for clinical deterioration, several findings of this thesis alongside existing literature can be considered. These include risk factors for PICU transfer, e.g., hemato-oncological diagnosis and hematopoietic stem cell transplantation (HSCT)[13-16]; the most common reasons for PICU admission, e.g., respiratory failure, sepsis and neurological deterioration[13 17 18] (**Chapter 5**); types of clinical deterioration missed by the modified BedsidePEWS score (**Chapter 5**); and frequently occurring organ dysfunction at PICU admission, that may benefit from early recognition and intervention (**Chapter 6**). In addition, the gut feeling of clinicians, nurses and parents should be incorporated. Nurses' sense of worry has been shown to be a strong prognostic factor for clinical deterioration, and family concern provides important information for detecting deteriorating patients.[19-21]

Larger sample sizes are required for the development of a more robust model.[22] A larger number of outcome events enables incorporating more variables, and more advanced modelling of escalation of care. The escalation of care at the wards may be considered as multiple clinical states of a patient. For example, a patient starts upon admission to the inpatient ward, then may require any intervention(s) because of clinical deterioration and/or may require an unplanned transfer to the PICU or CPR (see Figure 1). The evolution among these states can be described by estimating a multi-state model.[23] This class of models can estimate the effect of prognostic factors on the escalation of care, and the probability of transitioning from one state to another. Since multiple factors may influence the escalation of care, an adequate number of outcome events is essential to capture all clinical nuances. Possibilities for getting data from a larger number of patients will be discussed later in this chapter.

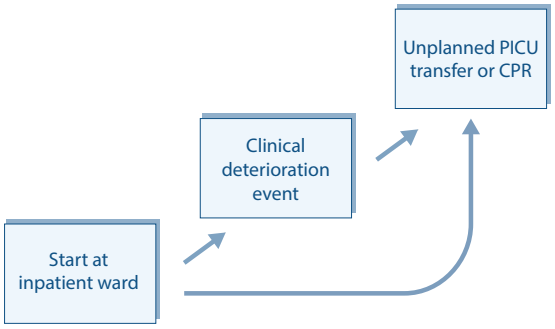

Figure 1. The escalation of care at the inpatient ward may be modelled by using multiple clinical states of a patient, where a patient starts at the inpatient ward, may experience a clinical deterioration event, and may subsequently be transferred to the PICU or require CPR, or may directly require a transfer to the PICU or cardiopulmonary resuscitation.

While it is essential to ensure that no patient deterioration goes unnoticed, as this may lead to adverse events[24], there are drawbacks in continuously monitoring the patients' condition throughout hospitalization, and triggering an evaluation upon risk of deterioration. Besides the financial costs, the burden of screening may include false positive alarms, administrative load, and frequent measurements of vital signs for patients.

First, the burden of false alarms is a significant but frequently overlooked concern in the use of PEWS scores, or risk prediction models for clinical deterioration [25-27], as we also found in **Chapter 5**. A high false alarm rate can be demanding for caregivers. It may lead to alarm fatigue, disengagement with the system, and, ultimately, risk missing signs of patient deterioration.[26-31] Therefore, in the development and validation of a prediction model, it is important to pay attentions to metrics reflecting (false) alarm rates [25], and to refine models prior to deployment to prevent large amounts of additional work-up.[27]

Second, monitoring all patients throughout hospitalization for potential clinical deterioration may be burdensome for nurses, specifically when all vital signs have to be manually registered. Directly incorporating vital signs into the EHR may reduce this burden. Preferably, only the inevitable items are manually registered. This may potentially free up clinical time for more important tasks, and may result in cost savings for hospitals and improved patient care.

Third, frequent measurements of vital signs may be burdensome for patients, for example nocturnal non-invasive blood pressure measurements that disturb patients' sleep. From a clinical perspective, it is undesirable for all patients to undergo the same frequency of vital sign measurements irrespective of their risk of deterioration. However, from a methodological perspective, utilizing the same frequency of measurements for each patient potentially at risk of deterioration would lead to a less biased risk estimation. Readily available clinical data could be used as much as possible in developing or optimizing a risk prediction model for clinical deterioration, to prevent patients from being burdened by additional screening. Such an approach requires some form of handling infrequently populated clinical data.

Currently, the Dutch PEWS score is used in our setting. This PEWS score itself is fairly similar to the modified BedsidePEWS score we validated. The difference lies in that the item of temperature has been removed, and some measurements are conducted stepwise. This means that saturation and blood pressure only need to be measured if other items within the breathing or circulation categories are abnormal. This may possibly reduce the burden of screening for patients compared to the modified BedsidePEWS. In addition to the PEWS score itself, other items (gut feeling and neurological deterioration) and risk categories were added. These items or risk categories function to increase the frequency of monitoring or prompt physician evaluation. The risk categories were defined based on clinicians' expertise, for example in our center one of the defined risk categories included patients with a central vascular access and fever. However, the Dutch PEWS is still a score-based tool that requires manual entry of all items, and it has not yet been validated in pediatric oncology patients. Moreover, to achieve accurate and timely prediction of clinical deterioration at all times during hospitalization, it would be preferable to analyze individual items in each other's context (e.g., by a multivariable analysis), and to incorporate the time-varying nature of the items.

Using more data with advanced modelling techniques for accurate risk prediction

The widespread implementation of modern electronic health records enables the use of large amounts of data and develop early warning systems that are not limited to simple scoring systems.[32] With these large datasets of clinical data, both traditional statistic and artificial intelligence (AI) models have the potential to allow more comprehensive, accurate and personalized risk prediction.[32-34] AI, which encompasses machine learning

(ML), is the scientific discipline that uses computer algorithms to learn from data, to help identify patterns in data, and make predictions.[35] Currently, AI and ML are generating excitement due to their ability to analyze large and complex data structures, including different types of data (such as free text notes).[34,36-38]

Moving from simple scoring systems towards more advanced risk prediction – at the inpatient ward

In adult (oncology) patients at the ward, a rapidly growing number of studies uses AI models to identify critical illness and deterioration at the inpatient ward.[39] Besides AI, traditional (advanced) statistical modelling techniques have been deployed aiming to provide more accurate risk prediction of clinical deterioration.[40] Various studies showed that models using patient data (e.g., vital signs, laboratory results) are more accurate in predicting unplanned ICU transfer, and have lower false alarm rates than standard early warning scores.[27 40-44] Moreover, accounting for trends over time may further improve accuracy.[45] A recent systematic review on AI-based prediction models for clinical deterioration in adult patients showed that these models have an overall good performance in predicting deterioration.[39] Nevertheless, this review also highlighted that future studies are required to assess their clinical utility and performance following implementation. A potential future benefit of AI is the use of real-time or integrated data to continuously update the model and incorporate treatment effects. Such an approach has not yet been widely employed in healthcare. The performance and effectiveness of models based on real-time data may be an interesting topic for future studies [39], also in hospitalized children.

In children, developing models that accurately detect clinical deterioration events while minimizing the burden of screening is more challenging, because clinical deterioration occurs less frequently compared to adults.[46] Nonetheless, various studies developed EHR-based models for hospitalized children that incorporated vital signs.[47-51] Some studies have also included additional clinical data such as patient characteristics or lab values.[52 53] These studies showed promising results in predicting PICU transfers[47-51 54], and cardiopulmonary arrest.[53] Specifically, the models showed superior accuracy for predicting cardiac arrest or unplanned PICU transfer compared to a modified PEWS score[47 53 54], as well as reduced false alarm rates.[53] With such promising results, it may be possible to increase accuracy of risk prediction for inpatient deterioration in pediatric oncology patients.

Notwithstanding these encouraging findings, some critical remarks must be considered regarding their clinical application. First, when developing a model, it is essential to think about its clinical use, preferably prior to model development.[55] Some of the studies in hospitalized children were limited in their clinical application to support decision making in daily care. For example, some studies considered only the first 24 hours of hospitalization[49 50], and therefore the model may not be applicable for the whole duration of a patient's hospital stay. Another study incorporated data that was not available

throughout hospitalization, such as discharge diagnosis.[48] Moreover, a complex model may not be easily interpretable by clinicians, and this may hamper its clinical use.[53] A matched case-control design from which the model was derived could pose the model at risk of bias, as the matching done during derivation may result in a model not applicable to a general population.[48 51] Before a model can be used at the bedside, it is important that it is interpretable, simple to automate and can be used to monitor patients' clinical condition throughout admission.[47]

Second, it is essential that all key aspects of model development and validation are evaluated and reported, also for AI models. AI is a rapidly growing field, and it has been suggested that AI can potentially revolutionize healthcare.[33] Yet, concerns have been raised that AI may be overhyped and, if not used with proper guidance, knowledge or expertise, studies may suffer from methodological shortcomings.[38] One of the concerns is overfitting (whereby too many predictors or features are included for a small data set, or merely a limited number of outcome events). Moreover, an AI model is often not compared to simpler modelling approaches (that may possibly yield a more parsimonious model).[35] Furthermore, external validation, which involves a robust assessment of the predictive accuracy of the model using data different from the ones used for development, is often lacking.[39] Most of these concerns are similar to those in 'regular', not AI-based, prediction models. Yet, a concern specific to AI is the lack of transparency of the algorithm, requiring thought on how to make the algorithm available to other researchers for independent validation or how to implement it in the clinical workflow.[35] To support complete and transparent reporting and critical appraisal of all key aspects of AI models, a new version of the TRIPOD (Transparent Reporting of multivariable prediction model of Individual Prognosis or Diagnosis) statement and Prediction model Risk Of Bias Assessment Tool (PROBAST) for AI will follow soon.[38]

Moving from simple scoring systems towards more advanced risk prediction - at the PICU

Currently, there is scarce data on the optimal standard of care for pediatric oncology patients at the PICU. At the PICU, large amounts of clinical data are being generated and digitized, including data from EHRs, bedside monitors, ventilators and medication pumps. These large amounts of clinical data, coupled with the complexity of critically ill patients and the need for an integrative approach in critical care research, make the PICU an appealing environment for deploying advanced modelling techniques, including AI.[34 46]

In routinely collected ICU data, AI techniques have been mainly deployed for predicting complications, mortality, and improving prognostic models.[56] However, in most studies, the sample size was too small to fully exploit the potential of AI methods.[56] In both adult and pediatric critical care, studies showed that AI models can identify groups of patients with similar trajectories that are not typically revealed by admission diagnosis or severity of illness scores.[57-62] These findings may have prognostic[58 62 63] and potentially therapeutic

relevance.[60-62] For example, one study in children with shock in the acute phase of critical illness identified different groups associated with different response to therapy and outcome.[62] Similarly, a study in critically ill children uncovered distinct and reproducible phenotypes of trajectories of multi organ failure during PICU stay.[63] This study reported that these phenotypes had distinct clinical characteristics, were independently associated with outcome of PICU mortality, and had different sets of organ dysfunction–based risk factors for death.[63] Such data-driven phenotyping may potentially help to develop precision medicine strategies that might reduce mortality and morbidity associated with multi organ dysfunction syndrome (MODS). Yet, further investigation into the value of this phenotyping approach in research and clinical care is warranted.[59 63]

In **Chapter 6**, we identified risk factors at PICU admission for new or progressive multi-organ dysfunction (NPMOD) during the first week of PICU stay. Yet, the risk of developing NPMOD may change throughout PICU admission. Modelling organ dysfunction throughout the PICU stay, thereby incorporating the interventions in patients with progressive organ dysfunction, could provide a more accurate risk prediction of NPMOD in pediatric oncology patients. In the general PICU population, several ML prognostic models have shown the ability to predict the risk of transition from no or a single organ dysfunction to multiple organ dysfunction throughout PICU admission.[64] An approach combining continuous evaluation of organ function and warning of development of MODS could contribute to the monitoring and ultimately the management of critically ill pediatric oncology patients.

So, both at the ward and the PICU the time has come to move from score-based screening tools towards more comprehensive models that can be used to support clinical decision making. However, to be able to capture all nuances and account for the whole richness of the clinical environment, we need large amounts of data – or merely more outcome events - and high-quality data. This will be discussed in the next section.

Possibilities and pitfalls of getting and using data for decision support

The possibilities of getting high quality data from larger amounts of patients

The most important impediment for developing more advanced models in pediatrics is the limited number of outcome events regarding patient deterioration. Using the EHRs of a single center may not provide sufficient outcome events, even when care has been nationally centralized. One way to tackle this barrier is through (international) multi-center studies, yet this may be hampered by national legislation. A recently launched, innovative opportunity for acquiring high quality data from many patients lies in the European Health Data Space (EHDS).[65] The EHDS encompasses a health-specific data sharing framework for research and innovation. Several stakeholders in cancer care recently welcomed this EHDS initiative, as leveraging EHR data and increased data sharing has great potential to

improve the care and prognosis of patients with cancer.[66] In the near future, using this kind of data sharing initiatives may yield more robust prediction models.

The quality of clinical data – useful examples of this thesis

The performance of the models, both traditional and AI models, relies on the quality of the data used to estimate or train them. Therefore, care should be taken during data preprocessing to ensure data accuracy and avoid disregarding potentially useful information.[46 67] However, as clinical data are primarily captured for the process of care, using these data for research purposes, and developing models can pose some challenges. In this thesis, we came across several challenges related to the use of clinical data. These included measurement errors or artefacts, missing data, selective measurements, time-series data with both granular data (e.g., data from monitor and equipment at a frequency of every minute) and interval data (e.g., laboratory values and observations), unlabeled data, and specifically considering pediatric patients age-related thresholds for vital signs. In preparing the data for statistical modeling, we made great efforts to ensure accuracy and reproducibility. Therefore, this thesis provides examples on how one may address these data-related challenges.

As there is no perfect solution to handle the abovementioned challenges in data preprocessing, we made assumptions from a clinical point of view. To illustrate, in **Chapter 6**, infrequently measured data (e.g., laboratory values) were interpolated based on clinical expertise for a limited amount of time. Moreover, we accounted for potential artefacts in vital signs by defining age-dependent thresholds. We then considered artefacts and missing data in the dimension reduction (from 1-minute to 1-hour windows). With this dimension reduction, we took effort to prevent one single aberrant data point to immediately flag organ dysfunction. For future studies, the classification of concomitant organ dysfunction could be further improved. Since the pre-specified criteria did not provide a time required to fulfil the criteria, we classified multi-organ dysfunction within 24-hour windows. Possibly, using and validating moving averages for a certain time-window, or modelling the optimal duration for fulfillment of the criteria to be classified as dysfunction could lead to better classification of concomitant organ dysfunction.

Not all relevant clinical data are available in structured format. Instead, they can be found in free text fields, such as clinicians' or nurses' notes or diagnostic reports.[68] This was a challenge we encountered in both our PEWS validation study (**Chapter 4 and 5**) and our PICU study (**Chapter 6**). Extracting data from free text fields is a cumbersome and time-consuming task. Therefore, we automatized this process to a considerable extent by using text mining with standardized search terms. We could then efficiently extract data, including escalation of care interventions. However, in the case of escalation of care interventions, we had to make assumptions for the starting point of some interventions as this was not always documented. For future studies, it would be even more advantageous to document the interventions along with the time of initiation.

The bigger picture

PEWS score as part of a system

Providing optimal care for deteriorating patients is a complex process that involves, besides measuring the PEWS score, several crucial elements. First, the ward staff must be able to timely recognize signs and symptoms of clinical deterioration. Second, they need to be empowered to promptly call for assistance. Third, the assistance must be readily available and provided by the appropriately skilled and equipped personal. Finally, the interventions arising from this response need to (ideally) improve patient outcomes.[69] Therefore, a PEWS score is often embedded within a system.[70] This system involves detection of a deteriorating child, response mechanisms, implementation, and organizational components.[9 70]

In addition to clinical factors, emotional factors may also influence the use of a PEWS score. A recent study among caregivers for pediatric oncology patients showed that an acutely elevated PEWS score often triggered concern, which usually resulted in increased attention.[71] However, persistently high PEWS scores manifested as alarm fatigue, resulting in a false sense of security, diminishing clinician attention and negatively impacting patient care. Nurses reported positive feelings in using a PEWS score, as it increased their confidence to alert a physician.[71] This confidence may promote earlier engagement between interdisciplinary team members and consideration of care escalation.

Overall, the PEWS score is one of several crucial components in the broader framework of clinical deterioration management. Evaluating the clinical value of the PEWS as a system, considering all relevant factors, can be challenging. Recently, a comprehensive mixed-method study has been undertaken in the United Kingdom to develop and implement an evidence-based PEWS improvement program. This project highlighted the difficulties in evaluating the PEWS score for quantitative clinical outcomes, as well as a variety of social, material, and contextual factors associated with implementation of a PEWS. It provided a framework that may be used for ongoing improvement of a PEWS in a whole-system approach.[70]

In a study validating a PEWS score, defining an outcome may be challenging.[70] The decision to transfer a patient to the PICU may be subjective, related to patient factors and resource availability.[72] However, the use of a hard outcome measure, such as CPR or death, is limited by the low occurrence rate.[73-75] Moreover, CPR or death may imply a late phase of clinical deterioration, and may indicate a lost opportunity for preventative action.

An interesting and new element of our study was the use of minor clinical deterioration events as a secondary outcome. This outcome measure reflected the escalation of care at the inpatient ward. Most studies validated a PEWS score for unplanned PICU admission or CPR – as did we. Yet, neither PEWS score validation studies in general pediatric patients

nor in pediatric oncology patients assessed escalation of care interventions at the ward.[2 9 69 76] Not all patients who clinically deteriorate require admission to the PICU. Moreover, the PEWS score was not initially developed to triage transfer to the PICU. It was designed to be a severity of illness score that can be used in routine care to discriminate between sick and less sick patients, aiming to facilitate early identification of patients at risk of clinical deterioration.[77] Escalation of care at the inpatient wards possibly comprises an outcome that captures the deteriorating patient at an early stage. Yet, it may still be subjective when exactly these interventions are started. Objectivity may be increased by incorporating organ dysfunction criteria as defined by the PODIUM criteria (ideally adjusted for pediatric oncology patients - **Chapter 6**). Escalation of care as an outcome may be valuable for future studies validating a PEWS score or a future model that predicts clinical deterioration at the ward, also in different settings or pediatric populations.

The impact of risk prediction models on clinical decision making

In this thesis, we have mainly focused on the predictive performance of the PEWS score itself. The PEWS score forms an essential link from a deteriorating patient to potentially life-saving actions. While we found evidence underlining the use of a PEWS score to support clinical decision making in escalation of care, it would be beneficial to further assess the impact of this PEWS score (or any other future model) on clinical decision making and patients' outcome.

Typically, prognostic models are evaluated with measures of predictive accuracy that do not address the clinical value of using the model, e.g., whether decisions based on the model actually result in an improvement of patient outcomes.[78-80] However, it is strongly recommended to quantify the impact on clinicians' behavior, patients' outcome or cost effectiveness of care. Herein, the impact of using such a model versus not using a model should be assessed, preferably before the model's implementation.[81] Yet, such impact studies are still infrequently performed. This is most likely due to their complexity, long follow-up and associated high costs.[81-84]

Correspondingly, limited data exist on the clinical impact of using a PEWS.[2 69] In general pediatric patients, two randomized multicenter trials were performed.[85 86] One trial compared two different PEWS scores, and concluded that there was no difference in prevention of critical events, yet suffered from low incidence rate of outcome events.[85] A second, large, randomized controlled trial assessed the effect of implementing the BedsidePEWS on all-cause mortality in hospitalized pediatric patients.[86] This study showed no reduction in all-cause mortality, but did show a significant reduction in critical deterioration events, a composite measure reflecting late ICU admission.[86] This study also suffered from a low incidence rate of the primary outcome of all-cause mortality. Consequently, it was argued that mortality might be an inappropriate outcome measure to assess the effect of PEWS implementation.[75]

Assessment of the true clinical impact of a prediction model typically requires an intervention study.[87] The preferred method for such a study would be a randomized controlled trial (RCT). However, as large amounts of patients are needed, logistical and economic challenges may hinder the feasibility of conducting a RCT. Alternative options include a "before-after" impact analysis, where outcomes are measured before, during, and after the use of the prediction model.[87] Nevertheless, this approach may still require a prolonged study period and be susceptible to temporal confounding.

Ultimately, clinicians and hospital policy makers have to weigh the benefits of earlier detection of clinical deterioration against potential burden, and resources required to implement changes in clinical practice.[27] To aid this weighing, the impact of a model on clinical care may be estimated by decision analytic techniques.[78 80 82 87 88] These techniques allow incorporation of clinical consequences, thus addressing the question of whether a model would do more good than harm, while requiring limited extra data.[78 80 88] A decision analytic study is a useful approach to estimate how decision making is expected to be improved when using the model, based on assumptions on how predictive information is used by clinicians in their decision-making.[78 88 89 90 91]

From model to actual successful support of clinical decision making

A potential future scenario in critically ill pediatric oncology patients may include that data-driven systems and clinicians work together. Advanced computational systems can analyze large amounts of data, and provide understandable and practical knowledge through user-friendly interfaces at the bedside. These systems can complement the clinician's decision-making process, by allowing them to make more informed decisions.[32 34 55]

A model that accurately and timely predicts the risk of clinical deterioration at the inpatient ward can facilitate appropriate escalation of care. Besides, accurate and timely predictions of the risk of unplanned PICU transfer may be useful in advanced care planning. In some cases, it may provide an opportunity to discuss patients' and families' wishes and goals surrounding unplanned PICU transfer possibly a bit earlier than the last moment where the patient must be urgently transferred to the PICU and medical interventions should be initiated to prevent critical decline or death.

In the case of facilitation of escalation of care, a model will need to be translated into a clinical decision support (CDS) tool to improve patient outcomes. However, taking models from inception to implementation to support decision making in daily care is a big challenge, as was discussed in this chapter. The process must be considered from the beginning, and the development and use of a CDS system requires the extensive expert knowledge of health care professionals alongside data and statistical experts.[55 92]

Summarizing, an effective model that supports clinical decision making should provide accurate information that the clinician is unlikely to know already. This information should be readily understandable, and provided within sufficient time for clinicians to be able to intervene.[55 93 94] The predictive performance of a CDS model should be assessed, based on data from which it was derived as well as external data.[82 95] Furthermore, as mentioned above, it is important to assess the impact of a model on clinical decision-making.[81] The implementation phase of a CDS includes the presentation of the algorithm in a specific way integrated in the workflow[55], interpretation by the health care professional, and eventually, the medical decision that is made.[92] The final decision (how) to use the CDS is up to the health care professional and their patient.[92]

In conclusion, this thesis has identified research priorities for critically ill pediatric oncology patients, provided valuable insights into the predictive performance of a PEWS score for detecting clinically deteriorating patients at the inpatient ward, and yielded risk factors for new or progressive multi-organ failure at the PICU. This research is an important step towards improving the timely identification of critically ill pediatric oncology patients, with the aim to improve outcome of these patients. Alongside our main findings, several future opportunities to optimize the risk prediction of clinical deterioration have been discussed, both at the inpatient ward and the PICU. Potentially, in the future care for critically ill pediatric oncology patients, data-driven systems and clinicians may work hand-in-hand. The goal would be to timely and accurately detect deteriorating patients with minimal burden of screening, and augment clinicians' decision making whereby data-driven systems provide appropriate information to enable adequate interventions. Alongside the expertise of our colleagues, we may be assisted by models in making complex decisions about escalation of care and resource allocation at busy wards. While there is still much work to be done, great opportunities lie ahead of us to turn this future scenario into a reality.

References

1. Soeteman M, Lekkerkerker CW, Kappen TH, et al. The predictive performance and impact of pediatric early warning systems in hospitalized pediatric oncology patients-A systematic review. *Pediatr Blood Cancer* 2022;69(5):e29636. doi: 10.1002/pbc.29636
2. Trubey R, Huang C, Lugg-Widger FV, et al. Validity and effectiveness of paediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalised children: a systematic review. *BMJ Open* 2019;9(5):e022105. doi: 10.1136/bmjopen-2018-022105
3. Gerry S, Bonnici T, Birks J, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. *BMJ* 2020;369:m1501. doi: 10.1136/bmj.m1501
4. Van Calster B, McLernon DJ, van Smeden M, et al. Calibration: the Achilles heel of predictive analytics. *BMC Med* 2019;17(1):230. doi: 10.1186/s12916-019-1466-7
5. Chapman SM, Oulton K, Peters MJ, et al. Missed opportunities: incomplete and inaccurate recording of paediatric early warning scores. *Arch Dis Child* 2019;104(12):1208-13. doi: 10.1136/archdischild-2018-316248
6. de Groot JF, Damen N, de Loos E, et al. Implementing paediatric early warning scores systems in the Netherlands: future implications. *BMC pediatrics* 2018;18(1):128. doi: 10.1186/s12887-018-1099-6
7. Tomasi JN, Hamilton MV, Fan M, et al. Assessing the electronic Bedside Paediatric Early Warning System: A simulation study on decision-making and usability. *Int J Med Inform* 2020;133:103969. doi: 10.1016/j.ijmedinf.2019
8. Sefton G, Lane S, Killen R, et al. Accuracy and Efficiency of Recording Pediatric Early Warning Scores Using an Electronic Physiological Surveillance System Compared With Traditional Paper-Based Documentation. *Comput Inform Nurs* 2017;35(5):228-36. doi: 10.1097/CIN.0000000000000305
9. Roland D, Powell C, Lloyd A, et al. Paediatric early warning systems: not a simple answer to a complex question. *Arch Dis Child* 2022 doi: 10.1136/archdischild-2022-323951
10. Goldstein SL, Dahale D, Kirkendall ES, et al. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. *Kidney Int* 2020;97(3):580-88. doi: 10.1016/j.kint.2019.10.015
11. Sanchez-Pinto LN, Goldstein SL, Schneider JB, et al. Association Between Progression and Improvement of Acute Kidney Injury and Mortality in Critically Ill Children. *Pediatr Crit Care Med* 2015;16(8):703-10. doi: 10.1097/PCC.0000000000000461
12. Weissman GE, Liu VX. Algorithmic prognostication in critical care: a promising but unproven technology for supporting difficult decisions. *Curr Opin Crit Care* 2021;27(5):500-05. doi: 10.1097/MCC.0000000000000855
13. Zinter MS, DuBois SG, Spicer A, et al. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014;40(10):1536-44. doi: 10.1007/s00134-014-3389-2
14. Zinter MS, Logan BR, Fretham C, et al. Comprehensive Prognostication in Critically Ill Pediatric Hematopoietic Cell Transplant Patients: Results from Merging the Center for International Blood and Marrow Transplant Research (CIBMTR) and Virtual Pediatric Systems (VPS) Registries. *Biol Blood Marrow Transplant* 2020;26(2):333-42. doi: 10.1016/j.bbmt.2019.09.027
15. Cheuk DK, Ha SY, Lee SL, et al. Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplant. *Hematol Oncol* 2004;22(1):1-9. doi: 10.1002/hon.724
16. Faraci M, Bagnasco F, Giardino S, et al. Intensive care unit admission in children with malignant or nonmalignant disease: incidence, outcome, and prognostic factors: a single-center experience. *J Pediatr Hematol Oncol* 2014;36(7):e403-9. doi: 10.1097/MPH.0000000000000048

17. Barking CTMM, Masjosthusmann K, Rellensmann G, et al. Treatment of Children With Cancer and/or Hematopoietic Stem Cell Transplantation in the Intensive Care Unit: Experience at a Large European Pediatric Cancer Center. *J Pediatr Hematol Oncol* 2020;42(7):e583-e88. doi: 10.1097/MPH.0000000000001718
18. Demaret P, Pettersen G, Hubert P, et al. The critically-ill pediatric hemato-oncology patient: epidemiology, management, and strategy of transfer to the pediatric intensive care unit. *Ann Intensive Care* 2012;2(1):14. doi: 10.1186/2110-5820-2-14
19. Romero-Brufau S, Gaines K, Nicolas CT, et al. The fifth vital sign? Nurse worry predicts inpatient deterioration within 24 hours. *JAMIA Open* 2019;2(4):465-70. doi: 10.1093/jamiaopen/ooz033
20. Bavare AC, Thomas JK, Elliott EP, et al. Family-Initiated Pediatric Rapid Response: Characteristics, Impetus, and Outcomes. *J Healthc Qual* 2018;40(2):103-09. doi: 10.1097/jhq.0000000000000096
21. Brady PW, Zix J, Brilli R, et al. Developing and evaluating the success of a family activated medical emergency team: a quality improvement report. *BMJ Qual Saf* 2015;24(3):203-11. doi: 10.1136/bmjqs-2014-003001
22. Vollmer S, Mateen BA, Bohner G, et al. Machine learning and artificial intelligence research for patient benefit: 20 critical questions on transparency, replicability, ethics, and effectiveness. *BMJ* 2020;368:l6927. doi: 10.1136/bmj.l6927
23. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;26(11):2389-430. doi: 10.1002/sim.2712
24. Pearson GA, Ward-Platt M, Harnden A, et al. Why children die: avoidable factors associated with child deaths. *Arch Dis Child* 2011;96(10):927-31. doi: 10.1136/adc.2009.177071
25. Romero-Brufau S, Huddleston JM, Escobar GJ, et al. Why the C-statistic is not informative to evaluate early warning scores and what metrics to use. *Crit Care* 2015;19(1):285. doi: 10.1186/s13054-015-0999-1
26. Romero-Brufau S, Huddleston JM, Naessens JM, et al. Widely used track and trigger scores: are they ready for automation in practice? *Resuscitation* 2014;85(4):549-52. doi: 10.1016/j.resuscitation.2013.12.017
27. Shah PK, Ginestra JC, Ungar LH, et al. A Simulated Prospective Evaluation of a Deep Learning Model for Real-Time Prediction of Clinical Deterioration Among Ward Patients. *Crit Care Med* 2021;49(8):1312-21. doi: 10.1097/CCM.0000000000004966
28. Cassidy CE, MacEachern L, Best S, et al. Barriers and Enablers to Implementing the Children's Hospital Early Warning Score: A Pre- and Post-Implementation Qualitative Descriptive Study. *J Pediatr Nurs* 2019;46:39-47. doi: 10.1016/j.pedn.2019.02.008
29. Bedoya AD, Clement ME, Phelan M, et al. Minimal Impact of Implemented Early Warning Score and Best Practice Alert for Patient Deterioration. *Crit Care Med* 2019;47(1):49-55. doi: 10.1097/CCM.0000000000003439
30. Mason BW, Edwards ED, Oliver A, et al. Cohort study to test the predictability of the NHS Institute for Innovation and Improvement Paediatric Early Warning System. *Arch Dis Child* 2016;101(6):552-55. doi: 10.1136/archdischild-2015-308465
31. Rasooly IR, Makeneni S, Khan AN, et al. The Alarm Burden of Excess Continuous Pulse Oximetry Monitoring Among Patients With Bronchiolitis. *J Hosp Med* 2021;16(12):727-29. doi: 10.12788/jhm.3731
32. Churpek MM, Edelson DP. Moving Beyond Single-Parameter Early Warning Scores for Rapid Response System Activation. *Crit Care Med* 2016;44(12):2283-85. doi: 10.1097/CCM.0000000000002105
33. Obermeyer Z, Emanuel EJ. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. *N Engl J Med* 2016;375(13):1216-9. doi: 10.1056/NEJMp1606181
34. Sanchez-Pinto LN, Luo Y, Churpek MM. Big Data and Data Science in Critical Care. *Chest* 2018;154(5):1239-48. doi: 10.1016/j.chest.2018.04.037
35. Collins GS, Moons KGM. Reporting of artificial intelligence prediction models. *Lancet*

2019;393(10181):1577-79. doi: 10.1016/S0140-6736(19)30037-6

36. Lehman LW, Saeed M, Long W, et al. Risk stratification of ICU patients using topic models inferred from unstructured progress notes. *AMIA Annu Symp Proc* 2012;2012:505-11. PMID: 23304322; PMCID: PMC3540429.
37. Ghassemi M, Naumann T, Doshi-Velez F, et al. Unfolding Physiological State: Mortality Modelling in Intensive Care Units. *KDD* 2014;2014:75-84. doi: 10.1145/2623330.2623742
38. Collins GS, Dhiman P, Andaur Navarro CL, et al. Protocol for development of a reporting guideline (TRIPOD-AI) and risk of bias tool (PROBAST-AI) for diagnostic and prognostic prediction model studies based on artificial intelligence. *BMJ Open* 2021;11(7):e048008. doi: 10.1136/bmjopen-2020-048008
39. Veldhuis LI, Woittiez NJC, Nanayakkara PWB, et al. Artificial Intelligence for the Prediction of In-Hospital Clinical Deterioration: A Systematic Review. *Crit Care Explor* 2022;4(9):e0744. doi: 10.1097/CCE.0000000000000744
40. Churpek MM, Yuen TC, Park SY, et al. Using electronic health record data to develop and validate a prediction model for adverse outcomes in the wards. *Crit Care Med* 2014;42(4):841-8. doi: 10.1097/CCM.0000000000000038
41. Romero-Brufau S, Whitford D, Johnson MG, et al. Using machine learning to improve the accuracy of patient deterioration predictions: Mayo Clinic Early Warning Score (MC-EWS). *J Am Med Inform Assoc* 2021;28(6):1207-15. doi: 10.1093/jamia/ocaa347
42. Churpek MM, Yuen TC, Winslow C, et al. Multicenter development and validation of a risk stratification tool for ward patients. *Am J Respir Crit Care Med* 2014;190(6):649-55. doi: 10.1164/rccm.201406-1022OC
43. Kipnis P, Turk BJ, Wulf DA, et al. Development and validation of an electronic medical record-based alert score for detection of inpatient deterioration outside the ICU. *J Biomed Inform* 2016;64:10-19. doi: 10.1016/j.jbi.2016.09.013
44. Hu SB, Wong DJ, Correa A, et al. Prediction of Clinical Deterioration in Hospitalized Adult Patients with Hematologic Malignancies Using a Neural Network Model. *PloS one* 2016;11(8):e0161401. doi: 10.1371/journal.pone.0161401
45. Churpek MM, Adhikari R, Edelson DP. The value of vital sign trends for detecting clinical deterioration on the wards. *Resuscitation* 2016;102:1-5. doi: 10.1016/j.resuscitation.2016.02.005
46. Shah N, Arshad A, Mazer MB, et al. The use of machine learning and artificial intelligence within pediatric critical care. *Pediatr Res* 2023;93(2):405-12. doi: 10.1038/s41390-022-02380-6
47. Mayampurath A, Jani P, Dai Y, et al. A Vital Sign-Based Model to Predict Clinical Deterioration in Hospitalized Children. *Pediatr Crit Care Med* 2020;21(9):820-26. doi: 10.1097/PCC.0000000000002414
48. da Silva YS, Hamilton MF, Horvat C, et al. Evaluation of Electronic Medical Record Vital Sign Data Versus a Commercially Available Acuity Score in Predicting Need for Critical Intervention at a Tertiary Children's Hospital. *Pediatr Crit Care Med* 2015;16(7):644-51. doi: 10.1097/PCC.0000000000000444
49. Rubin J, Potes C, Xu-Wilson M, et al. An ensemble boosting model for predicting transfer to the pediatric intensive care unit. *Int J Med Inform* 2018;112:15-20. doi: 10.1016/j.ijmedinf.2018.01.001
50. Zhai H, Brady P, Li Q, et al. Developing and evaluating a machine learning based algorithm to predict the need of pediatric intensive care unit transfer for newly hospitalized children. *Resuscitation* 2014;85(8):1065-71. doi: 10.1016/j.resuscitation.2014.04.009
51. Wellner B, Grand J, Canzone E, et al. Predicting Unplanned Transfers to the Intensive Care Unit: A Machine Learning Approach Leveraging Diverse Clinical Elements. *JMIR Med Inform* 2017;5(4):e45. doi: 10.2196/medinform.8680
52. Pimentel MA, Redfern OC, Malycha J, et al. Detecting Deteriorating Patients in Hospital: Development and Validation of a Novel Scoring System. *Am J Respir Crit Care Med* 2021 doi: 10.1164/rccm.202007-2700OC
53. Park SJ, Cho KJ, Kwon O, et al. Development

and validation of a deep-learning-based pediatric early warning system: A single-center study. *Biomed J* 2022;45(1):155-68. doi: 10.1016/j.bj.2021.01.003

54. Pimentel MAF, Redfern OC, Malycha J, et al. Detecting Deteriorating Patients in the Hospital: Development and Validation of a Novel Scoring System. *Am J Respir Crit Care Med* 2021;204(1):44-52. doi: 10.1164/rccm.202007-2700OC
55. Sanchez-Pinto LN, Bennett TD. Evaluation of Machine Learning Models for Clinical Prediction Problems. *Pediatr Crit Care Med* 2022;23(5):405-08. doi: 10.1097/PCC.0000000000002942
56. Shillan D, Sterne JAC, Champneys A, et al. Use of machine learning to analyse routinely collected intensive care unit data: a systematic review. *Crit Care* 2019;23(1):284. doi: 10.1186/s13054-019-2564-9
57. Vranas KC, Jopling JK, Sweeney TE, et al. Identifying Distinct Subgroups of ICU Patients: A Machine Learning Approach. *Crit Care Med* 2017;45(10):1607-15. doi: 10.1097/CCM.0000000000002548
58. Sanchez-Pinto LN, Bembea MM, Farris RW, et al. Patterns of Organ Dysfunction in Critically Ill Children Based on PODIUM Criteria. *Pediatrics* 2022;149(1 Suppl 1):S103-S10. doi: 10.1542/peds.2021-052888P
59. Seymour CW, Kennedy JN, Wang S, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA* 2019;321(20):2003-17. doi: 10.1001/*JAMA*.2019.5791
60. Nemati S, Holder A, Razmi F, et al. An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU. *Crit Care Med* 2018;46(4):547-53. doi: 10.1097/CCM.0000000000002936
61. Wong HR, Atkinson SJ, Cvijanovich NZ, et al. Combining Prognostic and Predictive Enrichment Strategies to Identify Children With Septic Shock Responsive to Corticosteroids. *Crit Care Med* 2016;44(10):e1000-3. doi: 10.1097/CCM.0000000000001833
62. Perizes EN, Chong G, Sanchez-Pinto LN. Derivation and Validation of Vasoactive Inotrope Score Trajectory Groups in Critically Ill Children With Shock. *Pediatr Crit Care Med* 2022;23(12):1017-26. doi: 10.1097/PCC.0000000000003070
63. Sanchez-Pinto LN, Stroup EK, Pendergrast T, et al. Derivation and Validation of Novel Phenotypes of Multiple Organ Dysfunction Syndrome in Critically Ill Children. *JAMA Netw Open* 2020;3(8):e209271. doi: 10.1001/*JAMA*networkopen.2020.9271
64. Bose SN, Greenstein JL, Fackler JC, et al. Early Prediction of Multiple Organ Dysfunction in the Pediatric Intensive Care Unit. *Front Pediatr* 2021;9:711104. doi: 10.3389/fped.2021.711104
65. European Health Data Space; https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en
66. Das M. Stakeholders welcome proposal on the European Health Data Space. *Lancet Oncol* 2022;23(12):1492. doi: 10.1016/S1470-2045(22)00691-X
67. Carra G, Salluh JIF, da Silva Ramos FJ, et al. Data-driven ICU management: Using Big Data and algorithms to improve outcomes. *J Crit Care* 2020;60:300-04. doi: 10.1016/j.jcrc.2020.09.002
68. Sjoding MW, Liu VX. Can You Read Me Now? Unlocking Narrative Data with Natural Language Processing. *Ann Am Thorac Soc* 2016;13(9):1443-5. doi: 10.1513/AnnalsATS.201606-498ED
69. Chapman SM, Wray J, Oulton K, et al. Systematic review of paediatric track and trigger systems for hospitalised children. *Resuscitation* 2016;109:87-109. doi: 10.1016/j.resuscitation.2016.07.230
70. Allen D, Lloyd A, Edwards D, et al. Development, implementation and evaluation of an early warning system improvement programme for children in hospital: the PUMA mixed-methods study. Southampton (UK) 2022.
71. Graetz DE, Giannars E, Kaye EC, et al. Clinician Emotions Surrounding Pediatric Oncology Patient Deterioration. *Front Oncol* 2021;11:626457. doi: 10.3389/fonc.2021.626457
72. Hsu BS, Hill V, Simone S. Executive Summary: Criteria for Critical Care of Infants and Children: PICU Admission, Discharge, and

Triage Practice Statement and Levels of Care Guidance. 2019 doi: 10.1542/peds.2019-2433
73. Menon K, McNally JD, Zimmerman JJ, et al. Primary Outcome Measures in Pediatric Septic Shock Trials: A Systematic Review. *Pediatr Crit Care Med* 2017;18(3):e146-e54. doi: 10.1097/pcc.0000000000001078
74. Ospina-Tascón GA, Büchele GL, Vincent JL. Multicenter, randomized, controlled trials evaluating mortality in intensive care: doomed to fail? *Crit Care Med* 2008;36(4):1311-22. doi: 10.1097/CCM.0b013e318168ea3e
75. Chapman SM, Wray J, Oulton K, et al. 'Death is not the answer': the challenge of measuring the impact of early warning systems. *Arch Dis Child* 2019;104(3):210-11. doi: 10.1136/archdischild-2018-315392
76. Lambert V, Matthews A, MacDonell R, et al. Paediatric early warning systems for detecting and responding to clinical deterioration in children: a systematic review. *BMJ Open* 2017;7(3):e014497. doi: 10.1136/bmjopen-2016-014497
77. Parshuram CS, Hutchison J, Middaugh K. Development and initial validation of the Bedside Paediatric Early Warning System score. *Crit Care* 2009;13(4):R135. doi: 10.1186/cc7998
78. Vickers AJ, Cronin AM, Elkin EB, et al. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak* 2008;8:53. doi: 10.1186/1472-6947-8-53
79. Van Calster B, Wynants L, Verbeek JFM, et al. Reporting and Interpreting Decision Curve Analysis: A Guide for Investigators. *Eur Urol* 2018;74(6):796-804. doi: 10.1016/j.eururo.2018.08.038
80. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* 2016;352:i6. doi: 10.1136/bmj.i6
81. Moons KG, Altman DG, Vergouwe Y, et al. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009;338:b606. doi: 10.1136/bmj.b606
82. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart* 2012;98(9):691-8. doi: 10.1136/heartjnl-2011-301247
83. Kappen TH, van Klei WA, van Wolfswinkel L, et al. Evaluating the impact of prediction models: lessons learned, challenges, and recommendations. *Diagn Progn Res* 2018;2:11. doi: 10.1186/s41512-018-0033-6
84. Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013;10(2):e1001381. doi: 10.1371/journal.pmed.1001381
85. Jensen CS, Olesen HV, Aagaard H, et al. Comparison of Two Pediatric Early Warning Systems: A Randomized Trial. *J Pediatr Nurs* 2019;44:e58-e65. doi: 10.1016/j.pedn.2018.11.001
86. Parshuram CS, Dryden-Palmer K, Farrell C, et al. Effect of a Pediatric Early Warning System on All-Cause Mortality in Hospitalized Pediatric Patients: The EPOCH Randomized Clinical Trial. *JAMA* 2018;319(10):1002-12. doi: 10.1001/*JAMA*.2018.0948
87. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med* 2006;144(3):201-9. doi: 10.7326/0003-4819-144-3-200602070-00009
88. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. *Diagn Progn Res* 2019;3:18. doi: 10.1186/s41512-019-0064-7
89. Kappen T, Peelen L. Prediction models: the right tool for the right problem. *Curr Opin Anaesthesiol* 2016;29:1. doi: 10.1097/ACO.0000000000000386
90. Koffijberg H, van Zaane B, Moons KG. From accuracy to patient outcome and cost-effectiveness evaluations of diagnostic tests and biomarkers: an exemplary modelling study. *BMC Med Res Methodol* 2013;13:12. doi: 10.1186/1471-2288-13-12
91. Jenniskens K, Lagerweij GR, Naaktgeboren CA, et al. Decision analytic modeling was useful to assess the impact of a prediction model on health outcomes before a randomized trial. *J Clin Epidemiol* 2019;115:106-15. doi: 10.1016/j.jclinepi.2019.07.010

92. Bezemer T, de Groot MC, Blasse E, et al. A Human(e) Factor in Clinical Decision Support Systems. *J Med Internet Res* 2019;21(3):e11732. doi: 10.2196/11732
93. Rudin C. Stop Explaining Black Box Machine Learning Models for High Stakes Decisions and Use Interpretable Models Instead. *Nat Mach Intell* 2019;1(5):206-15. doi: 10.1038/s42256-019-0048-x
94. Shortliffe EH, Sepulveda MJ. Clinical Decision Support in the Era of Artificial Intelligence. *JAMA* 2018;320(21):2199-200. doi: 10.1001/*JAMA*.2018.17163
95. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. *Heart* 2012;98(9):683-90. doi: 10.1136/heartjnl-2011-301246

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Summary

In the Netherlands, approximately 600 children are diagnosed with cancer every year. Cancer is a leading cause of death among children. Over the past decades, the overall 5-year survival of childhood cancer has significantly improved, as a result of better risk stratification, intensification of therapies and vigilant supportive care. Unfortunately, this improved survival was accompanied by the risk of complications, which may either arise from the cancer itself or toxicity of treatment. These complications may be life-threatening and may require admission to the pediatric intensive care unit (PICU).

Pediatric oncology patients who are admitted to the PICU have a worse prognosis compared to their non-cancer peers. Recent studies indicate that between 4 to 28% of pediatric oncology patients require at least one admission to the PICU during their treatment. Approximately two-thirds of these admissions are for planned post-operative care, primarily following tumor-resection. The other one-third comprises unplanned admissions, with respiratory failure, sepsis and neurological deterioration as main reasons for admission. The mortality rate at the PICU for pediatric oncology ranges from 7 to 39%, depending on specific patient categories. This range by far exceeds the PICU mortality of general pediatric patients (2%). Particularly unplanned PICU admissions, often preceded by a clinical deterioration event at the ward, are associated with a high PICU mortality.

Multi-organ dysfunction (MOD), i.e. the concomitant failure of two or more organ systems, is a major cause of death in critically ill children. The number of dysfunctional organ systems is associated with mortality, and each additional dysfunctional organ system increases the risk of death. Pediatric oncology patients are particularly susceptible to developing organ dysfunction. Their aggressive cancer pathophysiology and intensive treatment regimens may lead to organ infiltration, systemic toxicity, and prolonged immunosuppression. Early recognition and intervention in organ dysfunction provide the potential to modify its course and prevent further deterioration. Accordingly, it is important to accurately and timely recognize a patient who clinically deteriorates, to enable an intervention with the ultimate aim of improving the outcome.

Patients who require a transfer from the inpatient ward to the PICU often already have some extent of organ dysfunction at PICU admission. Consequently, it is important to consider the period preceding the PICU admission to initiate early interventions for organ dysfunction. Prior to this thesis, studies in adult oncology patients had shown that transfer to the intensive care unit shortly after onset of critical illness at the inpatient was associated with better short- and long-term outcomes. Similarly, it has been suggested that early interventions and early PICU transfer in clinically deteriorating pediatric oncology patients may be important steps in reducing morbidity and mortality.

This thesis focuses on the timely identification of clinically deteriorating patient, both at the inpatient ward and the PICU. Ultimately, we aim to improve the outcomes of critically ill pediatric oncology patients. Prior to the research presented in this thesis, there were

gaps of knowledge in the optimal standard of care for critically ill pediatric oncology patients, as well as how we can best recognize a deteriorating patient.

In the current context of scarce data on the optimal standard of onco-critical care, more studies are needed to advance our abilities to appropriately use life-sustaining therapies, and define new therapeutic approaches. To facilitate international harmonization of studies, we conducted a modified Delphi consensus study in **Chapter 2**, aiming to define and prioritize research topics. Based on broad consensus among pediatric intensivists and oncologists across Europe, we provided a top 5 research priorities for onco-critical care. This top 5 includes

1) the optimal timing of the use of life-sustaining therapies at the PICU;
2) the development of specific pediatric early warning scores for hospitalized pediatric oncology patients;
3) the role of non-invasive ventilation (NIV) in pediatric oncology patients;
4) exploring end-of-life care and ethical issues for children with cancer at the PICU; and
5) sepsis.

These topics may be used as a research framework for the next decade, aiming to increase survival and improve quality of life of critically ill pediatric oncology patients.

One of the priorities is the improvement of detection of clinically deteriorating patients at the inpatient ward. Deteriorating patients often show early signs prior to their critical decline. Yet, in daily practice, it may be challenging to adequately recognize these early signs. Pediatric early warning scores are often implemented to aid the recognition of clinically deteriorating patients. In these scores, values are assigned to the deviance from the normal range of vital signs or clinical observations, and combined into a numerical score. Typically, the score is assessed at regular intervals, and escalation of care is triggered when the score exceeds a prespecified threshold. The scores are often embedded within a system, including, for example, a rapid response team and implementation components – a so called Pediatric Early Warning System (PEWS).

Despite the widespread implementation of PEWS, few studies have validated a PEWS in pediatric oncology patients. Moreover, prior to this thesis, a systematic evaluation of the performance of PEWS in this specific population was lacking. Therefore, in **Chapter 3**, we summarized and critically appraised the existing evidence on 1) the ability of a PEWS to predict inpatient deterioration and 2) the effect of implementation of PEWS on patient outcomes in pediatric oncology patients. We identified limited evidence for both research questions. The validation studies reported good predictive performance the PEWS scores to detect clinical deterioration requiring unplanned PICU transfer in terms of high sensitivity, specificity and area under the curve. However, upon further assessment we found that all seven validation studies were at high risk of bias. The most important risks of bias included limited number of primary outcome events, the use of an unnested case-

control design - where 24-hour periods were sampled in patients experiencing and not experiencing the event -, and the use of a maximum PEWS value in the 24-hour periods. This could possibly bias the estimation of the predictive performance of a PEWS score for detecting clinical deterioration requiring PICU transfer. Therefore, a valid estimation of the predictive performance of a PEWS score in this specific population is warranted, and should ideally be performed in a large prospective cohort including all underlying malignancies.

In **Chapter 4**, we describe the study design of a prospective cohort study for the external validation of a modified BedsidePEWS score in hospitalized pediatric oncology patients. We aimed to determine the predictive performance of this modified BedsidePEWS score for the primary outcome of unplanned PICU admission or cardiopulmonary resuscitation (CPR), and secondary outcomes of minor clinical deterioration (e.g. the start of high flow oxygen, fluid bolus or urgent PICU consultation without requirement for PICU transfer) and any clinical deterioration (i.e. minor clinical deterioration and/or unplanned PICU transfer/CPR). A strength of this study design lies in the incorporation of all modified BedsidePEWS scores as documented in the electronic health records in all hospitalized pediatric oncology patients. This is the first study to account for the longitudinal, time-dependent nature of the PEWS score, since this score reflects the clinical condition of a patient and may vary per patient and during a hospital admission.

The main finding of this study, as described in **Chapter 5**, was that the modified BedsidePEWS score was significantly associated with both time to unplanned PICU admission or CPR, as well as minor or any clinical deterioration event. We also found several nuances to the use of this PEWS score as a clinical prediction model to timely detect clinical deterioration. We hereby found a moderate discriminative ability of the modified BedsidePEWS, that could be explained by the low incidence rate of the outcome event. Second, we found that not all clinical deterioration conditions were captured by the PEWS score – i.e. the score was below the threshold of triggering a patient evaluation, yet the patient still experienced an outcome event. Particularly patients with upper airway problems, unplanned post-operative care and neurological deterioration were not captured. Third, we found a high false alarm rate (low positive predictive value), which may risk alarm fatigue. These nuances may be valuable for future studies to further optimize the use of a PEWS score or clinical prediction model to timely detect deteriorating patients at the inpatient ward. Our study supports that the modified Bedside PEWS score is a valuable adjunct to clinical decision making in the escalation of care in hospitalized pediatric oncology patients.

In **Chapter 6**, the focus shifts from the inpatient ward to the PICU. Despite the crucial role of multi-organ dysfunction in PICU mortality, risk factors at start of PICU admission for developing MOD have not yet been identified. In a retrospective cohort of pediatric oncology patients at the PICU, we aimed to identify prognostic factors at PICU admission

for new or progressive multi-organ dysfunction (NPMOD) during the first week of PICU stay. We found that hemato-oncological diagnosis, an unplanned PICU admission and number of failing organs at PICU admission were significant prognostic factors for NPMOD. Moreover, during this study, we found opportunities to tailor the recently published organ dysfunction criteria (PODIUM criteria) to pediatric oncology patients. We hereby intended to flag critical illness-related organ dysfunction which is more likely to be part of a shared underlying pathway for MOD (e.g., as in sepsis), rather than the effect of chemotherapeutic treatment. We adjusted the criteria for renal dysfunction to capture early stages of acute kidney injury (AKI) and fluid overload, as AKI and fluid overload exceeding 10% are significantly associated with worse PICU outcomes. Following refinement of the organ dysfunction criteria for the oncology population, it became evident that endocrine, renal and severe cardiovascular dysfunction were the most frequently failing organ systems at the beginning of PICU admission in patients who develop NPMOD. These findings primarily have implications for the period preceding PICU admission and may offer opportunities for early surveillance at the inpatient ward. Hereby, the goal is to enable intervention and prevent the progression towards irreversible organ damage.

In conclusion, the research presented in this thesis contribute to the accurate and timely identification of clinically deteriorating pediatric oncology patients, both at the inpatient ward and the PICU. Our findings suggest several directions for future research, which are discussed in **Chapter 7**, aiming to optimize the risk prediction of clinical deterioration and increase the efficiency of escalation of care. Additionally, we have formulated a research framework in the field of onco-critical care, with a top 5 of priorities for the next decade. In all, this can be an important step towards the ultimate goal of improving survival rates and increasing quality of life in a vulnerable patient population.


S

Nederlandse samenvatting

In Nederland worden jaarlijks ongeveer 600 kinderen gediagnosticeerd met kanker. Kanker is een van de belangrijkste doodsoorzaken bij kinderen. In de afgelopen decennia is de algehele overleving van kinderkanker aanzienlijk verbeterd dankzij betere risicostratificatie, intensivering van behandelingen en ondersteunende zorg. Helaas is deze verbeterde overleving gepaard gegaan met het risico op complicaties, die kunnen voortkomen uit zowel de kanker zelf als de toxiciteit van de behandeling. Deze complicaties kunnen levensbedreigend zijn, en het kan nodig zijn dat een kind hiervoor op de kinder-intensive care (PICU) moet worden opgenomen.

Over het algemeen hebben kinderen met kanker die worden opgenomen op de PICU een slechtere prognose vergeleken met PICU patiënten zonder kanker. Recente studies laten zien dat 4 tot 28% van de kinderen met kanker ten minste één keer een PICU opname nodig heeft tijdens hun behandeling. Ongeveer twee derde deel van deze opnames zijn geplande opnames voor postoperatieve zorg, voornamelijk na het chirurgisch verwijderen van een tumor. Het overige deel betreft ongeplande opnames, waarbij respiratoir falen, sepsis en neurologische verslechtering de belangrijkste redenen voor opname zijn. De mortaliteit (sterfte) op de PICU voor kinderen met kanker varieert van 7 tot 39%, afhankelijk van specifieke patiëntencategorieën. Deze percentages overstijgen aanzienlijk de mortaliteit op de PICU van algemene pediatrische patiënten (2%). De ongeplande opnames, die vaak worden voorafgegaan door klinische achteruitgang op de afdeling, hebben met name een hoge PICU-mortaliteit.

Multi-orgaan falen (MOF), dat wil zeggen het gelijktijdig falen van twee of meer orgaansystemen, is een belangrijke doodsoorzaak bij ernstig zieke kinderen. Het aantal falende orgaansystemen is geassocieerd met een hogere mortaliteit, waarbij elk extra falend orgaansysteem het risico op overlijden verhoogt. Kinderen met kanker zijn bijzonder kwetsbaar voor het ontwikkelen van orgaanfalen. Enerzijds kan de kanker zelf de organen infiltreren of de afweer verminderen, anderzijds kan de intensieve behandeling leiden tot systemische bijwerkingen en langdurige immunosuppressie. Een vroegtijdige herkenning en interventie bij orgaanfalen kunnen het ziekteverloop veranderen en verdere verslechtering voorkomen. Het is daarom van groot belang om een patiënt die klinisch achteruitgaat tijdig te herkennen, met als uiteindelijk doel om de uitkomst te verbeteren.

Patiënten die vanuit de verpleegafdeling naar de PICU moeten worden overgeplaatst, vertonen vaak al een zekere mate van orgaanfalen bij opname op de PICU. Daarom is het van belang de periode voorafgaand aan de PICU opname te kunnen benutten, om een eventuele vroegtijdige interventie te starten. Eerdere studies bij volwassenen met kanker hebben aangetoond dat overplaatsing naar de intensive care kort na het begin van kritieke ziekte op de verpleegafdeling gepaard ging met betere korte- en langetermijnresultaten. Voor kinderen met kanker die klinisch verslechteren hebben meerdere studies eveneens gesuggereerd dat vroegtijdige interventie en overplaatsing naar de PICU belangrijke stappen kunnen zijn om morbiditeit (ziektelast) en mortaliteit te verminderen.

Dit proefschrift richt zich op de tijdige identificatie van kinderen met kanker die klinisch achteruitgaan, zowel op de verpleegafdeling als op de PICU. Ons uiteindelijke doel is de

prognose van kritiek zieke kinderen met kanker te verbeteren. Voorafgaand aan het onderzoek dat in dit proefschrift wordt gepresenteerd, bestonden er kennishiaten met betrekking tot de optimale zorg voor kritiek zieke kinderen met kanker en de herkenning van klinische achteruitgang op zowel de verpleegafdeling als de PICU.

Op dit moment hebben we vanuit de wetenschappelijke literatuur beperkte informatie over de optimale zorg voor ernstig zieke kinderen met kanker op de PICU. Meer onderzoek is nodig om levensondersteunende behandelingen op passende wijze in te kunnen zetten, en om nieuwe manieren van behandeling te kunnen ontwikkelen. In **Hoofdstuk 2** hebben we een aangepaste Delphi-consensusstudie uitgevoerd, teneinde internationale overeenstemming over de onderzoeksprioriteiten op dit gebied te vergemakkelijken. Deze studie had als doel om onderzoeksonderwerpen voor kritiek zieke kinderen met kanker te definiëren en prioriteren. Op basis van algemene overeenstemming onder kinderintensivisten en –oncologen in Europa, zijn de vijf belangrijkste onderwerpen vastgesteld. Deze top 5 omvat

1) het optimale tijdstip van het gebruik van levensondersteunende behandelingen op de PICU;
2) de ontwikkeling van specifieke scores voor vroegtijdige waarschuwing van achteruitgang bij patiënten die opgenomen liggen in het ziekenhuis;
3) de rol van niet-invasieve beademing (NIV)
4) het verkennen van palliatieve zorg en ethische kwesties; en
5) sepsis.

Deze onderwerpen kunnen worden gebruikt als leidraad voor onderzoek in het komende decennium, met als doel de overlevingskansen en kwaliteit van leven van kritiek zieke kinderen met kanker te verbeteren.

Een van de prioriteiten is het verbeteren van de herkenning van klinisch verslechterende patiënten op de verpleegafdeling. Patiënten die verslechteren vertonen vaak al vroege tekenen voordat hun toestand kritiek wordt. Toch kan het in de dagelijkse praktijk moeilijk zijn om deze vroege tekenen goed en tijdig te herkennen. Vroege waarschuwingsscores worden vaak gebruikt om te helpen bij die herkenning. In deze scores worden waarden toegekend aan de mate waarin een vitale functie of klinische observatie afwijkt van de normale waarde voor de leeftijd. Deze waarden worden samengevoegd tot een numerieke score. Doorgaans wordt de score op regelmatige tijdstippen beoordeeld en bij een oplopende score is er een trapsgewijze opschaling van de zorg. Met andere woorden, wanneer de score hoger wordt, moet deze vaker worden gemeten en wanneer de score een vooraf bepaalde drempel overschrijdt, dient de verpleegkundige een arts te waarschuwen en vindt er een evaluatie van de patiënt plaats. De scores zijn vaak geïntegreerd in een systeem, samen met een spoedinterventieteam en verschillende componenten die van belang zijn voor een goede implementatie. Zo'n systeem staat bekend als het Pediatric Early Warning System (PEWS).

Hoewel veel ziekenhuizen inmiddels een PEWS hebben geïmplementeerd, zijn er weinig studies die een PEWS bij kinderen met kanker hebben gevalideerd. Voorafgaand aan dit proefschrift ontbrak een systematische evaluatie van studies over de voorspellende

waarde en impact van PEWS bij klinisch opgenomen kinderen met kanker. In **Hoofdstuk 3** hebben we het bestaande bewijs samengevat en kritisch beoordeeld met betrekking tot: 1) de voorspellende waarde van een PEWS-score voor het detecteren van klinische achteruitgang die een PICU overplaatsing vereist en 2) het effect van de implementatie van PEWS op de uitkomst in deze populatie. Bij dit systematisch literatuuronderzoek vonden we beperkt bewijs voor beide onderzoeksvragen. De validatiestudies rapporteerden een goede voorspellende waarde van de PEWS-scores voor het detecteren van klinische verslechtering die een PICU overplaatsing vereist, met daarbij een hoge sensitiviteit, specificiteit en *area under the curve*. Echter, bij nadere beoordeling stelden we vast dat alle validatiestudies een hoog risico hadden op *bias* (vertekening). Dit kwam met name door de methodologie van de studies en het beperkt aantal uitkomstgebeurtenissen. Hierdoor kan er mogelijk een vertekening zijn geweest van de schatting van de voorspellende waarde van een PEWS-score voor het detecteren van klinische achteruitgang die een PICU-overplaatsing vereist. Een valide schatting van die voorspellende waarde is noodzakelijk in deze specifieke populatie met een hoog risico op klinische achteruitgang. Idealiter zou dit moeten worden uitgevoerd in een prospectieve cohortstudie, inclusief alle onderliggende maligniteiten.

In **Hoofdstuk 4** beschrijven we het onderzoeksontwerp van een prospectieve cohortstudie voor de externe validatie van een aangepaste BedsidePEWS-score bij klinisch opgenomen kinderen met kanker. Hierbij was het doel om de voorspellende waarde van deze PEWS-score te onderzoeken voor de primaire uitkomstmaat van ongeplande opname op de PICU of reanimatie, en de secundaire uitkomstmaten van a) klinische verslechtering op de afdeling (bijv. de noodzaak voor het starten van *high flow* zuurstoftherapie, een vochtbolus of een urgent consult van de PICU (zonder overplaatsing naar de PICU) en b) elke klinische verslechtering – d.w.z. een klinische verslechtering op de afdeling en/of een ongeplande overplaatsing naar de PICU of reanimatie. Een sterk punt van dit onderzoek is het gebruik van alle vastgelegde PEWS-scores in de elektronische patiëntendossiers van alle opgenomen kinderen met kanker. Het is de eerste studie die rekening houdt met de longitudinale, tijdafhankelijke aard van de PEWS-score; de score weerspiegelt de klinische toestand van een patiënt en dit kan per patiënt en ook gedurende een ziekenhuisopname variëren.

De belangrijkste bevinding van deze studie was dat de aangepaste BedsidePEWS-score significant geassocieerd was met de tijd tot zowel ongeplande opname op de PICU of reanimatie als klinische verslechtering (met of zonder PICU overplaatsing/reanimatie), zie **Hoofdstuk 5**. We vonden tevens verscheidende nuances omtrent het gebruik van deze PEWS-score als een klinisch voorspelmodel om klinische verslechtering te detecteren. Ten eerste vonden we een matig onderscheidend vermogen van de PEWS score. Dit kan worden verklaard doordat de uitkomstgebeurtenis relatief weinig voorkomt (lage incidentie van de uitkomstmaat). Ten tweede vonden we dat niet elk type klinische verslechtering werd 'gevangen' door de PEWS-score. Dat wil zeggen, de patiënt had wel een PICU opname of reanimatie nodig, maar de PEWS-score bleef onder de drempel die alarmeert dat een arts de patiënt dient te beoordelen. Met name patiënten met bovenste

luchtwegproblemen, neurologische verslechtering of die onverwachts na een operatie moesten worden opgenomen op de PICU werden niet gevangen door de PEWS-score. Ten derde constateerden we een hoog percentage van valse alarmen (een lage positief voorspellende waarde). Dit kan leiden tot alarm-moeheid, waarbij er niet of minder wordt gereageerd op alarmerende PEWS-scores. Deze nuances zijn waardevol voor toekomstige studies om het gebruik van een PEWS-score of voorspelmodel voor klinische achteruitgang verder te optimaliseren, teneinde verslechterende patiënten op de afdeling goed te kunnen herkennen. Samenvattend ondersteunt deze studie dat de aangepaste BedsidePEWS-score een waardevolle aanvulling is op de klinische besluitvorming bij het opschalen van de zorg in klinisch opgenomen kinderen met kanker.

In **Hoofdstuk 6** verschuift de focus van de verpleegafdeling naar de PICU. Multi-orgaanfalen speelt een significante rol bij de mortaliteit op de PICU. Echter, risicofactoren bij aanvang van PICU opname voor de ontwikkeling van MOF zijn nog niet vastgesteld. In een retrospectieve cohortstudie bij kinderen met kanker op de PICU, hebben we ons gericht op het vaststellen van risicofactoren bij aanvang van de PICU-opname die verband houden met het optreden van nieuw of progressief multi-orgaanfalen (NPMOF) gedurende de eerste week van de PICU-opname. De significante risicofactoren voor NPMOF waren een hemato-oncologische diagnose, een ongeplande PICU opname en het aantal falende organen bij PICU-opname. Tijdens deze studie zagen we kans om de recent gepubliceerde criteria voor orgaanfalen (PODIUM-criteria) aan te passen voor kinderen met kanker. We beoogden hiermee met name orgaanfalen vast te leggen dat gerelateerd is aan kritieke ziekte, en minder het orgaanfalen dat een immunosuppressie na de chemotherapie weerspiegelt. We hebben hierbij o.a. criteria voor nierfalen aangepast, om ook een vroeg stadium van nierfalen en overvulling te kunnen vastleggen dat geassocieerd is met een slechtere uitkomst op de PICU. Na aanpassing van de criteria voor orgaanfalen voor de kinderoncologische populatie, bleek dat endocrien falen, nierfalen, en ernstig cardiovasculair falen de meest voorkomende typen orgaanfalen zijn aan het begin van de PICU-opname bij patienten die NPMOF ontwikkelen. Deze bevindingen zijn vooral van belang voor de periode voorafgaand aan de PICU-opname. Ze bieden mogelijkheden voor vroegtijdige monitoring op de verpleegafdeling, met als doel vroegtijdig in te grijpen bij tekenen van orgaanfalen om de progressie naar onherstelbare orgaanschade te voorkomen.

In conclusie draagt het onderzoek in dit proefschrift bij aan een nauwkeurige en tijdige herkenning van klinische achteruitgang bij kinderen met kanker, zowel op de verpleegafdeling als op de PICU. Onze bevindingen geven diverse richtingen voor toekomstig onderzoek, met als doel de voorspelling van klinische achteruitgang te verbeteren en de efficiëntie in het opschalen van de zorg te vergroten. Deze toekomstperspectieven worden beschreven in **Hoofdstuk 7**. Daarnaast hebben we in dit proefschrift een top 5 onderzoeksprioriteiten voor kritiek zieke kinderen met kanker vastgesteld, welke kan dienen als leidraad voor het komende decennium. Dit vormt een belangrijke stap richting het uiteindelijke doel: het verbeteren van overlevingskansen en het verhogen van de kwaliteit van leven bij deze kwetsbare patiëntengroep.


A

Addendum

About the author
List of publications
PhD portfolio

Curriculum vitae

Marijn Soeteman was born on January 16th, 1988, in Someren, the Netherlands. After completing secondary school at Varendonck College in Asten in 2006, she pursued a degree in Medicine at the University of Maastricht. During her medical training, Marijn completed several internships abroad, at Unife University in Ferrara (Italy), Mater Misericordiae Hospital in Dublin (Ireland), and West Middlesex University Hospital in London (United Kingdom). She performed an elective clinical rotation in pediatrics at Clinica Universitaria Teletón in Bogotá, Colombia. Her final-year-clinical rotation was conducted in pediatrics at the Atrium Medical Center (now Zuyderland Medical Center), Heerlen, under the supervision of Dr. J.O. Busari. She did her research rotation at the department of pediatric pulmonology, Maastricht University Medical Center, in which she contributed to a study considering etiological factors of childhood asthma, under the supervision of Dr. E.M.M. Klaassen and prof. dr. E. Dompeling.

After graduating from medical school in 2012, Marijn began her medical career as a resident in pediatrics (ANIOS) at the Atrium Medical Center in Heerlen, after which she transitioned to the Wilhelmina Children's Hospital in Utrecht. Interested in emergency medicine, she thereafter worked as a resident at the Emergency Department of the Atrium Medical Center in 2014. In January 2015, Marijn started her specialist training in pediatrics in Utrecht, under the supervision of Prof. dr. J. Frenkel. The first part of her pediatric training took place at Meander Medical Center, Amersfoort, under the supervision of Dr. P. Hogeman. From January 2016 to December 2018, she continued her specialist training at the Wilhelmina Children's Hospital. Concurrently, from 2015 to 2018, Marijn was a member of the board representing all pediatric residents in the Netherlands (JA-NVK), participating in several committees of the Dutch Pediatric Society (NVK), including the council for pediatric training and education (Concilium Paediatricum), and the task force leading the implementation of the national training plan for pediatric residents (TOP2020). Since 2016, she has been an Advanced Pediatric Life Support (APLS®) instructor.

In December 2018, Marijn initiated her PhD research at the Princess Máxima Center for Pediatric Oncology (Utrecht), focusing on the identification of critically ill pediatric oncology patients. Under the guidance of Prof. dr. E.E.S. Nieuwenhuis, Prof. dr. W.J.E. Tissing, Prof. dr. M. Fiocco, and Dr. Wösten-van Asperen, this research forms the foundation of this thesis. Since January 2023, Marijn has resumed her specialist training in pediatrics at the Wilhelmina Children's Hospital, with current electives in pediatric oncology, neonatal and pediatric intensive care and emergency medicine.

Marijn resides in Houten with Fedde Rinsma and their sons Hidde (born in 2018) and Niels (born in 2021). In her spare time, she finds joy in learning to play the piano, and drawing. Recently, during the process of designing the cover and chapter pages of this thesis, she has developed a fresh enthusiasm for creating digital illustrations.

List of publications

This thesis

Soeteman M, Potratz J, Nielsen JSA, Willems J, Valla FV, Brierley J, Wösten-van Asperen RM; POKER (PICU Oncology Kids in Europe Research group) research consortium of ESPNIC (European Society of Paediatric Neonatal Intensive Care). Research priorities in pediatric onco-critical care: an international Delphi consensus study. *Intensive Care Med. 2019 Nov;45(11):1681-1683. doi: 10.1007/s00134-019-05706-x. PMID: 31444505.*

Soeteman M, Lekkerkerker CW, Kappen TH, Tissing WJ, Nieuwenhuis EE, Wösten-van Asperen RM. The predictive performance and impact of pediatric early warning systems in hospitalized pediatric oncology patients - A systematic review. *Pediatr Blood Cancer. 2022 May;69(5):e29636. doi: 10.1002/pbc.29636. PMID: 35253341.*

Soeteman M, Kappen TH, van Engelen M, Kilsdonk E, Koomen E, Nieuwenhuis EES, Tissing WJE, Fiocco M, van den Heuvel-Eibrink M, Wösten-van Asperen RM. Identifying the critically ill paediatric oncology patient: a study protocol for a prospective observational cohort study for validation of a modified Bedside Paediatric Early Warning System score in hospitalised paediatric oncology patients. *BMJ Open. 2021 May 19;11(5):e046360. doi: 10.1136/bmjopen-2020-046360. PMID: 34011596.*

Soeteman M, Kappen TH, van Engelen M, Marcelis M, Kilsdonk E, van den Heuvel-Eibrink MM, Nieuwenhuis EES, Tissing WJE, Fiocco M, van Asperen RMW. Validation of a modified bedside Pediatric Early Warning System score for detection of clinical deterioration in hospitalized pediatric oncology patients: A prospective cohort study. *Pediatr Blood Cancer. 2023 Jan;70(1):e30036. doi: 10.1002/pbc.30036. PMID: 36316817.*

Soeteman M, Fiocco MF, Nijman J, Bollen CW, Marcelis MM, Kilsdonk E, Nieuwenhuis EES, Kappen TH, Tissing WJE, Wösten-van Asperen RM. Prognostic factors for multi-organ dysfunction in pediatric oncology patients admitted to the pediatric intensive care unit. *Front Oncol. 2023 Jul 12;13:1192806. doi: 10.3389/fonc.2023.1192806. PMID: 37503310.*

Other

Hennus MP, Nusmeier A, van Heesch GGM, Riedijk MA, Schoenmaker NJ, **Soeteman M**, Wildschut ED, Fawns T, Ten Cate O. Development of entrustable professional activities for paediatric intensive care fellows: A national modified Delphi study. *PLoS One. 2021 Mar 18;16(3):e0248565. doi: 10.1371/journal.pone.0248565. PMID: 33735195.*

Soeteman M, Peters V, Busari JO. Improving patient experience in a pediatric ambulatory clinic: a mixed method appraisal of service delivery. *J Multidiscip Healthc. 2015 Mar 23;8:147-56. doi: 10.2147/JMDH.S81245. PMID: 25848303.*

Klaassen EM, van de Kant KD, **Soeteman M**, Damoiseaux J, van Eys G, Stobberingh EE, Stelma FF, Quaak M, van Schayck OC, Jöbsis Q, Dompeling E. CD14/Toll-like receptors interact with bacteria and regulatory T-cells in the development of childhood asthma. *Eur Respir J. 2014 Sep;44(3):799-802. doi: 10.1183/09031936.00020314. PMID: 25034561.*

Soeteman M, Willems RP, Busari JO. Herpes zoster ophthalmicus in an otherwise healthy 2-year-old child. *BMJ Case Rep. 2012 Oct 30;2012:bcr2012007015. doi: 10.1136/bcr-2012-007015. PMID: 23112258.*

PhD Portfolio

Name:	Marijn Soeteman
PhD period:	December 2017 – December 2022
Research School:	Clinical and Translational Oncology (Utrecht University)
Department:	Pediatric Oncology (Princess Máxima Center)
Promotors:	Prof. dr. E.E.S. Nieuwenhuis Prof. dr. W.J.E. Tissing Prof. dr. M. Fiocco
Co-promotor:	Dr. R.M. Wösten-van Asperen

PhD training	Year
Courses	
Adobe InDesign – from Dissertation Layout to Poster Design – GSLS, UU	2022
Analytic Storytelling – GSLS, UU	2022
Basic Course on Regulation and Organization for Clinical Investigators (BROK) - recertification - NFU	2022
Survival Analysis – Elevate, UU	2021
SQL fundamentals – (online – DataCamp) Intermediate SQL queries Joining data in SQL Data Manipulation in SQL	2021
Prognostic Research – Elevate, UU	2020
Writing a scientific paper – GSLS, UU	2020
Clinical Epidemiology – GSLS, UU	2020
Adobe Illustrator – GSLS, UU	2020
Introductory Biostatistics – GSLS, UU	2019
Data Science specialization – Foundations using R (online – Coursera) R programming Getting and Cleaning Data Exploratory Data Analysis Data visualization Reproducible Research	2018
Basic Course on Regulation and Organization for Clinical Investigators (BROK)	2018
Curriculum	
PhD Curriculum - Training Upcoming Leaders in Pediatric Science (TULIPS)	2019-2021

PhD training	Year
Seminars and Workshops	
Clinical and Translational Oncology PhD retreat	2019, 2020
Research Retreat Princess Máxima Center	2019
Weekly meetings Tissing Group	2019-2022
Weekly meetings Van den Heuvel-Eibrink Group	2017-2019
Conferences	
Oral presentations	
The 9th Congress of the European Academy of Paediatric Societies (EAPS), *Barcelona, Spain*	2022
Poster presentations	
32nd Annual Meeting of the of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC), *Athens, Greece*	2023
31st Annual Meeting of ESPNIC, *virtual*	2021
30th Annual Meeting of ESPNIC, *Salzburg, Austria*	2019
Teaching activities	
Supervising master students (UU, Medicine)	2019, 2020
Advanced Pediatric Life Support (APLS®) instructor - SSHK	2018 - now

Dankwoord

Het is gewoon gelukt!

Voor jullie ligt een exemplaar van mijn proefschrift. Het was een heel avontuur om tot dit punt te komen. Gelukkig heb ik die weg niet alleen afgelegd. Er zijn talloze mensen die me hebben geholpen en gesteund om de eindstreep te halen, en ik wil hen graag van harte bedanken.

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