Received: 21 September 2021 | Revised: 5 January 2022 | Accepted: 8 February 2022

DOI: 10.1002/pbc.29636

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

REVIEW

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

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Funding information

KiKa (a Dutch research charity foundation for pediatric oncology patients), Grant Number: KiKa 287

Abstract

Pediatric early warning systems (PEWS) arewidely 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 area under the receiver operating characteristics curve (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.

KEYWORDS

effect, impact, Pediatric Early Warning System, pediatric oncology, predictive performance, systematic review

1 | 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

Abbreviations: AUROC, area under the receiver operating characteristics curve; HSCT, hematological stem cell transplantation; PEWS, pediatric early warning systems; PICU, pediatric intensive care unit; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROBAST, Prediction model study Risk-Of-Bias Assessment Tool.

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% and 35%), and pediatric oncology patients have worse outcomes after cardiopulmonary arrest compared to other pediatric patients.[2,3] Early detection of deterioration coupled with 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 (a) the ability of PEWS to predict inpatient deterioration, and (b) the effect of implementation of PEWS on patient outcomes.

2 | METHODS

2.1 | Data sources and search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[14] (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 heading (MeSH) terms related to pediatrics, cancer, and pediatric early warning system or score. A complete description of the search is provided in 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.

2.2 | 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 0–21 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.

2.3 | Screening and selection process

After removal of duplicates, titles and abstracts of records were independently screened by two reviewers (Marijn Soeteman and Caroline W. Lekkerkerker). Subsequently, the full texts of 37 papers were reviewed (Marijn Soeteman and Caroline W. Lekkerkerker). Any discrepancies were resolved through discussion with a third reviewer (Roelie M. Wösten-van Asperen).

2.4 | Quality appraisal

Risk of bias and applicability concerns for validation studies were assessed by two reviewers (Marijn Soeteman and Teus H. Kappen) using Prediction model study Risk-Of-Bias ASsessment Tool (PROBAST).[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 (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 (Marijn Soeteman and Wim J. Tissing) using Cochrane Risk-of-Bias assessment for selection bias, attrition bias, detection bias, reporting bias, confounding bias, or other bias.[17]

2.5 | 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.

3 | 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 PEWS on clinical outcomes.[10,23] These nine studies together assessed seven different PEWS.[9–11,18,20–23]

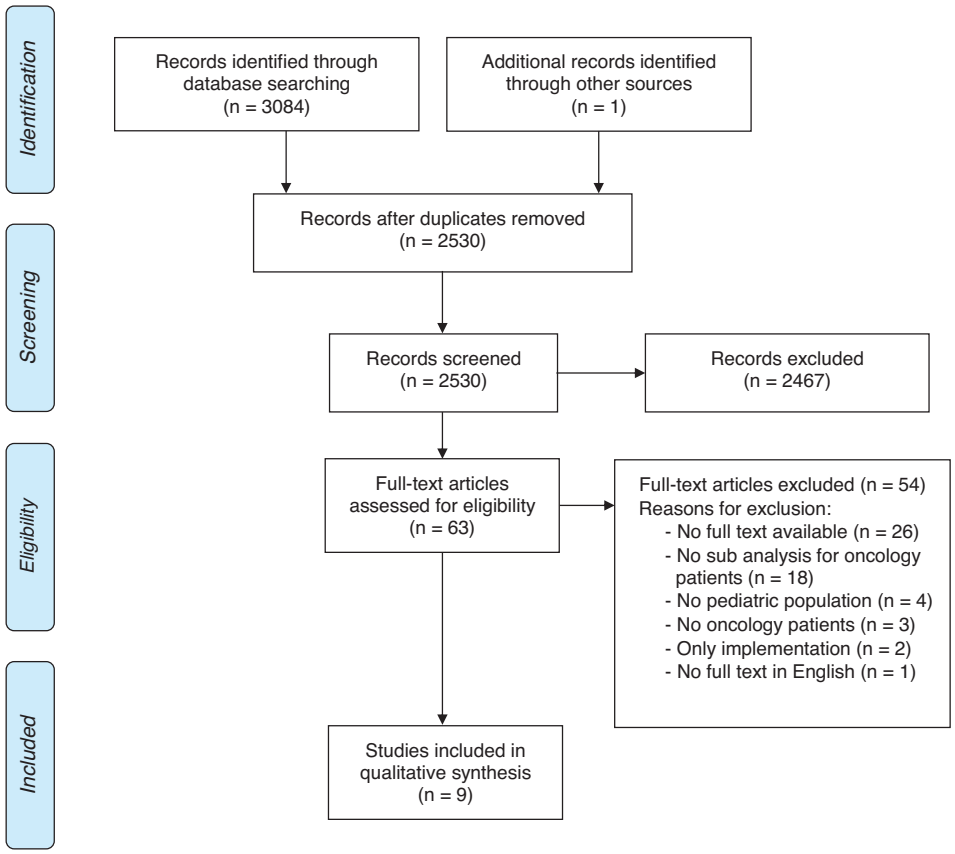

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart of search and selection of eligible studies

3.1 | 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 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, that is, one single parameter of the score is represented by a composite score of multiple different parameters.

3.2 | Results of validation studies

3.2.1 | 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 and 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 cutoff 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 cutoff score ≥8 was reported.[21] One study assessed the additional value of a new parameter to the PEWS.[20] In this study, an AUROC of 0.83 for BedsidePEWS cutoff 8 and 0.88 for BedsidePEWS cutoff 8 plus ≥7% weight gain in HSCT patients was reported; however, without 95% confidence intervals of the AUROCs, 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]

3.2.2 | 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

TABLE 1 Overview of study characteristics of the external validation studies

Paper, *Country*	Study design	Study inclusion criteria	Study population	System	Primary outcome	Score cutoff	Most important findings			Overall risk of bias
							Sensitivity (%)	Specificity (%)	AUROC (95% CI)	
Agulnik et al. (9), *USA*	Retrospective case–control	Patients aged 0–18 years admitted to oncology and HSCT ward	110 Cases, 220 controls	CHEWS	Unplanned PICU transfer	≥3	94	88	0.96 (0.93–0.98)	High[a,c]
						≥4	86	95	–	
Agulnik et al. (18), *Guatemala*	Retrospective case–control	Patients aged 0–18 years admitted to oncology ward	129 Cases, 129 controls	EVAT	Unplanned PICU transfer	≥3	93	85	0.94 (0.91–0.97)	High[a,c]
						≥4	88	97	–	
Cater et al. (20), *USA*	Retrospective cohort	Patients admitted to HSCT ward, aged 0–21 years	102 Patients	BedsidePEWS	PICU admission	≥8	76	90	0.83 *(0.77–0.89)*	High[b,c]
			(29 events)			≥8 + WG	28	99	0.88 *(0.82–0.94)*	
Dean et al. (11), *USA*	Retrospective cohort	Patients admitted to hemato-oncology/HSCT ward	5558 Patient-days (43 events)	Modified Brighton PEWS	Unplanned PICU transfer	≥3	88	90	0.93 (0.88–0.98)	High[b,c]
						≥4	79	96	–	
Fuijkschot et al. (21), *the Netherlands*	Retrospective case cohort	Patients admitted to pediatric oncology ward	1 Case, 118 controls	Modified PEWS	Unplanned PICU transfer	≥8	100	88	–	High[b,c]
Gawronski et al. (22), *Italy*	Prospective nested case–control	Patients aged 0–18 years, admitted to HSCT ward	19 Cases, 29 controls	BedsidePEWS	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		

(Continues)

TABLE 1 (Continued)

Paper, *Country*	Study design	Study inclusion criteria	Study population	System	Primary outcome	Score cutoff	Most important findings			Overall risk of bias
							Sensitivity (%)	Specificity (%)	AUROC (95% CI)	
Agulnik et al. (19), *Guatemala*	Retrospective chart review	Patients admitted to pediatric oncology ward	5 Cases, 34 controls	EVAT	Early PICU transfer (within 24 hours of IMCU transfer)	n.a.	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, $p = .03$)	High[b,c]		

Note: Risk-of-bias assessment for external validation studies with PROBAST. Major potential sources of bias: unnested case–control design; limited number of participants with the outcome; not all relevant performance parameters were measured appropriately. 95% Confidence interval in italics was calculated manually with data provided.

Abbreviations: CHEWS, Children's Hospital Early Warning Score; EVAT, Escala de Valoración de Alerta Temprana; HSCT, hematopoietic stem cell transplantation; IMCU, intermediate care unit; LOS, time from start hospital admission to PICU transfer; n.a., not assessed; PEWS, pediatric early warning system; PICU, pediatric intensive care unit; WG = ≥7% weight gain.

[a]Unnested case–control design.

[b]Limited number of participants with the outcome.

[c]Not all relevant performance parameters were measured appropriately.

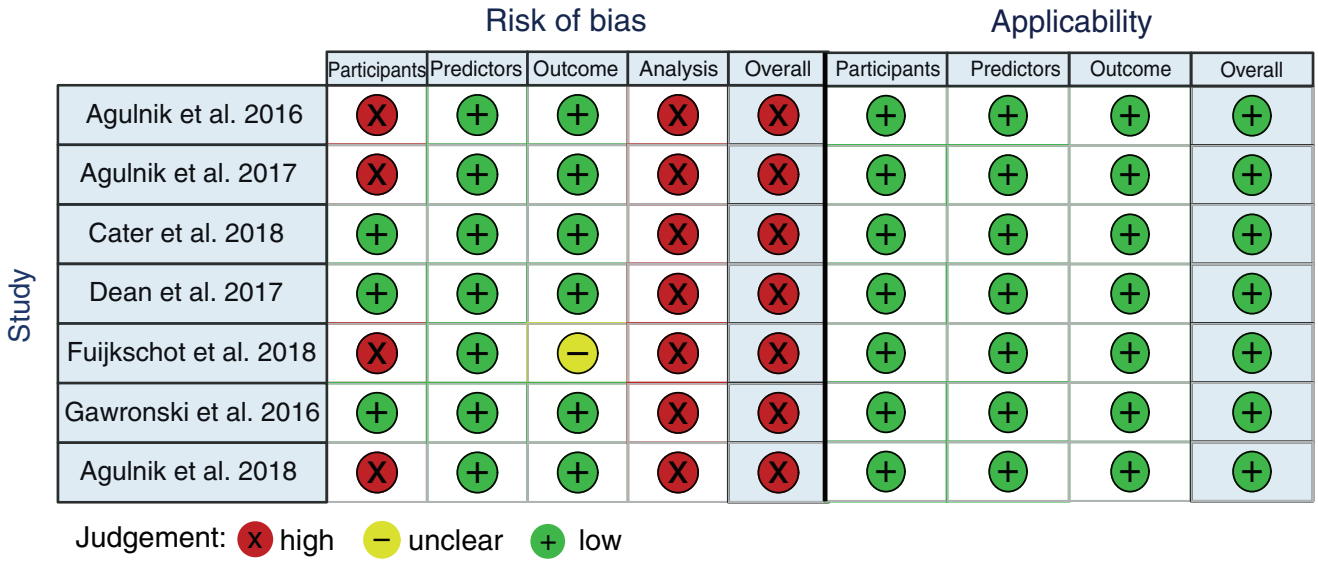

FIGURE 2 Risk of bias and applicability of the external validation studies as assessed by prediction model

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]

3.2.3 | 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 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 were at low risk of bias in all the 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 1–43 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 (Table S5 and Figure 2).

3.3 | Results of impact studies

3.3.1 | 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 24 hours of PICU admission after PEWS implementation, we found contradicting evidence in their results with no statistical difference for organ dysfunction within 24 hours of PICU admission. There was no reduction in use of invasive mechanical ventilation or vaso-active medication, PICU length-of-stay or mortality after PEWS implementation. The second study, a retrospective before-and-after study at the hemato/oncology ward of a tertiary hospital, reported a three-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.

3.3.2 | Risk-of-bias assessment impact studies

The risk-of-bias assessment of impact studies is displayed in Table S6. Our main concern for the first impact study was the use of an

TABLE 2 Overview of impact studies and risk-of-bias assessment

Paper, *Country*	Study design	Study population	System	Most important findings	Risk of biasSelection biasAttrition biasDetection biasReporting biasConfounding biasOther bias
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)	Modified EVAT	After PEWS implementation: - fewer unplanned PICU transfers after PEWS implementation (9.3 vs. 6.5 per 1000 patient-days, $p = .003$); - less PICU utilization for unplanned PICU transfer (1376 vs. 1088 total PICU patient-days, $p < .0001$); - decreased severe sepsis or septic shock on PICU transfer (3.9 vs. 2.7 per 1000 patient-days, $p = .044$); - no difference in mortality or PICU length of stay	a. Low b. Low c. Low d. Unclear e. Unclear[a] f. High[b]
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	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]

Note: Quality assessment with Cochrane Risk-of-Bias Tool.

Abbreviations: EVAT, Escala de Valoración de Alerta Temprana; PEWS, pediatric early warning system; PICU, pediatric intensive care unit.

[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.

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]

4 | DISCUSSION

This systematic review aimed to critically appraise the evidence on the ability of 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 of primary outcome events that 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 were 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.

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, discrimination and calibration, is required.[16,25,26]

Calibration of prediction models reflects the accuracy of risk estimates, relating to the agreement between the estimated and observed number of events.[27] None of the studies included in our review assessed calibration. Poorly calibrated 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. The response algorithms of PEWS, that is, the intensification of frequency of monitoring or calls for action, have not been assessed yet in an applied setting of pediatric oncology patients. It is therefore important to have valid, reliable risk estimates for clinical deterioration and to assess the impact of PEWS response algorithms on clinical decision-making 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 require large study sample size.[29] Significant clinical deterioration events, for example, 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 preventive action. Minor clinical deterioration events—that is, 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 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.

5 | 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.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: 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;69:e29636. 10.1002/pbc.29636