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PICU mortality of children with cancer admitted to pediatric intensive care unit a systematic review and meta-analysis

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ABSTRACT

Background: Outcomes for children diagnosed with cancer have improved dramatically over the past 20 years. However, although 40% of pediatric cancer patients require at least one intensive care admission throughout their disease course, PICU outcomes and resource utilization by this population have not been rigorously studied in this specific group.

Methods: Using a systematic strategy, we searched Medline, Embase, and CINAHL databases for articles describing PICU mortality of pediatric cancer patients admitted to PICU. Two investigators independently applied eligibility criteria, assessed data quality, and extracted data. We pooled PICU mortality estimates using random-effects models and examined mortality trends over time using meta-regression models.

Results: Out of 1218 identified manuscripts, 31 studies were included covering 16,853 PICU admissions with the majority being retrospective in nature. Overall pooled weighted mortality was 27.8% (95% confidence interval (CI), 23.7–31.9%). Mortality decreased slightly over time when post-operative patients were excluded. The use of mechanical ventilation (odds ratio (OR): 18.49 [95% CI 13.79–24.78], $p < 0.001$), inotropic support (OR: 14.05 [95% CI 9.16–21.57], $p < 0.001$), or continuous renal replacement therapy (OR: 3.24 [95% CI 1.31–8.04], $p = 0.01$) was significantly associated with PICU mortality.

Conclusions: PICU mortality rates of pediatric cancer patients are far higher when compared to current mortality rates of the general PICU population. PICU mortality has remained relatively unchanged over the past decades, a slight decrease was only seen when post-operative patients were excluded. This compared infavorably with the improved mortality seen in adults with cancer admitted to ICU, where research-led improvements have led to the paradigm of unlimited, aggressive ICU management without any limitations on resuscitations status, for a time-limited trial.

1. Introduction

Over the last decades, enhanced cancer therapy included the introduction of intensified multimodality treatment protocols, better stratification and advanced supportive care. Consequently, survival of children diagnosed with cancer has increased from an overall estimated 20% in the late 1980s to 70–80% survival today. (Bleyer, 1997; Petridou et al., 2013; Pritchard-Jones et al., 2006) However, intensified

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treatment regimens have also increased the incidence of treatment-related side effects and toxicities, many of which require intensive care treatment (Kress et al., 1999; Staudinger et al., 2000; Dalton et al., 2003; Tamburro et al., 2008) Recent studies showed that about 40% of all pediatric cancer patients require admission to the pediatric intensive care unit (PICU) at some point during their disease course, with acute respiratory failure and sepsis being the main admission reasons (Dalton et al., 2003; Tamburro et al., 2008; Hallahan et al., 2000; Rosenman et al., 2005)

Children with cancer requiring intensive care support are a highly complex and challenging group, with significantly worse outcomes compared to the overall PICU population. (Dalton et al., 2003; Tamburro et al., 2008), However, in adult cancer patients it has been shown that early institution of intensive care support rather than not intervening until late in the spiral of multi-organ failure, has significantly improved survival (Azoulay et al., 2013; Lengliné et al., 2012; Mokart et al., 2013)

PICU outcome and resource utilization in the pediatric cancer population have not been rigorously studied. Lack of this information is an important problem, as more knowledge could allow for better understanding of underlying mechanisms of organ dysfunction, identifying risk factors for clinical deterioration, more timely administration of life-saving therapies, and more cost-effective delivery of care and utilization of PICUs. So far, most of the existing data come from small, single-center retrospective studies.

In view of the limitations of the existing literature, we conducted a systematic review and meta-analysis using a comprehensive search strategy and meta-regression analysis to document PICU mortality for pediatric cancer patients, and to evaluate whether this PICU mortality has changed over time. Our aim is that in delineating the current situation we can then design prospective interventional trials.

2. Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (the PRISMA checklist is listed in eTable 1). (Moher et al., 2009, 2015), The protocol was registered on PROSPERO (ID: CRD42018091406).

2.1. Search strategy

A systematic comprehensive electronic search of MEDLINE, EMBASE, and CINAHL was undertaken, using a detailed search. All resources were searched from inception to March 2017. Databases were electronically searched for relevant publications using combinations of the following medical subject headings (MeSH) and keywords [Neoplasms] AND [Pediatric] AND [Intensive Care Unit, Pediatric] AND [Mortality]. Reviewing references of included studies and reviews expanded the search. Complete details of the study methods are provided in eTable2. The search was restricted to English-language articles.

2.2. Inclusion and exclusion criteria

To be included in the review, the study had to report PICU mortality in patients with a known malignancy who had been admitted to a PICU.

Conference proceedings, reviews, editorials, letters or case reports, publications in abstract form only, studies including only one subtype of cancer (e.g., AML), and duplicate reports were excluded. Also, studies including exclusively hematopoietic stem cell transplant patients were assessed whether data on cancer patients could be extracted as a large part of the reported patients have a non-malignant underlying disease. If not, these studies were excluded. In addition, studies from developing countries were excluded due to the reduced accessibility of resources and differences in standard of care compared to non-developing countries.

2.3. Selection of studies and data extraction

Titles and abstracts of all reports identified in the literature search were screened by two authors for further review with discrepancies resolved by consensus. Full text review of eligibility was conducted by two authors independently and relevant data was extracted from included studies to a standard piloted form.

For each study included in the final analysis, the following data were extracted: study design, years of study conduct, geographic location, patients' age and gender, underlying malignancy, and reason of PICU admission. The primary outcome was PICU mortality. Key secondary outcomes included length of PICU stay, PICU resources use such as invasive mechanical ventilation, inotropic/vasopressor support, and continuous renal replacement therapy (CRRT). We used the median year of the study enrollment period as the year of study conduct. Two studies provided mortality data for different cohorts (Butt et al., 1988; Heying et al., 2001); we included each cohort as an individual study.

Data of the study populations were summarized using proportions and weighted means. The mean and standard deviations in individual studies were estimated from those that were reported as median and interquartile range by using the method described by Wan et al. (Wan et al. (2014))

2.4. Assessment of quality

Methodological quality (risk of bias assessment) of each study was assessed using a 13-item list based on the STROBE guidelines. (Viswanathan et al., 2019; Sanderson et al., 2007; Vandenbroucke et al., 2007) Each item was scored as high quality (1 point) or low quality (0 points). The overall quality score is the percentage of items scored as high quality and is categorized in high ($> 80\%$) and low ($< 80\%$) quality studies.

2.5. Data analysis

We performed a meta-analysis using DerSimonian-Laird random effects models to obtain overall pooled weighted PICU mortality with 95% confidence intervals (CIs). A subgroup analysis was performed on a subset of studies in which post-operative patients were excluded and an analysis of this latter group including only studies in which no specific PICU admission reasons (e.g. patients with ARDS) were used, and on a subset of patients with sepsis at admission.

Heterogeneity of pooled data was assessed by using I^2 statistic. The I^2 statistic describes the percentage of total variation across studies due to true heterogeneity rather than chance. Values greater than 50% suggest substantial heterogeneity. (Higgins et al., 2003; Higgins and Geen, 2011), Publication bias was assessed by constructing a funnel plot and by using the Begg & Mazumdar's rank correlation test.

Separate random-effects logistic meta-regression analyses were used to explore the association between mortality, intervention-specific mortality (mechanical ventilation, inotropic support or CRRT), and year of study conduct. In addition, linear regression analysis was performed to explore the association of methodological quality of each study and year of publication. Finally, in a post hoc analysis, separate DerSimonain-Laird random effects models were used to explore the association between use of PICU resources and mortality. Other predisposing factors, such as underlying malignancy and PICU admission diagnosis, could not be explored due to the mixture of used definitions. Data are presented as odds ratios with p values.

A p-value of less than 0.05 was considered significant. All statistical analyses were performed using OpenMeta[analyst] (http://www.cebm.brown.edu/open-meta).

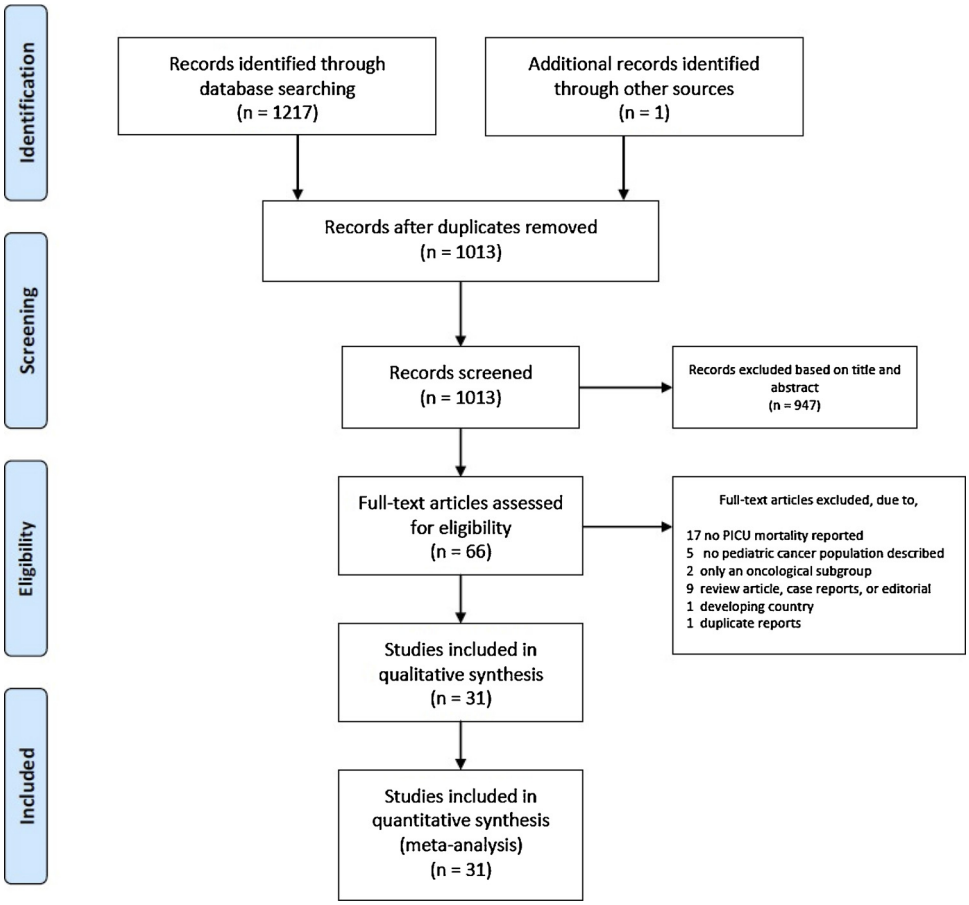

Fig. 1. Flow chart of study selection.

3. Results

3.1. Study selection

The search was conducted up to March 2017. The search identified a total of 1218 publications (Fig. 1). Overall inter-reviewer agreement for study selection was substantial (κ = 0.80). After duplicate removal and abstract screening, 66 articles were considered for full-text analysis. Among them, 35 were excluded because they did not turn out to meet inclusion criteria. The remaining 31 studies (total 14,312 patients with 16,853 PICU admissions) were included in our review. (Dalton et al., 2003; Tamburro et al., 2008; Hallahan et al., 2000; Butt et al., 1988; Heying et al., 2001; Meert et al., 1991; Sivan et al., 1991; van Veen et al., 1996; Heney et al., 1992; Parsons et al., 2001; Ben-Abraham et al., 2001; Ben Abraham et al., 2002; Keengwe et al., 1999; Fiser et al., 2005; Kutko et al., 2003; Khattab et al., 2005; da Silva et al., 2008; Pound et al., 2008; Tamburro et al., 2004; Pancera et al., 2008; Meyer et al., 2005; Haase et al., 2011; Schiller et al., 2009; Faraci et al., 2014; Owens et al., 2011; Dursun et al., 2009; Fausser et al., 2017; Ha et al., 2010; Garcia-Salido et al., 2015; Zinter et al., 2014; Agulnik et al., 2016)

3.2. Description of included studies

The characteristics of the included studies are summarized in Table 1. The majority of the studies were retrospective, single center cohort studies. Ten studies were conducted in North America, two in South

America, eleven studies in Europe, one in Asia, one in Australia, four in the Middle East, and two were combined studies (Canada/Australia and USA/Israel). Sample sizes ranged from 13 (Heying et al., 2001) to 10,365 (Zinter et al., 2014). In- and exclusion criteria varied significantly between the studies (Table 1 and eTable 3 for a detailed description of in- and exclusion criteria). Most studies included pediatric patients with a primary diagnosis of cancer who were admitted to the PICU. Ten studies included only a subgroup of pediatric cancer patients; four included only septic patients (Fiser et al., 2005; Kutko et al., 2003; da Silva et al., 2008; Pound et al., 2008), four studies included patients requiring mechanical ventilation (invasive or non-invasive) (Tamburro et al., 2008; Pancera et al., 2008; Schiller et al., 2009; Ha et al., 2010), one study included ARDS patients (Ben-Abraham et al., 2001), and finally one study included patients with respiratory insufficiency (Garcia-Salido et al., 2015). Ten studies excluded post-operative patients at the start of the study.

Twenty-nine studies reported the underlying oncological diagnosis. The main diagnoses included leukemia/lymphoma (46%), solid tumors (22%), brain and spinal cord tumors (30%), and other/non-malignant diseases (2%).

3.3. Methodological quality and risk of bias

Methodological quality of the included studies ranged from 58% to 100%. Eighteen out of the 31 included studies (58%) were considered to be of high quality. (Dalton et al., 2003; Tamburro et al., 2008; Hallahan et al., 2000; Ben-Abraham et al., 2001; Kutko et al., 2003; da Silva et al., 2008; Pound et al., 2008; Tamburro et al., 2004; Meyer et al., 2005; Haase et al., 2011; Schiller et al., 2009; Faraci et al., 2014; Dursun et al., 2009; Fausser et al., 2017; Ha et al., 2010; Garcia-Salido et al., 2015; Zinter et al., 2014; Agulnik et al., 2016) Detailed quality assessment of the included studies is provided in eTable 4. The quality of the studies improved over time (eFig. 1). We did not find significant publication bias (eFig. 2).

Table 1
Characteristics of included studies.

Author [ref]	Country	Study design	PICUs	Duration (mo)	Median year of conduct	No of patients	No of admissions	Age (mean ± SD or range; yrs)	Inclusion criteria	Underlying malignancy					HSCT patients included
										Leukemia & lymphoma	Solid tumors	Brain & spinal cord tumors	Others	Non-malignant	
Butt et al (Butt et al., 1988)	Canada	Retro	1	71	1981	67	67	NR	Primary diagnosis of cancer	83.6%	–	–	16.4%	–	NR
Butt et al (Butt et al., 1988)	Australia	Retro	1	55	1985	29	29	NR	Primary diagnosis of cancer	72.4%	17.2%	–	10.3%	6.9%	NR
Butt et al (Butt et al., 1988)	Australia	Retro	1	60	1984	37	37	NR	Primary diagnosis of cancer	56.8%	43.2%	–	–	–	NR
Meert et al (Meert et al., 1991)	USA	Retro	1	60	1986	155	183	6.9 ± 5.3	Primary diagnosis of cancer	27.3%	22.4%	46.4%	3.3%	0.005%	NR
Sivan et al (Sivan et al., 1991)	USA & Israel	Pros	2	36	1987	72	72	6.6 ± 6.6	Primary diagnosis of cancer	54.2%	37.5%	2.8%	–	5.6%	NR
van Veen et al (van Veen et al., 1996)	the Netherlands	Retro	1	120	1988	51	57	7.7 ± 3.7	Primary diagnosis of cancer Postoperative patients were excluded	NR	NR	NR	NR	NR	NR
Heney et al (Heney et al., 1992)	UK	Retro	1	79	1988	65	70	6.6	Primary diagnosis of cancer	78.6%	19%	–	–	5.6%	NR
Parsons et al (Parsons et al., 2001)	Canada	Retro	1	91	1988	134	171	6.9	Primary diagnosis of cancer	38.8%	31.3%	16.4%	6.7%	6.7%	Yes
Hallahan et al (Hallahan et al., 2000)	Australia	Retro	1	108	1992	150	206	7,23 ± 3,4	Primary diagnosis of cancer and/or HSCT	44.0%	44.0%	8.0%	–	4.0%	Yes
Ben-Abraham et al (Ben-Abraham et al., 2001)	Israel	Retro	1	120	1992	17	17	10.5 ± 5.1	Primary diagnosis of cancer & ARDS	100%	–	–	–	–	NR
Abraham et al (Ben Abraham et al., 2002)	Israel	Retro	1	120	1994	94	94	7.3 (range:2-21)	Primary diagnosis of cancer Postoperative patients were excluded	47.9%	22.3%	29.8%	–	–	NR
Keengwe et al (Keengwe et al., 1999)	UK	Retro	1	96	1994	74	74	5.4 (range 1 mo - 16 yrs)	Primary diagnosis of cancer	60.8%	37.8%	–	–	1.4%	NR
Fiser et al (Fiser et al., 2005)	USA	Retro	1	156	1996	359	446	NR	Primary diagnosis of cancer & severe sepsis	NR	NR	NR	NR	NR	Yes
Heying et al (Heying et al., 2001)	Germany	Retro	1	60	1997	13	13	6,9 ± 4,9	PICU admission at time of cancer diagnosis before start chemo Postoperative patients were excluded	84.6%	15.4%	–	–	–	No
Heying et al (Heying et al., 2001)	Germany	Retro	1	60	1997	35	35	9,1 ± 3,9	PICU admission during ongoing oncological treatment Postoperative patients were excluded	63.2%	18.4%	5.3%	13.2%	–	No
Dalton et al (Dalton et al., 2003)	USA	Pros	20	24	1997	802	802	8.3 ± 0.2	Primary diagnosis of cancer	19.1%	19.3%	51.6%	10.0%	–	NR
Kutko et al (Kutko et al., 2003)	USA	Retro	1	24	1998	57	68	NR	Sepsis or septic shock	30.9%	32.4%	5.9%	30.9%	–	Yes
Khattab et al (Khattab et al., 2005)	Saudi Arabia	Retro	1	50	1999	79	79	NR	Primary diagnosis of cancer Postoperative patients were excluded	84.8%	13.9%	–	0..01%	–	NR

(*continued on next page*)

Table 1 (*continued*)

Author [ref]	Country	Study design	PICUs	Duration (mo)	Median year of conduct	No of patients	No of admissions	Age (mean ± SD or range; yrs)	Inclusion criteria	Underlying malignancy					HSCT patients included
										Leukemia & lymphoma	Solid tumors	Brain & spinal cord tumors	Others	Non-malignant	
da Silva et al (da Silva et al., 2008)	Brazil	Retro	1	48	1999	155	155	8.4 ± 5,4	Primary diagnosis of cancer & sepsis	51.0%	49.0%	–	–	–	NR
Pound et al (Pound et al., 2008)	Canada	Retro	1	144	2000	69	69	7.8 (range 0-17.7)	Primary diagnosis of cancer & septic shock	63.8%	36.2%	–	–	–	NR
Tamburro et al (Tamburro et al., 2008)	USA	Retro	1	108	2000	329	401	9.5 ± 0.3	Cancer and/or HSCT requiring MV	59.1%	21.2%	10.5%	–	9.2%	Yes
Tamburro et al (Tamburro et al., 2004)	USA	Pros	1	21	2000	219	219	10.2 ± 0.5	Primary diagnosis of cancer and/or HSCT	61.6%	20.5%	11.9%	–	5.9%	Yes
Pancera et al (Pancera et al., 2008)	Brazil	Retro	1	96	2001	239	239	9.0	Primary diagnosis of cancer requiring MV or NIV	53.6%	46.4%	–	–	–	NR
Meyer et al (Meyer et al., 2005)	Germany	Retro	1	36	2002	32	32	11,3 ± 5,3	Primary diagnosis of cancer and/or BMT	62.5%	18.8%	18.6%	–	–	Yes
Haase et al (Haase et al., 2011)	Germany	Retro	1	144	2003	66	79	10.7 ± 7.2	Primary diagnosis of cancer, myelodysplastic syndrome or aplastic anemia excluding post-operative patients and interventions	54.4%	17.7%	17.7%	6.3%	3.8%	Yes
Schiller et al (Schiller et al., 2009)	Israel	Retro	1	89	2003	14	16	13,3 ± 5,3	Primary diagnosis of cancer requiring NIV for ARF	78.6%	21.4%	–	–	–	Yes
Faraci et al (Faraci et al., 2014)	Italy	Retro	1	142	2005	54	54	8,8 ± 4,2	Cancer and/or HSCT, non-malignant cases and children with CNS tumors were excluded in the analysis	64.8%	5.6%	–	–	29.6%	Yes
Owens et al (Owens et al., 2011)	Ireland	Retro	1	36	2005	55	66	1 month - 17 yrs	Primary diagnosis of cancer	54.5%	30.9%	10.9%	–	3.6%	Yes
Dursun et al (Dursun et al., 2009)	Turkey	Retro	1	48	2006	36	36	7.9 ± 4,8	Primary diagnosis of cancer Postoperative patients were excluded	66.7%	27.8%	5.6%	–	–	Yes
Fausser et al (Fausser et al., 2017)	France	Retro	6	132	2007	274	274	9 ± 3,9	Primary diagnosis of cancer Postoperative patients were excluded	70.1%	16.8%	9.1%	–	4.0%	Yes
Ha et al (Ha et al., 2010)	Korea	Retro	1	36	2007	54	54	5,9 ± 5.1	Primary diagnosis of cancer requiring MV > 72hrs Postoperative patients were excluded	75.9%	24.1%	–	–	–	Yes
Garcia-Salido et al (Garcia-Salido et al., 2015)	Spain	Retro	1	72	2009	69	88	8 ± 5,8	Primary diagnosis of cancer and/or HSCT with respiratory failure	52.2%	23.2%	–	–	24.6%	Yes
Zinter et al (Zinter et al., 2014)	USA	Retro	112	42	2011	10,365	10,365	NR	Primary diagnosis of cancer Postoperative patients were excluded	44.8%	21.4%	33.8%	–	–	Yes

(*continued on next page*)

Table 1 (*continued*)

Author [ref]	Country	Study design	PICUs	Duration (mo)	Median year of conduct	No of patients	No of admissions	Age (mean ± SD or range; yrs)	Inclusion criteria	Underlying malignancy					HSCT patients included
										Leukemia & lymphoma	Solid tumors	Brain & spinal cord tumors	Others	Non-malignant	
Agulnik et al (Agulnik et al., 2016)	USA	Retro	1	39	2012	42	42	NR	Primary diagnosis of cancer and/or HSCT; data only from oncological patients	64.3%	35.7%	–	–	–	Yes

Retro retrospective, *Pros* prospective, *PICU* pediatric intensive care unit, *mo* months, *yrs* years, *SD* standard deviation, *NR* not reported, *HSCT* hematopoietic stem cell transplant, *ARDS* acute respiratory distress syndrome, *BMT* bone marrow transplant, *MV* mechanical ventilation, *NIV* non-invasive ventilation.

3.4. PICU mortality

The overall pooled weighted PICU mortality was 27.8% (95% CI, 23.7–31.9) (Fig. 2). When excluding post-operative patients, pooled weighted PICU mortality increased to 33.5% (95% CI, 27.0–40.0) (Fig. 3).

As this latter cohort still contained studies with a variety of inclusion criteria, we performed an additional analysis on those studies that have included all PICU admission diagnoses, thereby representing a general PICU cohort of pediatric cancer patients. Pooled PICU mortality of this group was 35.4% (95% CI, 26.7–44.0) (Fig. 4). Among patients with sepsis, the estimated pooled PICU mortality was 46.2% (95% CI, 34.7–57.8) (Fig. 5). There was significant heterogeneity for PICU mortality across all studies (I^2 = 96%, p < 0.001), across studies excluding post-operative patients (I^2 = 97%, p < 0.001), and across studies including only septic patients (I^2 = 93%, p < 0.001).

Fig. 6 depicts the pooled weighted PICU mortality by year of study conduct. There was no association between the median year of study conduct and the reported PICU mortality (Fig. 56A). However, a slight, but significant, decrease in PICU mortality over time was found when post-operative patients were excluded (Fig. 56B). In the latter group in which only studies that have included all PICU admission diagnoses were selected (Fig. 56C) and in the subset of septic cancer patients, no significant decrease of PICU mortality over time was found (Fig. 56D).

3.5. Use of PICU resources

A majority of the studies (25 out of 31, 80.6%) reported on the use of PICU resources such as mechanical ventilation, inotropes, and/or CRRT. (Dalton et al., 2003; Tamburro et al., 2008; Hallahan et al., 2000; Butt et al., 1988; Heying et al., 2001; Meert et al., 1991; van Veen et al., 1996; Heney et al., 1992; Ben-Abraham et al., 2001; Ben Abraham et al., 2002; Keengwe et al., 1999; Fiser et al., 2005; Khattab et al., 2005; da Silva et al., 2008; Tamburro et al., 2004; Pancera et al., 2008; Meyer et al., 2005; Haase et al., 2011; Faraci et al., 2014; Owens et al., 2011; Dursun et al., 2009; Fausser et al., 2017; Ha et al., 2010; Garcia-Salido et al., 2015; Zinter et al., 2014) Thirty percent of the reported patients (4315/14142) received mechanical ventilation. The use of inotropes was described 21 studies. Forty percent (1240/3117) of the reported patients received inotropes. Only ten studies reported the use of CRRT during the PICU stay with 4,6% (382 of 8339 patients) requiring CRRT. Sixteen studies described PICU mortality by PICU treatment. Use of all three PICU resources was significantly associated with increased PICU mortality (mechanical ventilation odds ratio (OR) 18.49 [95% CI 13.79–24.78], $p < 0.001$; inotropic support OR 14.05 [95% CI 9.16–21.57], $p < 0.001$; CRRT OR 3.24 [95% CI 1.31–8.04], $p = 0.01$) (Table 2). Over time, intervention-specific PICU mortality improved, albeit only significant in patients who required inotropic support (eFig. 3).

4. Discussion

This systematic review of 31 observational studies over the past 30 years showed the mortality of pediatric cancer patients admitted to PICU is high (28%), five-fold higher than the current mortality rate of the general PICU population. (Heneghan and Pollack, 2017) When post-operative patients were excluded, PICU mortality increased to 33% and was even higher in septic patients (46%). Overall, mortality rates have remained static over time, although when post-operative patients were excluded, there is a slight significant decrease of PICU mortality over the past decades. For septic cancer patients, no association between the median year of study conduct and reported PICU mortality was found. The need for PICU resources (mechanical ventilation, inotropic support and CRRT) was significantly associated with PICU mortality.

Our findings are in line with previously reported high mortality rates of adult cancer patients requiring ICU admission. However, in

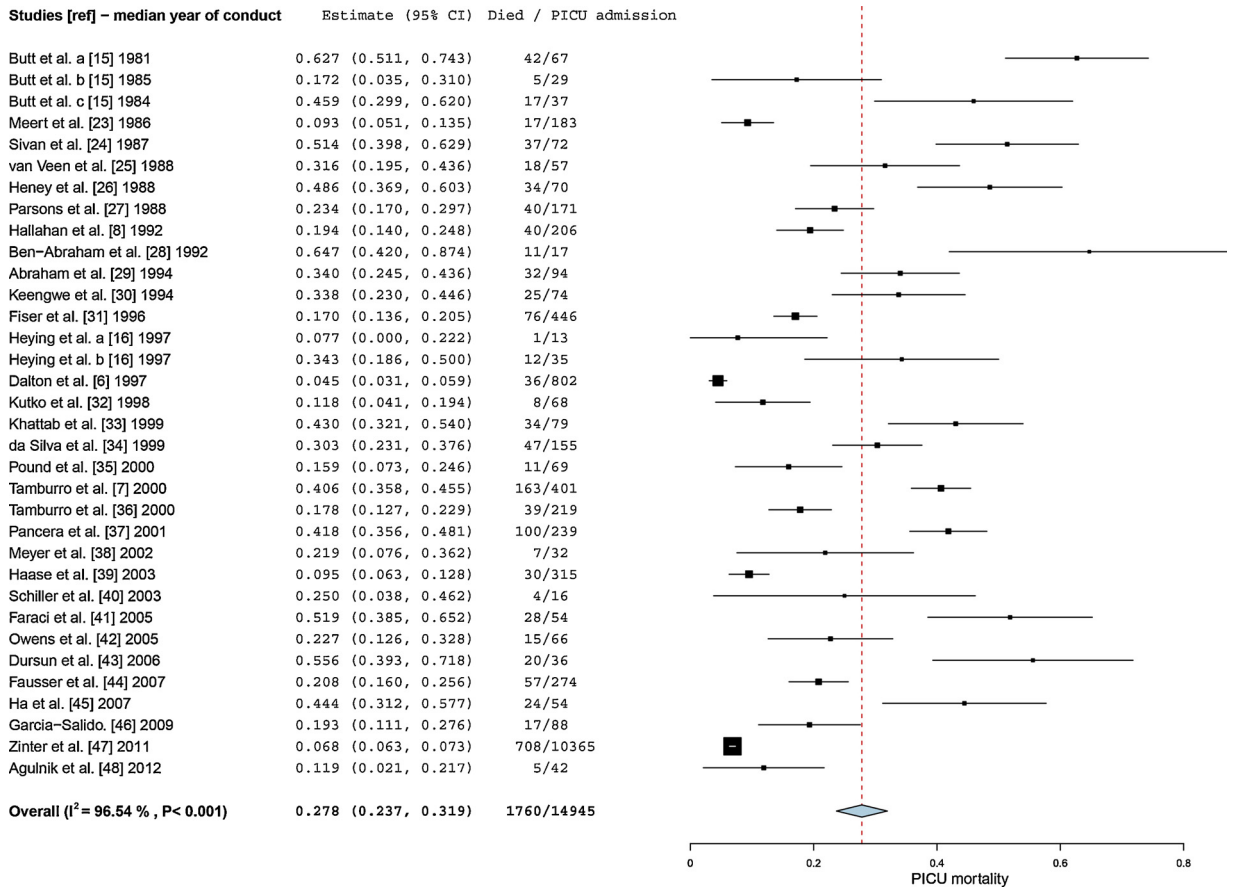

Fig. 2. Forest plot of PICU mortality using a random-effects model.Individual mortality for each study and the pooled weighted estimate shown with 95% confidence intervals (CI). Vertical dotted line represents the pooled weighted estimate. For studies providing PICU mortality for different time periods or cohorts, an individual point estimate is provided for each period.

contrast to our results, the ICU survival of adult patients has improved substantially over the corresponding time-frame. (Shimabukuro-Vornhagen et al., 2016) There are several differences between the approaches of adult and pediatric intensivists to critically ill cancer patients. One main explanation is that significant research into the management of critically ill adult cancer patients has occurred compared to children. This has resulted in changes to the point of view regarding admission of critically ill adult cancer patients to ICU over the past 15 years. (Azoulay et al., 2017) Time-limited trials of therapy, the so-called ICU-trials, have been one of these major changes (Shrime et al., 2016). The ICU-trial consists of unlimited, aggressive ICU management with full resuscitation status for a specific limited period. In one large French/Belgian study, critically ill patients with cancer, those 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 the comparable survival to unlimited aggressive care (Azoulay et al., 2013). In addition, it was demonstrated that ICU-admission shortly after the start of the critical care illness was associated with better survival rates. (Azoulay et al., 2013) Whether this approach would also improve PICU survival in pediatric cancer patients, needs to be determined.

Mortality trends over time offer important insights into the state of medical care for a particular disease or patient cohort. Mark Peters and Rachel Agbeko showed that the predicted risk of mortality for children with leukemia or lymphoma outside of first remission admitted to PICU due to sepsis-induced multiple organ dysfunction syndrome or ARDS has improved over the past decades. (Peters and Agbeko, 2014) However, our results suggest only slightly decreasing mortality rates over time when post-operative patients were excluded. Improved survival may be related to significant advances in ICU care, such as the introduction of early-goal directed therapy for sepsis and lung-protective ventilation. (Rhodes et al., 2017; Kneyber et al., 2017), Also, oncology treatments as well as supportive care such as immunomodulation have improved significantly in the past decades. Although guidelines exist to promote these practices, variable adherence may contribute to the observed lack of improvement in actual PICU outcomes of these patients. In addition, development of aggressive treatment regimens against cancer may have increased requirements of PICU support with the use of life-sustaining therapies for infectious or toxic chemotherapy-related events. This may imply that a higher-risk cohort of patients are being admitted to PICU over time, and because overall PICU care has improved, the mortality for these patients has not increased. As most studies did not report on severity of illness scores, such as PIM or PRISM scores, we were not able to verify this. In addition, it is possible that improved overall management of pediatric cancer patients means only those with more advanced disease or severe complications are now referred to PICU.

Not surprisingly, the need for PICU treatments such as mechanical ventilation, inotropic support and/or CRRT is associated with increased mortality. However, intervention-specific PICU mortality decreased over time. These results are consistent with findings in critically ill adult cancer patients where mortality has decreased over the past years. (Shimabukuro-Vornhagen et al., 2016; Azoulay et al., 2014), This may be attributable to improvements in early recognition of critically ill cancer patients, rapid implementation of aggressive ICU treatments, intensivists' skills in understanding the pathophysiology of organ dysfunction in this population and management of urgent complications

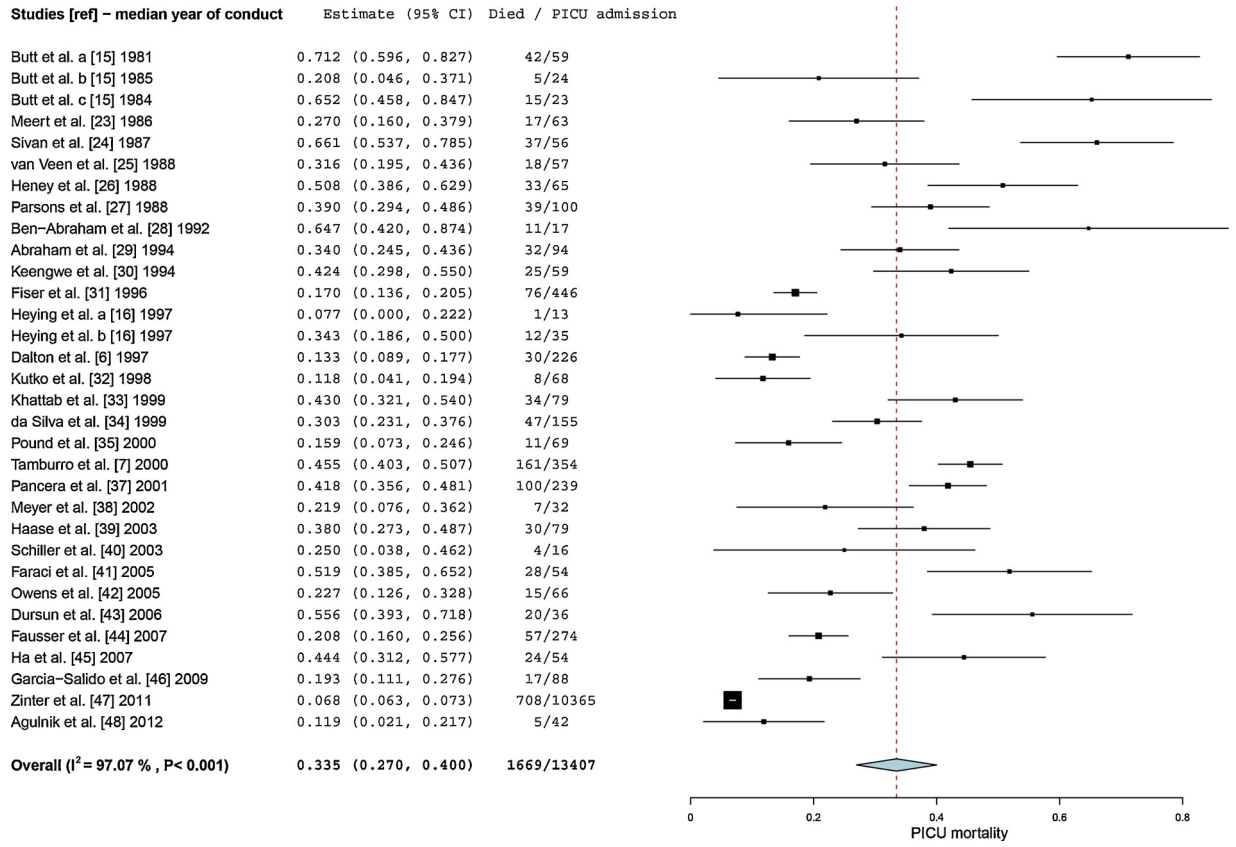

Fig. 3. Forest plot of PICU mortality for pediatric cancer patients excluding post-operative patients using a rondom-effects model.Individual mortality for each study and the pooled weighted estimate shown with 95% confidence intervals (CI). Vertical dotted line represents the pooled weighted estimate. For studies providing PICU mortality for different time periods or cohorts, an individual point estimate is provided for each period.

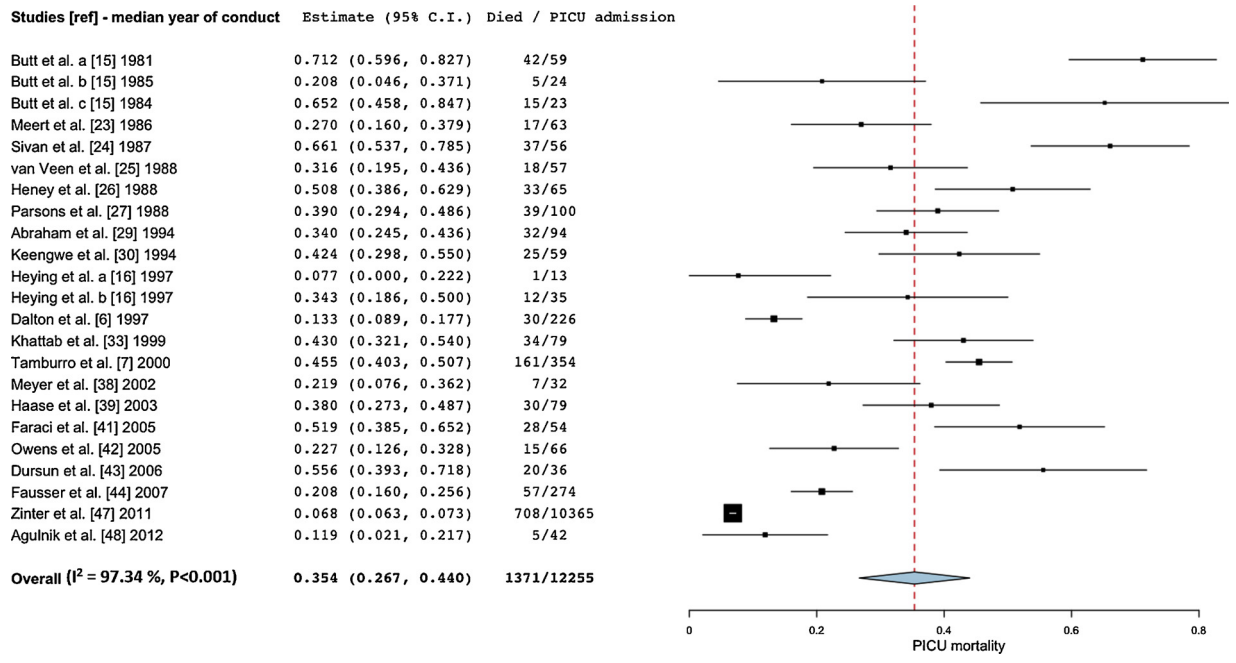

Fig. 4. Forest plot of PICU mortality for pediatric cancer patients, excluding post-operative patients using a rondom-effects model. Only studies that have included all PICU admission diagnoses were analyzed.Individual mortality for each study and the pooled weighted estimate shown with 95% confidence intervals (CI). Vertical dotted line represents the pooled weighted estimate. For studies providing PICU mortality for different time periods or cohorts, an individual point estimate is provided for each period.

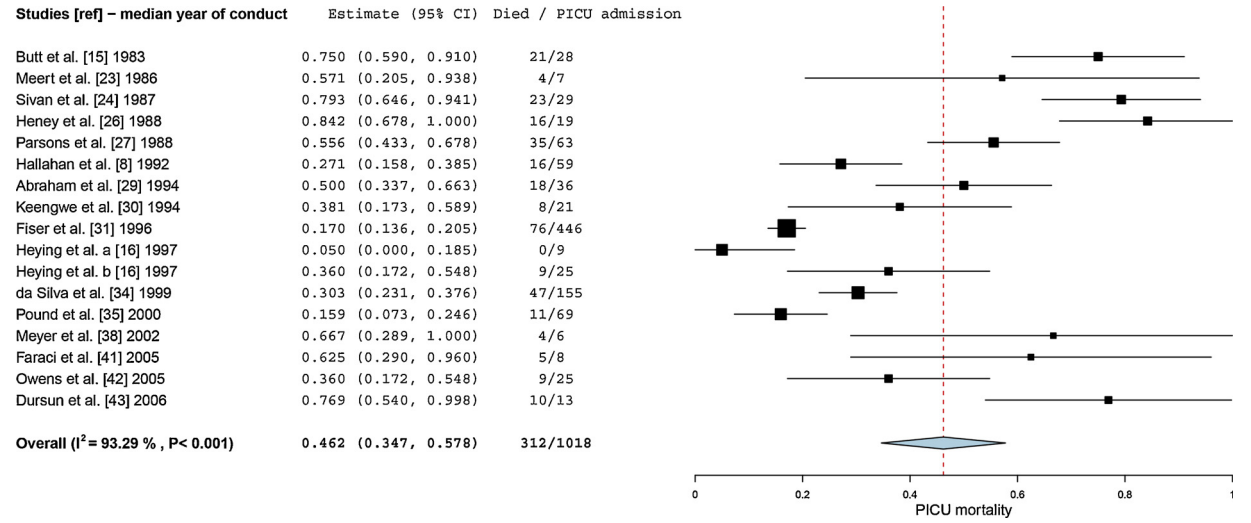

Fig. 5. Forest plot of PICU mortality for pediatric cancer patients with sepsis using a random-effects model.Individual mortality for each study and the pooled weighted estimate shown with 95% confidence intervals (CI). Vertical dotted line represents the pooled weighted estimate. For studies providing PICU mortality for different time periods or cohorts, an individual point estimate is provided for each period.

related to the malignancy. These developments must challenge pediatric intensivists and oncologists to achieve the same goals. To this aim, we need to collaborate intensively to generate prospective data on outcome, using identical criteria of underlying malignancies, admission diagnoses in order to determine risk factors on mortality.

Our study has important limitations. Our findings should be interpreted with caution due to the retrospective nature of the majority of the studies, which render them susceptible to potential flaws and bias. There was a considerable heterogeneity among published cohorts. This likely reflects differences in terms of case- mix, center characteristics, treatment strategies, and PICU admission criteria. Especially, in- and exclusion criteria of the included studies differed significantly. Moreover, the majority of the included studies didn't report on the inclusion of HSCT patients. Inclusion of these patients may have influenced PICU mortality rates over time. Almost all studies performed after 2000 reported inclusion of HSCT patients. `Previous studies have shown that these patients have a high PICU mortality (Pillon et al., 2017; An et al., 2016; Chima et al., 2012; van Gestel et al., 2008; Lamas et al., 2003). Increased numbers of included HSCT patients over time may form an explanation for the unchanged PICU mortality over the past decades. An individual patient data meta-analysis will be needed to adjust adequately for these confounders. In particular, we could not investigate the association between underlying malignancy or PICU admission diagnosis and mortality, because in the majority of the studies these data was not specified. For this reason, studies with only one subtype of cancer were excluded due to the fact that this data would not represent a general PICU mortality of pediatric cancer patients. Similarly, we could only investigate the association between use of PICU resources and mortality in a univariate analysis, as many studies did not report on the use of a combination of resources (e.g. mechanical ventilation with inotropes). Studies including exclusively hematopoietic stem cell transplant patients were also excluded. The majority of these studies included also children with a non-malignant disease without providing data of PICU mortality of the cancer patients separately. Moreover, this subpopulation of patients is known to have a high mortality rate, again not representing a general PICU mortality of pediatric cancer patients (Pillon et al., 2017; An et al., 2016; Chima et al., 2012; van Gestel et al., 2008; Lamas et al., 2003). We used the median year of conduct for each study as the independent variable in analyses of the effect of year on mortality. This was necessary because all studies were conducted over several decades. Finally, most studies reflect the experience of a single center thereby these results may be of limited generalizability to international healthcare systems with different practice patterns.

Our analysis may have important implications for pediatric intensivists and oncologists. We show that the improved overall survival rates of pediatric cancer patients are not reflected in the cohort referred to PICU. Although it cannot be excluded that over time this specific patient population forms a higher-risk cohort, an overall PICU mortality of almost 35% is too high and that is evidence enough to focus on tailoring research to improve outcomes in this patient population. Tantalizingly, the improvement in adult cancer patients in ICU suggests improvement is possible, but caution is warranted as we have little basic data on changes in the population referred. More research is needed to improve our ability to appropriately treat these patients. Recognizing the need for international collaboration on this issue, the PICU Oncology Kids in Europe Research group (POKER) was established to address these items ultimately to improve outcomes of children with cancer who are admitted to the PICU. As a first step, POKER aims to obtain consensus in determining the top research priorities and core outcome measures in the field of pediatric cancer patients at the PICU for the next 10 years.

In conclusion, our systematic review has shown that PICU mortality in pediatric cancer patients is sadly high and, unlike in adults with cancer, has remained relatively unchanged over the past decades. Our results highlight the need for urgent multicenter prospective interventional studies in this cohort. These studies may reveal risk factors for clinical deterioration and effective therapeutic interventions. In addition, data from these studies may help guide both intensivists and oncologists in risk stratification for patients, in the decision-making process of allocation of PICU resources, and may identify patients that may benefit from closer monitoring and early interventions. Finally, these studies may advance our understanding of critical illness in the context of pediatric oncology to further refine and reflect on our daily clinical practice.

Funding

None.

Declaration of Competing Interest

None.

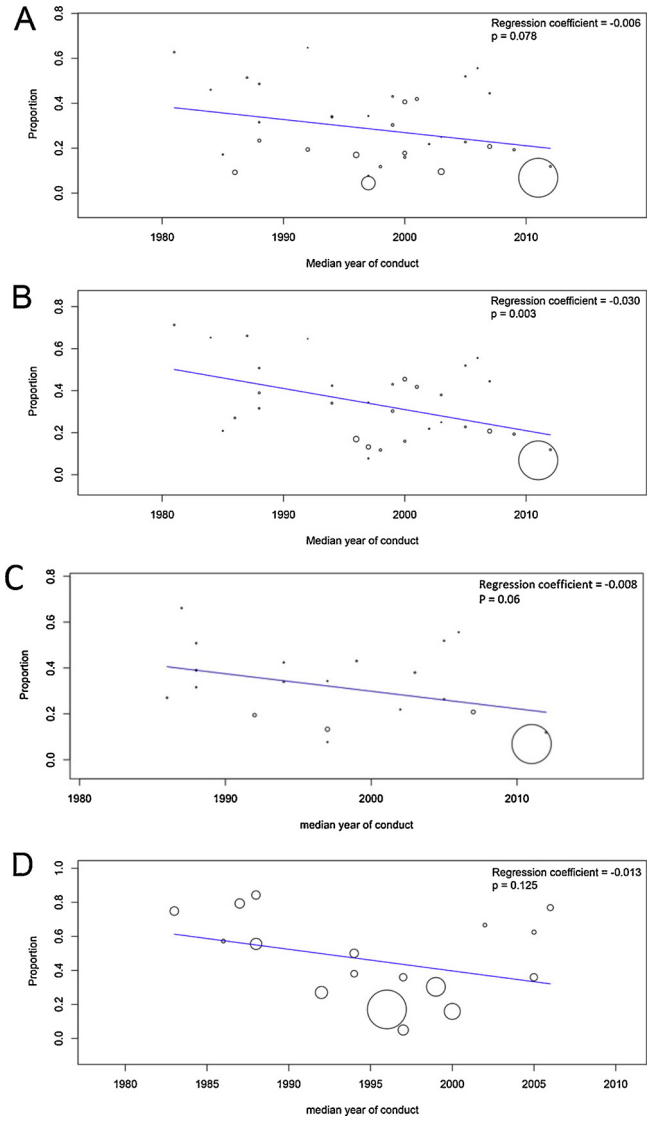

Fig. 6. Regression plot of PICU mortality of pediatric cancer patients over time. The solid line represents the regression line calculated with an univariate random-effects logistic meta-regression model of overall PICU mortality of pediatric cancer patients (**A**), PICU mortality excluding post-operative patients (**B**), PICU mortality reported in studies including all PICU admission diagnoses, post-operative patients excluded (**C**) and pediatric cancer patients with sepsis (**D**) presented by median year of study conduct. The studies are depicted as circles corresponding the weighted event rates.

Table 2
Random effects meta-analysis of the association between the use of PICU resources and PICU mortality estimates.

Mortality				
PICU resource use	Studies	Odds ratio [CI 95%]	p-value	I^2
Mechanical ventilation	14	18.49 [13.79-24.78]	< 0.001	6.09 %
Inotropic support	10	14.05 [9.16-21.57]	< 0.001	0%
CRRT	4	3.24 [1.31-8.04]	0.01	20.3%

CI = confidence interval; *CRRT* = continuous renal replacement therapy.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.critrevonc.2019.07.014.

References

Agulnik, A., Forbes, P.W., Stenquist, N., Rodriquez-Galindo, C., Kleinman, M., 2016. Validation of a pediatric early warning score in hospitalized pediatric oncology and hematopoietic stem cell transplant patients. Pediatr. Crit. Care Med. 17 (4), e146–e153.
An, K., Wang, Y., Li, B., et al., 2016. Prognostic factors and outcome of patients undergoing hematopoietic stem cell transplantation who are admitted to pediatric intensive care unit. BMC Pediatr. 16 (1), 138.
Azoulay, E., Mokart, D., Pène, F., et al., 2013. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium–a groupe de recherche respiratoire en réanimation onco-hématologique study. J. Clin. Oncol. 31 (22), 2810–2818.
Azoulay, E., Schellongowski, P., Darmon, M., et al., 2017. The intensive care medicine research agenda on critically ill oncology and hematology patients. Intensive Care Med. 43 (9), 1366–1382.
Azoulay, E., Lemiale, V., Mokart, D., et al., 2014. Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med. 40 (8), 1106–1114.
Ben Abraham, R., Toren, A., Ono, N., et al., 2002. Predictors of outcome in the pediatric intensive care units of children with malignancies. J. Pediatr. Hematol. Oncol. 24 (1), 23–26.
Ben-Abraham, R., Weinbroum, A.A., Augerten, A., et al., 2001. Acute respiratory distress syndrome in children with malignancy-can we predict outcome? J. Crit. Care 16 (2), 54–58.
Bleyer, W.A., 1997. The U.S. Pediatric cancer clinical trials programs: international implications and the way forward. Eur. J. Cancer 33 (9), 1439–1447.
Butt, W., Barker, G., Walker, C., Gillis, J., Kilham, H., Stevens, M., 1988. Outcome of children with hematologic malignancy who are admitted to an intensive care unit. Crit. Care Med. 16 (8), 761–764.
Chima, R.S., Daniels, R.C., Kim, M.O., et al., 2012. Improved outcomes for stem cell transplant recipients requiring pediatric intensive care. Pediatr. Crit. Care Med. 13 (6), e336–e342.
da Silva, E.D., Koch Nogueira, P.C., Russo Zamataro, T.M., de Carvalho, W.B., Petrilli, A.S., 2008. Risk factors for death in children and adolescents with cancer and sepsis/septic shock. J. Pediatr. Hematol. Oncol. 30 (7), 513–518.
Dalton, H.J., Slonim, A.D., Pollack, M.M., 2003. Multi-center outcome of pediatric oncology patients requiring intensive care. Pediatr. Hematol. Oncol. 20 (8), 643–649.
Dursun, O., Hazar, V., Karasu, G.T., Uygun, V., Tosun, O., Yesilipek, A., 2009. Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit. J. Pediatr. Hematol. Oncol. 31 (7), 481–484.
Faraci, M., Bagnasco, F., Giardino, S., et al., 2014. Intensive care unit admission in children with malignant or nonmalignant disease: incidence, outcome, and prognostic factors: a single-center experience. J. Pediatr. Hematol. Oncol. 36 (7), e403–e409.
Fausser, J.L., Tavenard, A., Rialland, F., et al., 2017. 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. 39 (5), e244–e248.
Fiser, R.T., West, N.K., Bush, A.J., Sillos, E.M., Schmidt, J.E., Tamburro, R.F., 2005. Outcome of severe sepsis in pediatric oncology patients. Pediatr. Crit. Care Med. 6 (5), 531–536.
Garcia-Salido, A., Mastro-Martinez, I., Cabeza-Martin, B., et al., 2015. Respiratory failure in children with hemato-oncological diseases admitted to the PICU: a single-center experience. J. Pediatr. Hematol. Oncol. 37 (6), 449–454.
Ha, E.J., Kim, S., Jin, H.S., et al., 2010. Early changes in SOFA score as a prognostic factor in pediatric oncology patients requiring mechanical ventilatory support. J. Pediatr. Hematol. Oncol. 32 (8), e308–e313.
Haase, R., Lieser, U., Kramm, C., et al., 2011. Management of oncology patients admitted to the paediatric intensive care unit of general children's hospital – a single center analysis. Klin. Padiatr. 223 (3), 142–146.
Hallahan, A.R., Shaw, P.J., Rowell, G., O'Connell, A., Schell, D., Gillis, J., 2000. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. Crit. Care Med. 28 (11), 3718–3721.
Heneghan, J.A., Pollack, M.M., 2017. Morbidity: changing the outcome paradigm for pediatric critical care. Pediatr. Clin. North Am. 64 (5), 1147–1165.
Heney, D., Lewis, I.J., Lockwood, L., Cohen, A.T., Bailey, C.C., 1992. The intensive care unit in paediatric oncology. Arch. Dis. Child. 67 (3), 294–298.
Heying, R., Schneider, D.T., Körholz, D., Stannigel, H., Lemburg, P., Göbel, U., 2001. Efficacy and outcome of intensive care in pediatric oncologic patients. Crit. Care Med. 29 (12), 2276–2280.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analysis. BMJ 327 (7414), 557–560.
Higgins, J.P.T., Geen, S. (Eds.), 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration Available at: http://www.cochrane-handbook.org. (Accessed 1 December 2012).
Keengwe, I.N., Stansfield, F., Eden, O.B., Nelhans, N.D., Dearlove, O.R., Sharples, A., 1999. Paediatric oncology and intensive care treatments: changing trends. Arch. Dis. Child. 80 (6), 553–555.
Khattab, T., Felimban, S., Fryer, C., Abutaleb, A., Helali, A., 2005. Pediatric oncology admission to paediatric intensive care unit: a 4 year experience. Haema 8 (3), 430–435.
Kneyber, M.C.J., de Luca, D., Calderini, E., et al., 2017. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 43 (12), 1764–1780.
Kress, J.P., Christenson, J., Pohlman, A.S., Linkin, D.R., Hall, J.B., 1999. Outcomes of

critically ill cancer patients in a university hospital setting. Am. J. Respir. Crit. Care Med. 160 (6), 1957–1961.
Kutko, M.C., Calarco, M.P., Flaherty, M.B., et al., 2003. Mortality rates in pediatric septic shock with and without multiple organ system failure. Pediatr. Crit. Care Med. 4 (3), 333–337.
Lamas, A., Otheo, E., Ros, P., et al., 2003. Prognosis of child recipients of hematopoietic stem cell transplantation requiring intensive care. Intensive Care Med. 29 (1), 91–96.
Raffoux, E., Lengliné, E., Lemiale, V., et al., 2012. Intensive care unit management of patients with newly diagnoses acute myeloid leukemia with no organ failure. Leuk. Lymphoma 53 (7), 1352–1359.
Meert, K., Lieh-Lai, M., Sarnaik, I., Sarnaik, A., 1991. The role of intensive care in managing childhood cancer. Am. J. Clin. Oncol. 14 (5), 379–382.
Gottschling, S., Meyer, S., Biran, T., et al., 2005. Assessing the risk of mortality in paediatric cancer patients admitted to the paediatric intensive care unit: a novel risk score? Eur. J. Pediatr. 164 (9), 563–567.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (4), 264–269.
Moher, D., Shamseer, L., Clarke, M., et al., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. (4), 1.
Schnell, D., Mokart, D., Lambert, J., et al., 2013. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. Leuk. Lymphoma 54 (8), 1724–1729.
Owens, C., Mannion, D., O'Marcaigh, A., Waldron, M., Butler, K., O'Meara, A., 2011. Indications for admission, treatment and improved outcome of paediatric haematology/oncology patients admitted to a tertiary paediatric ICU. Ir. J. Med. Sci. 180, 85–89.
Pancera, C.F., Hayashi, M., Fregnani, J.H., Negri, E.M., Deheinzelin, D., de Camargo, B., 2008. Noninvasive ventilation in immunocompromised pediatric patients: eight years of experience in a pediatric oncology intensive care unit. J. Pediatr. Hematol. Oncol. 30 (7), 533–538.
Parsons, S.J., Tomas, K., Wensley, D.F., 2001. Outcome and predictors of mortality in pediatric oncology patients requiring intensive care. J. Intensive Care Med. 16 (1), 29–34.
Peters, M.J., Agbeko, R.S., 2014. Optimism and no longer foolishness? Haematology/oncology and the PICU. Intensive Care Med. 40 (10), 1589–1591.
Petridou, E.T., Dimitrova, N., Eser, S., et al., 2013. Childhood leukFemia and lymphoma: time trends and factors affecting survival in five Southern and Eastern European Cancer Registries. Cancer Causes Control 24 (6), 1111–1118.
Pillon, M., Amigoni, A., Contin, A., et al., 2017. Risk factors and outcomes related to pediatric intensive care unit admission after hematopoietic stem cell transplantation: a single-center experience. Biol. Blood Marrow Transplant. 23 (8), 1335–1341.
Pound, C.M., Johnston, D.L., Armstrong, R., Gaboury, I., Menon, K., 2008. The morbidity and mortality of pediatric oncology patients presenting to the intensive care unit with septic shock. Pediatr. Blood Cancer 51 (5), 584–588.
Pritchard-Jones, K., Kaatsch, P., Steliarova-Foucher, E., Stiller, C.A., Coebergh, J.W., 2006. Cancer in children and adolescents in Europe: developments over 20 years and future challenges. Eur. J. Cancer 42 (13), 2183–2190.
Rhodes, A., Evans, L.E., Alhazzani, W., Levy, M.M., et al., 2017. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 43 (3), 304–377.
Rosenman, M.B., Vik, T., Hui, S.L., Breitfeld, P.P., 2005. Hospital resource utilization in childhood cancer. J. Pediatr. Hematol. Oncol. 27 (6), 295–300.
Sanderson, S., Tatt, I.D., Higgins, J.P., 2007. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int. J. Epidemiol. 36 (3), 666–676.
Schiller, O., Schonfeld, T., Yaniv, I., Stein, J., Kadmon, G., Nahum, E., 2009. Bi-level positive airway pressure ventilation in pediatric oncology patients with acute respiratory failure. J. Intensive Care Med. 24 (6), 383–388.
Shimabukuro-Vornhagen, A., Böll, B., Kochanek, M., Azoulay, É., von Bergwelt-Baildon, M.S., 2016. Critical care of patients with cancer. CA Cancer J. Clin. 66, 496–517.
Shrime, M.G., Ferket, B.S., Scott, D.J., et al., 2016. Time-limited trials of intensive care for critically ill patients with cancer: how long is long enough? JAMA Oncol. 2 (1), 76–83.
Sivan, Y., Schwartz, P.H., Schonfeld, T., Cohen, I.J., Newth, C.J.L., 1991. Outcome of oncology patients in the pediatric intensive care unit. Intensive Care Med. 17 (1), 11–15.
Staudinger, T., Stoiser, B., Müllner, M., et al., 2000. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. Crit. Care Med. 28 (5), 1322–1328.
Tamburro, R.F., Barfield, R.C., Shaffer, M.L., et al., 2008. Changes in outcomes (1996–2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. Pediatr. Crit. Care Med. 9 (3), 270–277.
Tamburro, R.F., West, N.K., Piercy 4th, J., Towner, G., Fang, H.B., 2004. Use of the nursing acuity score in children admitted to a pediatric oncology intensive care unit. Pediatr. Crit. Care Med. 5 (1), 35–39.
van Gestel, J.P., Bollen, C.W., van der Tweel, I., Boelens, J.J., van Vught, A.J., 2008. Intensive care unit mortality trends in children after hematopoietic stem cell transplantation: a meta-regression analysis. Crit. Care Med. 36 (10), 2898–2904.
Karstens, A., van Veen, A., van der Hoek, A.C., Tibboel, D., Hählen, K., van der Voort, E., 1996. The prognosis of oncologic patients in the pediatric intensive care unit. Intensive Care Med. 22 (3), 237–241.
Vandenbroucke, J.P., von Elm, E., Altman, D.G., et al., 2007. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Epidemiology 18 (6), 805–835.
Viswanathan, M., Ansari, M.T., Berkman, N.D., et al., 2019. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Agency for Healthcare Research and Quality (US), Rockville (MD), pp. 2008–2012.
Wan, X., Wang, W., Liu, J., Tong, T., 2014. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med. Res. Methodol. 14, 135.
Zinter, M.S., DuBois, S.G., Spicer, A., Matthay, K., Sapru, A., 2014. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. Intensive Care Med. 40 (10), 1536–1544.