## Review Article

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# Impact of palliative care on end-of-life care and place of death in children, adolescents, and young adults with life-limiting conditions: A systematic review

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## Abstract

**Objective.** To determine the impact of palliative care (PC) on end-of-life (EoL) care and the place of death (PoD) in children, adolescents, and young adults with life-limiting conditions.
**Method.** Eight online databases (PubMed, Medline, EMBASE, Cochrane Library, CINAHL, Airiti, GARUDA Garba Rujukan Digital, and OpenGrey) from 2010 to February 5, 2020 were searched for studies investigating EoL care and the PoD for pediatric patients receiving and not receiving PC.
**Results.** Of the 6,468 citations identified, 14 cohort studies and one case series were included. An evidence base of mainly adequate- and strong-quality studies shows that inpatient hospital PC, either with or without the provision of home and community PC, was found to be associated with a decrease in intensive care use and high-intensity EoL care. Conflicting evidence was found for the association between PC and hospital admissions, length of stay in hospital, resuscitation at the time of death, and the proportion of hospital and home deaths.
**Significance of results.** Current evidence suggests that specialist, multidisciplinary involvement, and continuity of PC are required to reduce the intensity of EoL care. Careful attention should be paid to the need for a longer length of stay in a medical setting late in life, and earlier EoL care discussion should take place with patients/caregivers, especially in regard to attempting resuscitation in toddlers, adolescents, and the young adult population. A lack of robust evidence has identified a gap in rigorous multisite prospective studies utilizing data collection.

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## Introduction

Life-limiting conditions are those for which there is no possibility of cure, where death is inevitable at some point in time during childhood or young adulthood (McNamara-Goodger and Feudtner, 2012; Fraser and Parslow, 2018). Pediatric palliative care (PC) is a multidisciplinary approach that improves the quality of life of this population and their families through preparing them for an anticipated death through providing physical, psychosocial, and spiritual supports, as well as managing complex conditions during the end of life (EoL; Chambers, 2018). The number of children, adolescents, and young adults with life-limiting conditions is increasing as a result of increased survival and earlier recognition of life-limiting diagnoses. The United Kingdom data suggest that 66.4 per 10,000 individuals in pediatric populations aged from 0 to 19 years were living with life-limiting conditions in 2017, and the prevalence is likely to rise to 84.2 per 10,000 by 2030 (Fraser et al., 2020). However, it was estimated that only 18.6% of them actually received PC before death (Widger et al., 2016).

The majority of this population goes through a prolonged period of inpatient admission, primarily in intensive care unit (ICU) settings during EoL, and die in the hospital (Gao et al., 2016; DeCourcey et al., 2018). Only 58% of children, adolescents, and young adults with cancer actually died at home as their place of preference (Stilwell et al., 2020). A growing body of evidence demonstrates that receiving early PC improves the quality of life and symptom control, facilitates earlier advanced care planning or planned withdrawal of ventilator support outside the ICU setting, and enables a choice in the place of death (PoD) outside of hospital (Abel et al., 2013; Laddie et al., 2014; Mitchell et al., 2017). Nevertheless, several patient and family-related factors influence the EoL decision-making and the PoD (Allen, 2014; Foster et al., 2016). Thus, there is limited scientific evidence by which to illustrate the impacts of PC on children, adolescents, and young adults with life-limiting conditions in terms of their healthcare circumstances and outcomes during the EoL.

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Recent systematic reviews suggest that access to PC is associated with reduced time in hospital and less invasive treatments (Marcus et al., 2020; Tayloy et al., 2020; Zuniga-Villanueva et al., 2020). However, these reviews specifically evaluated the outcomes of specialist PC services, which were developed mainly in the USA, Canada, the UK, and across Europe (Knapp et al., 2011). Thus, the evidence base is not yet able to offer a universal PC model, especially in the case of non-Western countries. Furthermore, these reviews aggregated the results for patients at earlier stages of their illness. The evidence of the impact on EoL care and the PoD, including studies on PC without further subdivisions of the general and specialist levels of services, remains unclear. The aim of this study is to determine the impact of PC on EoL care and PoD for children, adolescents, and young adults with life-limiting conditions.

## Methods

A systematic review was conducted to evaluate the academic literature related to PC in order to determine if the use of PC compared with not using it impacts on EoL care and the PoD. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocol (PRISMA-P) guidelines (Moher et al., 2015).

### Inclusion and exclusion criteria

We included studies if their target population was children up to 25 years of age with a life-limiting condition; the exposure of interest was self-described as "palliative care" and/or comprised at least two components of PC, including general and/or specialist PC, which means PC delivered by a healthcare team who are/are not PC specialists, as defined by the National Consensus Project for Quality Palliative Care (2018). The researchers provided a comparison between PC exposure and at least one of the outcomes of admission in terms of acute care beds, length of hospital stay, receiving cardiopulmonary resuscitation (CPR) before death, PoD, and the intensity of EoL care. Publications in English, Mandarin, or Bahasa were considered based on the language competencies of the reviewers.

Studies were excluded where the type of intervention was exclusively on only one component of comprehensive PC (e.g., providing opioid and sedation medications or advanced care planning) or included a mixed sample of adults aged over 25 years. Assessments of EoL care were not included if data in the last year of life could not be fully determined. Outcomes of the presence of limitations related to resuscitation orders were not included if the congruence of the presence of limitations of resuscitation orders and the actual CPR attempted at the time of death could not be fully determined. Cross-sectional descriptive studies and qualitative studies were excluded.

### Search strategy

The following online databases were searched: Medline, EMBASE, PubMed, Cochrane Library, CINAHL, Airiti, GARUDA Garba Rujukan Digital, and OpenGrey from 2010 to February 5, 2020, where a series of pediatric PC in various settings had been implemented over time. The search terms used included the recognized Medical Subject Heading (MeSH) and Embase subject headings (Emtree) with various combinations of the terms *children, adolescents, young adults, palliative, end-of-life, place of death,* and specific diagnoses from the International Classification of Disease (ICD10) coding framework (Fraser et al., 2012) (Supplementary Tables 1–5 in the Supplementary File for search strategy).

### Screening and selection

Retrieved references were imported using the EndNote. S.-C.L. and D.Y. screened and selected all articles by title and abstract independently using a prespecified screening and selection tool. Disagreements were discussed with M.-C.H. until a consensus was reached.

### Quality assessment

The quality of the individual studies was critically graded by applying the Joanna Briggs Institute (JBI) appraisal tools based on appropriate checklists. The checklists included assessment of the methodological quality of the study and any possibility of bias in its design, procedures, or analyses, scored as "yes" (2), "unclear" (1), "no" (0), or "not applicable." The summary scores for each study were derived by calculating the total scores of relevant items. S.-C.L. and D.Y. independently assessed all papers. Any disagreement was resolved through a discussion with M.-C.H.. Scores were expressed as a percentage, where >80% was considered strong; >70% was considered good; >50% was considered adequate, and ≤50% was considered limited. We did not exclude studies based on a quality assessment.

### Data extraction

Data extraction was conducted by one reviewer (S.-C.L.), using an extraction form piloted on three eligible studies. Key study characteristics, including the country of origin, setting, sample data, participant characteristics, intervention vs. control, outcomes, and measurement tools, were extracted. For this study, home and community PC was defined as any type of the availability of palliative home care services, 24-h on-call service, or a 24-h outreach pediatric PC team.

If the intervention effects were completely reported, pooled effect estimate (e.g., odds ratio and 95% confidence intervals) would be calculated using the random effects model in RevMan 5.4.1 where possible. Fisher's method for combining $p$-values or vote counting based on the direction of effects was used if there was minimal reporting of the data beyond $p$-values and the direction of effect, or the type of effect measure varied across the studies (McKenzie and Brennan, 2019).

## Results

### Study selection

A total of 6,461 studies were identified through electronic database searches, and seven studies were identified through reference lists. After duplicates were removed, title/abstract screening, and full-text screening, 15 studies met the eligibility criteria. A detailed illustration of the study selection process is presented in Figure 1.

### Risk of bias

The critical appraisal scores ranged between 45% and 95%. Seven of the 15 studies were judged to be of strong quality (Thienprayoon et al., 2013; Smith et al., 2015; Ullrich et al., 2016; Fraser et al., 2018; Widger et al., 2018; Revon-Rivière et al., 2019; Spraker-Perlman et al., 2019) (Tables 2 and 3).
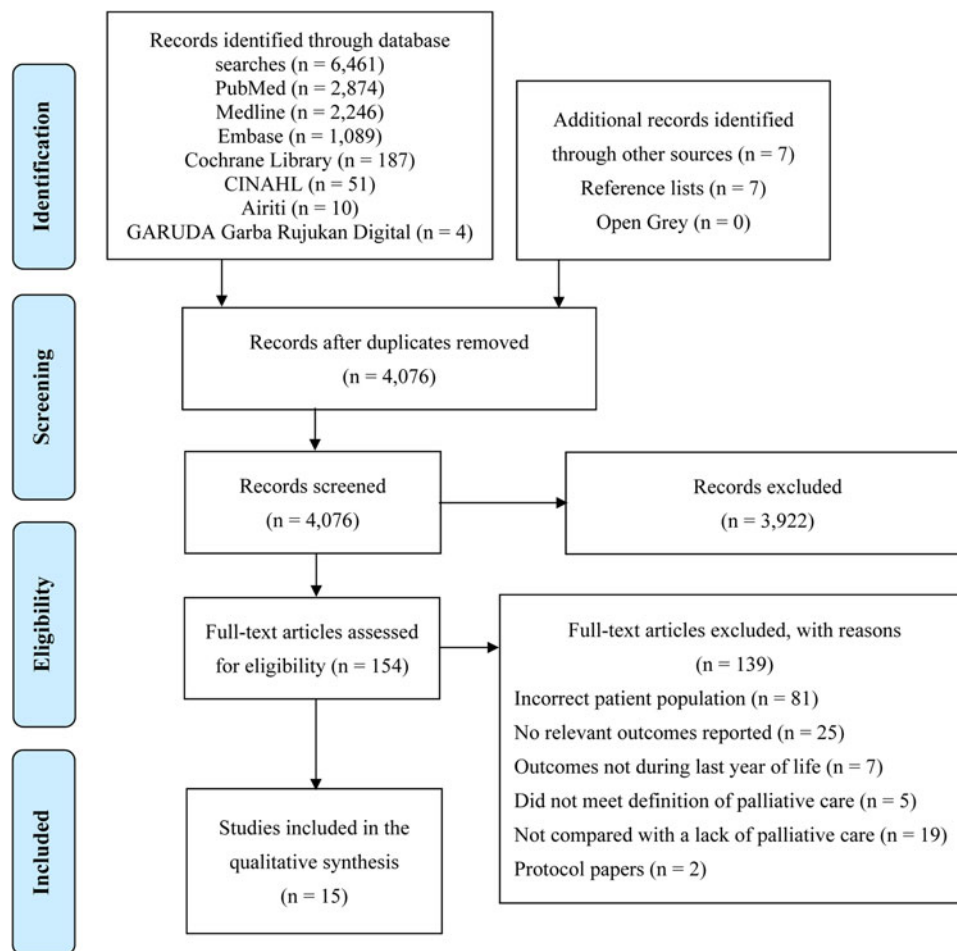
**Fig. 1.** PRISMA flow diagram.

### Study characteristics

Characteristics of the included studies are presented in Table 1. Of the 15 studies, nine were conducted in the USA, and one each was conducted in Canada, France, Germany, New Zealand, Singapore, and the UK. The studies were published from 2013 to 2019 as cohort studies ($n = 14$) and case series ($n = 1$).

### Participant characteristics

The study samples ranged from 60 to 24,342 for a total of 36,148 subjects. All studies considered both boys and girls. Subject aged from seven of the 15 studies ranged from 0 to 4 years old (67.7%), 5 to 14 years old (19.0%), and 15 to 25 years old (13.3%) (Chang et al., 2013; Keele et al., 2013; Snaman et al., 2017; Fraser et al., 2018; Widger et al., 2018; Revon-Rivière et al., 2019; Spraker-Perlman et al., 2019). Diagnoses of the subjects included neonatology/chromosome disorder (27.6%), respiratory disease (15.1%), hematology/oncology disease (15.4%), cardiology/circulatory disease (12.6%), neurological disease (8.1%), gastrointestinal/liver disease (5.4%), immunology/infectious disease (4.4%), trauma, and other (11.4%).

### Intervention/control characteristics

Eleven studies reported that PC was implemented in an inpatient hospital setting (Chang et al., 2013; Keele et al., 2013; Smith et al.,

2015; Vern-Gross et al., 2015; Osenga et al., 2016; Ullrich et al., 2016; Snaman et al., 2017; Fraser et al., 2018; Widger et al., 2018; Revon-Rivière et al., 2019; Spraker-Perlman et al., 2019); two studies implemented services in an inpatient hospice setting (Thienprayoon et al., 2013; Fraser et al., 2018), and 11 studies implemented services in home and community settings (Chang et al., 2013; Thienprayoon et al., 2013; Friedrichsdorf et al., 2015; Vern-Gross et al., 2015; Osenga et al., 2016; Ullrich et al., 2016; Chong et al., 2018; Fraser et al., 2018; Widger et al., 2018; Revon-Rivière et al., 2019; Zernikow et al., 2019). The control groups in all studies included subjects with either no PC team involvement or no active PC orders.

### Outcome characteristics

Data on demographics, hospital admission, LoS, CPR at the time of death, PoD, and intensity of EoL care were extracted from national databases, regional databases, medical records, and surveys. Significance was defined as $p < 0.05$.

### Number of admissions in acute care beds

The combination of $p$-values in three studies suggests that there was strong effect of PC in reducing the number of hospital admissions in at least one study ($p < 0.001$) (Chong et al., 2018; Revon-Rivière et al., 2019; Zernikow et al., 2019). Children and adolescents aged < 18 who received home-based PC had fewer

**Table 1.** Baseline characteristics of the included studies (*n* = 15)

| Author, year, country | Design | Data source, year of data[a] | Patient population[a] | How were life-limiting conditions assessed? | How were PC services identified? | Intervention, comparison, and delivery details | PC outcomes |
|---|---|---|---|---|---|---|---|
| Chang et al., 2013, New Zealand | Retrospective case series | Mortality records, 2006–2009 | PC *n* = 106; no PC *n* = 388 Aged 28 days–18 years included. 51.0% males Died from a life-limiting illness | ICD-10 codes C00-D48, D60-64, D80-89, E70-84, E88, G00-99, I42, J40-47, J80-84, J96.1, N18, Q00-99, P27, P91 | Records of a National Health Index number | Intervention: inpatient hospital, home, and community PC provided face-to-face services by a multidisciplinary team. PC provided advice to other healthcare services nationally. Comparison: no PC | PoD |
| Chong et al., 2018, Singapore | RCoh and single-group prospective cohort | Database of a nation-wide PPC program, 2012–2015 | PC *n* = 79; no PC *n* = 67 Mean age 9.3 years Aged <19 at diagnosis included No neonatal cases 62.3% males Life-limiting conditions Died in hospital | Verified by two physicians based on four criteria from Together for Short Lives | Record of enrollment in a specialist home-based PC service | Intervention: specialist home and community PC provided face-to-face services and 24/7 helpline support by a multidisciplinary team, with standardized referral criteria Extent of education/training of external professionals provided Comparison: no PC. | Number of hospital admissions, LoS, number of emergency room visits, healthcare expenditure, advance care planning discussions, patient's quality of life, caregiver burden |
| Fraser et al., 2018, U K | RCoh | PICU audit network dataset; death records, 2004–2014 | PC *n* = 566; no PC = 7,080 Aged 0–16+ included. Admitted to a PICU. 54.8% males | Any cause of death | Record of "discharge for palliative care" | Intervention: discharge for any PC area, including inpatient hospital, inpatient hospice, home, or community PC Comparison: had not been discharged for PC | Proportion of admissions to PICUs, LoS PICU, PICU death, survival in the year after PICU discharge |
| Friedrichsdorf et al., 2015, USA | RCoh | Survey for bereaved parents; medical records at one hospital; 2002–2008 | PC *n* = 30; no PC *n* = 30 Mean age 10.1 years 55% males Died of cancer at a tertiary pediatric institution | Cancer diagnosis, including leukemia, lymphoma, brain tumor, and other solid tumors | Not reported | Intervention: h-based PC provided face-to-face services by a multidisciplinary team. 24/7 for home visits was available. School visits and bereavement support were provided. Comparison: nexposure to the PPC program | Prevalence of distressing symptoms, level of suffering from symptoms, treatment success of symptoms, patient's quality of life, PoD, preferred PoD |
| Keele et al., 2013, USA | RCoh | Health information system database developed by hospital association; 2001–2004 and 2009–2011 | PC *n* = 919; no PC *n* = 23,423 Aged <18 included 54.9% males Hospitalized ≥5 days before inpatient death | Any cause of death. | ICD-10 code V66.7 | Intervention: inpatient hospital PC provided services by a multidisciplinary team. Comparison: no PC. | Medication use, procedures performed, PoD, proportion of ICU death, proportion of admissions to ICUs |

**Table 1.** (*Continued.*)

| Author, year, country | Design | Data source, year of data[a] | Patient population[a] | How were life-limiting conditions assessed? | How were PC services identified? | Intervention, comparison, and delivery details | PC outcomes |
|---|---|---|---|---|---|---|---|
| Osenga et al., 2016, USA | RCoh | Medical records at one hospital, 2012–2013 | PC n = 28; no PC n = 86 Mean age 2.8 years Aged 0–18 included 54.4% males Hospitalized ≥24 h before death | Any cause of death | Not reported | Intervention: inpatient hospital, outpatient clinic, home, and community PC provided face-to-face services by a multidisciplinary team, with standardized referral criteria. 24/7 physician and advanced practice nurse consults are available. Comparison: no PPC team involvement. | Diagnostic/ monitoring procedures, presence of DNR order, CPR, psychosocial and spiritual support, symptom prevalence, medication use, use of life support, and withdrawal of life support |
| Revon-Rivière et al., 2019, France | RCoh | National hospital database, 2014–2016 | PC n = 1,308; no PC n = 591 Aged 0–25 included 56.5% males Died from cancer-related causes Died in hospital | Cancer diagnosis, including brain tumor, hematological malignancies, and solid tumor | Authorization of palliative unit, bed care, or ICD-10 codes for PC (Z515 for acute care; 2303A01, 2303B1, 2303C1 for rehabilitation; MPP 04 for hospital-at-home) during the last 30 days of life | Intervention: inpatient hospital, home, and community PC provided face-to-face services by a multidisciplinary team Comparison: no PC | Presence of chemotherapy use, admissions to ICUs, >1 emergency room visit, >1 admission to acute care unit, use of life support, provision of HI-EoL, and/or most-invasive EoL care |
| Smith et al., 2015, USA | RCoh | Institutional administrative databases; medical records at one hospital; 2010 | PC n = 22; no PC n = 41 Age 0–16+ included High-cost inpatients | Any cause of death | Records from PPC team | Intervention: inpatient hospital PPC consultation provided face-to-face services by a multidisciplinary team, without standardized referral criteria Goals of care discussion, advance care planning, and symptom management were provided Comparison: no PPC consultation | Inpatient cost, hospital LoS, admissions to hospital, and ICUs |
| Snaman et al., 2017, USA | RCoh | Medical records at one hospital, 2008–2014 | PC n = 50; no PC n = 19 Mean age 17.3 years (range 14.7–25.2) 65% males Oncology patients Died in hospital | Any cause of death | Not reported | Intervention: inpatient hospital PC consultation and/or referral to hospice Comparison: no PC involvement | Presence and timing of DNR order, medication use, invasive procedures, prevalence of symptoms, chemotherapy use, use of life support, and PoD |

| Spraker-Perlman et al., 2019, USA | RCoh | Medical records at one hospital, 2012–2015 | PC n = 34, no PC n = 133 Aged 0–25 included 58.7% males Died during an inpatient stay (>48 h) at an academic pediatric hospital No known ICD-9 codes of complex chronic conditions at the time of final admission | Any cause of death | Records of PPC team consultation notes | Intervention: iinpatient hospital PC provided face-to-face services, PPC team consultation, and EoL planning by a multidisciplinary team, with standardized referral criteria Comparison: did not receive a PPC consultation | Hospital LoS, presence of care conference notes, presence and timing of EoL discussion and DNR order, and PoD |
|---|---|---|---|---|---|---|---|
| Thienprayoon et al., 2013, USA | RCoh | Cancer registry and neuro-oncology databases developed by a community oncology and hematology practice; databases of two hospice organizations, 2006–2010 | Hospice n = 95; no hospice n = 19 Aged 0–18 included 52% males Diagnosed with cancer or underwent bone marrow transplantation and died | Death related to cancer or complications of cancer treatment | Known enrollment in hospice to time of death | Intervention: enrollment in hospice, and having received inpatient hospice unit and/or outpatient home-based services Comparison: never enrolled in hospice | PoD |
| Ullrich et al., 2016, USA | RCoh | Medical records at one hospital, 2004–2012 | PC n = 37; no PC n = 110 Mean age 10.3 years 51.7% males Underwent stem cell transplantation and died | Any cause of death | Consult note included: "goals of care," "decision-making/ advanced care planning," "symptom management," and "support for the child and family, including psychosocial and spiritual support, home services, and quality of life." | Intervention: inpatient hospital, outpatient, and home PC provided face-to-face services by a multidisciplinary team, with standardized referral criteria Comparison: no PC. | Presence and timing of documented prognosis and resuscitation discussion, use of life support, hospice involved, and PoD |
| Vern-Gross et al., 2015, USA | Cross-sectional RCoh | Medical records at one hospital, 2001–2005 and 2007–2012 | PC n = 57; no PC n = 134 Aged <21 included 56% males Patients with advanced solid tumor malignancies | Any cause of death | Known enrollment in PC service to time of death | Intervention: institutional quality of life/PC program provided inpatient hospital, outpatient, home and community PC face-to-face services by a multidisciplinary team, with standardized referral criteria Hospice support services, EoL consultation, and bereavement support were provided. Comparison: did not implement quality of life/PC program. | Timing of EoL and DNR discussions, hospice enrollment, preferred PoD, presence of documented sibling counseling, bereavement support, and PoD |

*(Continued)*

**Table 1.** (Continued.)

| Author, year, country | Design | Data source, year of data[a] | Patient population[a] | How were life-limiting conditions assessed? | How were PC services identified? | Intervention, comparison, and delivery details | PC outcomes |
|---|---|---|---|---|---|---|---|
| Widger et al., 2018, Canada | RCoh | National administrative data; provincial childhood cancer registry; databases of three medical centers, 2000–2012 | SPPC n = 166; general PC n = 100; no PC n = 306. Aged 0–18 included. 57.2% males. Diagnosed with a primary cancer at <15 years of age, and subsequently died at age of ≦18 years | Cancer diagnosis. Died within 5 years of the latest pediatric cancer event | SPPC: known record in the SPPC database. General PC: known ≧2 billing or diagnosis codes reported by the physician | Intervention: hospital-based specialist PPC or general PC provided face-to-face service by a multidisciplinary team with standardized referral criteria Comparison: no PC | Presence of chemotherapy use, >1 hospitalization, >1 emergency room visit, number of ICU admissions, provision of HI-EoL care, use of life support, hospital death, and level of PC accessed |
| Zernikow et al., 2019, Germany | Repeated cross-sectional cohort | Survey for bereaved parents from six pediatric oncology departments in 2005, 16 departments in 2010, and 13 departments in 2015 | SPPC n = 64; no SPPC n = 60. Mean age 9.9 years. 71.8% males. Patients who died due to cancer | Any cause of death | Parents' reports of enrollment in SPPC | Intervention: specialist pediatric palliative home care provided face-to-face service by a physician and a nurse. Comparison: no specialist pediatric palliative home care | Proportion of symptoms and treatment of symptoms, quality of care, hospital stay in EoL, and PoD |

HI-EoL: high-intensity end-of-life care; PC: palliative care; PoD: place of death; PPC: pediatric palliative care; RCoh: retrospective cohort; SPPC: specialist pediatric palliative care.
[a]Information on the relevant data source, year of data, and sample included in the review.

hospital admissions during their last year of life, but no differences were found in the number of emergency visits (Chong et al., 2018). Studies also varied in terms of whether or not they found differences in the number of hospital admissions in the last month of life for children, adolescents, and young adults with cancer (Revon-Rivière et al., 2019; Zernikow et al., 2019) (Tables 2 and 3).

A consistent finding across studies was that children, adolescents, and young adults who received inpatient hospital PC, either with or without the provision of home and community PC, were less likely to be admitted to the ICU (Keele et al., 2013; Widger et al., 2018; Revon-Rivière et al., 2019). Among children, adolescents, and young adults who died for any reason, those who received PC had a 71% reduction in risk of ICU admission (Keele et al., 2013); for those who died with cancer, receiving PC was associated with a 6.25-fold decrease in the odds of ICU admission (OR, 0.16; 95% CI 0.13–0.20) (Widger et al., 2018; Revon-Rivière et al., 2019). If those who died due to treatment-related causes (e.g., acute toxicities) were excluded, there was a 3.33-fold decrease in the odds of ICU admission during the last month of life. However, general PC had no impact (Widger et al., 2018). These results are presented in Table 4.

## Length of hospital stay

The combination of $p$-values in five studies suggests that there was an effect in reducing the LoS in the EoL in at least one study ($p = 0.011$, five studies) (Keele et al., 2013; Smith et al., 2015; Osenga et al., 2016; Chong et al., 2018; Spraker-Perlman et al., 2019). Even an analysis restricted to studies where during intervention, only inpatient hospital PC was delivered, suggested an increased likelihood of shorter LoS in the PC group in at least one study ($p = 0.0167$, three studies) (Keele et al., 2013; Smith et al., 2015; Spraker-Perlman et al., 2019) (Table 5).

However, of the five studies examining LoS, in two of them, no differences in terms of cumulative LoS were observed in the last admission, last month, or last year of life [40% (95% CI 5–85%), $p = 1.625$] (Keele et al., 2013; Chong et al., 2018). Only one study excluded those who were hospitalized <5 days before death (Keele et al., 2013). Four of five studies did not exclude patients who died quickly after hospital admission, which may have created bias since those who received PC were more likely to have complex, critical illnesses with longer disease trajectories; on the contrary, those with short LoS or unexpected death usually lacked access to PC (Keele et al., 2013; Osenga et al., 2016). Therefore, the association between PC and LoS tended to be biased.

## CPR at the time of death

Of the three studies examining CPR at the time of death, all but one showed that patients who underwent hematopoietic stem cell transplants were less likely to undergo CPR at the EoL ($p = 0.03$) (Ullrich et al., 2016). However, studies on infants, or adolescents, and young adults, with a median age of 1.3 months and 17.3 years, respectively, found no difference in terms of CPR attempted at the time of death (Osenga et al., 2016; Snaman et al., 2017). Even though two of the three studies did find the median resuscitation discussion to be 5 days earlier ($p < 0.001$) or increased do-not-resuscitate (DNR) orders in place in patients followed by a PC team (AOR = 7.92, 95% CI 2.02–31.12) (Osenga et al., 2016; Ullrich et al., 2016). This result is presented in Table 6.

**Table 2.** Critical appraisal results of eligible studies using the JBI critical appraisal checklist for cohort studies (*n* = 14)

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chong et al., 2018 | N | Y | Y | Y | N | Y | Y | U | U | U | U | 14/22 = 64% (adequate) |
| Fraser et al., 2018 | Y | Y | Y | Y | Y | Y | Y | U | Y | N/A | Y | 19/20 = 95% (strong) |
| Friedrichsdorf et al., 2015 | N | Y | U | Y | N | Y | Y | U | N | N | N | 10/22 = 45% (limited) |
| Keele et al., 2013 | N | Y | Y | Y | N | Y | Y | U | Y | N/A | N | 13/20 = 65% (adequate) |
| Osenga et al., 2016 | N | Y | U | Y | Y | Y | Y | U | Y | N/A | Y | 16/20 = 80% (good) |
| Revon-Rivière et al., 2019 | U | Y | Y | Y | Y | Y | Y | U | U | U | Y | 18/22 = 82% (strong) |
| Smith et al., 2015 | N | Y | Y | Y | Y | Y | Y | U | Y | N/A | Y | 17/20 = 85% (strong) |
| Snaman et al., 2017 | U | Y | U | Y | N | Y | Y | U | U | U | Y | 15/22 = 68% (adequate) |
| Spraker-Perlman et al., 2019 | Y | Y | Y | Y | N | Y | Y | U | Y | N/A | Y | 17/20 = 85% (strong) |
| Thienprayoon et al., 2013 | Y | Y | Y | Y | N | Y | Y | U | Y | N/A | Y | 17/20 = 85% (strong) |
| Ullrich et al., 2016 | Y | Y | Y | Y | N | Y | Y | Y | U | U | Y | 18/22 = 82% (strong) |
| Vern-Gross et al., 2015 | N | Y | Y | Y | N | Y | Y | U | U | U | Y | 15/22 = 68% (adequate) |
| Widger et al., 2018 | U | Y | Y | Y | Y | Y | Y | U | Y | N/A | Y | 18/20 = 90% (strong) |
| Zernikow et al., 2019 | U | Y | Y | N | N | Y | Y | U | U | U | N | 12/22 = 55% (adequate) |

Y, yes; U, unclear; N, no; N/A, not applicable.
Y=2; U=1; *N* = 0 points
Q1= Were the two groups similar and recruited from the same population?
Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3 = Was the exposure measured in a valid and reliable way?
Q4 = Were confounding factors identified?
Q5 = Were strategies to deal with confounding factors stated?
Q6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7 = Were the outcomes measured in a valid and reliable way?
Q8 = Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
Q9 = Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
Q10 = Were strategies to address incomplete follow-up utilized?
Q11 = Was appropriate statistical analysis used?

**Table 3.** Critical appraisal results of eligible studies using the JBI critical appraisal checklist for case series (*n* = 1)

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chang et al., 2013 | N | Y | N | Y | Y | Y | Y | Y | Y | Y | 16/20 = 80% (good) |

Y, yes; U, unclear; N, no
Y=2; U=1; *N* = 0 points
JBI critical appraisal checklist for case series:
Q1 = Were there clear criteria for inclusion in the case series?
Q2 = Was the condition measured in a standard, reliable way for all participants included in the case series?
Q3 = Were valid methods used for the identification of the condition for all participants included in the case series?
Q4 = Did the case series have consecutive inclusion of participants?
Q5 = Did the case series have complete inclusion of participants?
Q6 = Was there clear reporting of the demographics of the participants in the study? Q7 = Was there clear reporting of clinical information of the participants?
Q8 = Were the outcomes or follow-up results of cases clearly reported?
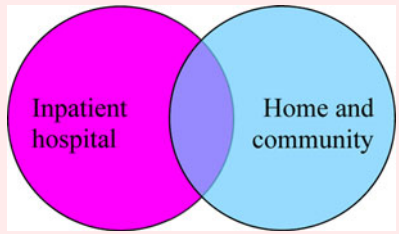Q9 = Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
Q10 = Was statistical analysis appropriate?

## Place of death

Even though PC was accessible in inpatient, home, and community settings, the examined studies varied in terms of whether the patients in the PC group were less likely to die in a medical setting (i.e., hospital and ICU), or more likely to die in the community (i.e., home, hospice, and home hospital services). Four of six studies indicated that the PC group had a smaller proportion of deaths in a medical setting [67% (95% CI 22–96%), *p* = 0.7] (Chang et al., 2013; Thienprayoon et al., 2013; Fraser et al., 2018; Widger et al., 2018); four of six studies showed PC to lead to a greater proportion of deaths in the community [67% (95% CI 22–96%), *p* = 0.7] (Thienprayoon et al., 2013; Friedrichsdorf et al., 2015; Fraser et al., 2018; Zernikow et al., 2019) (Table 7). In the case of children in the PICU, those who died after receiving PC at discharge who had either transferred hospitals or had moved into the community had an 8.06 times greater chance of not dying in a medical setting compared with those who were not discharged for PC (Fraser et al., 2018). However, if restricted to cancer patients, the possibility of dying in the hospital was comparable regardless of whether there was PC in inpatient, home, and community settings (Thienprayoon et al., 2013; Vern-Gross et al., 2015; Ullrich et al., 2016; Widger et al., 2018). Although home hospital services were accessible, and EoL discussions occurred earlier (median time from first discussion to death was 204 days earlier), there was no significant decrease in

**Table 4.** Description of the included papers comparing number of admissions in acute care beds for people with PC involvement vs. those without it (n = 5)



| Study | Outcome |
|---|---|
| *Hospital admission* | |
| Chong et al. | *Last year of life*: PC < no PC [mean (SD) 4.47(4.58) vs. 6.93(5.51), *p* < 0.004] |
| Revon-Rivière et al. | *Last month of life*: PC = no PC (OR = 1.40, 95% CI 0.99–1.99, *p* = 0.057) |
| Zernikow et al. | *Last month of life*: PC < no PC ( *p* < 0.001) *Proportion of patients stayed in the hospital*: PC < no PC (39.7% vs. 84.5%, *p* < 0.001) |
| *ER admission* | |
| Chong et al. | *Last year of life*: PC = no PC [mean (SD) 1.99(2.87) vs.1.81(2.23), *p* = 0.7] |
| *ICU admission* | |
| Keele et al. | *During the final hospital admission*: PC < no PC (OR = 0.04, 95% CI 0.03–0.05) |
| Revon-Rivière et al. | *Last month of life*: PC < no PC (OR = 0.16, 95% CI 0.13–0.21, *p* < 0.001) |
| Widger et al.[a] | *Last month of life*: PC < no PC (OR = 0.2, 95% CI 0.1–0.4, *p* < 0.001) |
| Subtotal[b] ($I^2$ = 98%, *p* < 0.001) | PC < no PC (OR = 0.11, 95% CI 0.04–0.32) |

CI, confidence interval; OR, odds ratio; PC, palliative care.
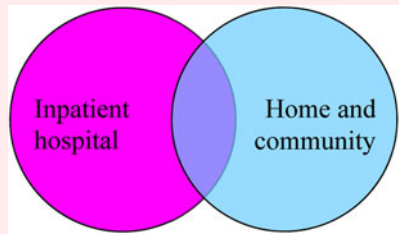Shading depicts the PC model.
[a]Data on the sample with all cause of death.
[b]Random-effects meta-analysis on the association between PC and the number of admissions in the ICU.

**Table 5.** Description of the included papers comparing length of hospital stay for people with palliative care involvement vs. those without it (n = 5)



| Study | Outcome |
|---|---|
| *Final admission (days)* | |
| Keele et al. | PC < no PC [median(IQR) 17(9/36) vs. 21(10/47), *p* < 0.001] |
| Osenga et al. | PC > no PC [mean(SD) 53.6(91.2) vs. 15.6(34.4), *p* = 0.002] |
| Spraker-Perlman et al. | PC = no PC (majority 21+ vs. 2–6, *p* = 0.16) |
| *During the year of death (days)* | |
| Smith et al. | PC = no PC [median(IQR) 36.8(18.7/64.3) vs. 22.4(14.3/55), *p* = 0.121] |
| *Last year of life (days)* | |
| Chong et al. | PC < no PC [mean(SD) 40.79(50.97) vs. 93.1(77.38), *p* < 0.05] |

IQR, interquartile range; PC, palliative care; SD, standard deviation.
Shading depicts the PC model.
[a]Data on the sample with all cause of death.

### Intensity of EoL care

Two studies reported results based on the intensity of EoL care summary scores (Widger et al., 2018; Revon-Rivière et al., 2019) (Table 8). Both defined high-intensity EoL care (HI-EoL) as the occurrence of at least one of the following four indicators: intra-hospital intravenous chemotherapy <14 days prior to death, ≥1 ICU admission, >1 emergency room visit, or >1 hospital admission in the last month of life. General PC was associated with a 1.67-fold decrease in the odds of HI-EoL (Widger et al., 2018), whereas specialist inpatient hospital PC, either with or without the provision of home and community PC, was associated with a 3.57-fold decrease in the odds of HI-EoL care during the last month of life for children aged 0–25 who died as a result of cancer (OR, 0.28; 95% CI 0.20–0.40) (Widger et al., 2018; Revon-Rivière et al., 2019). However, if those who died due to treatment-related causes were included, general PC alone was not associated with a lower intensity of the EoL care. These patients were more likely to have had hematologic malignancies and were significantly less likely to have accessed specialist PC services (Widger et al., 2018).

### Discussion

This review examined the impact of PC on EoL care and PoD in children, adolescents, and young adults with life-limiting conditions based on different models of care. The results demonstrated that those who receive PC are less likely to be admitted to ICUs,

inpatient deaths after the implementation of PC (Vern-Gross et al., 2015). However, if the intervention included the delivery of hospice care, PC was associated with being more likely to die at home (Thienprayoon et al., 2013; Fraser et al., 2018).

In at least one study, there was strong evidence suggesting that PC in reduces the proportion of ICU deaths in all hospital deaths ( *p* = 0.0017, two studies) (Ullrich et al., 2016; Snaman et al., 2017). Both with and without the delivery of inpatient hospice, home, and community PC, all four studies showed that inpatient hospital PC decreased the proportion of patients dying in an ICU (Keele et al., 2013; Ullrich et al., 2016; Snaman et al., 2017; Fraser et al., 2018). Furthermore, Ullrich et al. (2016) reported that there were no differences in receiving less or more than 1 month of PC before death in a cure-oriented stem cell transplantation setting.

**Table 6.** Description of the included papers comparing CPR at the time of death for people with PC involvement vs. those without it (n = 3)

| Study | Outcome | | | | |
|---|---|---|---|---|---|
| | Comparison | PC | No PC | *p*-value | Odds ratio (95% CI) |
| Inpatient hospital | | | | | |
|   Snaman et al. | PC = no PC | 8% | 21% | 0.203 | |
| Inpatient hospital, home, and community | | | | | |
|   Osenga et al. | PC = no PC | 25.0% | 30.2% | | 0.77 (0.29–2.03) |
|   Ullrich et al. | PC < no PC | 3% | 20% | 0.03 | |
| PC ≥1 month vs. PC <1 month | | | | | |
|   Ullrich et al. | PC = no PC | 0% | 5% | 1.0 | |

CI: confidence interval; PC: palliative care.

are less likely to receive HI-EoL care, and are less likely to die in ICUs. However, there was less evidence of effects of PC on LoS in the EoL, receiving CPR at the time of death, and the proportion of hospital and home deaths. Several possible explanations exist, including the fact that the symptom burden may be better managed in a medical setting than in the community during EoL (Clark et al., 2016; Zernikow et al., 2019) or that access to PC may have an impact on decisions to receive less intervention-focused care aimed at extending life (e.g., ICU care) but not on medical care during the EoL. This also suggests that intensivists and those providing acute care need to incorporate effective PC communication skills and improve team cohesiveness with the primary clinical team and specialist PC team (Richards et al., 2018).

Regarding the circumstances of death, mixed results were observed for the impact of CPR attempts at the time of death in the PC group. There was a lack of homogeneity across these studies in terms of the ages and diagnoses included in the samples, model of care, and the time between PC involvement and death. Although all studies indicated finding PC to have benefits in terms of promoting DNR orders in place (Osenga et al., 2016; Ullrich et al., 2016; Snaman et al., 2017), its impact on reductions in the number of pediatric patients undergoing CPR at the time of death at the request of the patient and/or caregiver showed little consensus. Comparable to previous studies (Mack et al., 2015; Johnston et al., 2017), studies in this review revealed that studies on toddlers, as well as adolescents and young adults with cancer, indicated that PC has little impact on reducing the number of cases with CPR attempts at the time of death (Osenga et al., 2016; Snaman et al., 2017). Several possible explanations exist, including the fact that adolescents and young adults have better competency related to expressing their desire to accept invasive treatments out of a desire to sustain their lives (Hinds et al., 2005). In goals of care and level of hope in patients receiving stem cell transplants may differ from those with complex chronic conditions, which has implications for EoL care decision-making.

Although previous studies have shown that an increase in home-based PC resources may reflect an increase in home deaths (Webber et al., 2019; Håkanson et al., 2017), the impact of inpatient, home, and community PC on increasing the number of home deaths is inconsistent in this review. However, studies where the intervention included the delivery of hospice care reported PC to be associated with being more likely to die at home as compared with no PC (Thienprayoon et al., 2013; Fraser et al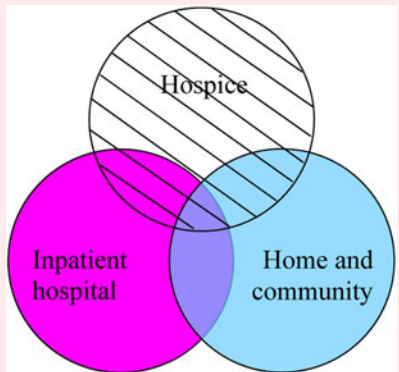., 2018). Complex symptoms may be better dealt with in hospitals or hospices than would be the case at home. The differences in the impact of PC on PoD may also related to the distance from a tertiary center (Kassam et al., 2017), different health system infrastructures, policies, socio-economic conditions (Håkanson et al., 2017), and cultural differences.
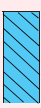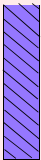
## Limitations of the included studies

Although this study adds to the literature through a systematic review intended to provide evidence for the association of PC with five important outcomes, the results should be interpreted cautiously given the lack of experimental evidence and the heavily reliance on unadjusted estimates based on observational studies. In 11 studies, there were concerns about the clarity of the inclusion and exclusion criteria or about similarities in the characteristics of the two groups under consideration (Chang et al., 2013; Keele et al., 2013; Friedrichsdorf et al., 2015; Smith et al., 2015; Vern-Gross et al., 2015; Osenga et al., 2016; Snaman et al., 2017; Chong et al., 2018; Widger et al., 2018; Revon-Rivière et al., 2019; Zernikow et al., 2019). Of the 14 cohort studies, outcomes were adjusted for demographic and clinical variables in the analyses in only five of them (Smith et al., 2015; Osenga et al., 2016; Fraser et al., 2018; Widger et al., 2018; Revon-Rivière et al., 2019). Possible confounding by family preference was not controlled for in any of the included studies. The duration of time from receiving PC to death was stated in only one study (Ullrich et al., 2016); therefore, there were concerns as to whether the follow-up time of the PC involvement in the intervention group was sufficiently long enough for outcomes to occur. This review was unable to reveal differences in the impact of PC among children, adolescents, and young adults referred to PC based on whether it occurred early and late in their illness trajectory.

There were concerns about the representativeness of samples. Subjects in seven of the 15 studies (46.7%) comprised only patients who had been hospitalized and died in hospital in order to collect accurate EoL care data (Keele et al., 2013; Osenga et al., 2016; Ullrich et al., 2016; Snaman et al., 2017; Chong et al., 2018; Revon-Rivière et al., 2019; Spraker-Perlman et al., 2019). Subjects in seven of the 15 studies (46.7%) used a single-site design (Friedrichsdorf et al., 2015; Smith et al., 2015; Vern-Gross et al., 2015; Osenga et al., 2016; Ullrich et al., 2016; Snaman et al., 2017; Spraker-Perlman et al., 2019). The primary diagnoses of the subjects varied, with the majority having

**Table 7.** Description of the included papers comparing *place of death* for people with PC involvement vs. those without it (*n* = 10)



| Place of death | PC model | Study | Results |
|---|---|---|---|
| ICU (proportion of all hospital death) | | Keele et al. | PC < no PC (60% vs. 88%, RR = 0.67; 95% CI 0.64–0.72) |
| | | Snaman et al. | PC < no PC (38% vs. 68%, *p* = 0.024) |
| | | Ullrich et al. | PC < no PC (58% vs. 80%, *p* = 0.03) |
| Hospital | | Chang et al. | PC < no PC (40.6% vs. 59.4%, *p* = 0.003; AOR = 0.60, 95% CI 0.38–0.96, *p* = 0.03) |
| | | Widger et al. | General PC = no PC (OR = 0.7; 95% CI 0.4–1.3, *p* = 0.26) SPPC < no PC (OR = 0.3; 95% CI 0.2–0.4, *p* < 0.001) |
| Home (proportion of all deaths) | | Friedrichsdorf et al. | PC > no PC (93% vs. 20%, *p* < 0.001) |
| | | Zernikow et al. | PC > no PC (78.1% vs. 19.0%, *p* < 0.005) |
| Home (proportion of all home and hospital deaths) | | Ullrich et al. | Home: PC = no PC (16% vs. 23%, *p* = 0.5) |
| Home vs. hospital (non-ICU) vs. ICU vs. other | | Ullrich et al. | Home: PC (16%), no PC (23%) Hospital: PC (35%), no PC (15%) ICU: PC (49%), no PC (62%) (*p* = 0.06) |
| | | Thienprayoon et al. | Home: PC (61%), no PC (0%) Hospital: PC (15%), no PC (47%) ICU: PC (5%), no PC (47%) (*p* < 0.001) |
| Home vs. hospital (non-ICU) vs. ICU vs. hospice vs. other vs. unknown | | Fraser et al. | Home: PC (23%), no PC (16%) Hospital: PC (29.5%), no PC (41.9%) ICU: PC (6.9%), no PC (34.8%) Hospice: PC (38.7%), no PC (6.3%) ($\chi^2$ = 797.2, *p* < 0.001) |
| Home vs. home hospital vs. inpatient vs. other vs. unknown | | Vern-Gross et al. | Home: PC (56%), no PC (54%) Home hospital: PC (9%), no PC (18%) Inpatient: PC (28%), no PC (13%) (*p* = 0.06) |

CI, confidence interval; OR, odds ratio; PC, palliative care; RR, relative risk.
Shading depicts the PC model.

neonatology/chromosome disorders, respiratory diseases, and hematology/oncology diseases. The distribution of diagnosis among the groups of subjects may have been different from the general pediatric population in different locations. There was a concentration of studies from the USA. Although studies involving Chinese and Bahasa populations were included, and Chinese and Indonesian databases were searched, no studies conducted using these languages were found. EoL care reflects child and family preferences, which is highly relationship-based (Hinds et al., 2005) and culturally related. Therefore, more population-based cohort studies assessing the impact of PC are needed in non-Western countries.

### Strengths and limitations of the review

This was the first systematic review to demonstrate the impact of PC on EoL care and PoD in children, adolescents, and young adults with life-limiting conditions. Since this review focused on studies published from 2010 to 2020, this increased the homogeneity of the progress of curative treatments and the recognition of the need for PC in the pediatric population. Only studies comparing those who actually received and did not receive PC were included, as opposed to comparing those with and without access to such services. This ensured that all subjects in the intervention groupf did receive PC. No included studies compared groups using a before–after design. This decreased the potential impact on the EoL care outcomes due to the progression of the illness. This review was not restricted to a specific PC model in order to allow a comparison of impacts across different components of intervention while also limiting the outcome of hospital admission and LoS to the last year of life. This widened the scope of the included studies and enriched the data synthesis, but the outcome may not be generalizable to a population at the early diagnosis stage.

Outcomes in this review may have been influenced by differences in the characteristics of the intervention and control groups. Patients who died due to any cause were considered as being in life-limiting conditions and were included in this review. For those who had better prognoses and received a significant amount of intensive care, but subsequently died with iatrogenic complications, caregivers and healthcare providers may have been less aware of the availability of specialist PC resources, or patients and caregivers may have been less likely to be referred for such care (Ullrich et al., 2016; Widger et al., 2018). These groups may have increased ICU admissions, HI-EoL, been denied PC team involvement, or died in the hospital, which led to a concern related to possible referral bias.

### Implications for clinical practice and research

Our results provide insights into PC resource allocation throughout the last year of life. To the best of our knowledge, there were

**Table 8.** Description of the included papers comparing composite high-intensity EoL care indicator for people with PC involvement vs. those without it (n = 2)

| Study | Outcome | |
| --- | --- | --- |
| | Restricted to cancer-related death | All causes of death |
| *Inpatient hospital* | | |
| Revon-Rivière et al. | PC < no PC (OR = 0.31, 95% CI 0.24–0.41, p < 0.001) | |
| *Inpatient hospital, home, and community* | | |
| Widger et al.[a] | PC < no PC (OR = 0.2, 95% CI 0.2–0.4, p < 0.001) | PC < no PC (OR = 0.2, 95% CI 0.1–0.3, p < 0.001) |
| Subtotal[b] ($I^2$ = 24%, p = 0.25) | PC < no PC (OR = 0.28, 95% CI 0.20–0.40, p < 0.0001) | |
| *General PC* | | |
| Widger et al.[a] | PC < no PC (OR = 0.6, 95% CI 0.4–0.9, p = 0.01) | PC = no PC (OR = 0.7, 95% CI 0.4–1.4, p = 0.34) |
| Overall[b] ($I^2$ = 80%, p = 0.007) | PC < no PC (OR = 0.35, 95% CI 0.20–0.61, p < 0.001) | |

CI, confidence interval; PC, palliative care.
[a]Data on the sample with all cause of death.
[b]Random-effects meta-analysis on the association between PC and the intensity of EoL care.

only two articles to date comparing HI-EoL care between oncology pediatric patients with and without PC. One randomized controlled trial examining the impact of PC on infants with prenatal single-ventricle diagnoses was excluded from this review because the outcomes did not meet the last year of life criteria (Hancock et al., 2018). More research is needed related to developing suitable indicators for the purpose of investigating the intensity of EoL care among non-cancer pediatric patients. Due to concerns about the heterogeneity of the populations, interventions, outcome measures, and study designs, it was not appropriate to conduct a further meta-analysis.

## Conclusion

In this work, PC was associated with a reduction in ICU admissions, ICU deaths, and HI-EoL care in the last month of life. The findings reveal an enormous ongoing gap in the understanding of whether pediatric PC is generally useful in reducing hospital admissions and LoS during EoL, reducing futile CPR, and avoiding hospital death. Based on this review, we make the following recommendations: first, specialist and multidisciplinary PC as well as the continuity of PC are required to reduce HI-EoL care. Second, careful attention should be paid to the need for a longer LoS in a medical setting late in life, and earlier EoL care discussion should take place with patients/caregivers especially in regard to attempting CPR in toddlers, adolescents, and the young adult population. Third, a lack of robust evidence led to identifying a gap in rigorous, comprehensive, and multisite prospective studies of data collection focusing on the impact of PC on EoL care and PoD for pediatric patients between 0 and 25 years of age. In addition, there may be reason to believe the patterns of utilization vary in different areas around the world, which necessitates the inclusion of cultural factors in future data collection.

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