Supportive Care in Cancer (2022) 30:10099–10109
https://doi.org/10.1007/s00520-022-07392-w

RESEARCH

All-cause mortality in cancer patients treated for sepsis in intensive care units: a systematic review and meta-analysis

Lama Nazer[1] · Maria A. Lopez-Olivo[2] · John A. Cuenca[3] · Wedad Awad[1] · Anne Rain Brown[4] · Aseel Abusara[1] · Michael Sirimaturos[5] · Rachel S. Hicklen[6] · Joseph L. Nates[3]

Received: 24 May 2022 / Accepted: 3 October 2022 / Published online: 10 October 2022

Abstract

Purpose Sepsis is a common complication in patients with cancer, but studies evaluating the outcomes of critically ill cancer patients with sepsis on a global scale are limited. We aimed to summarize the existing evidence on mortality rates in this patient population.

Methods Prospective and retrospective observational studies evaluating critically ill adult cancer patients with sepsis, severe sepsis, and/or septic shock were included. Studies published from January 2010 to September 2021 that reported at least one mortality outcome were retrieved from MEDLINE (Ovid), Embase (Ovid), and Cochrane databases. Study selection, bias assessment, and data collection were performed independently by two reviewers, and any discrepancies were resolved by a third reviewer. The risk of bias was assessed using the Newcastle–Ottawa scale. We calculated pooled intensive care unit (ICU), hospital, and 28/30-day mortality rates. The heterogeneity of the data was tested using the chi-square test, with a P value < 0.10 indicating significant heterogeneity.

Results A total of 5464 citations were reviewed, of which 10 studies met the inclusion criteria; these studies included 6605 patients. All studies had a Newcastle–Ottawa scale score of 7 or higher. The mean patient age ranged from 51.4 to 64.9 years. The pooled ICU, hospital, and 28/30 day mortality rates were 48% (95% CI, 43– 53%; $I^2 = 80.6\%$), 62% (95% CI, 58–67%; $I^2 = 0\%$), and 50% (95% CI, 38– 62%; $I^2 = 98\%$), respectively. Substantial between-study heterogeneity was observed.

Conclusion Critically ill cancer patients with sepsis had poor survival, with a hospital mortality rate of about two-thirds. The substantial observed heterogeneity among studies could be attributed to variability in the criteria used to define sepsis as well as variability in treatment, the severity of illness, and care across settings. Our results are a call to action to identify strategies that improve outcomes for cancer patients with sepsis.

Keywords Cancer · Neoplasms · Sepsis · Critical care · Mortality

✉ Lama Nazer
lnazer@khcc.jo

[1] Department of Pharmacy, King Hussein Cancer Center, Queen Rania Al-Abdallah StreetPO Box 1269, Amman 11941, Jordan

[2] Department of Health Services Research, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3] Department of Critical Care Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4] Department of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[5] Department of Pharmacy, Houston Methodist Hospital, Houston, TX, USA

[6] Research Medical Library, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction

Recent advances in cancer diagnosis and treatment have increased both the number of patients diagnosed with cancer and the number of cancer survivors [1]. The most recent statistics from the Global Cancer Observatory reported over 19 million new cancer cases worldwide in 2020 and a 5-year cancer prevalence of over 50 million patients [2]. This increasing population of patients with cancer is vulnerable to serious complications, such as sepsis [3, 4].

Sepsis is common in patients with cancer, who are especially vulnerable to severe infections owing to immune suppression associated with the malignancy itself and with cancer therapy [5]. Sepsis is one of the most common causes of admission to intensive care units (ICUs) among

cancer patients [6, 7]. Epidemiologic data show that 20% of patients with sepsis have cancer [8] and that nearly 1 in 10 cancer deaths is associated with severe sepsis [9].

Despite the vulnerability of patients with cancer to sepsis, studies evaluating sepsis outcomes in this population are limited and their findings are variable. Therefore, the aim of this systematic review and meta-analysis was to summarize the contemporary evidence on mortality rates in cancer patients with sepsis treated in ICUs (Fig. 2).

Methods

This meta-analysis was registered on PROSPERO (CRD42021236907). The 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) was followed to report our methods and results [10].

Eligibility criteria

Included studies were (a) prospective and retrospective observational studies; (b) published in English after January 2010; (c) evaluated adult (≥ 16 years old) cancer patients with sepsis, severe sepsis, and/or septic shock, as defined by the study investigators; (d) included patients treated in an ICU; and (e) reported at least one mortality outcome (i.e., ICU, hospital, or 28/30-day mortality rates).

We excluded studies that evaluated infections in critically ill patients that were not specifically defined as sepsis, severe sepsis, or septic shock and those that evaluated sepsis in cancer patients with COVID-19. In addition, to ensure that the reported outcomes were not biased toward a specific patient group, we excluded studies that exclusively evaluated (a) outcomes of a specific intervention (e.g., corticosteroids, antibiotics); (b) a specific subset of patients with sepsis (e.g., patients with renal failure, neutropenia, or specific lab results); (c) a specific age group (e.g., elderly patients); (d) a specific stage of malignancy (e.g., metastatic lung cancer, newly diagnosed acute lymphocytic leukemia); (e) patients who had undergone hematopoietic stem cell transplant (HSCT); or (f) patients admitted to the ICU for post-surgical care. When a study's cohort of cancer patients included HSCT or post-surgery patients along with other types of patients, the study was included if the proportion of HSCT or post-surgery patients did not exceed 30% of the study cohort each. We also excluded post hoc analyses of the included or interventional studies. If patient populations overlapped in two or more studies, we only included the study with the larger cohort and/or the wider time frame.

Information sources

The literature search was performed on February 21, 2021, and used the MEDLINE (Ovid), Embase (Ovid), and Cochrane databases. A search update was performed on September 20, 2021.

Search strategy

A systematic search of the literature was conducted and performed by a qualified medical librarian (RSH). The PRISMA literature search extension (PRISMA-S) guidelines were followed to report the literature search performed [11]. The databases were queried using controlled vocabulary and natural language terms for sepsis, critical illness, and cancer, as described in Appendix. The references of all selected eligible studies were screened for additional relevant citations. In addition, we used natural language keyword searches for cancer, critical illness, and sepsis to query Google Scholar and the websites of relevant societies and organizations (Sepsis Alliance, National Cancer Institute, American Cancer Society, Society of Critical Care Medicine, and the Critical Care Societies Collaborative). We checked studies retrieved via grey literature searching and citation chaining with our library of literature from the databases to identify any previously undiscovered studies. Conference abstracts were excluded, and results were limited to English-language citations published from January 1, 2010, to the date on which the search was conducted.

Selection process

Citations retrieved from the search were screened independently by two reviewers. An initial screening was based on titles and abstracts using the web application Rayyan [12]. Citations that were considered to be potentially relevant and those with a disagreement with the reviewers' assessments underwent further screening based on the full text. Discrepancies were resolved through discussion, and, if necessary, a third reviewer acted as an adjudicator.

Data collection process

Data extraction was performed independently by two pairs of reviewers. Corresponding authors were contacted if clarification was deemed necessary. If we were unable to reach the corresponding author, disagreements were resolved through discussion among the investigators to reach a final decision.

Data items

We collected the following characteristics of the included studies: study design; the country in which the study was conducted; the number of centers and ICUs involved in the study; study time frame and follow-up period; reported primary outcomes; criteria used to define sepsis, severe sepsis, or septic shock; and funding source(s). Patient characteristics were also recorded, including age, sex, and type of cancer (solid tumors or hematological malignancies), as well as several variables that may affect patient outcomes, including the severity of illness score, presence of neutropenia or thrombocytopenia, use of mechanical ventilation or dialysis, and treatment with vasopressors or inotropes. We also collected mortality rates (ICU, hospital, 28/30-day) and length of ICU stay.

Study risk of bias assessment

The risk of bias was assessed independently by two investigators. Disagreements were resolved through discussions or by a third reviewer. We used the Newcastle–Ottawa scale for cohort studies, which evaluates three domains of potential bias: selection, comparability, and outcome [13]. For the selection and outcome domains, a study can be awarded a maximum of 1 point for each numbered item, and for the comparability domain, a maximum of 2 points can be awarded. If the study controlled for the age, sex, and ICU severity of illness using any ICU prediction score, it was given a point. If the study was missing any of these three factors, no point was given. Studies that controlled for factors other than the three listed above received an additional point. Thus, a maximum score of 9 points could be obtained. Studies with scores of 7 or more points are generally regarded as having higher quality and a lower risk of bias [14].

Effect measures and synthesis methods

The primary outcome of the study was hospital mortality while the secondary endpoints were ICU mortality, 28/30 day mortality, and ICU length of stay for all patients in the included studies. For the mortality rates, we considered the total number of patients included in the study as the denominator and the number of patients who died in the hospital, in the ICU, or at 28/30 days as the numerator. To compare mortality outcomes between patients with hematological malignancies and solid tumors, we considered studies in which data for both subgroups of patients were reported. We also performed a post hoc analysis to test if the observed heterogeneity in mortality rates could be explained by the sepsis criteria used in the included studies.

To calculate the pooled mortality rates, we used the Freeman-Tukey arcsine transformation to stabilize variances and conducted all meta-analyses using inverse variance weights with a random-effects model. We determined the analytic mean length of ICU stay, weighting for the sample size in each study. When studies did not report a mean, we used the median value. Ranges were transformed into standard deviations using previously validated methods [15].

The heterogeneity of the data was formally tested by using the chi-square test, with a P value < 0.10 indicating significant heterogeneity, and the I-squared (I^2) statistic results were also assessed (a value greater than 50% was considered substantial heterogeneity). To explore heterogeneity in all outcomes, we used subgroup analysis to explore if the duration of follow-up or the type of study design had any impact on our findings. In addition, sensitivity analysis was used to determine if the use of imputation methods had an impact on the overall effect of the length of stay outcome. All analyses were performed using STATA 15 (StataCorp LP, College Station, TX).

Reporting bias assessment

We planned to perform a funnel plot and a regression asymmetry test to assess small-study bias for the meta-analysis. However, this was not possible due to the small number of studies per analysis ($n < 6$ studies).

Certainty assessment

A summary-of-findings table was created following the GRADE approach to rate the quality of the evidence for each outcome [16]. We expressed certainty using four categories: (i) high quality of evidence, that is, further research is very unlikely to change our confidence in the effect estimate; (ii) moderate quality, that is, further research is likely to have an important impact on our confidence in the effect estimate and may change the estimate; (iii) low quality, that is, further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate; and (iv) very low quality, that is, we are uncertain about the estimate.

Results

Study selection

The search strategy retrieved 8301 publications, among which 5464 were reviewed after the removal of duplicates (Fig. 1). A total of 10 studies met the inclusion criteria and were included in the meta-analysis [17–26].

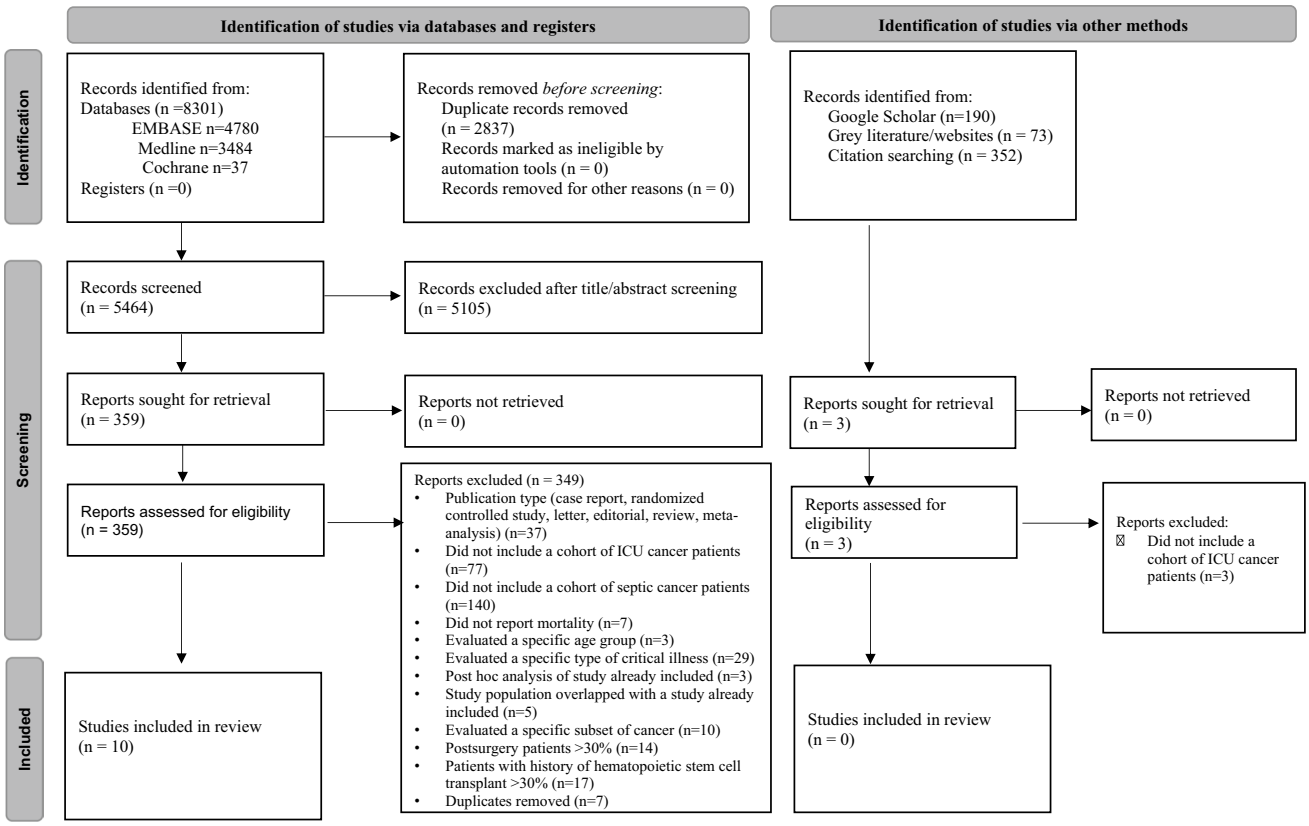

Fig. 1 Flow diagram showing study inclusion and exclusion

Study characteristics

Supplementary Table 1 summarizes the characteristics of the studies. Four studies were conducted in Asia, three in Europe, two in South America, and one in North America. Three studies had prospective cohorts, six had retrospective designs, and one included both retrospective and prospective data. Only two studies were multicenter; of the single-center studies, only two included two or more ICU units, and one did not report the number of units. The study time frames ranged from 3 months to 21 years. The total number of patients was 6605 (the smallest sample was 44 and the largest was 2062). Outcomes were assessed for several follow-up time spans: from ICU admission to hospital discharge ($n=3$), from ICU admission to 28 or 30 days ($n=2$), from ICU admission to 90 days ($n=1$), from ICU admission to 180 days ($n=3$), and from ICU admission to 1 year after ICU discharge ($n=1$).

The criteria used to define sepsis and septic shock varied among the studies, as outlined in Supplementary Table 2. Six studies used SEPSIS-3 [27] criteria to define sepsis, three used the SEPSIS-2 [28] criteria, and one study did not specify which criteria were used. For septic shock, four studies reported using the SEPSIS-2 definition, four studies reported using SEPSIS-3, and two studies did not report the number of patients with septic shock.

Characteristics of the participants

Table 1 outlines the characteristics of the patients included in each study. The analysis included a total of 6605 patients; 3731 had solid tumors, 2814 had hematological malignancies, and 60 patients had no type of malignancy defined. The mean age of the participants ranged from 51.4 to 64.9 years, and the percentage of males ranged from 45.5 to 69.5%. The percentage of patients with neutropenia ranged from 11.6 to 56.8%, that of patients receiving mechanical ventilation from 16.8 to 86.8%, that of patients receiving dialysis from 8.6 to 36.4%, and that of patients treated with vasopressors/inotropes from 17.9 to 100%. The percentage of participants with thrombocytopenia was reported in only two studies, which reported rates of 39.5% and 40.1%.

Risk of bias in studies

All included studies had a total Newcastle–Ottawa score of 7 or higher (Supplementary Table 3). The risks of selection, confounder, attrition, outcome, and missing data biases

Table 1 Patient characteristics

Study	Sample size (*n*)	Age, years mean (SD)	Sex, male *n* (%)	Metastasis *n* (%)	Severity of illness scale and score	Septic shock[a] *n* (%)	Neutropenia[b] *n* (%)	Thrombocytopenia[b] *n* (%)	Mechanical ventilation *n* (%)	Dialysis *n* (%)	Vasopressors/ inotropes[b] n (%)
Awad (2021)	1408 (total) H:453/ S: 955	56.8 (16.1)	821 (58.3)	733 (76.8)	APACHE II: mean 23 (SD 7.9)	1408 (100.0)	272 (19.3)	556 (36.5)	591 (42.0)	NR	1408 (100.0)
Camou (2020)	252 (total) H: 119/ S: 133	H: median 63 (IQR 49–68) S: median 65 (IQR 54–75)	152 (60.3)	78 (58.6)	SAPS II: median 56 H: 55 (46–68) S: 59 (44–81) SOFA: median 9 H: 10 (8–11) S: 8 (7–11)	252 (100.0)	78 (31.0)	NR	85 (33.7)	41 (16.3)	252 (100.0)
Dewi (2018)	60 (total) H: NR/ S: NR	51.4 (11.7)	32 (53.3)	NR	SOFA > 8: *n* = 29 (48.3%)	29 (48.3)	NR	NR	52 (86.7)	NR	29 (48.3)
Fang (2017)	95 (total) H: 12/ S: 83	62.2 (12.8)	61 (64.2)	NR	APACHE II: mean 23.8 (SD 8.3) SOFA: mean 9.4 (SD 3.9)	NR	NR	NR	NR	NR	NR
Kuo (2019)	279 (total) H: 24/ S: 255	63.4 (13.3) 37.9 (12.1) 63.5 (12.1)	194 (69.5)	169 (66.3)	NR	NR	66 (23.7)	112 (40.1)	225 (80.6)	24 (8.6)	147 (52.7)
Lemiale (2020)	2062 (total) H: 1700/ S: 362	median 59 (IQR 48–67)	1275 (61.8)	174 (48.1)	SOFA: median 6 (4–9)	NR	640 (31.0)	NR	1016 (49.3)	420 (20.4)	1172 (56.8)
Rosolem(2012)	563 (total) H: 127/ S: 436	59.2 (17.8)	301 (53.5)	88 (20.2)	SAPS II: mean 51 (SD 16.1) SOFA: mean 8 (5–11)	372 (66.1)	71 (12.6)	NR	489 (86.9)	110 (19.5)	372 (66.1)
Sippel (2015)	44 (total) H: 44/ S: 0	59.5 (NR)	20 (45.5)	NR	SAPS: mean 46	NR	25 (56.8)	NR	29 (65.9)	16 (36.4)	NR
Torres (2015)	268 (total) H: 35/ S: 233	63.1 (15)	126 (47.0)	79 (33.9)	SAPS II: mean 62.9 (SD 17.7) SOFA: median 9 (7–12)	126 (47)	31 (11.6)	NR	179 (66.8)	49 (18.3)	155 (57.8)
Wang (2018)	1574 (total) H: 300/ S: 1274	NR	908 (57.7)	NR	SAPS II: median 44 (36–54) SOFA: median 5 (3–8)	281 (17.9)	NR	NR	264 (16.8)	NR	281 (17.9)

Table 1 (continued)

Study	Sample size (*n*)	Lactate > 2 mmol/L *n* (%)	Performance status	Comorbidity index	Positive culture *n* (%)	Gram negative *n* (%)	AKI *n* (%)
Awad (2021)	1408 (total) H:453/ S: 955	918 (65.2%)	NR	NR	836 (59.4)	768 (54.5)	579 (41.1)
Camou (2020)	252 (total) H: 119/ S 133	NR	Median, H: 2 (1–3) S: 2 (2–3)	Median CCI, H: 5 (3–5) S: 8 (6–9)	168 (66.7)	103 (40.9)	
Dewi (2018)	60 (total) H: NR/ S: NR	NR	NR	NR	Not clear	NR	NR
Fang (2017)	95 (total) H: 12/ S: 83	NR	NR	NR	NR	NR	NR
Kuo (2019)	279 (total) H: 24/ S: 255	NR	N (%), 0–1: 132 (47.3) 2–4: 147 (52.7)	NR	NR	NR	118 (42.3)
Lemiale (2020)	2062 (total) H: 1700/ S: 362	NR	NR	NR	NR	NR	291 (14.1)
Rosolem (2012)	563 (total) H: 127/ S: 436	NR	N (%), 0–1: 269 (47.8) 2–4: 294 (52.2)	ACE 27, N (%): none-mild: 424 (75.3) moderate-severe: 139 (24.7)	383 (68.0)	297 (52.8)	NR
Sippel (2015)	44 (total) H: 44/ S: 0	NR	NR	NR	NR	NR	NR
Torres (2015)	268 (total) H: 35/ S: 233	NR	N (%), 0–1: 115 (42.9) 2–4: 153 (57.1)	ACE 27, N (%): none-mild: 128 (47.8) moderate-severe: 140 (52.2)	135 (50.4)	83 (31.0)	NR
Wang (2018)	1574 (total) H: 300/ S: 1274	NR	NR	NR	NR	668 (57.5)	NR

[a]Defined by each study

[b]Refers to values reported upon admission; if not reported, values reported during admission or at unspecified times were used

NR not reported, *H* hematological malignancies, *S* solid malignancies

were judged to be low for three of the six studies (50%) that reported ICU mortality outcomes. The remaining three studies were judged to have a high risk of confounding bias. For the hospital mortality outcome, all studies were judged to have an overall low risk of bias. For two of the five studies (40%) reporting the 28/30-day mortality outcome, the risks of selection, confounder, attrition, outcome, and missing data biases were judged to be low. The rest of the studies did not account for possible confounders and were judged to have a high risk of bias.

Results of syntheses

Mortality

Figure 2 shows the hospital, ICU, and 28/30 days mortality rates, respectively. Three studies reported on hospital mortality ($n = 2239$) [17, 23, 25]. The pooled hospital mortality rate was 62% for patients with sepsis (95% CI, 58–67%; $I^2 = 0\%$) (Fig. 2). Five studies reported on ICU mortality ($n = 2535$) [17, 18, 23–25]. One study reported a mortality rate without specifying a time frame; we assumed that this was ICU mortality ($n = 60$) [19]. The pooled ICU mortality rate was 48% for patients with sepsis (95% CI, 43–53%; $I^2 = 80.6\%$). Five studies reported on 28/30-day mortality ($n = 4262$) [19–22, 26]. The pooled mortality rate was 50% for patients with sepsis (95% CI, 38–62%; $I^2 = 98\%$). We did not find significant differences when grouping by study design at any of the reported mortality time frames (Supplementary Table 4). However, the 28/30-day mortality rate differed when grouped by follow-up time ($P < 0.001$) (Supplementary Table 4). Due to the limited number of studies that included data for both subgroups of patients with hematological and solid malignancies, we were unable to perform additional analysis to compare the mortality outcomes between the two groups.

A post hoc analysis was performed to evaluate the difference in mortality based on the sepsis criteria. For hospital mortality, all 3 studies used the same sepsis criteria. For the ICU mortality, there were only 2 subgroups (Sepsis 2: 46% [95% CI 41– 50%] vs Sepsis 3: 68% [95% CI 56–79%]); the difference between the groups was statistically significant. With regards to the 28/30 day mortality, there were 3 groups (Sepsis 2: 48% [95% CI 42– 54%] vs Sepsis 1/3: 51% [95% CI 41–60%] and Sepsis 3: 50% [33–67%]); the difference between the groups was not statistically significant (Supplementary Table 4).

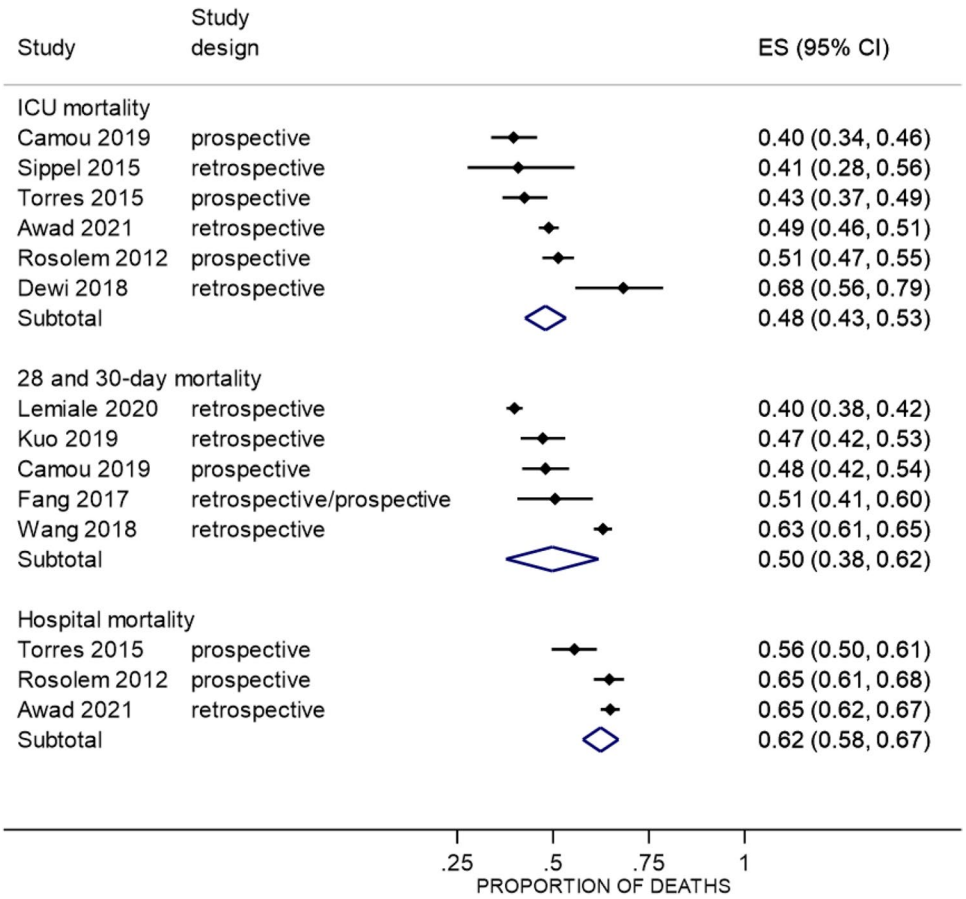

Fig. 2 Mortality rates in cancer patients treated in the intensive care units with sepsis

Length of ICU stay

Seven studies reported the length of ICU stay ($n=4169$) [17–19, 23–26]. The reported length of stay ranged from 3.3 to 20 days. The weighted mean length of stay was 7.01 days (95% CI, 5.61 to 8.42; $I^2=98.9\%$) (Fig. 3). There was substantial variability observed across studies with different designs and follow-up periods (Supplementary Table 1). Removing the study with imputed data did not influence our results.

Certainty of evidence

The evidence for the mortality rates was judged to be of moderate quality owing to limitations in study design (data from observational studies). Similarly, the evidence for the length of ICU stay was judged to be of low quality owing to similar study-design limitations (data from observational studies) and heterogeneity that could not be explained by subgroup analysis. (Supplementary Table 5).

Discussion

In this systematic review and meta-analysis of studies that included over 6000 patients, we determined the mortality rate of cancer patients with sepsis treated in ICUs. The reported pooled mortality rates were relatively high. The pooled hospital mortality rate for these patients was over 60%, higher than the rate of approximately 40% reported for patients without cancer treated for sepsis in ICUs [29]. However, we observed inconsistent definition criteria for sepsis and septic shock and differences among studies in the reported patient characteristics and clinical variables (e.g., use of mechanical ventilation, dialysis).

To our knowledge, this is the first meta-analysis to compile the available evidence on the mortality rate among critically ill cancer patients with sepsis. Given the vulnerability of patients with cancer to serious infections, the findings of this study provide insight into understanding the outcomes of this important subset of critically ill cancer patients. In addition, the findings are a call to action for clinical researchers to expand on research in this population to provide a better understanding of sepsis outcomes in critically ill cancer patients and to identify strategies that may improve these outcomes.

Outcomes for critically ill patients with cancer are improving [30]. However, a recent report showed that in a cohort of over 1 million US patients hospitalized with sepsis, the hospital mortality rate was substantially higher in patients with cancer-related sepsis than in patients with non–cancer-related sepsis (27.9% vs 19.5%) [31], although this study was not restricted to patients treated in ICUs. In addition, significantly more patients discharged after treatment for cancer-related sepsis required re-hospitalization than did patients with non-cancer-related sepsis (23.2% vs 20.1%, $P<0.001$).

In a meta-analysis of 44 randomized controlled trials of patients with severe sepsis and septic shock published between 2002 and 2016, the 28-day mortality rates over time ranged from 33.2 to 36.7% [32]. A more recent meta-analysis reported hospital mortality of hospital-acquired sepsis and sepsis with organ dysfunction of 35% and 24%, respectively [33]. Both meta-analyses showed lower mortality rates than the present study. Two factors could explain the difference. First, immune suppression associated with underlying malignancies and cancer-related therapies may lead to complications that pose an additional risk for mortality in critically ill cancer patients. Second, patients with cancer are generally frailer than non-cancer patients [34].

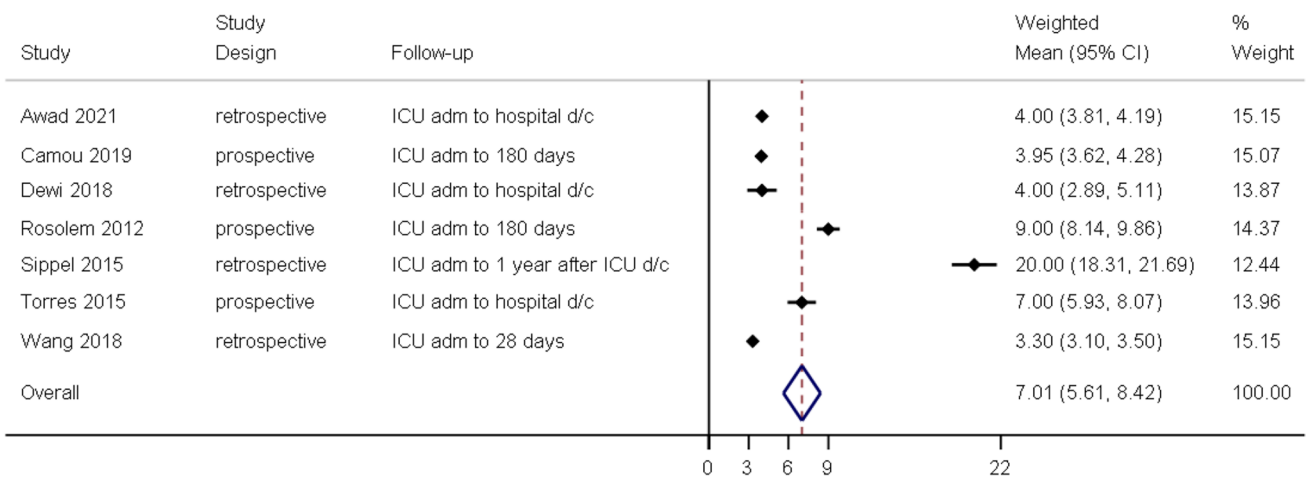

Fig. 3 Weighted mean length of stay

Frailty is an indirect surrogate of low physiological reserve and is associated with difficulties withstanding a critical illness such as sepsis [34].

We also found wide variability in the criteria used to define sepsis and the severity of illness measurement used by each study. This variability hampered direct comparisons between the studies; particularly for patients with septic shock. The SEPSIS-3 criteria defined septic shock as sepsis, hypotension refractory to fluid resuscitation, and a serum lactate level of greater than 2 mmol/L [27]. Applying the SEPSIS-3 definition increases the mortality rate by selecting the most severely ill patients with high lactate levels [35, 36]. This finding was also reflected in the ICU mortality we reported from studies that used the Sepsis 2 criteria versus the Sepsis 3. Despite the challenges to research involving critically ill cancer patients [37], our results are a call to action for clinical researchers to develop guidance for research in this population. Such guidance should specify the appropriate use of current sepsis definitions, establish the most appropriate severity of illness measure, and encourage reporting of either frailty or performance status.

The present systematic review and meta-analysis have limitations. First, our review included only English-language publications, and only 10 studies met the inclusion criteria. Second, substantial between-study heterogeneity was observed, which could be due to the variability in treatment, the severity of illness, and care across settings and countries. While it would have been important to account for such differences in the analysis, we were unable to do so due to the inconsistency in the type of data reported as well as an insufficient description of the management of sepsis and septic shock among the included patients. Third, since not all the studies used similar severity of illness, comorbidity, and performance status scores, we were also unable to perform adjustments for those variables.

In conclusion, this systematic review and meta-analysis of studies of outcomes in critically ill cancer patients with sepsis demonstrated a relatively high mortality rate, with in-hospital death reported in about two-thirds of the patients. The observed substantial heterogeneity among studies could reflect differences in treatments, definitions of sepsis, the severity of illness measures, and critical care practices across settings and countries. Our results are a call to action for clinical researchers to develop guidance for research in this population.

Appendix. Search strategy

1. exp Neoplasms/
2. exp MEDICAL ONCOLOGY/
3. (neoplas* or cancer* or carcinoma* or malignan* or tumor* or tumour* or oncolog* or metasta* or leukemi* or leukaemi* or lymphoma* or osteosarcoma* or sarcoma* or myeloma* or melanoma* or chemotherap* or chemo-therap* or antineoplas* or anti-neoplas*).ti,ab,kw.
4. colony-stimulating factors/ or exp granulocyte colony-stimulating factor/
5. exp Neutropenia/
6. Immunocompromised Host/
7. exp Immunosuppressive Agents/
8. exp Antineoplastic Agents/
9. exp Vinca Alkaloids/
10. exp Antimetabolites, Antineoplastic/
11. ("Granulocyte Colony-Stimulating" or Filgrastim or Lenograstim or "G-CSF" or GCSF or neutropenia* or neutropenic or Immunocompromis* or Immunosuppress* or anticancer* or anti-cancer* or antitumour* or anti-tumour* or antitumor* or anti-tumor* or Chemotherap*).ti,ab,kw.
12. or/1–11 [cancer terms]
13. exp Intensive Care Units/
14. exp Critical Care/
15. exp Critical Illness/
16. ("ICU" or "CCU").ab,ti.
17. (critical adj3 care).ab,kw,ti.
18. (intensive adj3 care).ab,kw,ti.
19. ("Coronary Care Unit*" or "Respiratory Care Unit*" or "burn unit*" or "recovery room*").ab,kw,ti.
20. or/13–19 [ICU terms]
21. exp Sepsis/ or exp Shock, Septic/
22. (sepsis or sepses).ti,kw,ab.
23. (septicemi* or bacteremi* or fungemi* or candidemi*).ti,kw,ab.
24. (septic or Pyemia* or Pyohemia* or Pyaemia* or "Blood Poison*").ab,kw,ti.
25. or/21–24 [sepsis terms]
26. 12 and 20 and 25 [cancer + ICU + sepsis]
27. limit 26 to conference abstract status
28. 26 not 27
29. limit 28 to (english language and yr = "2010 -Current")
30. limit 29 to human

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-022-07392-w.

Acknowledgements We appreciate the editorial contributions made by Amy Ninetto of the Research Medical Library at The University of Texas MD Anderson Cancer Center.

Author contribution All authors have contributed to the conceptualization (PROSPERO-protocol) of the meta-analysis. RSH performed the literature search. WA, AA, JAC, MS, LN, and ARB performed the literature evaluation and selection, data extraction, and risk of bias

assessment. MAL performed the statistical analysis. LN, JAC, and WA wrote the original draft of the paper, and all authors contributed to its review and editing.

Funding Dr. Nate's work is supported in part by a Cancer Center Support Grant from the NIH/NCI (award number P30CA016672). Dr. Lopez's work is supported by a career award from the NCI (#K08CA237619). The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Data availability All data used in the analysis is provided in the supplementary material. Any additional data may be requested directly from the corresponding author.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70(1):7–30
2. Sung H, Ferlay J, Siegel RL et al (2021) Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality-worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249
3. Roser M, Ritchie H, Ortiz-Ospina E. World population growth. Our World in Data 2019, University of Oxford. Available from: https://ourworldindata.org/world-population-growth. September 30, 2020.
4. Rozhok AI, DeGregori J (2016) The evolution of lifespan and age-dependent cancer risk. Trends in Cancer 2(10):552–560
5. Pavon A, Binquet C, Kara F et al (2013) Profile of the risk of death after septic shock in the present era: an epidemiologic study. Crit Care Med 41(11):2600–2609
6. 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
7. Hawari FI, Nazer LH, Addassi A et al (2016) Predictors of ICU admission in patients with cancer and the related characteristics and outcomes: a 5-year registry-based study. Crit Care Med 44(3):548–553
8. Rhee C, Dantes R, Epstein L et al (2017) Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. JAMA 318(13):1241
9. Williams MD, Braun LA, Cooper LM et al (2004) Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit Care 8(5):R291-298
10. Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
11. Rethlefsen ML, Kirtley S, Waffenschmidt S et al (2021) PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Syst Rev 10(1):39
12. Ouzzani M, Hammady H, Fedorowicz Z et al (2016) Rayyan—a web and mobile app for systematic reviews. Syst Rev 51 2016 5(1):1–10
13. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. September 3, 2021.
14. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
15. Wan X, Wang W, Liu J et al (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14(1):1–13
16. Holger Schünemann, Jan Brożek, Gordon Guyatt, et al. (Eds). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. The GRADE Working Group, 2013.
17. Awad WB, Nazer L, Elfarr S et al (2021) A 12-year study evaluating the outcomes and predictors of mortality in critically ill cancer patients admitted with septic shock. BMC Cancer 21(1):709
18. Camou F, Didier M, Leguay T et al (2020) Long-term prognosis of septic shock in cancer patients. Support Care Cancer 28(3):1325–1333
19. Dewi RS, Radji M, Andalusia R (2018) Evaluation of antibiotic use among sepsis patients in an intensive care unit: a cross-sectional study at a referral hospital in Indonesia. Sultan Qaboos Univ Med J 18(3):e367–e373
20. Fang W-F, Chen Y-M, Lin C-Y et al (2017) Immune profiles and clinical outcomes between sepsis patients with or without active cancer requiring admission to intensive care units. PLoS One 12(7):e0179749
21. Kuo W-K, Hua C-C, Yu C-C et al (2020) The cancer control status and APACHE II score are prognostic factors for critically ill patients with cancer and sepsis. J Formos Med Assoc 119(1):276–281
22. Lemiale V, Pons S, Mirouse A et al (2020) Sepsis and septic shock in patients with malignancies: a Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study*. Crit Care Med 48(6):822–829
23. Rosolem MM, Rabello LSCF, Lisboa T et al (2012) Critically ill patients with cancer and sepsis: clinical course and prognostic factors. J Crit Care 27(3):301–307
24. Sippel C, Kim Y, Wallau A et al (2015) AML versus ICU: outcome of septic AML patients in an intensive care setting. J Cancer Res Clin Oncol 141(9):1645–1651
25. Torres VBL, Azevedo LCP, Silva UVA et al (2015) Sepsis-associated outcomes in critically Ill patients with malignancies. Ann Am Thorac Soc 12(8):1185–1192
26. Wang Y, Zhou J, Wu K (2018) High 28-day mortality in critically ill patients with sepsis and concomitant active cancer. J Int Med Res 46(12):5030–5039
27. Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8):801–810
28. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 31(4):1250–1256
29. Buchman TG, Simpson SQ, Sciarretta KL et al (2020) Sepsis among medicare beneficiaries: 1. The Burdens of Sepsis 2012–2018. Crit Care Med 48(3):276–288
30. Zampieri FG, Romano TG, Salluh JIF et al (2021) Trends in clinical profiles, organ support use and outcomes of patients with

cancer requiring unplanned ICU admission: a multicenter cohort study. Intensive Care Med 47(2):170–179
31. Hensley MK, Donnelly JP, Carlton EF et al (2019) Epidemiology and outcomes of cancer-related versus non-cancer-related sepsis hospitalizations. Crit Care Med 47(10):1310–1316
32. Luhr R, Cao Y, Söderquist B et al (2019) Trends in sepsis mortality over time in randomised sepsis trials: a systematic literature review and meta-analysis of mortality in the control arm, 2002–2016. Crit Care 23(1):241
33. Markwart R, Saito H, Harder T, et al (2020) Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. Intensive Care Med
34. Ethun CG, Bilen MA, Jani AB et al (2017) Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 67(5):362–377
35. Sterling SA, Puskarich MA, Glass AF et al (2017) The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. Crit Care Med 45(9):1436–1442
36. Manjappachar NK, Cuenca JA, Ramírez CM et al (2022) Outcomes and predictors of 28-day mortality in patients with hematologic malignancies and septic shock defined by sepsis-3 criteria. J Natl Compr Cancer Netw 20(1):45–53
37. Reyes MP, Cuenca JA, Heatter J, et al (2021) Tribulations of conducting critically ill cancer patients research: lessons from a failed septic shock trial and Murphy's law. Med Intensiva