RESEARCH

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

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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.

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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].
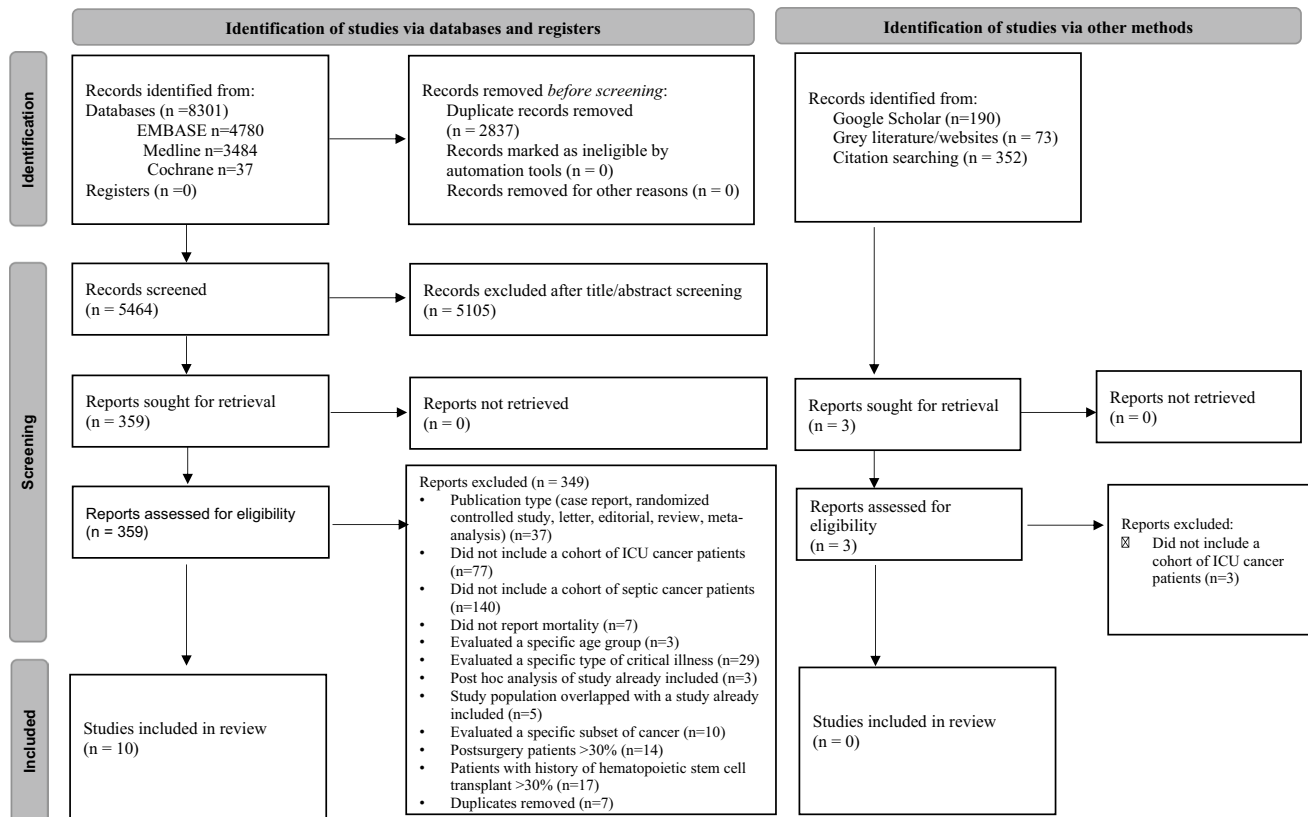
Fig. 1 Flow diagram showing study inclusion and exclusion

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.
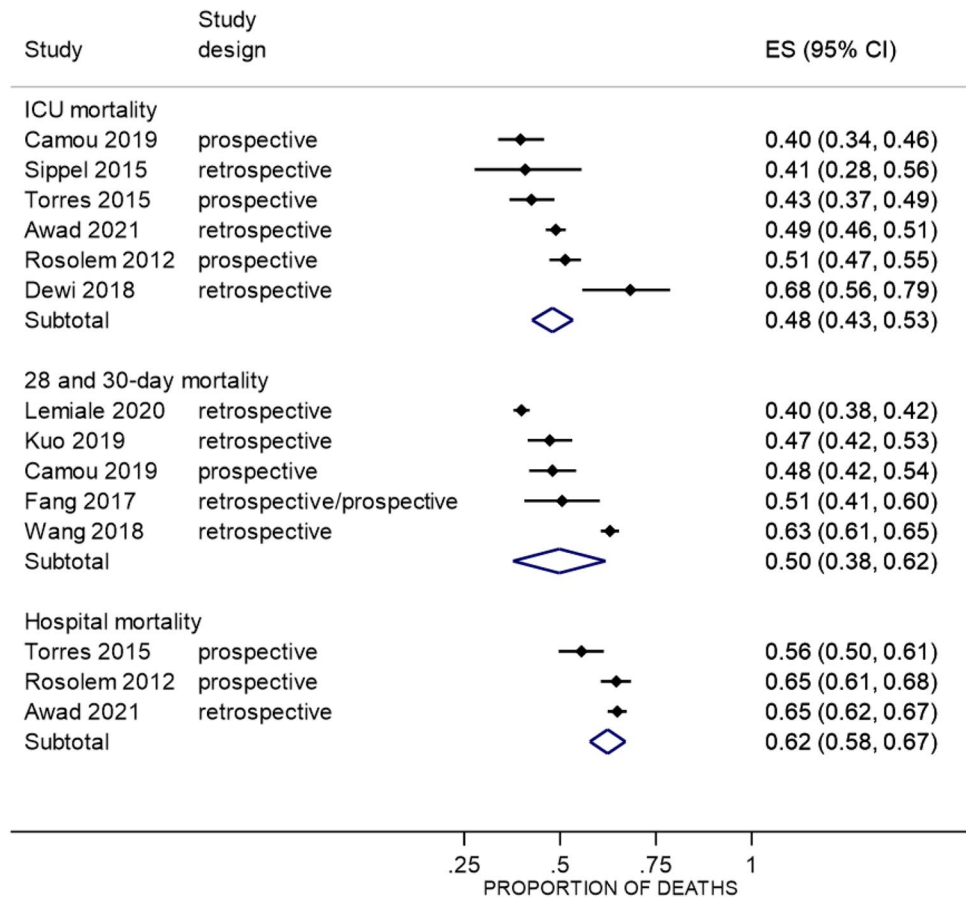
Results of syntheses

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

Study	Study design		ES (95% CI)
ICU mortality			
Camou 2019	prospective		0.40 (0.34, 0.46)
Sippel 2015	retrospective		0.41 (0.28, 0.56)
Torres 2015	prospective		0.43 (0.37, 0.49)
Awad 2021	retrospective		0.49 (0.46, 0.51)
Rosolem 2012	prospective		0.51 (0.47, 0.55)
Dewi 2018	retrospective		0.68 (0.56, 0.79)
Subtotal			0.48 (0.43, 0.53)
28 and 30-day mortality			
Lemiale 2020	retrospective		0.40 (0.38, 0.42)
Kuo 2019	retrospective		0.47 (0.42, 0.53)
Camou 2019	prospective		0.48 (0.42, 0.54)
Fang 2017	retrospective/prospective		0.51 (0.41, 0.60)
Wang 2018	retrospective		0.63 (0.61, 0.65)
Subtotal			0.50 (0.38, 0.62)
Hospital mortality			
Torres 2015	prospective		0.56 (0.50, 0.61)
Rosolem 2012	prospective		0.65 (0.61, 0.68)
Awad 2021	retrospective		0.65 (0.62, 0.67)
Subtotal			0.62 (0.58, 0.67)

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.25 .5 .75 1

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].
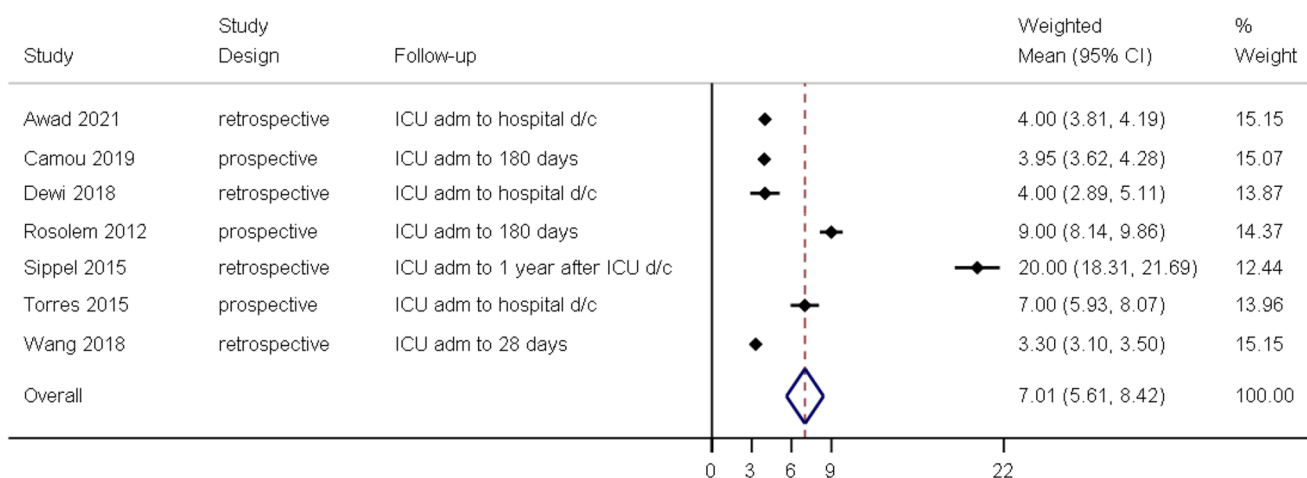

Study	Study Design	Follow-up		Weighted Mean (95% CI)	% Weight
Awad 2021	retrospective	ICU adm to hospital d/c		4.00 (3.81, 4.19)	15.15
Camou 2019	prospective	ICU adm to 180 days		3.95 (3.62, 4.28)	15.07
Dewi 2018	retrospective	ICU adm to hospital d/c		4.00 (2.89, 5.11)	13.87
Rosolem 2012	prospective	ICU adm to 180 days		9.00 (8.14, 9.86)	14.37
Sippel 2015	retrospective	ICU adm to 1 year after ICU d/c		20.00 (18.31, 21.69)	12.44
Torres 2015	prospective	ICU adm to hospital d/c		7.00 (5.93, 8.07)	13.96
Wang 2018	retrospective	ICU adm to 28 days		3.30 (3.10, 3.50)	15.15
Overall				7.01 (5.61, 8.42)	100.00

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

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.

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.

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