

A Systematic Review and Meta-Analysis Evaluating Geographical Variation in Outcomes of Cancer Patients Treated in ICUs

OBJECTIVES: The reported mortality rates of cancer patients admitted to ICUs vary widely. In addition, there are no studies that examined the outcomes of critically ill cancer patients based on the geographical regions. Therefore, we aimed to evaluate the mortality rates among critically ill cancer patients and provide a comparison based on geography.

DATA SOURCES: PubMed, EMBASE, and Web of Science.

STUDY SELECTION: We included observational studies evaluating adult patients with cancer treated in ICUs. We excluded non-English studies, those with greater than 30% hematopoietic stem cell transplant or postsurgical patients, and those that evaluated a specific type of critical illness, stage of malignancy, or age group.

DATA EXTRACTION: Two reviewers independently applied eligibility criteria, assessed quality, and extracted data. Studies were classified based on the continent in which they were conducted. Primary outcomes were ICU and hospital mortality. We pooled effect sizes by geographical region.

DATA SYNTHESIS: Forty-six studies were included ($n = 110,366$). The overall quality of studies was moderate. Most of the published literature was from Europe ($n = 22$), followed by North America ($n = 9$), Asia ($n = 8$), South America ($n = 5$), and Oceania ($n = 2$). Pooled ICU mortality rate was 38% (95% CI, 33–43%); the lowest mortality rate was in Oceania (26%; 95% CI, 22–30%) and highest in Asia (51%; 95% CI, 44–57%). Pooled hospital mortality rate was 45% (95% CI, 41–49%), with the lowest in North America (37%; 95% CI, 31–43%) and highest in Asia (54%; 95% CI, 37–71%).

CONCLUSIONS: More than half of cancer patients admitted to ICUs survived hospitalization. However, there was wide variability in the mortality rates, as well as the number of available studies among geographical regions. This variability suggests an opportunity to improve outcomes worldwide, through optimizing practice and research.

KEY WORDS: cancer; critical illness; meta-analysis; mortality; outcomes

Historically, patients with advanced cancers may not have been referred to the ICUs owing to their limited prognosis. However, novel treatments such as targeted therapies and immunotherapies, as well as advances in critical care management, have improved the outcomes of cancer patients, resulting in an increase in ICU admissions for the management of cancer- and noncancer-related critical illnesses (1, 2). Thus, it is essential to understand the prognosis of critically ill cancer patients to avoid excluding them from accessing vital clinical resources. Increasing epidemiologic evidence shows positive survival trends over time and improved outcomes associated with early ICU admission (3–5).

Reports on the mortality rates of cancer patients admitted to ICUs vary widely, making it difficult to understand the overall prognosis of this patient population.

Lama H. Nazer, PharmD, FCCM¹

Maria A. Lopez-Olivo, MD, PhD²

Anne Rain Brown, PharmD, FCCM³

John A. Cuenca, MD²

Michael Sirimaturos, PharmD,
FCCM⁴

Khader Habash, PharmD¹

Nada AlQadheeb, PharmD⁵

Heather May, PharmD⁶

Victoria Milano, PharmD⁷

Amy Taylor⁸

Joseph L. Nates, MD, MBA, MCCM²

Copyright © 2022 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000000757

Most previous studies have focused on specific patient populations or patients with a specific severity of illness or were limited by study size or center type (6–8). In addition, no studies have synthesized the characteristics and outcomes of critically ill cancer patients on the basis of geography. Therefore, we conducted a systematic review and meta-analysis to address this gap.

MATERIALS AND METHODS

This meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO), CRD42020179233. For reporting, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and the PRISMA literature search extension (PRISMA-S) (9, 10).

Eligibility Criteria

Eligible publications had to meet the following inclusion criteria: 1) observational studies with the main objective of evaluating outcomes of critically ill cancer patients, 2) published in English after January 2010, 3) included only adult patients, defined as those 16 years old or older, 4) included patients with cancer treated for critical illnesses in the ICU, and 5) reported at least 1 mortality outcome, that is, ICU or hospital mortality.

To ensure that the reported outcomes were not biased toward a specific patient group, we excluded studies that exclusively evaluated the outcomes of a specific intervention (e.g., corticosteroids, mechanical ventilation), age group (e.g., older adult patients), type of critical illness (e.g., sepsis, respiratory failure), or stage of malignancy (e.g., metastatic lung cancer, newly diagnosed acute lymphocytic leukemia). For the same reason, we also excluded studies in which more than 30% of the cohort consisted of patients with a history of hematopoietic stem cell transplant or patients admitted to the ICU after surgery. In addition, we excluded studies conducted during the COVID-19 pandemic, defined as starting January 2020.

In addition, interventional studies and post hoc analyses of included studies were excluded. If studies had overlapping patient populations, the study with the larger cohort and/or the wider time frame was included, and the others were excluded from this analysis.

Information Sources

We searched Medline (PubMed), Web of Science (Clarivate), and EMBASE (Ovid) on December 31, 2019. A search update was performed by rerunning the search on February 26, 2021.

Search strategy

An experienced medical librarian (A.T.) developed the search strategy (**Appendix A**, <http://links.lww.com/CCX/B54>). No limits or filters were added to the search strategy. Following the literature search, deduplication was performed using EndNote (Clarivate, London, United Kingdom).

Selection Process

Retrieved citations were reviewed independently by two reviewers. First, reviewers screened titles and abstracts for relevance using Rayyan, a web application for screening literature for systematic reviews (11). Second, citations deemed relevant and those in which there was a discrepancy between the reviewers underwent full-text assessment independently by two reviewers. Any discrepancies were discussed between the two reviewers and, if necessary, a third reviewer.

Data Collection Process

Data extraction was performed independently by teams of two reviewers, who utilized Microsoft Excel (Microsoft Corp, Redmond, WA) for data entry. Any discrepancies between the reviewers were discussed, and if necessary, a third reviewer was involved.

Data Items

The characteristics of the eligible studies and patients were recorded, as well as the outcomes reported in the studies. Studies that included both patients with hematologic and solid malignancies had the outcomes recorded for each, if available.

Risk-of-Bias Assessment

Each study was assessed for risk of bias independently by two investigators, with disagreements resolved through discussions or review by a third investigator. We used the Newcastle-Ottawa scale for cohort studies, which evaluates three domains of potential bias:

selection, comparability, and outcome (12). For the comparability domain, if a study controlled for age, sex, and severity of critical illness, it was given 1 point. Studies that controlled for factors other than the three listed above received an additional point. A maximum score of 9 points could be obtained; studies with scores of 7 points or higher were regarded as having higher quality and lower risk of bias (12).

Effect Measures

The primary outcomes of the meta-analysis were ICU and hospital mortality rates for cancer patients in the included studies. We determined the outcomes for the entire cohort of cancer patients for each continent. In addition, we reported separately the outcomes for patients with hematologic malignancies and those with solid tumors within each continent.

We also compared outcomes between patients with hematologic malignancies and solid tumors. For such comparison, we considered only studies in which data for both subgroups of patients were reported. We calculated the relative risk (RR) to compare dichotomous outcomes, the mean difference for continuous outcomes, and the 95% CIs.

Synthesis Methods

For the pooled mortality rates, we used the Freeman-Tukey arcsine transformation to stabilize variances and conducted a meta-analysis using inverse variance weights with a random-effects model. Studies were categorized based on the continent in which they were conducted: Asia, Africa, Europe, North America, Oceania, or South America.

We calculated the RR to compare dichotomous outcomes, the mean difference (MD) for continuous outcomes, and 95% CIs. We determined the pooled weighted mean (WM) and median length of ICU stay. When studies did not report means, we used the median values. Ranges were transformed into SDs using validated methods (13). For studies not reporting SDs for the hematologic or solid cancer cohorts, we used the SD for the entire cohort. When no SD was available, we used the estimated weighted SD from all the included studies reporting a SD.

Heterogeneity of the data was formally tested by using the chi-square test, with a *p* value of less than 0.10 indicating significant heterogeneity. We performed meta-regressions and sensitivity analysis to evaluate

the effect of patient characteristics and the variability in the defined criteria on the reported outcomes. A cumulative meta-analysis was also performed to evaluate if the pooled ICU mortality rate differed every time the results of a new study were published. All analyses were performed using STATA 15 (StataCorp LP, College Station, TX).

Reporting Bias Assessment

We performed a funnel plot and a regression asymmetry test to assess small-study bias for comparisons of outcomes between patients with hematologic malignancies and solid tumors.

Certainty Assessment

We followed the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to rate the quality of evidence for each outcome (14).

RESULTS

Study Selection

The search retrieved 49,352 publications, among which 35,398 were reviewed after removal of duplicates. A total of 46 publications met the inclusion criteria and were included in the meta-analysis (**Fig. 1**).

Study Characteristics

The characteristics of the 46 included studies are described in **eTable 1** (<http://links.lww.com/CCX/B54>). Most of the published literature was from Europe (*n* = 18) (15–32), followed by Asia (*n* = 12) (33–44), North America (*n* = 9) (4, 45–52), South America (*n* = 5) (5, 53–56), and Oceania (*n* = 2) (57, 58). On the other hand, studies from North America contributed the highest number of patients (*n* = 37,255), followed by South America (*n* = 32,723), Asia (*n* = 23,540), Europe (*n* = 16,149), and Oceania (*n* = 478).

The majority of the studies were retrospective (*n* = 38; 83%), conducted in single centers (*n* = 29; 63%), and initiated between 2000 and 2009 (*n* = 28; 61%). Follow-up was calculated in various manners, most commonly was time from ICU admission until hospital discharge (18 studies; 39%) or until 1 year after discharge (11 studies; 24%).

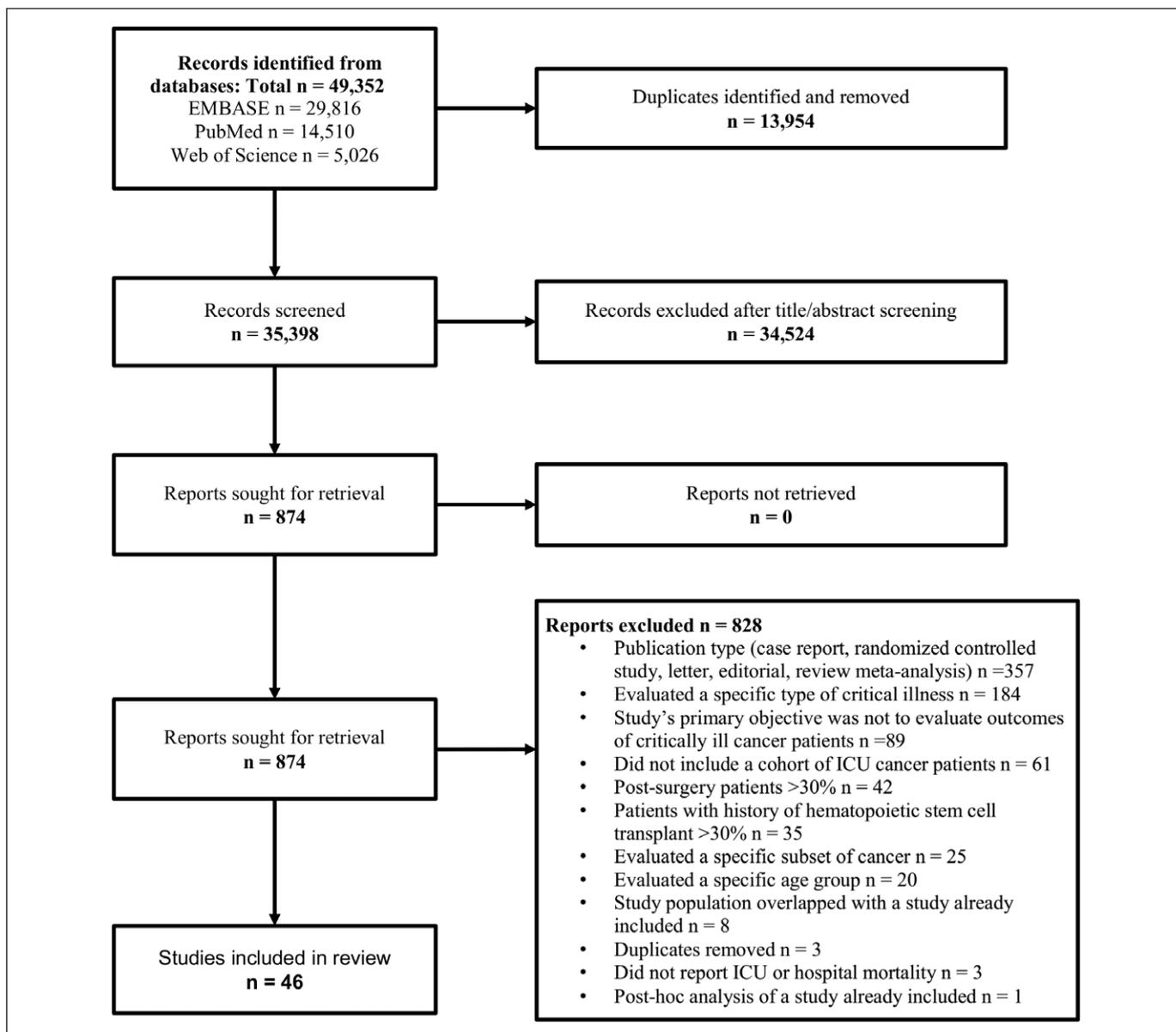


Figure 1. Flow diagram showing study inclusion and exclusion.

Participant Characteristics

The included studies had a total of 110,145 patients with cancer who were treated in ICUs, among whom 70,759 patients (64%) had solid tumors and 39,386 (36%) had hematologic malignancies. The characteristics of the patients included in each study are provided in **eTable 2** (<http://links.lww.com/CCX/B54>). The studies varied in the characteristics that they reported. For example, although use of mechanical ventilation was reported by most studies, the time at which this feature was recorded varied. In addition, characteristics such as neutropenia, thrombocytopenia, and the use of dialysis and vasopressors/inotropes were not reported by all studies.

Table 1 summarizes differences in the characteristics of patients from each continent. The WM age of patients was highest in South America (69 yr; 95% CI, 67–71) and lowest in North America (58 yr; 95% CI, 55–60). Asia had the highest proportion of patients who received mechanical ventilation (57%), whereas South America had the lowest (15%).

Risk of Bias in Studies

All studies had a total Newcastle-Ottawa score of 7 or higher, indicating a low risk of bias (**eTable 3**, <http://links.lww.com/CCX/B54>). Among the 46 studies, five did not report ICU mortality data (42, 47, 48, 52, 54).

TABLE 1.
Patient Characteristics and Outcomes Reported for All Included Studies by Continent

Characteristics ^a	Overall (46 Studies)	Europe (18 Studies)	Asia (12 Studies)	North America (9 Studies)	South America (5 Studies)	Oceania (2 Studies)
Patients	110,145	16,149	23,540	37,255	32,723	478
Study type, <i>n</i>						
Retrospective	37	15	10	6	4	2
Prospective	8	2	2	3	1	0
Retrospective/prospective	1	1	0	0	0	0
Age, weighted mean (95% CI), yr	64 (62–65)	64 (62–65)	66 (63–70)	58 (55–60)	69 (67–71)	62 (59–65)
Male sex	61,272 (56)	9,643 (60)	14,285 (61)	20,477 (55)	16,585 (51)	282 (59)
Type of malignancy						
Solid tumor	70,759 (64)	5164 (32)	21,928 (93)	14,094 (38)	29,481 (90)	92 (19)
Hematologic	39,386 (36)	10,985 (68)	1,612 (7)	23,161 (62)	3,242 (10)	386 (81)
Surgery ^b	1,833 (3)	429 (3)	100 (7)	460 (9)	802 (2)	42 (15)
Hematopoietic stem cell transplant ^b	3,078(10)	630 (7)	18 (6)	2,371 (11)	0	59 (22)
Neutropenia ^b	1,760(24)	638(25)	747(21)	170 (34)	91 (25)	114 (42)
Thrombocytopenia ^b	1,334 (32)	54 (11)	1,154 (33)	126 (83)	NR	NR
Mechanical ventilation ^b	28,166 (36)	7,667 (47)	13,306 (57)	2,128 (39)	4,912 (15)	153 (32)
Dialysis	4,754 (7)	2,046 (20)	551 (3)	265 (5)	1,815 (5)	77 (16)
Vasopressors/inotropes	12,921 (23)	6,038 (38)	813 (51)	1,302 (29)	4,492 (14)	276 (58)
ICU length of stay, median (range), d	5.66 (2.74–23.65)	6.0 (2.74–15.75)	6.67 (4.50–23.65)	4.87 (3.50–9.40)	5.05 (3.47–6.33)	3.84 (3.67–4.00)
Pooled ICU mortality rate (95% CI), %	38 (33–43)	34 (29–39)	51 (44–57)	33 (26–40)	37 (14–64)	26 (22–30)
Pooled hospital mortality rate (95% CI), %	45 (41–49)	45 (40–50)	54 (37–71)	37 (31–43)	46 (23–69)	40 (35–44)

NR = not reported.

^aValues are determined based on studies that reported each of the listed outcomes.

^bData are presented as number of patients (%) unless otherwise indicated.

The risks of selection, attrition, outcome, and missing data biases were judged to be low for all included studies. Among the 41 studies reporting ICU mortality, the risk of confounding bias was judged to be low for 19 studies (46%).

Ten studies did not report hospital mortality data (18, 22, 32, 34, 35, 37, 38, 41, 46, 53). The risks of selection, attrition, outcome, and missing data biases were considered low for the 36 studies reporting on hospital mortality. The risk of confounding bias was judged to be low for 22 studies (61%).

Results of Synthesis

ICU Mortality. In the 41 studies that reported ICU mortality rates, the pooled ICU mortality rate was 38% (95% CI, 33–43%; range, 13–70%) (Fig. 2). Studies from Asia reported a significantly higher ICU mortality rate (51%; 95% CI, 44–57%) among cancer patients than did those from Europe (34%; 95% CI, 29–39%; $p < 0.001$), Oceania (26%; 95% CI, 22–30%; $p < 0.001$), and North America (33%; 95% CI, 26–40%; $p = 0.003$) (Fig. 3) (eTable 4, <http://links.lww.com/CCX/B54>).

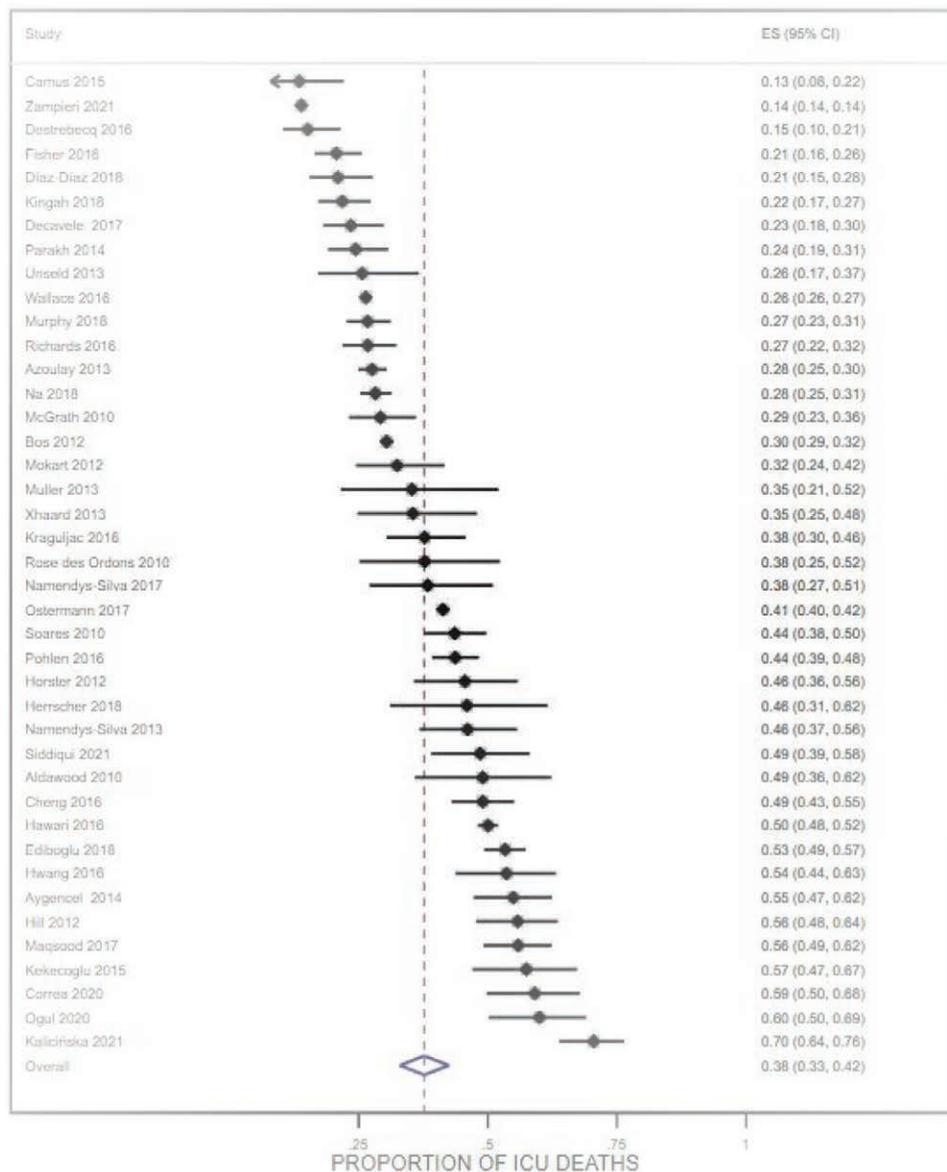


Figure 2. ICU mortality rates in critically ill patients with cancer. *Horizontal bars* indicate 95% CIs; *black diamonds* indicate effect estimates (ES) for ICU mortality; and *blue diamond* indicates pooled ICU mortality rate.

Table 2 outlines the ICU mortality rates for each continent based on the type of malignancy.

Supplementary Figures 1 and **2** (<http://links.lww.com/CCX/B54>) show the pooled ICU mortality rates for patients with hematologic and solid malignancies. Ten studies reported data that could be compared directly between these subgroups (4, 16, 18, 23, 34, 35, 37, 39, 44, 57). Overall, patients with hematologic malignancies were 37% more likely to die in the ICU than were patients with solid malignancies (RR, 1.4; 95% CI, 1.13–1.73; $I^2 = 94.4\%$) (**Supplementary Fig. 3**, <http://links.lww.com/CCX/B54>).

Hospital Mortality. Thirty-six studies reported data on hospital mortality. The pooled hospital mortality rate was 45% (95% CI, 41–49%; range, 24–81%) (**Fig. 4**). The pooled hospital mortality rates were highest in Asia (54%; 95% CI, 37–71%) and lowest in North America (37%; 95% CI, 31–43%), but no statistically significant differences were found (**Fig. 3**) (eTable 4, <http://links.lww.com/CCX/B54>). **Table 2** outlines the hospital mortality rates for each continent based on the type of malignancy.

Supplementary Figures 4 and **5** (<http://links.lww.com/CCX/B54>) show the pooled hospital mortality rates for patients with hematologic and solid

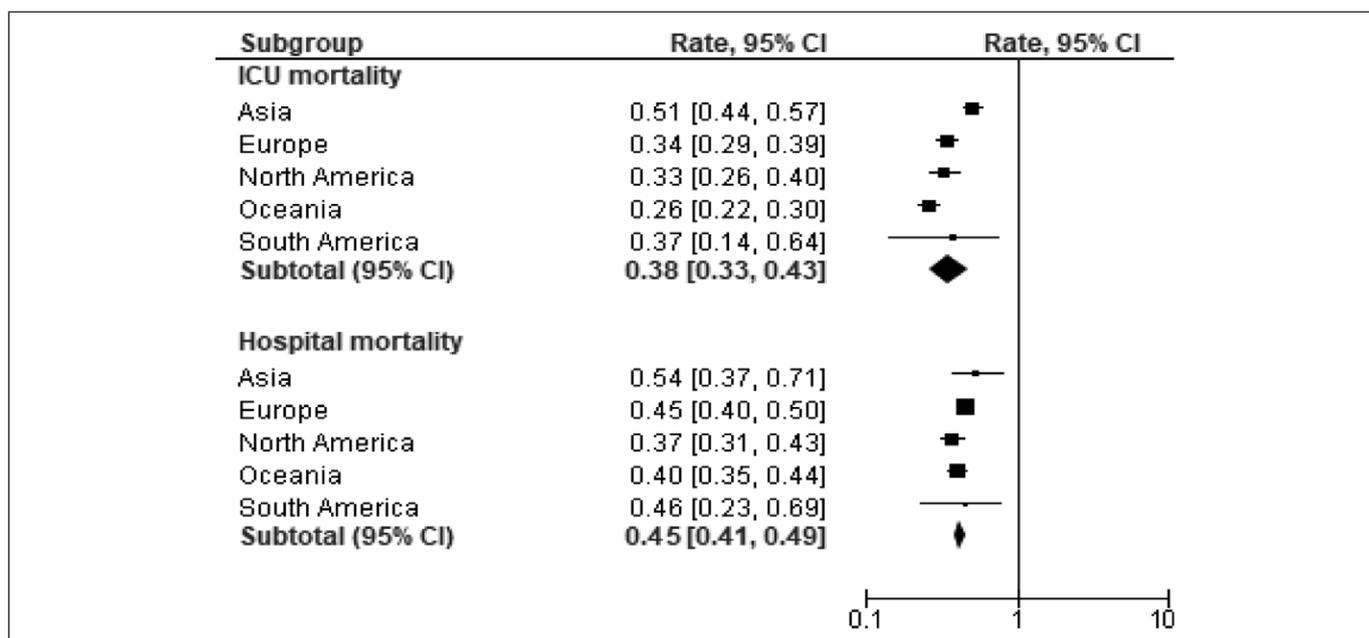


Figure 3. ICU (A) and hospital (B) mortality rates by continent. Boxes represent mortality rates, and the upper and lower ends of the boxes represent 95% CIs.

malignancies. Seven studies reported data enabling direct comparison of these subgroups (4, 14, 21, 26, 42, 50, 55). Patients with hematologic malignancies were 43% more likely to die in the hospital than were patients with solid malignancies (RR, 1.43; 95%

CI, 1.13–1.81; $I^2 = 96.3\%$) (**Supplementary Fig. 6**, <http://links.lww.com/CCX/B54>).

Length of ICU Stay. Thirty-seven studies reported data on length of stay in the ICU (4, 5, 16–19, 21, 23–25, 28, 29, 32–36, 38–52, 54–58). The WM length of

TABLE 2.

ICU and Hospital Mortality Rates for Patients With Hematologic and Solid Malignancies

Continent	Hematologic Malignancies			Solid Malignancies		
	No. of Studies	Pooled Mortality Rate (95% CI), %	I^2 , %	No. of Studies	Pooled Mortality Rate (95% CI), %	I^2 , %
ICU mortality						
Asia	7	54 (48–60)	68.4	9	48 (39–57)	95.1
Europe	10	44 (37–50)	96	9	23 (19–27)	80.1
South America	1	59 (50–68)	NA	1	35 (21–52)	NA
North America	4	38 (33–43)	53.5	3	24 (16–32)	98
Oceania	2	27 (23–31)	0	1	21 (14–30)	NA
Hospital mortality						
Asia	3	57 (51–63)	0	4	46 (35–57)	95.6
Europe	8	54 (47–61)	96.5	9	37 (32, 42)	84.3
South America	NA	NA	NA	2	56 (50–62)	0
North America	5	43 (42–45)	58.8	4	28 (21–36)	93.1
Oceania	2	41 (36–46)	0	1	33 (24–43)	NA

NA = not available.

Differences between groups $p < 0.0001$.

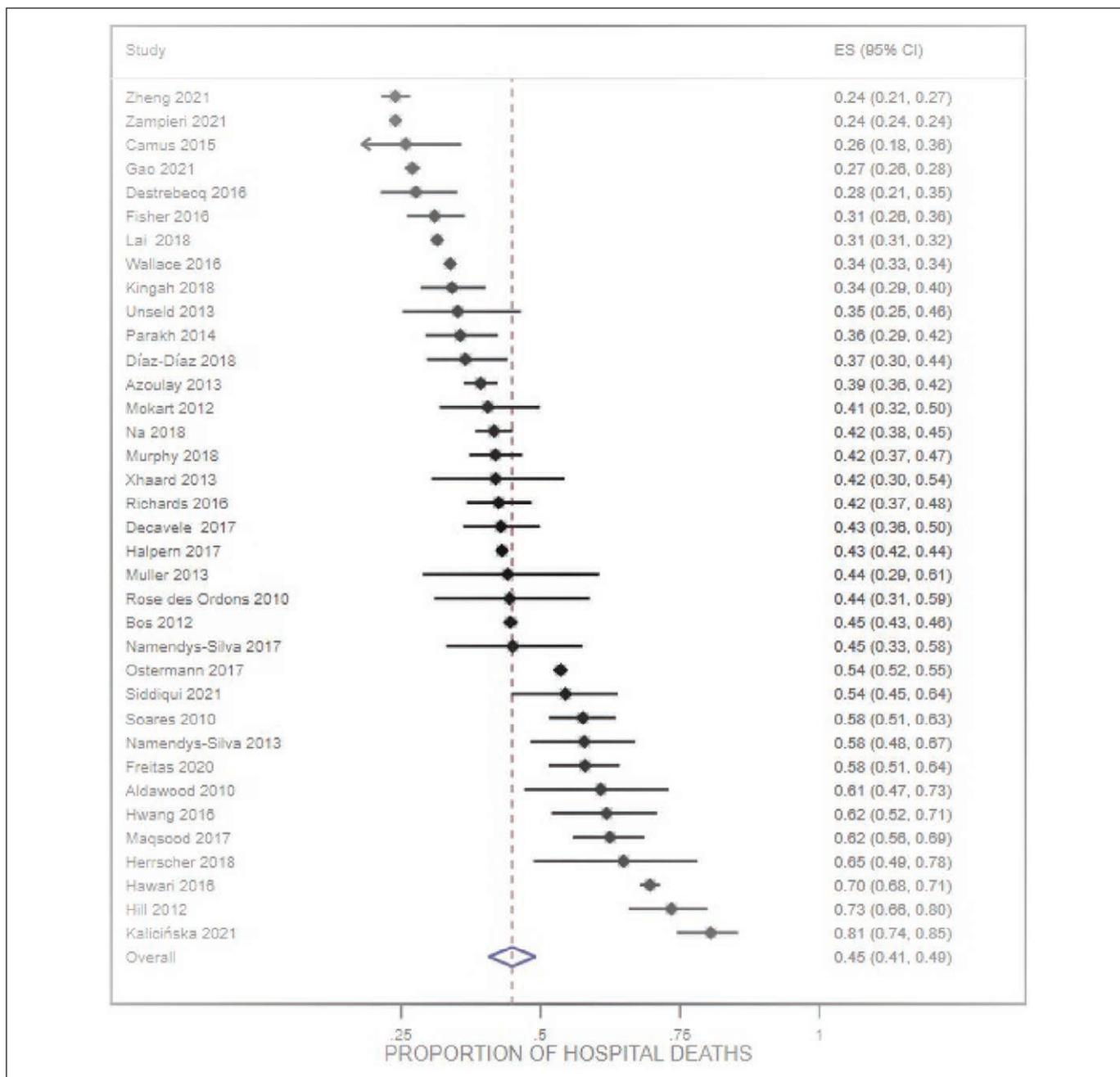


Figure 4. Hospital mortality rates in critically ill patients with cancer. *Horizontal bars* indicate 95% CIs; *black diamonds* indicate effect estimates (ES) for hospital mortality; and *blue diamond* indicates pooled hospital mortality rate.

stay was 5.9 days (95% CI, 5.3–6.5 d), and the median was 5.7 days (range, 2.7–23.7 d). By continent, the WM ICU lengths of stay (95% CI) and the medians (ranges) were (in days) as follows: Oceania, 3.81 (3.48–4.14) and 3.84 (3.67–4.00); Europe, 4.75 (3.27–6.24) and 6.0 (2.74–15.75); Asia, 5.4 (4.54–6.33) and 6.67 (4.50–23.65); South America, 6.08 (5.81–6.35) and 5.05 (3.47–6.33); North America, 6.55 (5.00–8.12) and 4.87 (3.50–9.40).

The WM length of ICU stay for patients with hematologic malignancies (considering 18 studies that provided data with or without a comparison group) was 6.8 days (95% CI, 5.7–7.9 d), and the median was 5.8 days (range, 3.7–15.8 d). The WM length of ICU stay for patients with solid tumors (considering 18 studies that provided data with or without a comparison group) was 4.6 days (95% CI, 3.8–5.5 d), and the median was 5.4 days (range, 2.2–23.7 d). The MD in ICU length of

stay between patients with hematologic malignancies and those with solid tumors (including only studies where the groups were directly compared) is shown in **Supplementary Figure 7** (<http://links.lww.com/CCX/B54>). Seven studies reported data for a direct comparison of these subgroups (4, 16, 18, 23, 34, 44, 57). A statistically significant difference in length of ICU stay was found between patients with hematologic and solid malignancies; on average, patients with hematologic malignancies had longer ICU stays (by more than a day) than did patients with solid malignancies (MD, 1.10; 95% CI, 0.49–1.70; $I^2 = 94.9\%$).

Reporting Bias and Exploration of Heterogeneity

There was no evidence of small-study effects (Egger test $p = 0.31$) in the funnel plot for the primary outcome assessed, namely risk of mortality in the ICU (**Supplementary Fig. 8**, <http://links.lww.com/CCX/B54>). Removing studies with a risk of confounding bias from the analyses did not change the direction of the results. Neither the median patient age nor the percentage of male patients included in the studies had an impact on the results. No differences were observed between groups when the mean length of stay was estimated with the quantile method or when studies with extrapolated data were removed from the analysis. After performing meta-regressions and correcting for multiple comparisons, we found that none of the patient characteristics had a statistically significant effect on our results. Sensitivity analysis showed that when studies analyzing ICU readmissions (not number of patients) or those without information on the type of data analyzed were removed, the pooled mortality rates remained similar, with no significant changes in the magnitude of the effect (ICU mortality, 36%; 95% CI, 27–45% and hospital mortality, 43%; 95% CI, 37–50%). Furthermore, when analyzing the cumulative evidence since 2010, the pooled ICU mortality rate remains virtually identical in all subsequent years until 2021 (37% in 2010 and 38% in 2021).

Certainty of Evidence

The evidence for the mortality rates and length of stay was judged to be of low quality due to limitations in study design (data from observational studies).

DISCUSSION

In this meta-analysis of 46 studies and over 100,000 patients, we found high ICU mortality rate (38%) and hospital mortality rate (45%). Compared with patients with solid tumors, patients with hematologic malignancies were 43% more likely to die in the hospital. In addition, we found wide variation in mortality rates by continent, and there were no studies from Africa were found.

Despite ongoing improvements in cancer patients' overall survival, the mortality rates of critically ill cancer patients remain high (59). A previous systematic review and meta-analysis of 30 studies published between 2005 and 2015 reported an overall hospital mortality rate of 47.7% in 7,515 critically ill cancer patients (59). Although mortality rates remained high, that analysis showed an annual decrease in mortality, consistent with previous reports of a downward trend in mortality in this patient population (4, 5). In spite of these reported improvements, patients with hematologic malignancies have higher mortality rates, compared with patients with solid tumors. In a study of a large single-center cohort of 387,306 cancer patients over 20 years, Wallace et al (4) reported ICU and hospital mortality rates of 18.3% and 25.2%, respectively, for solid tumor patients and 34.6% and 42.6% for patients with hematologic cancers.

In contrast to these high rates of mortality among cancer patients in ICUs, overall ICU mortality rates for noncancer patients are lower. The worldwide Intensive Care Over Nations (ICON) audit, which included 10,069 patients from 730 centers and 84 countries, reported ICU and hospital mortality rates of 16.2% and 22.4%, respectively (60). The more recent and likewise worldwide End-of-Life Practices in European Intensive Care Units (ETHICUS) II study reported a mortality rate 12% in a prospective cohort of 87,951 patients admitted to 199 ICUs in 36 countries (61). These two studies also showed that cancer patients had a lower ICU utilization rate than noncancer patients (14.2% and 9.6%, respectively), and this difference alone may explain the difference between these reported mortality rates and ours (60, 61).

Notably, both the ICON and ETHICUS II studies showed significant differences in mortality across regions, aligning with our results. ICU mortality was lowest in Oceania and highest in Asia, ranging from 13% to 70% across regions. Hospital mortality rates

were lowest in North America, followed closely by Oceania, and highest again in Asia, ranging from 24% to 81% across continents. These differences could be associated with regional or national differences in ICU admission policies and practices, healthcare access, and severity of illness, among other factors. For example, previous observations suggested that ICU patients in North America may be less severely ill than those in other regions, as up to 40% of North American ICU admissions were for monitoring purposes (62). The markedly higher ICU bed capacity in countries with the highest gross national income and the limited availability of ICU care in countries with lower national incomes could have also played a role in the observed differences (60).

We reported higher mortality rates and longer ICU stays in patients with hematologic malignancies compared with those with solid tumors. These results remained unchanged even after adjustment for sample size, age, sex, and follow-up period. However, we were unable to determine if this difference was related to a difference in the severity of critical illnesses or the underlying malignancy. Future studies are necessary to provide a better understanding of such observations.

Compared with the rest of the world, the number of publications evaluating critically ill cancer patients from Europe was disproportionately higher, compared with the other continents. In addition, no studies were published from Africa, which represents the second largest continent in the world. This disparity may lead to an underestimation of the burden of critical illness in regions that are not proportionately represented in the literature and may suggest that the literature does not provide a true representation of the burden of critical illness worldwide. An earlier study assessed worldwide scientific contributions in the field of critical care medicine (63). Although the study evaluated the time frame between 1995 and 2003 and was not limited to critical care oncology, the authors found substantial differences in research productivity between regions; research productivity was highest in Western Europe and the United States and lowest in Africa. Variability in research productivity has also been reported among countries within the same region. Despite the difficulties encountered (64), developing research capacity-building programs in countries with low research productivity is essential to better understand critical illnesses and to improve the outcomes of patients worldwide (65, 66).

This study has some limitations due to the observational nature of its data. The included studies may have been affected by selection bias and by institution-specific admission criteria that were not clearly defined in the studies. Potential confounding bias was another possibility, given that several variables that may affect patient outcomes, such as the stage of malignancy, patients' baseline performance status, underlying comorbidities, duration of organ support, and changes to code status in the ICU. In addition, the pathogenesis of various critically ill conditions and details of the therapeutic and medical management of patients may very likely vary among countries. Nonetheless, data from observational studies can help to inform a question when randomized trials are not available. Furthermore, we classified countries based on the continents, which has its limitations since there are various differences in healthcare and resources among countries within the same continent. Although we understand that there is no specific classification that would include a homogenous group of countries, we chose the classification based on continents to provide findings that may help in developing strategic initiatives at a regional level.

CONCLUSIONS

In this large meta-analysis evaluating mortality in critically ill cancer patients, although there was high ICU and hospital mortality rates, more than half of the patients survived hospitalization. Compared with patients with solid tumors, patients with hematologic malignancies had higher mortality rates and longer ICU stays. In addition, there was wide variability in both mortality rates and the number of available studies among geographical regions. This variability suggests an opportunity to improve outcomes worldwide, through optimizing practice and research.

ACKNOWLEDGMENTS

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

- 1 Department of Pharmacy, King Hussein Cancer Center, Amman, Jordan.
- 2 Department of Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX.

- 3 Department of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX.
- 4 Department of Pharmacy, Houston Methodist Hospital, Houston, TX.
- 5 Department of Pharmacy, King Fahad Specialist Hospital, Dammam, Saudi Arabia.
- 6 Department of Pharmacy, Mayo Clinic, Rochester, MN.
- 7 Department of Pharmacy, University of New Mexico Hospitals, Albuquerque, NM.
- 8 Medical Library, Houston Methodist Hospital, Houston, TX.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejournal>).

Dr. Nates's work is supported in part by a Cancer Center Support Grant from the National Institutes of Health/National Cancer Institute (award number P30CA016672). Dr Lopez's work is supported by a career award from the National Cancer Institute (no. K08CA237619). The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: lnazer@khcc.jo

REFERENCES

1. Nates JL, Wallace SK, Price KJ: The authors reply. *Crit Care Med* 2016; 44:e1254–e1255
2. Azoulay E, Shimabukuro-Vornhagen A, Darmon M, et al: Critical care management of chimeric antigen receptor T cell-related toxicity. Be aware and prepared. *Am J Respir Crit Care Med* 2019; 200:20–23
3. Siegel RL, Miller KD, Goding Sauer A, et al: Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; 70:145–164
4. Wallace SK, Rathi NK, Waller DK, et al: Two decades of ICU utilization and hospital outcomes in a comprehensive cancer center. *Crit Care Med* 2016; 44:926–933
5. Zampieri FG, Bastos LSL, Soares M, et al: The association of the COVID-19 pandemic and short-term outcomes of non-COVID-19 critically ill patients: An observational cohort study in Brazilian ICUs. *Intensive Care Med* 2021; 47:1440–1449
6. Azoulay E, Soares M, Darmon M, et al: Intensive care of the cancer patient: Recent achievements and remaining challenges. *Ann Intensive Care* 2011; 1:5
7. Manjappachar NK, Cuenca JA, Ramírez CM, et al: Outcomes and predictors of 28-day mortality in patients with hematologic malignancies and septic shock defined by sepsis-3 criteria. *J Natl Compr Canc Netw* 2022; 20:45–53
8. Awad WB, Nazer L, Elfarr S, et al: A 12-year study evaluating the outcomes and predictors of mortality in critically ill cancer patients admitted with septic shock. *BMC Cancer* 2021; 21:709
9. Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71
10. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al: PRISMA-S Group: PRISMA-S: An extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev* 2021; 10:39
11. Ouzzani M, Hammady H, Fedorowicz Z, et al: Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016; 5:210
12. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al: The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 3, 2021
13. Wan X, Wang W, Liu J, et al: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14:135
14. Holger S, Jan B, Gordon G, et al; The GRADE Working Group: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013. Available at: <https://gdt.grade.org/app/handbook/handbook.html>. Accessed August 20, 2022.
15. Azoulay E, Mokart D, Pène F, et al: Outcomes of critically ill patients with hematologic malignancies: Prospective multi-center data from France and Belgium—a groupe de recherche respiratoire en réanimation onco-hématologique study. *J Clin Oncol* 2013; 31:2810–2818
16. Bos MM, de Keizer NF, Meynaar IA, et al: Outcomes of cancer patients after unplanned admission to general intensive care units. *Acta Oncol* 2012; 51:897–905
17. Kalicińska E, Kuszczak B, Dębski J, et al: Hematological malignancies in Polish population: What are the predictors of outcome in patients admitted to intensive care unit? *Support Care Cancer* 2021; 29:323–330
18. McGrath S, Chatterjee F, Whiteley C, et al: ICU and 6-month outcome of oncology patients in the intensive care unit. *QJM* 2010; 103:397–403
19. Mokart D, Etienne A, Esterni B, et al: Critically ill cancer patients in the intensive care unit: Short-term outcome and 1-year mortality. *Acta Anaesthesiol Scand* 2012; 56:178–189
20. Murphy K, Cooksley T, Haji-Michael P: Short- and long-term outcomes of patients with solid tumours following non-surgical intensive care admission. *QJM* 2018; 111:379–383
21. Ostermann M, Ferrando-Vivas P, Gore C, et al: Characteristics and outcome of cancer patients admitted to the ICU in England, Wales, and Northern Ireland and national trends between 1997 and 2013. *Crit Care Med* 2017; 45:1668–1676
22. Pohlen M, Thoennissen NH, Braess J, et al: Patients with acute myeloid leukemia admitted to intensive care units: Outcome analysis and risk prediction. *PLoS One* 2016; 11:e0160871
23. Unseld S, Schuepbach RA, Maggiorini M: ICU, hospital and one year mortality of patients suffering from solid or haematological malignancies. *Swiss Med Wkly* 2013; 143:w13741
24. Xhaard A, Epelboin L, Schnell D, et al: Outcomes in critically ill chronic lymphocytic leukemia patients. *Support Care Cancer* 2013; 21:1885–1891
25. Camus MF, Ameye L, Berghmans T, et al: Rate and patterns of ICU admission among colorectal cancer patients: A single-center experience. *Support Care Cancer* 2015; 23:1779–1785
26. Decavèle M, Weiss N, Rivals I, et al: Prognosis of patients with primary malignant brain tumors admitted to the intensive care unit: A two-decade experience. *J Neurol* 2017; 264:2303–2312
27. Destrebécq V, Lieveke A, Berghmans T, et al: Are intensive cares worthwhile for breast cancer patients: The experience of an oncological ICU. *Front Med (Lausanne)* 2016; 3:50

28. Díaz-Díaz D, Villanova Martínez M, Palencia Herrejón E: Oncological patients admitted to an intensive care unit. Analysis of predictors of in-hospital mortality. *Med Intensiva* 2018; 42:346–353
29. Fisher R, Dangoisse C, Crichton S, et al: Short-term and medium-term survival of critically ill patients with solid tumours admitted to the intensive care unit: A retrospective analysis. *BMJ Open* 2016; 6:e011363
30. Herrscher H, Artzner T, Severac F, et al: Intensive care for patients with gastric cancers: outcome and survival prognostic factors. *J Gastrointest Oncol* 2019; 10:292–299
31. Hill QA, Kelly RJ, Patalappa C, et al: Survival of patients with hematological malignancy admitted to the intensive care unit: prognostic factors and outcome compared to unselected medical intensive care unit admissions, a parallel group study. *Leuk Lymphoma* 2012; 53:282–288
32. Horster S, Stemmler HJ, Mandel PC, et al: Mortality of patients with hematological malignancy after admission to the intensive care unit. *Onkologie* 2012; 35:556–561
33. Aldawood AS: Prognosis and resuscitation status of critically ill patients with lung cancer admitted to the intensive care unit. *Anaesth Intensive Care* 2010; 38:920–923
34. Aygencel G, Turkoglu M, Turkoz Sucak G, et al: Prognostic factors in critically ill cancer patients admitted to the intensive care unit. *J Crit Care* 2014; 29:618–626
35. Oğul A, Paydas S, Karacoç E, et al: Factors predicting prognosis with oncology patients followed in the intensive care unit. *Cukurova Med J* 2020; 45:1267–1275
36. Siddiqui SS, Narkhede AM, Chaudhari HK, et al: Clinicodemographic and outcome predictors in solid tumor patients with unplanned intensive care unit admissions: An observational study. *Indian J Crit Care Med* 2021; 25:1421–1426
37. Cheng Q, Liu J, Yang Q, Wang E, Shen X, Khoshnood K, et al: Factors affecting the prognosis of cancer patients in general intensive care units in a Chinese population. *Int J Clin Exp Med* 2016;9:14294–14303
38. Ediboğlu Ö, Kirakli SC, Yazicioğlu Moçin Ö, Güngör G, Anar C, Çimen P, et al: Predictors of mortality in cancer patients who need intensive care unit support: A two center cohort study. *Turkish J Med Sci* 2018;48:744–749
39. Hawari FI, Nazer LH, Addassi A, et al: Predictors of ICU admission in patients with cancer and the related characteristics and outcomes: A 5-year registry-based study. *Crit Care Med* 2016; 44:548–553
40. Hwang KE, Seol CH, Hwang YR, et al: The prognosis of patients with lung cancer admitted to the medical intensive care unit. *Asia Pac J Clin Oncol* 2016; 12:e118–e124
41. Kekecoglu A, Dalar L, Omaygenc DO, et al: Intensive care in cases with thoracic and extrathoracic malignant solid tumours: Indications and survival. *Pneumon* 2015; 28:222–229
42. Lai CC, Ho CH, Chen CM, et al: Risk factors and mortality of adults with lung cancer admitted to the intensive care unit. *J Thorac Dis* 2018; 10:4118–4126
43. Maqsood S, Badar F, Hameed A: Characteristics and outcomes of patients with hematological malignancies admitted for intensive care - A single centre experience. *Asian Pac J Cancer Prev* 2017; 18:1833–1837
44. Na SJ, Ha TS, Koh Y, et al: Validation of Simplified Acute Physiology Score 3 in Korean Intensive care unit (VSKI) study group; Korean Study Group On Respiratory Failure (KOSREF): Characteristics and clinical outcomes of critically ill cancer patients admitted to Korean intensive care units. *Acute Crit Care* 2018; 33:121–129
45. Kingah P, Alzubaidi N, Yafawi JZD, et al: Factors associated with mortality in patients with a solid malignancy admitted to the intensive care unit - A prospective observational study. *J Crit Care Med (Targu Mures)* 2018; 4:137–142
46. Kraguljac AP, Croucher D, Christian M, et al: Outcomes and predictors of mortality for patients with acute leukemia admitted to the intensive care unit. *Can Respir J* 2016; 2016:3027656
47. Gao S, Wang Y, Yang L, et al: Characteristics and clinical subtypes of cancer patients in the intensive care unit: A retrospective observational study for two large databases. *Ann Transl Med* 2021; 9:13–13
48. Halpern AB, Culakova E, Walter RB, et al: Association of risk factors, mortality, and care costs of adults with acute myeloid leukemia with admission to the intensive care unit. *JAMA Oncol* 2017; 3:374–381
49. Namendys-Silva SA, González-Herrera MO, García-Guillén FJ, et al: Outcome of critically ill patients with hematological malignancies. *Ann Hematol* 2013; 92:699–705
50. Namendys-Silva SA, Barragán-Dessavre M, Bautista-Ocampo AR, et al: Outcome of critically ill patients with testicular cancer. *Biomed Res Int* 2017; 2017:3702605
51. Roze des Ordon AL, Chan K, Mirza I, et al: Clinical characteristics and outcomes of patients with acute myelogenous leukemia admitted to intensive care: A case-control study. *BMC Cancer* 2010; 10:516
52. Zheng B, Reardon PM, Fernando SM, et al: Costs and outcomes of patients admitted to the intensive care unit with cancer. *J Intensive Care Med* 2021; 36:203–210
53. Corrêa LC, Teles D, Silva OBD, et al: Predictors of mortality among patients with acute leukemias admitted to an intensive care unit specialized in patients with hematological disease at a Brazilian hospital. *Hematol Transfus Cell Ther* 2020; 42:33–39
54. de Freitas ICL, de Assis DM, Amendola CP, et al: Characteristics and short-term outcomes of patients with esophageal cancer with unplanned intensive care unit admissions: A retrospective cohort study. *Rev Bras Ter Intensiva* 2020;32:229–234
55. Müller AM, Gazzana MB, Silva DR: Outcomes for patients with lung cancer admitted to intensive care units. *Rev Bras Ter Intensiva* 2013; 25:12–16
56. Soares M, Caruso P, Silva E, et al: Brazilian Research in Intensive Care Network (BRICNet): Characteristics and outcomes of patients with cancer requiring admission to intensive care units: A prospective multicenter study. *Crit Care Med* 2010; 38:9–15
57. Parakh S, Piggan A, Neeman T, et al: Outcomes of haematology/oncology patients admitted to intensive care unit at the Canberra Hospital. *Intern Med J* 2014; 44:1087–1094
58. Richards S, Wibrow B, Anstey M, et al: Determinants of 6-month survival of critically ill patients with an active hematologic malignancy. *J Crit Care* 2016; 36:252–258

59. Darmon M, Bourmaud A, Georges O, et al: Changes in critically ill cancer patients' short-term outcome over the last decades: Results of systematic review with meta-analysis on individual data. *Intensive Care Med* 2019; 45:977–987
60. Vincent JL, Marshall JC, Namendys-Silva SA, et al; ICON investigators: Assessment of the worldwide burden of critical illness: The intensive care over nations (ICON) audit. *Lancet Respir Med* 2014; 2:380–386
61. Avidan A, Sprung CL, Schefold JC, et al; ETHICUS-2 Study Group: Variations in end-of-life practices in intensive care units worldwide (Ethicus-2): A prospective observational study. *Lancet Respir Med* 2021; 9:1101–1110
62. Zimmerman JE, Kramer AA: A model for identifying patients who may not need intensive care unit admission. *J Crit Care* 2010; 25:205–213
63. Michalopoulos A, Kasiakou SK, Falagas ME: The significance of different formulations of aerosolized colistin. *Crit Care* 2005; 9:417–418; author reply 417
64. Reyes MP, Cuenca JA, Heatter J, et al: Tribulations of conducting critically ill cancer patients research: Lessons from a failed septic shock trial and Murphy's law. *Med Intensiva* 2021. doi: HYPERLINK "https://www.medintensiva.org/es-tribulations-conducting-critically-ill-cancer-avance-S0210569121002709"10.1016/j.medin.2021.10.007
65. Elaibaid M, Nazer LH, Shaikha L, et al: Evaluating the published critical care research from the World Health Organization eastern mediterranean region. *BMC Res Notes* 2019. doi:10.1186/s13104-019-4093-7
66. Nazer LH, Kleinpell R, Olsen K, et al: Capacity building for research in critical care: A pilot program in the eastern mediterranean region. *Crit Care Explor* 2021; 3:e0315