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SYSTEMATIC REVIEW

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Survival in solid cancer patients following intensive care unit admission

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Abstract *Purpose:* One in seven patients admitted to intensive care units (ICU) has a cancer diagnosis but evidence on their expected outcomes after admission has not been synthesised. *Methods:* Systematic literature review of solid cancer adult patients admitted to ICU from 2000 onwards using EMBASE and MEDLINE electronic databases. *Results:* There were 48 papers identified that reported survival in ICU patients with solid cancers. ICU mortality was reported in 35 studies comprising a total sample of 25,339 patients and ranging from 4.5 to 85 %. The average mortality of the distribution of reported mortality rates within ICU was 31.2 % (95 % CI 24.0–39.0 %). Hospital mortality was reported in 31 studies across a total sample of 74,061 patients. The average hospital mortality was 38.2 % (33.8–42.7 %) and ranged from 4.6 to 76.8 %. Poorer physiological score, invasive mechanical ventilation and poor functional status were associated with higher mortality. *Conclusions:* Several factors have been associated with poor survival in ICU cancer patients; however, primary research is still needed to describe outcomes in cancer patients with sufficient case mix and treatment details to be of prognostic value to clinicians.

Keywords Cancer · Intensive care · Critical illness · Co-morbidity

Introduction

Advances in oncology have led to a dramatic reduction in mortality rates in cancer patients over the past few decades [1]. However, this has come at the cost of using more complex and intensive cytotoxic and immunosuppressive regimens, in addition to undertaking major surgical procedures in patients who would previously received palliative care. As a result, there is an increasing demand for critical care input to support patients through these therapies or the complications that arise as a consequence.

Around one in seven patients admitted to general intensive care units (ICU) in Europe have a malignancy, the majority being solid tumours [2]. Multiple organ support can be offered but the burden of treatment can be significant for patients and therefore it is only undertaken when there is a reasonable expectation of survival [3]. Much of the controversy regarding ICU care of cancer patients surrounds expected survival in this group of patients. It may not always be appropriate to provide intensive care and organ support to patients with a reversible illness but an otherwise terminal process. In

cancer patients, there are increasing questions about whether too much effort is made to prolong life at the cost of poorer quality in the last few months of life. For those patients approaching the end of their life, it has been recognised that care should be less medicalised and occur outside the hospital environment [4].

Due to these concerns, the presence of cancer is the second most common reason cited by intensive care physicians for refusal of ICU admission [5]. However, there may be a cohort of cancer patients who would benefit from an ICU admission but are refused on the basis of prejudices against this patient population. Cancer is one of many chronic comorbid conditions that are common in the ICU population. It is likely that the presence of chronic conditions has an influence on prognosis, and it has been recognised elsewhere that further work is required to determine the impact of cancer and other comorbidities on ICU outcomes [6].

The challenge facing ICU physicians is to identify which cancer patients are likely to benefit from ICU care and in which patients the expected outcome is unacceptable to justify the burdens of ICU. With an enhanced understanding of what happens to cancer patients with critical illness, clinicians would be in a better position to give prognostic information regarding expected outcomes. This would facilitate open discussion and better inform patients and relatives as well as physicians when making admission decisions pertaining to cancer patients.

While there have been a number of reports on outcomes of cancer patients after admission to ICU, to our knowledge there has been no attempt to systematically review their findings and assess the quality of evidence currently available. The aim of our study was to assess mortality among cancer patients admitted to ICU by carrying out a systematic review of published studies and to synthesise the results using both a narrative synthesis and the distribution of published mortality.

Methods

We carried out a systematic review of published literature and summarised the distribution of reported mortality using preferred reporting items for systematic reviews and meta-analyses guidelines [7].

Study identification and eligibility criteria

To be included in the review, the study had to report survival outcomes in patients with known malignancy (solid tumours) who had been admitted to a critical care area, that is, intensive care (or treatment) unit. We limited the study to solid cancers as survival in haematological cancers has been associated with consistently poorer ICU survival that has varied with time.

Two electronic databases (OVID MEDLINE and EMBASE to April 2014) were searched using a combination of medical subject headings (MeSH), title and abstract keywords. The MeSH terms "neoplasm" and "critical care"/"intensive care"/"ICU"/"critical illness" were exploded and articles containing both terms were combined. We then searched for the terms "death", "mortality", "surviv$", "prognos$", "hospital$" or "outcome". Articles that featured in both searches were then limited to those human studies published in English. We excluded paediatric studies and review articles from the search.

Study selection and data extraction

From the initial search results, a title review was performed by two separate reviewers (K.P., D.S.M.). Editorials, letters or case reports were excluded. Studies were required to report survival outcomes in patients with solid tumours admitted to ICU/critical care. Where only one reviewer felt that the title may represent an article of interest, the abstract was sought. The abstracts were then scrutinised by both reviewers before obtaining the full text of all relevant articles. Where additional potential studies were identified by hand-searching or expert recommendation, they were reviewed for eligibility in the same way as studies identified from electronic databases.

Studies were excluded if the study population entirely pre-dated 1 January 2000, if outcomes were reported for solid tumours mixed with haematological tumours, or if the study reported outcomes from a study population that had already been included in another study. This date was chosen to ensure data were contemporaneous with current ICU management practices [8–10].

Data describing the study population were collected from each paper. Several studies only reported the average age and severity of illness scores for a mixed cohort of patients with solid and haematological tumours and did not differentiate patients with solid tumours. We did not place any restrictions on these studies. Reported survival data were collected, which was most commonly ICU mortality, hospital mortality, 6-month mortality and 1-year mortality. The authors were contacted for additional information when clarification was required.

STROBE criteria were used to examine what was reported in each study including study design, variables, data sources, participants, descriptive data and outcome data [11].

Distribution of mortality estimates

ICU and hospital mortality with exact 95 % confidence intervals (CIs) were calculated for each study. The

distribution of mortality rates was examined and summarised using the Freeman–Tukey double arcsine transformation to estimate the average of the mortality distribution with 95 % CIs. Random-effects estimates were used to take account of heterogeneity between studies.

Consistency between study outcomes was assessed using the Chi square test for homogeneity. The extent of variation between study outcomes was measured using the I^2 statistic. This indicates the proportion of the total variation across study outcomes attributable to heterogeneity. Values greater than 50 % suggest substantial heterogeneity.

Regression and stratified analyses were used to examine the role of selected study-level characteristics (for example, location, setting and severity) in contributing to differences between study outcomes. There was insufficient study information to generate informative results from multivariable meta-regression and only univariable analyses were performed. All statistical analyses were performed using Stata v.13.1 (Stata, College Station, TX, USA).

Results

Electronic database searches identified 668 references to April 2014 of which 48 papers were included in the final selection. The studies broadly fell into two groups: those reporting on a mixture of solid cancers together, and those reporting on specific tumour types. Details of the selection processes are described in Fig. 1.

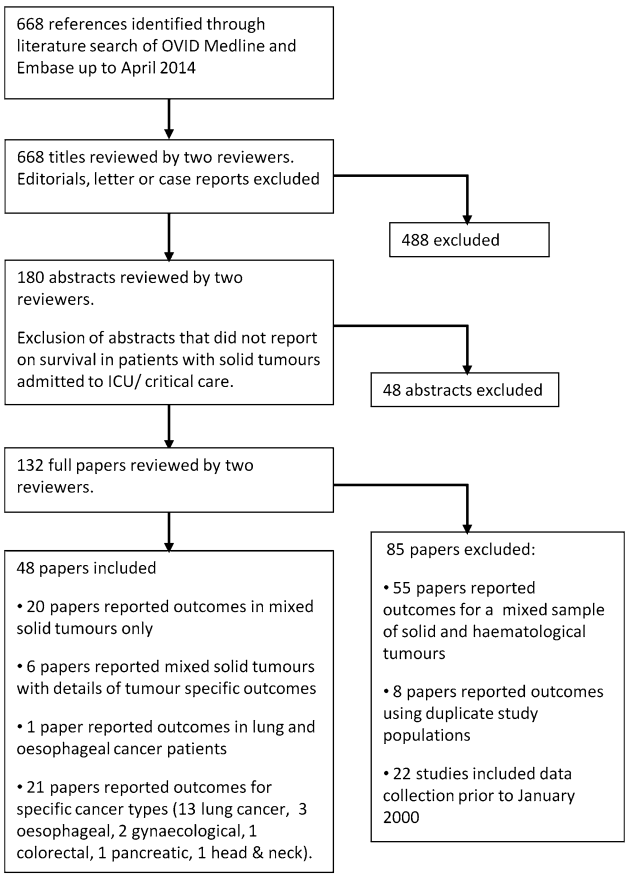

Fig. 1 Flowchart of study selection

Study characteristics

We identified 48 studies that reported mortality (including short-term ICU or in-hospital mortality) for patients with solid tumours after admission to ICU (Table 1) [2, 12–58]. While the inclusion criteria required that admissions from 2000 onward were reported, the studies spanned admissions between 1997 and 2011. Where cancer site-specific outcomes were reported, the commonest (20 studies) were for lung cancers. Four papers each reported head and neck and colorectal cancers; oesophageal, breast and pancreatic cancers were each reported in three papers; stomach and gynaecological cancers each had two papers; and single papers were identified for upper gastrointestinal, all gastrointestinal, urological, prostate and melanomas. Soares et al. has published several outcome studies on a cohort of patients from May 2000 variously to December 2004 [59], to December 2005 [60], and to January 2004 [47, 61], and we chose the single most comprehensive of these papers [47].

The mean age of patients, where given, ranged from 47 to 75 years and, unless tumours were sex-specific, patients comprised a mixture of men and women. Where the presence of metastatic disease was reported, this ranged from 0–100 %. Twenty-two studies were from Europe, ten were from Brazil and nine from North America. Slatore's study was the largest [46], with 49,373 patients whilst Azoulay et al., Darmon et al., and Song et al. reported on all cancer patients of which solid tumours made up 10, 12 and 13 patients, respectively [16] [25] [52]. The majority of the studies (36/48, 75 %) included a measure of physiological status, and there was wide variation between them; 20 studies provided mean SAPS II scores, ranging from 25.1 to 63.4, and 15 studies gave mean APACHE II scores, ranging from 10.3 to 25.6.

We considered bias in each of the studies, using information reported under PRISMA criteria. With respect to information or measurement biases, it is possible that studies misclassified whether or not patients had cancer, or misclassified the site of the primary tumour. However, because no additional sources of information were available to validate the classification, we were unable to evaluate the extent, if any, of such biases. As all studies reported total and not cause-specific mortality, misclassification of outcomes is unlikely, although the timing of death may have been incorrect. Mortality could

Table 1 Characteristics of studies reporting short term mortality for patients with solid cancers admitted to ICU

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
Adam et al. [12]	USA 1998–2005; single centre general ICU	Retrospective	139 lung cancer patients admitted to MICU	ICU stay <24 h, routine postoperative care, cancer remission >2 years, ICU readmission	139; NSCLC (69 %), SCLC (13 %)	40	SAPS III 41.8 (22.9), APACHE III 59.0 (25.1)	64.2 (10.2)
Aldawood [13]	Saudi Arabia 1999–2009; single centre general ICU	Prospective	51 ICU patients with lung cancer	Postoperative lung resection patients, age <16 years, brain death victims	51; NSCLC (51 %) SCLC (14 %)	–	APACHE II 25.6 (8.13)	58 (16.2)
Andréjak et al. [14]	France 1996–2006; 2 general MICUs	Retrospective	76 patients with advanced lung cancer (no curative surgical option, stage 3B, 4 NSCLC or SCLC) requiring MICU admission	Lung cancer diagnosed/ staged after ICU admission, disease remission >5 years, ICU stay <24 h (except if died), routine postoperative care, readmissions	76; NSCLC (64.5 %), SCLC (38.2 %)	59.2	SAPS II 43 (16.5), APACHE II 22 (7.7)	63.0 (9.9)
Anisoglou et al. [15]	Greece 2008–2011; single centre oncological ICU	Retrospective	105 lung cancer patients with acute respiratory failure requiring ICU	ICU stay <24 h, routine postoperative care	105 lung cancer patients; 80 % NSCLC, 13 % SCLC	72.4	APACHE II 23.4, SOFA 9.4	68.3 (10.4)
Azoulay et al. [16]	France 1997–2002; single centre general ICU Prospective		203 patients with haematological/ solid tumours admitted to ICU with acute respiratory failure	Nil	19; lung (52.6 %), breast (47.4 %)	–	–	53[a] (41-63)
Bissell et al. [17]	UK 1998–2009; single centre general ICU	Retrospective	43 patients requiring readmission to ICU following elective oesophagectomy for malignancy	Nil	43 oesophageal cancer patients; adenocarcinoma (90.7 %), squamous cell (4.7 %), GIST (4.7 %)	0	–	65 (1.6)
Bonomi et al. [18]	USA 1992–2005; multicentre ICUs	Retrospective	1,134 patients with NSCLC stage IIIB/IV admitted to MICU with respiratory, cardiac, or neurological diseases, renal failure, or sepsis	Age < 65 years	1134 NSCLC; adenocarcinoma (45.4 %), squamous cell (32.2 %), large cell (8.6 %), other (13.8 %)	54.5	–	73 (69–78)
Bos et al. [19]	Netherlands 2007–2011; 80 general ICUs	Retrospective	15,211 patients with an APACHE IV diagnosis of haematological or solid tumour and an unplanned admission to ICU	Elective ICU admission	12,290 patients with solid tumours	30	APACHE IV 88.1 (36.3)[a]	–

Table 1 continued

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
Caruso et al. [20]	Brazil; single centre oncological ICU	Retrospective	83 patients with metastatic solid cancer admitted to ICU during 1 calendar year	Readmissions	83; breast (19.3 %), lung (14.5 %), head & neck (8.4 %), colon (6 %), stomach (6 %), melanoma (6 %), prostate (6 %), pancreas (4.8 %)	100	SAPS II 47.5 (40–60)	61.4 (51–71)
Cense et al. [21]	Netherlands 1994–2000; 2 general ICUs	Prospective	109 patients undergoing a transthoracic resection for adenocarcinoma of the middistal esophagus or gastric cardia	Age <18 years, ASA >3	109; oesophageal (100 %)	14.7	–	62
Chawla et al. [22]	USA 2004–06, single centre oncological ICU	Retrospective	25 patients with solid/ haematological cancer admitted to ICU within 48 h of planned or actual hospital discharge	Nil	21; bladder (14.3 %), colorectal (7.1 %), lung (14.3 %), pancreatic (7.1 %)	–	–	63.9 (15.9)
Chou et al. [23]	Taiwan 2007–2008, single general ICU	Retrospective	70 patients with stage III–IV lung cancer requiring mechanical ventilator support for sepsis-related respiratory failure	Nil	70; lung (100 %)		APACHE II 24.3 (6.7) SOFA 7.1 (3.1)	74.5 (12.0)
Christodoulou et al. [24]	Greece 2001-05; single centre general ICU	Retrospective	69 patients with solid tumours admitted to ICU	Routine postoperative monitoring	69; lung (39.1 %), colorectal (13 %), ovarian (8.6 %), breast (7.2 %), pancreas (5.8 %), prostate (5.8 %), brain (4.3 %), nasopharynx (4.3 %), bladder (4.3 %), kidney (2.9 %), stomach (2.9 %), oesophagus (1.4 %)	89.9	APACHE II 18.1 (8.3)	61.3 (13.3)
Darmon et al. [25]	France 1997–2003; single centre general ICU	Prospective	100 patients with organ failure, inoperable solid tumour or hematologic malignancy diagnosed < 30 days before ICU admission, in immediate need of chemotherapy and eligible to receive chemotherapy	Previous chemotherapy	12; sarcoma (33 %), breast (17 %), testicular (17 %), NSCLC (8 %)	–	SAPS II 39 (30–48)	47 (32–61)

Table 1 continued

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
de Almeida et al. [26]	Brazil 2009; single centre oncology ICU	Prospective	122 patients with solid or haematological tumour admitted to ICU	Age < 18 years old, palliative care, haemorrhagic shock, end-stage renal disease, patients in other studies, expected death within 24 h, discharged within 24 h	106; not specified	35.2	APACHE II 14 (10–20)[a]	63 (61–65)[a]
Ertan et al. [27]	Turkey 1998–2004; single centre general ICU	Not stated	102 patients who underwent emergency surgery for colorectal cancer and admitted to ICU	Diagnostic uncertainty or insufficient clinical data	102; colorectal (100 %)	–	–	61 (18–97)
Jennens et al. [28]	Australia 1993–2001; 3 general ICUs	Retrospective	20 patients with lung cancer (SCLC) admitted to ICU	Nil	20; SCLC (100 %)	–	–	67
Kopterides et al. [29]	Greece 2005–07; 2 general ICUs	Prospective	126 patients with solid/ haematological cancer admitted to ICU	Age < 18 years, ICU readmissions, routine post-op monitoring	90; lower GI (33.3 %), upper GI (25.6 %), urogenital (14.4 %), lung (12.2 %), breast (8.9 %)	–	SOFA 8.0 (5.0), SAPS II 45.1 (22.2), APACHE II 18.8(10.1)	65.3 (14.4)
Leath et al. [30]	USA 1999–2004; single centre general ICU	Retrospective	185 gynaecological oncology patients admitted to ICU following surgery	Patients undergoing outpatient procedures or surgery at a different centre or non-surgical admissions	185; Ovarian (39 %), Endometrial (21 %), cervical (12 %), other (8 %), benign disease (20 %)	–	APACHE II 11.6	60
Lecuyer et al. [31]	France 2001–04, single general ICU	Prospective	188 consecutive patients with solid/haematological cancer requiring mechanical ventilation and presence of at least one other organ failure	HIV, allogenic stem cell transplant recipients	56; lung and breast (46 %)	–	–	51.5[a]
Libório et al. [32]	Brazil 2006-08; single centre oncological ICU	Prospective	288 patients with solid/ haematological cancer admitted to ICU	ESRF, previous renal transplant, obstructive nephropathy, ICU stay <24 h, ICU readmissions	258; gastrointestinal (30.2 %), urological (25.6 %), head & neck (16.3 %), lung (6.9 %), breast (6.9 %)	–	SOFA 5.8 (3.4), SAPS II 35 (19.4), APACHE II 10.3 (5.9)	58.8 (17.4)
Maccariello et al. [33]	Brazil 2004–08; 14 general ICUs in 3 centres	Prospective	773 consecutive (118 with cancer) patients requiring renal replacement therapy for AKI in ICU	ESRF, ICU stay <24 h, ICU readmissions, non-AKI indication for RRT	86; lower GI (29 %), urogenital (20.9 %), liver/biliary (17.4 %), upper GI (12.8 %), lung (7 %)	31.4	SOFA 9 (7–11), SAPS II 49.3 (12.7)	70.0 (13.9)
McGrath et al. (2010) [34]	UK 2004–08; single centre oncological ICU	Retrospective 2004–06; Prospective 2006–08	185 patients with solid/ haematological cancer admitted to ICU	Routine post-op monitoring	70; lung (21.4 %), breast (15.7 %), oesophagus (11.4 %), ovarian (5.7 %)	41.4 %	SOFA 5.5, APACHE II 17.1	57.1 (12.8)

Table 1 continued

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
Mendoza et al. [35]	USA 2003–04, single centre general ICU	Retrospective	147 patients with solid cancer admitted to ICU	Nil	147; lung (23 %), colorectal (12 %), breast (7 %), prostate (6 %), pancreas (5 %)	51.7	–	63.5 (13.5)
Mokart et al. [36]	France 2008; single centre oncological ICU	Prospective	111 consecutive ICU patients with previous or current history of haematological or solid organ malignancy	Nil	24; not specified	79	SAPS II 45 (33–55)[a]	60 (50–68)[a]
Mourad et al. [37]	France 2009–2011; single oncology ICU	Prospective	76 cancer patients with septic shock and persistent hypotension requiring vasopressor therapy	Age < 18 years, valvular heart disease, regional myocardial ischaemia or previous MI, therapeutic limitation decision prior to admission	26; not specified	–	SAPS II 57 (45.7–69)[a], SOFA 11 (9–13)[a]	58 (49–66)[a]
Namendys-Silva et al. [38]	Mexico 2007; single centre oncological ICU	Prospective	177 patients with solid cancer admitted to ICU	Age < 16 years, routine post-operative care, ICU readmissions	177; GI (22.6 %), head and neck (20.3 %), lung (2.3 %), genitourinary (5.1) %, gynaecological (29.4 %), breast (3.4 %), gem-cell (5.6 %), prostate (1.1 %), sarcoma (4 %) skin and soft tissue (6.2 %)	–	SOFA 3 (1–8), APACHE II 12 (11–14)	52.4 (17.3)
Namendys-Silva et al. [39]	Mexico 2008–10; single centre oncological ICU	Prospective	82 patients with solid/ haematological cancer with septic shock in ICU	Age < 18 years, ICU readmissions	56; colorectal (17.9 %), cervix (17.9 %), sarcoma (12.5 %), upper GI (12.5 %), breast (8.9 %)	33.9	SOFA 10.2 (3.2)[a], APACHE II 16.2[a]	52.5 (14.7)[a]
Namendys-Silva et al. [40]	Mexico 2007; single centre oncological ICU	Prospective	92 patients with gynaecological cancer admitted to ICU	Age < 16 years, routine post-operative care, ICU readmissions	92; cervix (67.3 %), ovarian (21,2 %)	–	SOFA 4.4 (4), APACHE II 12.4 (2)	56.5 (12.8)
Oeyen et al. [41]	Belgium 2008–2009; single centre general MICU & SICU	Prospective	483 patients with solid or haematological malignancy admitted to ICU	Readmissions, remission >5 years, post op cardiac surgery	398; lower GI (26 %), upper GI (25 %), lung (15 %), urogenital (8.5 %), brain (8 %), head and neck (7 %), breast (4 %)	46	SOFA 3 (2–5), APACHE II 13 (11–18)	62 (54–69)
Okiror et al. [42]	UK 2003–2008, single centre thoracic ICU	Retrospective	30 patients with lung cancer admitted to ICU as an emergency following lung resection	Nil	30; 100 % NSCLC	–	–	71 (7)

Table 1 continued

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
Park et al. [43]	UK 1995–2007; 181 general ICUs	Retrospective	7,227 patients admitted to ICU following elective oesophageal surgery for malignancy	Nil	7,227; oesophageal (100 %)	–	SAPS II 25.1 (10.5), APACHE II 13.9 (4.8)	64.3 (9.9)
Reichner et al. [44]	USA 2002–04; single centre general ICU	Retrospective	47 patients with lung cancer admitted to ICU	Nil	47; NSCLC (83 %), SCLS (15 %)	64	SOFA 4.7 (3.3)	65 (10)
Roques et al. [45]	France 1997–2006; single centre general ICU	Prospective	105 lung cancer patients admitted to ICU	Postoperative lung resection patients, ICU readmission	105; NSCLC (83 %), SCLC (17 %)	64	SAPS II 40 (21) SOFA 4.4 (4.7)	64.8 (10.6)
Slatore et al. [46]	USA 1992–2007; multicentre ICUs	Retrospective	49,373 patients with lung cancer admitted to ICU within 5 years of diagnosis	Age < 66 years at diagnosis, patient with incomplete or without Medicare billing information, routine postoperative ICU admission, in situ cancer, diagnosis of cancer post mortem	49,373; NSCLC (80.3 %), SCLC (13.1 %), Other (6.6 %)	45.7	–	75 (71–79)
Soares et al. [47]	Brazil 2000–04; single centre oncological ICU	Prospective	772 consecutive patients with solid/haematological cancer admitted to ICU	Cancer remission >5 years, ICU stay <24 h, acute coronary syndrome, routine postoperative care, ICU readmissions	642; GI (17.1 %), head & neck (16.2 %), brain (16.2 %), lung (11.8 %), upper GI (11.4 %), urogenital (10.1 %), breast (5.9 %)	21.4	SOFA 6.5 (3.9), SAPS II 43.6 (18.9)	57.6 (16.4)
Soares et al. [48]	Brazil 2000–2005; single centre oncological ICU	Prospective	121 patients with head and neck cancer admitted to ICU because of severe acute complications	ICU stay <24 h, routine postoperative care, readmission, complete cancer remission >5 years	121; oral cavity (30 %); larynx (25 %), pharynx (14 %), thyroid (9 %), salivary gland (7 %), paranasal sinuses (6 %), other (9 %)	35	SAPS II 49.6 (17.8), SOFA 7.2 (3.6)	63.3 (14.7)
Soares et al. [49]	Brazil & France 2000–05; 1 oncology & 1 general ICU	Retrospective	152 lung cancer patients admitted to ICU	Age < 18 years, cancer remission >5 years, ICU stay <24 h, routine postoperative care, ICU readmission	143; squamous-cell carcinoma (39 %), adenocarcinoma (34 %), SCLC (17 %), large cell (6 %), other (3 %)	31	SAPS II 47.4 (21.0)	61.6 (9.9)
Soares et al. (2010) [50]	Brazil 2007; 28 ICUs	Prospective	753 patients with solid/ haematological cancer admitted to ICU	Age < 18 years, cancer remission >5 years, ICU stay <24 h, routine postoperative care, ICU readmission	667; lower GI (18.3 %), urogenital (12.3 %), upper GI (12.3 %), lung (8.7 %), brain (8.5 %), head & neck (8.4 %), breast (7.5)	29.1	SAPS II 32.1 (7.2)[a], SAPS III 48.7 (19.0)[a] SOFA 7 (5 –10)[a]	61.2 (15.4)[a]

Table 1 continued

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
Song et al. [51]	South Korea 2001–05; single centre oncological ICU	Retrospective	94 patients who underwent resection for lung or oesophageal cancer and subsequently required readmission to ICU	Single wedge resection	94; oesophageal (39.4 %), lung cancer (60.6 %)	–	APACHE III 53.8 (24.5)	65.9 (7.3)
Song et al. [52]	South Korea 2002–08; single centre general ICU	Retrospective	62 consecutive patients with solid/haematological cancer who received chemotherapy in ICU	Patients receiving prior ongoing chemotherapy or treatment with corticosteroids only	13; lung (46.2 %), sarcoma (23 %), bladder (7.7 %), breast (7.7 %), gastric (7.7 %), germ cell (7.7 %)	–	SOFA 10 (6–14), SAPS II 53 (41–68)	50 (37–63)
Song et al. [53]	South Korea 2010; single centre oncological ICU	Retrospective	199 solid/haematological cancer patients admitted to ICU via medical emergency team intervention	Limitation of care decision or refusal of ICU admission	104; not specified	–	SAPS III 80 (67–93)[a], SOFA 8 (5–11)[a]	60 (51–70)[a]
Souza-Dantas et al. [54]	Brazil 2000–07; single centre oncological ICU	Prospective	94 patients with solid/ haematological cancer and neutropenia admitted to ICU matched to 94 non-neutropenic patients	Age < 18 years, cancer remission >5 years, ICU stay <24 h, routine postoperative care, ICU readmissions	60; GI (26.7 %), urogenital (16.7 %)	–	SOFA 11 (8–14), SAPS II 61.6 (16.5)	50 (32–65)
Taccone et al. [2]	24 European countries 2002; 198 general ICUs	Prospective	473 patients with solid/ haematological cancer admitted to ICU	Age < 15 years old, routine postoperative observation if >24 h, ICU readmissions	404; not specified	24.8	SOFA 4.6 (3.6), SAPS II 36.8 (17.6)	66.4 (12.1)
Toffart et al. [55]	France 2000–07; 3 general ICUs	Retrospective	103 ICU patients with a past or present history of non-resectable lung cancer	Postoperative care	103; squamous cell (32 %), adenocarcinoma (25 %), SCLC (20 %), large cell (11 %)	61	SAPS II 33 (25–46) LOD 3 (1–4)	61 (54–68)
Unseld et al. [56]	Switzerland 2002; single centre MICU	Retrospective	74 patients with solid/ haematological malignancy admitted to MICU	Nil	42; urogenital (42 %), lung (24 %), gastrointestinal (16 %), head (9 %), other (7 %)	–	SAPS II 39 (28–53), SOFA 5 (3–9)	66 (57–73)
Welsch et al. [57]	Germany 2001–2008; single centre general ICU	Prospective	96 patients with pancreatic head adenocarcinoma admitted to ICU post operatively for >24 h	Patients with ampullary adenocarcinomas, intraductal papillary mucinous neoplasms, distal bile duct carcinomas, and other malignant and benign pancreatic pathologies	96; pancreas (100 %)	7	–	–

Table 1 continued

References	Setting	Design	Study population	Exclusions	Number of solid tumour patients; tumour types (%)	Metastatic disease (%)	Severity of illness mean (SD) or median (IQR)	Average age mean (SD) or median (IQR)
Zuber et al. [58]	France 1997–2008; 41 general ICUs	Secondary analysis of prospective database of 22,5481 ICU patients	3,437 patients with solid/haematological cancer admitted to ICU with septic shock	ICU readmission	2,119; lung (16.8 %), GI (16.6 %), genitourinary (16.3 %), metastatic (41.9 %)	–	SAPS II 63.4 (25.1)	62.2 (14.3)

APACHE acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment, *SAPS* simplified acute physiology score, *LOD* logistic organ dysfunction score, *ASA* American Society Anaesthesiologists, *ICU* Intensive Care Unit, *MICU* medical intensive care unit, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *GIST* Gastro-intestinal stromal tumour, *MI* myocardial infarction, *ESRF* end stage renal failure, *AKI* acute kidney injury

[a] Includes haematological cancer patients

be misrepresented in those studies that excluded routine postoperative patients, patients with ICU stays of less than 24 h, readmissions or only inclusion of patients requiring specific interventions, such as renal replacement therapy or mechanical ventilation.

Overall mortality up to 5 years after ICU admission

Mortality was reported for ICU, hospital and up to 5 years after ICU admission [Table 1, Electronic Supplementary Material (ESM)]. ICU mortality was reported in 35 studies and ranged widely from 4.5 to 85 %. Hospital mortality was reported in 31 studies ranging from 4.6 to 76.8 %. Mortality at 1 year was reported in five studies and ranged from 35.9 to 88.0 %, and a single study by Bissell reported 62.8 % survival at 5 years [17]. ICU and hospital mortality are plotted showing the average of the distribution of rates in Fig. 2. The average mortality summarises only those studies using independent samples, so that where several papers reported on the same group of patients, only one representative paper was used. The overall average mortality within ICU was 31.2 % (95 % CI 24.0–39.0 %) based on a total sample of 25,339 patients with a solid tumour, of which Bos's study comprised nearly half of the patients. There was substantial variation between studies in the proportion of patients who died in ICU ($I^2 = 99.1$ %, $\chi^2 = 3{,}483$, $df = 31$, $p < 0.001$). The average hospital mortality was 38.2 % (33.8–42.7 %) among a total sample of 74,061 patients with solid tumours, of which Slatore's study comprised two-thirds of the patients. There was substantial variation in hospital mortality between studies ($I^2 = 98.8$ %, $\chi^2 = 1{,}829$, $p < 0.001$). ESM Fig. 1 provides summary average mortality estimates at all follow-up periods.

Predictors of survival

When the effects of risk factors associated with survival in multivariable analyses were reported these have been described in Table 2. Severity of illness scores were generally associated with greater risks of mortality with each unit increase; the relatively larger effect size reported by Song et al. [52] reflects the comparison between patients with SOFA scores of $\leq$10 and >10. The relationship between higher severity of illness score and increased mortality was reported up to 90 days after admission and was of a similar magnitude to its effect on shorter-term mortality. This may suggest that it imposes little additional risk after the initial ICU admission period.

Cancer patients who are admitted as medical, as opposed to surgical admissions had increased risk of ICU mortality of between two- and fourfold, and increased risks of in-hospital mortality of between six- and eightfold. WHO Performance Status, which is used to quantify

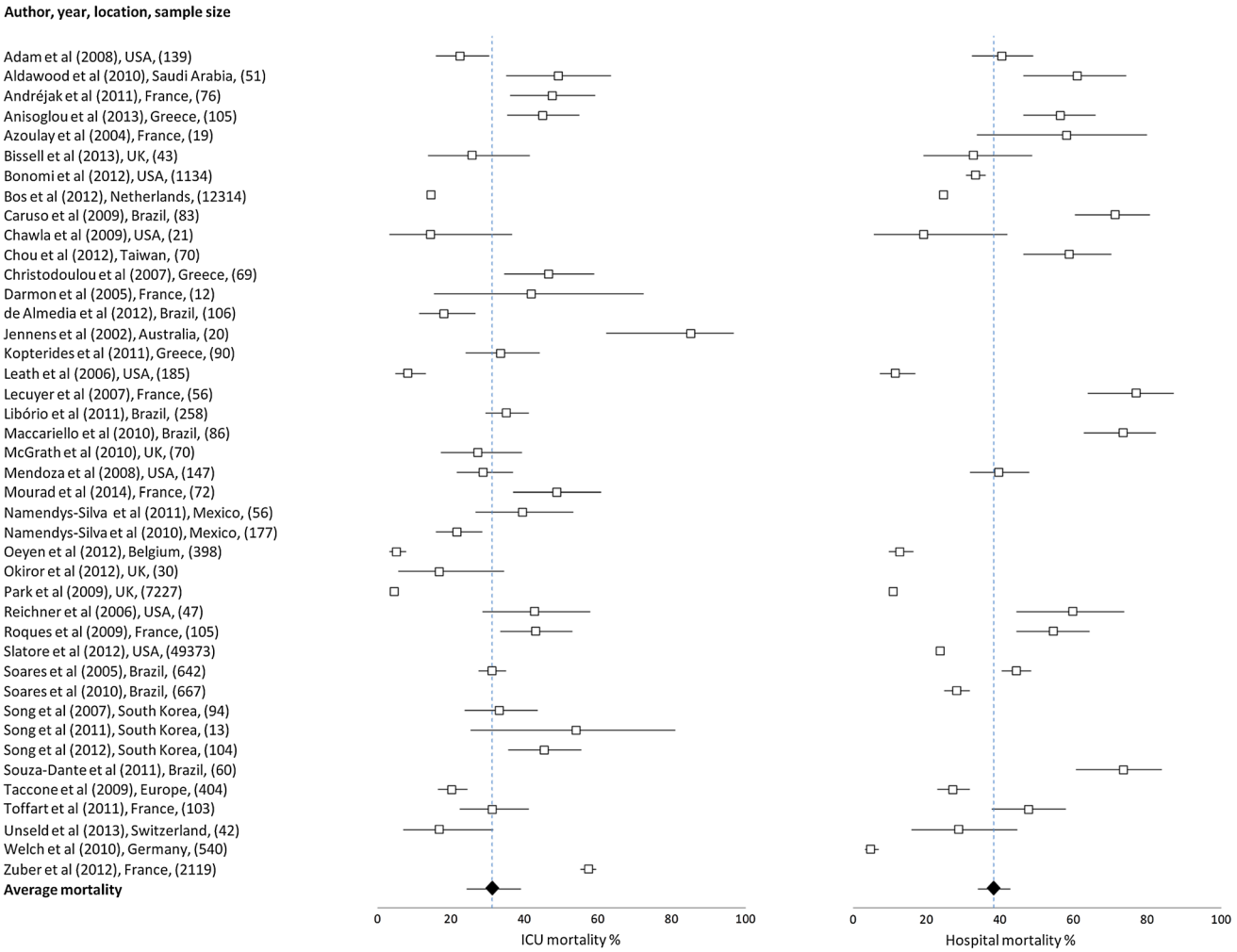

Fig. 2 ICU and hospital mortality among ICU patients with solid tumours

cancer patients' general health and functioning, was associated with survival. Generally, papers compared patients with scores of 3 and 4 (from capable of only limited self-care to completely disabled and confined to bed or chair) with those of 0, 1 and 2; where alternative thresholds were used, these have been indicated in Table 2. Poorer performance status was associated with increased ICU mortality of between four- and sevenfold, and increased mortality by two- to threefold at 90 days after ICU admission. Sepsis increased ICU mortality by fivefold and in-hospital mortality between two- and fivefold. Mechanical ventilation increased ICU mortality by around sixfold in most studies; Mourad's much higher figure of nearly 17-fold increased ICU mortality included haematological patients and the confidence interval around the estimate was wide [37]. Use of vasopressors increased the risks of both ICU and in-hospital mortality. The increased mortality at 30 days reported by Darmon is of a similar magnitude to that reported in ICU by several authors, and again this may suggest that its effects are not sustained beyond ICU [25].

The impact of cancer stage has been inconsistently associated with mortality. Mendoza's study of 147 patients with mixed solid tumours found metastatic disease to be independently predictive of hospital mortality on multivariate analysis [35]. Soares' study of patients with head and neck cancer identified that those with stage IV disease had a higher risk of in-hospital death with OR 3.8 (95 % CI 1.28–11.28) [62]. A further study by Soares of cancer patients receiving >24 h of invasive mechanical ventilation found that hospital mortality was associated with recurrence/progression of cancer status (OR 3.43, 95 % CI 1.81–6.53 compared with controlled cancer) and airway/pulmonary involvement by the tumour as the reason for ventilation (OR 5.73 CI 1.92–17.08) [61]. However, an additional three papers did not find an association between metastatic disease and short-term outcomes such as ICU or hospital mortality [2, 24, 33].

Table 2 Multivariable prognostic factors associated with survival among ICU cancer patients

Outcome	References	Model	SAPS	SOFA	APACHE II	Medical admission	Performance status 3–4	Sepsis/ septic shock	Mechanical ventilation	Vasopressors	Other factors
ICU mortality	Adam et al. [12]									8.7 (2.8–27)	Multi-organ system failure >2 40.8 (5.1–328.3)
	Andréjak et al. [14]								6.61 (1.44–30.5)	6.81 (1.77–26.26)	Platelet count <100,000/mm^3 5.13 (1.17–22.5); admission for complication of cancer management 0.206 (0.058–0.738)
	de Almedia et al. [26]				1.15 (1.05–1.26)						LIS 2.23 (1.29–3.87); positive fluid balance >1100 ml/ 24 h 5.14 (1.45–18.24)
	Kopterides et al. [29]	I		1.2 (1.05–1.38)		3.84 (1.14–12.92)	3.88 (1.22–12.39)				Infection on admission 3.9 (1.17–13.05)
		II	1.04 (1.01–1.08)				6.67 (2.12–21.00)	4.75 (1.00–22.73)			Anaemia on admission 4.06 (1.30–12.65)
		III			1.16 (1.07–1.26)		6.70 (2.18–20.60)	5.51 (1.16–26.10)			
	Mokart et al. [36][b]										Logistic organ dysfunction 1.32[a] (1.11–1.57); viral infection/ reactivation 2.8[a]5 (1.10–7.40)
	Mourad et al. [37][b]			1.35 (1.05–1.75)					16.6 (3.60–77.15)		Diastolic dysfunction ($e' \leq 8$ cm/s) 16.6 (3.28–84.6)
	Namendys-Silva et al. [38]				1.92 (1.43–2.58)					22.66 (6.09–84.22)	
	Song et al. [52]			9.66[d] (1.43–65.47)					6.26 (1.12–34.95)		
	Zuber et al. [58]		1.04 (1.03–1.04)			1.73 (1.29–2.32)			5.52 (4.04–7.54)		Renal replacement therapy 1.74 (1.30–2.33); fungal infection 1.95 (1.18–3.21); unknown microorganism 1.64 (1.27–2.11); admission to high vs low volume unit 0.63 (0.46–0.87)
Hospital mortality	Azoulay et al. [16][b]									3.19 (1.28–7.95)	Congestive heart failure 0.16 (0.03–0.72); invasive aspergillosis 3.78 (1.05–14.24); no definite diagnosis 3.85 (1.26–11.70); NIMV only 1.58 (0.37–6.70); NIMV followed by conventional MV 17.46 (5.04–60.52); First-line conventional MV 8.75 (2.35–32.54); late NIMV failure 10.64 (1.05–107.83)

Table 2 continued

Outcome	References	Model	SAPS	SOFA	APACHE II	Medical admission	Performance status 3–4	Sepsis/ septic shock	Mechanical ventilation	Vasopressors	Other factors
	Bonomi et al. [18]							5.06 (3.04–8.43)	4.69 (3.02–7.30)		Renal failure 2.28 (1.02–5.10); admission related to respiratory conditions 2.34 (1.43–3.82)
	Caruso et al [20]		1.09 (1.01–1.18)								Thrombocytopenia 26.2 (2.6–267.9)
	Christodoulou et al. [24]						5.44 (1.48–19.99)				
	Chou et al. [23]			1.360 (1.038–1.782)							
	Lecuyer et al. [31]										No significant independent predictors of hospital mortality
	Libório et al. [32]		1.05 (1.02–1.08)	1.69 (1.37–2.09)	1.65 (1.34–2.03)						RIFLE score 4.86 (1.68–14.06)
	Maccariello et al. [33]					6.55 (2.29–18.73)					Associated organ dysfunction 2.14 (1.25–3.65); ICU days until start of renal 1.42 (0.97–2.09)
	Mendoza et al. [35]									$p < 0.001$	Metastatic disease ($p < 0.001$)
	Namendys-Silva et al. [40]				1.43 (1.01–2.09)					8.6 (2.05–36)	
	Park et al. [43]								1.24 (1.03–1.50)		Age ($p < 0.001$); P/F ratio ($p < 0.001$); Serum urea ($p = 0.016$); Serum creatinine ($p = 0.014$);Serum albumin ($p < 0.001$); Lowest arterial pH ($p < 0.001$)
	Roques et al. [45]						3.6[c] (1.5–8.7)				Acute respiratory failure 3.5 (1.5–8.4)
	Slatore et al. [46]								6.95 (6.89–7.01)		
	Soares et al. [48]						5.17[c] (1.84–14.53)				Stage IV 3.80 (1.28–11.28); number of acute organ failures 2.87 (1.83–4.50); oral cavity 2.19 (0.55–8.74); pharynx 4.43 (0.84-23.41), other 3.7 (1.01-13.51) ref larynx cancer
	Soares et al. [48]										Age 1.08 (1.02-1.15); cancer status-uncontrolled newly diagnosed 1.53 (0.45–5.28). Uncontrolled recurrence/progressive 8.81 (1.56–49.67); airway obstruction by cancer 3.55 (1.02–12.32); number of organ failures 1.95 (1.16–3.28)

Table 2 continued

Outcome	References	Model	SAPS	SOFA	APACHE II	Medical admission	Performance status 3–4	Sepsis/ septic shock	Mechanical ventilation	Vasopressors	Other factors
	Soares et al. [50]			1.25 (1.17–1.34)		5.66 (3.43–9.33)	3.40[c] (2.19–5.26)		2.42 (1.51–3.87)		Emergency surgical 2.46 (1.28–4.73); hospital stay 1.18 (1.01–1.37); active-new diagnosed cancer 2.75 (1.19–6.32), active-recurrence/ progression 2.42 (1.51–3.87)
	Song et al. [51]										Renal support 3.611 (1.096–11.895); Duration of ventilation ≥ 5 7.859 (2.375–26.006); APACHE III ≥ 50 12.100 (2.859–51.206)
	Song et al. [53][b]			1.18 (1.03–1.35)			1.28 (0.56–2.90)		1.31 (0.54–3.14)	0.77 (0.31–1.90)	Age 1.03 (1.00–1.06); gender (male) 0.93 (0.42–2.05); haematological malignancy 0.59 (0.24–1.45); stem cell transplantation 2.54 (0.79–8.15); MET criteria (3+) 3.09 (1.32–7.23); Time to intervention (hours) 1.45 (1.22–1.72); infection 2.17 (0.90–5.24); PF ratio 1.00 (1.00–1.01)
	Souza-Dantas et al. [54]	I	1.06 (1.03–1.09)			7.82 (1.75–34.88)	2.43[c](1.03–5.70)	4 (1.37–11.73)			Neutropenia at admission 0.64 (0.24–1.75) 0.66 (0.08–5.30); chemo before admission 0.19 (0.05–0.78); Hospital days before admission 1.50 (1.08–2.07);
		II		1.19 (1.06–1.33)		7.06 (1.68–29.63)	2.84[c] (1.26–6.40)	3.53 (1.20–10.33)			Neutropenia at admission 0.52 (0.20–1.38) 1 (0.14–7.10); chemo before admission 0.3 (0.08–1.14); hospital days before admission 1.49 (1.09–2.04);
	Taccone et al. [2]		1.07 (1.05–1.08)					2.1 (1.2–3.7)	2.4 (1.2–4.7)		ARDS 2.5 (1.2–5.3)

Table 2 continued

Outcome	References	Model	SAPS	SOFA	APACHE II	Medical admission	Performance status 3–4	Sepsis/ septic shock	Mechanical ventilation	Vasopressors	Other factors
30 day/1 month mortality	Darmon et al. [25]								6.36 (1.76–22.94)	6.01 (1.86–19.4)	Hepatic failure 7.76 (1.25–48.27)
90 day/3 month mortality	Namendys-Silva [39][a]			1.11[a] (1.02–1.19)			1.84[a,c] (1.03–3.29)				
	Toffart et al. [55][a]	I	1.03 (1.02–1.05)				1.96[a] (1.11–3.46)				
		II					2.65[a] (1.43–4.88)				Metastasis at ICU admission 1.90 (1.08–3.33); LOD, per point 1.19 (1.08–1.32)
	Roques et al. [45]								3.6 (1.35–9.4)		Cancer progression 6.1 (2.2–17)
	Slatore et al. [46]								1.21 (1.16–1.26)		
180 days/ 6 month mortality	Soares et al. [47]								1.34 (1.00–1.78)		Age 40–70 1.66 (1.24–2.23), >70 years 2.07 (1.49–2.88); Surgical patient 0.69 (0.55–0.86); Cancer status-Newly-diagnosed 1.46 (1.11–1.91); Recurrence, progression 2.20 (1.72–2.82); Number of acute organ failures 1–2 1.77 (1.29–2.43) >2 3.89 (2.73–5.53)
	Soares et al. [47]								1.36 (1.02–1.81)		
1 year mortality	Mokart[a] et al. [36]										Acute leukemia 0.19 (0.06–0.55); multiple myeloma 0.1 (0.01–0.56)
Mortality after discharge	Namendys-Silva[a] [38]									2.79[a] (1.06–7.33)	Length of stay in ICU 1.10[a] (1.007–1.02); CCI > 2 5.81[a] (1.35–25.03)
Mortality	Bissell et al. [17]										Age 1.05[a] (1.01–1.09); renal support 5.63[a] (4.0–7.2)

[a] Hazard ratios
[b] Includes haematological malignancies
[c] ≥2
[d] SOFA >10

The impact of leukopenia and neutropenia has been assessed in many of the studies and was not found to be associated with short-term mortality [2, 25, 29, 32, 54].

Studies varied widely in their mean acute illness scores (Table 1) and reported mortality (ESM Table 1). Generally, studies with higher acute illness score reported higher ICU mortality (ESM Fig.2). However, there was some variation in mortality between studies with similar acute illness scores, and these reflect differences in other patient characteristics, particularly cancer site.

ICU and hospital mortality for specific tumour sites

Figure 3 summarises short-term mortality where this has been described for specific tumour sites, indicating the site-specific average and overall average (additional data are provided in ESM Table 2). It is apparent from Fig. 3 that survival varies between studies on the same cancer site and between different cancer sites. Precision of estimates varied considerably between studies. Generally, mortality was highest for patients with lung cancers and lowest for patients with gynaecological cancers (average ICU mortality 40.1 %, 95 % CI 28.6–52.2 and 12.0 %, 95 % CI 7.4–10.4, respectively). Other individual tumours were less frequently reported with four papers reporting outcomes for colorectal cancer (average hospital mortality 35.0 %), four papers in head and neck tumours (average hospital mortality 54.7 %), three papers for oesophageal malignancy (average hospital mortality 19.9 %) and four papers for breast cancer (average hospital mortality 57.7 %).

Discussion

This systematic literature review identified a set of studies that describe contemporary outcomes in non-haematological cancer patients after admission to ICU. The 48 papers that reported on solid cancers were characterised by a wide range of case-mix variables both in terms of critical illness and in tumour types. The broad range of observed outcomes, with ICU mortality ranging from 4.5 to 85 %, reflects the heterogeneity of patients described in

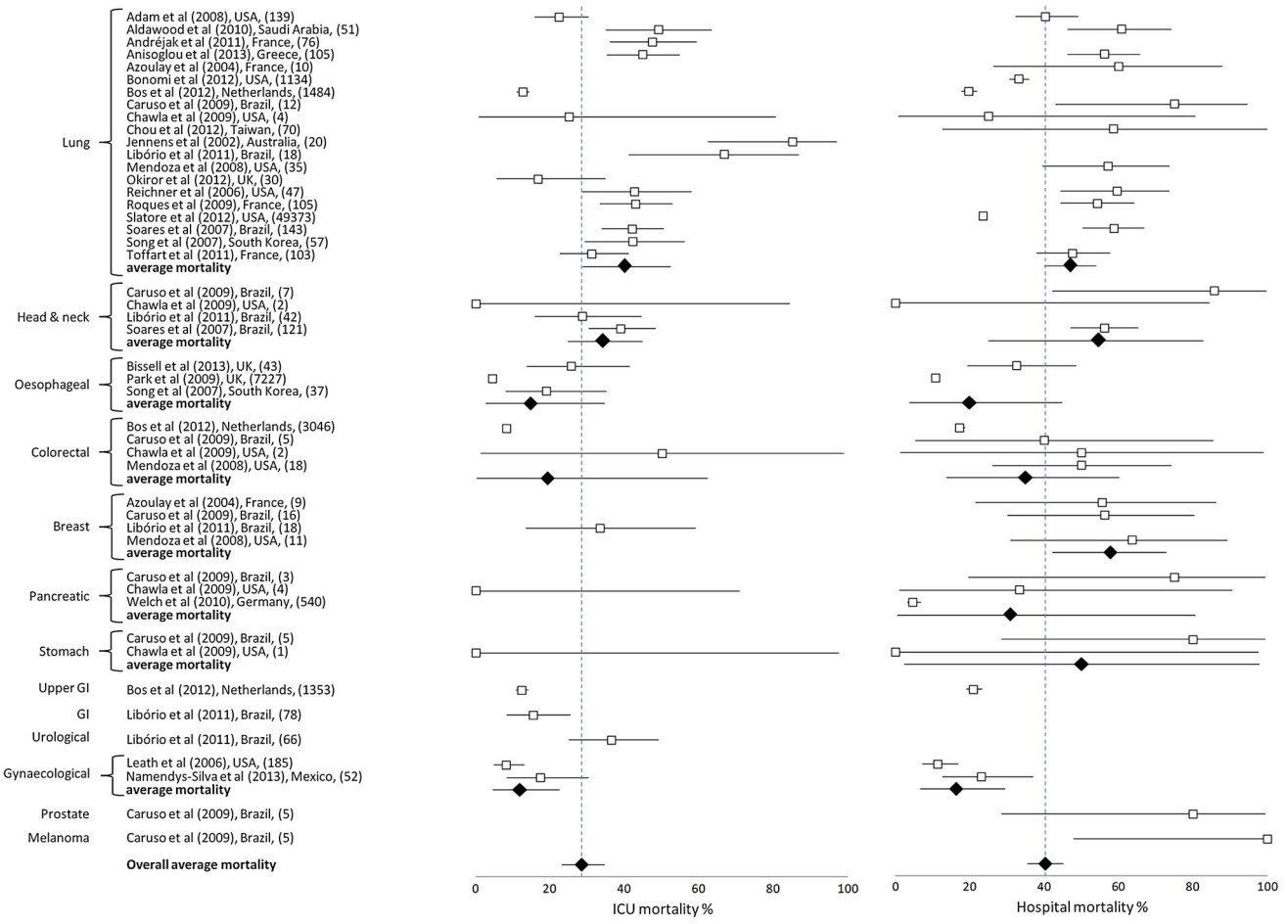

Fig. 3 ICU and hospital mortality among ICU patients with specific tumours

the available literature. However, average mortality across all included studies with ICU mortality of 31.2 % and hospital mortality of 38.2 % is considerably lower than that which has been historically reported. Cancer patients should therefore not be excluded from ICU exclusively based on having an underlying malignancy, and instead those factors known to be associated with survival should be taken into account.

A number of studies looked at factors associated with survival. Poorer physiological status was associated with poorer ICU and hospital survival, but the range of different scoring systems employed, and the absence of any measure from some studies, makes summary estimates difficult in this patient group. All types of organ failure were associated with a poorer outcome; however, of these, requirement for invasive mechanical ventilation had the strongest effect on mortality. In addition, poor chronic health or limited functional status have been demonstrated to be associated with poorer survival. These findings are consistent with those seen in the general ICU population and are not specific to cancer patients. Whilst tumour type has not been demonstrated to be associated with mortality in any of the individual studies, the average mortality by tumour types described in this systematic review suggests that there is variation. The impact of disease stage and presence of metastasis has been inconsistently associated with mortality and the exact role these factors play is uncertain. Thus, despite around 15 % of ICU admissions being for patients with known malignancies [2], current literature is unable to predict likely survival of the individual cancer patient after ICU admission; however, it can guide prognostication.

Our study has strengths and weaknesses. It is the first systematic review on outcomes among cancer patients admitted to ICU. We have used established systematic review procedures, PRISMA guidelines [7], and STROBE criteria for assessing observational studies [11]. Unlike narrative reviews, our study has a specific, explicit and therefore reproducible methodological strategy for identifying and synthesising relevant papers and is not based on the subjectivity of the authors. Our analysis adds to current literature by consolidating and summarising a large amount of information from primary published sources which many busy practicing ICU clinicians would not have time to identify or read. As such, its strength lies in pooling this information in an accessible form while highlighting the paucity and heterogeneity of information available on specific cancer outcomes.

The principal weakness of our study is that we have included all studies within this field whether the focus was on the general ICU cancer population or a subgroup such as those with sepsis, a specific organ failure or an individual tumour type. As a result, there are large differences between the study populations of the included papers which is reflected in the distribution of mortality rates that they report. The differences in terms of patient population, type of cancer, or type of patients (surgical vs. non-surgical) are confounding biases and contribute towards the heterogeneity we report. There are vast differences in the outcomes associated with surgical admissions versus medical admissions to ICU, and this effect seems to be exaggerated within the oncological population. For example, the three studies with the lowest mortality [30, 41, 43] includes mainly elective surgical patients. In contrast, the studies with higher mortality [20, 31, 33, 54] includes only a few surgical patients, and instead selected patients based on their severity (mechanical ventilation plus at least one organ failure) [31]: only patients requiring renal replacement therapy [33], the extent of the underlying disease [20] or both. The difference in reported mortality is therefore to be expected.

Bos et al. [19] noted that many studies which report on prognostic factors mainly involve specialised oncological ICUs, making it difficult to extrapolate to general ICUs where the mixture of tumour types and expertise is different. They suggested that their own study was most appropriately compared to papers by Taconne et al. and Soares et al. [2, 50]. But even in this limited comparison, there were important differences in terms of study size, duration, and discrimination of emergency admissions, medical and surgical patients. Given the paucity and variability of the published literature, we felt that it would have been even less informative to have further restricted our inclusion criteria as this would have lost more than half of the published data with no increase in precision. This is important because, although we have summarised the distribution of reported mortality using the average mortality with 95 % confidence intervals, the mortality reference range of published studies is justifiably very wide.

As the incident number of cancers will continue to increase globally [63], driven largely by aging populations but in some countries by increased exposures to risk factors, demand for ICU support for cancer patients and for information to guide admission policies will also rise. Our work adds to current literature because it draws together different strands of international research and highlights the ways in which these studies of cancer patients in ICU differ. We feel that current evidence on outcomes of cancer patients after admission to ICU would be improved with additional clinical details such as treatment intent, cancer staging/histology or pre-ICU clinical pathways. Targets for future research should build upon the work that has already been published by reporting outcomes in clearly defined groups and producing further prognostic information on those factors that are associated with poorer survival.

Whilst oncological ICUs provide a large patient population in which to study these patients, they may not be representative of the general ICU cancer population and therefore additional studies require to be performed on both groups. Where patients are admitted to general ICUs, there is a value in reporting comparative outcomes for non-cancer patients to allow calculation of the additional risk posed by

having cancer. In addition to describing survival over the short, medium and longer terms, research is needed to describe whether cancer patients are likely to receive planned anti-cancer therapy after discharge from ICU, as admissions are currently assumed to be suitable for ongoing treatment following successful discharge. Because there are international variations in the definition of ICUs and in the case-mix of patients they treat, it will be important for future research to clearly define staffing levels, interventions provided, and patient characteristics, so that results can be usefully generalised [64].

Conflicts of interest All authors declare no conflicts of interest.

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