Prognostic factors in oncological patients with solid tumours requiring intensive care unit admission

RAQUEL BOSCH-COMPTE[1], LAURA VISA[2,3], ALEJANDRO RIOS[2], XAVIER DURAN[4], MARIA FERNÁNDEZ-REAL[1,4], GEMMA GOMARIZ-VILALDACH[1,4] and JOAN RAMON MASCLANS[1,4,5]

Departments of [1]Critical Care Medicine and [2]Medical Oncology, Hospital del Mar, 08003 Barcelona; [3]Network Biomedical Research Center in Cancer, Ministry of Science and Innovation, Government of Spain, 28029 Madrid; [4]Hospital del Mar Medical Research Institute Foundation, 08003 Barcelona; [5]Department of Medicine and Life Sciences, Pompeu Fabra University, 08002 Barcelona, Spain

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Abstract. The aim of the present study was to identify factors predicting in-hospital mortality in patients with cancer admitted to a medical Intensive Care Unit (ICU), and to evaluate their functional status and survival during follow-up at the oncology service in the initial 12 months after hospital discharge. A retrospective observational study was performed on 129 consecutive oncological patients with solid tumours admitted to the medical ICU of the Hospital del Mar (Barcelona, Spain) between January 2016 and June 2018. Demographics, and clinical data in-ICU and in-hospital mortality were recorded. Post-hospital discharge follow-up was also carried out. ICU and hospital mortality rates were 24% (n=31) and 40.3% (n=52), respectively. Sequential Organ Failure Assessment (SOFA) score (HR, 1.20; 95% CI, 1.01-1.42; P=0.037), neutropenia on admission (HR, 8.53; 95% CI, 2.15-33.82; P=0.002), metastatic disease (HR, 3.92; 95% CI, 1.82-8.45; P<0.001), need for invasive mechanical ventilation (HR, 5.78; 95% CI, 1.61-20.73; P=0.007), surgery during hospital admission (HR, 0.23; 95% CI, 0.09-0.61; P=0.003) and ICU stay (>48 h) (HR, 0.11; 95% CI, 0.04-0.29; P<0.001) were the independent risk factors for ICU mortality. Overall, 59.5% of the survivors had good functional status at hospital discharge and 28.7% of patients with cancer admitted to the ICU were alive 1 year after hospital discharge, most of them (85.7%) with good functional status (Eastern Cooperative Oncology Group 0-1). In conclusion, hospital mortality may be associated with SOFA score at ICU admission, the need for invasive mechanical ventilation, neutropenia and metastatic disease. Only 40% of patients with oncological disease admitted to the ICU died during their hospital stay, and >50% of the survivors presented good functional status at hospital discharge. Notably, 1 year after hospital discharge, 28.7% of patients were alive, most of them with a good functional status.

Correspondence to: Ms. Raquel Bosch-Compte, Department of Critical Care Medicine, Hospital del Mar, 25-29 Passeig Marítim de la Barceloneta, 08003 Barcelona, Spain
E-mail: raquelbosch13@gmail.com

Abbreviations: ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; APACHE II, Acute Physiology and Chronic Health Evaluation II; LTE, limitation of therapeutic effort; ARF, acute respiratory failure; SD, standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NR, not reported; ENT, ear-nose-throat; CPA, cardiopulmonary arrest; PaO_2/FiO_2, arterial oxygen partial pressure to inspiratory oxygen fraction

Key words: critical illness, in-hospital mortality, long-term follow-up, oncological patients, prognostic factors

Introduction

In recent years, the incidence of oncological patients has risen in line with the increase in the elderly population. Advances in early diagnosis and the progress of new treatments for various types of cancer, such as immunotherapy or targeted molecular therapies, and the development of support treatment have improved prognosis and increased survival in these patients, achieving an acceptable quality of life. As a result, the number of cancer patients requiring ICU admission is rising, be it for management of tumour-related complications or due to the side effects of cancer treatment or medical conditions independent of the cancer itself (1-6). It is widely accepted that admitting oncological patients to the ICU is usually futile and costly in terms of recovery (both short and long term), with a worse prognosis and a higher mortality rate than critically ill non-cancer patients; therefore, the indication of their admission to the ICU has been questioned. However, recent studies have reported that the current prognosis for the critically ill cancer patients has significantly improved (6-9). Therefore, in view of the increase in life expectancy among these patients, studies investigating clinical factors predicting the short-term prognosis of cancer patients with critical complications are needed in order to guide the admission criteria and design new management strategies in the ICU (10-14). In addition, most of the studies of prognosis in critical care units have included both patients with solid tumours and patients with

haematological malignancies, and this heterogeneity in terms of the nature and curability of the neoplasm has limited the validity of the results (6,12,15-19). For this reason, we carried out an analysis of patients with solid tumours admitted to a university hospital ICU in Spain, in order to determine their characteristics and outcomes and to identify the risk factors associated with in-hospital mortality. Unlike other studies, we also included a 12-month follow-up period after hospital discharge to assess the survival and functional status of these patients.

Patients and methods

Study design. A retrospective observational study conducted in the 18-bed ICU at the University Hospital del Mar in Barcelona, Spain, between January 2016 and June 2018.

Adult patients (≥18 years old) admitted to the ICU due to acute illness with the diagnosis of active solid tumour (defined as cancer diagnosis in the five years prior to ICU admission). Patients with haematological malignancy were excluded. To assess in-hospital mortality, in patients with multiple ICU admissions only the last admission was recorded.

The following information was recorded: Demographic data, comorbidities, body mass index (BMI), the healthcare service of origin and health functional status, using the Eastern Cooperative Oncology Group (ECOG) scale to quantify patients' general well-being. Variables related to tumour status were also recorded, namely site of the primary malignancy, local or metastatic extension, disease status at the time of ICU admission by radiological assessment two months prior to admission [non-progressive or progressive disease, no evidence of relapse or recent diagnosis (during admission)] and antineoplastic therapy received. The reason for ICU admission and the treatment received in the ICU were also recorded [vasoactive support, ventilatory support (including invasive mechanical ventilation and non-invasive ventilatory support such as non-invasive mechanical ventilation or high-flow nasal cannula), renal replacement therapy, blood product transfusion, parenteral nutrition and tracheostomy, as well as the need for surgery (scheduled or urgent)] during hospital admission. The severity of the underlying disease and the number of organ failures were calculated on the first day of admission according to the SOFA and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. At the time of admission, laboratory data and vital signs (mean blood pressure, heart rate, temperature, respiratory rate, gasometric data, lactate, hemogram, sodium, C-reactive protein, procalcitonin, creatinine, calcium, albumin, bilirubin, glucose, neutrophils and prothrombin time) were collected. Furthermore, the sequential SOFA was also recorded at 48 h and on days 5, 10 and 14. Both ICU and hospital length of stay, ICU and in-hospital mortality rate, as well as the cause of death [septic, respiratory, haemorrhagic, cardiac, brain death or limitation of therapeutic effort (LTE)] were recorded. The LTE decision was made in accordance with the ICU protocol, which was indicated after verifying that the patient's clinical situation was irreversible or terminal, always by consensus of the intensive care team and with the participation of the patient and relatives. Finally, the oncology team followed up the surviving patients after hospital discharge and collected treatment data and functional status after two months. Further follow-up controls were carried out at 6 and 12 months to be able to assess patients' survival and functional status.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Ethics Committee of Hospital del Mar (approval no. 2022/10570).

Statistical analysis. Continuous variables were described through means and standard deviations, and comparisons between groups were assessed through the unpaired Student's t-test. Levene's test was used to check group homoscedasticity. Qualitative variables were described as frequencies (number and percentage) and comparisons were assessed through χ^2 or Fisher exact test, as appropriate. The McNemar test was used to check changes in ECOG score in the follow-up after hospital discharge in comparison with the score at ICU admission, and during the follow-up after hospital discharge. Univariate and multivariate Cox regression was used in the analysis of the variables related to in-hospital mortality. Results of these analyses were expressed by means of hazard ratios. The variables associated with higher risk of mortality ($P<0.05$) in the univariate analysis were used in the multivariate analysis, controlling for collinearity (linear relations between explanatory covariates) and the clinical significance of these covariates. The proportional hazard assumption, checked by examining Schoenfeld residuals (for the model overall and variable by variable), was not violated. A post-hoc power analysis was performed for in-hospital mortality and taking as main factor of interest the SOFA score at admission. Regarding this variable, a threshold of 7 (approximately the mean in the non-survivor group) was used to perform a Kaplan Meier survival curve comparing both groups (above and below threshold). Log-rank test was used to check differences between survival curves.

STATA version 15.1 (StataCorp, College Station, TX, USA) was used for statistical analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of the study population. A total of 1,741 patients were recruited during the study period, of whom 129 (7.4%) had an active solid tumour at ICU admission. Patients with haematological malignancy were excluded. Fig. 1 shows the flowchart of the study. The main patient characteristics and malignancy-related data are summarized in Table I.

Most patients were men (79%) and mean age was 67 years. The most frequent comorbidities at the time of admission were hypertension (55.8%), cardiovascular diseases (35.7%), chronic obstructive pulmonary disease (31.8%) and diabetes mellitus (24.8%). Most patients were admitted to our medical ICU from the emergency service (46.5%) or from a hospital ward (43.4%). Fifty-seven patients had good functional health status according to ECOG score (ECOG 0-1) before ICU admission. The most common reasons for ICU admission were acute respiratory failure (ARF) (39.5%) and shock (38.9%), especially septic shock (27.9%).

Lung tumours were the most frequent (29.5%) followed by gastrointestinal (28.7%) and genitourinary cancer (21.7%). Seventy-four patients (57.4%) had localized disease on ICU

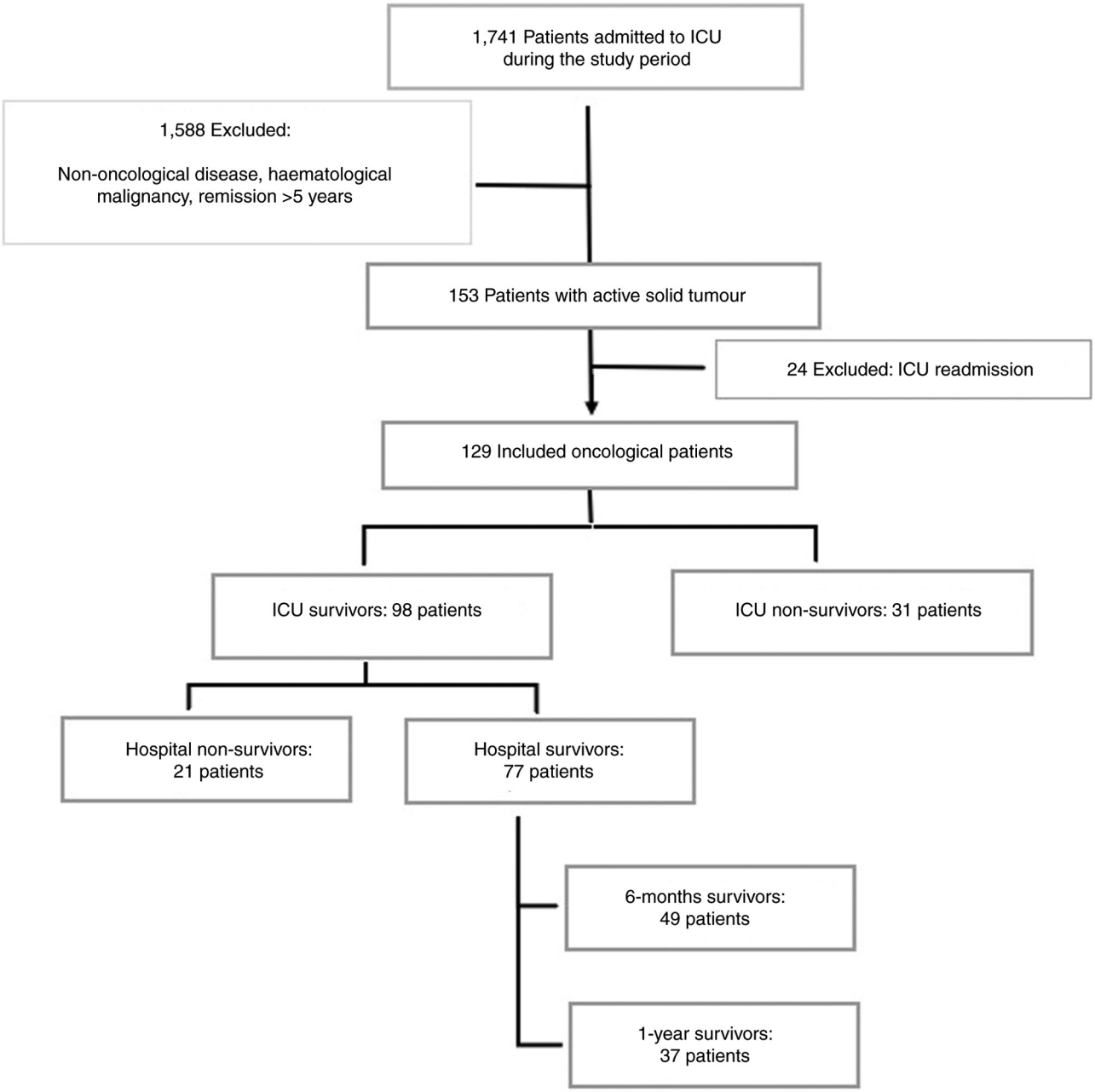

Figure 1. Flowchart of the study. ICU, Intensive Care Unit.

admission, while 46 (35.7%) had metastasis, the most frequent being hepatobiliary (20.9%), peritoneal (18.6%), bone (14%) and pulmonary (13.2%). In most patients the cancer onset coincided with the time of ICU admission (44.2%), while 21.7% of patients had progressive and 11.6% non-progressive disease. Finally, 20.2% of patients had no evidence of relapse during ICU admission. Fifty-seven patients (44.1%) had received antineoplastic therapy within the two months before ICU admission, while 71 (55%) had not received cancer-specific treatment in this time period.

During the ICU stay most patients received life-supporting therapies, such as vasopressors (48.8%), mechanical ventilation (either invasive or non-invasive ventilatory support, 68.2%), renal replacement therapy (7.8%) and parenteral nutrition (11.6%). Thirty-eight patients (29.5%) required surgery during hospital admission (57.9% urgent and 42.1% scheduled). The characteristics and reasons for surgery are found in Table SI.

The mean APACHE II and SOFA severity scores at ICU admission were 23 (SD 8.3) and 5.8 (SD 3.6) respectively. The mean APACHE II scores were higher in cancer patients than in non-cancer patients admitted to the ICU in the same period of time [22.99 (SD 8.34) vs. 18.81 (SD 10.28), P<0.001].

The median duration of ICU stay was five days (IQR, 3-10), and more than 80% of cancer patients had an ICU stay of more than 48 h. The median duration of hospital stay was 20 days (IQR, 11-40).

Finally, 21 patients (16.28%) were readmitted to the ICU, 14 (10.85%) during the same hospital admission. Three cases were readmitted to ICU up to three times.

Table I. Characteristics of ICU patients with solid tumours.

Variable	Value
Number	129
Male sex, n (%)	102 (79.07)
Mean age, years (SD)	66.97 (10.29)
Mean BMI, kg/m^2 (SD)	26.33 (5.40)
Comorbidity, n (%)	
High blood pressure	72 (55.81)
Cardiovascular disease[a]	46 (35.66)
COPD	41 (31.78)
Diabetes mellitus	32 (24.81)
Chronic kidney failure	13 (10.08)
Immunosuppressed[b]	9 (6.98)
Healthcare service of origin, n (%)	
Emergency service	60 (46.51)
Hospital ward	56 (43.41)
Others[c]	13 (10.08)
ECOG prior to ICU admission, n (%)	
0-1	57 (44.19)
≥2	26 (20.16)
NR	46 (35.66)
Type of tumour, n (%)	
Lung	38 (29.46)
Gastrointestinal	37 (28.68)
Genitourinary	28 (21.71)
Gynaecological and breast	14 (10.85)
ENT	13 (10.08)
Central nervous system	2 (1.55)
Other tumours[d]	3 (2.33)
Oncological assessment prior to ICU admission, n (%)[e]	
Debut/first appearance	57 (44.19)
Progressive disease	28 (21.71)
No evidence of relapse	26 (20.16)
Non-progressive disease[f]	15 (11.63)
NR	3 (2.33)
Stage at diagnosis, n (%)[g]	
Located disease	74 (57.36)
Metastatic disease	46 (35.66)
NR	9 (6.98)
Metastasis, n (%)	
Hepatobiliary	27 (20.93)
Peritoneal	24 (18.60)
Bone	18 (13.95)
Pulmonary	17 (13.18)
Brain	9 (6.98)
Suprarenal	9 (6.98)
Antineoplastic therapy, n (%)[e]	
No	71 (55.04)
Chemotherapy	25 (19.38)
Others[h]	14 (10.85)
Chemotherapy + Radiotherapy	9 (6.98)
Immunotherapy	9 (6.98)
NR	1 (0.78)
Reason for intensive care unit admission, n (%)	
ARF	51 (39.53)
Shock	50 (38.88)
Septic	36 (27.91)
Hypovolemic and cardiogenic	9 (6.98)
Anaphylactic	5 (3.88)
CPA	10 (7.75)
Surveillance and monitoring	10 (7.75)
Coma	4 (3.10)
Acute kidney failure	4 (3.10)
Life-supporting therapies, n (%)	
Vasopressors	63 (48.84)
Invasive mechanical ventilation	45 (34.88)
Non-invasive mechanical support	43 (33.33)
Blood transfusion	36 (27.91)
Tracheostomy	17 (13.19)
Parenteral nutrition	15 (11.63)
Renal replacement therapy	10 (7.75)
Surgical intervention	38 (29.46)
Median ICU stay, days (IQR)	5 (3-10)
≤48 h	24 (18.60)
>48 h	105 (81.40)
Median hospital stay, days (IQR)	20 (11-40)
Mean severity scores SD	
APACHE II	22.99 (8.34)
$SOFA_0$	5.81 (3.60)
$SOFA_{48\ h}$	3.76 (3.40)
$SOFA_{5\ D}$	3.17 (2.78)

[a]Heart failure and vasculopathy; [b]HIV and chronic steroids treatment; [c]Day hospital, resuscitation unit, another hospital, operating room; [d]Melanoma and carcinoma of unknown primary source; [e]2 months prior to ICU admission; [f]Non-progressive disease: Partial/complete response (n=10) + stable disease (n=5); [g]Located (stage I-III) or metastatic disease (stage IV); [h]Radiotherapy (n=9), hormone therapy (n=3) (letrozole, enzalutamide, abiraterone), target agents (n=2) (vemurafenib, cetuximab). ICU, Intensive Care Unit; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; NR, not reported; ENT, ear-nose-throat; ARF, acute respiratory failure; CPA, cardiopulmonary arrest; IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; $SOFA_0$, SOFA at admission; $SOFA_{48\ h}$, SOFA at 48 h; $SOFA_{5\ D}$, SOFA at 5th day.

Outcome and prognostic factors. Of the 129 patients, 52 died during their hospital stay (hospital mortality rate 40.3%), 31 of them in the ICU, with an ICU mortality rate of 24%

Table II. Characteristics of hospital survivor and non-survivor cancer patients.

Variable	Survivors (n=77)	Non-survivors (n=52)	HR (95% CI)	P-value
Male sex, n (%)	62 (80.52)	40 (76.92)	0.75 (0.39-1.43)	0.376
Mean age, years (SD)	66.19 (9.54)	68.12 (11.31)	1.00 (0.97-1.03)	0.992
Mean BMI, kg/m^2 (SD)	25.93 (5.19)	26.98 (5.74)	1.04 (0.98-1.10)	0.161
Comorbidity, n (%)				
High blood pressure	41 (53.25)	31 (59.62)	0.97 (0.56-1.70)	0.923
Cardiovascular disease	27 (35.06)	19 (36.54)	0.93 (0.53-1.63)	0.792
COPD	20 (25.97)	21 (40.38)	1.24 (0.71-2.17)	0.442
Diabetes mellitus	15 (19.48)	17 (32.69)	1.50 (0.84-2.68)	0.17
Chronic kidney failure	7 (9.09)	6 (11.54)	0.99 (0.42-2.33)	0.985
Immunosuppression	2 (2.60)	7 (13.46)	1.72 (0.77-3.83)	0.183
ECOG prior to ICU admission, n (%)				
0-1	34 (75.56)	23 (60.53)	1	
≥2	11 (24.44)	15 (39.47)	1.06 (0.54-2.07)	0.874
Type of tumour, n (%)				
Lung	17 (22.08)	21 (40.38)	2.06 (1.18-3.60)	0.011
Gastrointestinal	21 (27.27)	16 (30.77)	1.04 (0.58-1.87)	0.903
Genitourinary	22 (28.57)	6 (11.54)	0.52 (0.22-1.21)	0.13
Gynaecological and breast	8 (10.39)	6 (11.54)	1.34 (0.57-3.14)	0.502
ENT	11 (14.29)	2 (3.85)	0.21 (0.05-0.87)	0.031
Central nervous system	0 (0)	2 (3.85)	1.94 (0.47-8.00)	0.362
Other tumours	1 (1.30)	2 (3.85)	1.88 (0.45-7.76)	0.385
Oncological assessment prior to ICU admission, n (%)				
No evidence of relapse	16 (21.33)	10 (19.61)	1	
Non-progressive disease	10 (13.33)	5 (9.80)	1.24 (0.42-3.67)	0.7
Progressive disease	19 (25.33)	9 (17.65)	0.99 (0.4-2.43)	0.978
Debut/first appearance	30 (40.00)	27 (52.94)	1.53 (0.74-3.16	0.252
Stage at diagnosis, n (%)				
Located disease	53 (73.61)	21 (43.75)	1	
Metastatic disease	19 (26.39)	27 (56.25)	2.36 (1.33-4.19)	0.003
Metastasis, n (%)				
Hepatobiliary	14 (18.18)	13 (25)	2. 17 (1.14-4.15)	0.019
Peritoneal	14 (18.18)	10 (19.23)	2.21 (1.09-4.49)	0.028
Bone	9 (11.69)	9 (17.31)	2.03 (0.97-4.26)	0.06
Pulmonary	12 (15.58)	5 (9.62)	0.99 (0.39-2.51)	0.982
Brain	5 (6.49)	4 (7.69)	1 (0.36-2.80)	0.994
Suprarenal	4 (5.19)	5 (9.62)	2.01 (0.79-5.12)	0.139
Antineoplastic therapy, n (%)				
No	41 (53.25)	30 (58.82)	1	
Chemotherapy	14 (18.18)	11 (21.57)	2.01 (0.98-4.12)	0.057
Others	10 (12.99)	4 (7.84)	0.51 (0.18-1.44)	0.202
Chemotherapy + radiotherapy	6 (7.79)	3 (5.88)	0.95 (0.29-3.13)	0.935
Immunotherapy	6 (7.79)	3 (5.88)	2.13 (0.64-7.09)	0.217
Reason for ICU admission, n (%)				
Acute respiratory failure	33 (42.86)	18 (34.62)	0.53 (0.3-0.94)	0.03
Shock	32 (41.56)	18 (34.62)	1.08 (0.61-1.92)	0.792
CPA	2 (2.60)	8 (15.38)	2.81 (1.32-6.01)	0.008
Surveillance and monitoring	6 (7.79)	4 (7.69)	1.53 (0.55-4.28)	0.416
Coma	1 (1.30)	3 (5.77)	1.34 (0.41-4.33)	0.626
Acute kidney failure	3 (3.90)	1 (1.92)	1.21 (0.16-8.89)	0.85

Table II. Continued.

Variable	Survivors (n=77)	Non-survivors (n=52)	HR (95% CI)	P-value
Life-supporting therapies, n (%)				
Vasopressors	29 (37.66)	34 (65.38)	1.91 (1.08-3.39)	0.027
Invasive mechanical ventilation	18 (23.38)	27 (51.92)	1.67 (0.75-3.70)	0.21
Non-invasive mechanical support	26 (33.77)	17 (32.69)	1.38 (0.59-3.21)	0.456
Blood transfusion	18 (23.38)	18 (34.62)	1.12 (0.63-1.99)	0.689
Tracheostomy	10 (12.99)	7 (13.46)	0.55 (0.24-1.22)	0.142
Parenteral nutrition	10 (12.99)	5 (9.62)	0.39 (0.15-0.98)	0.045
Renal replacement therapy	4 (5.19)	6 (11.54)	1.34 (0.57-3.16)	0.498
Surgical patients, n (%)	24 (31.17)	14 (26.92)	0.37 (0.20-0.70)	0.002
ICU stay, n (%)				
≤48 h	10 (12.99)	14 (26.92)	1	
>48 h	67 (87.01)	38 (73.08)	0.16 (0.08-0.31)	<0.001
Severity scores, mean (SD)				
APACHE II	21.16 (7.26)	25.71 (9.13)	1.04 (1.01-1.07)	0.003
$SOFA_0$	4.74 (2.89)	7.40 (3.97)	1.17 (1.09-1.26)	<0.001
$SOFA_{48\ h}$	2.77 (2.58)	5.45 (3.96)	1.17 (1.07-1.28)	<0.001
$SOFA_{5\ D}$	2 (1.82)	5.21 (3.01)	1.34 (1.16-1.54)	<0.001
Analytic and vital signs at ICU admission, median (IQR)				
Mean blood pressure, mmHg	63 (53-80)	61 (44-80)	0.99 (0.98-1.00)	0.05
Heart rate, beats/min	110 (88-120)	110 (80-128)	0.99 (0.99-1.00)	0.035
Temperature, ˚C	36 (36-37)	36 (35.8-36.5)	0.86 (0.67-1.10)	0.226
Respiratory rate, breaths/min	25 (18-31)	26.5 (18-35)	0.99 (0.96-1.02)	0.513
PaO_2/FiO_2, mmHg	295 (185-380)	205 (150-300)	1.00 (1.00-1.00)	0.154
Lactate, mmol/l	2.3 (1.3-4.2)	2.7 (1.9-5.6)	1.07 (1.02-1.12)	0.005
Haemoglobin level, g/dl	9.8 (8.2-11.4)	9.9 (8.4-11.5)	1.06 (0.94-1.20)	0.352
Leukocytes, $10^3/mm^3$	11.2 (7.7-19.5)	14.6 (10.6-23.8)	1.01 (0.99-1.04)	0.303
Thrombocytes ($10^5/mm^3$)	2.2 (1.3-3)	2.1 (1.3-2.8)	0.74 (0.58-0.94)	0.013
Procalcitonin, ng/ml	1.5 (0.3-6.3)	1 (0.3-15)	1.01 (1.00-1.02)	0.127
C-reactive protein, mg/l	12.2 (3.6-24)	11.1 (5.8-28.3)	1.01 (0.99-1.03)	0.219
Creatinine, mg/dl	1.1 (0.7-1.9)	1.2 (0.7-1.9)	1.06 (0.94-1.19)	0.376
Albumin, g/dl	3 (2.4-3.6)	3.1 (2.5-3.3)	1.38 (0.83-2.29)	0.21
Calcium, mg/dl	8.3 (7.8-8.9)	8.2 (7.7-8.7)	0.95 (0.72-1.25)	0.725
Bilirubin, mg/dl	0.4 (0.3-0.7)	0.6 (0.4-1.3)	1.20 (1.04-1.38)	0.012
Glucose, mg/dl	132 (113-170)	154.5 (120-268)	1.01 (1.00-1.01)	<0.001
Prothrombin time, %	81.2 (59-97.6)	72 (54.6-86.5)	0.99 (0.98-1.00)	0.008
Neutropenia, <1,000/mcl	5 (6.49)	5 (9.62)	4.45 (1.69-11.72)	0.003

HR, hazard ratio; ICU, Intensive Care Unit; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; ENT, ear-nose-throat; CPA, cardiopulmonary arrest; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; $SOFA_0$, SOFA at admission; $SOFA_{48\ h}$, SOFA at 48 h; $SOFA_{5\ D}$, SOFA at 5th day; PaO_2/FiO_2, arterial oxygen partial pressure to inspiratory oxygen fraction.

(18 due to LTE). Table II displays the characteristics of the cancer survivors and non-survivors.

Among the demographic and cancer-associated variables, statistical analysis revealed that gender, age, BMI, comorbidities, ECOG at ICU admission, oncological assessment and antineoplastic therapy were not associated with a worse prognosis. On the other hand, high severity-scores (APACHE II, SOFA) and neutropenia were related to a higher mortality rate. Patients with higher SOFA at ICU admission were more likely to die during hospital stay (P=0.013; Fig. S1).

The length of ICU stay was significantly shorter in non-survivors than in survivors. Mortality was significantly associated with metastatic disease, lung tumour and the need for vasopressors during the ICU stay. Cardiopulmonary arrest (CPA) on ICU admission was significantly more common

Table III. Factors associated with hospital mortality in critically ill cancer patients. Results from multivariate analysis.

Variable	HR (95% CI)	P-value
$SOFA_0$	1.22 (1.07-1.39)	0.003
Neutropenia	9.16 (2.33-36.04)	0.002
ICU stay (>48 h)	0.13 (0.06-0.29)	<0.001
Stage at diagnosis (metastatic disease)	4.23 (2.05-8.70)	<0.001
Invasive mechanical ventilation	4.83 (1.43-16.26)	0.011
Surgical intervention	0.22 (0.09-0.50)	<0.001

Variables included: Lung tumours, age, Acute Physiology and Chronic Health Evaluation II, SOFA, neutropenia, surgical intervention, metastatic disease, need for mechanical ventilation and ICU stay. HR, hazard ratio; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment.

in non-survivors. Bilirubin, glucose and lactate levels were significantly associated with mortality.

ENT tumours were significantly more frequent in survivors. Survivors were also more likely to have acute respiratory failure as the reason for ICU admission and to require surgery during their hospital stay. Platelet count, mean blood pressure, heart rate and coagulation rate were significantly higher in survivors.

Multivariate analysis. The multivariate analysis showed that the risk factors for hospital mortality were the severity of organ failure at admission using the SOFA score (HR, 1.22; 95% CI, 1.07-1.39; P=0.003), neutropenia (HR, 9.16; 95% CI, 2.33-36.04; P=0.002) and metastatic disease at ICU admission (HR, 4.23; 95% CI, 2.05-8.70; P=0.000), as well as the need for invasive mechanical ventilation (HR, 4.83; 95% CI, 1.43-16.26; P=0.011). In addition, the ICU stay [>48 h] (HR, 0.13; 95% CI, 0.06-0.29; P=0.000) and the need for surgery during hospital stay (HR, 0.22; 95% CI, 0.09-0.50; P=0.000) were identified as good prognostic factors (Table III).

Results of the power calculation for the multivariate model showed a power of 91.56.

Follow-up. The destination of survivors discharged from hospital (77 patients) was home in 70% of cases, a convalescence unit in 16.8% and a palliative care unit in 11.5%. Forty-two discharged patients (54.5%) were evaluated by a medical oncologist on an outpatient basis within two months of discharge, twenty-five of whom (59.5%) presented good functional status (ECOG score 0-1).

However, comparing the evolution of the ECOG score between ICU admission and the first oncological visit at discharge, we observed that of the 13 patients who presented poor functional status at hospital discharge (ECOG ≥2), nine (32.1% of the follow-up cohort) had presented good general condition prior to ICU admission (ECOG 0-1). They showed a statistically significant deterioration during their ICU stay (P=0.034; Table IV).

Table IV. ECOG score at the first hospital discharge visit vs. pre-ICU admission.

ECOG previous to ICU admission	ECOG at hospital discharge (within 2 months)			P-value[a]
	0-1	≥2	Total	
0-1	13 (59.09)	9 (40.91)	22 (100)	0.0348
≥2	2 (33.33)	4 (66.67)	6 (100)	
Total	15 (53.57)	13 (46.43)	28 (100)	

Data are presented as number (%) of patients. [a]P-value was determined using McNemar test.

Table V. Description of ECOG evolution in survivors over time.

ECOG classification	Discharge (n=77)	6 months (n=49)	12 months (n=37)
Oncological follow-up	42 (54.54)	28 (57.15)	21 (56.76)
ECOG 0-1	25 (59.52)	23 (82.14)	18 (85.71)
ECOG 2-3	17 (40.48)	5 (17.86)	3 (14.29)

Data are presented as number (%) of patients.

In the post-discharge follow-up, 49 survivors discharged from hospital (63.6%) were alive at six months, and 37 (48.1%) at one year. In relation to all the 129 patients admitted to the ICU, this represents a one-year survival rate after discharge of 28.7%. Three cases were lost to follow-up due to a change of country or health region. Moreover, 28 of the 49 survivors at six months (57.2%) were monitored by the oncology service, and 23 of these 28 (82.1%) had good functional status (ECOG 0-1). A similar trend was observed in survivors at one year, since 18 of the 21 patients followed by the oncology service (85.7%) presented good functional status (Table V).

Finally, Fig. 2 shows the changes in ECOG score between different time points in the follow-up: first oncological visit after hospital discharge, after six months, and after 12 months. No significant changes in functional status were observed over time.

Discussion

The main objectives of the current study were to determine the outcome of solid cancer patients admitted to an ICU in Spain, and to identify factors predicting in-hospital mortality. The study also sought to analyse the evolution of these patients inside and outside the hospital, evaluating their survival and functional status at one year after hospital discharge.

In-hospital and ICU mortality rates were 40 and 24% respectively. In the multivariate analysis, these rates were negatively influenced by high SOFA score, neutropenia and metastatic disease at ICU admission and the need for invasive mechanical

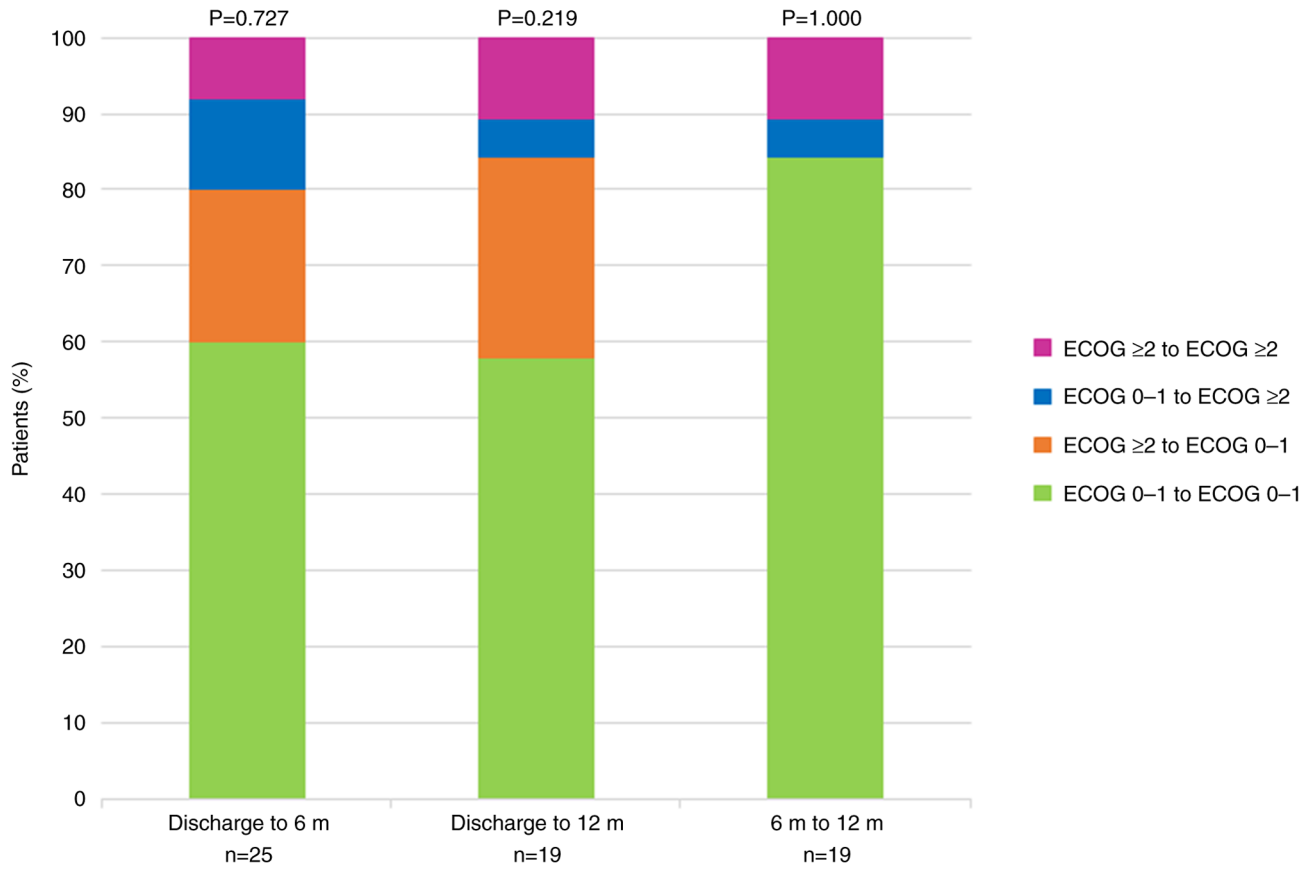

Figure 2. Changes in ECOG score in the follow-up 12 months after hospital discharge. P-values were obtained using the McNemar test. ECOG, Eastern Cooperative Oncology Group; m: months.

ventilation. In addition, a longer ICU stay and the need for surgery during hospital stay were identified as protective factors.

Our ICU mortality rate in cancer patients was 24% and, though higher than the overall ICU mortality rate of 16.3%, the difference was not substantial. Therefore, the diagnosis of malignancy should not automatically contraindicate ICU admission. Previous studies have reported ICU mortality rates in solid tumours of between 10 and 50%. This large variation in rates between studies makes comparisons difficult: it is due to the heterogeneity of the cancer population, with different types of cancer and oncologic treatments, different specific reasons for ICU admission and differences in the implementation of end-of-life decisions (2,10,20,21).

In the critical care setting, scoring systems for quantifying severity of illness and organ failure such as APACHE II or SOFA scores have proved to be valuable tools for identifying patients at high risk for hospital mortality. So, the decision to admit cancer patients to the ICU should be based on the severity of the acute illness, as some authors have indicated (2,6,12,13,19,22,23). In our study, we also found that SOFA score at ICU admission, which identifies organ dysfunction, is one of the main prognostic factors in critically ill patients with cancer. Previous studies have proposed an admission and treatment modality called the ICU trial, which consists in initial full intensive care without limitations and mandatory daily assessments of organ failures and their evolution during the first 3-7 days, with particular attention to the development of multiple organ dysfunction during the ICU stay. The ICU trial may help in making decisions in a complex situation and in prompting early palliative and end-of-life discussions, especially in patients who do not progress toward recovery in the first days of ICU care, and in those in whom symptom palliation would improve quality of life (13,18,24,25). In our study, we observed that sequential SOFA between day 2 and day 5 continues to be a good prognostic marker of in-hospital mortality. It is recommended that follow-up be carried out by an interdisciplinary team (ICU specialists, oncologists, and palliative care specialists if appropriate). Quality of life, the patient's wishes and the family's opinion should also be taken into account.

As many as 80% of cancer patients are admitted to our ICU due to shock or ARF, that is, organ failures requiring life-supporting therapies. Lung cancer is the most common solid tumour in our critically ill patients. ARF is one of the most frequent reasons for ICU admission in cancer patients. There are many possible causes of ARF, including the local effect of the tumour, pneumonia, acute respiratory distress syndrome and congestive heart failure. Supplemental oxygen and treatment of the underlying disorder is the fundamental approach to ARF, but severe cases require ventilatory support. However, despite significant advances in ventilatory support and cancer management, numerous studies have found invasive mechanical ventilation for more than 24 h to be associated with high mortality rates (13,18,19,22,26). Mortality may be related to multiple factors including complications of ventilation such as ventilator-induced lung injury or ventilator-associated pneumonia. Moreover, the local and systemic effects of tumour may also play a role.

Neutropenia remains a common side effect of cancer chemotherapy and, although transient and expected, may lead to immune dysfunction in oncological patients. Beyond specific cancer therapies, several additional factors including lung injury, sepsis, underlying malignancy and its stage are habitually associated with neutropenia duration. ICU admission is frequently required in these patients as a consequence of severe sepsis or ARF. In the general ICU population with septic shock, neutropenia is an independent predictor of mortality. In cancer patients in this setting the influence of neutropenia on outcome is uncertain; however, some recent systematic reviews and meta-analyses have shown it to be associated with an increase in mortality in critically ill cancer patients (27,28). In our study, the presence of neutropenia on ICU admission was also significantly associated with the risk of hospital death.

In most studies, the characteristics of the underlying cancer have little impact on short-term survival, and are not enough to rule out ICU admission (2,10,29). Similarly, in our study, only metastatic disease emerged as a prognostic factor for in-hospital mortality; the oncological assessment prior to ICU admission (i.e., no evidence of relapse, progressive disease, first appearance or non-progressive disease) or the antineoplastic treatment received had no influence. In this regard, it must not be forgotten that immunotherapy can improve the prognosis of patients with metastatic disease, and indeed its use has increased exponentially in recent years. In our study only nine patients received immunotherapy. In addition, the heterogeneity of the types of cancer makes the interpretation of survival data more difficult.

In our study, an ICU stay of more than 48 h was a protective factor. The reason for this may be that, in contrast to other studies, we included patients with admissions of less than 24 h, and 88% of these patients died. Moreover, in 8% of all cases, the reason for ICU admission was CPA and the chances of survival after CPA in patients with advanced cancer are low. Consequently, in our series, 50% died in the first 48 h of ICU admission, due to brain death, multiorgan dysfunction or LTE.

In contrast, we found that undergoing surgery during hospitalization was related to good prognosis. It is difficult to extrapolate these results to other settings, given the heterogeneous nature of the cancer patients who undergo surgery and the differences in surgical goals; there may also be a selection bias, since the majority of surgical patients are admitted to the resuscitation service. More than 40% of these surgeries are scheduled, mainly primary tumour surgeries in patients with a recent diagnosis and treated with curative intent. In addition, more than 50% of the surgical patients are operated upon more than 72 h prior to admission to the ICU, and so the reason for ICU admission is medical. In our study, only one patient received palliative surgery.

Finally, in our study, functional status prior to ICU admission as defined by the ECOG scale was not found to be a predictor of mortality, in contrast to other studies (11-13,17,19,30). This is probably because most of our patients had a recent oncological diagnosis (without previous oncological evaluation), and the sample size for this variable was small. Nevertheless, patients with poor ECOG tend to have worse survival results. As a general rule, patients with good ECOG in situations in which life-extending treatment options are available should be routinely admitted to the ICU. Moreover, in our study we analysed the evolution of ECOG at hospital discharge and follow-up at the oncology department over the following 12 months, and concluded that even though ICU stay significantly worsens the functional capacity of cancer patients in 32.1% of cases, more than half of the survivors (59.5%) with follow-up after discharge had good functional status. With subsequent follow-up, we can affirm that most patients (more than 80%) who survive and undergo oncological follow-up at 6 and 12 months maintain good functional status (ECOG 0-1); the group with worse functional status (ECOG ≥2) had the highest mortality. There were no significant changes in their functional status during the follow-up period. This suggests that patients with cancer and good ECOG should receive full intensive care, but it should be borne in mind that ICU treatment entails a short-term functional worsening, and so ECOG is a simple and highly effective clinical tool for assessing patients' overall health status.

Our study has several limitations that should be considered. First, it is a descriptive retrospective observational study at a single centre with a sample that is small and very heterogeneous from the oncological point of view, a circumstance that limits the reliability of the statistical analysis and the extrapolation of the results to other samples. It is also difficult to compare crude mortality in different studies due to the high variability of the underlying oncological disease, admission criteria, and treatment decision criteria. Furthermore, certain oncological data such as the ECOG scale are not available in patients admitted to the ICU with a recent cancer diagnosis who have not been evaluated previously by oncologists. In addition, the ICU mortality rate may suffer from a sampling bias because patients who are repeatedly admitted to the ICU were recorded only once. Moreover, factors such as ethnic origin and toxic habits were not been recorded. Finally, this series is a few years old, since during the pandemic we were unable to proceed with the study and publish the findings.

In conclusion, only 40% of patients with cancer requiring ICU admission died during hospitalization, and more than half of the survivors presented good functional status at hospital discharge. Moreover, the similar ICU mortality rate observed in cancer patients and critically ill non-cancer patients supports a broader policy on ICU admission in this population. The survival rate of oncological patients admitted to the ICU one year from hospital discharge was 28.7%. Most of the patients (85.7%) who survived at one year and who were controlled by the oncology service had good functional status (ECOG 0-1).

The prognosis of critically ill adult patients with cancer is best determined by the nature and number of organ failures with the SOFA score, rather than by the stage of the underlying oncological malignancy. Therefore, admission should not be limited to patients with an active tumour. Need for invasive mechanical ventilation, neutropenia and metastatic disease were variables related to in-hospital mortality. ICU stay (>48 h) and the need for surgery during hospital admission were protective variables.

Further multicentre and prospective studies should now be conducted to determine the prognostic factors of critical patients with solid tumours and their later post-hospital evolution.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RBC and LV contributed to the study design. RBC, MFR and GGV collected the critical patient data. LV and AR collected the oncological and follow-up data. RBC and LV confirm the authenticity of all the raw data. RBC was the major contributor in writing the manuscript. RBC, LV, JRM and XD contributed to the discussion, analysis and interpretation of the results obtained. XD contributed to the statistical analysis. JRM supervised the project. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the ethical principles of The Declaration of Helsinki, and was approved by the Ethics Committee of Hospital del Mar (No. 10570). The Clinical Research Ethics Committee understood that it was not necessary to obtain informed consent to participate in the study since the data were collected and analysed anonymously, and due to the observational character of the trial.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

ORCID: Raquel Bosch-Compte. https://orcid.org/0000-0002-7861-9474.

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