

BMJ Open Are patients with cancer with sepsis and bacteraemia at a higher risk of mortality? A retrospective chart review of patients presenting to a tertiary care centre in Lebanon

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ABSTRACT

Objective: Most sepsis studies have looked at the general population. The aim of this study is to report on the characteristics, treatment and hospital mortality of patients with cancer diagnosed with sepsis or septic shock.

Setting: A single-centre retrospective study at a tertiary care centre looking at patients with cancer who presented to our tertiary hospital with sepsis, septic shock or bacteraemia between 2010 and 2015.

Participants: 176 patients with cancer were compared with 176 cancer-free controls.

Primary and secondary outcomes: The primary outcome of this study was the in hospital mortality in both cohorts. Secondary outcomes included patient demographics, emergency department (ED) vital signs and parameters of resuscitation along with laboratory work.

Results: A total of 352 patients were analysed. The mean age at presentation for the cancer group was 65.39±15.04 years, whereas the mean age for the control group was 74.68±14.04 years ($p<0.001$). In the cancer cohort the respiratory system was the most common site of infection (37.5%) followed by the urinary system (26.7%), while in the cancer-free arm, the urinary system was the most common site of infection (40.9%). Intravenous fluid replacement for the first 24 hours was higher in the cancer cohort. ED, intensive care unit and general practice unit length of stay were comparable in both the groups. 95 (54%) patients with cancer died compared with 75 (42.6%) in the cancer-free group. The 28-day hospital mortality in the cancer cohort was 87 (49.4%) vs 46 (26.1%) in the cancer-free cohort ($p=0.009$). Patients with cancer had a 2.320 (CI 95% 1.225 to 4.395, $p=0.010$) odds of dying compared with patients without cancer in the setting of sepsis.

Conclusions: This is the first study looking at an in-depth analysis of sepsis in the specific oncology population. Despite aggressive care, patients with cancer have higher hospital mortality than their cancer-free counterparts while adjusting for all other variables.

Strengths and limitations of this study

- First study looking at the toll of sepsis in the high-risk oncological population.
- 176 patients with cancer with sepsis were compared with 176 patients with non-oncological sepsis. Both cohorts were similar in terms of demographics.
- Multivariate analysis conducted to minimise confounding bias.
- A retrospective chart review cohort study, and is subjected to bias.
- Single-centre study with a referral tertiary emergency department that deals with regional complicated cases, therefore the applicability of the results would be affected.

INTRODUCTION

Sepsis is one of the leading and most lethal medical emergencies, with a mortality rate reaching 25%.¹ In the USA, sepsis is responsible for 9% of all cancer-related deaths.² When compared with the non-oncological population, patients with cancer presenting with sepsis or septic shock are more likely to be hospitalised and have worse outcomes.^{3 4} The higher sepsis risk in patients with cancer, terminal or otherwise, is probably due to their state of immunosuppression, often due to the disease burden itself and to the effects of chemotherapy.⁴ There are no studies that looked at the emergency department's (ED) management of oncological patients, their in-hospital mortality from sepsis or septic shock, or the value of the systemic inflammatory response syndrome (SIRS) criteria in this subset of population. Therefore, the rationale behind this study is to evaluate sepsis outcomes in the oncological population compared with the

cancer-free population presenting to the ED with sepsis or septic shock; and to report on their hospital, 72-hour, and 28-day mortality as primary outcomes, as well as to report the differences in ED management, microbiology and parameters of resuscitation.

METHODS

Study design and patient selection

This was an Institutional Review Board approved (IRB# GA.ER.05), single-centre, retrospective, chart review, cohort study. All patients presenting to the ED of a tertiary care hospital between July 2010 and April 2015 were retrieved from the hospital's electronic health records. Inclusion criteria were a final diagnosis of sepsis, septic shock or bacteraemia. Sepsis and septic shock were defined according to the Surviving Sepsis Campaign guidelines.⁵ Sepsis was defined as having a documented/presumed infection with two or more of the following: temperature >38 or <36 °C, heart rate (HR) of >90 bpm, respiratory rate of >20 breaths/min or arterial carbon dioxide tension <32 mm Hg, white cell count $>12 \times 10^9$ cells/L or $>10\%$ bands. Septic shock was defined as having sepsis with any of the following: systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure <65 mm Hg or lactate >2 mmol/L after an initial fluid challenge. Bacteraemia was defined as two positive blood culture bottles with skin flora pathogens or one positive blood culture bottle with non-skin flora pathogens. The exclusion criteria were incomplete charts, patients younger than 18 years of age, pregnant or presenting secondary to trauma.

During the selected study period 1017 patients were identified as per our study criteria. Of those, 176 (17.3%) had an active solid or haematological malignancy, defined as currently receiving chemotherapy and/or radiation therapy, and were considered as the positive risk factor group in the cohort study. Of the 841 patients who were cancer free, 176 were selected using computer software for random number generation with the intent of producing demographic comparability between the two groups.

The medical records of the chosen oncological and non-oncological septic or septic shock patients were used to retrieve the patients' age, gender, history of comorbidities, type of cancer and history of bone marrow transplantation (BMT). Patients' vital signs and laboratory results were collected at initial presentation to the ED. Causative microorganisms and presence of bacteraemia were retrieved, as well as time to antibiotics, and amount of fluid resuscitation within the first 6 and 24 hours. Duration and type of vasopressors and steroids administration, as well as antibiotic type were collected to determine the appropriateness of antibiotic choice. Appropriate use of antibiotics was defined as a broad-spectrum antibiotics regimen covering Gram-positive and Gram-negative bacteria including pseudomonas and anaerobic bacteria. Furthermore, disposition from the ED, length of stay in the ED, intensive care unit (ICU)

or general practice unit (GPU), in addition to hospital, 72-hour and 28-day mortality were noted.

Statistical analysis

A two-tailed sample t-test was used to compare the differences in age, lengths of stay, time to and duration of vasoactive agent therapy, antibiotic and steroid therapy, fluid administration at 6 and 24 hours, vital signs at presentation, as well as electrolytes and blood work between oncological and non-oncological patients. Pearson's χ^2 test was used to compare the difference in distribution of bacteraemia, comorbidities, microbiology, use and appropriateness of antibiotics, disposition from the ED, use of vasopressor therapy, use of steroids, lactate level, and hospital, 72-hour and 28-day mortality between the same groups stated above. Statistical analyses were performed using SPSS Statistics for Windows V.21.0. (Armonk, New York, USA: IBM Corp).

In the bivariate analysis, Student's t-test and Pearson's χ^2 test were used to assess the significance of the statistical association between the independent variables (continuous and categorical) and hospital mortality; the dependent variable. Both tests were interpreted at a pre-determined significance level ($\alpha=0.05$). Furthermore, the magnitude of association between the predictor variables and hospital mortality was determined through calculating the ORs and their corresponding 95% CIs. A multivariate analysis was performed using logistic regression to find the best model that fits the data and that explains the association between the two groups in terms of the outcome variable and all predictor factors. A backward selection procedure, with significance level for removal from the model set at 0.1, was conducted by fitting hospital mortality with all risk factors found to be significant in the bivariate level, in addition to those considered clinically meaningful (age, gender, medical history (diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HTN), cerebrovascular accident (CVA), chronic kidney disease (CKD) on haemodialysis (HD), and systolic heart failure (HF), time to antibiotics, SBP, HR, blood urea nitrogen (BUN), and oncology status)).

RESULTS

Total cohort and oncological cohort characteristics

The mean age at presentation for the cancer group was 65.39 ± 15.05 years, with the mean age for the control group being 74.68 ± 14.04 years ($p < 0.001$). There was a higher number of male patients in the oncological arm (63.6%) than in the non-oncological arm (51.7%). The diagnosis of septic shock in both groups was statistically similar. Furthermore, there was a higher percentage of patients with HTN (71% vs 53.4%), diabetes (44.3% vs 30.1%), CAD (44.3% vs 23.3%) and non-systolic HF (29% vs 19.3%) in the non-oncological arm compared with the oncological arm. In terms of infection characteristics, both groups were similar regarding the

Table 1 Patient demographic characteristics

	Oncological (N=176)	Non-oncological (N=176)	p Value
Age (years) (mean±SD)	65.39±15.046	74.68±14.044	<0.001
Male sex n (%)	112 (63.6)	91 (51.7)	0.023
Diagnosis n (%)			
Septic shock	109 (61.9)	101 (57.4)	0.385
Sepsis	67 (38.1)	75 (42.6)	
HTN n (%)	94 (53.4)	125 (71.0)	0.001
DM n (%)	53 (30.1)	78 (44.3)	0.006
CAD n (%)	41 (23.3)	78 (44.3)	<0.001
Non-systolic CHF: EF≥40% n (%)	34 (19.3)	51 (29.0)	0.034
Systolic CHF: EF<40% n (%)	25 (14.2)	34 (19.3)	0.199
COPD/emphysema n (%)	24 (13.6)	27 (15.3)	0.650
CKD on HD n (%)	9 (5.1)	23 (13.1)	0.009
CVA n (%)	8 (4.5)	37 (21.0)	<0.001
Bacteraemia n (%)	66 (37.5)	63 (35.7)	0.740
Site of infection n (%)			<0.001
Lung	66 (37.5)	67 (38.1)	
Gastrointestinal	23 (13.1)	12 (6.8)	
Urine	47 (26.7)	72 (40.9)	
Skin	5 (2.8)	13 (7.4)	
Oral cavity	1 (0.6)	0 (0.0)	
Catheter	4 (2.3)	4 (2.3)	
Bile	5 (2.8)	4 (2.3)	
Liver	1 (0.6)	1 (0.6)	
Undetermined	24 (13.6)	3 (1.7)	
Microbiology isolates			
CoNS*	13 (7.4)	11 (6.3)	0.672
<i>Staphylococcus aureus</i>	9 (5.1)	6 (3.4)	0.429
<i>Escherichia coli</i>	60 (34.1)	77 (43.8)	0.063
<i>Klebsiella pneumoniae</i>	23 (13.1)	12 (6.8)	0.050
<i>Pseudomonas aeruginosa</i>	12 (6.8)	16 (9.1)	0.431
<i>Acinetobacter baumani</i>	8 (4.5)	11 (6.3)	0.479
<i>Enterococcus</i> spp.	7 (4.0)	7 (4.0)	1.000
<i>Proteus mirabilis</i>	4 (2.3)	9 (5.1)	0.158
<i>Streptococcus</i> spp.	7 (4.0)	12 (6.8)	0.238
<i>Clostridium</i> spp.	3 (1.7)	1 (0.6)	0.312
Others†	22 (12.5)	17 (9.7)	0.396

*Coagulase-negative staphylococci.

†Others included: *Bacteroides fragilis*, *Candida albicans*, *Citrobacter*, *Diphtheroids* spp., *Enterobacter cloacae*, *Haemophilus influenzae* (type B), *Haemophilus parainfluenzae*, *Legionella pneumophila*, *Leuconostoc*, *Morganella morgani*, *Peptococcus* spp., *Providencia stuartii*, *Serratia marsescens*, *Stenotrophomonas maltophilia*.

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; EF, ejection fraction; HD, haemodialysis; HTN, hypertension.

percentage of bacteraemic patients (37.5% vs 35.7%, $p=0.704$). In the cancer cohort, the respiratory system was the most common site of infection (37.5%), followed by the urinary system (26.7%) and the gastrointestinal system (13.1%). In the cancer-free arm, the urinary system was the most common site of infection (40.9%), followed by the respiratory system (38.1%) and the integumentary system (7.4%). The site of infection was not identified in 13.6% of patients with cancer compared with only 1.7% of patients who were cancer free. With regard to microbiology isolates, both groups were comparable with *Escherichia coli* being the most prevalent in both groups. The information presented is summarised in table 1.

The oncological cohort, as shown in table 2, was comprised of 19.9% haematological tumours and 80.1% solid tumours. Lung cancer (18%) was the most prevalent type of cancer, followed by acute and chronic leukaemia (11.9%), and breast cancer (11.4%). In terms of therapy, 22.8% of the haematological patients underwent BMT previously, and out of the total cancer cohort, 83.5% recently underwent chemotherapy and 35.2% received radiation therapy. When hospital, 72-hour and 28-day mortality analysis was conducted for the patients who underwent BMT compared with those who did not, no differences were noted between the two subgroups. Similar analysis was performed between haematological tumours and solid tumours, and likewise, no significant mortality difference was noted.

Table 2 Type of malignancy and treatments in the oncological cohort

	Oncology patients N=176
Total haematological tumours n (%)	35 (19.9)
Leukaemia*	20 (10.9)
Lymphoma	13 (7.1)
Multiple myeloma	2 (1.1)
Underwent BMT†	8 (22.8)‡
Total solid tumours n (%)	141 (80.1)
Lung cancer	32 (17.5)
Breast cancer	20 (10.9)
Pancreatic cancer	14 (7.7)
Bladder cancer	13 (7.1)
Prostate cancer	12 (6.6)
Ovarian cancer	8 (4.4)
Colon cancer	8 (4.4)
Cholangiocarcinoma	8 (4.4)
Liver cancer	7 (3.8)
Rectal cancer	6 (3.3)
Laryngeal cancer	4 (2.2)
Other‡	16 (8.7)
Current chemotherapy regiment n (%)	147 (83.5)
Current radiation therapy n (%)	62 (35.2)

*Includes acute and chronic leukaemia.

†Percentage is out of the total of haematological malignancy patients (ie, N=35).

‡Gastric, kidney, thyroid, brain, oesophageal, sarcoma, nasopharyngeal, thymus and anal cancer.

BMT, bone marrow transplantation.

Vital signs and laboratory studies on ED presentation

Compared with the cancer-free group, patients with cancer had a significantly lower average SBP (99.64 vs 110.33 mm Hg, respectively, $p<0.001$), and a significantly higher HR at presentation to the ED (110.32 vs 98.48 bpm, $p<0.001$). Moreover, 38.1% of the patients with cancer had a SBP at presentation lower than 90 mm Hg compared with 23.6% in the cancer-free arm. With respect to laboratory studies, notably lactic acid levels at presentation to the ED (drawn on 102 patients with cancer and 100 of the patients who were cancer free) were slightly higher in the cancer cohort as compared with the control group (4.37 vs 3.80 mg/dL). In the cancer arm, 44.1% of patients had a lactate level above 4 mg/dL, compared with 26% in the control group ($p=0.007$). Furthermore, there was a significant difference in the average haemoglobin levels between patients with cancer and patients who were cancer free (10.1 vs 11.4 g/dL, respectively, $p<0.001$). These findings are summarised in table 3.

Sepsis treatment variables and patients' length of stay

Patients with cancer required more fluids, with the cancer cohort receiving at 6 hours an average of 3.34 L compared with 2.69 L in the cancer-free group ($p=0.003$) and at 24 hours, 6.24 L compared with 5 L in the cancer-free group ($p<0.001$). Regarding vasopressor use, a total of 51.7% of patients with cancer required vasopressors at one point during their hospital admission compared with only 39.2% of the patients who were

Table 3 Vital signs and laboratory parameters on presentation to the ED

	Oncological (N=176)	Non-oncological (N=176)	p Value
SBP (mm Hg) (mean±SD)	99.6±23.4	110.3±26.6	<0.001
DBP (mm Hg) (mean±SD)	57.1±15.3	60.3±18.0	0.069
MAP (mm Hg) (mean±SD)	71.3±16.5	76.8±19.1	0.002
HR (bpm) (mean±SD)	110.3±24.9	98.3±23.2	<0.001
O ₂ saturation (%) (mean±SD)	93.8±8.2	93.4±6.7	0.570
Temperature (°C) (mean±SD)	37.2±1.1	37.6±1.2	0.004
RR (breaths/min) (mean±SD)	23.5±7.2	23.4±6.8	0.889
Glucose (mg/dL) (mean±SD)	154.2±81.5	166.5±103.3	0.249
Lactate (mmol/L) (mean±SD)	4.37±3.27	3.80±3.69	0.252
WCC ($\times 10^9$ cells/L) (mean±SD)	14.28±16.62	15.10±8.76	0.565
Haemoglobin (g/dL) (mean±SD)	10.07±2.11	11.42±2.05	<0.001
Haematocrit (%) (mean±SD)	29.98±6.46	34.14±6.13	<0.001
Bicarbonate (mmol/L) (mean±SD)	19.80±5.64	20.36±6.05	0.370
BUN (mg/dL) (mean±SD)	38.43±24.52	49.17±35.69	0.001
Creatinine (mg/dL) (mean±SD)	1.75±1.54	2.26±1.79	0.004
Arterial pH (mean±SD)	7.35±0.11	7.35±0.12	0.704
INR (mean±SD)	1.71±1.06	1.93±1.41	0.192
Lactate*			
≥4 (mmol/L) (%)	44.1%	26.0%	0.007

*Lactate levels were drawn on 102 patients with cancer and 100 patients who are cancer-free.

BUN, blood urea nitrogen; DBP, diastolic blood pressure; ED, emergency department; HR, heart rate; INR, international normalised ratio; MAP, mean arterial pressure; RR, respiration rate; SBP, systolic blood pressure; WCC, white cell count.

cancer free. Of the cancer cohort, 44.3% of patients required vasopressor therapy in the first 24 hours, compared with 34.7% of patients from the control group. Antibiotics were administered after an average of 4.73 hours in the patients with cancer and 2.77 hours in the control patients, with the majority of patients in both groups receiving their antibiotics in the ED (93.2% and 92%, respectively). Of note, both groups had similar ED, ICU and GPU length of stays. Table 4 summarises the differences in the ED management between the two arms of the study.

Patient mortality and hospital mortality logistic regression

During their hospital stay, a total of 96 (54%) patients with cancer died compared with 75 (42.6%) patients in the cancer-free group ($p=0.033$). The 72-hour mortality was higher in the cancer group, as 26 (14.7%) of the patients with cancer died compared with only 11 (6.3%) of the control patients ($p=0.009$). Furthermore, patients with cancer had a significantly higher 28-day mortality compared with control patients (49.4% vs 26.1% respectively, $p<0.001$).

Table 5 shows the logistic regression done, with hospital mortality as the dependent variable, to determine the major predictors of this primary outcome. Age, sex, comorbidities (DM, CAD, HTN, CVA, CKD on HD, and

HF), previous use of steroids, time to antibiotic initiation, SBP and HR on presentation along with BUN were chosen as factors to be controlled for, due to their clinical meaningfulness and statistical difference between oncological and non-oncological patients. The multivariate analysis showed statistical significance only for being an oncological patient as a predictor of hospital mortality. While adjusting for all other variables, oncological patients had 2.32 higher odds of hospital mortality than their cancer-free counterparts in the setting of either sepsis or septic shock.

DISCUSSION

In 2001, the Early Goal Directed Therapy (EGDT) protocol, by Rivers *et al*⁶ was the first major study that tackled sepsis-related mortality and led to a shift towards a protocol-based, more aggressive sepsis care in the ED. Recent published data have advocated for earlier recognition of sepsis, with an early emphasis on fluid resuscitation and antibiotic administration.⁷⁻⁹ The majority of sepsis studies, however, have looked at the general population and neglected to look at high-risk patient populations such as the oncological patients.¹⁰⁻¹³ The aim of this study was to look at patients with cancer who presented to the ED with sepsis or septic shock and to compare them to patients who were cancer free with a

Table 4 Sepsis treatment variables and patients' LOS

	Oncological (N=176)	Non-oncological (N=176)	p Value
IV fluid requirement in first 6 hours (L) (mean±SD)	3.34±2.17	2.69±1.87	0.003
IV fluid requirement in first 24 hours (L) (mean±SD)	6.24±3.11	5.00±2.59	<0.001
Vasopressor use: levophed (%)	51.7%	39.2%	0.019
Vasopressor use: dopamine (%)	6.8%	10.2%	0.252
Inotrope use: dobutamine (%)	0.6%	2.8%	0.100
Vasopressor/inotrope use within the first 24 hours (%)	44.3%	34.7%	0.064
Time to vasopressor/inotrope use within first 24 hours (hours) (mean±SD)	7.03±5.72	6.77±5.84	0.792
Vasopressors/inotrope treatment duration within first 24 hours (hours) (mean±SD)	15.73±6.39	16.02±6.85	0.801
Steroid use (%)	32.4%	29.0%	0.488
Antibiotics use* (%)	99.4%	98.9%	0.562
Appropriate antibiotic†‡ (%)	92.1%	92.2%	0.979
Antibiotics initiated in ED (%)	93.2%	92.0%	0.684
Antibiotics initiated in ICU (%)	1.1%	1.7%	0.652
Antibiotics initiated in GPU (%)	5.1%	5.7%	0.814
Time to initiation of antibiotics (hours) (mean±SD)	4.73±12.71	2.77±2.70	0.047
ED LOS (hours) (mean±SD)	23.07±38.48	23.48±35.84	0.917
ICU LOS (days) (mean±SD)	10.16±12.55	14.93±30.31	0.184
GPU LOS (days) (mean±SD)	9.40±10.07	9.88±13.39	0.798
Hospital LOS (days)§ (mean±SD)	15.43±17.41	16.45±29.71	0.790

*Variable was calculated for patients who are bacteraemic that received antibiotics (N=128, with 66 patients with cancer and 63 patients without cancer).

†Variable was calculated only for patients who are bacteraemic that received antibiotics, and had an available bacterial sensitivity (N=127, with 65 patients with cancer and 63 patients without cancer).

‡Appropriate use of antibiotics was defined as a broad-spectrum antibiotics regimen covering Gram-positive, Gram-negative bacteria including pseudomonas and anaerobic bacteria.

§Hospital LOS days were calculated only for those that did not expire in hospital (as shorter LOS times may be associated with early deaths). ED, emergency department; GPU, general practice unit; ICU, intensive care unit; IV, intravenous; LOS, length of stay.

Table 5 Multiple logistic regression for hospital mortality

	Oncological (N=176)	Non-oncological (N=176)	Crude*		Adjusted†	
			OR (CI 95%)	p Value	OR (CI 95%)	p Value
Hospital mortality n (%)	95 (54)	75 (42.6)	1.579 (1.036 to 2.405)	0.033	2.320 (1.225 to 4.395)	0.010

*Reference group is being non-oncological.

†While controlling for all statistically significant and clinically relevant variables from the bivariate analysis in table 1.

similar presentation, with an emphasis on demographics, ED management and mortality.

While there is a paucity of the literature on sepsis in the oncological patients, some researchers have tackled this issue. Angus *et al*¹⁴ showed that one in six patients with severe sepsis have an underlying malignancy. Williams *et al*⁸ constructed a database of patients with cancer admitted to the hospital and compared patients with cancer with severe sepsis to patients with non-severe sepsis. They found that patients with cancer with severe sepsis were older, had more comorbid conditions and a higher mortality than patients with cancer without severe sepsis; however, they did not compare patients with cancer to patients who are cancer free. According to our results, patients with septic cancer are younger and have less comorbid conditions than the general population and are more haemodynamically unstable at presentation.

Angus *et al*¹⁴ reported a 30% increase in mortality in patients with cancer with severe sepsis. Furthermore, Williams *et al*⁸ reported that the overall hospital mortality for patients with severe sepsis with cancer was 52% higher than that of patients with non-cancer severe sepsis (37.8% vs 24.9%, respectively) and was five times greater than the non-severe sepsis cancer hospital mortality. In our study, the in-hospital mortality was higher in the oncological group (54%) compared with the control group (42.6%; $p < 0.001$). Similar to the Angus study, we found that patients with cancer had a 29% increase in in-hospital mortality, and that an underlying malignancy in a patient with sepsis increased the odds of dying by 2.32 times. This increased risk of death could be explained by the burden the tumour imposes on the host, through the production of cytokines or secondary to localised obstruction, as well as chemotherapy and the ensuing immunosuppressed state that significantly decreases the host's immune system and predisposes the host to opportunistic infections.^{3 15}

In their registry of patients, Williams *et al*⁸ found that the incidence of severe sepsis was higher in haematological tumours than in solid tumours; however, they noted that both cancer types had a similar mortality. This finding of similar haematological/solid tumour mortality is echoed in our study as well. Moreover, they found that lung cancer was associated with the highest mortality. The highest mortality in our cancer cohort was associated with gastrointestinal (GI) infections, which could probably be explained by the tumour obstructing GI structures and acting as a nidus for infection and continuous bacterial seeding. Infections in

these sites generally require complex surgical interventions, which may not be possible due to the nature, location and prognosis of the disease.¹⁶

At the time of this study, there was no sepsis management protocol at our institution. Patients with cancer received on average 3.34 ± 2.17 L of fluids at 6 hours, which is in line with the 30 cc/kg fluid resuscitation guidelines set by the Surviving Sepsis Campaign guidelines.¹⁷ Broad-spectrum antibiotics were initiated in all cases of sepsis and septic shock with a combination of vancomycin and carbapenems being the most commonly used antibiotics. However, the time to antibiotic administration from presentation was longer than the 3 hours set guideline, with an average of 4.73 ± 12.72 hours in the oncological cohort as opposed to 2.77 hours in the cancer-free cohort. The delay in antibiotics administration in the cancer cohort could have possibly contributed to our high mortality.¹⁸ Metersky *et al*¹⁹ found that the main reason for delay of antibiotics in their patient population was an incoherent presentation, such as normal vital signs and non-specific localising symptoms that delayed diagnosis. In our study, the delay could have been due to several reasons; on one hand, the presenting temperature in the cancer cohort was lower than the non-cancer cohort, while on the other hand, the presence of non-infectious acute inflammatory disorders can mimic sepsis in patients with malignancies and confound the clinical picture. For instance, patients with acute monocytic leukaemia often have pulmonary infiltrates.²⁰ Furthermore, induction treatments may precipitate tumour lysis syndrome, which may result in multiorgan dysfunction. All of these non-infectious processes might have influenced the clinicians and lead to the delay in diagnosis.

According to the literature, the length of stay of patients with severe sepsis cancer was almost three times as long as that of the patients with septic cancer and the incurred hospitalisation costs was three times as much.³ While we did not conduct a cost analysis, we had very similar lengths of stay between the two cohorts. It is important to note that there is a limited amount of ICU beds at our institution; and very often, patients requiring an ICU admission tend to remain in the ED for an extended period of time. This in part explains our long ED length of stay and our high GPU admission rate.

Finally, the majority of patients in both cohorts presented with two or more SIRS criteria, showing that in accordance with the literature, SIRS criteria have a high sensitivity.²¹ However, there was no correlation between

the number of SIRS criteria and mortality in either group. Of the patients with cancer who were admitted and were treated for sepsis during their hospital stay, 27 (15%) were found to have <2 SIRS criteria at presentation, with a total of 13 patients (48.1%) dying during their hospital stay. SIRS-negative sepsis has been described in the literature, with the latest studies showing that about 12% of patients with sepsis have <2 SIRS criteria at presentation.^{4 14} Though it may not fulfil the definition of sepsis, emergency physicians should always be vigilant and have a low threshold to suspect sepsis in patients with cancer given that these patients can present with normal vital signs, deteriorate during their admission and end up with a diagnosis of sepsis.

Limitations

This was a retrospective chart review cohort study and as such authors are aware of the inherent limitations of such a type of study. To minimise biases from this, frequent meetings were held between the principal investigator and data collectors to standardise the way in which data are collected, entered and cleaned. The increased mortality seen in the oncological cohort could be due to several reasons. First and foremost, the study is from a referral tertiary centre ED that deals with regional complicated cases, which could limit the generalisability of the results to the whole oncological subpopulation. Second, the delay in antibiotic administration in the oncological cohort might have led to the increased mortality. In the analysis stage, the equally numbered groups were found to be unmatched and possibly difficult to compare and conclude meaningful evidence from. In an effort to correct for this, bivariate analysis was performed, and characteristics that were statistically different between the populations along with clinically meaningful elements were controlled for in the multivariate analysis in order to minimise confounding variables. One possible confounding factor not accounted for is oncological patients being diagnosed with terminal cancer, as these patients would have higher mortality rates than other patients with cancer thus limiting our conclusion. According to the literature, the most common definition for terminal illness is an expected 3-month cut-off for survival in addition to inutility of chemotherapy or current regimen in treating the disease.^{22–24} However, in accordance with the local culture and setting of the study, patients are not labelled terminal and services such as hospice care are not available, and patients typically receive chemotherapy until the end of their disease. Resolving all the aforementioned issues poses a problem outside the scope of this article but the authors concede that the mortality might have been falsely elevated given the fact that some patients might have expired from their advanced cancer as well as sepsis.

CONCLUSION

This study is one of the first studies looking at sepsis and septic shock in the oncological versus the non-

oncological population. It shows that in the setting of sepsis or septic shock in the ED, patients with cancer (haematological or solid) have higher hospital mortality than their cancer-free counterparts while adjusting for all other variables. Patients with cancer with sepsis or septic shock, are usually younger and have less comorbidities at presentation, but tend to have a higher mortality despite aggressive care. We hope that this study sheds light on this topic and stimulates further research on sepsis in vulnerable patient population.

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REFERENCES

1. Jaimes F, Garcés J, Cuervo J, *et al.* The systemic inflammatory response syndrome (SIRS) to identify infected patients in the emergency room. *Intensive Care Med* 2003;29:1368–71.
2. Hartnett S. Septic shock in the oncology patient. *Cancer Nurs* 1989;12:191–201.
3. Williams MD, Braun LA, Cooper LM, *et al.* Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care* 2004;8:R291–8.
4. Chanock S. Evolving risk factors for infectious complications of cancer therapy. *Hematol Oncol Clin North Am* 1993;7:771–93.
5. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.
6. Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
7. Peake SL, Delaney A, Bailey M, *et al.*, ARISE Investigators; ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014;371:1496–506.
8. Yealy DM, Kellum JA, Huang DT, *et al.*, ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683–93.
9. Mouncey PR, Osborn TM, Power GS, *et al.* Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372:1301–11.
10. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. *Crit Care* 2004;8:222–6.
11. Wang HE, Shapiro NI, Angus DC, *et al.* National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 2007;35:1928–36.

12. Gaieski DF, Edwards JM, Kallan MJ, *et al*. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167–74.
13. Martin GS, Mannino DM, Eaton S, *et al*. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–54.
14. Angus DC, Linde-Zwirble WT, Lidicker J, *et al*. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303–10.
15. Allegretta GJ, Weisman SJ, Altman AJ. Oncologic emergencies II. Hematologic and infectious complications of cancer and cancer treatment. *Pediatr Clin North Am* 1985;32:613–24.
16. Bosscher MR, van Leeuwen BL, Hoekstra HJ. Mortality in emergency surgical oncology. *Ann Surg Oncol* 2015;22:1577–84.
17. Levy MM, Dellinger RP, Townsend SR, *et al*. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010;38:367–74.
18. Gaieski DF, Mikkelsen ME, Band RA, *et al*. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045–53.
19. Metersky ML, Sweeney TA, Getzow MB, *et al*. Antibiotic timing and diagnostic uncertainty in Medicare patients with pneumonia: is it reasonable to expect all patients to receive antibiotics within 4 hours? *Chest* 2006;130:16–21.
20. Azoulay É, Canet E, Raffoux E, *et al*. Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. *Eur Respir J* 2012;39:648–53.
21. Comstedt P, Storgaard M, Lassen AT. The Systemic Inflammatory Response Syndrome (SIRS) in acutely hospitalised medical patients: a cohort study. *Scand J Trauma Resusc Emerg Med* 2009;17:67.
22. Kaukonen KM, Bailey M, Pilcher D, *et al*. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015;372:1629–38.
23. Viganò A, Dorgan M, Buckingham J, *et al*. Survival prediction in terminal cancer patients: a systematic review of the medical literature. *Palliat Med* 2000;14:363–74.
24. Aabom B, Kragstrup J, Vondeling H, *et al*. Defining cancer patients as being in the terminal phase: who receives a formal diagnosis, and what are the effects? *J Clin Oncol* 2005;23:7411–16.