RESEARCH ARTICLE

Cancer Patients Are at High Risk of Mortality if Presenting with Sepsis at an Emergency Department

Thidathit Prachanukool[1], Panvilai Tangkulpanich[1], Possawee Paosaree[1], Kittisak Sawanyawisuth[2,3], Yuwares Sitthichanbuncha[1]*

Abstract

Background: Sepsis is an emergency condition with high mortality and morbidity rate. There are limited data on the association of cancer as a risk factor for mortality in sepsis patients in the emergency department (ED). Materials and Methods: This retrospective study was conducted at the ED, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. The study period was between January 1st and December 31st, 2014. The inclusion criteria were as follows: adult patients over 15 years of age who presented at the ED with suspicion of sepsis, received treatment at the ED, and whose blood culture was found to be positive. Clinical data were recorded from medical records including the Mortality in Emergency Department Sepsis score (MEDS score). The primary outcome of this study was mortality at one month. Multivariate logistic regression analysis was used to identify independent factors associated with death. Results: During the study period, there were 775 eligible patients. The two most common pathogens identified from blood cultures were *Staphylococcus aureus* (193 patients; 24.9%) and *Escherichia coli* (158 patients; 20.4%). At one month after presenting at the ED, 110 patients (14.2%) had died. There were four significant factors for death, having cancer, being on an endotracheal tube, initial diagnosis of bacteremia, and high MED scores. Having cancer had an adjusted OR of 2.12 (95% CI of 1.29, 3.47). Conclusions: Cancer patients have double the risk of mortality if presenting with sepsis at the ED.

Keywords: Sepsis - cancer - death - predictors - emergency department

Asian Pac J Cancer Prev, **17 (7)**, 3423-3426

Introduction

Sepsis is a common emergency condition and requires prompt management (Lakshmikanth et al., 2016). It is defined by the presence of at least two abnormalities of systemic inflammatory response syndrome (Dellinger et al., 2013). The incidence of sepsis is 240-300 patients/100,000 population in the United States of America and it causes 215,000 deaths per year (Angus et al., 2001; Martin et al., 2003). The mortality rate of sepsis may be as high as 34.3-54.1% in Thailand where medical resources are limited (Angkasekwinai et al., 2009; Khwannimit and Bhurayanontachai, 2009).

Several factors are reported to be associated with mortality in sepsis such as hypoxemia, shock, or early antibiotic treatment (within three hours) at the ED visit (Angkasekwinai et al., 2009). Emergency physicians may play an important role in terms of early detection and early treatment of sepsis. The Emergency Department (ED), therefore, is a key factor in in saving patients' lives. Despite good protocol on early resuscitation for severe sepsis at the ED, the mortality rate is still about one-in-four (Drumheller et al., 2016).

Cancer is a common condition and has an increasingly high number of incidences and mortalities (Jemal et al., 2010). Sepsis may be one important cause of death in cancer patients. There are limited data on the association of cancer as a risk factor for mortality in sepsis patients at the ED. A study from an intensive care unit in China found that sepsis patients who had cancer had an increased a risk of death by 2.246 times (Zhou et al., 2014). This study aimed to evaluate if cancer is a risk factor for mortality in sepsis patients treated at the ED.

Materials and Methods

This study was a retrospective study and conducted at the ED, Faculty of Medicine, Ramathibodi hospital, Bangkok, Thailand. The study period was between January 1st and December 31st, 2014. The inclusion criteria were as follows: adult patients over 15 years of age who presented at the ED with suspicion of sepsis, received treatment at

*[1]Department of Emergency Medicine, Faculty of Medicine, Ramathibodi Hospital Mahidol University, Bangkok, [2]Department of Medicine, Faculty of Medicine, [3]Research Center in Back, Neck Other Joint Pain and Human Performance (BNOJPH), Khon Kaen University, Khon Kaen, Thailand *For correspondence: yuwares.sit@mahidol.ac.th*

the ED, and whose blood culture was found to be positive. We excluded patients who had incomplete medical records, did not meet the sepsis criteria, or received any treatment prior to participation in the study.

Clinical data were recorded from medical records including age, sex, co-morbid disease, vital signs, areas of the ED in which they were treated (resuscitation room or observation room), Mortality in Emergency Department Sepsis score (MEDS score), diagnosis made by initial ED physicians, initial laboratory tests, blood cultures, and initial treatment at the ED. The MEDS score has been described elsewhere (Shapiro et al., 2003). This score was used to divide patients into five categories; very low risk, low risk, moderate risk, high risk, and very high risk. The primary outcome of this study was mortality at one month.

Patients were divided into two groups according to whether or not they had survived at one month. Data were compared between both groups using descriptive statistics. Univariate logistic regression analyses were applied to calculate the crude odds ratios (ORs) of individual variables for death. All significant variables by univariate

Table 1. Causative Agents in Sepsis Treated at the Emergency Room by Positive Blood Culture (n = 775)

Causative organism	n (%)
Gram Negative Bacteria	411 (53.0%)
Escherichia coli	158 (38.4%)
Escherichia coli (ESBLs)	79 (19.2%)
Klebsiella pneumoniae	41 (9.9%)
Acinetobacter baumannii	15 (3.6%)
Pseudomonas aeruginosa	15 (3.6%)
Salmonella spp.	15 (3.6%)
Others	88 (21.4%)
Gram Positive Bacteria	355 (45.8%)
Staphylococcus spp.	193 (54.4%)
Streptococcus spp.	88 (24.8%)
Bacillus spp.	18 (5.0%)
Enterococcus spp.	17 (4.8%)
Micrococcus luteus	15 (4.2%)
Others	24 (6.8%)
Fungus	9 (1.2%)
Candida spp.	4 (44.4%)
Cryptococcus neoformans	4 (44.4%)
Penicillium marneffei	1 (11.1%)

Table 2. Clinical Factors of Sepsis Patients Treated at the Emergency Department Categorized by Mortality at One Month

Factors	Survival (n=665)	Death (n=110)	p-value
Age, years	68 (17,100)	67 (16,99)	0.12
Male gender	262 (39.4%)	60 (54.5%)	0.003
MED score			< 0.001
very low	246 (37.0%)	8 (7.3%)	
low	148 (22.3%)	12 (10.9%)	
moderate	209 (31.4%)	46 (41.8%)	
high	35 (5.3%)	29 (26.4%)	
very high	27 (4.1%)	15 (13.6%)	
ER place			< 0.001
Resuscitation room	116 (17.4%)	61 (55.5%)	
Observation room	549 (82.6%)	49 (44.5%)	
No underlying disease	71 (10.7%)	4 (3.6%)	0.021
DM	219 (32.9%)	28 (25.5%)	0.119
HT	286 (43.0%)	43 (39.1%)	0.441
CKD	137 (20.6%)	17 (15.5%)	0.21
HIV infection	12 (1.8%)	3 (2.7%)	0.515
COPD	24 (3.6%)	7 (6.4%)	0.172
Cancer	183 (27.5%)	57 (51.8%)	< 0.001
Transplant patients	13 (2.0%)	0 (0.0%)	0.139
Bed-ridden	96 (14.4%)	27 (24.5%)	0.007
Cerebrovascular diseases	100 (15.0%)	17 (15.5%)	0.91
Liver disease	59 (8.9%)	10 (9.1%)	0.941
Heart disease	116 (17.4%)	18 (16.4%)	0.781
Terminal illness	123 (18.5%)	55 (50.0%)	< 0.001
Systolic blood pressure, mmHg	129 (0, 243)	113.5 (0, 194)	0.968
Diastolic blood pressure, mmHg	69 (0,164)	61.5 (0,100)	0.1
Mean arterial pressure, mmHg	89 (0,170)	80 (0,129)	0.342
Heart rate, bpm	104 (0,185)	109 (0,170)	< 0.001
Respiratory rate, tpm	22 (0,46)	24 (0,56)	< 0.001
Body temperature, oC	38.2, (35.0,41.2)	37.6, (35.0,42.0)	0.001
Site of infections			
Upper Respiratory tract	3 (0.5%)	0 (0.0%)	0.48
Lower Respiratory tract	132 (19.8%)	36 (32.7%)	0.002
GU tract	207 (31.1%)	13 (11.8%)	<0.001
Abdominal	112 (16.8%)	17 (15.5%)	0.717
Skin & Soft tissue	83 (12.5%)	13 (11.8%)	0.845
Bacteremia	125 (18.8%)	29 (26.4%)	0.065
CNS	9 (1.4%)	4 (3.6%)	0.084
Unknown	6 (0.9%)	0 (0.0%)	0.317
Lab			
Mean hematocrit, %	32.8 (7.3)	31.2 (7.8)	0.228
White blood cells, x103/mm3	11.5 (7-15)	11.0 (4-21)	< 0.001
Mean band form, %	0.75 (2.4)	1.49 (3.6)	< 0.001
Mean platelet, x106/mm3	218 (114)	180 (141)	0.028

*Data is presented as median (range), numbers (percentage), or mean (S.D.); MED: Mortality in Emergency Department Sepsis score; ER: emergency room; DM: diabetes mellitus; HT: hypertension; CKD: chronic kidney disease; HIV: human immunodeficiency virus; COPD: chronic obstructive airway disease; GU: genitourinary; CNS: central nervous system; bold type indicates statistically significant numbers; 0 indicated patients presented with cardiac arrest

Table 3. Treatment Factors of Sepsis Patients Treated at the Emergency Department Categorized by Mortality at One Month

Treatment	Survival (n=665)	Death (n=110)	p-value
Antibiotic			< 0.001
Ceftriazone	287 (43.2%)	22 (20.0%)	
Piperacillin/tazobactam	54 (8.1%)	27 (24.5%)	
Meropenam	39 (5.9%)	11 (10.0%)	
Amoxicillin/clavulanic acid	29 (4.4%)	9 (8.2%)	
Levofloxacin	33 (5.0%)	4 (3.6%)	
Ceftazidime	29 (4.4%)	4 (3.6%)	0.991
Others	179 (26.9%)	32 (29.1%)	
No antibiotics at the ER	15 (2.3%)	1 (0.9%)	
Mean time of antibiotic treatment, min	194.1 (203.9)	176.3 (208.9)	
Norepinephrine	58 (8.7%)	28 (25.5%)	< 0.001
Dopamine	1 (0.2%)	2 (1.8%)	0.009
Steroids	19 (2.9%)	2 (1.8%)	0.534
On endotracheal tube	34 (5.1%)	33 (30.0%)	< 0.001
Blood transfusions	52 (7.8%)	15 (13.6%)	0.044

Table 4. Significant Factors Associated with death in Sepsis Patients Treated at the Emergency Department (n = 775)

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
ER place		
Resuscitation room	5.89 (3.84, 9.02)	2.62 (1.57, 4.37)
Observation room	1	1
Cancer	2.83 (1.87 – 4.27)	2.12 (1.29 – 3.47)
On endotracheal tube	7.95 (4.66 – 13.57)	4.60 (2.44 – 8.68)
Bacteremia	2.49 (1.48 – 4.18)	2.83 (1.51 – 5.29)
MED score		
Very low	1	1
Low	2.38 (0.93, 6.05)	1.82 (1.69, 4.76)
Moderate	7.12 (3.29, 15.41)	4.00 (1.76, 9.07)
High	25.99 (11.01, 61.36)	12.78 (4.95, 32.97)
Very high	17.43 (6.77, 44.86)	5.36 (1.81, 15.88)

logistic analysis were included in subsequent stepwise multivariate logistic regression analyses. Analytical results were presented as unadjusted ORS, adjusted ORs, and 95% confidence intervals (CIs). All analyses were performed by SPSS software (Chicago, Illinois, USA).

Results

During the study period, there were 947 eligible patients. Of those, 172 patients were excluded due to having previously been treated at other hospitals (55 patients), failure to meet SIRS criteria (53 patients), age of less than 15 years (42 patients), and incomplete medical records (22 patients). In total, there were 775 patients in this study. The two most common pathogens identified from blood cultures were Staphylococcus aureus (193 patients; 24.90%) and Escherichia coli (158 patients; 20.39%). Details of other identified pathogens were shown in table 1 and categorized by type of pathogen.

At one month after presenting at the ED, 110 patients (14.19%) died. Characteristics of patients in the survival and death groups are shown in Table 2. There were several factors of which there were significantly higher proportions in the death group including males, high MED scores, being at the resuscitation room, having a lower respiratory tract infection, having cancer/bed ridden status, or having terminal illness (Table 2).

Regarding treatment at the ED, there was a significant difference between the two groups in the antibiotics prescribed at the ED but no difference in the time from first presentation at the ED to the time given antibiotics (194 vs 176 minutes; p value 0.991). A higher proportions of patients in the death group received norepinephrine (25.5% vs 8.7%), dopamine (1.8% vs 0.2%), endotracheal tubes (30.0% vs 5.1%), and blood transfusions (13.6% vs 7.8%) than the survival group (Table 3).

According to multivariate logistic regression analysis, there were four significant factors for death (Table 4) including place of ER care, having cancer, being on an endotracheal tube, initial diagnosis of bacteremia, and high MED scores. Having cancer had an adjusted OR of 2.12 (95% CI of 1.29, 3.47).

Discussion

Among the 12 co-morbid diseases in this study, only cancer was an independent factor associated with death in sepsis patients who had positive blood cultures and were treated at the ED (Table 2 and 4). The risk doubled if the patients had a history of cancer. Most studies performed at the ED did not find this association (Shapiro et al., 2003; Angkasekwinai et al., 2009; Khwannimit and Bhurayanontachai, 2009; Zhou et al., 2014). The recent study with a smaller sample size than this study (378 sepsis patients) also showed a positive correlation between history of cancer and mortality in sepsis patients at the ED

(Drumheller et al., 2016). The adjusted OR was somewhat higher than in this study (4.31 *vs* 2.12). Another study performed in the intensive care unit in China also found this association with an adjusted OR of 2.246 (Zhou et al., 2014).

Other independent factors for death in sepsis patients treated at the ED in this study were mostly similar to previous studies (Shapiro et al., 2003; Angkasekwinai et al., 2009; Khwannimit and Bhurayanontachai, 2009; Zhou et al., 2014). These factors included the patient having received endotracheal tube, having a high MED score, and being treated at the resuscitation room. These factors indicated a severe sepsis condition (Drumheller et al., 2016). Initial diagnosis of bacteremia was not statistically significant according to univariate logistic analysis (Table 2), but became a significant independent factor after adjustment for other factors (Table 4). These findings indicated that it is a real significant factor because multivariate analysis is more robust and can control for confounding factors. Thus, the initial clinical evaluation as bacteremia by ER physicians may be also important in identifying high-risk sepsis patients (Angkasekwinai et al., 2009).

The main limitation in this study is that the status and details of the patients' cancer were not well described. Further studies should be performed using cancer patients who presented at the ED with sepsis. The types and status of the patients' cancer should be studied. However, the results of this study may encourage ER physicians to be aware that cancer patients presenting at the ED with sepsis may be at higher risk for death and need prompt management, particularly for those cancer patients who have good functional status suggesting good prognosis from cancer.

In conclusion, Cancer patients have double the risk of mortality if presenting with sepsis at the ED.

Acknowledgements

The authors would like to thank the Thailand Research Fund (TRF) for kind support (IRG 5780016). This research was also funded in part by grants from the Higher Education Research Promotion National Research University Project of Thailand, Office of the Higher Education Commission through the Health Cluster (SHeP-GMS), Thailand; the Faculty of Medicine, Khon Kaen University grant number TR57201; and the TRF Senior Research Scholar Grant, Thailand Research Fund grant number RTA5880001.

References

Angkasekwinai N, Rattanaumpawan P, Thamlikitkul V (2009). Epidemiology of sepsis in Siriraj Hospital 2007. *J Med Assoc Thai*, **92**, 68-78.

Angus DC, Linde-Zwirble WT, Lidicker J, et al (2001). Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*, **29**, 1303-10.

Dellinger RP, Levy MM, Rhodes A, et al (2013). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*, **39**, 165-228.

Drumheller BC, Agarwal A, Mikkelsen ME, et al (2016). Risk factors for mortality despite early protocolized resuscitation for severe sepsis and septic shock in the emergency department. *J Crit Care*, **31**, 13-20.

Jemal A, Center MM, DeSantis C, Ward EM (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*, **19**, 1893-907.

Khwannimit B, Bhurayanontachai R (2009). The epidemiology of, and risk factors for, mortality from severe sepsis and septic shock in a tertiary-care university hospital setting. *Epidemiol Infect*, **137**, 1333-41.

Lakshmikanth CL, Jacob SP, Chaithra VH, de Castro-Faria-Neto HC, Marathe GK (2016). Sepsis: in search of cure. Inflamm Res, [Epub ahead of print].

Martin GS, Mannino DM, Eaton S, Moss M (2003). The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*, **348**, 1546-54.

Putra BE, Tiah L (2013). The mortality in Emergency Department Sepsis Score as a predictor of 1-month mortality among adult patients with sepsis: weighing the evidence. *ISRN Emergency Medicine*, 896802.

Shapiro NI, Wolfe RE, Moore RB, et al (2003). Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med*, **31**, 670-5.

Zhou J, Qian C, Zhao M, et al (2014). Epidemiology and outcome of severe sepsis and septic shock in intensive care units in mainland China. *PLoS One*, **9**, 107181.