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ORIGINAL ARTICLE

Risk Factors for Severe Outcomes in Extended-Spectrum Beta-Lactamase (ESBL) Bacteremia: A Single-center Study

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ABSTRAK

Bakteremia beta-laktamase spektrum diperluas (ESBL) sering menyebabkan hasil yang teruk seperti kematian dan kegagalan rawatan. Kajian ini bertujuan untuk mengenalpasti faktor risiko bagi pesakit bakteremia ESBL. Analisis kohort retrospektif telah dijalankan terhadap pesakit yang berumur 13 tahun ke atas dan dimasukkan ke Hospital Canselor Tuanku Muhriz (HCTM) untuk bakteremia ESBL dalam tempoh Januari 2015 hingga Ogos 2019. Pesakit dengan bakteria polimikrobial dikecualikan. Kadar kematian pesakit di HCTM ialah sebanyak 30.2%, manakala kadar kematian berkaitan jangkitan ialah 22.5%. Faktor risiko kematian di hospital termasuklah hipertensi, diabetes mellitus, jangkitan kulit dan tisu lembut (SSTI), kateterisasi kencing dan pengudaraan mekanikal. Faktor risiko bebas yang dikaitkan dengan kematian ialah pengudaraan mekanikal (AOR 3.12; CI 1.06-9.18; p = 0.04). Tiada perkaitan ditemui antara rawatan antibiotik empirik yang sesuai dengan kematian (p = 0.74), kejayaan rawatan (p = 0.71), dan tempoh rawatan di hospital (p = 0.84). Walau bagaimanapun, rawatan definitif yang sesuai dikaitkan dengan kadar kematian yang lebih rendah (p<0.01) dan kejayaan rawatan yang lebih tinggi (p<0.01). Pengudaraan mekanikal adalah satu-satunya faktor risiko bebas yang dikaitkan secara signifikan dengan kematian, manakala rawatan definitif yang sesuai dikaitkan dengan kadar kematian yang lebih rendah dan kejayaan rawatan yang lebih tinggi.

Kata kunci: bakteremia, ESBL, faktor risiko, hasil, kematian

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ABSTRACT

Expanded-spectrum beta-lactamase (ESBL) bacteremia often leads to severe outcomes like mortality and treatment failure. This study aimed to identify risk factors in patients with ESBL bacteremia. A retrospective cohort analysis was conducted among patients aged 13 years and above who were admitted to Hospital Canselor Tuanku Muhriz (HCTM) due to ESBL bacteremia between the period of January 2015 and August 2019. Patients with polymicrobial bacteremia were excluded. The all-cause in HCTM mortality rate was 30.2%, while the infection-related mortality rate was 22.5%. The risk factors of all-cause in-hospital mortality include hypertension, diabetes mellitus, skin and soft tissue infections (SSTIs), urinary catheterisation and mechanical ventilation. The independent risk factor associated with mortality was mechanical ventilation (AOR 3.12; CI 1.06-9.18; p = 0.04). No association found between appropriate empirical antibiotic treatment with mortality (p = 0.74), treatment success (p = 0.71) or length of hospital stay (p = 0.84). However, appropriate definitive treatment was associated with a lower mortality rate (p<0.01) and higher treatment success (p<0.01). Mechanical ventilation was the only independent risk factor significantly associated with mortality, while appropriate definitive treatment was associated with a lower mortality rate and higher treatment success.

Keywords: bacteremia, ESBL, mortality, outcome, risk factors

INTRODUCTION

The emergence of extended-spectrum beta-lactamase (ESBL) bacteremia become increasingly challenging for clinicians, primarily due to its limited therapeutic option. The ESBL is a plasmid-mediated enzyme which can hydrolyse and inactivate numerous beta-lactam antibiotics. Examples of microorganisms that produce ESBL include *Escherichia coli (E. coli)*, *Klebsiella* species, *Proteus* species, *Enterobacter* species., and *Acinetobacter* species (Paterson & Bonomo 2005; Turner 2005).

The prevalence of ESBL bacteremia varies geographically. According to a study involving nine regions in the United States (U.S.), the prevalence of ESBL bacteremia was 12.2%, with the frequency rate of 16.0% for *Klebsiella pneumoniae (K. pneumoniae)*, 11.9% for *E. coli*, 10.0% for *Klebsiella oxytoca*, and 4.8% for *Proteus mirabilis* (Castanheira et al. 2014). As the ESBL bacteremia is increasing in the U.S., it is expected to reach statistic of 11.1 to 22.1 infections out of 100,000 people within six years (Thaden et al. 2016). A higher prevalence of ESBL bacteremia has been reported in Asia, the Middle East and Latin America (18.0-40.0%), particularly associated with intra-abdominal and urinary tract infections (Morrissey et al. 2013). Malaysia has a

high prevalence of ESBL bacteremia, and it was estimated to be between 7.0 to 19.0% for *E. coli* and 27.0 to 38.0% for *K. Pneumonia*e in 2001 (Consensus Guidelines for Management of Infections 2001).

Most of the previous studies had shown that the risk factors for ESBL bacteremia include previous antibiotic exposure, history of hospital admission within three months, prolonged hospital stay, advanced age, nursing home residents, malignancy, mechanical ventilation, urinary catheterisation and central line insertion (Kang et al. 2008; Kang et al. 2012).

It is essential to recognise ESBL bacteremia, as it is commonly associated with higher mortality rates, extended hospital stays, increased treatment costs and the potential emergence of resistant organisms (Nguyen et al. 2015). Additionally, ESBL-producing organisms have a higher mortality rate than non-ESBL-producing organisms, as evidenced in a meta-analysis of 32 studies of bacteremia of *Enterobacteriaceae* (OR 2.35, 95.0% CI 1.90-2.91) (Rottier et al. 2012). Therefore, identifying the risk factors provides valuable knowledge for clinicians in detecting those at higher risk of mortality.

The study main objective was to determine risk factors for the all-cause in-hospital and infection-related mortality associated with ESBL bacteremia in patients admitted to Hospital Canselor Tuanku Muhriz (HCTM) between January 2015 and August 2019. Other objectives included identifying the sources of ESBL bacteremia in the study population and determining the association between the appropriateness of empirical and definitive treatments of ESBL bacteremia with all-cause mortality in-hospital, infection-related mortality, prolonged hospital stay; and treatment outcome (successful versus unsuccessful).

MATERIALS AND METHODS

Patient Population and Study Design

A retrospective cohort study was performed on patients aged 13 years and above who were admitted to HCTM, Kuala Lumpur, due to diagnosis of ESBL bacteremia between January 2015 and August 2019. Polymicrobial patients were excluded from this study. A total of 181 patients were initially identified, but only 129 patients were included in this study. Fifty-one patients were excluded due to polymicrobial infection (21 patients), not having ESBL bacteremia (6 patients), missing/incomplete data (4 patients), and duplicate entries (20 patients).

Study Definitions

Expanded-spectrum beta-lactamase bacteremia was defined as positive of ESBL organism blood culture and clinical features was compatible with sepsis (Kang et al. 2012; Consensus Guidelines for Management of Infections 2001). Community-acquired bacteremia was defined as bacteremia that had developed 48 hours before hospitalisation (Kang et al. 2012),

while nosocomial bacteremia was defined as bacteremia that developed after 48 hours of admission (Garner et al. 1991). Healthcare-associated infection was defined if any of the following conditions were present; hemodialysis in the previous 30 days; antibiotic treatment in the previous 30 days; or a history of more than 48 hours of hospitalisation (including nursing home and long-term care facility) in the previous 90 days (Kang et al. 2012). Primary bacteremia was defined as confirmed bloodstream infection without an identifiable source of infection and no concurrent positive culture from another site at the time of diagnosis (Renaud & Brun-Buisson 2001). On the other hand, secondary bacteremia was defined as confirmed bloodstream infection, with an identifiable source of infection and a concurrent positive culture from another site (Renaud & Brun-Buisson 2001). Recurrent bacteremia was defined as any new episode of documented infection due to the same pathogen occurring at least two weeks after the initial episode, which blood culture was negative (Michalopoulos et al. 2011).

Catheter-related bloodstream infection (CRBSI) was an infection with at least one of the same organism from peripheral blood culture and catheter tip culture. Another two definitions define CRBSI as (i) a positive ESBL organism blood culture from the peripheral blood vessel and the catheter; (ii) a similar organism was grown from the catheter two hours before the peripheral blood culture (Mermel et al. 2009). Septic shock was defined as sepsis and the use of vasopressor therapy to increase the mean arterial pressure to ≥65 mmHg, and lactate to >2 mmol/L, despite adequate fluid resuscitation (Shankar-Hari et al. 2016; Singer et al. 2016).

According to Peralta et al. (2012), immunosuppression was considered in patients with any one of the following conditions; neutropenia, which was defined as an absolute neutrophil count of <500 neutrophils/mm^3 (Kang et al. 2012); undergoing immunosuppression therapy; or AIDS, which was defined as an HIV infection with AIDS-defining diagnosis and CD4 cell count <200 cells/uL (Malaysian Consensus Guidelines on Antiretroviral Therapy 2017). In addition, a quick-pitt bacteremic score of over two was defined as critically ill (Battle et al. 2019).

Treatment was considered successful if all the signs and symptoms of infection due to ESBL bacteremia were absent at the end of the antimicrobial therapy (Hawkey & Infection 2008). Conversely, it was considered unsuccessful if the patient lacked of clinical improvement or had recurrent bacteremia with the same pathogen (Hawkey & Infection 2008). Appropriate empirical therapy was defined as a treatment regimen that included one or more antibiotics against microorganisms undergoing in vitro susceptibility testing, providing the dosage and the route of administration were according to the current medical standards (Kang et al. 2012). On the other hand, appropriate definitive therapy was the continuation or modification of the antimicrobial

therapy administered to a susceptible agent after the susceptibility results are available (Peralta et al. 2012; Rodriguez-Bano et al. 2012). Exposure to antimicrobial was defined as the usage of antimicrobial for more than 72 hours or 30 days before ESBL bacteremia diagnosis (Xiao et al. 2019).

In-hospital mortality was defined as the all-cause mortality during hospitalisation. Infection-related mortality was attributed to ESBL bacteremia whereby there was an active infection at the time of death without other apparent causes (Schwaber et al. 2006).

Data Collection and Study Outcomes

Demographical and clinical data regarding essential characteristics, treatment, clinical outcomes and laboratory data were reviewed and retrieved from patients' medical records during the study period. Prior to this study, ethical approval (Research Code: FF-2020-435) was obtained from the Research Committee, Faculty of Medicine, Universiti Kebangsaan Malaysia.

Statistical Analysis

IBM SPSS Statistics for Windows (Version 26, IBM Corp., Armonk, NY) was used for statistical analysis. Normally distributed continuous variables were expressed as mean standard deviation (SD), and skewed data were expressed as median interquartile range (IQR). In addition, Pearson's Chi-squared test and Fisher's exact test were used to evaluate categorical variables.

A p-value of <0.05 was considered as statistically significant. Thus, the multivariate binary logistic regression model was used for variables with significant p-value (<0.05) from the univariable analysis. This was done to determine the independent risk factors for the all-cause in-hospital mortality and infection-related mortality. The results were presented as odds ratio (OR) with 95% confidence interval (CI).

RESULTS

A total of 129 patients were included in this study. The distribution of gender was comprised of 65 males (50.4%) and 64 females (49.6%). The median age of the study population was 65 years old (IQR 54-76). Therefore, the patients were primarily elderly which aged 60 years old and above (62.0%). Most patients were Malay (55.0%), followed by Chinese (33.3%), Indian (9.3%) and others (2.4%).

These patients suffered primarily from hypertension (69.8%), followed by diabetes mellitus (58.9%) and cardiovascular diseases (44.2%). Other comorbidities included hematological diseases (26.4%), end-stage renal disease (15.5%), immunodeficiency (14%), solid organ malignancies (9.3%), pulmonary diseases (8.5%) and chronic liver disease (3.9%).

The main isolated *Enterobacteriaceae* were ESBL *Klebsiella* spp. and ESBL *E. coli*, which made up about 52.7% and 43.4%, respectively. Others included *Enterobacter* sp. (3.1%), *Proteus mirabilis*

(1.6%) and *Citrobacter fruendii* (0.8%). Urinary tract infection was found to be the most common source of infection (30.2%), followed by pneumonia (24.8%), primary bloodstream infection (16.3%), intraabdominal infection (11.6%), catheter-related bloodstream infection (9.3%) and skin and soft tissue infections (SSTIs)(7.0%).

According to the results, the all-cause in-hospital mortality rate was 30.2%, while the infection-related mortality rate was 22.5%. Approximately 79.2% of the patients had been successfully treated, while 26.4% experienced treatment failure. Table 1 and 2 show the associations between the risk factors and mortality. Diabetes mellitus (p = 0.02), hypertension (p = 0.02), SSTIs (p = 0.02), urinary catheterisation (p = 0.02) and mechanical ventilation (p = 0.01) were significantly associated with in-hospital mortality. Diabetes mellitus (p = 0.03), hypertension (p

Table 1: Association of the risk factors for in-hospital mortality

Factors	Number (%)	All-cause in-hospital mortality		Chi-square/ Mann Whitney test value	P-value
		Non-survivor (n = 39)	Survivor (n = 90)		
Age (years), n (%)					
Young < 60	49 (40.0)	11 (22.4)	38 (77.6)	2.27	0.13
Elderly > 60	80 (60.0)	28 (35.0)	52 (65.0)		
Gender, n (%)					
Male	65 (50.4)	17 (26.2)	48 (73.8)	1.03	0.31
Female	64 (49.6)	22 (34.4)	42 (65.6)		
Comorbidities, n (%)					
Hypertension	90 (69.8)	33 (36.7)	57 (63.3)	5.84	0.02*
Diabetes Mellitus	76 (58.9)	29 (38.2)	47 (61.8)	5.51	0.02*
Cardiovascular disease	57 (44.2)	21 (36.8)	36 (63.2)	2.12	0.15
Hematological disease	34 (26.4)	8 (23.5)	26 (76.5)	0.98	0.32
End-stage renal failure	20 (15.5)	4 (20.0)	16 (80.0)	1.18	0.28
Immunodeficiency	18 (14.0)	6 (33.3)	12 (66.7)	0.10	0.76
Solid-organ malignancy	12 (9.3)	6 (50.0)	6 (50.0)		0.18[a]
Pulmonary disease	11 (8.5)	5 (45.5)	6 (54.5)		0.31[a]
Chronic liver disease	5 (3.9)	1 (20.0)	4 (80.0)		1.00[a]
If immunodeficiency, n (%)					
Neutropenia	31 (24.0)	9 (29.0)	22 (71.0)	0.03	0.87
Chemotherapy	34 (26.4)	10 (29.4)	24 (70.6)	0.02	0.90
Immunosuppressive	33 (25.6)	6 (18.2)	27 (81.8)	3.05	0.08
Severe acquired immune deficiency syndrome	4 (3.1)	2 (50.0)	2 (50.0)		0.58[a]
Ethnicity, n (%)					
Malay	71 (55.0)	24 (33.8)	47 (66.2)	0.95	0.33
Non-malay	58 (45.0)	15 (25.9)	43 (74.1)		
Prolonged hospital stay, n (%)					
Yes	64 (49.6)	17 (26.6)	47 (73.4)	0.81	0.37
No	65 (50.4)	22 (33.8)	43 (66.2)		
Length of prior hospital stay (days)					
Median (IQR)	5.5 (1.0-15.0)	8 (1.0-17.0)	4 (1.0-15.0)		
Range	1 - 80			-1.06	0.29

Total quick Pitt bacteremia score, n (%)					
≥ 2	48 (37.2)	30 (62.5)	18 (37.5)	1.91	0.17
< 2	81 (62.8)	60 (74.1)	21 (25.9)		
The possible source of bacteremia, n (%)					
Urinary tract infection	39 (30.2)	9 (23.1)	30 (76.9)	1.36	0.24
Pneumonia	32 (24.8)	10 (31.3)	22 (68.8)	0.02	0.89
Primary bloodstream infection	21 (16.3)	3 (13.6)	19 (86.4)	3.46	0.06
Intraabdominal infection	15 (11.6)	8 (53.3)	7 (46.7)		0.07[a]
Catheter-related bloodstream infection	12 (9.3)	3 (25.0)	9 (75.0)		1.00[a]
SSTIs	9 (7.0)	6 (66.7)	3 (33.3)		0.02[a]
Type of infection, n (%)					
Community-acquired	23 (17.8)	6 (26.1)	17 (73.9)	0.23	0.63
Nosocomial	106 (82.2)	33 (31.1)	73 (68.1)		
Urinary catheterisation	115 (89.1)	39 (33.3)	78 (66.7)	5.73	0.02
Central line catheterisation	72 (55.8)	22 (30.6)	50 (69.4)	0.01	0.93
Mechanical ventilation	18 (14.0)	10 (55.6)	8 (44.4)	6.36	0.01
Surgical procedure	5 (3.9)	0 (0.0)	5 (100.0)		0.32[a]
ICU care, n (%)					
Yes	16 (12.4)	3 (18.8)	13 (81.3)		0.39[a]
No	113 (87.6)				
Previous exposure to antibiotics, n (%)					
Yes	80 (62.0)	24 (30.0)	56 (70.0)	0.01	0.94
No	49 (38.0)				

[a]Fisher's exact test; *Statistically significant, p<0.05.

Table 2: Association of the risk factors for infection-related mortality

Factors	Number (%)	Infection-related mortality		Chi-square/ Mann Whitney test value	P-value
		Non-survivor (n = 29)	Survivor (n = 100)		
Age (years), n (%)					
Young	49 (40.0)	7 (14.3)	42 (85.7)	3.05	0.08
Elderly	80 (60.0)	22 (27.5)	58 (72.5)		
Gender, n (%)					
Male	65 (50.4)	12 (18.5)	53 (31.9)	1.21	0.27
Female	64 (49.6)	17 (26.6)	47 (23.0)		
Comorbidities, n(%)					
Hypertension	90 (69.8)	25 (27.8)	65 (72.2)	4.79	0.03*
Diabetes Mellitus	76 (58.9)	22 (28.9)	54 (71.1)	4.44	0.04*
Cardiovascular disease	57 (44.2)	15 (26.3)	42 (73.7)	0.86	0.35
Hematological disease	34 (26.4)	6 (17.6)	28 (82.4)	0.62	0.43
End-stage renal failure	20 (15.5)	2 (10.0)	18 (90.0)		0.24[a]
Immunodeficiency	18 (14.0)	5 (27.8)	13 (72.2)		0.55[a]
Solid-organ malignancy	12 (9.3)	5 (41.7)	7 (58.3)		0.14[a]
Pulmonary disease	11 (8.5)	2 (18.2)	9 (81.8)		1.00[a]
Chronic liver disease	5 (3.9)	1 (20.0)	4 (80.0)		1.00[a]

Factors	Number (%)	Infection-related mortality		Chi-square/ Mann Whitney test value	P-value
		Non-survivor (n = 29)	Survivor (n = 100)		
If immunodeficiency, n (%)					
Neutropenia	31 (24.0)	7 (22.6)	24 (77.2)	0.00	0.99
Chemotherapy	34 (26.4)	8 (23.5)	26 (76.5)	0.03	0.86
Immunosuppressive	33 (25.6)	4 (12.1)	29 (87.9)	2.73	0.10
Severe acquired immune deficiency syndrome	4 (3.1)	2 (50.0)	2 (50.0)		0.22[a]
Ethnicity, n (%)					
Malay	71 (55.0)	18 (25.4)	53 (74.6)	0.75	0.39
Non-malay	58 (45.0)	11 (19.0)	47 (81.0)		
Prolonged hospital stay, n (%)	64 (49.6) 65 (50.4)	9 (14.1)	55 (85.9)	5.17	0.02*
Length of prior hospital stay (days)					
Median (IQR)	5.5 (1-15)	6 (1.0-18.0)	5 (1.0-14.0)	-0.67	0.50
Range	1 - 80				
Total quick Pitt bacteremia score, n (%)					
≥ 2	48 (37.2)	35 (72.9)	12 (27.1)	0.93	0.34
< 2	81 (62.8)	65 (80.2)	16 (19.8)		
The possible source of bacteremia, n (%)					
Urinary tract infection	39 (30.2)	7 (17.9)	32 (82.1)	0.66	0.42
Pneumonia	32 (24.8)	9 (28.1)	23 (71.9)	0.78	0.38
Primary bloodstream infection	21 (16.3)	1 (4.5)	20 (95.5)		0.03[a]
Intraabdominal infection	15 (11.6)	7 (46.7)	8 (53.3)		0.04[a]
Catheter-related bloodstream infection	12 (9.3)	0 (0.00)	12 (100.0)		0.07[a]
SSTIs	9 (7.0)	5 (55.6)	4 (44.4)		0.03[a]
Type of infection, n (%)					
Community-acquired	23 (17.8)	4 (17.4)	19 (82.6)	0.42	0.52
Nosocomial	106 (82.2)	25 (23.6)	81 (76.4)		
Invasive procedure during the infectious period, n (%)					
Urinary catheterisation	115 (89.1)	29 (24.8)	88 (75.2)	0.86	0.07[a]
Central line catheterisation	72 (55.8)	14 (19.4)	58 (80.6)		0.35
Mechanical ventilation	18 (14.0)	7 (38.9)	11 (61.1)		0.12[a]
Surgical procedure	5 (3.9)	0 (0.00)	5 (100.0)		0.59[a]
ICU care, n (%)	16 (12.4)	2 (12.5)	14 (87.5)		0.52[a]
Previous exposure to antibiotics, n (%)	80 (62.0)	19 (23.8)	61 (76.2)	0.20	0.66

[a]Fisher's exact test; *Statistically significant, p<0.05.

= 0.04), prolonged hospital stay (p = 0.02), primary bloodstream infection (p = 0.03), intraabdominal infection (p = 0.04) and SSTIs (p = 0.03) were found to be the risk factors associated with the infection-related mortality.

Table 3 to 5 show the associations between appropriate empirical and definitive treatments and their outcomes (i.e. mortality, treatment outcome and prolonged hospital stay). Appropriate definitive treatment was significantly associated ($p < 0.01$) with treatment success and mortality reduction (in-hospital mortality and infection-related mortality). However, the appropriate empirical antibiotics were not significantly associated with

Table 3: Association between appropriate empirical and definitive treatments with mortality

Factors		n	Non-Survivor, n (%)	Survivor, n (%)	X statistic	p-value
Receive empirical treatment (all-cause in-hospital mortality)	No	108	76 (70.4)	32 (29.6)	0.11	0.74
	Yes	21	14 (66.7)	7 (33.3)	1	
Received empirical treatment (infection-related mortality)	No	108	83 (76.9)	25 (23.1)		0.78[a]
	Yes	21	17 (81.0)	4 (19.0)		
Definitive treatment (in-hospital mortality mortality)	No	11	3 (27.3)	8 (73.7)		<0.01*
	Yes	118	87 (73.7)	31 (26.3)		
Definitive treatment (infection-related mortality)	No	11	3 (27.3)	8 (73.7)		<0.01*
	Yes	118	97 (82.2)	21 (17.8)		

[a]Fisher's exact test; *Statistically significant, p<0.05

Table 4: Association between appropriate empirical and definitive treatments with treatment outcomes

Factors	n	Treatment Failure, n (%)	Treatment Success, n (%)	X statistic	p-value
Empirical treatment (no)	108	30 (27.8)	78 (72.8)	0.14	0.71
Empirical treatment (yes)	21	5 (23.8)	16 (76.2)	1	
Definitive treatment (no)	11	9 (81.8)	2 (19.2)		<0.01*
Definitive treatment (yes)	118	26 (22.0)	92 (28.0)		

*Statistically significant, p<0.05

Table 5: Association between appropriate empirical and definitive treatments with length of stay

Factors	n	Without prolonged hospital stay, n (%)	Prolonged hospital stay, n (%)	X statistic	p-value
Empirical treatment (no)	108	54 (50.0)	54 (50.0)	0.40	0.84
Empirical treatment (yes)	21	11 (52.4)	10 (47.6)	1	
Definitive treatment (no)	11	8 (72.7)	3 (27.3)	2.401	0.12
Definitive treatment (yes)	118	57 (48.3)	61 (51.7)	1	

*Statistically significant, p<0.05

Table 6: Multivariate analysis using binary logistic regression model on the independent risk factors for all-cause in-hospital mortality in patients with ESBL bacteremia

Variables	Adjusted OR	OR (95% CI)	X stat. (df)	p-value
Diabetes mellitus	1.62	0.55 (4.76)	0.76 (1)	0.38
Hypertension	1.95	0.56 (6.73)	1.09 (1)	0.30
SSTIs	3.32	0.73 (15.07)	2.43 (1)	0.12
Mechanical ventilation	3.12	1.06 (9.18)	4.27 (1)	0.04*

*Statistically significant, p<0.05

any of the outcomes. Finally, Table 6 shows that mechanical ventilation was the only independent risk factor associated with in-hospital mortality (AOR 3.12; CI 1.06-9.18; $p = 0.04$).

DISCUSSION

The mortality rate of ESBL bacteremia in the present study was found to be relatively high. Previous studies showed that 30-days mortality rate from ESBL bacteremia ranged between 30.6 and 34.0%, while the all-cause in-hospital mortality was found to be between 14.5 and 37.9% (Anunnatsiri et al. 2012; Chopra et al. 2015; Datta & Kontomichalou 1965; Du et al. 2002). Our finding (30.2% of our patients passed away) is in line with the previous studies which showed the importance of identifying the risk factors associated with mortality in patients with ESBL bacteremia.

In the present study, the significant risk factors associated with mortality include hypertension ($p = 0.02$), diabetes mellitus ($p = 0.02$), SSTIs ($p = 0.02$), urinary catheterisation ($p = 0.02$), and mechanical ventilation ($p = 0.01$). Furthermore, our multivariate analysis showed that mechanical ventilation was the only independent risk factor for all-cause in-hospital mortality among patients with ESBL bacteremia. These findings were unique to our study, as others found the severity of sepsis, intensive care unit (ICU) admission and presence of septic shock as the independent risk factors for mortality (Freeman et al. 2012; Kang et al. 2008).

Only a few patients were categorised as critically ill (only 37.2% had quick-pitt bacteremic score of more than 2). The present study also found a lower number of septic shock patients (upon presentation) and a lower ICU admission history than other studies. The variations can be explained by geographical differences, especially in the choice of antibiotics used, different patient backgrounds and timing of antibiotic initiation, making the results more heterogeneous and infeasible compared to other studies.

Apart from that, Malaysia had a higher prevalence of diabetes mellitus (16.7%) and hypertension (ranked 5th) compared to the other South-East Asian countries (Malaysian Healthcare Performance Unit 2020). Moreover, diabetes mellitus and hypertension were associated with higher mortality rates, contributing to an overall increased in the mortality rate (Oh et al. 2017; Escobedo-de la Peña et al. 2021).

The present study also showed a

significant association between SSTIs and the all-cause in-hospital mortality. Even though SSTIs were rare as the sources of bacteremia when compared to other sources such as urinary tract infection, they were associated with increased risk for mortality, once complicated with bacteremia. Micek et al. (2010) claimed that bacteremia was an independent risk factor for mortality in patients with SSTIs (AOR 6.37; 95% CI 3.34 - 12.12). In addition, antimicrobial-resistant Gram-negative SSTIs were associated with a poorer prognosis (Kofteridis et al. 2012; Ioannou et al. 2018).

The present study did not find any significant association between appropriate empirical antibiotic therapy with reducing mortality rate, treatment success and prolonged hospital stay. This finding was not surprising, as other studies have shown that appropriate empirical antibiotics in ESBL bacteremia were not associated with a lower mortality rate (Chaubey et al. 2010; Palacios-Baena et al. 2017; Ko et al. 2018). Despite some studies suggested that appropriate empirical antibiotics were associated with a lower mortality rate or treatment success, most of these studies were retrospective in setting, indicating the need for more randomised controlled trials to look into this matter (Chaubey et al. 2010; Peralta et al. 2012).

As expected, the appropriate definitive antibiotic using carbapenem group was significantly associated with a lower mortality rate and higher treatment success, as recommended by the Infectious Diseases Society of America (IDSA) Guidelines on treating antimicrobial-resistant Gram-negative infections (Tamma et al. 2021). Although there were multiple attempts for carbapenem-sparing therapy, such as the MERINO trial, they failed to show the non-inferiority of piperacillin-tazobactam in the 30-days mortality rate, in comparison to meropenem in ESBL bacteremia patients (Harris et al. 2018). Thus, the present study was in good agreement with the previous studies.

Nonetheless, the present study possessed several limitations. Firstly, it was a retrospective single-center study. Hence, comparison between groups may be biased, and there were also some missing data. Secondly, the study concentrated mainly on the clinical analysis of treatment outcomes. We did not analyse epidemiology, laboratory detection methods or molecular characterisation of the ESBL-producing bacteria. Despite these limitations, the study hadits strengths. To the best of our knowledge, this was the first study in Malaysia that looked into the risk factors for mortality in ESBL bacteremia within the Malaysian population. Thus, the study offered valuable information in treating patients with ESBL bacteremia and identifying patients at a higher risk of mortality.

CONCLUSION

In conclusion, the risk factors for mortality in patients with ESBL bacteremia were diabetes mellitus, hypertension, urinary catheterisation, mechanical ventilation and SSTIs. Mechanical ventilation was the only

independent risk factor associated with all-cause in-hospital mortality. There was no significant association between appropriate empirical antibiotics, treatment success, mortality and prolonged hospital stay. However, the use of the carbapenem group as a definitive therapy was associated with a reduction in mortality and increased treatment success. These findings were valuable for clinicians to identify patients at a relatively higher risk of mortality so that better interventions can be provided for a better prognosis.

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