SURVIVAL TIME AND PROGNOSTIC FACTORS OF MORTALITY AMONG PATIENTS WITH CATHETER-RELATED BLOODSTREAM INFECTION AT HOSPITAL PAKAR UNIVERSITI SAINS MALAYSIA

NOR AINI BINTI HAMIDI

UNIVERSITI SAINS MALAYSIA

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by

NOR AINI BINTI HAMIDI

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SYMBOLS

<	Less than
>	More than
≤	Less than or equal to
≥	More than or equal to
=	Equal
/	Or
α	Alpha (Level of significance)
B	Regression coefficient
%	Percentage
n	Number of samples
1 - β	Power

LIST OF ABBREVIATIONS

BSI	Bloodstream infection
CI	Confidence interval
CLABSI	Central line-associated bloodstream infection
CRBSI	Catheter-related bloodstream infection
CRE	Carbapenem-resistant *Enterobacterales*
CVC	Central venous catheter
DTP	Differential time to positivity
ESBL	Extended-spectrum beta-lactamase
HCAI	Healthcare-associated infection
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
LML	Log minus log
LOS	Length of hospital stay
MDR	Multidrug-resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
OR	Odds ratio
PICC	Peripherally inserted central catheter
SPSS	Statistical Package for the Social Science
TPN	Total parenteral nutrition
USM	Universiti Sains Malaysia
VIF	Variance inflation factor

XDR	Extensively drug-resistant

LIST OF APPENDICES

MASA KELANGSUNGAN HIDUP DAN FAKTOR PROGNOSTIK YANG MEMPENGARUHI KEMATIAN DALAM KALANGAN PESAKIT DENGAN JANGKITAN ALIRAN DARAH BERKAITAN KATETER DI HOSPITAL PAKAR UNIVERSITI SAINS MALAYSIA

ABSTRAK

Pengenalan: Jangkitan aliran darah berkaitan kateter (CRBSI) merupakan antara jangkitan berkaitan penjagaan kesihatan (HCAI) yang paling kerap dilaporkan di fasiliti penjagaan kesihatan. Jangkitan yang serius namun boleh dicegah ini berkait rapat dengan kadar morbiditi dan mortaliti yang tinggi. Sehingga kini, data tempatan dan peringkat dunia berkaitan masa kelangsungan hidup median dan kadar kelangsungan hidup pesakit dengan jangkitan CRBSI adalah terhad. **Objektif:** Kajian ini bertujuan untuk mengetahui masa kelangsungan hidup dan faktor prognostik yang mempengaruhi kematian pesakit dengan jangkitan CRBSI. **Metodologi:** Kajian ini merupakan kajian retrospektif di satu pusat yang melibatkan 181 orang pesakit dengan jangkitan CRBSI di Hospital Pakar USM dari tahun 2018 sehingga 2022. Data yang dikumpulkan untuk kajian ini termasuk faktor berkaitan pesakit, faktor berkaitan kateter, faktor berkaitan klinikal, and faktor berkaitan organisma. Pemboleh ubah hasil bagi kajian ini adalah masa kelangsungan hidup. Peristiwa utama dalam kajian ini merujuk kepada kematian akibat semua sebab dalam tempoh 90 hari selepas waktu permulaan CRBSI, manakala pemerhatian tersensor merujuk kepada pesakit yang masih hidup di akhir tempoh kajian, tidak mengalami peristiwa utama atau gagal dikesan semasa susulan. Analisis anggaran Kaplan Meier dan jadual hayat digunakan untuk mengetahui masa kelangsungan hidup median dan kadar kelangsungan hidup. Analisis regresi Cox dijalankan untuk mengetahui faktor prognostik kematian yang

signifikan. **Keputusan:** Secara keseluruhan, jumlah pesakit yang mati disebabkan CRBSI dan faktor lain yang berkaitan dalam masa 90 hari selepas waktu permulaan CRBSI adalah 35.4%. Masa kelangsungan hidup median tidak dapat diketahui daripada lengkung Kaplan-Meier kerana kelangsungan hidup yang tinggi dalam kalangan pesakit dengan jangkitan CRBSI yang mungkin berkaitan dengan diagnosis awal dan rawatan yang efektif di pusat ini. Kadar kelangsungan hidup bagi satu, tiga, dan enam bulan adalah masing-masing 77.4% (95% CI: 70.5, 82.8), 65.2% (95% CI: 57.8, 71.6), dan 64.6% (95% CI: 57.2, 71.1). Faktor-faktor prognostik yang mempengaruhi kelangsungan hidup pesakit CRBSI secara signifikan dalam kajian ini adalah sepsis atau renjatan septik (aHR: 5.95; 95% CI: 2.88, 12.28), ventilasi mekanikal (aHR: 5.94; 95% CI: 3.29, 10.71), tempoh tinggal di hospital yang lebih singkat (aHR: 1.13; 95% CI: 1.10, 1.17), jantina perempuan (aHR: 2.71; 95% CI: 1.60, 4.58), dan jangkitan organisma Gram-negatif, yang berkaitan dengan risiko kematian lebih rendah (aHR: 0.31; 95% CI: 0.18, 0.55). **Kesimpulan:** Analisis regresi bahaya berkadar Cox pelbagai menunjukkan bahawa sepsis atau renjatan septik, penggunaan ventilatisi mekanikal, tempoh tinggal di hospital lebih singkat, jantina perempuan, dan jangkitan dengan organisma Gram-negatif (berkaitan dengan risiko kematian yang lebih rendah) adalah faktor prognostik kematian yang signifikan dalam kalangan pesakit dengan jangkitan CRBSI. Dapatan ini memberikan pengetahuan yang lebih mendalam tentang hasil klinikal CRBSI yang boleh membantu pakar perubatan dalam membuat keputusan klinikal serta pengurusan CRBSI.

SURVIVAL TIME AND PROGNOSTIC FACTORS OF MORTALITY AMONG PATIENTS WITH CATHETER-RELATED BLOODSTREAM INFECTION AT HOSPITAL PAKAR UNIVERSITI SAINS MALAYSIA

ABSTRACT

Introduction: Catheter-related bloodstream infection (CRBSI) is considered as one of the most frequently reported healthcare-associated infections (HCAIs) in the healthcare settings. This serious yet preventable infection is associated with high morbidity and mortality rate. To date, the local and global data on median survival time and survival rate of CRBSI is limited. **Objective:** This study aimed to determine the survival time and prognostic factors that influence the mortality of patients with CRBSI. **Methodology:** This study was a single-centre retrospective study which involving 181 patients with CRBSI at Hospital Pakar USM from 2018 until 2022. Data collected for this study included patient-related factors, catheter-related factors, clinical-related factors, and organism-related factors. The outcome variable of this study was the survival time. The primary event referred to all-cause mortality of CRBSI patients within 90 days after onset, while censored observation referred to the patient who was still alive at the end of study, did not experience event or lost to follow up. Kaplan Meier estimate and life table analysis were used to determine median survival time and survival rate. Cox regression analysis was performed to determine the significant prognostic factors of mortality. **Results:** In total, the number of patients who died due to CRBSI and other related causes within 90 days after onset was 35.4%. The median survival time could not be determined by the Kaplan-Meier curve due to a high survival among CRBSI patients which may be related to early diagnosis and effective treatment in this centre. The one-, three- and six- month survival rate were

77.4% (95% CI: 70.5, 82.8), 65.2% (95% CI: 57.8, 71.6), and 64.6% (95% CI: 57.2, 71.1) respectively. The prognostic factors that significantly affect survival of CRBSI patients were sepsis or septic shock (aHR: 5.95; 95% CI: 2.88, 12.28), mechanical ventilation (aHR: 5.94; 95% CI: 3.29, 10.71), shorter length of hospital stay (aHR: 1.13; 95% CI: 1.10, 1.17), female gender (aHR: 2.71; 95% CI: 1.60, 4.58), and infection with Gram-negative organism, which was linked to lower mortality risk (aHR: 0.31; 95% CI: 0.18, 0.55). **Conclusions:** Multiple Cox proportional hazards regression showed that sepsis or septic shock, use of mechanical ventilation, shorter hospital stay, female gender, and infection with Gram-negative organism (associated with a lower risk of death) were significant prognostic factors of mortality among patients with CRBSI. These findings provide a greater understanding of CRBSI outcomes which can assist physicians in the clinical decision making and CRBSI management.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Healthcare-associated infections (HCAIs), previously known as hospital-acquired infections or nosocomial infections, refer to infections that acquired by patients directly from the healthcare interventions such as medical or surgical procedure, and it may also develop as a result of being in contact with the healthcare setting (National Institute for Health and Care Excellence (NICE), 2011). Patients can develop HCAIs while receiving treatment for other diseases and even after they have been discharged (Khan, Baig & Mehboob, 2017). Many HCAIs are caused by implants and prostheses, in addition to infections at surgery sites, infections caused by cross-contamination between patients and healthcare personnel, and patients being more susceptible to infections due to weakened immune systems (Haque *et al.*, 2018).

It has been estimated that in every 100 admission, 7 patients in high-income countries and 15 patients in low- and middle-income countries will develop at least one HCAI during their hospitalization in acute-care hospitals (WHO, 2022). The overall prevalence of HCAIs in Southeast Asia is 21.6% which is considered as substantially high (Wah Goh *et al.*, 2023). Based on the national data from 2018, the prevalence of HCAIs in Malaysia was 4.5% per 100 hospital admissions, whereby bloodstream infection (BSI), pneumonia and surgical site infection (SSI) are the most prevalent type of HCAIs observed from the survey (TheSun Daily, 2019).

According to Chaves *et al*. (2018), catheter-related bloodstream infection (CRBSI) was considered as one of the most frequently reported HCAIs in the healthcare settings. CRBSI refers to an infection diagnosed in a patient with a central venous

catheter (CVC) in place or removed within 48 hours prior to diagnosis, who develops symptoms and has the same microorganism isolated from both peripheral blood sample culture and catheter tip culture (Zhang *et al.*, 2023). This serious yet preventable infection is associated with reduced patients' quality of life, leading to high morbidity and mortality rate, and also increase the healthcare costs (Musu *et al.*, 2017).

The estimated incidence rate of CRBSI can ranging from 0.5 – 5 infections per 1000 catheter-days (Ngo Bell *et al.*, 2024). According to International Nosocomial Infection Control Consortium Report which provided data for 2010 – 2015 across 50 countries including Southeast Asia, the pooled crude ICU mortality among central line-associated bloodstream infection patients was 38.4% (Rosenthal *et al.*, 2016).

In Malaysia, CRBSI rate was 0.3 per 1000 catheter days as reported by the Malaysian Registry of Intensive Care Unit (Rajandra *et al.*, 2025). A local study done by Shahar *et al.* (2021) in Universiti Kebangsaan Malaysia Medical Centre reported that overall mortality of haemodialysis patients with CRBSI was 1.1%.

Similar to other HCAIs, CRBSI can affect any individuals, however some patients are more likely than others to become infected. Older age, reinsertion of new catheter, high APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sequential Organ Failure Assessment) scores, high Charlson Comorbidity Index score, *S. aureus* and *Candida spp*. infection were among the reported significant prognostic factors that increase hazard of death or case-fatality rates of CRBSI in both ICU and non-ICU settings (Saliba *et al.*, 2018; Zhong *et al.*, 2021).

Antibiotic lock therapy (ALT) is recommended in selected cases of CRBSI with long-term catheter use when there are no signs of exit site or tunnel infection, and the aim is to retain the catheter (Baang *et al.*, 2023). It is most effective when combined with systemic antimicrobial therapy. ALT delivers a high concentration of antibiotic

directly into the catheter lumen for an extended length of time, helping in the elimination of biofilm, and improving treatment outcomes. ALT may be considered for infections caused by *coagulase-negative staphylococci* with negative peripheral blood cultures, but it is not indicated for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Candida spp*., when catheter removal is strongly recommended.

1.2 Problem statement and study rationale

According to the World Health Organization (WHO), HCAIs are considered as the most common adverse event in terms of healthcare service where there is no country or health system can declare to be free from this global issue. Each year, it has been estimated that millions of patients were affected by HCAIs worldwide, including the CRBSI. CRBSI contribute to many negative outcomes including prolonged length of hospital stay, increased hospital costs and financial burden, as well as increased morbidity and mortality (Chaves *et al.*, 2018).

Based on the current knowledge, there are limited studies that explore the median survival time, overall survival rate as well as the prognostic factors of patients with CRBSI in general, either in Malaysia or other countries. Most of the previous studies that determining the survival rate or risk factors of mortality among patients with CRBSI had focusing on specific organism that causes CRBSI or specific ward such as ICU and non-ICU (Cheewinmethasiri *et al.*, 2014; Saliba *et al.*, 2018; Y. Lee *et al.*, 2018; Zhong *et al.*, 2021). This study may provide additional information regarding the survival rate and factors that may affect the survival time of patients with CRBSI in the context of local population.

The mortality related to CRBSI can be influenced by the relevant prognostic factors. Hence, the accurate prediction of prognostic factors is important for the clinical decision making so that some subgroup of patient will receive specific and appropriate therapeutic application. This study allows physicians to identify factors that affect the survival and hence able to deliver the best care for high-risk patients in order to reduce mortality due to CRBSI.

1.3 Research questions

1. What is the median survival time of patients with CRBSI at Hospital Pakar USM?
2. What are the one-, three- and six- month survival rates for patients with CRBSI?
3. What are the prognostic factors that influence the mortality of patients with CRBSI at Hospital Pakar USM?

1.4 Objectives

1.4.1 General:

The general objective of this study is to assess the survival time and prognostic factors that influence the mortality of patients with CRBSI at Hospital Pakar USM.

1.4.2 Specific:

1. To determine the overall median survival time of patients with CRBSI at Hospital Pakar USM.
2. To estimate the one-, three- and six- month survival rate of patients with CRBSI.
3. To identify the prognostic factors that influence the mortality of patients with CRBSI at Hospital Pakar USM.

1.5 Research hypothesis

There are significant prognostic factors (patient-related factors, catheter-related factors, clinical-related factors, and organism-related factors) that influence the mortality of patients with CRBSI at Hospital Pakar USM.

CHAPTER 2

LITERATURE REVIEW

2.1 Background and diagnosis of CRBSI

Globally, CRBSI is considered as one of the most common types of HCAIs. Based on İnce *et al.* (2020), CRBSI is the third leading HCAIs, after ventilator-associated pneumonia (VAP) and catheter-related urinary tract infection (CAUTI). According to Zhang *et al*. (2023), CRBSI is defined as an infection diagnosed in a patient with a CVC in place or removed within 48 hours prior to diagnosis, who develops symptoms and has the same microorganism isolated from both peripheral blood sample culture and catheter tip culture.

In modern medicine, CVCs are commonly used for the purpose of administration of medications, intravenous fluids, parenteral nutrition, blood products as well as to monitor hemodynamic status and to provide haemodialysis (Chaves *et al.*, 2018). Compared to other types of medical devices, CVCs contribute to the highest risk of device-related infections and associated with morbidity and mortality (Gahlot *et al.*, 2014).

The terms CRBSI and CLABSI are sometimes used interchangeably; however, both terms have distinct definitions and purposes (Centres for Disease Control and Prevention (CDC), 2024). CRBSI is a clinical definition in the diagnosis and treatment of patients which involves specialized laboratory tests that specifically determine the catheter as the source of bloodstream infection. Contrarily, CLABSI is a surveillance definition used for reporting purposes in which a primary bloodstream infection was developed in a patient who had a central line within 48 hours prior to the onset of infection; and it is not secondary to another source within the body. Unlike CRBSI,