DISTRIBUTION AND PROGNOSTIC FACTORS FOR MORTALITY OF INVASIVE CANDIDIASIS, AND COST-EFFECTIVENESS ANALYSIS OF THREE DIAGNOSTIC MODALITIES IN SELECTED MALAYSIAN HOSPITALS

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by

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TABLE OF CONTENTS

ACKNOWLEDGMENTS ii

TABLE OF CONTENTS iii

LIST OF TABLES xii

LIST OF FIGURES xiv

LIST OF SYMBOLS xvi

LIST OF ABBREVIATION xvii

LIST OF APPENDICES xx

ABSTRAK xxii

ABSTRACT xxiv

CHAPTER 1 1

INTRODUCTION 1

1.1 Invasive Candidiasis 1

1.1.1 Pathophysiology 2

1.1.2 Burden of Invasive Candidiasis 2

1.1.3 Risk Factors and Populations at Risk 3

1.2 Clinical Presentation 4

1.3 Diagnostic Methods 4

1.3.1 Blood culture 5

1.3.2 Non-culture method 7

1.3.3 Imaging 8

1.4 Treatment 8

1.4.1 Antifungal Resistance and Treatment Challenges 9

1.5 Prognosis 11

1.6 Cost-Effectiveness Analysis 11

1.6.1 Significance of CEA in the Management of Invasive Candidiasis 12

1.7 Statement of Problem 14

1.8 Rationale 15

1.9 Research Questions 17

1.10 Study Objectives 17

1.10.1 General objective 17

1.10.2 Specific objectives 17

1.11 Research Hypotheses 18

CHAPTER 2 19

LITERATURE REVIEW 19

2.1 Invasive Candidiasis in Malaysia 19

2.2 Clinical Presentation 20

2.3 Prognostic Factors for IC Mortality 22

2.3.1 Sociodemographic 22

2.3.2 Clinical Conditions 23

2.3.3 Treatment and Procedures 25

2.3.4 *Candida* species 27

2.4 Diagnostic Modalities 28

2.4.1 Polymerase chain reaction 28

2.4.2 Mannan Anti-Mannan 29

2.4.3 beta-D-glucan assay (BDG) 31

2.4.4 T2Candida 32

2.4.5 Diagnostic Performance Metrics 32

2.5 Cost-effectiveness of Invasive Candidiasis Diagnostic Methods 34

2.5.1 Costing 34

2.5.2 Outcome 36

2.5.3 Past studies on CEA of diagnostic methods 37

2.6 Research Gaps 39

2.7 Conceptual Framework 41

CHAPTER 3 43

METHODOLOGY 43

3.1 Part One 43

3.1.1 Study Design 43

3.1.2 Study Area 43

3.1.3 Study Period 45

3.1.4 Study Population 45

3.1.5 Sampling Frame 45

3.1.6 Study Criteria 46

3.1.7 Sample Size Calculation 46

3.1.8 Case Identification and Selection 48

3.1.9 Source of Data 48

3.1.10 Research Tools and Variables 50

3.1.11 Data Collection 51

3.1.12 Data Entry 52

3.1.13 Statistical Analysis 52

3.1.14 Operational Definitions 58

3.2 Part Two 59

3.2.1 Analytic Technique 59

3.2.2 Study Area 59

3.2.3 Study Population 63

3.2.4 Sample Size Estimation 63

3.2.5 Study Criteria 64

3.2.6 Study Perspective 64

3.2.7 Study Period 64

3.2.8 Time Horizon 65

3.2.9 Sampling Frame 65

3.2.10 Selection Comparator 65

3.2.11 Retrieval of Effectiveness Evidence 65

3.2.12 Measuring Outcomes 65

3.2.13 Resource Use and Cost 66

3.2.14 Discount Rate 71

3.2.15 Currency, Price Date, and Conversion 71

3.2.16 Data Analysis and Presentation of Results 72

3.2.17 Sensitivity Analysis 74

3.2.18 Study Assumptions 74

3.3 Study Fowchart 75

3.4 Ethical Consideration 76

3.4.1 Subject Vulnerability 77

3.4.2 Declaration of Absence of Conflict of Interest 77

3.4.3 Privacy and Confidentiality 77

3.4.4 Community Sensitivities and Benefits 77

3.4.5 Honorarium and Incentives 78

3.4.6 Ethical Review Board Approval 78

CHAPTER 4 79

RESULTS 79

4.1 Descriptive Analysis of Invasive Candidiasis Cases in Kedah 79

4.1.1 Distributions of Invasive Candidiasis 79

4.1.2 Trend of Invasive Candidiasis Cases 83

4.1.3 Antifungal Sensitivity Test 86

4.2 Survival Prognostic factors of Invasive Candidiasis 89

4.2.1 Socio-demographic and Clinical Characteristics of Patients 89

4.2.2 Survival Rate 92

4.2.3 Median Survival Time.....95

4.2.4 Simple Proportional Hazards Cox Regression.....106

4.2.5 Multiple Proportional Hazards Cox Regression 110

4.3 Cost-Effectiveness Analysis (CEA).....112

4.3.1 Background of the Study Respondents 112

4.3.2 Outcome of the Diagnostic Methods: Lab Turnaround Time.....114

4.3.3 Cost of Diagnostic Methods.....114

4.3.4 Average cost-effectiveness ratio (ACER).....123

4.3.5 Incremental cost-effectiveness ratio (ICER).....125

4.3.6 Sensitivity analysis.....127

CHAPTER 5 130

DISCUSSION 130

5.1 Trend of Invasive Candidiasis Cases 130

5.1.1 Burden of Invasive Candidiasis 130

5.1.2 Diagnostic accuracy 131

5.1.3 Uptrend and downtrend of cases 132

5.1.4 *Candida* species among special populations.....134

5.1.5 Shift of the species patterns 135

5.1.6 Antifungal sensitivity test (AFST) 137

5.2 Survival Study 138

5.2.1 Survival Rate 139

5.2.2 Median survival time 140

5.2.3 Prognostic factor for mortality 144

5.3 Cost-effectiveness Study 161

5.3.1 Study Respondents 161

5.3.2 Lab turnaround time 161

5.3.3 Cost of diagnostic methods 162

5.3.4 Incremental cost-effectiveness ratio (ICER) analysis 166

CHAPTER 6 170

CONCLUSION AND RECOMMENDATION 170

6.1 Conclusion 170

6.2 Strength 173

6.3 Limitation 175

6.4 Recommendations 177

6.4.1 Clinical practice and patient care 177

6.4.2 Hospital Epidemiology and Health Financing 178

6.4.3 Future research 180

REFERENCES 182

APPENDICES 218

LIST OF TABLES

Table 3.1: Sample size calculation for survival analysis 48

Table 4.1: Demographic and microbiological characteristics of IC (*n* = 1138). 80

Table 4.2: Distributions of aetiological agents according to departments (*n*=1138). 82

Table 4.3: Percentage of tested species according to the year (*n*=1138). 85

Table 4.4 Percentage of fluconazole sensitivity according to species (*n* = 665). 86

Table 4.5: Percentage of amphotericin B sensitivity according to species (*n*=808). .87

Table 4.6: Percentage of micafungin sensitivity according to species (*n*=792).....87

Table 4.7: Percentage of caspofungin sensitivity according to species (*n*=790). 87

Table 4.8: Percentage of itraconazole sensitivity according to species (*n*=5). 88

Table 4.9: Percentage of flucytosine sensitivity according to species (*n*=805). 88

Table 4.10: Percentage of voriconazole sensitivity according to species (*n*=709). ...88

Table 4.11: Patient demographic of patients in HSB from 2017-2023 (n=445).....89

Table 4.12: Laboratory Data of patients in HSB from 2017-2023 (*n*=445) 90

Table 4.13: Risk factors of patients in HSB from 2017-2023 (n=445).....91

Table 4.14: Clinical presentation of patients in HSB from 2017-2023(*n*=445).....91

Table 4.15: Complication and associated outcome of patients in HSB(n=445) 92

Table 4.16: Overall survival rate of patients in HSB from 2017-2023 (n=445).....92

Table 4.17: Survival rate patients in HSB according to selected variables (n=445) .93

Table 4.18: Univariate analysis of the prognostic factor of mortality. 108

Table 4.19: The final model of prognostic factor of mortality 110

Table 4.20: Patient demographic and clinical characteristics of patients (*n*=13) 114

Table 4.21: Mean lab turn around time (LTAT) for IC diagnostic methods 114

Table 4.22: Derivation of unit cost for salary in running PCR testing. 116

Table 4.23: Cost of equipment used for PCR testing.....117

Table 4.24: Cost of consumables for PCR testing 118

Table 4.25: Total cost of PCR per test. 118

Table 4.26: Derivation of unit cost for salary in running Mn A-Mn testing.....119

Table 4.27: Cost of consumables for Mn A-Mn testing.....119

Table 4.28: The cost of equipment used for the Mn A-Mn testing.....121

Table 4.29: Cost of equipment shared with another testing.....121

Table 4.30: Total cost of Mn A-Mn per test 122

Table 4.31: Comparison of diagnostic approaches in IC diagnostic.....122

Table 4.32: The ACER of the diagnostic approaches based sample quantity. 124

Table 4.33: ICER of the diagnostic approaches based on 250samples.....125

Table 4.34: ICER of the diagnostic approaches based on 1000samples.....126

Table 4.35:ICER of the diagnostic approaches (2000samples) 126

Table 4.36: M2 vs M1 sensitivity analysis for 250 test samples (±5%) 127

Table 4.37: M3 vs M1 sensitivity analysis for 250 test samples (±5%) 128

Table 4.38: M2 vs M1 sensitivity analysis for 2000 test samples of (±5%).....128

Table 4.39: M3 vs M1 sensitivity analysis for 2000 test samples (±5%) 129

LIST OF FIGURES

Figure 2.1: Conceptual framework of this study.....42

Figure 3.1: Picture of Hospital Sultanah Bahiyah, Alor Setar, Kedah.....44

Figure 3.2: Study design in survival analysis.....54

Figure 3.3: Location of Hospital Kuala Lumpur next to major roads.....61

Figure 3.4: Map of HSIS, Serdang and HSAAS,UPM. 63

Figure 3.5: Flow chart of part one and part two of the study.....76

Figure 4.1: Trend of IC cases from 2017- 2023.....83

Figure 4.2: Trends of main *Candida* species from the year 2017-2023.....84

Figure 4.3: Survival probabilities of overall IC patients.....95

Figure 4.4: Survival probability patient age ≥ 65 (*p*-value = 0.05). 96

Figure 4.5: Survival probability based on hospital department 97

Figure 4.6: Survival probability based on *Candida* species.....98

Figure 4.7: Survival probability of hypertension patients (*p*-value =0.002).....99

Figure 4.8: Survival probability of diabetic patients (*p*-value = 0.132).....100

Figure 4.9: Survival probability of respiratory disease patients (*p*-value = 0.284)..100

Figure 4.10: Survival probability patients presented with fever (*p*-value <0.001)..101

Figure 4.11: Survival probability patients with septic shock (*p*-value <0.001).....102

Figure 4.12: Survival probability patients with leukocytosis (*p*-value = 0.001).....102

Figure 4.13: Survival probability patients with GIT symptoms (*p*-value = 0.07). ..103

Figure 4.14: Survival probability patients with kidney injury (*p*-value <0.001). 104

Figure 4.15: Survival probability of patients with treatment (p-value <0.01). 105

LIST OF SYMBOLS

<	Less than
>	More Than
≤	Less than or Equal
≥	More than or Equal
=	Equal to
α	Alpha (type 1 error)
β	Beta (type II error)
n	Sample
%	Percentage
p	*p*-value

LIST OF ABBREVIATION

A-Mn	Anti-Mannan Antibodies
Adj. HR	Adjusted Hazard Ratio
Adj.OR	Adjusted Odd Ratio
AFST	Antifungal Susceptibility Testing
APC	Aerobic Plate Count
BA	Behavioural Attitude
BDG	beta-D-glucan
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CNS	Central Nervous System
CRRT	Continuous Renal Replacement Therapy
DALYs	Disability-Adjusted Life Years
HAI	Healthcare-Associated Infection
HbA1c	Hemoglobin A1C
HER	Electronic Health Record
HIS	Hospital Information System
HIV	Human Immunodeficiency Virus
HKL	Hospital Kuala Lumpur
HSAAS	Hospital Sultan Abdul Aziz Shah
HSB	Hospital Sultanah Bahiyah

HSIS	Hospital Sultan Idris Shah
IC	Invasive Candidiasis
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IQR	Interquartile Range
JEPEM	Jawatankuasa Etika Penyelidikan Manusia (Human Research Ethics Committee)
LDP	Latihan Dalam Perkhidmatan (Training During Service)
LIS	Lab Information System
LTAT	Lab Turnaround Time
M1	Fungal Blood Culture
M2	Fungal Blood Culture with PCR
M3	Fungal Blood Culture with Mn and A-Mn
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionisation-Time of Flight
MIC	Minimum Inhibitory Concentration
Mn	Mannan Antigen
NMRR	National Medical Research Register
NPV	Negative Predictive Value
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
PS Software	Power and Sample Size Calculation Software

PWID	Persons Who Inject Drugs
QALYs	Quality-Adjusted Life Years
RM	Ringgit Malaysia
SDA	Sabouraud Dextrose Agar
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
sp.	Species
T2MR	T2 Magnetic Resonance
UPM	Universiti Putra Malaysia
US	United States of America
USM	Universiti Sains Malaysia
WTP	Willingness-To-Pay

LIST OF APPENDICES

Appendix A	Approval letter from the Human Research Ethics Committee, Universiti Sains Malaysia (JEPeM).
Appendix B	Approval letter from Ministry of Health Ethics Committee: Medical Research and Ethics Committee (MREC).
Appendix C	Approval letter from the Universiti Putra Malaysia UPM ethics committee: Jawatankuasa Etika Universiti Untuk Penyelidikan Melibatkan Manusia (JKEUPM).
Appendix D	Approval letter from the director of Kedah Health State Department (JKN Kedah).
Appendix E	Approval letter from the director of Hospital Sultanah Bahiyah (HSB), Alor Setar
Appendix F	Approval letter from the director of Hospital Sultan Idris Shah (HSIS), Serdang
Appendix G	Approval letter from the director of Hospital Sultan Abdul Aziz Shah (HSAAS), UPM.
Appendix H	Proforma for data collection.
Appendix I	Micro costing form.

ABSTRAK

TABURAN DAN FAKTOR PROGNOSTIK BAGI KEMATIAN CANDIDIASIS INVASIF, DAN ANALISIS KEBERKESANAN UNTUK KOS TIGA KAEDAH DIAGNOSTIK DI HOSPITAL TERPILIH DI MALAYSIA

Candidiasis invasif (IC) adalah jangkitan kulat yang teruk dengan kadar kematian yang tinggi serta kos penjagaan kesihatan yang ketara. Walaupun terdapat kemajuan dalam kaedah diagnostik, terdapat cabaran yang berterusan bagi mencapai diagnosa yang tepat pada masanya dan kos yang wajar, terutamanya dalam persekitaran dengan sumber yang terhad. Kaedah diagnostik tanpa kultur yang lebih maju menawarkan keputusan yang lebih pantas tetapi menghadapi penerimaan yang terhad di Malaysia disebabkan oleh isu kos. Kajian ini bertujuan untuk mengkaji taburan dan trend IC, menganggar kadar kelangsungan hidup, mengenal pasti faktor prognostik yang mempengaruhi kematian, dan menilai keberkesanan kos kaedah diagnostik untuk memperbaiki keadaan pesakit dan memaklumkan dasar penjagaan kesihatan.

Kajian ini terdiri daripada dua bahagian. Bahagian pertama menggunakan reka bentuk kohort retrospektif untuk menyiasat trend IC, masa kelangsungan hidup median, dan faktor prognostik dalam kalangan 445 pesakit yang didiagnosis antara tahun 2017 dan 2023. Analisis kelangsungan hidup menggunakan anggaran Kaplan-Meier menonjolkan kadar kelangsungan hidup median berdasarkan pemboleh ubah demografi dan klinikal, manakala regresi berkadar Cox mengenal pasti faktor kematian yang ketara. Bahagian kedua memberi tumpuan kepada analisis keberkesanan kos tiga kaedah diagnostik: kultur (M1), kultur dengan tindak balas rantai polimerase (PCR) (M2), dan kultur dengan Mannan Anti-Mannan (M3),

menggunakan pendekatan mikro-kos. Keberkesanan dinilai berdasarkan masa pemprosesan makmal (LTAT), dengan mengira nisbah keberkesanan kos purata (ACER) dan nisbah keberkesanan kos tambahan (ICER).

Spesies yang paling kerap ditemui adalah *Candida albicans* (32.2%), diikuti oleh spesies bukan albicans seperti *C. tropicalis* (25.3%) dan *C. parapsilosis* (20.3%). Kadar kematian yang tinggi dapat diperhatikan, terutamanya dalam kalangan pesakit ICU, dengan kadar kelangsungan hidup 30 hari sebanyak 26.1%. Anggaran Kaplan-Meier menunjukkan masa kelangsungan hidup median selama 21 hari. Faktor prognostik yang signifikan bagi kematian termasuk kecederaan buah pinggang, hipertensi, dan sepsis. M2 dan M3 menunjukkan masa pemprosesan makmal yang lebih pantas (LTAT < 2 hari) berbanding M1 (> 5 hari). Nisbah keberkesanan kos purata (ACER) untuk jumlah 2000 spesimen menunjukkan M2 memerlukan kos sebanyak RM33.25 bagi setiap hari pengurangan LTAT, manakala M3 memerlukan RM41.79. Nisbah keberkesanan kos tambahan (ICER) menunjukkan diagnosis IC menggunakan PCR atau Mn A-Mn adalah kos efektif.

Penemuan kajian ini menonjolkan spesies *Candida* bukan *albicans* adalah patogen yang dominan, serta kepentingan meningkatkan diagnostik dan strategi rawatan yang disesuaikan. Kaedah diagnostik yang menggabungkan PCR dan Mn A-Mn menawarkan pendekatan yang kos efektif untuk menambahbaik pengurusan IC dan memberi panduan bagi dasar penjagaan kesihatan.

ABSTRACT

DISTRIBUTION AND PROGNOSTIC FACTORS FOR MORTALITY OF INVASIVE CANDIDIASIS, AND COST-EFFECTIVENESS ANALYSIS OF THREE DIAGNOSTIC MODALITIES IN SELECTED MALAYSIAN HOSPITALs

Invasive candidiasis (IC) is a severe fungal infection associated with high mortality and substantial healthcare costs. Despite advancements in diagnostic methods, challenges persist in achieving timely and economically viable diagnosis, particularly in resource-limited settings. Advanced non-culture diagnostics offer faster results but face limited adoption in Malaysia due to cost concerns. This study aimed to examine the distribution and trends of IC, estimate survival rates, identify prognostic factors influencing mortality, and assess the cost-effectiveness of diagnostic methods to improve patient outcomes and to inform healthcare policy.

This study comprised two parts. Part one used a retrospective cohort design to investigate IC trends, median survival time, and prognostic factors among 445 patients diagnosed between 2017 and 2023. Survival analysis, employing Kaplan-Meier analysis, revealed median survival rates stratified by demographic and clinical variables, while Cox proportional hazards regression identified significant mortality prognostic factors. Part two focused on a cost-effectiveness analysis of three diagnostic modalities: culture (M1), culture with polymerase chain reaction (M2), and culture with Mannan/anti-Mannan (M3), using a micro-costing approach. Effectiveness was assessed through lab turnaround time (LTAT), with average cost-effectiveness ratios (ACER) and incremental cost-effectiveness ratios (ICER) calculated.

The most prevalent species was *Candida albicans* (32.2%), followed by non-albicans species such as *C. tropicalis* (25.3%) and *C. parapsilosis* (20.3%). High mortality rates were observed, particularly among ICU patients, with a 30-day survival rate of 26.1%. Kaplan-Meier estimates revealed a median survival time of 21 days. Significant prognostic factors of mortality included kidney injury, hypertension, and sepsis. M2 and M3 demonstrated faster (LTAT < 2 days) compared to M1 (> 5 days). Average cost-effectiveness ratios for 2000 specimens quantity M2 achieved a cost of RM33.25 per day reduction in LTAT, while M3 required RM41.79. Incremental cost-effectiveness ratios demonstrated diagnosis IC using PCR or Mn A-Mn is cost-effective

The findings highlight the dominance of non-albicans Candida species and highlighted the importance of improved diagnostics and tailored treatment strategies. Incorporating PCR and Mn A-Mn diagnostics offers a cost-effective approach to enhance IC management and guide healthcare policies.

CHAPTER 1

INTRODUCTION

This chapter introduces the main concepts of the study to ease the understanding of the topic. The study objectives were twofold. It first examined the prognostic factor of Invasive Candidiasis (IC) aimed to improve the patients' management and outcomes. In part two, a cost-effectiveness analysis was conducted on diagnostic modalities to determine their cost and their outcome in order to prioritise the diagnostic tool with maximum impact. Calculating these costs is essential in public health, as they enable effective resource allocation by identifying interventions with the highest benefit relative to cost. This approach, which evaluates both the economic and clinical value of diagnostic tools, supports informed decision-making to enhance disease surveillance, expand access to critical diagnostics, and promote financial sustainability, particularly in resource-limited settings.

This chapter begins with an introduction to IC, its prevalence, and prognosis. To enhance understanding, the chapter offers an overview of diagnostic methods for IC and cost-effectiveness analysis (CEA). The chapter wraps up by presenting the study's research questions, rationale, and objectives.

1.1 Invasive Candidiasis

Invasive candidiasis is a severe systemic *Candida* infection characterised by the hematogenous dissemination or spread to several viscera of *Candida*. This condition refers to candidemia, the presence of *Candida* species in the bloodstream,

or the involvement of various organs such as the heart, liver, or kidneys. Deep-seated or visceral candidiasis without candidemia, candidemia with visceral *Candida* infection, and candidemia without visceral involvement are key categories of IC (Clancy & Nguyen, 2013).

Although candidemia does not occur in all cases of IC, it is one of the most common and clinically recognised forms of invasive *Candida* infection. As a result, the terms 'invasive candidiasis' and 'candidemia' are sometimes used interchangeably, though they are not synonymous.

1.1.1 Pathophysiology

Candida species such as *Candida albicans* are typically regarded as constituents of the natural microbiota in the human gastrointestinal and genitourinary tracts, yet they possess as an opportunistic fungal pathogen and have the capacity to initiate disease when a disruption occurs in their usual ecological environment (Jenkinson, Julia & Affiliations, 2002). Interestingly, *Candida albicans* contributed to more than 50% of the IC cases (Pappas *et al.*, 2018). In addition to the patient's normal endogenous flora, candida infection may be acquired during nosocomial transmission, especially in the intensive care unit (Pfaller & Diekema, 2007).

1.1.2 Burden of Invasive Candidiasis

Invasive candidiasis (IC) is the most common fungal disease in hospitalised adult and pediatric patients (Kullberg & Arendrup, 2015). It was estimated that there were 10 to 30 IC cases per 100,000 population in the United States of America cities between 2008 and 2013 (Cleveland *et al.*, 2015). In Malaysia, the estimated incidence

of candidemia alone was 5 cases per 100,000 population in 2017 (Velayuthan *et al.*, 2018a). Despite the significant burden of IC, actual cases are likely underreported due to the lack of population-based epidemiological data and systematic fungal surveillance in Malaysia. Around 20% of IC cases in a tertiary care hospital in Malaysia from 2001 to 2018 were caused by *Candida albicans* (Haydar & Tajuddin, 2018; Yamin *et al*., 2020).

Beyond its clinical impact, IC imposes a substantial financial burden on healthcare systems due to prolonged hospital stays, increased ICU admissions, and the high cost of antifungal therapy (Ananda-Rajah *et al.*, 2011). Additionally, the need for invasive medical procedures, and frequent patient monitoring and investigations, further escalates hospital expenditures.

1.1.3 Risk Factors and Populations at Risk

Immunocompromised individuals are at a significantly higher risk of developing IC due to their weakened ability to mount an effective immune response against *Candida* infections (Dropulic & Lederman, 2016). Patients with prolonged hospitalisation, particularly those in intensive care units (ICU), face increased susceptibility due to factors such as broad-spectrum antibiotic use, mechanical ventilation, and exposure to invasive medical devices like central venous catheters (Jung *et al.*, 2020; Ramirez *et al.*, 2020) High-risk populations include transplant recipients, individuals undergoing chemotherapy for malignancies, and patients with uncontrolled diabetes mellitus(Shoham & Marr, 2012; Rodrigues et al., 2019; Soriano et al., 2023). In critically ill patients, the combination of multiple risk factors, including sepsis and multi-organ failure, further exacerbates their vulnerability to the infection.

1.2 Clinical Presentation

Invasive candidiasis presents clinically with non-specific subtle symptoms resembling other infections, making timely diagnosis challenging (Pappas *et al.*, 2018). Patients might experience fever, chills, and rigour in addition to not being responsive to antibiotics. Hematogenous spread involving various organs leads to fatigue, malaise, and weight loss. Complications like endophthalmitis, central nervous system (CNS) involvement, peritonitis, and cutaneous manifestations add to the complexity.

1.3 Diagnostic Methods

The diagnosis of IC relies on a combination of clinical assessment, and microbiological tests, supported by imaging techniques in certain conditions. Despite advancements in diagnostic tools, several limitations persist, including delays in definitive diagnosis, variability in the sensitivity of different methods, and financial constraints that hinder accessibility, particularly in resource-limited settings.

In the course of a physical examination, observable signs such as typical eye lesions (chorioretinitis), skin lesions, and atypically muscle abscesses may suggest potential hematogenous dissemination of *Candida* (Pappas *et al.*, 2018). Nevertheless, these clinical signs may be subtle and easily overlooked, particularly in critically ill or immunocompromised patients. In cases where localised signs, such as skin lesions or parenchymal involvement, are evident of IC, a biopsy is conducted to facilitate staining, culture, and histopathological analysis. Expedited techniques with enhanced sensitivity are deemed imperative for critically ill patients.

Invasive candidiasis is diagnosed using fungal culture and non-culture methods (Pappas *et al.*, 2018). Fungal culture methods will use blood or tissues. Blood cultures are the simplest and most reliable way to diagnose IC since they grow the organism directly from blood. Non-culture methods are Mannan anti-Mannan (Mn A-Mn), beta-D-glucan (BDG), T2 Magnetic Resonance (T2MR), Polymerase Chain Reaction (PCR), microscopy, and histopathology.

1.3.1 Blood culture

The gold standard method for diagnosing IC is the culture method, particularly the fungal blood culture method, where the identification of *Candida* sp. in a fungal blood culture signifies a potential metastatic or deep-seated infection, warranting careful consideration rather than dismissal as a contaminant (Fridkin, 2005).

Unfortunately, the blood culture method's detection capability is limited, capturing only approximately 50% of all cases, a constraint attributed to live *Candida* cells in the bloodstream (Barantsevich & Barantsevich, 2022).With a sensitivity of about 50% and a specificity often exceeding 90%, the positive predictive value (PPV) remains high in high-prevalence settings; however, the negative predictive value (NPV) is compromised, meaning that a negative result does not reliably exclude invasive candidiasis. The LTAT is approximately four (4) days for culture methods

The fungal blood culture method involves carefully collecting blood samples from suspected patients, followed by introducing the blood samples into a blood culture bottle that contains specific nutrients suitable for fungal growth. These bottles are then incubated for a period of time, usually in automated systems that continuously monitor for microbial growth. If fungal growth is detected, the sample is removed

from the bottle and subjected to gram staining to assess morphology (Nawrot *et al.*, 2015).

Subsequent subculturing is performed on specialised agar plates, specifically Sabouraud Dextrose Agar (SDA) and Blood Agar (BA). These plates are then placed in a controlled environment with a defined temperature and atmospheric conditions, facilitating the proliferation of fungi. After sufficient growth on the plates, additional tests, such as biochemical assays or MALDI-TOF mass spectrometry, are used to precisely identify the fungal species (Lau, 2021). Antifungal susceptibility testing (AFST) is then performed to determine the appropriate treatment regimen.

Blood culture is a crucial prerequisite for conducting drug susceptibility tests, specifically the AFST (Choi *et al.*, 2017). The primary objective of AFST is to identify antifungal resistance and establish optimal treatment strategies tailored to the particular fungal strain. Employing broth microdilution techniques in AFST facilitates generating minimum inhibitory concentration (MIC) values, providing a quantitative assessment of drug efficacy. Clinicians depend on these methodologies to determine the most effective antifungal agents for treating infections and to gain insights into the epidemiology of antifungal resistance (Wiederhold, 2021).

Contamination, notably from skin flora, which can lead to false-positive results, remains a persistent problem in fungal blood culture procedures (Weinstein, 2003). Effectively addressing this concern necessitates the stringent application of aseptic techniques during blood collection. Additionally, ensuring the accuracy of fungal blood cultures requires utilising specialised culture media, such as SDA, designed to minimise contamination risks through bacterial proliferation inhibition using its acidity and moisture profile. These precautionary measures are of utmost

significance in guaranteeing the collection of reliable and uncontaminated samples, thereby optimising the accuracy of fungal infection diagnosis in clinical settings.

Certain fungal species present diagnostic complexities due to their slow growth. Extending the incubation time of fungal blood cultures is an effective strategy to improve the test's sensitivity, increasing the chances of detecting fungal infections. However, these measures may inadvertently result in potential delays in achieving timely diagnoses. To address such delays, the supplementation of blood culture with sophisticated non-culture techniques is recommended, aiming to achieve a more precise and prompt identification of fungal infections (Nawrot *et al.*, 2015; Pappas *et al.*, 2018; Fang *et al.*, 2023). From a cost perspective, the blood culture method is relatively affordable compared to advanced non-culture methods; however, the need for extended incubation times and repeated testing might contribute to increased hospital costs and resource utilisation.

1.3.2 Non-culture method

The emergence of non-culture methods such as mannan and anti-mannan antibody, BDG, T2 Magnetic Resonance (T2MR), and Polymerase Chain Reaction (PCR) assays have the advantage of diagnosing the disease in a shorter time frame (up to one hour) and with a higher positivity rate, addressing the limitations of conventional blood cultures (Barantsevich & Barantsevich, 2022). However, these advanced diagnostic methods come with higher costs, making them less accessible in resource-limited settings, especially in most government hospitals in Malaysia. Balancing diagnostic effectiveness with affordability remains a significant challenge in managing IC.

1.3.3 Imaging

Although imaging studies are not diagnostic tools for IC, they serve as valuable adjuncts, particularly when deep-seated infections are suspected. Computed tomography (CT) and magnetic resonance imaging (MRI) aid in detecting abscesses, hepatosplenic candidiasis, and end-organ involvement, providing crucial insights into the extent of dissemination (Cornely, Bangard & Jaspers, 2015). Additionally, echocardiography (transthoracic or transesophageal) plays a key role in identifying cardiac complications such as *Candida* endocarditis (Henriquez *et al.*, 2023). However, imaging findings alone are non-specific and must be interpreted alongside microbiological and serological tests to establish a definitive diagnosis. Additionally, the above-mentioned imaging modalities are costly, often requiring specialised equipment and radiology expertise, which limits their routine use in low-resource settings.

1.4 Treatment

The 2016 Infectious Diseases Society of America (IDSA) guidelines suggest that empiric antifungal medication should be considered for critically sick patients with persistent, unexplained fever and risk factors for IC (Pappas *et al.*, 2015). Based on the current clinical practice, IC treatment must be continued for two weeks after the first negative result for candidiasis or *Candida* clearance (Pappas *et al.*, 2018). The estimated minimum duration for the treatment of IC is around 18 days, as the median (IQR) *candida* clearance time is 6 days (5) after the initiation of the antifungal treatments, and the median (IQR) length of stay of patients is 25.5 days (40) (Elbaz *et al.*, 2022).

Echinocandins (caspofungin, micafungin, anidulafungin) and fluconazole are used to treat candidemia more commonly than amphotericin B formulations due to their toxicity (Gafter-Gvili *et al.*, 2008). Echinocandins noncompetitively inhibit 1,3-BDG production, an essential component of fungal cell walls (Morris & Villmann, 2006).

Fluconazole is widely used in treating IC because it may be used intravenously or orally, has a low risk of side effects, and comes in a generic form, thus making it affordable (Rex *et al.*, 2003). Other available azoles include Voriconazole, Posaconazole, Itraconazole, and Isavuconazole. The azoles inhibit the lanosterol 14-alpha-demethylase cytochrome P450-dependent enzyme (Zonios & Bennett, 2008). This enzyme is required to convert lanosterol to ergosterol, a vital component of the cellular membrane of fungi.

Amphotericin B, a polyene antifungal drug, binds to sterols, particularly ergosterol, and forms pores that leak cellular components, disrupting fungal cell wall formation (Pappas *et al.*, 2015). Amphotericin B formulations are avoided due to their higher toxicity than azoles and echinocandins. They are beneficial when resistance to other antifungal classes is suspected or established.

1.4.1 Antifungal Resistance and Treatment Challenges

The rise of antifungal resistance presents a significant hospital epidemiology concern, as IC is frequently acquired in healthcare settings, particularly in ICU, transplant wards, and oncology units (Wiederhold, 2017). The widespread use of antifungals in prophylactic and empirical antifungal therapy has further accelerated resistance development, underscoring the need for robust antifungal stewardship

programs. In addition, the absence of rapid diagnostic tools in many healthcare settings leads to delays in targeted therapy, prolonged reliance on empirical antifungal therapy and, consequently, driving antifungal resistance.

The emergence of multidrug-resistant (MDR) *Candida* species, such as *Candida auris*, poses a significant concern due to its ability to cause outbreaks in healthcare facilities and its resistance to multiple antifungal classes (Garcia-Bustos *et al.*, 2021). These outbreaks are often associated with nosocomial transmission, driven by breaches in infection control, prolonged hospital stays, and the widespread use of invasive medical devices such as central venous catheters and endotracheal tubes (Chakrabarti *et al.*, 2022).

Beyond the challenge of antifungal resistance, the management of IC is further complicated by issues such as drug toxicity, drug interactions, and the limited accessibility of newer antifungal agents in resource-limited settings (Roemer & Krysan, 2014). These factors collectively contribute to the growing burden of IC in healthcare settings, underscoring the need for comprehensive infection control strategies, improved antifungal stewardship, and equitable access to effective treatment options.

1.5 Prognosis

Invasive candidiasis causes significant health concerns as it is one of the leading causes of bloodstream infection. Its diagnosis is often only established when patients are in a critical stage (Kullberg & Arendrup, 2015; Pappas *et al.*, 2018).

The 30-day mortality rate of IC is significantly alarming, ranging between 29% and 75% (Ng *et al.*, 2015; Al-Rashdi *et al.*, 2021). A local study in Malaysia also found that the overall mortality rate of hospitalised IC patients from 2010 until 2014 was 59% (Haydar & Tajuddin, 2018). This statement is supported by other multi-centric studies that found median survival time for IC patients ranges between three to 30 days (Bienvenu *et al.*, 2020; Kutlu *et al.*, 2022). This can be interpreted as half of the IC patients will die within three to 30 days from the date of diagnosis or start of treatment.

Early treatment of infected individuals is crucial since delays in effective medication significantly influence outcomes (Labelle *et al.*, 2008). Late diagnosis of IC is attributed to non-specific clinical presentations, below-average performance, availability of laboratory methods, and the nature of the disease itself (Clancy & Nguyen, 2013; Vergidis *et al.*, 2016).

1.6 Cost-Effectiveness Analysis

Economic evaluation is a systematic comparative analysis of various interventions or strategies, examining both their costs and consequences. It aids decision-making in resource allocation by providing input on health interventions or technologies that provide the greatest value for money (Bertram *et al.*, 2021). Existing evidence, disease patterns, and the healthcare system's capabilities will be considered during the evaluation process (Kim & Basu, 2021).

Economic evaluations can be partial or full; the latter include CEA, cost-utility analysis, cost-minimisation analysis and cost-benefit analysis. The selection of CEA as the choice of analysis was primarily due to the measurement of its outcome in natural units, in relation to the cost of health intervention and compares it with other interventions (Turner *et al.*, 2021). It has been used in many studies to analyse various healthcare interventions, such as pharmaceuticals, surgeries, and public health initiatives. Recently, CEA has also been increasingly used to assess the cost-effectiveness of diagnostic methods, helping to identify the most efficient approaches for timely and accurate diagnoses within constrained budgets (Walker *et al.*, 2016; Pagès *et al.*, 2017; Snowsill, 2023).

1.6.1 Significance of CEA in the Management of Invasive Candidiasis

The treatment of IC is very costly. The costs are 100% higher compared to a similar diagnosis-related group without IC due to the number of hospital stays of the patients, which contributes to the high cost of treatment (Gagne *et al.*, 2006). As a reference, the cost of hospital stays in Malaysia contributes more than 50% of the total cost of patient care (Wan Ismail *et al.*, 2020). Given these economic implications, optimising diagnostic strategies is essential to reducing unnecessary healthcare expenditures.

Diagnostic-driven IC has been found to decrease the length of stay and subsequently decrease the cost of hospitalisation (Machado *et al.*, 2021), decrease the consumption and cost of anti-fungi medication, and improve(Patch *et al.*, 2018; Kawaguchi *et al.*, 2019; Samura *et al.*, 2020). Even though the gold standard diagnostic method of IC (blood culture method) is a relatively cheap, reliable, dependable, and straightforward method and is able to cultivate *Candida* from blood,

it has low sensitivity and takes a few days to complete. Other non-culture diagnostic methods offer significantly better lab turnaround time (LTAT) than the culture method. Unfortunately, these non-culture methods are unable to cultivate the *Candida* (needed for AFST) and are very costly.

Given the inherent trade-offs between cost and LTAT reduction across different diagnostic modalities, CEA is the most appropriate economic evaluation approach for this study. Cost-effectiveness analysis is particularly useful when comparing interventions that produce the same clinical outcome but with different costs, making it well-suited for evaluating IC diagnostic methods where the primary objective is early and accurate detection rather than long-term health utility measurements such as quality-adjusted life years (QALYs), which are typically assessed using cost-utility analysis (CUA).

The framework of CEA offers a systematic approach to assess the financial viability of various IC diagnostic modalities so that it can determine which diagnostic technique offers the best value for money because healthcare resources tend to be scarce. The analysis spans beyond cost consideration to include the assessment of health outcomes. The outcomes may include rapid and accurate diagnosis, allowing for prompt treatment, subsequently decreased morbidity and death, and reduced length of stay, thus reducing the total cost of the healthcare system. This helps to ensure that resources are allocated to a diagnostic modality with the greatest potential to improve patient outcomes.

1.7 Statement of Problem

In Malaysia, with a population of 33 million people, it was estimated in 2017 that the total burden of candidiasis is half a million cases annually, of which 1,533 are candidemia cases (Velayuthan et al., 2018). Immunocompromised patients and multiple comorbidities are prognostic factors for candidemia or IC and its mortality.

The morbidity and mortality rates of IC are very significant, depending on the specific patient population, as most IC patients have underlying medical conditions. In addition, the mortality rate varies geographically. Typically, the mortality rates range from 29% to as high as 75% (Hirano *et al.*, 2015; Pappas *et al.*, 2018). Assuming that the mortality rate of IC in Malaysia is on average, 50%, it will translate into approximately more than 700 deaths nationwide annually. To put it in perspective, the number of death among IC patients is higher than the number of deaths from dengue fever in Malaysia. Dengue fever recorded between 100 to 200 deaths in 2016 from over 100,000 cases annually (Ahmad *et al.*, 2018).

Currently, blood culture is the gold standard diagnostic method for IC. However, the blood culture test is relatively insensitive and takes days (Barantsevich & Barantsevich, 2022). Furthermore, the blood culture test must be performed repeatedly because of the long course of anti-fungi treatment, which needs to be continued for another two weeks after the first negative diagnostic test result. Attending clinicians often treat suspected patients for IC empirically without a definite diagnosis due to the long duration for diagnosis when using the blood culture method. This empirical treatment will increase the cost of treatment and the chances for side effects of antifungal drugs and worsening current drug resistance. Antifungal resistance has lately been dubbed a silent crisis (Kainz *et al.*, 2020). It is due to the

long-term therapeutic application and prophylactic use of antifungal drugs in high-risk patients.

Even though non-culture methods can give a definitive early diagnosis, these methods cannot produce a viable fungus for susceptibility tests. Among these methods, only PCR and T2MR can identify the *Candida* species (Kourkoumpetis *et al.*, 2012; Nguyen & Clancy, 2018). Thus, combining blood culture and non-culture methods will give an early diagnosis and drug susceptibility advantages compared to blood culture or non-culture alone. However, these non-culture methods have not been adopted in Malaysia, as their cost-effectiveness has not yet been evaluated.

Invasive candidiasis has also been shown to have a substantial economic impact on individuals and the healthcare system. It was estimated that the mean total cost per patient and mean cost per hospitalisation of IC patients range from $48,487 to $157,574 and $10,216 to $37,715, respectively (Wan Ismail *et al.*, 2020) In 2017, it was estimated that the total economic burden due to IC in the United States is nearly two billion dollars yearly (Benedict *et al.*, 2019). The financial costs reported are an underestimation of the actual costs since they excluded unnecessary tests and inappropriate therapy before a diagnosis of a fungal infection is made.

1.8 Rationale

It is essential to address IC as it imposes significant health, mortality, and economic risks. There is currently limited study that analyses the distribution and trend of IC in Malaysia in recent years. There are also no available data on the median mortality time and prognostic factors for IC in Malaysia. Identifying median mortality time and prognostic factors contributing to mortality is essential to facilitate further

improvement in patient care, guiding clinical intervention and strengthening hospital-based infection control measures.

The introduction of several non-culture methods that improve diagnostic timing and early diagnosis of IC in clinical practice has been widely accepted and used worldwide. Despite their availability in the market, the application is not fully adopted in Malaysia due to cost constraints. Currently, their use is primarily restricted to university hospitals—mainly for research purposes—and selected private hospitals. Unfortunately, economic evaluation studies of IC diagnostic methods are also limited. No prior study has been done in Malaysia on this matter leaving policymakers and hospital administrators without data to justify their widespread adoption.

The economic evaluation will provide information regarding the significance of supplementing the current culture method testing with non-culture methods (PCR and Mn A-Mn) in diagnosing IC. Given that CEA is widely used to evaluate healthcare interventions, this study will employ CEA to compare diagnostic costs and clinical outcomes (LTAT), identifying which method offers the highest value for money, further guiding resource allocation and clinical decision-making.

This study is expected to provide evidence for a more cost-effective and sustainable laboratory strategy for IC diagnosis in Malaysian hospitals. By evaluating the financial feasibility and clinical benefits of non-culture methods, this research will offer a structured framework for decision-making, ensuring that healthcare resources are allocated efficiently. This research will benefit IC patients, clinicians, and hospital administrators. It will also be a guide in the more efficient use of the limited healthcare resources by focusing on a more viable, cost-effective alternative in improving the outcome of IC patients.

1.9 Research Questions

1. What is the distribution, trend and antifungal susceptibility of IC in Kedah from 2017 to 2023?

2. What is the median mortality time of patients with IC in Hospital Sultanah Bahiyah from 2017 to 2023?

3. What are the prognostic factors for mortality among patients with IC in Hospital Sultanah Bahiyah from 2017 to 2023?

4. Which diagnostic method for IC is the most cost-effective?

1.10 Study Objectives

1.10.1 General objective

To study the distribution and prognostic factors of invasive candidiasis mortality and the cost-effectiveness of its diagnostic method.

1.10.2 Specific objectives

1. To describe the distribution, trend and antifungal susceptibility of invasive candidiasis cases in Kedah from 2017 to 2023.

2. To estimate the survival rate and the median survival time for mortality among patients with invasive candidiasis in Hospital Sultanah Bahiyah from 2017 to 2023.

3. To identify the prognostic factors associated with mortality among patients with invasive candidiasis in Hospital Sultanah Bahiyah from 2017 to 2023.

4. To determine the cost-effectiveness of three modalities of diagnostic methods for invasive candidiasis in Hospital Sultan Abdul Aziz Shah, UPM.

1.11 Research Hypotheses

1. There are significant prognostic factors that led to mortality among patients with invasive candidiasis.

2. The non-culture methods such as Mannan anti-Mannan (Mn A-Mn) and Polymerase Chain Reaction (PCR) are cost-effective diagnostic modalities for invasive candidiasis.

CHAPTER 2

LITERATURE REVIEW

This chapter contains a review of the literature on topics related to the study objectives. The literature search used online databases and search engines, namely Scopus, PubMed, Google Scholar, Springer Link, Web ISI, and Science Direct. Various search techniques were used, including the usage of Boolean operators such as "AND", "OR", and "NOT". Invasive Candidiasis, Mortality, Diagnostic Method, and Economic Evaluation are the keywords utilised.

2.1 Invasive Candidiasis in Malaysia

The epidemiology of IC in Malaysia remains inadequately studied, with limited systematic data available. Is was estimated that approximately 1,533 cases of candidemia recorded annually, with 460 cases occurring in ICU and 1,073 cases among cancer patients in Malaysia (Velayuthan *et al.*, 2018). This suggests that IC is predominantly a healthcare-associated infection, disproportionately affecting immunocompromised and critically ill patients. However, the absence of population-based surveillance limits the accuracy of these estimates.

Unlike Western cohorts, where ICU-acquired candidemia is predominant, 39.6% of cases in Malaysia were reported in non-ICU settings, possibly due to delayed diagnosis and late initiation of antifungal therapy, which often exceeded 48 hours in medical wards (Haydar & Tajuddin, 2018). The high 30-day mortality rate (59%) underscores the urgent need for improved epidemiological surveillance, early diagnostic strategies, and optimised antifungal stewardship to mitigate the burden of

IC in Malaysia. Moreover, global trends indicate that developing countries, including Malaysia, may experience a disproportionately high IC burden due to limited diagnostic infrastructure and inconsistent infection control measures (Kaur *et al.*, 2020). Addressing these gaps through enhanced surveillance and early intervention is crucial for improving patient outcomes and reducing mortality.

2.2 Clinical Presentation

Invasive candidiasis presents with non-specific systemic symptoms that overlap with bacterial sepsis, often delaying diagnosis and appropriate treatment. Persistent fever unresponsive to broad-spectrum antibiotics is the most prevalent clinical manifestation, reported in 72–89% of cases, complicating differential diagnosis in critically ill patients (Kullberg & Arendrup, 2015; Pappas *et al.*, 2018). Hypotension, observed in 33–45% of cases, further mimics bacterial sepsis, potentially leading to inappropriate initial management. Additionally, hematogenous dissemination of *Candida* species can result in organ-specific complications, including hepatosplenic abscesses and endophthalmitis, increasing morbidity and mortality risks.

A laboratory-based multicenter study conducted between 2008 and 2010 across 21 tertiary hospitals in seven Latin American countries reported that 68% of IC patients (including neonates, adults, and elderly individuals) developed fever and septic shock, while 22% experienced metastatic complications such as endophthalmitis (Nucci et al., 2013).

In India, ICU-acquired candidemia commonly presents with fever and septic shock, often leading to multi-organ complications. However, while renal abscesses

and cutaneous lesions have been reported in some cases, large-scale studies have not extensively documented their prevalence. This nationwide study across 27 ICUs conducted between April 2011 and September 2012 found that ICU-acquired candidemia predominantly affects non-neutropenic patients, with *Candida tropicalis* being the most prevalent pathogen. While delayed antifungal therapy significantly contributes to high mortality (44.7%) within 30 days (Chakrabarti *et al.*, 2015).

A local retrospective study (2001–2018) highlighted fever as a predominant symptom in IC patients, with many patients experiencing prolonged febrile episodes despite antibiotic therapy. While septic shock is a recognised complication of candidemia, the study does not specify the exact proportion of patients who progressed to this stage (Yamin et al., 2020). In the same setting, another retrospective study of IC patients in the ICU from 2010 to 2014 found that the patients commonly presented with persistent fever and sepsis, often unresponsive to antibiotics. Additional documented symptoms included hypotension, altered mental status, and multi-organ dysfunction, indicating systemic dissemination (Haydar & Tajuddin, 2018).

Invasive candidiasis can result in systemic fungal dissemination, including ocular involvement in the form of endogenous fungal endophthalmitis. This condition typically presents with blurred vision, floaters, red painful eyes, and photophobia, progressing to choroiditis, vitreous haze, and intraretinal haemorrhages (Ly & Sallam, 2025).

2.3 Prognostic Factors for IC Mortality

Prognostic factors for mortality in IC play a crucial role in patient outcomes. Identification and complete appraisal of prognostic factors below are critical for directing targeted intervention and improving overall prognosis in IC-infected patients.

2.3.1 Sociodemographic

An older age was shown to be a significant risk for 30-day mortality in Turkish research, with a Hazard Ratio of 1.02, 95% CI 1.01, 1.04, and p-value <0.05 (Kutlu *et al.*, 2022). Population-based surveillance shows that candidemia incidence is highest among neonates (<1 year: 33.8 cases per 100,000 person-years) and older adults (≥65 years: 55.7 cases per 100,000), highlighting extreme age as a key prognostic factor for mortality in invasive candidiasis (Kullberg & Arendrup, 2015).

Males were also shown to be a significant prognostic factor for 30-day mortality in one research done in Brazil (Adj. OR 5.85, 95% CI 1.19, 28.83) (Rodrigues *et al.*, 2019). This finding highlights the potential influence of sex-specific factors on outcomes, but further large-scale studies are warranted to confirm this association and to elucidate the underlying mechanisms. This gender disparity may stem from biological factors such as hormonal influences, as well as behavioural and environmental exposures that differ between males and females (Ivan et al., 2023). Populations in resource-limited settings often encounter significant barriers, including delayed diagnosis, inadequate laboratory infrastructure, and limited access to antifungal therapy, which can amplify the adverse effects of age and gender on IC prognosis (AlMaghrabi *et al.*, 2023).

2.3.2 Clinical Conditions

Recent research demonstrates that the clinical condition of patients, particularly immunocompromised individuals with multiple comorbidities, is a critical prognostic factor for mortality in IC. Moreover, the emergence of multidrug-resistant fungal strains and the complications associated with invasive medical devices underscores the urgent need for novel antifungal strategies and standardised diagnostic protocols (Kainz *et al.*, 2020).

One of the clinical conditions is neutropenia, which is associated with 30-day mortality (Adj. HR 3.28, 95% CI 1.69, 6.33), suggesting it may reflect a broader state of immunosuppression in these patients (Elbaz *et al.*, 2022). Neutropenia occurs when the patient have low numbers of circulating neutrophils (one type of white blood cell) responsible for immunity. Neutropenia is caused by blood malignancy (leukaemia), autoimmune disease, and malnutrition.

A study in China found that chronic renal disease(Adj. HR 2.02, 95% CI 1.23, 3.30) and patients on mechanical ventilation (Adj HR 1.95, 95% CI 1.31, 2.91) are associated with 28-day mortality in patients with IC (Zheng *et al.*, 2021). However, the association with mechanical ventilation may partly reflect overall disease severity rather than serving solely as an independent prognostic factor.

A study conducted in the Middle East revealed that critically ill patients requiring renal replacement therapy following an IC diagnosis faced significantly higher mortality risks (Adj. OR 5.42, 95% CI 2.16,13.56) (Al-Dorzi *et al.*, 2020). While these findings highlight the link between renal dysfunction and poor outcomes, it is important to note that the need for renal replacement therapy may serve as a

surrogate for severe multiorgan failure, and the observational design limits causal inference.

Another significant factor that predicts the 30-day mortality of IC patients is pre-existing heart disease (Adj. OR 11.55, 95% CI 2.53,52.66) (Rodrigues *et al.*, 2019). This 2019 study was conducted in Brazil and emphasises the critical impact of cardiovascular comorbidities on the outcomes of critically ill patients. The wide confidence interval is likely due to the relatively small number of patients with cardiovascular disease in the study.

Invasive candidiasis is particularly prevalent among critically ill patients, especially in ICU settings, where risk factors such as central venous catheterisation, prolonged broad-spectrum antibiotic use, and elevated Acute Physiology and Chronic Health Evaluation (APACHE) scores indicate severe illness. Additionally, recent abdominal surgery and significant trauma or burns further increase susceptibility to this life-threatening infection (Chow *et al.*, 2008; Kullberg & Arendrup, 2015).

Prolonged ICU stays are linked to an increased risk of invasive candidiasis (Soriano *et al.*, 2023). This relationship is likely driven by the cumulative impact of extended exposure to invasive procedures and broad-spectrum antibiotics, compounded by increased disease severity that makes critically ill patients more susceptible to fungal infections. This same study, which was conducted at a clinic in Barcelona, found that IC mortality rates are disproportionately higher among ICU patients than in general wards, further illustrating the critical impact of these conditions on patient outcomes.

In a retrospective study (2009–2016) conducted at a university hospital in Brazil, the use of corticosteroids among patients is associated with 30-day mortality