Survival Outcomes in Invasive Candidiasis: Exploring the Role of Chronic Disease Prevention and Healthy Lifestyle in Malaysia

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ABSTRACT

Invasive candidiasis (IC) is a life-threatening fungal infection, particularly prevalent among patients with non-communicable diseases (NCDs). The rising incidence of NCDs in Malaysia poses a significant challenge to IC management and patient survival. The objective of this study was to determine the median survival time of IC patients in Malaysia and explore the relationship between survival outcomes, and chronic disease prevention. This retrospective cohort study analyzed data from 445 patients diagnosed with IC at a tertiary hospital in Malaysia. Data on sociodemographics, comorbidities, clinical presentation, Candida species, treatment, and patient outcomes were collected and analyzed using Kaplan-Meier survival estimates. The median survival time for IC patients was 21 days, with significant variations based on age, ethnicity, and comorbidities. Patients with diabetes on insulin therapy exhibited a lower mortality risk, likely due to better glycemic control and higher health-seeking behavior. *Candida* parapsilosis infections were associated with higher survival rates, while *Candida glabrata* and *Candida tropicalis* infections were linked to poorer outcomes. These findings highlight the importance of tailored treatment strategies that consider patient comorbidities and the specific *Candida* species involved. Integrating preventive measures for NCDs and promoting healthy lifestyle practices are crucial for improving IC patient survival.

Keywords: Invasive Candidiasis, Survival, Non-communicable diseases

INTRODUCTION

Invasive candidiasis (IC) is a life-threatening fungal infection with poor survival outcomes, with mortality rates ranging from 29 to 75 percent(Pappas et al., 2018). It is particularly associated with high morbidity and mortality in individuals with immunosuppressive conditions and non-communicable diseases (NCDs) (Velayuthan et al., 2018). The impact of IC is further intensified by the increasing prevalence of NCDs, such as diabetes, cardiovascular disease, and renal disease, which weaken the immune

system and increase susceptibility to severe infections (Hsu et al., 2018). The interplay between IC and NCDs is complex, as NCDs not only predispose individuals to IC but also complicate its clinical management, leading to suboptimal treatment responses and ultimately poorer survival rates (Pappas et al., 2018).

The rising incidence of non-communicable diseases (NCDs) or lifestyle-related diseases in Malaysia presents a significant challenge in healthcare and raises concerns about its potential impact on IC patient outcomes (Ismail et al., 2024). Given the alarming 30-day mortality rates and the short median survival time for IC patients—ranging from three (3) to 30 days—there is an urgent need to explore and integrate more effective preventive and management strategies (Elbaz et al., 2022; Kutlu et al., 2022). Therefore, comprehensive strategies are critically needed that address not only the immediate treatment of IC but also focus on the prevention and management of underlying NCDs.

Healthy lifestyle practices, such as proper nutrition, regular physical activity, and stress management, have been shown to reduce the risk of NCDs, and improve their control, thereby enhancing overall immune function and potentially strengthening the body's natural defenses against infections (Khaw et al., 2023). The integration of these healthy lifestyle practices could play a pivotal role in both the prevention and management of IC, potentially improving survival outcomes.

This study aims to determine the median survival time for mortality among IC patients in Malaysia, with a particular focus on lifestyle-related diseases. By exploring the relationship between them, this research seeks to identify strategies that could enhance patient survival.

METHODS

Study Setting and Design

This retrospective cohort study utilized secondary data obtained from hospital patient records in Kedah State, Malaysia. The hospital, serving as a tertiary referral center for the state with more than two million population, offers a comprehensive range of services. Core areas include general medicine, surgery, obstetrics and gynecology, orthopedics, pediatrics, ophthalmology, otorhinolaryngology (ORL), and intensive care. Additionally, the hospital provides specialized care in infectious diseases, endocrinology, cardiology, nephrology, rheumatology, gastroenterology, hematology, and oncology, ensuring a multidisciplinary approach to patient care.

In this study, confirmed cases of IC admitted to the hospital from 2017 to 2023 were

extracted from the hospital's lab information system (LIS) database and then matched with electronic records of patient case notes.

Data collected included sociodemographic variables such as age, gender, ethnicity, and department. Risk factors recorded were diabetes mellitus (DM), respiratory disease, kidney diseases, solid tumors, cardiovascular disease (CVD), and cerebrovascular accident (CVA). The study also documented clinical factors, including presenting symptoms, the patient's previous medication, and the patient's status upon discharge. Microbiological and treatment-related data, including *Candida* species and duration of survival, were systematically captured.

Study Population and Sample Size

The study focuses on hospitalized patients diagnosed with IC using fungal blood cultures from 2017 to 2023. The research period spans from November 2023 to March 2024, with inclusion criteria for patients who tested positive for IC between January 1, 2017, and December 31, 2023. Exclusion criteria included patients with missing data, those under 18 years old, a recent history of IC within 30 days, and non-citizens.

Although the estimated sample size was 239, calculated using the single proportion formula based on an IC prevalence of 0.17, a confidence interval of 1.96, and a precision of 0.05 (with an additional 10% to account for incomplete data), all available samples were included in the study. This approach was possible because the study used secondary data, allowing the inclusion of the entire dataset without compromising the analysis's integrity. As a result, no sampling method was employed.

This study received approval from the Medical Research and Ethics Committee (NMRR ID-23-02219-UMZ (IIR)), the Ethics Committee for Research Involving Human Subjects at Universiti Putra Malaysia (JKEUPM-2022-1038), and the Human Research Ethics Committee (JePEM) of Universiti Sains Malaysia (USM/JEPeM/KK/23010104).

Study Instrument and Data Collection and Analysis

The study exclusively utilized patient case notes, with no direct involvement of patients. Initially, written authorization to access and use the data was obtained from the hospital’s director. Subsequently, a list of patients diagnosed with IC was provided by the hospital’s microbiology laboratory department. This list was then cross-referenced with hospitalized patient records to ensure data accuracy.

Data collection was systematically conducted using a standardized data proforma. The final line listing was securely stored in a password-protected Microsoft Excel file. Before

analysis, all duplicate entries were eliminated, and patient names and identification numbers were anonymized and coded to ensure confidentiality. This approach maintained strict adherence to ethical standards and safeguarded patient privacy throughout the research process.

A comprehensive range of *Candida* species was tested, including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and other species grouped under "others." The clinical condition, microbiological, and treatment-related data will be documented as categorical variables (yes/no). Duration of survival will be defined as the number of days from the date of the first positive specimen to the date of discharge/ death (within 30 days).

The data were analyzed using IBM SPSS Statistics for Windows, version 26. Descriptive statistics summarised key information about IC, with categorical data reported as frequencies and percentages. Kaplan-Meier survival estimates were employed to determine the median survival time for mortality among patients with IC.

RESULTS

Demographic

The study cohort had a median age of 58 years old, with a median length of stay of 24 days, and a slight predominance of male patients as shown in Table 1. Key risk factors identified included diabetes mellitus, kidney disease, and hypertension. High incidences of fever, septic shock, and gastrointestinal symptoms were prevalent among the patients. Nearly half of the patients succumbed within 30 days of admission.

Table 1. Sociodemographic, Risk Factors, and Presentation of patients (*n*=445)

Variables	*n* (%)	Censored *n* (%)	Dead *n* (%)
Age (Years)[1]	58 (41 – 66)	57.0 (37 – 64)	59 (46 – 68)
Age > 65			
Yes	124 (27.9)	55 (44.4%)	69 (55.6%)
No	321 (72.1)	179 (55.8%)	142 (44.2%)
Gender			
Female	198 (44.5)	105 (53.0)	93 (47.0)
Male	247 (55.5)	129 (52.2)	118 (47.8)
Received Treatment	328 (73.7)	192 (58.5)	136 (41.5)
Risk Factors			

Diabetes Mellitus (DM)	240 (53.9)	122 (50.8)	118 (49.2)
Insulin Use	56 (12.6)	39 (69.6)	17 (30.4)
Hypertension (HPT)	207 (46.5)	100 (48.3)	107 (51.7)
Respiratory Disease	61 (13.7)	26 (42.6)	35 (57.4)
Kidney Disease	147 (33.0)	80 (54.4)	67 (45.6)
Solid Tumor	47 (10.6)	23 (48.9)	24 (51.1)
Clinical Presentation			
Fever	192 (43.1)	125 (65.1)	67 (34.9)
Septic shock	308 (69.2)	124 (40.3)	184 (59.7)
Gastrointestinal Symptoms	53 (11.9)	24 (45.3)	29 (54.7)

Patients infected with *Candida parapsilosis* had the highest survival rate, with 77.9% censored (alive), while those with *Candida tropicalis* and *Candida glabrata* had the lowest survival rates, with 58.0% and 56.5% dead, respectively as shown in Table 2.

Table 2. Culture result of patients' specimens (n=445)

Variables	**n (%)**	**Censored n(%)**	**Dead n(%)**
Organism			
albican	102 (22.9)	46 (45.1)	56 (54.9)
tropical	162 (36.4)	68 (42.0)	94 (58.0)
parapsilosis	95 (21.3)	74 (77.9)	21 (22.1)
glabrata	69 (15.5)	30 (43.5)	39 (56.5)
Others	17 (3.8)	16 (94.1)	1 (5.9)

Kaplan–Meier analysis

The study's overall median survival time is 21 days (Figure 1). Survival times vary significantly by age. Patients under 65 have a median survival of 24 days, while those aged 65 and older have a median survival of 16 days as shown in Figure 2. Median survival times vary significantly by organism, with *C. albicans* at 21 days, *C. tropicalis* at 13 days, and *C. glabrata* at 15 days (Figure 3).

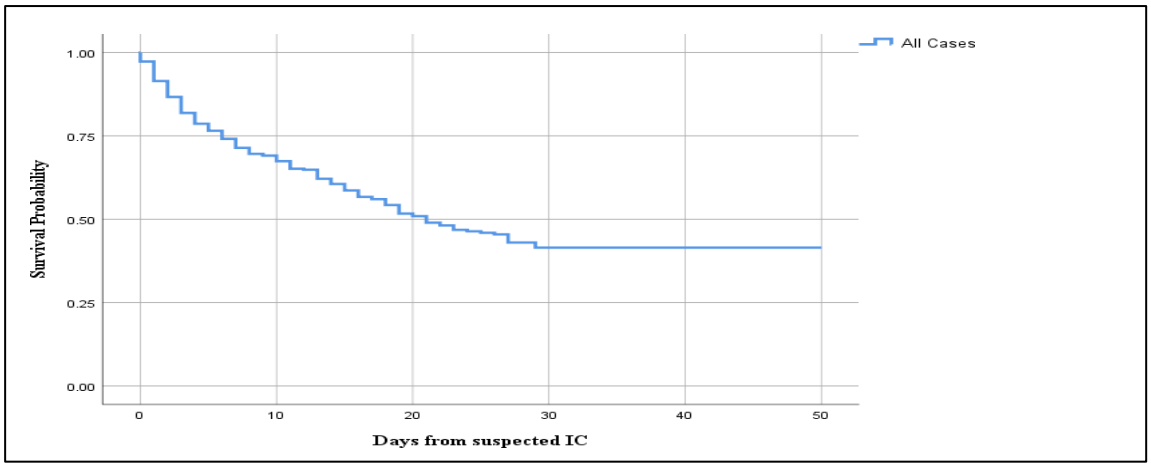

Figure 1: . Survival probabilities of overall IC patients.

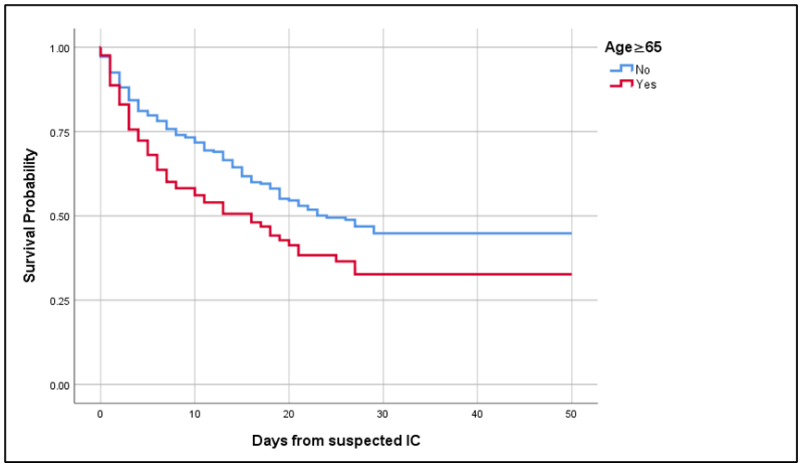

Figure 2: . Survival probability patient age ≥ 60 years old (*p*-value <0.05)

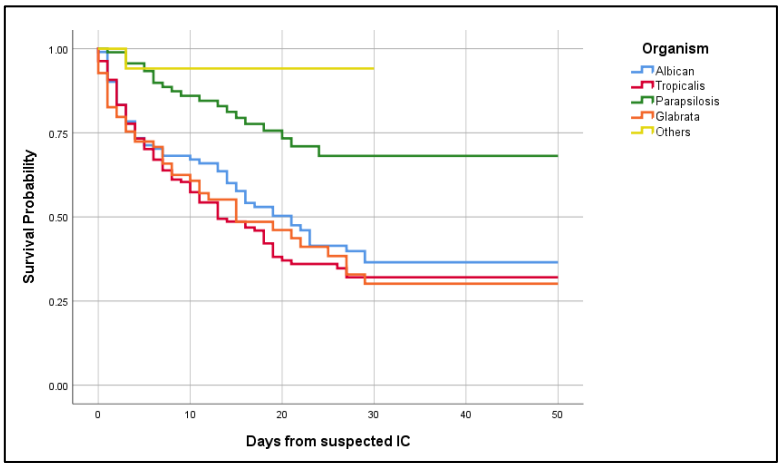

Figure 3: Survival probability based on *Candida* species (*p*-value <0.05

Several clinical factors influenced survival outcomes. Diabetic patients had a median survival of 21 days, slightly less than the 22 days observed in non-diabetic patients

(Figure 4). Patients on insulin were found to have better survival time compared to patients not on insulin (Figure 5). Hypertension was associated with poorer survival outcomes, with a median survival time of 16 days (Figure 6). Similarly, respiratory disease was linked to a median survival of 18 days, compared to 22 days for those without such conditions (Figure 7).

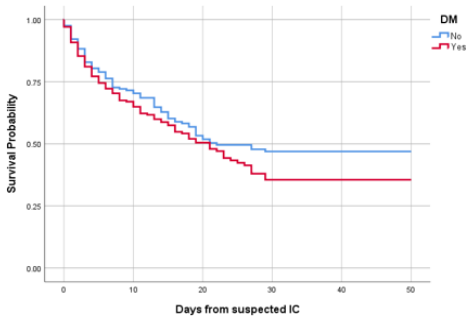

Figure 4: Survival probability of diabetic patients (p-value >0.05)

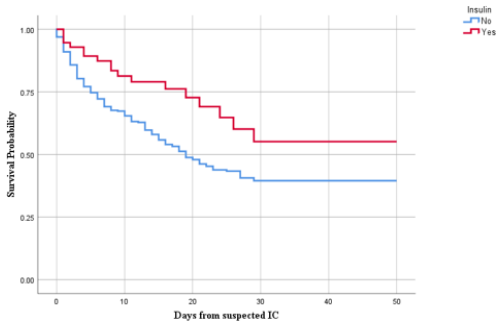

Figure 5: Survival probability of patients on insulin (p-value <0.05).

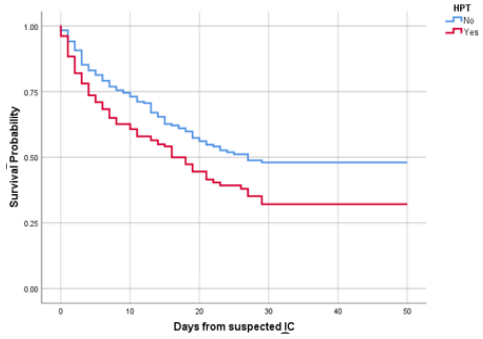

Figure 6: Survival probability of hypertension patients (p-value <0.05).

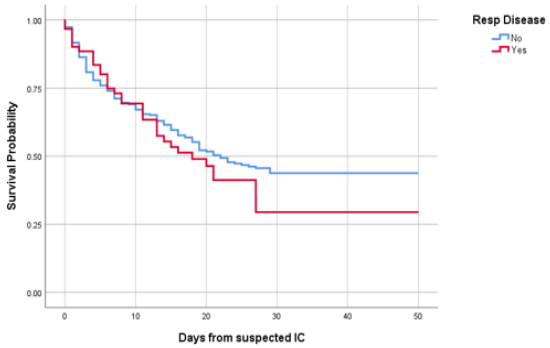

Figure 7: Survival probability of respiratory disease patients (p-value >0.05).

Patients presenting with fever showed a survival advantage shown in Figure 8. Septic shock was associated with a notably lower median survival of 16 days compared to higher survival times in those without septic shock (Figure 9). Patients with gastrointestinal symptoms had lower survival rates compared to those without(Figure 10). Untreated patients had a median survival of just 3 days, while treated patients showed a median survival of 27 days (Figure 11).

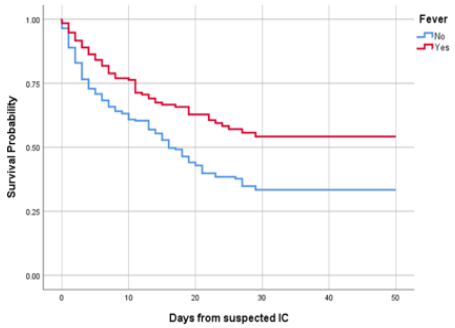

Figure 8: Survival probability patients presented with fever (*p*-value <0.05)

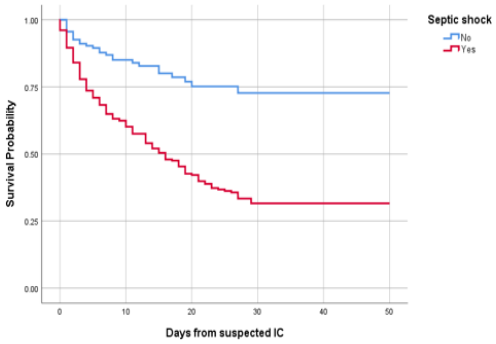

Figure 9: Survival probability of patients with septic shock (*p*-value <0.05).

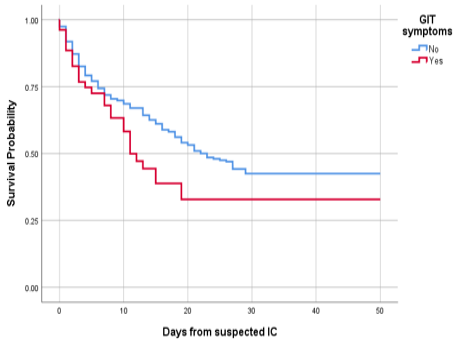

Figure 10: Survival probability of patients with GIT symptoms (*p*-value >0.05).

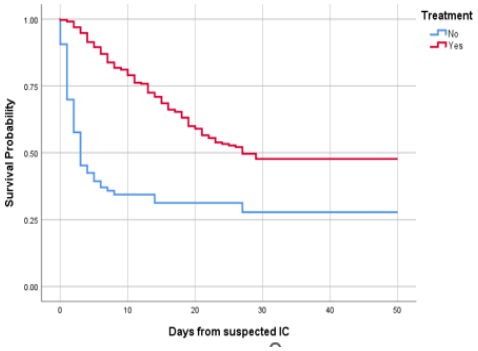

Figure 11: Survival probability of patients who underwent treatment for IC (*p*-value <0.05)

DISCUSSION

Median survival of 21 days reflects the serious nature and high mortality risk of invasive candidiasis, underscoring its severity compared to other high-mortality diseases. This short survival time indicates a significant disease burden, placing substantial strain on healthcare resources and highlighting the crucial need for early diagnosis and prompt, effective treatment to improve outcomes and extend survival.

Patient demographic

Younger patients (under 65) showed better median survival compared to 16 days for those 65 and older, which likely reflects the generally stronger immune systems and fewer comorbidities in younger individuals, consistent with existing literature on fungal infections, making the older population relatively vulnerable to severe infections and

complications (Gong et al., 2020; Hohmann et al., 2023).

Patients clinical conditions

The Kaplan-Meier survival plots clearly illustrate that diabetes and hypertension are associated with poorer prognosis in IC patients. This is consistent with the understanding that diabetes mellitus impairs phagocytic activity and alters cytokine production, which are crucial for effective immune responses against fungal infections (Nyunt et al., 2020). Diabetic patients are more susceptible to severe infections due to compromised immune function and other related complications such as kidney disease and other end-organ damage, which could explain the lower survival rates observed (Geerlings & Hoepelman, 1999). Moreover, patients with cardiovascular disease or renal impairment often require multiple medications, some of which may interact with antifungal agents, leading to reduced efficacy or risk of drug toxicity (Ghezzi et al., 2020). While the difference in median survival times between diabetic and non-diabetic patients is modest, the overall trend suggests that diabetes contributes to a decreased survival probability.

The median mortality time was reduced in patients receiving insulin therapy before IC, as reflected in the higher survival probability of this group over time. This is likely due to their overall better health-seeking behavior. Patients on insulin therapy generally exhibit greater engagement in managing their diabetes, adhering to a regimen that requires regular injections, frequent blood glucose monitoring, and clinic follow-ups (Roberts et al., 2021). This proactive approach not only enhances their ability to manage diabetes but also prepares them to handle critical health conditions such as IC. By complying with insulin therapy, these patients ensure that their blood sugar levels remain under control, preventing complications like diabetic ketoacidosis, which can further weaken the immune system and exacerbate infections.

The improved survival outcomes seen in the insulin-treated group may be attributed to insulin's critical role in glycemic control. Proper blood sugar regulation helps to prevent conditions associated with diabetes, such as microvascular damage and immune dysfunction, both of which can worsen the prognosis of infections like IC (Nyunt et al., 2020). Patients with better-controlled diabetes are less likely to experience hyperglycemia-related complications, which not only strengthens their immune response but also reduces the severity of the infection(Chávez-Reyes et al., 2021). Consequently, patients receiving insulin therapy have a better chance of surviving IC due to their enhanced ability to manage diabetes and avoid life-threatening complications related to both their chronic condition and the infection itself.

Hypertension is a major risk factor that complicates infectious diseases by straining the cardiovascular system and weakening the immune response, making infections more severe. These comorbidities create a challenging clinical scenario that can lead to shorter survival times due to compounded health issues and treatment complexities (Zhang et al., 2023).

Patients presented with fever had significantly higher survival rates compared to those without fever. The absence of fever might delay the suspicion and diagnosis of IC, allowing the infection to worsen before treatment begins, leading to poorer outcomes (Ghrenassia et al., 2019). This finding reinforces the importance of early symptom recognition and suggests that even subtle clinical signs should not be overlooked in at-risk populations.

Microbiological and Treatment-Related Outcomes

The differences in *Candida* species reveal significant variations in patient survival outcomes. *Candida albicans*, the most common species associated with IC, exhibited survival outcomes in line with the overall median survival of IC patients. Patients infected with *Candida parapsilosis* showed the highest survival probability over time, suggesting it may have a less aggressive infection profile or be more easily managed (Horn et al., 2010). The poor outcomes in *Candida glabrata* cases may be attributable to its known resistance to common antifungal treatments, complicating management and reducing treatment efficacy (Soriano et al., 2023). Similarly, the lower median survival time in *Candida tropicalis* cases is likely due to its ability to cause severe systemic infections that are less responsive to standard therapies (Keighley et al., 2024). These species-specific differences emphasize the necessity for precise identification and tailored treatment strategies based on the infecting species.

Antifungal treatment has a significant impact on survival outcomes for patients with IC. There is a notable difference in median survival time between those who received antifungal therapy (27 days) and those who did not (3 days). The sharp decline in survival probability among untreated patients highlights the aggressive nature of IC and underscores the critical importance of timely intervention. Without any antifungal therapy, the infection can progress rapidly, resulting in substantially higher mortality rates (Cahan & Deville, 2011).

This finding is consistent with studies advocating for early and precise antifungal interventions to improve survival probability (Kanj et al., 2022). This highlights the need for healthcare providers to maintain a high level of vigilance for IC, ensuring that

treatment is initiated as soon as the infection is suspected. Delays in treatment significantly lower survival probabilities, making early diagnosis and rapid test results crucial for timely Intervention to prevent infection progression, reduce the risk of complications, and ultimately decrease mortality rates.

CONCLUSION

The study highlights the severe nature of IC, with a median survival time of just 21 days, emphasizing the importance of early diagnosis and timely treatment. The data provides valuable insights into the factors influencing survival outcomes in patients with invasive candidiasis (IC) within a Malaysian hospital setting. Key factors identified include advanced age, specific *Candida* species, and the presence of comorbidities like diabetes and hypertension, all of which are associated with poorer survival outcomes. These findings underscore the need for tailored treatment strategies that address these variables to enhance patient survival.

Recommendations

Based on these findings, healthcare providers must prioritize early detection and immediate initiation of antifungal therapy, especially in high-risk patients. Implementing species-specific management strategies alongside effective comorbidity management and targeted interventions in critical care could significantly improve patient outcomes. Additionally, promoting preventive measures for NCDs, such as encouraging healthy lifestyle practices that maintain good overall health and organ function, is crucial. These strategies, if adopted, could lead to better survival rates and an improved quality of life for IC patients.

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