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Epidemiology and risk factors of fungal pathogens in sepsis: a prospective nationwide multicenter cohort study

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Abstract

Background The incidence of sepsis with identified fungal pathogens is increasing and is associated with higher morbidity and mortality. Co-infection with fungal infections in COVID-19 patients is attracting clinical attention. This study examines the epidemiology, risk factors, and outcomes among sepsis patients with identified fungal pathogens.

Methods We conducted a nationwide cohort study of adult patients with sepsis from the Korean Sepsis Alliance Database in South Korea between September 2019 and December 2021. We identified 407 patients with documented fungal pathogens, categorized according to the presence of hemato-oncologic malignancies.

Results Of the 11,981 patients with sepsis, fungal pathogens were identified in 3.4% of cases. Among these patients, 38.3% had co-existing hematologic or solid organ cancer. Older age, higher clinical frailty scale scores, and underlying conditions, such as chronic kidney disease, cerebrovascular disease, and dementia, were more prevalent in patients without hemato-oncologic malignancies. The most common fungal pathogens were *Candida albicans* (47.9%), *Candida glabrata* (20.6%), and *Candida tropicalis* (13.5%). Only 6.6% of the patients with confirmed fungal pathogens received antifungal treatment. The presence of hemato-oncologic malignancies did not significantly affect patient outcomes. Factors associated with the presence of identified fungal pathogens included chronic kidney disease (Odds ratio [OR] 1.662; 95% confidence interval [CI] 1.216–2.273; $p=0.001$), connective tissue disease (OR 1.885; 95% CI 1.058–3.358; $p=0.032$), immunocompromised status (OR 2.284; 95% CI 2.186–3.753; $p=0.001$), and invasive mechanical ventilation (OR 2.864; 95% CI 2.186–3.753; $p<0.001$).

Conclusions Sepsis identified fungal pathogen are associated with chronic kidney disease, immunocompromised status and other risk factors, demonstrating the need for early detection, targeted management and improved antifungal strategies to improve patient outcomes.

Keywords Disease, Fungus, Epidemiology, Sepsis

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Introduction

Sepsis, a life-threatening condition caused by an infection, remains a major challenge for the healthcare community. Sepsis can also be caused by fungal pathogens, which are known to be associated with high morbidity and mortality [1, 2]. The incidence of fungal sepsis is higher than expected, particularly in certain high-risk populations [3, 4]. These issues have been further highlighted in the context of the COVID-19 pandemic [5–7], where co-infections, including those caused by fungal pathogens, have emerged as a serious concern.

The causes and risk factors for fungal infections in sepsis are diverse and complex [8]. *Candida* and *Aspergillus species* are among the most identified fungal pathogens in patients [4, 9, 10]. While hematologic malignancies and immunocompromised states are well-established risk factors [11, 12], there is growing recognition that non-traditional factors such as older age, intensive care unit (ICU) admission, frailty, and chronic comorbidities (e.g., kidney disease and diabetes) also contribute to the development and outcome of fungal infections [13].

Therefore, a better understanding of the epidemiology of sepsis associated with fungal organisms is needed. This includes identifying the most common fungal pathogens, understanding their distribution in different patient populations, and recognizing the factors that contribute to their presence and their impact on patient outcomes. Rather than distinguishing between fungal sepsis and fungal colonization, this study aims to describe the characteristics of sepsis patients in whom fungal pathogens have been identified. Using a large multicenter cohort from the Korean Sepsis Alliance database, this study examines the prevalence and types of fungal pathogens detected in sepsis patients and explores the risk factors associated with fungal pathogen detection and their potential influence on patient prognosis.

Materials and methods

Adult patients (aged ≥ 19 years) who met the diagnostic criteria for sepsis and septic shock, as defined by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), were prospectively identified and enrolled in the Korean Sepsis Alliance national multicenter registry between September 2019 and December 2021. The study was conducted at 20 tertiary and university hospitals in South Korea, all of which had established sepsis education programs. To ensure data accuracy and quality, the research team at Asan Medical Center, Seoul, conducted regular audits.

The study was approved by the institutional review board (IRB) of each participating hospital, including Chungnam National University Hospital (IRB No. 2019–11-048). Given the observational nature of the study, which involved standard data collection with minimal risk and no interventions, the requirement for informed consent was waived.

Data recruitment and definition

All patients admitted to a general ward or emergency department during the study period were screened for eligibility. Sepsis was diagnosed when the following criteria were met: 1) a probable or confirmed diagnosis of infection, and 2) a change in the total Sequential Organ Failure Assessment (SOFA) score of 2 or more since infection. Septic shock was characterized by persistent arterial hypotension, requiring vasopressors to maintain a mean arterial pressure greater than 65 mmHg and a serum lactate level greater than 2 mmol/L, despite adequate fluid resuscitation. The patients were followed up until death or discharge. The data were prospectively collected by the study coordinator at each participating center using an electronic case report form (http://sepsis.crf.kr/). The collected information included demographic data, such as age, sex, and comorbidities; disease severity (SOFA score and hemodynamic and laboratory variables at baseline); source and type of infection; positive culture results; treatment, including ICU admission; and outcome data, including ICU- and 28-day mortality. For patients admitted to the ICU, we assessed medical events and medical resource use during the ICU stay.

Patients with hemato-oncologic malignancies were defined as those patients with an underlying hematologic malignancy (leukemia, lymphoma, multiple myeloma, etc.) and/or solid cancers (breast, colon, lung, prostate, and skin). Sepsis identified fungal pathogens was defined as cases in which a fungal pathogen was identified by at least one of the following diagnostic methods: culture, polymerase chain reaction (PCR), or antigen (Ag) testing. Culture-based methods were used to isolate fungal species from clinical specimens, while PCR was used to detect fungal deoxyribo nucleic acid in patient samples. In addition, antigen tests, such as β-D-glucan or galactomannan assays, were used to aid in the identification of fungal pathogens. Diagnostic tests were included in the analysis if they were performed within 48 h before or after the onset of sepsis to ensure their relevance to the acute phase of sepsis. These diagnostic methods were routinely performed as part of standard clinical practice at the participating hospitals, and the results were extracted from the medical records for analysis.

Statistical analysis

All statistical analyses were performed using SPSS version 25 software (IBM Corp., Armonk, NY, USA). Categorical variables are represented as numbers with percentages, and continuous variables are represented as means with

standard deviations. The Student's t-test or Mann–Whitney U test was used to compare continuous variables, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. A logistic regression analysis was performed to evaluate the factors associated with fungal infections, and all sepsis data were used to evaluate the factors associated with the identification of fungal pathogens. A Cox regression analysis was performed to assess the factors associated with mortality. Factors with a p-value < 0.05 in the univariate analysis were identified and included in the multivariate analysis. The risk factors for fungal infection are presented as odd ratio (OR) and 95% confidence interval (CI), and factors associated with mortality are represented as hazard ratio (HR) and 95% CI. The statistical significance was defined as $p < 0.05$.

Results

Basic characteristics of the study population

Among the 11,981 patients with sepsis, we analyzed 407 (3.4%) patients in whom a fungal pathogen was identified, excluding the remaining 11,574 patients with no detected fungal pathogens (Fig. 1). Of these, 251 (61.7%) patients had no hematological malignancies or solid tumors, and 156 (38.3%) patients had hematological malignancies and/or solid tumors.

The baseline patient characteristics are shown in Table 1. Patients with non-hemato-oncologic malignancies were older (72.7 ± 13.7 vs. 67.7 ± 13.0, years, $p < 0.001$), had a lower Charlson comorbidity index (5.0 [4.0–6.0] vs. 7.0 [6.0–10.0], $p < 0.001$), and had a higher clinical frailty scale (6.0 [4.0–7.0] vs. 5.5 [3.0–7.0], $p = 0.016$) compared to those in patients with hemato-oncologic malignancies. Chronic kidney disease (24.7% vs. 13.5%, $p = 0.006$), cerebrovascular disease (23.9% vs. 12.2%, $p = 0.004$), and dementia (19.5% vs. 7.7%, $p = 0.001$) were more common in patients with non-hemato-oncologic malignancies than in patients with hemato-oncologic malignancies.

Pathogens and antifungal agents in sepsis

Table 2 (Fig. 2) shows the fungal pathogens identified in patients with sepsis and the antifungal agents used. The most common fungal pathogens identified were *Candida albicans* (47.9%), *Candida glabrata* (20.6%), *Candida tropicalis* (13.5%), *Pneumocystis jirovecii* (7.9%), and *Aspergillus* (3.7%). No statistically significant differences exist in the fungal pathogens between the two groups. Antifungal agents were used in 6.6% of the patients. No differences exist in the antifungal agents between the two groups, except that echinocandins were more commonly used in patients with hemato-oncologic malignancies than in patients with non-hemato-oncologic diseases (3.2% vs. 0.4%, $p = 0.022$).

Primary sites of infection and culture sites

Additional Table 1 presents the primary sites of infection and culture results. Pulmonary infections were more frequently observed in patients with non-hemato-oncologic malignancies, whereas abdominal and catheter-related infections were more prevalent in those with hemato-oncologic malignancies. With regard to culture results, sputum samples were collected more frequently in patients with non-hemato-oncologic malignancies,

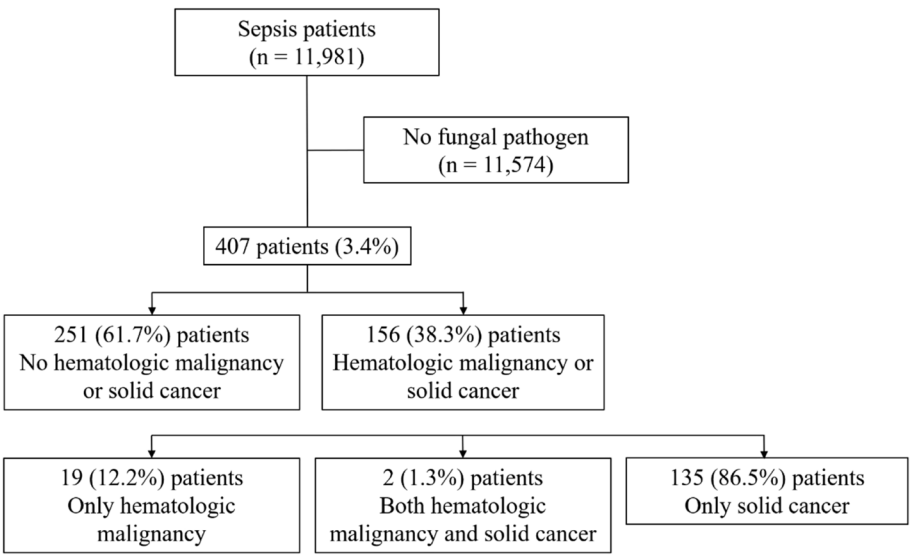

Fig. 1 Flowchart of enrolled patients

Table 1 Baseline characteristics of enrolled patients

Characteristics	All patients	Non-hemato-oncologic patients	Hemato-oncologic patients	*P*-value
Patients (n)	407	251	156	
Age, yr	70.8 ± 13.6	72.7 ± 13.7	67.7 ± 13.0	< 0.001
Male	213 (52.3)	129 (51.4)	84 (53.8)	0.630
Body mass index, kg/m^2	21.8 ± 4.2	21.7 ± 4.4	22.0 ± 3.9	0.493
Charlson comorbidity index	6.0 (4.0 – 7.0)	5.0 (4.0 – 6.0)	7.0 (6.0 – 10.0)	< 0.001
Clinical frailty scale	6.0 (4.0 – 9.0)	6.0 (4.0 – 7.0)	5.5 (3.0 – 7.0)	0.016
SOFA score	6.0 (4.0 – 9.0)	6.0 (4.0 – 9.0)	6.0 (4.0 – 9.0)	0.430
Underlying disease				
Diabetes Mellitus	172 (42.3)	107 (42.6)	65 (41.7)	0.848
Chronic kidney disease	83 (20.4)	62 (24.7)	21 (13.5)	0.006
Chronic liver disease	44 (10.8)	23 (9.2)	21 (13.5)	0.175
Heart failure	28 (6.9)	20 (8.0)	8 (5.1)	0.271
Chronic obstructive lung disease	40 (9.8)	29 (11.6)	11 (7.1)	0.138
Cerebrovascular disease	79 (19.4)	60 (23.9)	19 (12.2)	0.004
Dementia	61 (15.0)	49 (19.5)	12 (7.7)	0.001
Connective tissue disease	19 (4.7)	14 (5.6)	5 (3.2)	0.270
Laboratory findings				
White blood cell, × 10^3/uL	10.35 (6.25 – 16.48)	11.10 (7.68 – 16.78)	8.63 (3.35 – 15.98)	0.006
Hemoglobin, g/dL	10.2 ± 2.4	10.5 ± 2.5	9.8 ± 1.9	0.001
Platelet, × 10^3/uL	154.0 (74.8 – 250.3)	172.0 (95.0 – 269.3)	134.0 (57.0 – 203.0)	0.001
Total bilirubin, mg/dL	0.8 (0.5 – 1.6)	0.7 (0.5 – 1.3)	1.0 (0.6 – 1.8)	0.291
Albumin, g/dL	2.6 ± 0.6	2.8 ± 0.6	2.5 ± 0.6	< 0.001
Creatinine, mg/dL	1.36 (0.81 – 2.15)	1.41 (0.81 – 2.38)	1.30 (0.80 – 1.92)	0.015
CRP, ng/mL	10.67 (4.50 – 18.02)	10.26 (4.11 – 18.14)	11.51 (5.11 – 18.21)	0.439
Lactate, mmol/L	2.4 (1.5 – 4.8)	2.2 (1.3 – 4.1)	3.4 (1.9 – 5.4)	0.028

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated

APACHE II Acute physiology and chronic health evaluation, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CRP* C-reactive protein

while blood, bile, and ascitic fluid cultures were collected more frequently in patients with hemato-oncologic malignancies.

Patient outcomes and management in the ICU

The patient outcomes and management in the ICU are shown in Table 3. ICU admission was more common in patients with non-hemato-oncologic malignancies than in patients with hemato-oncologic malignancies (61.8% vs. 48.1%, $p = 0.007$). Otherwise, there were no statistically significant differences in the outcomes or ICU management between the two groups.

Factors related to patients with identified fungal pathogens

The factors that were associated with patients in whom fungal pathogens were identified are shown in Table 4. In multivariate analysis, the factors that were associated with identified fungal pathogen in septic patients included chronic kidney disease (OR 1.662; 95% CI 1.216–2.273; $p = 0.001$), connective tissue disease (OR 1.885; 95% CI 1.058–3.358; $p = 0.032$), immunocompromised patients (OR 2.284; 95% CI 2.186–3.753; $p = 0.001$), and use of invasive mechanical ventilation (OR 2.864; 95% CI 2.186–3.753; $p < 0.001$).

Factors associated with the outcome of patients

The factors associated with in-hospital mortality are shown in Additional Table 2. In the multivariate analysis, older age (HR 1.016; 95% CI 1.000–1.032; $p = 0.055$), higher clinical frailty scale score (HR 1.253; 95% CI 1.131–1.388; $p < 0.001$), higher SOFA score (HR 1.104; 95% CI 1.049–1.163; $p < 0.001$), and higher laboratory lactate level (HR 1.073; 95% CI 1.028–1.120; $p = 0.001$) were associated with in-hospital mortality.

The factors associated with ICU mortality are shown in Additional Table 3. In multivariate analysis, higher SOFA scores, underlying hematological malignancy, a higher laboratory lactate level, and the implementation of CRRT in the ICU were associated with ICU mortality.

Table 2 Pathogen and antifungal agents in enrolled patient cohort

Characteristics	All patients	Non-hemato-oncologic patients	Hemato-oncologic patients	*P*-value
Pathogens				
Candida albicans	195 (47.9)	123 (49.0)	72 (46.2)	0.576
Candida glabrata	84 (20.6)	48 (19.1)	36 (23.1)	0.338
Candida parasilosis	11 (2.7)	5 (2.0)	6 (3.8)	0.262
Candida tropocalis	55 (13.5)	31 (12.4)	24 (15.4)	0.384
Candida krusei	4 (1.0)	3 (1.2)	1 (0.6)	0.582
Other candida	14 (3.4)	10 (4.0)	4 (2.6)	0.445
Cryptococcus neoformans	4 (1.0)	4 (1.6)	0 (0)	0.113
Aspergillus spp.	15 (3.7)	10 (4.0)	5 (3.2)	0.685
Pneumocystis jirovecii	32 (7.9)	20 (8.0)	12 (7.7)	0.920
aOther fungus	24 (5.9)	15 (6.0)	9 (5.8)	0.931
Antifungal agents	27 (6.6)	15 (6.0)	12 (7.7)	0.499
Fluconazole	6 (1.5)	4 (1.6)	2 (1.3)	0.800
Amphotericin B	1 (0.2)	1 (0.4)	0 (0)	0.430
Voriconazole	1 (0.2)	1 (0.4)	0 (0)	0.430
Echinocandin	6 (1.5)	1 (0.4)	5 (3.2)	0.022
TMP/SMX	13 (3.2)	8 (3.2)	5 (3.2)	0.992

[a] Trichosporon asahii, Rhizopus spp, Paecilomyces variotii, Fungus species; Yeast form, Paecilomyces variotii

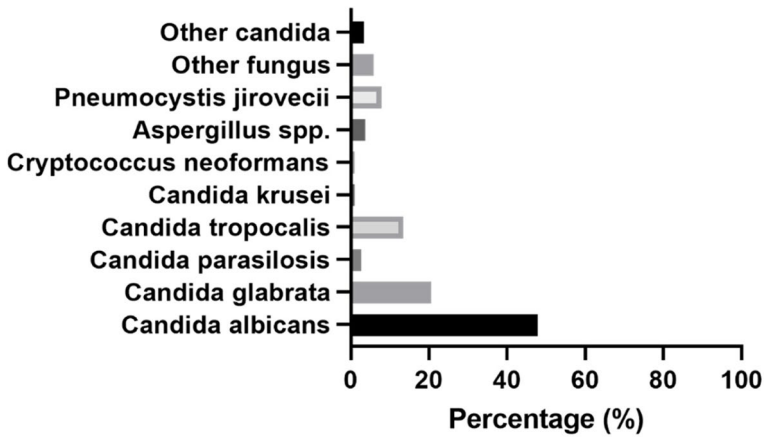

Fig. 2 Distribution of identified fungal pathogens

Discussion

In our study, fungal pathogens were identified in 3.4% of sepsis patients. Our analysis showed that conditions such as chronic kidney disease, cerebrovascular disease, and immunosuppressive status in patients with non-hemato-oncologic diseases influenced the susceptibility to fungal pathogens in sepsis. In addition, older age, high frailty, high SOFA scores, and high lactate levels influenced the patient outcomes. This highlights the need for a personalized approach to the management of septic patients with identified fungal pathogen, considering their different clinical backgrounds.

Fungal infections predominantly affect patients with compromised immune systems [8, 14]. As a result, individuals with hematologic malignancies [15, 16], transplant recipients [17, 18], and individuals with immunodeficiencies [12] are at increased risk. In this study, we examined the identification of the fungal pathogens in patients with and without hemato-oncologic malignancies and identified the types of fungi present and their distribution in these patient groups. Patients with non-hemato-oncologic malignancies were typically older and frailer and more commonly had comorbidities such as chronic kidney disease, cerebrovascular disease, and

Table 3 Outcomes and interventions of the patients

Characteristics	All patients	Non-hemato-oncologic patients	Hemato-oncologic patients	*P*-value
Vasopressors	195 (47.9)	127 (50.6)	68 (43.6)	0.169
Norepinephrine	195 (47.9)	127 (50.6)	68 (43.6)	0.169
Epinephrine	41 (10.1)	21 (8.4)	20 (12.8)	0.147
Vasopressin	86 (21.1)	47 (18.7)	39 (25.0)	0.132
Dopamine	17 (4.2)	14 (5.6)	3 (1.9)	0.073
Inotropic	22 (5.4)	17 (6.8)	5 (3.2)	0.122
Dobutamine	21 (5.2)	16 (6.4)	5 (3.2)	0.160
Transfusion	140 (34.4)	92 (36.7)	48 (30.8)	0.224
Antibiotics	406 (99.8)	250 (99.6)	156 (100.0)	0.999
Steroid	98 (24.1)	64 (25.5)	34 (21.8)	0.396
Admission to the ICU	230 (56.5)	155 (61.8)	75 (48.1)	0.007
Interventions in the ICU ($n=230$)				
Invasive mechanical ventilation	164 (71.3)	111 (71.6)	53 (70.7)	0.882
NIV	20 (8.7)	16 (10.3)	4 (5.3)	0.208
HFNC	81 (35.2)	49 (31.6)	32 (42.7)	0.100
Continuous renal replacement therapy	83 (36.1)	59 (38.1)	24 (32.0)	0.369
ECMO	11 (4.8)	7 (4.5)	4 (5.3)	0.785
Hemodialysis	15 (6.5)	8 (5.2)	7 (9.3)	0.230
Tracheostomy	27 (11.7)	18 (11.6)	9 (12.0)	0.932
Clinical outcomes				
ICU mortality	69 (30.0)	49 (31.6)	20 (26.7)	0.443
ICU stay, days	7.0 (3.0 – 15.0)	8.0 (4.0 – 15.0)	6.0 (3.0 – 12.0)	0.849
In-hospital mortality	160 (39.3)	95 (37.8)	65 (41.7)	0.443
Hospital stay, days	19.0 (10.0 – 39.5)	18.0 (10.0 – 36.3)	21.0 (11.0 – 44.0)	0.751

Data are presented as median and interquartile range or number (%), unless otherwise indicated

ICU intensive Care Unit, *HFNC* high flow nasal cannula, *ECMO* extracorporeal membrane oxygenation

dementia. Several studies have investigated fungal infections in patients without hematological diseases. These studies provided information on the prevalence, risk factors, and outcomes of fungal infections in this specific patient population. In addition, these studies have identified additional risk factors for fungal infections, including old age [19], immunocompromised state [8], ICU admission [13, 20], the presence of indwelling catheters [21], high acute physiology and chronic health evaluation score II [1, 13], and underlying medical conditions [12, 22], such as liver cirrhosis [23], chronic kidney disease [24], and chronic obstructive pulmonary disease [25]. Solid organ transplant recipients are at increased risk for Candida infections, including urinary tract candidiasis, peritonitis, intra-abdominal candidiasis, and candidemia [26]. Furthermore, the emergence of fluconazole-resistant Candida species highlights the importance of early identification, susceptibility testing, and antifungal stewardship to optimize treatment outcomes [26]. However, the lack of molecular characterization and antifungal susceptibility testing in our data set limits our ability to assess emerging Candida species and antifungal resistance patterns. Future studies incorporating these elements would provide a more detailed epidemiologic and clinical understanding of fungal infections in critically ill patients. Despite these limitations, our findings expand the understanding of fungal infections beyond traditionally recognized high-risk groups. The identification of fungal pathogens in sepsis patients, regardless of hematologic malignancy status, underscores the importance of early detection, risk stratification, and tailored antifungal therapy in critically ill patients. A more standardized approach to diagnostic testing and resistance monitoring is needed to improve clinical decision-making and patient outcomes in this population.

In this study of sepsis patients, the most commonly identified fungal pathogens were *Candida species,* followed by *Pneumocystis jirovecii* and *Aspergillus species*. These findings are consistent with previous studies and indicate a consistent pattern of fungal pathogen prevalence in critically ill patients. A study by Montagna et al. reported an overall incidence of invasive fungal infections

Table 4 Univariate and multivariate logistic analysis of factors associated with identified fungal pathogens

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age, yr	0.997	0.990 – 1.004	0.445			
Male	1.248	1.024 – 1.521	0.028	1.256	0.967 – 1.631	0.088
Body mass index, kg/m^2	0.999	0.975 – 1.023	0.917			
Charlson comorbidity index	1.049	1.010 – 1.089	0.013	0.991	0.938 – 1.048	0.760
Clinical frailty scale	1.075	1.025 – 1.127	0.003	1.036	0.974 – 1.103	0.258
SOFA score	1.050	1.018 – 1.082	0.002	0.996	0.956 – 1.038	0.855
Underlying disease						
Diabetes Mellitus	1.387	1.135 – 1.695	0.001	1.185	0.909 – 1.545	0.209
Chronic kidney disease	1.796	1.402 – 2.300	< 0.001	1.662	1.216 – 2.273	0.001
Hematologic malignancy	0.815	0.522 – 1.273	0.369			
Solid cancer	0.900	0.730 – 1.109	0.323			
Chronic obstructive lung disease	1.605	1.148 – 2.243	0.006	1.521	0.969 – 2.388	0.068
Connective tissue disease	1.815	1.130 – 2.917	0.014	1.885	1.058 – 3.358	0.032
Immunocompromised	2.739	1.835 – 4.087	< 0.001	2.284	2.186 – 3.753	0.001
Interventions in the ICU						
Steroid	1.739	1.378 – 2.195	< 0.001	1.150	0.859 – 1.540	0.347
Invasive mechanical ventilation	2.895	2.214 – 3.785	< 0.001	2.864	2.186 – 3.753	< 0.001
Continuous renal replacement therapy	1.772	1.352 – 2.324	< 0.001	1.063	0.786 – 1.439	0.692

SOFA sequential organ failure assessment, *ICU* intensive care unit, *OR* odd ratio, *CI* confidence interval

of 18.9 cases per 1,000 ICU admissions, with yeasts and molds accounting for 87.6% and 12.4% of cases, respectively [27]. Similarly, Lehrnbecher et al. identified *Candida* and *Aspergillus species* as the most common fungal pathogens in a university hospital setting [28]. In patients with hematologic malignancies, *Aspergillus non-fumigatus* was the most common cause of invasive aspergillosis, followed by candidemia and mucormycosis [29]. Another study by Rayens et al. reported that infections caused by *Aspergillus, Pneumocystis,* and *Candida species* accounted for 76.3% of diagnosed fungal infections and 81.1% of associated healthcare costs [3].

Fungal infections in sepsis patients often originate from different anatomical sites, reflecting their ability to disseminate systemically. In our study, the most common culture sites for fungal pathogens were sputum, urine and blood, similar to previous findings. The lungs are frequently identified as the primary site of fungal infection [28, 30], while the bloodstream is an emerging site of systemic fungal infection, particularly in hospitalized patients with central venous catheters or those receiving parenteral nutrition [31, 32].

According to our analysis, patients with non-hematologic malignancies were more likely to be admitted to the ICU than patients with hematologic malignancies. This suggests that a significant burden of sepsis in this population is associated with fungal pathogens. This finding is consistent with previous studies reporting that ICU admission, mechanical ventilation, hemodialysis, central venous catheterization, and prolonged ICU stay are associated with an increased risk of fungal infections [1, 2, 13, 33–35]. However, beyond ICU admission rates, we did not observe significant differences in clinical outcomes or ICU management strategies between the two groups. This finding suggests a consistent approach to sepsis management across patient demographics, despite differences in underlying conditions. Several studies have examined fungal infections in non-haematological patients, providing insight into prevalence, risk factors, and clinical outcomes. A meta-analysis of candidemia cases in Iran identified surgery, malignancy, and broad-spectrum antibiotic use as major risk factors for fungal infections. *Candida parapsilosis* (30.8%) was the predominant species, followed by *Candida albicans* (27.3%) and *Candida glabrata* (18.2%) [36]. Similarly, our study identified chronic kidney disease, connective tissue disease, immunocompromised status, and invasive mechanical ventilation as significant risk factors for identified fungal pathogens in sepsis, underscoring the complex interplay of underlying conditions in critically ill patients. These findings underscore the multiple and overlapping risk factors for fungal infections observed in previous studies. Factors such as immunosuppressive status [8, 16], neutropenia [12, 30], prolonged antibiotic use [22], total parenteral

nutrition [2, 27] and previous surgery [13] have all been associated with increased susceptibility to fungal infections. The coexistence of multiple risk factors further complicates the management of fungal sepsis and underscores the importance of early detection and tailored prevention strategies.

Several factors influenced in-hospital mortality, including older age, higher Clinical Frailty Scale, higher SOFA scores, and higher laboratory lactate levels. Consistent with our findings, previous studies have identified comorbidities [37, 38], the extent of organ dysfunction [39], and the severity of the patient's condition [38–40], as important predictors of mortality, reinforcing a consistent pattern across patient populations. These indicators, along with those identified in our research, may be important for initial risk stratification of patients with sepsis in whom fungal pathogens have been identified.

Limitations

This study has several limitations, primarily related to the challenges of accurately distinguishing true fungal pathogens from commensals in sepsis patients. A major limitation is that the presence of a fungal pathogen does not necessarily indicate invasive fungal sepsis. Although our study was prospective in design, data were collected from medical records and laboratory results, and it was not always possible to perform direct clinical reassessment of each case. As a result, we were unable to apply standardized criteria to definitively differentiate invasive fungal infections from colonization. This limitation may have led to potential misclassification, affecting the analysis of the prevalence and risk factors associated with fungal infections in sepsis. However, it is important to note that fungal colonization itself has been identified as a potential risk factor for invasive infections in previous studies [13, 34, 35], which underscores the clinical significance of our findings despite this limitation. Furthermore, the time interval between the detection of fungal pathogens and the onset of sepsis could not be precisely determined in our data set, limiting our ability to assess the temporal relationship between fungal infection and the development of sepsis. Another important limitation is that our study did not include antifungal susceptibility testing or drug susceptibility data. Given the increasing reports of fluconazole-resistant Candida species and other antifungal-resistant pathogens, the lack of drug susceptibility data prevents a more in-depth analysis of treatment efficacy and resistance trends. Future studies incorporating antifungal susceptibility testing would provide important insights into emerging resistance patterns and optimal treatment strategies. In addition, the retrospective nature of our study, which relies on the accuracy and completeness of medical records, is an inherent limitation. Data inconsistencies and missing information may introduce potential bias in data interpretation. However, we attempted to minimize this by using structured data collection methods and involving experienced researchers in data verification. In addition, variability in patient demographics and clinical practices among participating hospitals introduced heterogeneity into the data set. Differences in baseline characteristics, treatment protocols, and institutional policies may have influenced the observed epidemiologic trends and risk factors, potentially affecting the generalizability of our findings.

Recognition of these limitations is essential for accurate interpretation of our results and for guiding future research toward a more standardized approach to assessing fungal infections in sepsis patients. Future studies should incorporate prospective designs, standardized diagnostic criteria, and antifungal susceptibility testing to further refine our understanding of the clinical impact of fungal infections in critically ill patients.

Conclusion

In conclusion, this study identified fungal pathogens in 3.4% of sepsis patients, demonstrating the need for improved detection and treatment strategies, particularly in patients with chronic kidney disease, immunocompromised status, and other established risk factors. The low rate of antifungal treatment observed in this cohort suggests a potential under-recognition of fungal infections in clinical practice and highlights the need for increased clinical awareness, timely diagnosis and prompt intervention. Given the growing concern about antifungal resistance, future research should include standardized diagnostic criteria, antifungal susceptibility testing, and treatment outcome assessment to optimize therapeutic strategies and improve patient outcomes. A multidisciplinary approach involving infectious disease specialists, critical care physicians, and microbiologists is essential to facilitate early detection, effective risk stratification, and targeted antifungal therapy. Strengthening these collaborative efforts will be critical to reducing the burden of fungal infections in sepsis patients and improving overall survival.

Abbreviations

ICU	Intensive care unit
IRB	Institutional review board
SOFA	Sequential Organ Failure Assessment
PCR	Polymerase chain reaction
Ag	Antigen
OR	Odd ratio
CI	Confidence interval

HR Hazard ratio

Supplementary Information

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Supplementary Material 1.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
This study was approved by the Clinical Research Ethics Committee of Chungnam National University Hospital (approval number: 2019–11-048) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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