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Original Article

Clinical characteristics and outcomes of patients with candidemia during the COVID-19 pandemic: Insights from experience in the Omicron era

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KEYWORDS
SARS-CoV-2;
Candida;
Mortality;
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Abstract *Background:* In Taiwan, COVID-19 outbreaks caused by the Omicron variant occurred in 2022. We investigated the incidence of candidemia during COVID-19 pandemic and the mortality of candidemia patients with COVID-19 in Taiwan.
Methods: The incidence of candidemia and fluconazole susceptibility of *Candida* species before (2015—2019) and during COVID-19 pandemic (2020—2023) at Kaohsiung Chang Gung Memorial Hospital were investigated. The associated factors with mortality in candidemia patients during COVID-19 pandemic were analyzed. Candidemia patients who had COVID-19 within the prior 90 days (case group, n = 34) were propensity-score matched for age, ICU admission, and abdominal surgery in a 1:4 ratio with candidemia patients without COVID-19 (control group, n = 136).
Results: Age (adjusted odds ratio [AOR] = 1.02, 95% CI: 1.01—1.03), ICU stay (AOR = 1.84, 95% CI: 1.29—2.62), higher Charlson comorbidity index (AOR = 1.08, 95% CI: 1.03—1.13), corticosteroid use (AOR = 1.50, 95% CI: 1.04—2.17) were associated with increased risk of mortality; abdominal surgery (AOR = 0.47, 95% CI: 0.29—0.74) and infected by *Candida parapsilosis* (AOR = 0.61, 95% CI: 0.38—0.98) were associated with decreased risk of mortality. After

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matching, there was no significant difference in mortality rates between the case and control groups. The incidence of candidemia increased from 196 to 278 patients/100,000 admissions during COVID-19 pandemic, while the causative species of candidemia and fluconazole susceptibility rates were similar.
Conclusion: While the incidence of candidemia increased during COVID-19 pandemic, there was no significant difference in mortality between candidemia patients with and without COVID-19 in the Omicron era.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a substantial mortality rate globally. SARS-CoV-2 has infected more than 770 million people and caused over 6.9 million deaths since December 2019.[1] In Taiwan, nationwide COVID-19 outbreaks emerged in 2022, characterized by three pandemic waves.[2] During the COVID-19 pandemic, there has been an increase in the reports of fungal infections associated with COVID-19, such as pulmonary aspergillosis, mucormycosis, and candidiasis.[3—5] In the US, over 13,000 people died of fungal infections between 2020 and 2021, representing an increase in the numbers and rates of death from fungal infections compared with previous years.[6] Invasive candidiasis in patients with COVID-19 was first described shortly after the emergence of COVID-19 in China.[7] COVID-19 patients, especially those who are in the intensive care unit (ICU), receiving parenteral nutrition and systemic corticosteroids, and requiring mechanical ventilation, are at a higher risk of developing candidemia.[3,8] Studies have revealed a two-to tenfold higher incidence of candidemia in COVID-19 patients compared to those without COVID-19.[8—10] The pathogenesis of COVID-19-associated candidemia is complicated and involves multiple factors. Among individuals diagnosed with COVID-19, there is a reduction in the expression of human leucocyte antigen DR (HLA-DR) in circulating monocytes, which serves as an indicator of immune dysfunction.[3] Moreover, COVID-19 patients often exhibit lymphopenia, characterized by diminished levels of CD4 and CD8 T-cells.[3,11] The compromised immune response in these individuals may create an environment conducive for *Candida* spp. to subvert and elude immune defenses, thereby heightening the susceptibility to fungal infections.[3,11] This state of immune dysregulation could persist for a period of at least three months.[12]

Previous studies conducted before the COVID-19 pandemic indicated that independent mortality predictors of candidemia patients included increasing age, ICU admission, and abdominal surgery.[13,14] Candidemia patients with COVID-19 had worse outcomes compared to those without COVID-19.[8—10] A cohort study involving 10 surveillance sites in the US revealed that the all-cause in-hospital mortality rate among candidemia patients with COVID-19 was nearly twice the rate among those without COVID-19 (62.5% vs. 32.1%, $p < 0.001$).[15] Thus, COVID-19 appears to have a significant impact on the outcome of candidemia patients.

Candida albicans is the most frequently reported *Candida* species in critically ill patients with COVID-19.[9,15] However, in some geographical areas, the emerging *Candida* species that were fluconazole-resistant, such as *Candida parapsilosis* and *Candida auris*, cause sporadic cases or outbreaks.[5,16—20] Outbreaks caused by fluconazole-resistant *Candida* species were demonstrated to be associated with high mortality rates and could persist in the environment despite strict infection control strategies.[18,21]

Taiwan experienced a relatively lower incidence of COVID-19 before 2022. The viral strains of COVID-19 were dominated by the Omicron variant.[2] It is important to note that previous studies on the impact of COVID-19 on the outcome of patients with candidemia were conducted during periods when prevalent viral strains were Alpha or Delta.[8—10] It is uncertain whether the findings in the Alpha or Delta variants era can be directly applied to the current situation in the Omicron era. Our study aimed to examine the differences in the clinical characteristics and outcomes between candidemia patients who had experienced COVID-19 and those who had no COVID-19. Additionally, this study compared the incidence of candidemia, susceptibility to fluconazole, and distribution of *Candida* species between the COVID-19 pre-pandemic and pandemic periods.

Methods

Study population and design

In this retrospective cohort study, we included adult patients (≥18 years old) with candidemia who were admitted to Kaohsiung Chang Gung Memorial Hospital (KCGMH) from January 2020 to December 2023. If the patients had more than one episode of candidemia, only the first episode was included. The characteristics of patients who survived candidemia and those who died were compared to explore the associated factors with mortality in candidemia patients during the COVID-19 pandemic. Considering post-COVID-19 immune dysregulation,[12] the case group was defined as patients infected with COVID-19 within 90 days before candidemia onset while the control group was defined as those who had no COVID-19 before candidemia. Previous studies conducted before the COVID-19 pandemic indicated that independent mortality predictors of

candidemia patients included age, ICU admission, and abdominal surgery.[13,14] These three varieties were employed for propensity score matching to select the control group in a 1:4 ratio, aiming to mitigate the potential confounding factors in assessing the clinical impact of COVID-19 on candidemia. To understand the impact of COVID-19 on the incidence of candidemia, distribution of *Candida* species, and the susceptibility to fluconazole of *Candida* species, we collected the annual incidence and mortality rates of hospitalized patients with candidemia and the susceptibility rates of *Candida* species to fluconazole before (2015—2019) and during COVID-19 pandemic (2020—2023). This study was approved by the Ethics Committee of the Chang Gung Memorial Hospital, Kaohsiung, Taiwan, following the Declaration of Helsinki (IRB number 202300309B0).

Data collection and definitions

The information on demographic and clinical features was collected, which included age, sex, body mass index (BMI), the severity of COVID-19, underlying diseases, Charlson comorbidity index (CCI), oral and parenteral antibiotics use before the onset of candidemia within 14 days, immunosuppressives before the onset of candidemia within 30 days, parenteral nutrition use, abdominal surgery before candidemia, duration of the central venous catheter (CVC) placement, the occurrence of septic shock prior to candidemia, use of mechanical ventilation, days of ICU admission before candidemia, days of hospitalization, length of stay after candidemia, oral and parenteral anti-fungal agents use after the onset of candidemia, causative *Candida* species of candidemia, and in-hospital mortality rate. The diagnosis of COVID-19 was made with the use of a polymerase-chain-reaction (PCR) assay or rapid antigen test for SARS-CoV-2.

The severity of COVID-19 was defined according to Infectious Diseases Society of America Guideline.[22] Candidemia was identified as the detection of one or more *Candida* species in at least one blood culture in patients who have findings compatible with infection. Corticosteroid use was defined using $\geq$10 mg prednisone-equivalent daily for $\geq$3 days. Other immunosuppressives included T cell-directed medications, B cell-directed medications, cytokines targeting medications, chemokines and cell adhesion targeting medications, and multiple cellular targeting medications. Septic shock was defined as sepsis with persisting hypotension and requiring vasopressor therapy to maintain mean arterial pressure at $\geq$ 65 mm Hg or serum lactate level greater than 2 mmol/L ($>$18 mg/dL) despite adequate fluid resuscitation.[23] The exposure to antibiotics recorded before candidemia onset included glycopeptides (vancomycin and teicoplanin), carbapenems (ertapenem, imipenem, doripenem, and meropenem), aminopenicillin/beta-lactamase inhibitor (ampicillin/sulbactam and amoxicillin/clavulanate), first to third generation of cephalosporins (cefazolin, cefuroxime, flomoxef, and ceftriaxone), antipseudomonal cephalosporins (ceftazidime, cefoperazone/sulbactam and cefepime) and fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin). Echinocandins for the treatment of candidemia included micafungin, anidulafungin, and caspofungin.

Identification of *Candida* isolates and fluconazole susceptibility testing

Candida isolates were identified to the species level using Matrix-assisted laser desorption ionization time-of-flight mass spectrometry biotyper system and biotyper 2.3 software (MALDI-TOF MS; Bruker Daltonics). *C. albicans, Candida tropicalis, and C. parapsilosis* isolates were subject to antifungal susceptibility testing of fluconazole using the E-test method, which was performed according to the manufacturer's instructions with a yeast suspension equivalent to 0.5 McFarland, Roswell Park Memorial Institute (RPMI) 1640 agar plates (Sigma-Aldrich®) and fluconazole E-test strips (bioMerieux Marcy-l'E toile, France). All plates were incubated at 35 °C, and susceptibility was recorded after 48 h. *Candida parapsillosis* ATCC 22019 and *Candida krusei* ATCC 6258 were used as quality control strains. Susceptibility was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[24]

Statistical analysis

Descriptive statistics were presented as frequency and percentages for categorical variables, and average with standard deviation for continuous variables. Categorical variables were compared using the Chi-square test in parametric conditions. Student's t-test and Mann-Whitney U test were used in the comparison of continuous variables for normally distributed and non-normally distributed data, respectively. Multivariable logistic regression analysis was conducted on the significant variables identified in the univariate analysis among surviving and deceased candidemia patients. After propensity score matching was conducted, standardized mean differences (SMD) less than 0.2 indicated they were well-matched.[25,26] Statistical analyses were performed with IBM SPSS V.25 software version (IBM Corp., Armonk, NY, USA). A *p*-value of less than 0.05 was considered statistically significant.

Results

During the COVID-19 pandemic period, a total of 6260 patients with COVID-19 were admitted to KCGMH; and a diagnosis of candidemia was made in 663 patients, regardless of COVID-19. Of these patients with candidemia, 20 patients were aged less than 18 years; 49 patients had COVID-19 before developing candidemia; and 594 patients had had no COVID-19 before candidemia. The first patient who had COVID-19 before developing candidemia was diagnosed in May 2022. After excluding 15 patients who were diagnosed with candidemia more than 90 days after COVID-19, the case group comprised 34 patients. Another 136 patients with candidemia without COVID-19 were selected as the control group after propensity score matching.

In Table 1, we analyzed the associated factors for mortality among these 643 adult patients with candidemia during the COVID-19 pandemic. Multivariable logistic

Table 1 Associated factors for mortality in candidemia patients during the COVID-19 pandemic.

Variables	Mortality (n = 391)	Survival (n = 252)	*p*-Value	Multivariable analysis		
				AOR	95% CI	*p*-Value
Demographics						
Age (years), mean ± SD	68.7 ± 13.5	64.4 ± 13.2	*<0.001	1.02	1.01−1.03	*0.001
Sex (male), n (%)	226 (57.8)	164 (65.1)	0.065			
BMI (kg/m2), mean ± SD	22.8 ± 4.9	23.3 ± 4.9	0.216			
Abdominal surgery, n (%)	47 (12.0)	59 (23.4)	*<0.001	0.47	0.29−0.74	*0.001
ICU admission before candidemia, n (%)	232 (59.3)	124 (49.2)	*0.012	1.84	1.29−2.62	*<0.001
Charlson comorbidity index, mean ± SD	6.2 ± 3.9	5.4 ± 3.8	*0.008	1.08	1.03−1.13	*<0.001
Admission diagnosis, COVID-19, n (%)	20 (5.1)	14 (5.6)	0.808			
Severe or critically ill COVID-19, n (%)	15 (3.8)	5 (2.0)	0.187			
Candidemia occurred in the year of 2022−2023, n (%)	209 (53.5)	124 (49.2)	0.293			
Immunosuppressive drugs (within the last 30 days), n (%)						
Chemotherapy	79 (20.2)	43 (17.1)	0.321			
Corticosteroids ≥ 3 days	149 (38.1)	64 (25.4)	*<0.001	1.50	1.04−2.17	*0.030
Other immunosuppressants	13 (3.3)	10 (4.0)	0.668			
Parenteral nutrition ≥ 2 days before candidemia, n (%)						
Peripheral parenteral nutrition	151 (38.6)	113 (44.4)	0.117			
Total parenteral nutrition	63 (16.1)	55 (21.8)	0.808			
***Candida* species distribution, n (%)**						
Candida albicans	149 (38.1)	100 (39.7)	0.689			
Candida tropicalis	113 (28.9)	50 (19.8)	*<0.001			
Candida glabrata	95 (24.3)	45 (17.9)	0.053			
Candida parapsilosis	39 (10.0)	50 (19.8)	*<0.001	0.61	0.38−0.98	*0.042
Fluconazole non-susceptible species	111 (28.4)	55 (21.8)	0.063			
Antifungal therapy						
Time to antifungal therapy ≤2 days	256 (80.0)	186 (76.5)	0.323			
Echinocandins	252 (78.8)	178 (73.3)	0.128			
Fluconazole	66 (20.6)	67 (27.6)	0.055			
Voriconazole or posaconazole	15 (4.7)	4 (1.7)	0.059			
Amphotericin B	2 (0.6)	0	0.509			
Inappropriate empiric antifungal therapy[a]	15 (4.7)	9 (3.7)	0.567			

[a] Inappropriate empirical antifungal therapy means the empirical use of fluconazole that exhibited non-susceptibility in the final susceptibility assessment. If amphotericin B or echinocandin was administered empirically, it is regarded as appropriate empirical antifungal therapy.

The asterisk (*) indicates statistically significant differences, specifically where the p-value is less than 0.05.

Abbreviation: COVID-19, coronavirus disease 2019; AOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation; BMI, body mass index; ICU, intensive care unit.

regression analysis showed that age (adjusted odds ratio [AOR] = 1.02, 95% CI: 1.01−1.03, $p = 0.001$), ICU stay (AOR = 1.84, 95% CI: 1.29−2.62, $p < 0.001$), higher CCI (AOR = 1.08, 95% CI: 1.03−1.13, $p < 0.001$), corticosteroid use (AOR = 1.50, 95% CI: 1.04−2.17, $p = 0.030$) were factors associated with an increased risk of mortality, whereas having undergone abdominal surgery (AOR = 0.47, 95% CI: 0.29−0.74, $p = 0.001$), and infected by *C. parapsilosis* (AOR = 0.61, 95% CI: 0.38−0.98, $p = 0.042$) were associated with a decreased risk of mortality.

The clinical characteristics of propensity score matched candidemia patients are described in Table 2. The mean age of the case group was 68.5 years and 67.7% were male. The mean interval from the diagnosis of COVID-19 to the identification of candidemia was 20.3 days and the proportion of severe or critically ill COVID-19 was 58.8%. There were no significant differences in the use of oral and parenteral antibiotics within the last 14 days before candidemia between the two groups, except for a higher exposure to glycopeptides in the case group compared to the control group (41.2% vs. 20.6%, $p = 0.013$). In the use of immunosuppressives within the last 30 days, only the case group had a significantly higher rate of exposure to other immunosuppressives than the control group (8.8% vs. 0.7%, $p = 0.02$). There were no significant differences between the case and control groups regarding BMI, duration of ICU stay before candidemia, comorbidities, CCI, exposure to parenteral nutrition, presence of CVC, mechanical ventilation, previous septic shock, *Candida* isolates distribution and mortality rate.

Table 2 The characteristics of candidemia patients with and without COVID-19 after propensity score matching.

Variables	COVID-19 patients with candidemia (n = 34)	Non-COVID-19 patients with candidemia (n = 136)	*p*-Value
Demographics			
Age (years), mean ± SD	68.5 ± 15.3	68.7 ± 14.3	0.952
Sex (male), n (%)	23 (67.7)	100 (73.5)	0.493
BMI (kg/m2), mean ± SD	21.7 ± 4.0	22.7 ± 5.0	0.289
Abdominal surgery, n (%)	7 (20.6)	25 (18.4)	0.769
ICU admission before candidemia, n (%)	16 (47.1)	59 (43.4)	0.699
Days of ICU stay before candidemia, mean ± SD	11.1 ± 9.6	15.8 ± 18.7	0.662
Days of admission to candidemia, mean ± SD	22.2 ± 22.1	21.5 ± 22.2	0.874
Days of COVID-19 to candidemia, mean ± SD	20.3 ± 18.2		
Severe or critically ill COVID-19, n (%)	20 (58.8)		
Comorbidities, n (%)			
Myocardial infarction	1 (2.9)	9 (6.6)	0.689
Congestive heart failure	7 (20.6)	20 (14.7)	0.401
Peripheral vascular disease	2 (5.9)	22 (16.2)	0.170
Cerebrovascular disease	9 (26.5)	22 (16.2)	0.164
Dementia	4 (11.8)	10 (7.4)	0.483
Chronic pulmonary disease	8 (23.5)	21 (15.4)	0.262
Rheumatic disease	3 (8.8)	2 (1.5)	0.055
Peptic ulcer disease	7 (20.6)	35 (25.7)	0.534
Liver disease	10 (29.4)	25 (18.4)	0.155
Diabetes mellitus	13 (38.2)	44 (32.4)	0.516
Renal disease	11 (32.4)	40 (29.4)	0.738
Solid or hematological cancer	15 (44.1)	71 (52.2)	0.399
Charlson comorbidity index, mean ± SD	5.2 ± 3.6	5.8 ± 3.6	0.431
Antibiotics ≥ 2 days (within the last 14 days), n (%)			
Glycopeptides	14 (41.2)	28 (20.6)	*0.013
Carbapenems	13 (38.2)	51 (37.5)	0.937
Aminopenicillin/beta-lactamase inhibitor	6 (17.7)	16 (11.8)	0.393
Piperacillin/tazobactam	15 (44.1)	40 (29.4)	0.101
1st-3rd generation of cephalosporins	8 (23.5)	33 (24.3)	0.929
Antipseudomonal cephalosporins	9 (26.5)	40 (29.4)	0.735
Fluoroquinolones	7 (20.6)	25 (18.4)	0.769
Immunosuppressive drugs (within the last 30 days), n (%)			
Chemotherapy	7 (20.6)	27 (19.9)	0.924
Corticosteroids ≥ 3 days	14 (41.2)	41 (30.2)	0.219
Other immunosuppressants	3 (8.8)	1 (0.7)	*0.026
Parenteral nutrition ≥ 2 days before candidemia, n (%)			
Peripheral parenteral nutrition	11 (32.4)	35 (25.7)	0.437
Total parenteral nutrition	3 (8.8)	25 (18.4)	0.179
Other associated conditions, n (%)			
CVC at place	28 (82.4)	113 (83.1)	0.919
Days of CVC use, mean ± SD	19.2 ± 15.4	19.8 ± 21.0	0.597
Mechanical ventilation	18 (52.9)	63 (46.3)	0.490
Previous septic shock	5 (14.7)	24 (17.6)	0.683
***Candida* species distribution, n (%)**			
Candida albicans	18 (51.4)	56 (39.4)	0.198
Candida tropicalis	4 (11.4)	30 (21.1)	0.192
Candida glabrata	10 (28.6)	29 (20.4)	0.297
Candida parapsilosis	3 (8.6)	22 (15.5)	0.418
Others[a]	0	5 (3.6)	1
Clinical outcomes			
Septic shock due to candidemia, n (%)	12 (35.3)	38 (27.9)	0.400
Mortality, n (%)	20 (58.8)	78 (57.4)	0.877
Length of stay after candidemia, mean ± SD	19.5 ± 29.3	20.1 ± 22.1	0.919
Days of hospitalization, mean ± SD	41.7 ± 41.6	41.6 ± 32.5	0.985

Variables	Unmatched cohort			PSM cohort		
	COVID-19 patients with candidemia (n = 34)	Non-COVID-19 patients with candidemia (n = 609)	SMD	COVID-19 patients with candidemia (n = 34)	Non-COVID-19 patients with candidemia (n = 136)	SMD
Age (years), mean ± SD	68.5 ± 15.3	66.9 ± 13.4	0.118	68.5 ± 15.3	68.7 ± 14.3	0.014
Abdominal surgery, n (%)	7 (20.6)	99 (16.3)	0.157	7 (20.6)	25 (18.4)	0.078
ICU admission before candidemia, n (%)	16 (47.1)	338 (55.5)	0.238	16 (47.1)	59 (43.4)	0.105

[a] Others included *C. lusitaniae* (n = 2), *C. krusei* (n = 2), *C. dubliniensis* (n = 1).
The asterisk (*) indicates statistically significant differences, specifically where the p-value is less than 0.05.
Abbreviation: COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; ICU, intensive care unit; CVC, central venous catheter, PSM, propensity score match; SMD, standardized mean difference.

The annual incidence of candidemia among hospitalized patients with COVID-19 was 0.57% in 2022 and 0.51% in 2023. The annual incidence of candidemia among hospitalized patients without COVID-19 was 0.26% in 2022 and 0.16% in 2023. The incidence of candidemia and mortality of patients with candidemia between 2015 and 2023 are shown in Fig. 1. Compared with the incidence of candidemia before the COVID-19 pandemic, there was an upward trend in the incidence of candidemia from 2019 to 2022 (196 patients/100,000 admissions to 278 patients/100,000 admissions) ($p < 0.001$). As the pandemic eased in 2023, the incidence of candidemia declined (147 patients/100,000 admissions). In contrast, the mortality rate of patients with candidemia from 2015 to 2023 remained at around 55%, with no significant changes before and during the COVID-19 pandemic ($p = 0.892$).

From 2015 to 2023, *C. albicans* remained the predominant species, followed by *C. tropicalis*, *Candida glabrata*, and *C. parapsilosis* (Fig. 2). However, less than 40% of candidemia cases were caused by *C. albicans* during the COVID-19 pandemic. The trends of non-susceptible rates of different *Candida* species to fluconazole from 2015 to 2023 are shown in Fig. 3. During this period, the fluconazole non-susceptible rate of *C. tropicalis* ranged from 3% to 18%. *C. albicans* maintained susceptibility to fluconazole, with an annual non-susceptible rate of less than 3.5%. Although fluconazole non-susceptible isolates of *C. parapsilosis* were observed, only two isolates were classified as non-susceptible (one in 2017 and one in 2020). There were no significant changes in the fluconazole non-susceptible rates among these three *Candida* species before and during the COVID-19 pandemic (Fig. 3).

Discussion

In this study, we analyzed candidemia patients during the COVID-19 pandemic and observed a significant increase in

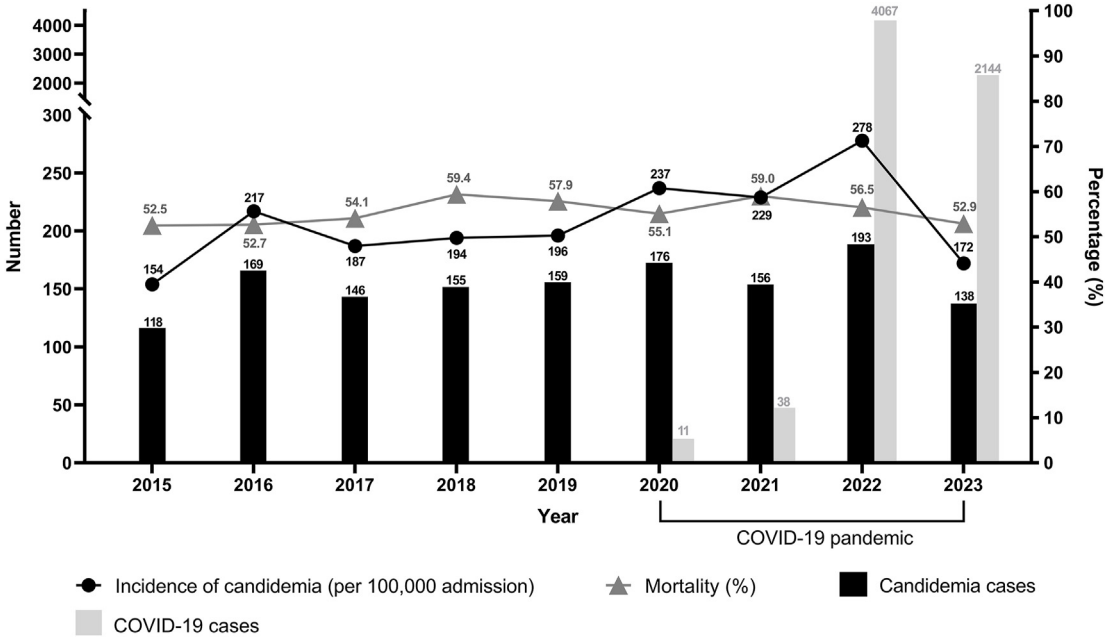

Figure 1. Annual incidence and mortality rate of patients with candidemia in Kaohsiung Chang Gung Memorial Hospital from 2015 to 2023. From 2019 to 2022, there was a significant ascending trajectory in the incidence of candidemia ($p < 0.001$), which corresponded to the periods of COVID-19 pre-pandemic and pandemic. Subsequently, as the pandemic subsided in 2023, the incidence of candidemia decreased. From 2015 to 2023, the annual mortality rate did not exhibit significant differences ($p = 0.892$).

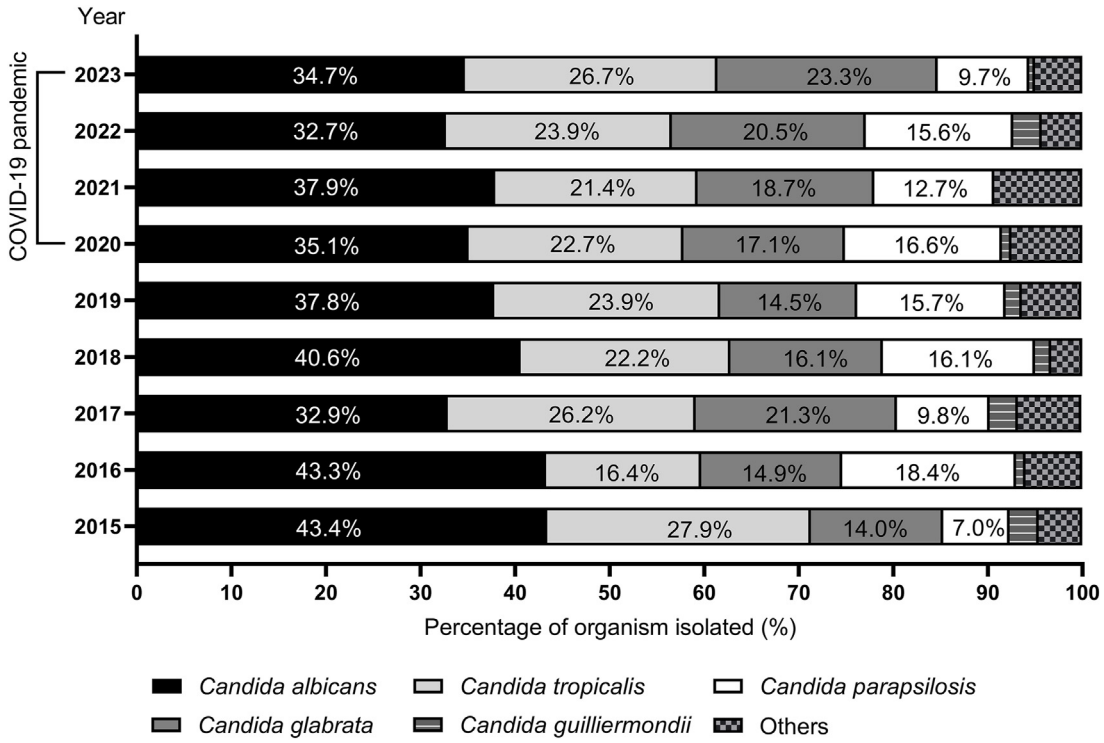

Figure 2. Identified *Candida* species distribution from patients with candidemia in Kaohsiung Chang Gung Memorial Hospital from 2015 to 2023. Before and during the COVID-19 pandemic, *C. albicans* remained the predominant species, followed by *C. tropicalis*, *C. glabrata* and *C. parapsilosis*. However, the proportion of *C. albicans* decreased during the COVID-19 pandemic compared to the period before the pandemic.

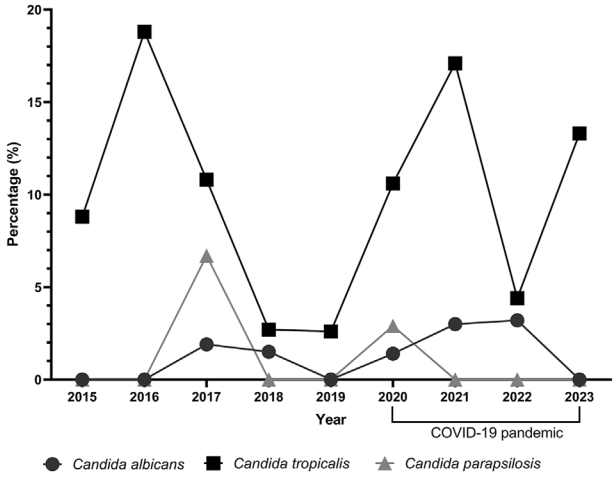

Figure 3. Fluconazole non-susceptible rates of different *Candida* species from patients with candidemia in Kaohsiung Chang Gung Memorial Hospital from 2015 to 2023. *C. albicans* maintained an annual non-susceptible rate of less than 3.5 %. The fluconazole non-susceptible rate of *C. tropicalis* ranged from 3% to 18%. Fluconazole non-susceptible isolates of *C. parapsilosis* were found in 2017 and 2020. There was no significant change in the fluconazole non-susceptible rate among these three *Candida* species before and during the COVID-19 pandemic.

the incidence of candidemia during this period. Our study found that the incidence of candidemia in patients with COVID-19 was 0.51—0.57%, which was two to fourfold higher than the rate of 0.16—0.26% in those without COVID-19. This finding is in agreement with previous studies that revealed an incidence of candidemia in patients with COVID-19 of 0.22—1.18%, which was two-to ten-fold higher than the rate of 0.11—0.14% in those without COVID-19.[8—10] The heightened exposure to corticosteroids and broad-spectrum antibiotics poses an increased susceptibility for COVID-19 patients in acquiring candidemia.[8,9] Moreover, the reduction in overall hospital admissions amid the pandemic could have potentially contributed to the elevated incidence of candidemia. Over the study period, hospitalizations decreased from 81,280 in 2019 to 69,532 in 2022, predominantly impacting non-critically ill patients. Conversely, the number of patients in critical condition and those in the ICU, with a higher predisposition to candidemia, remained steady throughout this timeframe. These occurrences may result in an upward trajectory in candidemia incidence from 2019 to 2022, followed by a substantial decline in 2023. As the COVID-19 pandemic eased in 2023, the incidence of candidemia declined in our study (Fig. 1). However, further large-scale studies are required to draw valid conclusions.

Previous studies indicated that candidemia patients with COVID-19 had a higher mortality rate than those without

COVID-19.[9,10,15] In the analysis of associated factors with mortality among candidemia patients (Table 1), we found that a prior history of COVID-19 before developing candidemia had no impact on the mortality rate of candidemia patients. After propensity-score matching for age, abdominal surgery, and ICU stay (Table 2), we found no statistically significant difference in mortality rates between candidemia patients with and without COVID-19. The initial wave of the COVID-19 pandemic was caused by the original strain, Alpha or Delta variants, during the global outbreak in 2020 and 2021.[1] Taiwan faced a nationwide COVID-19 outbreak starting from April 2022, which has been dominated by the Omicron variant.[2] Compared to previous strains of the COVID-19 virus, the Omicron variant tends to infect the upper airway and has been associated with milder respiratory symptoms,[27,28] resulting in lower severity of COVID-19 related complications. In view of 34 candidemia patients with COVID-19 in our study, nearly 60% had severe or critically ill COVID-19. Compared to candidemia patients with mild COVID-19, those with severe or critically ill COVID-19 had poor outcomes (35.7% vs.75.0%, $p = 0.022$). However, the diagnosis of COVID-19 and severity of COVID-19 were not independently associated factors with mortality in our candidemia patients. In our study, Older age, ICU stay before candidemia, a higher CCI and corticosteroid use were associated with an increased risk of mortality, while having undergone abdominal surgery and infection by *C. parapsilosis* were associated with a decreased risk of mortality. The factors identified to be associated with mortality of candidemia patients in the COVID-19 pandemic in our study were consistent with the findings of studies conducted before the COVID-19 pandemic.[13,14,29,30]

While many studies have indicated *C. albicans* as the predominant pathogen of candidemia in patients with COVID-19,[3,15,31] there was also evidence of an increasing occurrence of fluconazole-resistant species, such as *C. auris*.[17] Additionally, some studies have found that the fluconazole-resistant rate is increasing in certain species like *C. parapsilosis*[18,20] and *C. tropicalis*.[32] Therefore, understanding the distribution of *Candida* species and their susceptibility to antifungal therapy is important in specific periods including the era of COVID-19. This highlights the need for appropriate therapeutic strategies. In our study, whether before or during the COVID-19 pandemic, *C. albicans* remained the most predominant etiology of candidemia (Fig. 2). The distribution of Candida species has been changing over the last decade. Progressive shifts from *C. albicans* to non-albicans Candida spp. have been observed globally before the COVID-19 pandemic.[29,33] The proportion of *C. albicans* decreased during the COVID-19 pandemic compared to the period before the pandemic. Notably, *C. auris* was not detected in this study during the pandemic.

Compared to the period before the COVID-19 pandemic, the fluconazole non-susceptible rates of *C. parapsilosis* and *C. tropicalis* have shown a significant increase in some regions of the world during the COVID-19 pandemic.[19,20,32] Studies revealed that outbreaks of fluconazole-resistant *C. parapsilosis* infections might be due to the horizontal transmission of infection, as evidenced by the phylogenetic clustering of resistant strains that show similar genotypes.[18,20] The clinical management of the patients might have contributed to the selection of preexisting resistant clones circulating in the hospitals. In our study, there was no significant difference in the fluconazole non-susceptible rate among the *Candida* species before and during the COVID-19 pandemic (Fig. 3).

Overall, the mortality rate of patients with candidemia has been around 30%—50%,[14,29,34—36] whereas the mortality rate in our study has exceeded 50%. Factors that affect the mortality rate of candidemia patients include older age, the use of immunosuppressives, pre-existing renal dysfunction and other comorbidities, retained central venous catheters, delayed diagnosis of candidemia, delayed initiation of appropriate antifungal treatment, and the infecting *Candida* species.[13,14,29,30] Studies suggest that infections with *C. tropicalis* are associated with worse outcomes and higher mortality, whereas infections with *C. parapsilosis* are associated with better outcomes.[13,14,29,37] Compared to other studies,[29,34—36] the proportion of *C. tropicalis* in our cohort is higher. This may be one of the reasons why the mortality rate is higher in our study. Other potential factors contributing to the mortality in our cohort are beyond the scope of this investigation. Nevertheless, the presence of COVID-19 does not impact the outcome of our candidemia patients after propensity-score matching for age, abdominal surgery, and ICU stay.

Our study has some limitations. First, it is a single-center retrospective study, and the results observed may not be generalizable to patients with COVID-19 who developed candidemia at other hospitals. Second, the information was retrieved from the medical records, which may result in information bias. Third, the sample size of the case group was small, which may limit the power of this study to identify significant differences between the case group and control group. Fourth, there has been no clear definition of the time between a COVID-19 diagnosis and the identification of candidemia to be considered as candidemia associated with COVID-19. While our study defined candidemia associated with COVID-19 as candidemia diagnosed within 90 days after COVID-19, the median and mean interval between COVID-19 and subsequent candidemia was 15 days and 20.3 days, varying from 0 to 63 days. Whether a longer time interval chosen might affect the impact of COVID-19 on candidemia remains unknown. Five, although COVID-19 is considered a notifiable infectious disease in Taiwan, the reportable COVID-19 standards varied over time. Hence, it was plausible that individuals diagnosed with candidemia in the absence of COVID-19 could have been categorized differently.

Conclusion

We observed a significant increase in the incidence of candidemia during the COVID-19 pandemic. Contrary to previous findings, candidemia with COVID-19 diagnosis did not lead to a higher mortality in our study conducted in the Omicron era. The factors associated with mortality of candidemia in the setting of the COVID-19 pandemic were largely consistent with traditionally associated factors with mortality in candidemia patients.

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CRediT authorship contribution statement

Geng-Lou Lin: Writing — original draft, Conceptualization. **Po-Hsun Chang:** Software, Data curation. **Ing-Kit Lee:** Conceptualization. **Yi-Chun Chen:** Writing — review & editing, Supervision, Conceptualization. **Chen-Hsiang Lee:** Writing — review & editing, Supervision, Funding acquisition.

Declaration of competing interest

I declare that I have no financial or non-financial conflicts of interest that could influence the outcome or interpretation of this manuscript. All authors have reviewed the final version of the manuscript and approve it for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.07.014.