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Different epidemiological characteristics between patients with non-hospital-onset and hospital-onset candidemia: a retrospective cohort study

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Abstract

Candidemia is a life-threatening infectious disease that has varying incidences. Previous studies revealed the differences in clinical characteristics and outcomes between non-hospital-onset (NHO) and hospital-onset (HO) candidemia. This 4-year retrospective research included adult patients with candidemia in a tertiary medical centre in Taiwan, and cases were categorised as NHO and HO candidemia. Survival analysis and risk factors associated with in-hospital mortality were performed using the Kaplan–Meier method and multivariate Cox proportional-hazards models. The analysis included 339 patients, and the overall incidence was 1.50 per 1,000 admission person-year. Of the cases, 82 (24.18%) were NHO candidemia, and 57.52% (195/339) of patients were diagnosed with at least one malignancy. *C. albicans* was the most commonly isolated species, accounting for 52.21%. Patients with NHO candidemia had a higher proportion of *C. glabrata* but a lower ratio of *C. tropicalis* in comparison to the HO group. The all-cause in-hospital mortality rate was 55.75%. Multivariate Cox proportional-hazards models showed that NHO candidemia was a better outcome predictor (adjusted hazard ratio, 0.44). The administration of antifungal therapy within 2 days was a protective factor. In conclusion, NHO candidemia showed distinct microbiological characteristics and a better outcome than HO candidemia.

Introduction

Candidemia, associated with extended hospitalisation and high mortality, poses a global threat, particularly among immunocompromised patients [1–4]. The reported incidence of candidemia ranged from 1.7 to approximately 10 cases per 100,000 person-years or nearly 1.22 episodes per 1,000 discharges [5–8]. Previous studies have identified several risk factors associated with candidemia, including indwelling catheters, usage of steroids, disrupted gut or cutaneous barriers, hemodialysis, and injection drug use, especially in the United States [9–13]. It is worth noting that the distribution of *Candida* species varies across different countries and patient populations with various underlying diseases [7, 14]. The SENTRY antifungal surveillance program reported a decrease in the isolation of *C. albicans* to less than half but an increase in the isolation of *C. glabrata* and *Candida parapsilosis* [15]. Nevertheless, *C. tropicalis* presented high rates of resistance to fluconazole in the Asia-Pacific region and was more likely to be isolated in hemato-oncology wards [7, 15].

Non-hospital-onset (NHO) candidemia, which is defined as the onset of candidemia occurring in outpatient settings or within 2 days after hospital admission, has been previously recognised as community-onset and is an emerging issue [14, 16, 17]. The reported proportion of NHO candidemia among all candidemia varied from 0 to 31.14%, highlighting the need for studies to address NHO candidemia due to the discrepant epidemiological results [14, 18–21]. Furthermore, an American study found that NHO candidemia was more likely to result from *C. parapsilosis* and had a lower 30-day case-fatality rate compared with those with hospital-onset (HO) candidemia [14]. However, there is a lack of data on candidemia, especially NHO candidemia, in Asian countries. Therefore, we conducted this 4-year retrospective study to explore the characteristics of people with candidemia.

Methods

Study design, patient settings, and definitions

We designed a retrospective observational cohort study on adult patients (age ≥ 20 years old) who were hospitalised for two or more days and were diagnosed with candidemia. We reviewed all

electronic medical charts and microbiological data from the laboratory management information system in the Taichung Veterans General Hospital Research Database (registered number: F20424) between 1 January 2015 and 31 December 2018. This study was approved by the Institutional Review Board (IRB) I & II of the Taichung Veterans General Hospital, and the IRB serial is CE19376A. Informed consent was waived because all data obtained from individual patients were anonymised before the analysis.

Candidemia was defined as the presence of at least one set of blood cultures of *Candida* species with relevant clinical symptoms and signs during hepatisation. The onset of candidemia was defined as the day when patients received blood culture tests. Patients with candidemia were further categorised as NHO candidemia (defined as patients with candidemia experiencing onset of disease outside of the hospital, in the emergency department, or within 2 days after hospital admission) or HO candidemia (defined as the first episode of candidemia occurring after 2 days of hospitalisation) [14, 16, 17]. Bacterial concomitant bloodstream infection (BSI) was defined as one or more positive bacterial blood cultures isolated collectively or within 48 h of the time of candidemia [22, 23]. The presence of non-tunnel catheters was defined as central venous catheters (CVC) being in place for more than 24 h prior to the onset of candidemia [24]. Initial antifungal therapy was regarded as inadequate if *Candida* species were resistant or if no related minimum inhibitory concentration (MIC) was reported. Patients who died or were discharged in critical condition were classified as in-hospital mortality. The aim of this study was to investigate the epidemiological characteristics of candidemia, explore the involved *Candida* species, and identify risks for mortality in patients with candidemia.

Laboratory identification, susceptibility test of Candida species

Five to 10 millilitres of blood samples were collected from patients with related symptoms and signs by aseptic procedure into blood culture flasks (Becton, Dickinson and Company), transferred to the Clinical Microbiology Department, and then incubated appropriately. Whenever positive cultures were noted, the pathogens were further identified by using VITEK 2 (bioMérieux, Marcy l'Etoile, France) yeast identification card system (VITEK® 2 YST ID card) or matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS). The antifungal susceptibility testing was performed by using the VITEK® 2 Yeast Susceptibility Card, AST-YS05 (bioMérieux, Marcy l'Etoile, France) and SensiTitre™ YeastOne™ (microbroth dilution test using alamarBlue). The susceptibility of *Candida* species was regrouped with updated breakpoints described in the Clinical and Laboratory Standards Institute (CLSI; M60-ED2:2020 performance standards for antifungal susceptibility testing of yeasts, 2nd edition).

Statistical analyses

Continuous variables were presented as the mean ± standard deviation (SD) or median with interquartile range (IQR), and further compared using a Student's *t*-test or Mann–Whitney *U* test whenever appropriate based on the check of the normality assumption. Categorical variables among groups were compared using counts and percentages. Statistical comparisons between groups were made by χ^2 test or Fisher's exact. The Simpson's diversity index was applied to express the diversity of *Candida* species in NHO or HO candidemia [25]. The dependent variable was all-cause in-hospital mortality. On the contrary, the independent variables were those risk factors and underlying comorbidities potentially affecting the clinical outcomes. The Kaplan–Meier survival analysis with log-rank tests was applied for survival differences of all-cause in-hospital mortality from the onset of candidemia to discharge. We incorporated variables of interest to build a full Cox proportional-hazards model to identify predictors of in-hospital mortality, and then the adjusted hazard ratios (aHRs) of each individual factor were calculated. A *p*-value of 0.05 was used to determine statistical significance. *Rstudio* (2022.02.2 +485) in R version 4.1.0 (18 May 2021) with appropriate packages was used for the statistical analysis in this study.

Results

Demographics and clinical characteristics of patients with NHO and HO candidemia

A total of 339 patients were identified in this study (Figure 1), resulting in an overall incidence of 1.50 per 1,000 admission

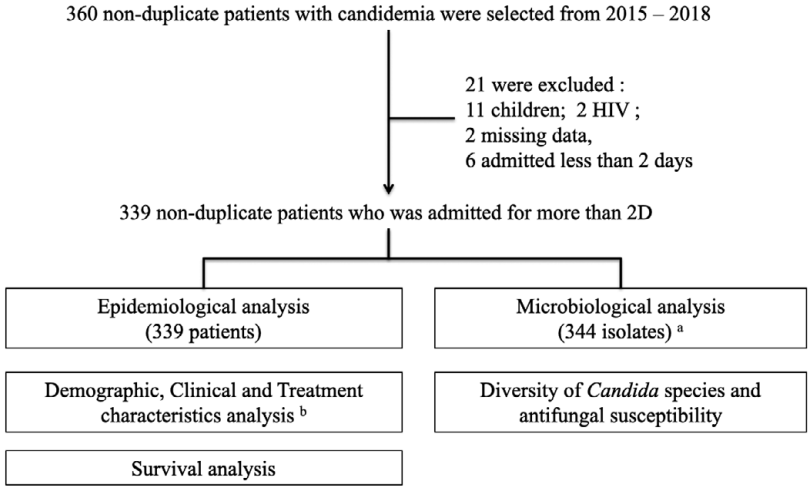

Figure 1. Flows of the study design. This study was approved by the Institutional Review Board I & II of Taichung Veterans General Hospital (CE19376A), Taichung, Taiwan. During the study period from 1 January 2015 to 31 December 2018, a total of 339 adult hospitalized patients (age = 20-year-old) were identified after excluding 21 patients from a total of 764 positive blood cultures for Candida species within 11,128 positive blood cultures by the commercial identification system (VITEK® 2) in this retrospective observational study. Further epidemiological and microbiological analyses were performed for these 339 patients and 344 isolates. Kaplan-Meier survival curves with a log-rank test were applied for survival analysis. Note:a Among 339 patients, five patients were noted to have two different Candida species isolated from their blood samples, summing up 344 isolates. The criteria of breakpoint of antifungal susceptibility were on the basis of the Clinical and Laboratory Standards Institute guidelines (CLSI; M60-ED2:2020 performance standards for antifungal susceptibility testing of yeasts, 2nd edition). b Comparison of demographic, clinical, and treatment characteristics were executed between community-onset candidemia (n=83) and nosocomial candidemia (n=256).

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Table 1. The comparison of demographics and clinical characteristics of patients with candidemia between NHO and HO candidemia (n = 339)

Patient demographics[a]	Total n = 339	NHO n = 82	HO n = 257	p-Value
Sex				
Male	219 (64.60)	54 (65.85)	165 (64.20)	0.785
Age, years, mean (SD)	64.24 (15.16)	66.95 (14.28)	63.38(15.35)	0.063
Age, years, median (IQR)	64 (54–76)	65.5(58–79.8)	63 (53–75)	0.10
Previous admission within 30 days	123 (36.28)	31 (37.81)	92 (35.80)	0.742
The onset of candidemia after admission, days, median (IQR)	14 (3–30)	0 (−1 – 0)[b]	20 (11–35)	<0.001*
Terminal disease registry	131 (38.64)	25 (30.49)	106 (41.25)	0.082
Any risks of candidemia development[c]	310 (91.45)	64 (78.05)	246 (95.72)	<0.001*
Presence of a non-tunnel catheter	123 (36.28)	7 (8.54)	116 (45.14)	<0.001*
Status of chemo port				0.002*
Without a chemo port implant	231 (68.14)	62 (75.61)	169 (65.76)	
With chemo port, removal	60 (17.70)	18 (21.95)	42 (16.34)	
With chemo port without removal	48 (14.16)	2 (2.44)	46 (17.90)	
Ever received steroid within 7 days before candidemia	136 (40.12)	16 (19.51)	120 (46.69)	<0.001*
Ever received chemotherapy within 1 month before candidemia	60 (17.70)	12 (14.63)	48 (18.68)	0.404
Simultaneous bacteremia				0.233
Monomicrobial	29 (8.55)	4 (4.88)	25 (9.73)	
Polymicrobial	3 (0.88)	0 (0.00)	3 (1.17)	
Underlying comorbidities				
Charlson comorbidity index, mean (SD)	5.56 (2.78)	5.73 (2.70)	5.56 (2.80)	0.619
Malignancy	195 (57.52)	40 (48.78)	155 (60.31)	0.066
Haematology disease	19 (5.61)	6 (7.31)	13 (5.06)	0.439
Solid-organ tumour	178 (52.51)	36 (43.90)	142 (55.25)	0.073
Post-organ transplant	13 (3.83)	1 (1.22)	12 (4.67)	0.157
Hollow organ perforation	32 (9.44)	12 (14.63)	20 (7.78)	0.065
Severe skin defects[d]	7 (2.06)	0 (0.00)	7 (2.72)	0.131
Diabetes mellitus	104 (30.68)	35 (42.68)	69 (26.85)	0.007*
Hypertension	117 (34.51)	32 (39.02)	85 (33.07)	0.324
Cirrhosis	30 (8.85)	9 (10.98)	21 (8.17)	0.436
HBV carrier	30 (8.85)	8 (9.76)	22 (8.56)	0.74
HCV carrier	13 (3.83)	4 (4.88)	9 (3.50)	0.572
Renal function impairment	66 (19.47)	17 (20.73)	49 (19.07)	0.74
COPD	15 (4.42)	5 (6.10)	10 (3.89)	0.398
Any rheumatic disorders	20 (5.90)	6 (7.32)	14 (5.45)	0.532
Any CNS disorder	35 (10.32)	10 (12.20)	25 (9.73)	0.523
Pancreatitis	9 (2.65)	1 (1.22)	8 (3.11)	0.353
TPN	7 (2.06)	1 (1.22)	6 (2.33)	0.536
Clinical complications				
Acute respiratory failure	106 (31.27)	33 (40.24)	73 (28.40)	0.044*
Acute kidney injury	46 (13.57)	10 (12.20)	36 (14.01)	0.676
Acute liver failure	18 (5.31)	3 (3.66)	15 (5.84)	0.444
Sepsis	39 (11.50)	13 (15.85)	26 (10.12)	0.156

(*Continued*)

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Table 1. (*Continued*)

Patient demographics[a]	Total *n* = 339	NHO *n* = 82	HO *n* = 257	*p*-Value
Septic shock	89 (26.25)	24 (29.27)	65 (25.29)	0.476
Clinical outcome				
Hospital stay, days, mean (SD)	46.12 (50.02)	31.43 (25.20)	50.81 (54.88)	0.002*
Hospital stay, days, median (IQR)	35 (23–56)	27 (13–44)	40 (26–60)	< 0.001*
In-hospital mortality	189 (55.75)	29 (35.37)	160 (62.26)	<0.001*
30-day mortality	165 (48.67)	24 (29.27)	141 (54.86)	<0.001*
90-day mortality	194 (57.23)	32 (39.02)	162 (63.04)	<0.001*

Note: Data are presented as no. (%) unless indicated in the specific patient demographics.
Abbreviations: ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; ESRD, end-stage renal disease; HO, hospital-onset; IQR, interquartile range; NHO, non-hospital-onset; SD, standard deviation; TPN, Total parenteral nutrition.
[a]Demographics are presented at the patient level.
[b]The negative value presented days prior to admission.
[c]The risks of candidemia development include any risk below: the presence of a non-tunnel catheter, chemo port implant, receiving steroids within 7 days before candidemia, receiving chemotherapy within 1 month before candidemia, malignancy, severe skin defect, CKD or ESRD, and hollow organ perforation.
[d]Includes patients with burn injury and toxic epidermal necrolysis.
*$p < 0.05$.

person-years. The median age of patients was 64 years old, and 64.60% of patients were male. There was no age ($p = 0.10$) or gender ($p = 0.785$) difference between NHO and HO. The onset of HO was 28.53 days after admission (see Table 1). About, 57.52% (195/339) of patients were diagnosed with at least one kind of malignancy with no significant difference between NHO and HO (48.78% vs. 60.31%, $p = 0.066$). The HO group had a higher proportion of patients with non-tunnel catheters compared to the NHO group (45.14% vs. 8.54%, $p < 0.001$). Patients with HO candidemia had a significantly higher proportion of chemo port existence but a lower proportion of chemo port removal after the onset of candidemia compared to those with NHO candidemia (16.34% vs. 21.95%, $p = 0.002$). The overall Charlson comorbidity index (CCI) ± SD was 5.60 ± 2.78 in this cohort, showing no significant difference between patients in the NHO and the HO group (5.73 ± 2.70 vs. 5.56 ± 2.80, $p = 0.619$). 90.56% (307/339) of patients with candidemia had at least one risk factor, including the presence of a non-tunnel catheter or a chemo port implant, receiving steroids within 7 days before candidemia, receiving chemotherapy within 1 month prior to the onset of candidemia, or the presence of malignancy or chronic kidney disease (CKD) or end-stage renal disease (ESRD). The risks of acquiring candidemia were significantly higher in patients with HO candidemia compared to NHO candidemia (95.72% vs. 74.39%, $p < 0.001$). Most characteristics of comorbidities were similar, except for a higher proportion of diabetes mellitus (DM) in NHO candidemia (42.68% vs. 26.85%, $p = 0.007$).

Diversity of Candida species and antifungal susceptibility among these 339 patients with candidemia

C. albicans (52.21%, 177) accounted for the most common isolated species, followed by *C. tropicalis* (17.11%, 58), *C. glabrata* (16.22%, 55), and *C. parapsilosis* (8.26%, 22). No adult patients were infected by *Candida krusei*; however, three *C. krusei* infections occurred in children, but these were excluded due to the study design. Five patients (1.47%) were found to be infected by more than one species, all consisting of *C. albicans*.

The Simpsons diversity index showed similar species diversity between NHO and HO candidemia (0.698 vs. 0.642). However, the proportion of *Candida* species was significantly different between NHO and HO (Table 2, $p = 0.002$). In patients with NHO candidemia, a higher proportion of *C. glabrata* (25.61% vs. 13.23%), *C. parapsilosis* (10.98% vs. 7.39%), and *Candida pelliculosa* (6.10% vs. 2.72%) were isolated, while there were fewer isolations of *C. albicans* (47.56% vs. 53.70%) and *C. tropicalis* (4.88% vs. 21.01%) than in the HO group. By analysing further by species, we found a higher percentage of *C. glabrata* isolated from patients with NHO candidemia than those in the HO group (26.83% vs. 13.62, $p = 0.005$), whereas the isolation of *C. tropicalis* showed the opposite result (4.88% vs. 21.01%, $p = 0.001$).

The antifungal susceptibility test results of 344 *Candida* species among 339 patients with candidemia are summarised in supplement Table 1. *C. albicans* (176, 96.7%) still demonstrated high susceptibility to fluconazole. The antifungal resistance of fluconazole ($p = 0.784$) and voriconazole ($p = 0.598$) showed no statistical significance between NHO and HO candidemia.

Treatment characteristics among 339 patients with candidemia

Echinocandin was the most commonly prescribed initial antifungal therapy, and a higher proportion of patients with NHO candidemia accepted antifungal treatment compared to those with HO candidemia (95.12% vs. 84.83%, $p = 0.016$; Table 3). The gap between the onset of candidemia and initiation of antifungal therapy was 2.58 days, with a longer delay in the NHO group (3.49 vs. 2.56 days, $p = 0.001$). Less than half (48.08%, 163/339) of patients with candidemia received antifungal therapy on or before 2 days after candidemia, and with no significant difference in antifungal therapy between groups ($p = 0.366$). The proportion of inadequate initial antifungal therapy due to resistance, without related MIC report or no antifungal therapy during the whole hospitalisation was significantly higher in the HO group than in the NHO group (19.07% vs. 9.76%, $p = 0.05$). Finally, a longer antifungal therapy duration, including initial treatment (14.15 ± 9.68 days vs. 10.46 ± 8.96 days, $p = 0.002$) and total therapy duration (20.51 ± 17.34 vs. 14.98 ± 13.26 days, $p = 0.003$), was noted in the NHO group than in the HO group.

The outcomes of 339 patients with candidemia

The all-cause in-hospital mortality rate was 55.75% (189/339, Table 1). Survival analysis showed a significantly better outcome for patients with NHO candidemia than for those with HO

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Table 2. Diversity and resistance characteristics of *Candida* species among 339 patients with candidemia

	Total patients	NHO	HO	
	n = 339	*n* = 82	*n* = 257	*p*-Value
Candida species				0.002*
C. albicans	177 (52.21)	39 (47.56)	138 (53.70)	
C. glabrata	55 (16.22)	21 (25.61)	34 (13.23)	
C. krusei	0 (0)	0 (0)	0 (0)	
C. parapsilosis	28 (8.26)	9 (10.98)	19 (7.39)	
C. tropicalis	58 (17.11)	4 (4.88)	54 (21.01)	
C. guilliermondii	1 (0.29)	0 (0.00)	1 (0.39)	
C. lusitaniae	1 (0.29)	0 (0.00)	1 (0.39)	
C. pelliculosa	12 (3.54)	5 (6.10)	7 (2.72)	
C. famata	1 (0.29)	0 (0.00)	1 (0.39)	
C. rugosa	1 (0.29)	1 (1.22)	0 (0.00)	
C. albicans + *C. glabrata*	2 (0.59)	1 (1.22)	1 (0.39)	
C. albicans + *C. parapsilosis*	2 (0.59)	2 (2.44)	0 (0.00)	
C. albicans + *C. tropicalis*	1 (0.29)	0 (0.00)	1 (0.39)	
Isolation of *C. albicans*	182 (53.69)	42 (51.22)	140 (54.47)	0.607
Isolation of *C. glabrata*	58 (17.11)	22 (26.83)	35 (13.62)	0.005*
Isolation of *C. tropicalis*	58 (17.11)	4 (4.88)	54 (21.01)	0.001*
Isolation of *C. parapsilosis*	30 (8.85)	11 (13.42)	19 (7.39)	0.095
Antifungal therapy resistance				
Fluconazole resistance	7 (2.06)	2 (2.44)	5 (1.95)	0.784
Voriconazole resistance	6 (1.77)	2 (2.44)	4 (1.56)	0.598

Note: Data are presented as no. (%).
Abbreviations: HO, hospital-onset; NHO, non-hospital-onset.
*$p < 0.05$.

candidemia (Figure 2a, $p < 0.001$). This survival advantage of NHO candidemia remained after stratifying *Candida* species with *C. albicans*, *C. tropicalis,* and *C. glabrata* (Figure 2b–d).

The multivariate Cox proportional-hazards model for risk factors associated with in-hospital mortality showed that NHO candidemia was a better predictor of outcome (adjusted hazard ratio, 0.44; 95% CI, 0.29–0.67, Table 4) regardless of age, sex, and CCI. Other variables that can predict poor clinical outcomes included recent steroid use, retained chemo port, acute liver failure, and the occurrence of septic shock during hospitalisation. On the contrary, antifungal therapy initiation within 2 days was a protective factor, reducing 40% and 38% mortality risk by using either triazole or echinocandin.

Discussion

In this retrospective study, we investigated the differences in clinical and mycological characteristics and outcomes between patients with NHO and HO candidemia. Patients with NHO candidemia were more likely to be infected by *C. glabrata*; nonetheless, *C. tropicalis* was more commonly isolated from patients with HO candidemia. After adjusting for covariates, patients with NHO candidemia were independently associated with lower in-hospital mortality. We also identified a number of mortality-relevant risk factors, including recent steroid use, presence of a chemo port without removal, acute liver failure, and septic shock. On the other hand, initiation of antifungal therapy within 2 days with either triazole or echinocandin was a protective factor for in-hospital mortality.

The global distribution of *Candida* species showed a decline in the isolation of *C. albicans* accompanied by rises in the isolation of *C. parapsilosis* and *C. glabrata* in the SENTRY antifungal surveillance program, including in Asia countries [15]. However, our data revealed that *C. albicans* was still the most numerous species, followed by *C. tropicalis*, *C. glabrata*, and *C. parapsilosis.*

Table 3. Treatment characteristics among 339 patients with candidemia

	Total patients	Community-onset	Nosocomial	
Treatment characteristic[a]	*n* = 339	*n* = 82	*n* = 257	*p*-Value
Antifungal therapy during hospitalisation				0.016*
Without any treatment	43 (12.68)	4 (4.88)	39 (15.18)	
Triazole as initial therapy	92 (27.14)	19 (23.17)	73 (28.40)	
Echinocandin as initial therapy	204 (60.18)	59 (71.95)	145 (56.42)	
Treatment gap after the onset of candidemia, days, mean (SD)	2.58 (2.87)	3.49 (3.47)	2.252 (2.56)	0.001*
Treatment initiation within 2 days after onset of candidemia	163 (48.08)	36 (43.90)	127 (49.42)	0.366
Treatment with triazole class	44 (12.98)	7 (8.54)	37 (14.40)	
Treatment with echinocandin class	119 (35.10)	29 (35.37)	90 (35.02)	
Inadequate initial antifungal therapy	57 (16.81)	8 (9.76)	49 (19.07)	0.05
Initial therapy duration, days, mean (SD)	11.35 (9.26)	14.15 (9.68)	10.46 (8.96)	0.002*
Total therapy duration, days, mean (SD)	16.32(14.52)	20.51 (17.34)	14.98(13.26)	0.003*

Note: Data are presented as no. (%) unless indicated in the specific treatment characteristic.
Abbreviations: IQR, interquartile range; SD, standard deviation.
[a]Demographics are presented at the patient level.
*$p < 0.05$.

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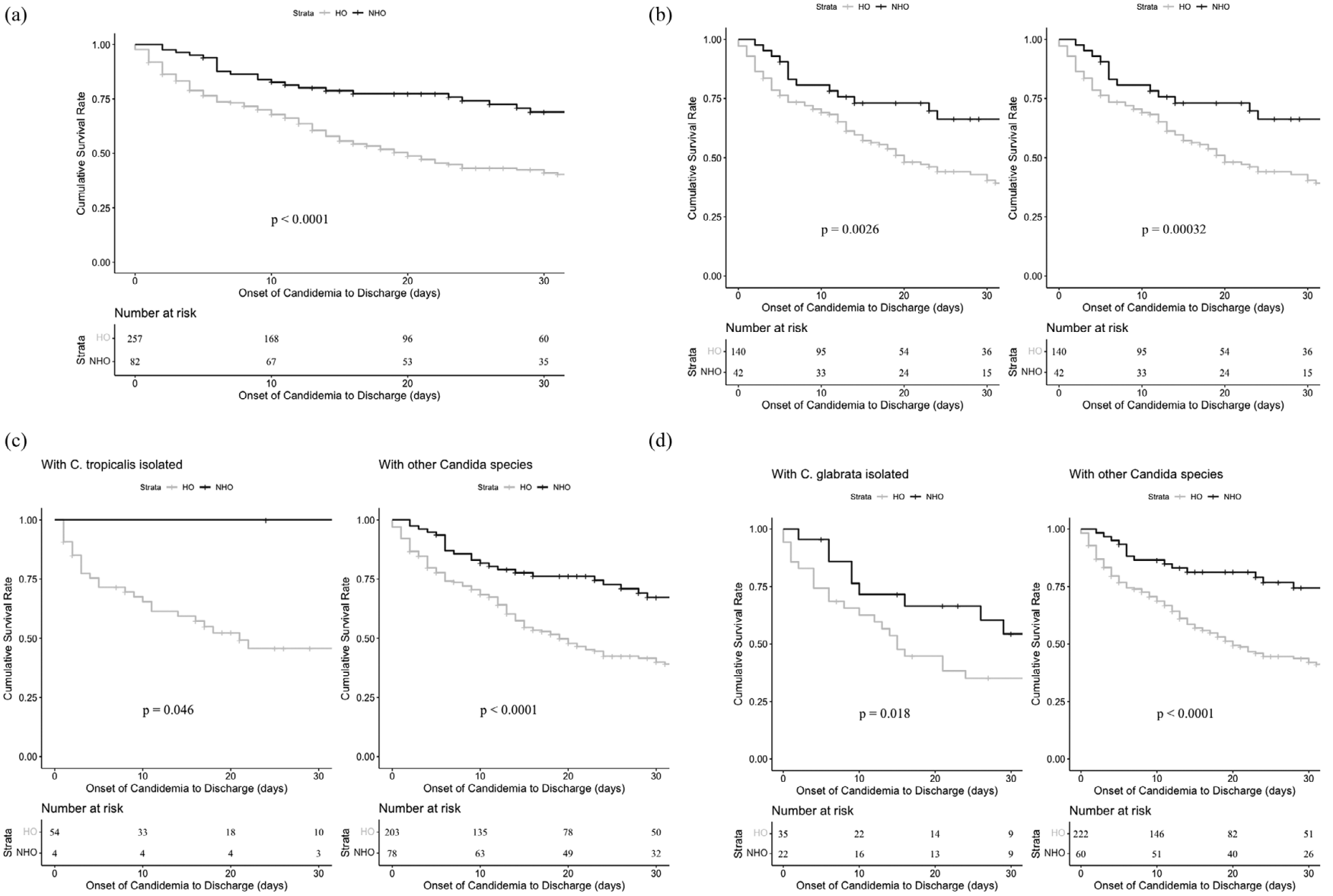

Figure 2. Survival curves analysis. A log-rank test was applied to assess the statistical significance, and a p value less than 0.05 was considered statistically significant. (a) survival comparison between non-hospital-onset (NHO) candidemia and hospital-onset (HO) candidemia within all patients. (b) survival comparison between NHO candidemia and HO candidemia within groups based on isolation of C. albicans vs. other species. (c) survival comparison between NHO candidemia and HO candidemia within groups based on isolation of C. tropicalis vs. other species. (d) survival comparison between NHO candidemia and HO candidemia within groups based on isolation of C. glabrata vs. other species. Abbreviations: NHO, non-hospital-onset; HO, hospital-onset

Table 4. Univariate and multivariate analysis of risk factors associated with in-hospital mortality by Cox proportional-hazards model

	Univariate result		Multivariate result	
	HR (95% CI)	*p*-Value	aHR (95% CI)	*p*-Value
Age	1.001 (0.99–1.01)	0.76	1 (0.99–1.01)	0.884
Male sex	1.19 (0.88–1.61)	0.259	1.1 (0.8–1.52)	0.54
Charlson comorbidity index	1.06(1.012–1.12)	0.016*	1.04 (0.97–1.11)	0.288
Status of chemo port				
No chemo port	Reference		Reference	
With chemo port followed by removal	0.85 (0.57–1.3)	0.41	1.13 (0.73–1.75)	0.577
With chemo port without removal	2.28(1.57–3.3)	<0.001*	2.25 (1.46–3.46)	<0.001*
Ever received steroid within 7 days before candidemia	2.05 (1.5–2.7)	<0.001*	1.64 (1.18–2.27)	0.003*
Acute respiratory failure	1.60 (1.2–2.1)	0.0016*	1.04 (0.73–1.5)	0.813
Acute kidney injury	1.94 (1.4–2.8)	<0.001*	1.26 (0.84–1.9)	0.269
Acute liver failure	2.28 (1.4–3.8)	0.0013*	2.08 (1.20–3.59)	0.009*
Septic shock	2.03 (1.5–2.73)	<0.001*	1.77 (1.24–2.54)	0.002*
Treatment within 2 days				
No antifungal therapy within 2 days	Reference		Reference	
Triazole within 2 days	0.71 (0.44–1.13)	0.146	0.6 (0.37–0.98)	0.042*
Echinocandin within 2 days	0.72 (0.53–0.99)	0.043*	0.62 (0.45–0.86)	0.005*
Non-hospital (vs. hospital-onset)	0.40 (0.27–0.59)	<0.001*	0.44 (0.29–0.67)	<0.001*

Abbreviations: aHR, adjusted Hazard ratio; HR, hazard ratio.
*$p < 0.05$.

Meanwhile, Sofair et al. [14] conducted an active, population-based surveillance study involving 1,143 patients with candidemia in the United States, showing the association between strain types and epidemiologic classification. The study reported that while *C. albicans* accounted for the most common species, particularly in HO candidemia, *C. parapsilosis* was more proportionally associated with NHO candidemia, especially in cases where hospitalization occurred further in the past [14]. In our study, we found a relatively high proportion of *C. glabrata* among those with NHO candidemia, which may reflect the predominance of *C. glabrata* colonisation among patients in the community. This is in accordance with the SENTRY program, which ranked *C. glabrata* as the second most predominant species between 1997 and 2016 [15]. Furthermore, *C. tropicalis* appears to be predominant in patients exposed to the hospitalised environment. This high percentage of *C. tropicalis* could be associated with a relatively higher proportion of underlying disease with malignancy in the patients with HO candidemia compared with NHO candidemia (60.31% vs. 48.78%, $p = 0.066$), as shown in previous studies [6, 7, 26]. Taken together, these pieces of evidence demonstrate that *C. albicans* remains the most commonly isolated species in patients with candidemia, and those with NHO candidemia are more likely to be affected by *C. glabrata.* The differences observed between HO and NHO candidemia can aid in identifying risk factors, predicting species, selecting appropriate treatment, and ultimately improving outcomes by addressing modifiable risks.

In spite of various antifungal therapy, candidemia is still a lethal infectious disease, leading to as high as 55.75% of in-hospital mortality in our cohort, which was comparable to previous studies [3, 27–29]. A previous study [14] showed that patients with NHO candidemia had a lower risk of 30-day mortality compared with those with HO candidemia (RR, 0.64; 95% CI: 0.53–0.78, $p < 0.01$); however, Kato reported that NHO candidemia was not a protective factor [16]. In our study, patients with NHO candidemia presented a 56% reduction of hazard ratio for in-hospital mortality compared with those with HO candidemia in multivariate Cox proportional-hazards models involving other variables. Despite the fact that a higher proportion of patients with malignancy and more patients in the NHO group were diagnosed with DM than those in the HO candidemia group, these two factors did not have an impact on the in-hospital mortality advantage of NHO over HO candidemia by using Kaplan–Meier survival curves, including different *Candida* species (log-rank tests, all $p < 0.05$). Whether there is an impact of different *Candida* species on clinical outcomes, particularly mortality, is still debatable. While some studies revealed no association between species and outcome [30–32], others have reported that infection caused by different species might be associated with mortality [3, 4, 33]. *C. parapsilosis* fungemia was found to be associated with a better outcome compared with other species or mixed fungemia by the Kaplan–Meier survival curve analysis ($p = 0.044$). However, such a benefit was not noted in a multivariate logistic regression analysis of 30-day mortality (aOR, 0.63, 95% CI: 0.29–1.34, $p = 0.23$) in Japan [16]. Unlike Kato's study, our study reported that candidemia due to different species did not reveal significant influences on in-hospital mortality and the superiority of NHO candidemia (Figure 2b–d).

Some recent studies revealed the incidence of candidemia had been decreasing [34, 35] in comparison to previous epidemiologic reports in the 2000s. Suzuki et al. [17] reported a 77.1% reduction in incidence rates in HO candidemia since its peak in 2004, after a series of infection control interventions. Regardless, the fact that the onset of nosocomial candidemia can occur for as long as 20 days

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from hospital admission has highlighted the importance of healthcare-associated infection control interventions. The percentage of NHO candidemia ranged from 17% to 31.14% [14, 16] and varied with time and countries [21]. This small proportion of NHO candidemia might be highlighted after a descent of HO candidemia by introducing multifaceted infection control interventions. Thus, it is crucial to pay more attention to these distinct characteristics and clinical outcomes of NHO and HO candidemia to customise treatment strategies. The different characteristics observed in HO and NHO candidemia could be extremely useful for clinicians to judge the most possible risk factors, select the most appropriate treatment, and ultimately improve clinical outcomes.

There were several limitations in our study. First, this was a retrospective cohort study which may have introduced potential bias due to non-standardised data collection procedures. Second, no other in-vitro resistance mechanism was explored in this study. Not all isolates had antifungal breakpoints reference based on CLSI, though those strains without breakpoints were only 4.65% (16/344, Supplementary Table 1). Further studies are also necessary for elucidating the resistance mechanism of those strains.

Conclusion

In conclusion, NHO candidemia accounted for 24.18% of all candidemia cases and was associated with a lower in-hospital mortality. A higher percentage of *C. glabrata* was isolated from those with NHO candidemia, while *C. tropicalis* was more prevalent in the HO group. Patients with organ failure, retained chemo port, or septic shock, or those who received steroids had significantly higher mortality. Nonetheless, initiation of antifungal therapy within 2 days of diagnosis was a protective factor against in-hospital mortality.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268823000894.

Data availability statement. All collected data used for the analysis in this study are available from the corresponding author at reasonable request.

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Competing interest. The authors have no competing interest to declare.

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