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Persistent candidemia caused by different *Candida* species: Data from a multicenter contemporary cohort

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SUMMARY

Objectives: To explore persistent candidemia by different Candida spp.
Methods: Observational, retrospective, multicenter study including patients with candidemia (Jan 2018–Dec 2022) from 3 hospitals in Italy and Spain. The primary outcome was persistent candidemia, defined as positive blood culture (BC) yielding the same Candida spp≥5 days from the start of active antifungals. Patients with no available follow-up BCs were excluded. A competing risk analysis (competing risk of death) was performed using Fine and Gray regression models.
Results: Among 1188 patients, 298 (25.1%) had persistent candidemia. Cancer (sHR 1.335, 95% CI 1.037–1.633, p=0.011), total parenteral nutrition (sHR 1.440, 95%CI 1.062–1.818, p=0.006), Candida parapsilosis (sHR 1.312, 95% CI 1.075–1.633, p=0.03) and Candida auris (sHR 1.549, 95% CI 1.155–2.159, p=0.029) compared to Candida albicans, were associated with increased risk of persistent candidemia, whereas primary candidemia (sHR 0.573, 95% CI 0.321–0.825, p < 0.001) and early source control (sHR 0.557, 95% CI 0.401–0.713, p < 0.001) were protective. Persistent candidemia was associated with higher 30-day mortality (aHR 1.605, 95% CI 1.176–2.191, p=0.003).
Conclusions: Persistent candidemia affects one in four patients with Candida BSI. Infections caused by Candida parapsilosis or Candida auris require individualized management, with early source control being essential to reduce the risk of persistence.

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Introduction

Persistent candidemia represents a clinically relevant yet underexplored condition. Existing evidence is limited,[1–4] and some available studies involve immunocompromised patients or neonates.[5] A key limitation is the lack of consensus on the time threshold defining persistence, resulting in variability across studies and hindering accurate estimation of its incidence and outcomes.[1–5]

Recognizing persistent candidemia is critical, as it should prompt investigation for occult foci such as thrombophlebitis, endocarditis, or deep-seated infections.[1] However, the impact of persistence candidemia on mortality remains unclear. The attributable mortality rate in patients with candidemia remains as high as 40%[6,7] and their management remains challenging both in intensive care unit (ICU) and outside ICU.[8–11] Therefore, timely recognition and optimal management of persistent candidemia may be essential to prevent poor clinical outcomes. Current guidelines recommend obtaining daily follow-up blood cultures until three consecutive days yield negative results.[12] Adherence to this recommendation facilitates early identification of patients with persistent candidemia and enables prompt implementation of further diagnostic evaluation.

Another knowledge gap concerns the potential association between certain *Candida* species, such as *Candida parapsilosis* and *Candida tropicalis*, and occurrence of persistent candidemia.[4] Over recent decades, non-albicans *Candida* species have become more prevalent, with emerging fluconazole-resistant strains like *Candida parapsilosis* and *Candida auris*.[13–18] Although some recent studies showed that these species are not associated with increased risk of mortality,[6,7,19,20] data on their complications and clinical features remain limited.

This study aimed to assess the risk of persistent candidemia in patients with bloodstream infections (BSIs) caused by different *Candida* species, using a large, contemporary cohort.

Methods

Study design

We performed a retrospective, observational, multicenter cohort study including consecutive patients with BSI caused by *Candida* spp, diagnosed between January 1st, 2018, and December 31st, 2022, in 3 tertiary-care academic hospitals in Italy (Azienda Ospedaliero Universitaria Pisana, Pisa; San Martino Hospital, Genoa), and Spain (Hospital General Universitario Gregorio Marañón, Madrid). At each site, antifungal stewardship policies recommending follow-up blood cultures (BC) every 24–48 h until mycological clearance were implemented.

Inclusion criteria were:

i) adult inpatients (age ≥ 18 years).

ii) a confirmed diagnosis of BSI caused by *Candida* spp.

Exclusion criteria were:

i) mixed fungemia, defined as the isolation of > 1 *Candida* spp from BC obtained less than 48 h[21].

ii) unavailable data on *Candida* spp and/or susceptibility to antifungal agents.

The study was approved by the local Ethical Committee and was conducted in accordance with the Declaration of Helsinki.

Outcome measures

The primary endpoint was persistent candidemia. Persistent candidemia was defined as ≥1 positive blood culture with the same *Candida* species ≥5 days from the start of active antifungal treatment, consistent with previous studies that have adopted this threshold.[1–4]

Secondary endpoint was 30-day mortality rate.

Data collection and definitions

According to a pre-established protocol, the following variables were collected: age, sex, hospital ward stay at the time of *Candida* BSI onset, underlying conditions, risk factors for *Candida* BSI, source of *Candida* BSI, source control. Hidden foci of infections were not systematically investigated. However, screening with echocardiography, ophthalmological examination and Central vein Doppler ultrasound to identify deep-seated or metastatic foci was performed according to attending physician judgment. Data about ocular candidiasis, endocarditis, septic thrombophlebitis were collected when available. Patients were followed up until death or for up to 30 days from *Candida* BSI diagnosis.

An episode of *Candida* BSI was defined as at least one BC positive for *Candida* spp. obtained from a patient with signs and/or symptoms of infection during hospitalization. Sepsis or septic shock were defined according to current criteria[22] and recorded on the day of *Candida* BSI onset. Source of candidemia was defined according to Centers for Disease Control and Prevention definitions[6,23] and were categorized as follows: i) primary candidemia (defined as candidemia without a clear focus of infection such as an abdominal, urinary, or catheter-associated infection)[24]; ii) catheter-related candidemia; iii) abdominal; iv) other sources. Source control measures included the removal of central venous catheter (CVC) and peripherally inserted central catheter (PICC), as well as surgical or radiological procedures to drain abscesses or fluid collections deemed to be the source of *Candida* infection.[25] Early source control was defined as control of the infection source within 24 h from positive BCs.[26]

Microbiological methods

Candida spp identification and *in vitro* antifungal activity were evaluated using standard local methods. Identification of *Candida* spp. was performed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Antifungal susceptibility testing was conducted using a commercial microdilution method (Sensititre™ YeastOne™, ThermoFisher Scientific Inc., Waltham, MA, USA), following the manufacturer's instructions. Interpretive breakpoints were based on the Clinical and Laboratory Standards Institute (CLSI) performance standards for antifungal susceptibility testing of yeasts (M60, 2nd edition).[27] As *Candida auris*-specific susceptibility breakpoints have not yet been established, tentative breakpoints proposed by the CDC were used.[28]

Statistical analysis

Continuous variables were compared by the Student *t* test if normally distributed and the Mann-Whitney U test if non-normally distributed. Categorical variables were evaluated using the $\chi 2$ or the 2-tailed Fisher exact test, as appropriate. Values for continuous and categorical variables are expressed as the median (interquartile range [IQR]) and percentage, respectively.

According to the primary endpoint analysis, as follow-up BC might not always be obtained on consecutive days, only patients with available follow-up blood cultures at Day 5 were included in the analysis. To address immortal time bias, a landmark analysis was conducted, excluding patients who died before the start of active antifungal treatment (Supplementary Fig. S1).[29] Moreover, since the event "death" during the first 5 days from the start of antifungal treatment may preclude the occurrence of the event of interest ("persistent candidemia"), a competing risk analysis was performed using the sub-distribution hazard model (Supplementary Fig. S1). To appropriately handle the competing risk of death, which precludes the occurrence of persistent candidemia, we used Fine and Gray subdistribution hazard models (sHR). This approach estimates the

occurrence of persistent candidemia while accounting for the effect of the competing event *"early death"*. Covariates with univariate p < 0.1 were entered in the model. Active antifungal therapy within 24 h from candidemia onset was included due to clinical relevance. The variance inflation factor (VIF) value was calculated to control the influence of collinearity, assuming a lack of multicollinearity if all variables had a VIF value < 2. No collinearity was detected among the variables included in the final model. Subdistributional hazardratios (sHR) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association.

As for secondary endpoint analysis, factors associated with 30-day mortality were explored using a multivariable Cox regression analysis. The final multivariable model was constructed using a forward stepwise procedure. Adjusted hazard ratios (aHR) and 95% CIs were calculated.

All data were statistically analyzed using two commercially available statistical software packages (SPSS, version 29.0; SPSS Inc., Chicago, IL, United States and R, version 3.4.2; R development core team, Vienna, Austria). All tests were two-tailed, and a p value of < 0.05 was considered statistically significant.

Results

Study population

Among 1691 eligible patients, 124 were excluded as they did not meet the inclusion criteria (97 mixed candidemia, 27 no complete mycological data). After the exclusion of 135 patients who died before receiving active antifungal therapy and 244 due to unavailability of follow-up BCs on Day 5 from the start of active antifungal therapy, a total of 1188 patients were included (*Study flow chart,* Fig. 1). The comparison of included patients and those excluded due to unavailable follow-up BC is reported in Supplementary Table S1.

Clinical characteristics of the study population are shown in Table 1. Most BSIs occurred in medical wards (563/1188, 47.4%), followed by ICU (332/1188, 27.9%), surgery (239/1188, 20.1%) and onco-hematology (54/1188, 4.5%). The most common *Candida* spp were *Candida albicans* (490/1188, 41.2%), followed by *Candida parapsilosis* (453/1188, 38.1%), *Candida tropicalis* (63/1188, 5.3%), *Candida glabrata/Nakaseomyces glabratus* (60/1188, 5.1%), *Candida auris/Candidozyma auris* (60/1188, 5.1%), *Candida krusei/Pichia kudriavzevii* (22/1188, 1.9%) and other *Candida* spp (40/1188, 3.4%). Resistance to fluconazole was observed in 29.4% of all isolates (349/1188): 100% (n=60/60) among *Candida auris*, 81.7% (n=49/60) among *Candida glabrata/Nakaseomyces glabratus,* 45.7% (207/453) among *Candida parapsilosis*, 6.3% (n=4/63) among *Candida tropicalis,* 10% (n=4/40) among other *Candida* spp. and 0.6% (n=3/490) among *Candida albicans* isolates. Resistance to amphotericin B was detected in 56.6% (n=34/60) of *Candida auris.* All *Candida auris* isolates were susceptible to echinocandins. No resistance to echinocandins or amphotericin B was observed in other *Candida* spp. Supplementary Fig. S2 shows the distribution of *Candida* spp among different hospital wards.

Primary outcome

A total of 42/1188 (3.5%) died within 5 days from the start of active antifungal therapy, 298/1188 (25.1%) had persistent candidemia, whereas 848/1188 (71.4%) achieved clearance of *Candida* from the bloodstream within 5 days from start of active antifungal therapy (*Study flow chart*, Fig. 1). Fig. 2 shows the rates of persistent candidemia according to *Candida* spp. The rate of persistent candidemia did not significantly differ according to initial antifungal therapy (therapy received during the first 24 h from candidemia onset): 25.9% (n=83/321) in patients who received echinocandins, 30% (n=18/60) in those who received azoles and 33.3% (3/9) in subjects treated with liposomal amphotericin B as initial therapy (p=0.949) (Supplementary Fig. S3).

A comparison of patients with and without persistent candidemia is reported in Table 2. On multivariable analysis (Table 3), accounting for the competing risk of death, solid cancer (sHR 1.335, 95% CI 1.037–1.633, p=0.011), total parenteral nutrition [TPN] (sHR

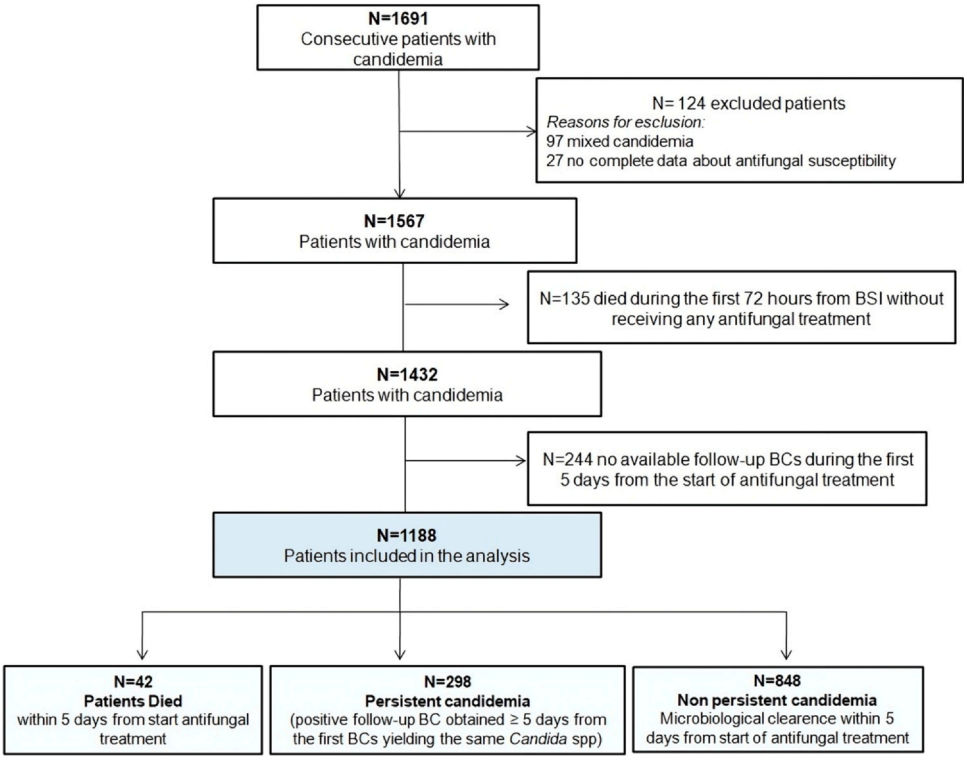

Fig. 1. Study flow chart.

Table 1
Baseline demographic and clinical characteristics of patients with candidemia (Jan 2018–Dec 2022) included in the study.

Variables	N= 1188 (%)
Demographics	
Age, years, median (IQR)	72 (60–80)
Male sex	693 (58.3)
Hospital ward at the time of candidemia	
Intensive care unit	332 (27.9)
Medicine ward	563 (47.4)
Surgical ward	239 (20.1)
Onco-hematology unit	54 (4.5)
Underlying conditions	
Cardiovascular disease	612 (51.5)
Neurological disease	414 (34.8)
Solid cancer	334 (28.1)
Chronic kidney disease	242 (20.4)
Diabetes mellitus	270 (22.7)
Hematological malignancy	96 (8.1)
Charlson Comorbidity Index, median (IQR)	3 (2–6)
Risk factors for candidemia	
Previous antibiotic therapy, last 30 days	1014 (85.4)
Previous corticosteroid therapy, last 30 days	326/1173 (27.8)
Chemotherapy, last 90 days	110/1180 (9.3)
Immunosuppressive therapy, last 30 days	102/1177 (8.7)
Previous intra-abdominal surgery, last 90 days	271/1173 (23.1)
TPN at time of candidemia	757/1158 (65.4)
Central Lines	
CVC or PICC at time of candidemia	745 (62.7)
Septic shock at time of candidemia	193 (16.2)
Source of candidemia	
Catheter-related	591 (49.7)
Primary candidemia	483 (40.7)
Abdominal	50 (4.2)
Other	64 (5.4)
***In vitro* active antifungal therapy within 24 h from positive BC**	412 (34.7)
Infection source control	
Source control	790/909 (86.9)
Early source control	258/909 (28.4)
Time to source control from first positive BCs, days, median, (IQR)	2.5 (1–5)
***Candida* spp**	
Candida albicans	990 (41.2)
Candida parapsilosis	453 (38.1)
Candida auris/ Candidozyma auris	60 (5.1)
Candida glabrata/Nakaseomyces glabratus	60 (5.1)
Candida krusei/Pichia kudriavzevii	22 (1.9)
Candida tropicalis	63 (5.3)
Others*	40 (3.4)
Fluconazole-resistance	349 (29.4)
Complementary screening for hidden foci of infection	
Ophthalmologic examination	527 (44.4)
Echocardiography	641 (54)
Central vein Doppler ultrasound	1013 (85.3)
Outcomes	
Death within 5 days from start of active antifungal therapy	42 (3.5)
Persistent candidemia (defined at day 5 from active antifungal therapy)	298 (25.1)
Thirty-day mortality	344 (29)

BC: Blood cultures; CVC: central venous catheter; IQR: Interquartile range; PICC: peripherally inserted central catheter; TPN: total parenteral nutrition.
Source control was defined as "early" when performed within 24 h from positive blood cultures.
*Other *Candida* species included: 16 *Candida othopsilosis*; 8 *Candida guillermondii/ Meyerozyma guilliermondii;* 5 *Candida lusitaniae/Clavispora lusitaniae;* 4 *Candida dubliniensis;* 4 *Candida kefyr|Kluyveromyces marxianus;* 1 *Candida famata/Debaryozyma hansenii;* 1 *Candida metapsilosis*, 1 *Candida pelliculosa|Wickerhamomyces anomalus.*

1.440, 95% CI 1.062–1.818, p=0.006), *Candida parapsilosis* (sHR 1.312, 95% CI 1.075–1.633, p=0.03) and *Candida auris* (sHR 1.549, 95% CI 1.155–2.159, p=0.029) compared to *Candida albicans* were factors independently associated with increased risk of persistent candidemia, while primary candidemia (sHR 0.573, 95% CI 0.321–0.825, p < 0.001) and early source control (sHR 0.557, 95% CI 0.401–0.713, p < 0.001) were protective factors.

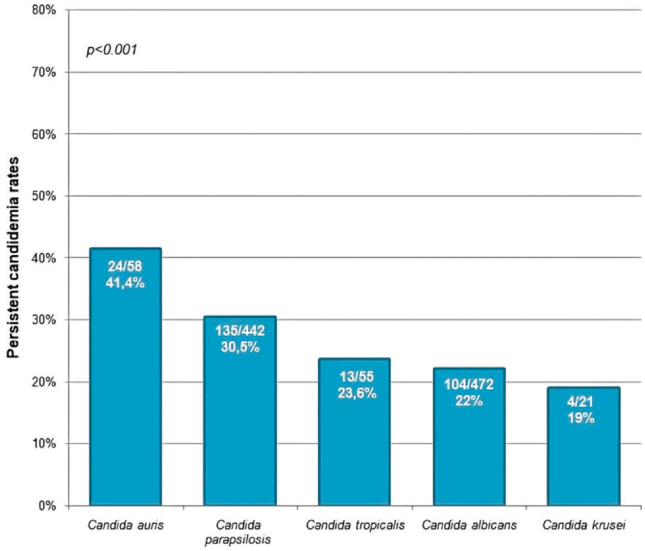

Fig. 2. Persistent candidemia according to *Candida* spp.

Management, complications and outcome of patients with persistent candidemia

Patients with persistent candidemia were more likely to have central vein septic thrombophlebitis and ocular candidiasis compared to controls, whereas endocarditis did not differ between the 2 groups (Table 4). Compared to patients without persistent candidemia, those with persistent candidemia had higher mortality rate (32.6% versus 24.2%, p=0.005) (Table 4). A comparison of patients who died and those who survived is reported in Supplementary Table S2. On Cox regression multivariable analysis (Supplementary Table S3), age (aHR 1.030, 95% CI 1.018–1.043, p < 0.001), septic shock (aHR 2.475, 95% CI 1.692–3.622, p < 0.001), primary candidemia (aHR 1.642, 95% CI 1.14–2.365, p < 0.001) compared to catheter-related candidemia and persistent candidemia (aHR 1.605, 95% CI 1.176–2.191, p=0.003) were factors independently associated with 30-day mortality. Hospitalization in surgical wards (aHR 0.271, 95% CI 0.150–0.489, p < 0.001), *Candida parapsilosis* (aHR 0.573, 95% CI 0.403–0.815, p=0.002) and *Candida auris* (aHR 0.414, 95% CI 0.188–0.910, p=0.028) were independently associated with reduced 30-day mortality.

Discussion

Our study shows that a significant proportion of patients with *Candida* BSI develop persistent candidemia and that two species, *Candida parapsilosis* and *Candida auris*,[30] are independently associated with increased risk of persistent candidemia and a more complicated hospital course.

The rate of persistent candidemia (25.1%) in our study was higher than previously reported in the literature.[1–4] Some factors may explain our findings: first, our cohort included a large proportion of solid cancer patients (28%), which was identified as a predictor of persistent candidemia; second, a significant number of episodes were caused by *Candida parapsilosis* and *Candida auris*, that have higher propensity to cause persistent candidemia; finally, patients who did not undergo follow-up BCs were excluded from the analysis, leading to a smaller denominator compared to other studies. All *Candida* spp are able to adhere to surfaces and form biofilm.[8] However, *Candida parapsilosis* and *Candida auris* appear to have

Table 2
Comparison of patients with persistent candidemia and those without.

Variables	Persistent candidemia N=298	Non persistent candidemia N=848	p value
Demographics			
Age, years, median (IQR)	70 (59–80)	72 (60–81)	0.148
Male sex	164 (55)	505 (59.6)	0.173
Hospital ward at the time of candidemia			
Intensive care unit	86 (28.9)	230 (27.1)	0.564
Medicine ward	142 (47.7)	399 (47.1)	0.859
Surgical ward	54 (18.1)	185 (21.8)	0.177
Onco-hematology unit	16 (5.4)	34 (4)	0.323
Underlying conditions			
Cardiovascular disease	147 (49.3)	443 (52.2)	0.387
Neurological disease	110 (36.9)	288 (34)	0.357
Solid cancer	97 (32.6)	227 (26.8)	0.057
Chronic kidney disease	54 (18.1)	178 (21)	0.289
Diabetes mellitus	74 (24.8)	187 (22.1)	0.325
Hematological malignancy	22 (7.4)	68 (8)	0.725
Charlson Comorbidity Index; median [IQR]	3 (2–6)	3 (1.25–6)	0.592
Risk factors for candidemia			
Previous antibiotic therapy, last 30 days	266 (89.3)	713 (84.1)	*0.029*
Previous corticosteroid therapy, last 30 days	82/294 (27.9)	230/838 (27.4)	0.883
Chemotherapy, last 90 days	32/297 (10.8)	74/842 (8.8)	0.311
Immunosuppressive therapy, last 30 days	23/295 (7.8)	72/841 (8.6)	0.683
Previous intra-abdominal surgery, last 90 days	71/293 (24.2)	190/838 (22.7)	0.586
TPN at time of candidemia	219/294 (74.5)	510/822 (62)	*< 0.001*
Central Lines			
CVC or PICC at time of candidemia	208 (69.8)	516 (60.8)	0.006
Septic shock at time of candidemia	52 (17.4)	126 (14.9)	0.288
Source of candidemia			
Catheter-related	178 (59.7)	407 (48)	*< 0.001*
Primary candidemia	91 (30.5)	361 (42.6)	*< 0.001*
Abdominal	16 (5.4)	32 (3.8)	0.392
Other	13 (4.4)	48 (5.7)	0.455
***In vitro* active antifungal therapy within 24 h from positive BC**	104 (34.9)	286 (33.7)	0.713
Infection source control			
Source control	215/245 (87.8)	552/635 (86.9%)	0.743
Early source control*	48/245 (19.6)	203/635 (32)	*< 0.001*
Time to source control from first positive BCs, days, median, (IQR)	4 (2–7)	2 (1–4)	*< 0.001*
***Candida* spp**			*0.002*
Candida albicans	104 (34.9)	368 (43.4)	
Candida parapsilosis	135 (45.3)	307 (36.2)	
Candida auris/ Candidozyma auris	24 (8.1)	34 (4)	
Candida glabrata/Nakaseomyces glabratus	8 (2.7)	52 (6.1)	
Candida krusei/Pichia kudriavzevii	4 (1.3)	17 (2)	
Candida tropicalis	13 (4.4)	42 (5)	
Others[a]	10 (3.4)	28 (3.3)	
Fluconazole resistance	96 (32.2)	244 (28.8)	0.263

BC: Blood cultures; CVC: central venous catheter; IQR: Interquartile range; PICC: peripherally inserted central catheter; TPN: total parenteral nutrition.
* Source control was defined as "early" when performed within 24 h from positive blood cultures.
[a] Other *Candida* spp: a) in patients who died within 5 days there were 1 *Candida guillermondii/Meyerozyma guilliermondii* and 1 *Candida kefyr|Kluyveromyces marxianus*; b) in patients with persistent candidemia there were 4 *Candida orthopsilosis*, 2 *Candida guillermondii/Meyerozyma guilliermondii*, 1 *Candida famata/Debaryozyma hansenii*, 1 *Candida lusitaniae/Clavispora lusitaniae*, 1 *Candida dubliniensis*, 1 *Candida kefyr|Kluyveromyces marxianus*; c) in patients of non persistent candidemia there were 12 *Candida orthopsilosis*, 5 *Candida guillermondii|Meyerozyma guilliermondii*, 4 *Candida lusitaniae|Clavispora lusitaniae*, 3 *Candida dubliniensis*, 2 *Candida kefyr/Kluyveromyces marxianus*, 1 *Candida metapsilosis*, 1 *Candida pelliculosa|Wickerhamomyces anomalus*.

adhesion-related mechanisms, including cell wall proteins, adhesion factors and regulatory genes involved in biofilm formation.[31,32] These features contribute to their survival in hospital environments, ability to cause outbreaks, and ultimately, may be responsible for persistent candidemia in infected patients.[31,32]

A potential bias could be that these two *Candida* species may represent a surrogate marker of delayed source control of the infection. However, in our study, *Candida auris* or *Candida parapsilosis* remain independently associated with increased risk of persistent candidemia, even after adjustment for early focus removal (within 24 h from candidemia onset), which suggests the importance of a tailored management of patients with candidemia caused by *Candida auris* or *Candida parapsilosis*.

Indeed, our findings may have clinical implications for the management of patients with BSI caused by *Candida parapsilosis* and *Candida auris*. A central vein Doppler ultrasound should be considered in the presence of intravascular lines, whereas fundus oculi should be performed in all patients with persistent candidemia, especially if they are receiving echinocandins. Echocardiography may be reserved for patients with an implantable cardiac device or prosthetic valve. An early source control remains one of the most important protective factors to reduce the risk of dissemination of infection to distant sites. Thus, delay in focus removal should be avoided, especially in patients with BSIs caused by *Candida auris* or *Candida parapsilosis*.

Unlike previous studies,[33] we did not find an association between the initial antifungal therapy (echinocandins vs fluconazole) and the risk of persistent candidemia. Further studies are needed to explore whether a potential association with the type of initial antifungal therapy may exist.

The impact of persistent candidemia on patient outcome remains controversial.[1] However, we found that patients with persistent candidemia needed a longer course of antifungal therapy compared to those without, leading to prolonged hospitalization and increased healthcare costs.[34] Moreover, patients with persistent candidemia in our study had higher risk of 30-day mortality. This finding is highly

Table 3
Multivariable analysis of risk factors for persistent candidemia (taking into account the competing risk of death within the first 5 days from positive BCs).

	sHR (95% CI)	p value
Solid cancer	1.335 (1.037–1.633)	*0.011*
Previous antibiotic therapy	1.351 (0.813–1.889)	0.140
TPN	1.440 (1.062–1.818)	*0.006*
CVC/PICC at time of candidemia	0.824 (0.453–1.195)	0.4
Source of candidemia		
Central venous catheter	*reference variable*	-
Abdominal	1.051 (0.542–1.560)	0.84
Primary candidemia	0.573 (0.321–0.825)	0.013
Other	0.56 (0.185–0.935)	0.09
***In vitro* active antifungal therapy within 24 h from first positive BC**	1.213 (0.942–1.484)	0.09
Early source control	0.557 (0.401–0.713)	*< 0.001*
***Candida* spp**		
Candida albicans	*reference variable*	ref
Candida parapsilosis	1.312 (1.075–1.633)	*0.03*
Candida auris/ Candidozyma auris	1.549 (1.155–2.159)	*0.029*
Candida glabrata/Nakaseomyces glabratus	0.599 (0.141–1.057)	0.19
Candida krusei/Pichia kudriavzevii	1.091 (0.129–2.053)	0.85
Candida tropicalis	0.803 (0.273–1.333)	0.51
Others	1.005 (0.304–1.706)	0.99

Variables included in the model: all variables with $p < 0.1$ at univariate analysis. Active antifungal therapy within 24 h from positive BCs was included due to its clinical relevance. Source control was defined as "early" when performed within 24 h from positive blood cultures.
CVC: central venous catheter; IQR: Interquartile range; PICC: peripherally inserted central catheter; TPN: total parenteral nutrition.

Table 4
Complications and outcome of patients with persistent candidemia compared to those without persistent candidemia.

Variables	Persistent candidemia N=298	Non persistent candidemia N=848	p value
Complementary diagnostic screening			
Ophthalmologic examination	146 (49)	375 (44.2)	0.155
Echocardiography	182 (61.1)	456 (53.8)	*0.029*
Central vein Doppler ultrasound	265 (88.9)	719 (84.8)	0.078
Complications			
Ocular candidiasis	12/146 (8.2)	13/375 (3.5)	*0.037*
Endocarditis	6/182 (3.3)	17/456 (3.7)	1.0
Septic thrombophlebitis	30/265 (11.3)	34/719 (4.7)	< 0.001
Thirty-day mortality	97 (32.6)	205 (24.2)	*0.005*

significant as it highlights the importance of implementing a targeted management approach in patients with candidemia, particularly by identifying previously undetected foci of infection. Future studies are needed to assess the impact of different antifungal regimens on the outcome of patients with persistent candidemia.

This study has several limitations. First, due to its retrospective design, the potential impact of unmeasured confounders cannot be excluded. Although some relevant variables were collected (such as the removal of indwelling venous catheters and its timing, which we included under the definition of early source control), other important factors may not have been consistently assessed. These include the presence of mycotic aneurysms, prosthetic valves, cardiac implantable electronic devices (e.g., pacemakers or ICDs), or other deep hidden foci of infection, which may have contributed to candidemia persistence in some cases, but were not systematically investigated. Variability in clinical practices across hospitals may be occurred. Diagnostic procedures for detection of hidden foci of candidemia were not consistently performed across all patients. However, our study reflects the real-world practice. Moreover, all the participating centers implemented antifungal stewardship policies (e.g. follow-up blood cultures every 24–48 h until mycological clearance, infectious disease consultation for all *Candida* BSI).

Another limitation may be due to the exclusion of patients with unavailable follow-up BC. We found that these subjects were more frequently hospitalized in internal medicine wards compared to those included in the final analysis. This finding may reflect a lower adherence to candidemia management guidelines, including the implementation of bundled care practices, in medical wards compared to ICU, surgical, or onco-hematology settings. Of importance, the excluded patients had higher mortality rate compared to those included in the analysis. Several factors may explain this finding: 1) these patients were older; 2) they may have received suboptimal management, as suggested by the lack of follow-up BC and less common source control; 3) some patients may have died before a follow-up BC could be obtained, thus precluding assessment of persistence; 4) in some cases, especially in older or terminally ill patients, diagnostic workup (including follow-up BC) may have been intentionally omitted due to poor prognosis or transition to palliative care; 5) the absence of follow-up BC may have negatively impacted patient outcomes by delaying the recognition and treatment of persistent candidemia and associated deep-seated infections. Although the exclusion of these patients may have led to underestimation of the true incidence of persistent candidemia, it strengthens the robustness of our data, as it ensures accurate classification of persistent candidemia, which is the primary endpoint of our study.

Furthermore, although the overall cohort was large, the number of cases with persistent candidemia was relatively limited, which may reduce the statistical power to detect associations for less common risk factors. Differences in local epidemiology, antifungal resistance patterns, and source control practices may limit the generalizability of our findings and introduce residual confounding. Our study population has a high prevalence of *Candida parapsilosis* and *Candida auris*. These species-specific epidemiological features may have influenced the observed risk of persistent candidemia and limit the generalizability of our findings. Thus, caution is warranted when extrapolating these results to institutions with a different *Candida* epidemiology, particularly where *Candida albicans* remains predominant.

Although our observational study is prone to potential selection bias, we addressed immortal time bias by using a Landmark analysis

and performed a competing risk analysis to account for the competing risk of death and persistent candidemia. We did not investigate molecular characteristics or circulating clones of *Candida* isolates in our hospitals. Therefore, our findings should be validated in different epidemiological settings.

In conclusion, persistent candidemia is relatively common in clinical settings with high prevalence of *Candida parapsilosis* and *Candida auris.* Solid cancer and the use of TPN are additional risk factors, whereas early source control remains the most important protective factor. Nosocomial spread of difficult-to-treat and persisting *Candida* spp, such as *Candida parapsilosis* and *Candida auris,* should be prevented through strict infection control and surveillance programs.

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Author contributions

GT, AV, MF and MB conceived of the presented idea. AF, MC, CB, CM, PE collected data. GT performed the statistical analysis. All authors discussed the results and significantly contributed to the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Outside the submitted work, GT declares personal fees for speaker/advisor from Shionogi, Menarini, MSD, Gilead, Angelini. Outside the submitted work, AV reports personal fees for speaker/advisor from Pfizer Inc, Shionogi, Tillotts Pharma, Menarini, Gilead Italia, Merck. Outside the submitted work, DRG reports investigator-initiated grants from Pfizer Inc, Shionogi, BioMérieux, Tillotts Pharma, Menarini, and Gilead Italia, personal fees for speaker/advisor from Pfizer, Menarini, BioMérieux, and Tillotts Pharma. Outside the submitted work, MB reports research grants and/or personal fees for advisor/consultant and/or speaker/ chairman from Bayer, BioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, and Shionogi. JSG has received speaker honoraria by Gilead, Menarini, and Pfizer; travel grant by AstraZeneca and has been advisory board for Pfizer, outside of the submitted work. Outside the submitted work, PM reports investigator-initiated grants from Pfizer Inc, Shionogi, Tillotts Pharma, Menarini, and Gilead. Outside the submitted work, VDP reports payments for participation in a company sponsored speaker's bureau from A.d.a, consulting fee from Biorad, supports for attending meetings from Arrow Diagnostics. Outside the submitted work, MF declares unconditional grants from MSD and grants/or speaker honoraria from Angelini, Shionogi, Pfizer, Menarini, Gilead and Nordic Pharma. The other authors report no conflicts of interest relevant to this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106586.

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