**Introduction**

Candidemia is the most common fungal infection among hospitalized patients, associated with high morbidity and mortality. Persistent candidemia (PC), defined as the repeated isolation of *Candida* spp. from blood cultures after a specified period, is a frequent complication and has been linked to worse clinical outcomes. However, the definition of PC varies widely between studies, and the lack of systematic follow-up blood cultures, often limits accurate identification of persistence. We aimed to investigate the risk factors associated with PC within what is, to our knowledge, the largest cohort analysed to date.

**Methods**

We conducted a retrospective study at a 900-bed tertiary hospital in Valencia, Spain, including all patients with ≥1 positive peripheral blood culture for *Candida* spp. between January 2010 and September 2024. PC was defined as positive blood cultures ≥ 5 days after initiation of appropriate antifungal therapy. Non–PC was defined as a negative follow-up culture <5 days antifungal therapy initiation. Species were identified using MALDI-ToF, and antifungal susceptibility tested by Sensititre Yeast One® (ThermoFisher, USA) according to CLSI guidelines. A random sample of 100 non-PC cases was selected as controls. Clinical and microbiological characteristics, complications and 30-day mortality were compared between PC and non-PC groups. Categorical variables were analysed using chi-squared or Fisher’s exact tests, and continuous variables were compared using t-tests or Mann–Whitney U tests, as appropriate. Variables with a p-value <0.1 in univariate analysis or deemed clinically relevant, were considered as candidate predictors for multivariate logistic regression. Final model was obtained using a backward stepwise selection approach to identify factors independently associated with PC.

**Results**

A total of 652 candidemia episodes were identified during the study period, 481 (73.8%) had follow-up blood cultures. Among the 171 patients without follow-up, 99 (57.9%) died within the first 7 days of antifungal therapy. PC occurred in 100/481 cases (20.8%). Compared to non-PC, PC patients had a significantly higher Candida score (2.0 vs. 1.5, *p*=0.008), more frequent parenteral nutrition (62% vs. 47%, *p*=0.047), central venous catheter presence (81% vs. 66%, *p*=0.025), previous multisite colonization (58% vs. 36%, *p*=0.003), and ICU-acquired candidemia (53% vs. 36%, *p*=0.023). Early catheter removal (58.4% vs. 27.3%, *p*<0.001) and resolution of other foci (81.8% vs. 31.2%, *p*=0.003) were more common in non-PC. Thirty-day mortality was higher in PC cases (30% vs. 15%, *p*=0.018). Full clinical comparisons between groups are detailed in Table 1. No significant differences were found between groups regarding *Candida* species distribution or antifungal susceptibility profiles (Table 2).

In the multivariate logistic regression analysis, central venous catheter (OR 2.64[1.09–6.42] *p*=0.032) and previous multisite colonization (OR 2.31[1.10–4.84] *p*=0.027) were independently associated with an increased risk of PC. Early catheter removal (within 48 h) was independently associated with a reduced risk (OR 0.18[0.08–0.41] *p*<0.001).

**Conclusion**

Multiple colonization prior to candidemia and the presence of parenteral nutrition were independently associated with persistent candidemia, while early catheter removal was independently associated with a lower risk. These findings support the implementation of candidemia management bundles to ensure timely source control and improve outcomes.

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| **Table 1. Clinical characteristics, management, and outcomes of patients with persistent vs. non-persistent candidemia** |
| **Variable, n (%)** | **Total (n = 200)** | **NPC (n = 100)** | **PC (n = 100)** | **p-value** |
| Candida score, mean (sd) | 1.8 (1.2) | 1.5 (1) | 2 (1.2) | **0.00836** |
| Charlson, mean (sd) | 5.5 (3.7) | 5.8 (4) | 5.3 (3.3) | 0.366 |
| Age, mean (sd) | 56.2 (22.8) | 58.7 (22) | 53.7 (23.3) | 0.125 |
| Sex: Male | 130 (65%) | 71 (71%) | 59 (59%) | 0.103 |
| Surgery in the past 30 days | 108 (54%) | 47 (47%) | 61 (61%) | 0.0651 |
| Previous therapy |  |  |  |  |
| Corticosteroid therapy | 49 (24.5%) | 22 (22%) | 27 (27%) | 0.511 |
| Other immunosuppresive therapy | 37 (18.5%) | 13 (13%) | 24 (24%) | 0.0686 |
| Broad spectrum antibiotics | 173 (86.5%) | 82 (82%) | 91 (91%) | 0.0978 |
| Prophylactic antifungal therapy | 31 (15.5%) | 10 (10%) | 21 (21%) | 0.0507 |
| Risk factors |  |  |  |  |
| Central venous catheter | 147 (73.5%) | 66 (66%) | 81 (81%) | **0.0249** |
| Parenteral nutrition | 109 (54.5%) | 47 (47%) | 62 (62%) | **0.0468** |
| Severe sepsis | 49 (24.5%) | 26 (26%) | 23 (23%) | 0.742 |
| Previous candidemia | 4 (2%) | 3 (3%) | 1 (1%) | 0.621 |
| Previous multisite colonization | 94 (47%) | 36 (36%) | 58 (58%) | **0.00293** |
| Profound neutropenia (<500 cells/mL) | 21 (10.5%) | 13 (13%) | 8 (8%) | 0.356 |
| Candidemia during ICU stay | 89 (44.5%) | 36 (36%) | 53 (53%) | **0.0228** |
| Invasive mechanical ventilation | 49 (24.5%) | 20 (20%) | 29 (29%) | 0.188 |
| Initial antifungal agent |  |  |  | 0.456 |
| Amphotericin B | 23 (11.5%) | 9 (9%) | 14 (14%) |  |
| Anidulafungin | 100 (50%) | 47 (47%) | 53 (53%) |  |
| Caspofungin | 34 (17%) | 20 (20%) | 14 (14%) |  |
| Fluconazole | 33 (16.5%) | 21 (21%) | 12 (12%) |  |
| Micafungin | 7 (3.5%) | 3 (3%) | 4 (4%) |  |
| Treatment duration | 25.2 (13.3) | 21.2 (11.7) | 29.2 (13.7) | **<0.001** |
| Infection focus |  |  |  | 0.137 |
| Catheter | 97 (48.5%) | 45 (45%) | 52 (52%) |  |
| Unknown | 45 (22.5%) | 27 (27%) | 18 (18%) |  |
| Ventricular device | 4 (2%) | 1 (1%) | 3 (3%) |  |
| Soft tissue infection | 9 (4.5%) | 7 (7%) | 2 (2%) |  |
| Abdominal infection/abscess | 23 (11.5%) | 8 (8%) | 15 (15%) |  |
| Urinary | 22 (11%) | 12 (12%) | 10 (10%) |  |
| Management approach to candidemia |  |  |  |  |
| Antifungal therapy within 48h | 171 (85.5%) | 86 (86%) | 85 (85%) | 1 |
| Catheter removed within 48 h  | 66 (42.9%) | 45 (58.4%) | 21 (27.3%) | **<0.001** |
| Non-catheter focus resolution within 48h  | 23 (60.5%) | 18 (81.8%) | 5 (31.2%) | **0.0026** |
| Metastatic infection | 20 (10%) | 6 (6%) | 14 (14%) | 0.099 |
| Chorioretinitis | 2 (10%) | 0 (0%) | 2 (14.3%) |  |
| Endocarditis | 5 (25%) | 1 (16.7%) | 4 (28.6%) |  |
| Hepatosplenic infection | 5 (25%) | 2 (33.3%) | 3 (21.4%) |  |
| Meningitis | 3 (15%) | 0 (0%) | 3 (21.4%) |  |
| Osteomyelitis | 3 (15%) | 1 (16.7%) | 2 (14.3%) |  |
| Other late complications | 2 (10%) | 2 (33.3%) | 0 (0%) |  |
| 30-days mortality | 45 (22.5%) | 15 (15%) | 30 (30%) | **0.0178** |
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| **Table 2. Microbiological characteristics of patients with persistent vs. non-persistent candidemia.** |
| **Species** | **Total** | **Non-PC** | **PC** |  | **p** |  |  |
|  *Candida albicans* | 45 (22.5%) | 27 (27%) | 18 (18%) |  | 0.366 |  |  |
|  *Candidozyma auris* | 44 (22%) | 18 (18%) | 26 (26%) |  |  |  |  |
|  *Nakaseomyces glabratus* | 26 (13%) | 16 (16%) | 10 (10%) |  |  |  |  |
|  *Candida parapsilosis* | 71 (35.5%) | 32 (32%) | 39 (39%) |  |  |  |  |
|  *Candida tropicalis* | 6 (3%) | 3 (3%) | 3 (3%) |  |  |  |  |
|  Otras candidas | 8 (4%) | 4 (4%) | 4 (4%) |  |  |  |  |
| **Antifungal agent** | **MIC 50 non-PC** | **MIC90 non-PC** | **MIC50 PC** | **MIC90 PC** | **p** |  |  |
| Amphotericin B | 0.5 | 1 | 0.5 | 0.5 | 0.172 |  |  |
| Fluconazole | 1 | 256 | 2 | 256 | 0.166 |  |  |
| Itraconazole | 0.06 | 0.5 | 0.125 | 0.5 | 0.736 |  |  |
| Voriconazole | 0.03 | 2 | 0.125 | 2 | 0.070 |  |  |
| Caspofungin | 0.06 | 0.5 | 0.125 | 0.5 | 0.418 |  |  |
| Anidulafungin | 0.125 | 2 | 0.125 | 2 | 0.163 |  |  |
| Micafungin | 0.03 | 2 | 0.06 | 2 | 0.083 |  |  |
| Posaconazole | 0.03 | 1 | 0.06 | 0.5 | 0.989 |  |  |
| Isavuconazole | 0.03 | 0.6 | 0.047 | 1.5 | 0.429 |  |  |
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