doi:10.4149/neo_2020_200204N105

Etiology of candidemia in patients with solid tumors - 7 years of experience of one oncology center

M. SZYMANKIEWICZ[1,*], T. NOWIKIEWICZ[2,3]

[1]*Department of Microbiology, Prof. F. Lukaszczyk Center of Oncology in Bydgoszcz, Bydgoszcz, Poland;* [2]*Clinical Department of Breast Cancer and Reconstructive Surgery, Prof. F. Lukaszczyk Center of Oncology in Bydgoszcz, Bydgoszcz, Poland;* [3]*Department of Diagnosis and Treatment of Breast Diseases, Department of Oncological Surgery, Collegium Medicum UMK in Toruń, Toruń, Poland*

**Correspondence: szymankiewiczm@co.bydgoszcz.pl*

Received February 4, 2020/ Accepted March 30, 2020

Although the candidemia still remains a serious health problem, the study of candidemia in cancer patients is limited. We conducted a retrospective analysis of candidemia among 31 adult patients hospitalized in one oncological center. The mean annual incidence of candidemia was 0.14±0.05/1000 patient-days (range 0.04-0.91). In 10 patients (32.3%), the catheter-related infection was diagnosed; in the remaining 21 patients (67.7%), it was a secondary infection. From 31 patients of candidemia, 15 died (48.4% 30-day mortality), but an overall mortality rate during hospital stay was 61.3% (19 cases). Patients with secondary candidemia, ASA=IV and complicated postoperative course, had poorer 1-year survival probability compared with patients with catheter-related infection (p=0.004), ASA<IV (p=0.0393), and uncomplicated postoperative course (p=0.0009). *C. glabrata* (n=13, 41.9%) was the most frequently isolated species, followed by *C. albicans* (n=12, 38.7%) and *C. parapsilosis* (n=3, 9.7%). *C. lusitaniae* (n=2, 6.5%), and *C. tropicalis* (n=1, 3.2%) were sporadically isolated. Within *C. glabrata*, there was no resistance to anidulafungin, two strains (15.4%) were resistant to fluconazole, while the others showed intermediate susceptibilities to this drug. A total of 58.0% of all *Candida* spp. strains were sensitive to fluconazole, and 90.0% of the strains were sensitive to anidulafungin. Mortality in candidemia among patients with solid tumors undergoing surgery remains high. The complicated postoperative course requiring reoperation and secondary origin of candidemia are factors for poor prognosis. The demonstrated dominant role of *C. glabrata* in inducing candidemia is becoming a serious clinical and therapeutic problem.

Key words: candidemia, solid tumors, mortality, etiologic agents, sensitivity to antimycotics

The increasing incidence of candidemia among cancer patients and poor prognosis encourages the undertaking of research on the current etiological agents of candidemia. While there are quite numerous reports of candidemia among patients with hematological cancers, only a few publications are dealing with this problem among patients with solid tumors [1–3].

It is known, however, that the species structure of candidemia has changed in recent years [4]. In Europe, a decrease in the frequency of isolation of *Candida albicans* (*C. albicans*) has been observed, although it often remains the dominant species in candidemia in intensive care units, and there has been an increase in the incidence of non-*albicans Candida*, with varying percentages of individual species [5].

Candidemia occurs in patients at increased risk of developing a fungal infection, and the likelihood of it developing depends on the accumulation of many risk factors. Cancer patients are more likely to develop candidemia. Immunodeficiencies, especially periodic neutropenia and lymphopenia, mainly related to CD4 + lymphocytes, resulting from the underlying disease and chemotherapy and immunotherapy used in treatment, help infections to overcome the immune barrier and develop [4, 6, 7]. Surgical operations during advanced stages of cancer are often extensive, frequently requiring gastrointestinal opening and subsequent anastomosis. This increases the risk of candidemia from the surgical site. Also, long-term central venous catheters used in cancer patients, a stay in an intensive care unit, and vancomycin or piperacillin/tazobactam treatment also promote fungal infections [3, 8, 9].

Antifungal treatment strategies distinguish empirical, pre-emptive, and targeted treatment. About 80.0% of patients who develop invasive fungal infections receive empirical treatment [10]. For empirical treatment, the IDSA (Infec-

tious Diseases Society of America) and ESCMID (European Society of Clinical Microbiology and Infectious Diseases) recommend triazoles or echinocandins [11, 12].

The aim of our work is a retrospective analysis of the epidemiology of candidemia among patients with solid tumors, analysis of the participation of individual *Candida* species in inducing candidemia, as well as assessing the sensitivity of isolated pathogens to fluconazole and anidulafungin. We also calculate the 30-day mortality rate and 1-year survival probability.

Patients and methods

Patients and criteria of candidemia. A retrospective study covered 31 adult patients, hospitalized in one oncological center with >300 beds, in 3 surgical departments, as well as in the intensive care unit, in which candidemia was diagnosed in the period from 01/2013–09/2019. The source of demographic data (age, sex, and body mass index-BMI index) and clinical data of the analyzed group of patients (including the results of microbiological tests) was the hospital medical documentation of the patients.

An infection associated with the stay in the ward was deemed to be candidemia that had developed 48 h after admission to the ward. Candidemia was diagnosed when at least one positive blood culture showed the presence of *Candida* fungi. Blood infection was considered to be catheter-related when its origin was causally related to the presence of a venous catheter and the same *Candida* species was isolated from the blood and the removed central catheter. Secondary infection was diagnosed when the same fungal species was cultured from blood and other sites or infection sites (gastrointestinal tract, respiratory system, urinary tract, and other sites). Cases where no microbiological confirmation of the origin of the candidemia was obtained (but catheter-related infection was ruled out) were classified as a secondary without microbiological confirmation. Secondary infections confirmed microbiologically and without such confirmation were jointly referred to as secondary infections. The day of taking the blood sample for the test, which was positive, was considered to be the day of candidemia diagnosis. In accordance with the hospital's standard practice, the placement and management of the central venous catheter were covered by the applicable standard of care, aimed at the prevention of infection. If catheter infection was suspected, the catheter was immediately removed and the tip of the catheter was sent for microbiological examination.

Microbiological analysis. Blood for testing was collected in *BacT/ALERT* FN Plus and FA Plus bottles with culture medium, and incubated in an automated *BacT/ALERT 3D* system (bioMérieux, US) based on colorimetry. In the case of obtaining a positive signal from the analyzer, a Gram-stained preparation was made and plated in a laminar chamber on solid media: Columbia agar + 5% sheep blood and chocolate agar with Vitox (Thermo Scientific, Germany). The grown microorganisms were identified using VITEK 2 YST cards for the VITEK 2 Compact system (bioMérieux, France). The sensitivity of fungi to fluconazole and anidulafungin was assessed using gradient strips impregnated with antibiotic with the E-test system (bioMérieux, France) on RPMI agar (bioMérieux, France). Incubation was carried out in an incubator at 35°C for 24–48 hours (until growth was obtained). MIC (minimal inhibitory concentration) results were interpreted in accordance with current EUCAST version 9, valid from 12.02.2018, and previous versions of documents (EUCAST, European Committee on Antimicrobial Susceptibility Testing). MIC_{50} (lowest inhibitory concentration of 50.0% isolates) and MIC_{90} (lowest inhibitory concentration of 90.0% isolates) were also evaluated.

Since 2016, in positive blood cultures, microbial genetic material has been additionally detected by multiplex PCR using a blood culture identification panel (BCID) in the FilmArray system. FilmArray (BioFire Diagnostics, Salt Lake City, US) is an automated *in vitro* diagnostic system that uses nested multiplex polymerase chain reaction (nmPCR) and high resolution melting analysis to simultaneously detect and recognize many specific nucleic acid sequences found in a clinical sample. Within *Candida*, the test detects the five most common species: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*. The first positive blood culture obtained from a patient in the course of diagnosis of a generalized infection was qualified for the multiplex PCR test. PCR samples were prepared according to the manufacturer's instructions. All positive results in the multiplex PCR method were confirmed by positive cultures and identification as described above.

In the event of suspected catheter infection, the catheter tip, taken into a sterile container, was inoculated onto Columbia agar + 5% sheep blood (Thermo Scientific, Germany) in a quantitative and semi-quantitative manner according to Maki et al. [13] through rolling. After the incubation period, colonies were counted. Fungi were identified using the VITEK 2 Compact system (bioMérieux, France). Growth of microorganisms of the same species ≥15 colonies in the semi-quantitative method, and in the quantitative method $>10^3$ CFU/ml, was interpreted as a positive result.

Groups created for analysis. Depending on the origin of the candidemia, two groups of patients were distinguished. The first group included patients with secondary candidemia (n=21), the second group includes patients with catheter-derived candidemia (n=10). The frequency of occurrence of risk factors in both groups was compared.

In the examined patients, the causes of deaths were analyzed. To this end, groups of patients qualified for surgery due to *de novo* malignant disease or due to recurrence or progression of the underlying disease were identified, cases with different primary tumor locations (gastrointestinal tract, urinary tract, gynecological neoplasms), and groups of patients with normal or complicated (necessity of

reoperation) postoperative course. The clinical significance of preoperative systemic treatment (or radiotherapy) was also determined.

30-day mortality was defined as the death occurring within 30 days after the day of candidemia diagnosis. The mortality during the hospital stay was also given.

Statistical analysis. Statistical analysis for categorical variables was carried out using chi-square test with Yates correction or Fisher's exact test with Freeman-Halton correction. A Mann-Whitney U test was used to analyze continuous variables. Survival analysis was conducted using Statistica (data analysis software system, TIBCO Software Inc., www.statistica.io, version 13.3). The Kaplan-Meyer model with a log-rank test was adopted to compare survival between groups. The results were analyzed for the endpoints: death or the last visit to the hospital, which data was available in the medical reports. Differences were accepted as statistically significant when the significance level was less than 0.05 ($p<0.05$). The results are also shown as % and median.

The study received approval from the Bioethical Commission at the Collegium Medicum of Nicolaus Copernicus University in Toruń (KB approval number 830/2019).

Results

The annual incidence of candidemia. In almost seven years, 31 cases of candidemia were found. The mean annual incidence of candidemia in relation to four departments reporting its occurrence was 0.14±0.05/1000 patient-days (range 0.04–0.91). The highest average annual incidence rate was recorded in the intensive care unit 0.91±1.00/1000 patient-days (range 0.0–2.54).

Characteristics of patients. The median age of the patients analyzed was 66.0 years (in the range of 38 to 86 years), median BMI 25.3 kg/m^2 (range 15.1–36.0). Twenty-one of the 31 patients (67.7%) were women. Seven patients (22.6%) had a level ASA=IV (risk associated with the occurrence of serious complications or death assessed according to the American Society of Anesthesiology (ASA)). All patients underwent surgery due to a malignant diagnosis. Sixteen out of 31 patients (51.6%) underwent surgery up to 30 days before the onset of candidemia. In 17 patients (54.8%), the primary tumor was localized in the gastrointestinal tract, in 12 patients (38.7%) – in the female genital tract, in the remaining cases it was localized in the urinary tract (n=2, 6.4%).

In 20 cases, the diagnosis of candidemia (64.5%) concerned patients undergoing surgical treatment for a newly diagnosed primary malignant tumor. In 10 patients, the indications for surgery were the progression symptoms of a previously diagnosed neoplastic disease, while in one case – local complications (entero-vaginal fistula and entero-bladder fistula) in the patient during palliative treatment (35.5% in total).

In 13 patients, preoperative systemic treatment or CHTH (chemotherapy) combined with RTH (radiotherapy) was used. Slightly more than 4/5 of the analyzed patients (n=26, 83.9%) received parenteral nutrition in the past. Up to 30 days before the diagnosis of candidemia, 27 of 31 patients (87.1%) were treated with broad-spectrum antibiotics, including 17 patients (54.8%) using at least one of the following antibiotics: vancomycin or piperacillin with tazobactam. In contrast, 20 out of 31 patients (65.0%) received empirical antifungal therapy using fluconazole and/or echinocandins.

Epidemiology of candidemia, *Candida* species distribution. The median of days of hospitalization up to candidemia was 36 (range 7–70). The characteristics of patients with regard to the division into the origin of candidemia are presented in Table 1. In 10 patients (32.3%), the catheter-related infection was diagnosed, in the remaining 21 patients (67.7%), it was a secondary infection, with a primary focus located in the gastrointestinal tract, respiratory system, urinary tract or in other sites. In 11 patients (35.5%), candidemia was diagnosed in the intensive care unit, and in the remaining 20 patients (64.5%) in the surgical wards. Bacterial and fungal co-infection was found in 5 requirements (16.1%). However, cultured bacterial strains were not the subject of analyzes in this work. Confirmation of the microbiological source of the candidemia was obtained in 22/31 (72.0%) patients, in all cases associated with catheter-induced disease (10/10, 100.0%) and in 12/21 cases (57.1%) of secondary infection.

31 *Candida* strains were cultured from patients, including 12 (38.7%) *C. albicans* strains and 19 (61.3%) non-*albicans Candida* strains. Among non-*albicans Candida*, *C. glabrata* (n=13) was the most numerous, which was also the most frequently isolated species and constituted 41.9% of all isolated *Candida* fungi. Other isolated species are *C. parapsilosis* (3/31, 9.7%), *C. lusitaniae* (2/31, 6.5%), and *C. tropicalis* (1/31, 3.2%). The distribution of *Candida* species responsible for candidemia is shown in Table 2.

***Candida* susceptibility to fluconazole and anidulafungin.** No strains resistant to fluconazole (MIC<1.0 mg/l) and anidulafungin (MIC<0.02 mg/l) were found within *C. albicans*. Among non-*albicans Candida*, a species dominated that shows low susceptibility to triazoles, *C. glabrata*. According to EUCAST criteria, two *C. glabrata* strains showed fluconazole resistance (MIC=96 and MIC>256 mg/l), the remaining 11 strains were intermediate (MIC 3–24 mg/l). All strains from this species showed sensitivity to echinocandins – anidulafungin (MIC<0.023 mg/l). Among *C. parapsilosis*, no fluconazole resistant strains (MIC<1.0 mg/l) were found, while all strains showed reduced sensitivity to echinocandins – anidulafungin (MIC 0.75–1.50), remaining intermediately susceptible to this antibiotic. *C. lusitaniae* strains remained sensitive to fluconazole (MIC<0.75 mg/l). The *C. tropicalis* strain was sensitive to fluconazole (MIC 0.19 mg/l) and anidulafungin (MIC 0.008 mg/l). The MIC, MIC50 and MIC90 values are shown in Table 3. In total, 58.0% of all *Candida* strains were sensitive to fluconazole and 90.0% of the strains were sensitive to anidulafungin.

Table 1. Demographics and clinical characteristics of patients with candidemia.

Parameter/Group	Number of patients (%) n = 31	Secondary candidemia[4] Number of patients n = 21 (67.7%)	Catheter-related candidemia Number of patients n = 10 (32.3%)	p-value
Age (years), median, range	66 (38-86)	67 (59-86)	63 (38-76)	0.107
Sex (n), %				
Female	21 (67.7)	13 (61.9)	8 (80.0)	0.551
Male	10 (32.3)	8 (38.1)	2 (20.0)	
BMI (kg/m^2), median, range	25.3 (15.1-36.0)	26.5 (15.1-36.0)	23.8 (21,2-35,4)	0.711
Type of cancer (n), %				
Gynecologic tumor[1]	12 (38.7)	5 (23.8)	7 (70.0)	**0.042**
Gastrointestinal tract tumor[2]	17 (54.8)	14 (66.7)	3 (30.0)	
Urinary tract tumor[3]	2 (6.4)	2 (9.5)	0 (0.0)	
ASA score				
<IV	24 (77.4)	15 (71.4)	9 (90.0)	0.248
IV	7 (22.6)	6 (28.6)	1 (10.0)	
Previous surgery				
<30 days	16 (51.6)	10 (47.6)	6 (60.0)	0.795
≥30 days	15 (48.4)	11 (52.4)	4 (40.0)	
Malignancy status (Type of surgery)				
Recent diagnosis (primary surgery)	20 (64.5)	14 (66.7)	6 (60.0)	0.969
Progression (secondary surgery) and palliative status (palliative surgery)	11 (35.5)	7 (33.3)	4 (40.0)	
Days in hospital until *Candida* BSI diagnosis, median, range	36 (7-70)	38 (7-70)	29 (12-62)	0.865
Hospitalization before candidemia in ICU no less than 48 h, n (%)	11 (35.5)	10 (47.6)	1 (10.0)	0.100
Prior exposure to broad-spectrum antibiotics, within 30 days before diagnosis of candidemia	27 (87.1)	19 (90.5)	8 (80.0)	0.810
Prior exposure to at least one of these antibiotics: vancomycin or piperacillin + tazobactam, within 30 days before diagnosis of candidemia	17 (54.8)	14 (66.7)	3 (30.0)	0.126
Anti-fungal empiric therapy receiving (fluconazole and/or anidulafungin), within 30 days before diagnosis of candidemia	20 (65.0)	14 (66.7)	6 (60.0)	0.969
TPN (Total parenteral nutrition) receiving	26 (83.9)	18 (85.8)	8 (80.0)	0.906
Bacterial-co infections (bacteremia)	5 (16.1)	4 (19.0)	1 (10.0)	0.906
30-day mortality	15 (48.4)	14 (66.7)	1 (10.0)	**0.006**
Overall mortality rate during hospital stay	19 (61.3)	17 (80.6)	2 (20.0)	**0.002**

[1]Gynecologic tumor (ovarian cancer, cervical cancer, endometrial cancer, vulvar cancer); [2]Gastrointestinal tract tumor (colon cancer, stomach cancer, bile ducts cancer, esophagus cancer); [3]Urinary tract tumor (urinary bladder cancer); [4]Secondary source (pulmonary tract, digestive tract, urinary tract, other non-catheter – related origin of candidemia); ASA score - American Society of Anesthesiologists score; BMI - body mass index

Table 2. Distribution of *Candida* species.

Candida species	No. (%) of patients from whom the pathogen was isolated		
	Total	Secondary candidemia	Catheter-related candidemia
C. glabrata	13 (41.9)	10 (47.6)	3 (30.0)
C. albicans	12 (38.7)	6 (28.6)	6 (60.0)
C. parapsilosis	3 (9.7)	3 (14.3)	–
C. lusitaniae	2 (6.5)	2 (9.5)	–
C. tropicalis	1 (3.2)	–	1 (10.0)
Total	31 (100.0)	21 (100.0)	10 (100.0)

30-day mortality and one-year survival probability. During hospitalization, a total of 19 deaths (61.3%) occurred in the study group and 15 deaths (48.4%) within 30 days following the day of candidemia diagnosis. Among the patients who died within their hospital stay, the complicated postoperative course (reoperation required) and secondary type of candidemia were more common than among the patients who lived (p=0.001 and p=0.004, respectively). Table 4 lists the most important risk factors for patients' deaths. 1-year survival probability after diagnosis with respect to postoperative course, the origin of candidemia, *Candid*a species, and ASA score is shown in Figures 1 A–D.

Discussion

In our work, we presented an almost 7-year retrospective analysis of the occurrence of candidemia among patients undergoing surgery for solid tumors. Infections of fungal

etiology caused by *Candida* strains are not frequently encountered (in the presented clinical material the incidence of candidemia was 0.14±0.05/1000 patient-days/year). However, due to the long duration of treatment and high mortality, they still remain a serious health problem.

Candidemia was most common in the intensive care unit, and the average incidence rate of 0.91±1.00/1000 patient-days was slightly higher than reported in the paper by Nawrot et al. [14], where for intensive care units it was 0.76±0.56/1000 patient-days/year. However, the studies concerned different groups of patients.

Multiple studies have unambiguously demonstrated that deaths due to sepsis in cancer patients and 30-day mortality remain high. In the group of patients we analyzed, the 30-day mortality rate was 48.4%, which is close to the maximum value obtained in other studies concerning patients with solid tumors, where the authors showed mortality at the level of 28.0–56.0% [1, 2, 15–18]. In the control study among cancer patients, conducted by The European Organization for Research and Treatment of Cancer, the overall 30-day mortality rate was 39.0% and was associated with the age and severity of the underlying disease [19]. According to other

Table 3. Antifungal susceptibility test results of *Candida* species.

Candida species	Number of strains	Antifungal agent	MIC range	% isolates susceptible to antifungal	% isolates resistant to antifungal	MIC_{50} (mg/l)	MIC_{90} (mg/l)
C. glabrata	13	Fluconazole	3 – >256	0.0	15.4*	8	96
		Anidulafungin	0.006 – 0.023	100.0	0.0	0.012	0.016
C. *albicans*	12	Fluconazole	0.038–1.0	100.0	0.0	0.380	0.750
		Anidulafungin	0.002–0.02	100.0	0.0	0.004	0.012
C. parapsilosis	3	Fluconazole	0.5–1.0	100.0	0.00	0.500	1.0
		Anidulafungin	0.75–1.50	0.00	0.00	0.750	1.500
*C. lusitaniae***	2	Fluconazole	0.25–0.75	100.0	0.00	–	–
		Anidulafungin		–			
C. tropicalis	1	Fluconazole	0.12	100.0	0.00	–	–
		Anidulafungin	0.008	100.0	0.00		

MIC_{50} (minimal inhibitory concentration inhibits 50.0% of isolates); MIC_{90} (minimal inhibitory concentration inhibits 90.0% of isolates); *2 isolates showed MIC values of 96 and 256 mg/l; **non-species related breakpoints

Table 4. Analysis of causes of confirmed deaths of patients.

Parameter/Group	Patients died n=19 (%)	Patients cured n=12 (%)	p-value
Type of candidemia:			
Catheter-related	2 (20.0)	8 (80.0)	**0.004**
Secondary	17 (81.0)	4 (19.0)	
Type of cancer lesions:			
New diagnosis	13 (65.0)	7 (35.0)	0.852
Tumor recurrence/progression	6 (54.5)	5 (45.5)	
Primary tumor location:			
Digestive tract	11 (64.7)	6 (35.3)	0.530
Gynecologic tract	6 (50.0)	6 (50.0)	
Urinary tract	2 (100)	0 (0)	
Postoperative course:			
Uncomplicated	0 (0)	6 (100)	**0.001**
Complicated (reoperation required)	19 (76.0)	6 (24.0)	
Preoperative CHTH (CHTH+RTH / RTH):			
yes	7 (53.8)	6 (46.2)	0.727
no	12 (66.7)	6 (33.3)	
Need to open the lumen of the gastrointestinal tract during the procedure preceding the candidiasis:			
yes	18 (66.7)	9 (33.3)	0.295
no	1 (25.0)	3 (75.0)	
ASA:			
<IV	13 (54.2)	11 (45.8)	0.286
IV	6 (85.7)	1 (14.3)	

CHTH - chemotherapy; RTH - radiotherapy; Percentage was calculated in rows - not in columns

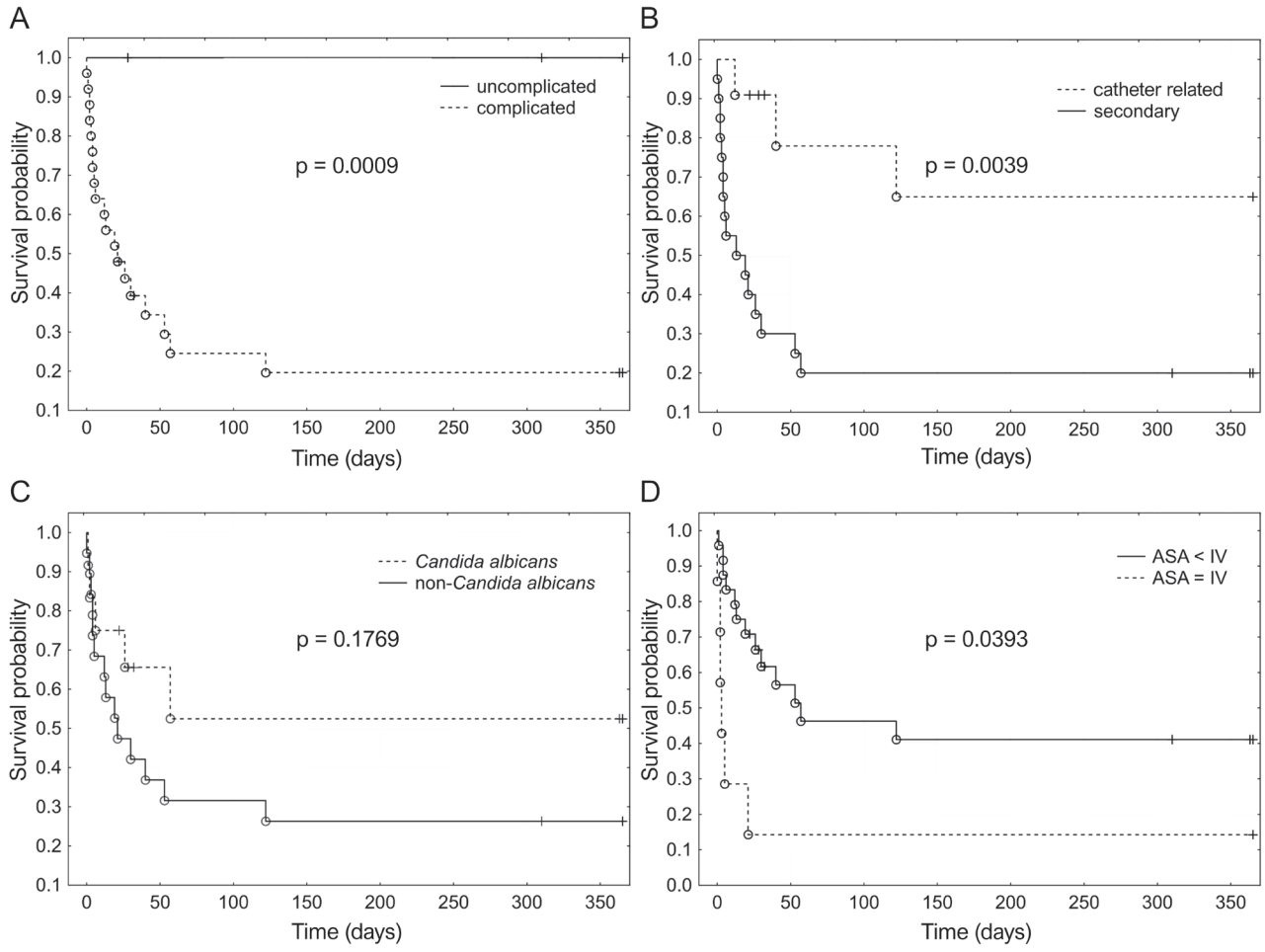

Figure 1. 1-year survival probability after candidemia diagnosis by parameter: A) postoperative course, B) origin of candidemia, C) *Candida* species, D) ASA score (American Society of Anesthesiologists score)

authors, the mortality rate was also influenced by previous intra-abdominal surgery and stays in an intensive care unit [20], and also the occurrence of the septic shock and the use of mechanical ventilation > 48 h [18]. It is worth emphasizing that in our work, the 30-day mortality rate in the group of patients with catheter infection was low (1/10, 10.0%) compared to the rate in patients with secondary infection (14/31, 66.7%, p=0.006). Such a large difference in mortality can be explained by the clinical condition of patients after surgery. In the group of patients with catheter-related candidemia, only 1 out of 10 patients before the diagnosis had been in the intensive care unit, while in the group of patients with secondary candidemia, hospitalization in the intensive care unit was noted in about 1/2 of the patients. However, the differences between the groups were not statistically significant (p=0.100).

According to various authors, candidemia usually comes from a central catheter or another site, or sites of infection. In the case of catheter infection, the infection route is most often endogenous (the patient's skin and mucous membranes), but an exogenous route, where the source of infection is the hands of the staff, cannot be excluded. In the previously cited prospective CANDIPOP study conducted in 2010–2011 in 29 Spanish hospitals, Puig-Asensio et al. [1] showed that catheter-related candidemia accounts for about 1/3 of all candidemia for solid tumor patients. We also received convergent results regarding the share of catheter-derived candidemia in our work. In addition, we observed different species distribution depending on the origin of the candidemia. Catheter infection was dominated by *C. albicans*, with a lower proportion of *C. glabrata* than in secondary infections, but the differences between the groups were not statistically significant.

In our work, slightly more than 1/5 of patients were classified in IV category according to the ASA classifications. Half of the patients were > 66 years old. Approximately 35% of patients had disease progression, which was associated with the need for extensive surgery. A similar percentage of

patients required preoperative chemotherapy (in some cases also radiation therapy). Almost 90.0% of patients received broad-spectrum antibiotic treatment. These are recognized factors that disturb the balance in the intestinal microbiome, causing damage to the intestinal mucosa. Platinum derivatives used in anticancer treatment cause lumps in the ileum and large intestine, which are already visible within 96 hours of cisplatin administration, and also have an antibiotic activity [21]. Damage to the integrity of the intestinal mucosa is the cause of microbial translocation and invasive infections [22, 23]. Our analysis has shown that the location of the tumor and, consequently, subsequent treatment, affects the origin of the candidemia. Patients with primary gastrointestinal neoplasms had significantly more frequent secondary candidemia than those with neoplasms in the female reproductive organs (p=0.042).

The majority of patients who died had a complicated postoperative course, required reoperation and had candidemia of secondary origin. Lower probability of 1-year survival was associated with complicated postoperative course, ASA=IV and secondary candidemia. The species of *Candida* did not affect the probability of survival. However, due to the small number of patients, this does not allow for unambiguous conclusions and requires further investigations.

Species distribution showed that *C. glabrata* (41.9%) was more frequently reported by us than in previous Polish studies. Mnichowska-Polanowska et al. [24], in studies conducted among approximately 950 non-neutropenic intensive care patients, found 59 candidemia cases. Among the etiological agents, *C. albicans* dominated, constituting 45.0%; the share of *C. glabrata* was 31.7%, but as in our work, *C. parapsilosis* was in third place, constituting 10.0%. According to Nawrot et al. [14], *C. glabrata* may constitute from 0.0 to 18.7%, depending on the ward, with the highest frequency of occurrence in surgical wards.Due to the low invasiveness of *C. glabrata*, infections with this species of *Candida* usually occur after the anatomical barriers have been broken, during surgery, the use of catheters, and cytostatic treatment [25]. It is worth noting that in our work all patients underwent surgery, and in over 1/3 of patients it was surgery due to recurrence of the cancer process. Almost 84% of patients had a central catheter and 35.5% of patients had previously been treated with cytostatics. *C. glabrata* has naturally reduced sensitivity to fluconazole, which means that in approximately 50.0% of the cases of secondary infections we have discussed, empirical treatment with this drug would be ineffective. In intra-abdominal candidemia, which is a complication of surgery, intestinal perforation or anastomotic leakage, as well as mucosal damage, it is necessary to take into account the possibility of fluconazole-resistant species due to the selection of existing resistant strains, as well as the replacement of etiological agents of infection with other species resistant to the drugs used [26, 27]. According to Lin et al. [8], also frequent use of vancomycin and piperacillin with tazobactam may cause changes in the microbiota of the skin and gastrointestinal tract, and thus select low-invasive microorganisms such as *C. glabrata*. In our work, over half of the patients received at least one of these antibiotics. Furthermore, *C. glabrata* is in danger of developing strains resistant to echinocandins due to the ability of this species to develop resistance and acquire various mutations under drug pressure [28]. Anidulafungin resistance is estimated to be 5.2–6.0% for *C. glabrata* [3, 29]. However, in our work, despite the empirical use of antifungal drugs, in about 2/3 of the patients, we did not find strains resistant to anidulafungin, and the minimum inhibitory concentration of 90.0% of isolates of this species was 0.016 mg/l and was low.

We showed a lower share of *C. albicans* (38.8%) in our study than in the studies cited above: a retrospective Polish candidemia study [14] and a prospective Spanish study [1], respectively 50.0 and 44.4%. In turn, in single-center Swedish studies, *C. albicans* constituted as much as 65.0% of isolated *Candida* fungi [29]. However, the participation of individual species may vary depending on the patient group and institution [5, 9, 30, 31].

The share of species other than *C. glabrata* and *C. albicans* in inducing candidemia was definitely lower in our study. *C. parapsilosis* was the third most common species in our work. Strains of this species have naturally reduced sensitivity to echinocandins [11]. The strains we isolated were intermediately susceptible to this drug. The MIC values of fluconazole in the tested strains were low and the strains remained susceptible to this drug.

C. lusitaniae and *C. tropicalis* species appeared sporadically. There are few reports in the literature regarding the occurrence of *C. lusitaniae*. Nevertheless, its share in causing candidemia is estimated at 0–3.0%. The risk factor for this species is neutropenia and increased use of antifungal drugs. In our work, 2/31 (6.5%) cases of candidemia caused by this species were found that might develop resistance to amphotericin B during treatment. Such a phenomenon has been described during the cytostatic treatment [32–34]. Species-specific breakpoints are not available for *C. lusitaniae*, which is why the MIC value was only determined for fluconazole as recommended by EUCAST. Test strains were sensitive to this drug.

We showed in our work that postoperative course requiring reoperation and secondary origin of candidemia are poor prognosis factors among patients with candidemia. The results of our analysis also showed the dominant role of *C. glabrata* in inducing candidemia among patients with solid tumors who underwent surgery. The established dominance of *C. glabrata* is worrying and poses a serious clinical and therapeutic problem, especially since this species has naturally reduced sensitivity to fluconazole. This presents the risk of therapeutic failure if the drug is used empirically. On the other hand, it is known that some strains of *C. glabrata* are resistant to echinocandins and although we have not found such strains in our work, this situation should be taken into account.

Knowledge of *Candida* species occurring among cancer patients, taking into account the study group, risk factors, and the origin of candidemia, is necessary to determine the appropriate empirical therapy. All the more, because the distribution of species may depend on the origin of the candidemia. However, the limitations of our study should be emphasized. The study was conducted in one center specializing in the treatment of patients with solid tumors. Both the population of patients treated in our center, as well as the surgical procedures and antifungal treatment used may have an impact on our results. Another limitation of our work is the small number of cases analyzed. Therefore, further investigation is needed in this study.

References

[1] PUIG-ASENSIO M, RUIZ-CAMPS I, FERNÁNDEZ-RUIZ M, AGUADO JM, MUÑOZ P et al. CANDIPOP Project; GEIH-GEMICOMED SEIMC; REIPI. Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain. Clin Microbiol Infect 2015; 21: 491.e1–10. https://doi.org/10.1016/j.cmi.2014.12.027

[2] CORNEJO-JUÁREZ P, VILAR-COMPTE D, GARCÍA-HORTON A, LÓPEZ-VELÁZQUEZ M, ÑAMENDYS-SILVA S et al. Hospital-acquired infections at an oncological intensive care cancer unit: differences between solid and hematological cancer patients. BMC Infect Dis 2016; 16: 274. https://doi.org/10.1186/s12879-016-1592-1

[3] PING-FENG W, WEI-LUN L, MIN-HAN H, ING-MOI H, YU-LIN L et al. Epidemiology and antifungal susceptibility of candidemia isolates of non-*albicans Candida* species from cancer patients. Emerg Microbes Infect 2017; 6: e87. https://doi.org/10.1038/emi.2017.74

[4] KULLBERG BJ, ARENDRUP MC. Invasive candidiasis. N Engl J Med 2015; 373: 1445–1456. https://doi.org/10.1056/NEJMra1315399

[5] MONTAGNA MT, LOVERO G, BORGHI E, AMATO G, ANDREONI S et al. Candidemia in intensive care unit: a nationwide prospective observational survey (GISIA-3 study) and review of the European literature from 2000 through 2013. Eur Rev Med Pharmacol Sci 2014; 18: 661–674.

[6] MCCARTHY MW, WALSH TJ. Candidemia in the cancer patient: diagnosis, treatment, and future directions. Expert Rev Anti Infect Ther 2018; 16: 849–854. https://doi.org/10.1080/14787210.2018.1536546

[7] LI D, XIA R, ZHANG K, BAI CH, LI Z et al. Evaluation of candidemia in epidemiology and risk factors among cancer patients in a cancer center of China: an 8-year case-control study. BMC Infect Dis 2017; 17: 536. https://doi.org/10.1186/s12879-017-2636-x

[8] LIN MY, CARMELI Y, ZUMSTEG J, FLORES EL, TOLENTINO J et al. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and *Candida krusei* fungemia: a case-case-control study. Antimicrob Agents Chemother 2005; 49: 4555–4560. https://doi.org/10.1128/AAC.49.11.4555-4560.2005

[9] NUCCI M, BRAGA PR, NOUÉR SA, ANAISSIE E. Time of catheter removal in candidemia and mortality. Braz J Infect Dis 2018; 22: 455–461. https://doi.org/10.1016/j.bjid.2018.10.278

[10] DOLIN HH, PAPADIMOS TJ, XIAOHUAN C, ZHIXING KP. Characterization of pathogenic sepsis etiologies and patient profiles: a novel approach to triage and treatment. Microbiol Insights 2019;12: 1178636118825081. https://doi.org/10.1177/1178636118825081

[11] BEN-AMI R. Treatment of invasive candidiasis: a narrative review. J Fungi (Basel) 2018; 4: 97. https://doi.org/10.3390/jof4030097

[12] PAPPAS PG, KAUFFMAN CA, ANDES DR, CLANCY CJ, MARR KA et al. Executive Summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62: 409–417. https://doi.org/10.1093/CID/CIV1194

[13] MAKI DG, WEISE CE, SARAFIN HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 1977; 296: 1305–1309.

[14] NAWROT U, PAJĄCZKOWSKA M, FLEISCHER M, PRZONDO-MORDARSKA H, SAMET A et al. Candidaemia in polish hospitals–a multicentre survey. Mycoses 2013; 56: 576–581.

[15] BASSETTI M, TARAMASSO L, NICCO E, MOLINARI MP, MUSSAP M et al. Epidemiology, species distribution, antifungal susceptibility and outcome of nosocomial candidemia in a Tertiary Care Hospital in Italy. PLoS One 2011; 6: e24198. https://doi.org/10.1371/journal.pone.0024198

[16] ZIRKEL J, KLINKER H, KUHN A, ABELE-HORN M, TAPPE D et al. Epidemiology of *Candida* blood stream infections in patients with hematological malignancies or solid tumors. Medical Mycology 2012; 50: 50–55. https://doi.org/10.3109/13693786.2011.587211

[17] SABINO R, VERÍSSIMO C, BRANDÃO J, ALVES C, PARADA H et al. Epidemiology of candidemia in oncology patients: a 6-year survey in a Portuguese central hospital. Medical Mycology 2010; 48: 346–354. https://doi.org/10.3109/13693780903161216

[18] POVES-ALVAREZ R, CANO-HERNÁNDEZ B, MUÑOZ-MORENO MF, BALBÁS-ALVAREZ S, ROMÁN-GARCÍA P et al. Impact of empirical treatment with antifungal agents on survival of patients with candidemia. Rev Esp Quimioter 2019; 32: 6–14.

[19] VISCOLI C, GIRMENIA C, MARINUS A, COLLETTE L, MARTINO P et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999; 28: 1071–1079.

[20] BERGAMASCO MD, GARNICA M, COLOMBO A, NUCCI M. Epidemiology of candidemia in patients with hematologic malignancies and solid tumours in Brazil. Mycoses 2013; 56: 256–63. https://doi.org/10.1111/myc.12013

[21] PERALES-PUCHALT A, PEREZ-SANZ J, PAYNE KK, SVORONOS N, ALLEGREZZA MJ et al. Microbiota reconstitution restores intestinal integrity after cisplatin therapy. J Leukoc Biol 2018; 103: 799–805. https://doi.org/10.1002/JLB.5HI1117-446RR

[22] VAN VLIET MJ, HARMSEN HJ, DE BONT ES, TISSING WJ. The role of intestinal microbiota in the development and severity of chemotherapy-induced mucositis. PLoS Pathog 2010; 6: e1000879. https://doi.org/10.1371/journal.ppat.1000879

[23] TAUR Y, PAMER EG. Microbiome mediation of infections in the cancer setting. Genome Med 2016; 8: 40. https://doi.org/10.1186/s13073-016-0306-z

[24] MNICHOWSKA-POLANOWSKA M, ADAMOWICZ M, JAROSZ K, BILSKA I, WILK M et al. Prevalence and characteristics of *Candida* bloodstream infection in non-neutropenic patients of intensive care unit in West Pomeranian region. Int J Inf Control 2018; 14: 54–55.

[25] KUMAR K, ASKARI F, SAHU MS, KAUR R. *Candida glabrata*: a lot more than meets the eye. Microorganisms 2019; 7: 39. https://doi.org/10.3390/microorganisms7020039

[26] MAGILL SS, SHIELDS C, SEARS CL, CHOTI M, MERZ WG. Triazole cross – resistance among *Candida* spp.: case Report, occurrence among bloodstream isolates, and implications for antifungal therapy. J Clin Microbiol 2006; 44: 529–535. https://doi.org/10.1128/JCM.44.2.529-535.2006

[27] VERGIDIS P, CLANCY CJ, SHIELDS RK, PARK SY, WILDFEUER BN et al. Intra-abdominal candidiasis: The importance of early source control and antifungal treatment. PLoS One 2016; 11: e0153247. https://doi.org/10.1371/journal.pone.0153247

[28] RIVERO-MENENDEZ O, NAVARRO-RODRIQUEZ P, BERNAL-MARTINEZ L, MARTIN-CANO G, LOPEZ-PEREZ L et al. Clinical and laboratory development of echinocandin resistance in *Candida glabrata:* molecular characterization. Front Microbiol 2019; 10: 1585. https://doi.org/10.3389/fmicb.2019.01585

[29] LINDBERG E, HAMMARSTRÖM H, ATAOLLAHY N, KONDORI N. Species distribution and antifungal drug susceptibilities of yeasts isolated from the blood samples of patients with candidemia. Scientific Reports 2019; 9: 3838. https://doi.org/10.1038/s41598-019-40280-8

[30] TORTORANO AM, PRIGITANO A, LAZZARINI C, PASSERA M, DEIANA ML et al. A 1-year prospective survey of candidemia in Italy and changing epidemiology over one decade. Infection 2013; 41: 655–662. https://doi.org/10.1007/s15010-013-0455-6

[31] BUTTA H, SARDANA R, MENDIRATTA L, SIBAL A, GUPTA V et al. Time to detection of yeast isolates in pediatric and adult patients with fungemia and its relevance to clinical profile and outcome. Indian J Crit Care Med 2019; 23: 27–30. https://doi.org/10.5005/jp-journals-10071-23108

[32] ATKINSON BJ, LEWIS RE, KONTOYIANNIS DP. *Candida lusitaniae* fungemia in cancer patients: risk factors for amphotericin B failure and outcome. Med Mycol 2008; 46: 541–546. https://doi.org/10.1080./13693780801968571

[33] JUNG DS, FARMAKIOTIS D, JIANG Y, TARRAND YY, KONTOYIANNIS DP. Uncommon *Candida* species fungemia among cancer patients, Houston, Texas, USA. Emerg Infect Dis 2015; 21:1942–1950. https://doi.org/10.3201/eid2111.150404

[34] PINTO-MAGALHÃES S, MARTINS A, LACERDA S, FILIPE R, PRISTA-LEÃ B et al. Candidemia in a Portuguese tertiary care hospital: Analysis of a 2-year period. J Mycol Med 2019; 29: 320–324. https://doi.org/10.1016/j.mycmed.2019.08.002