Abstract. This study aimed to identify the risk factors of candidemia and assess possible clinically significant differences between *Candida parapsilosis* and other *Candida* species in a Chinese tertiary cancer center over six years. A total of 323 cancer patients were enrolled and analyzed from 2012 to 2018. Among the isolates, the species most frequently isolated was *C. parapsilosis* (37.15%, 120/323), and *C. albicans* only accounted for 34.37%. Based on statistical analysis, when candidemia patients who had *C. parapsilosis* were compared with other *Candida* spp., the following factors were found to be significantly associated with *C. parapsilosis* fungemia: parenteral nutrition (p < 0.001), neutropenia (p < 0.001), receipt of chemotherapy (p = 0.002), and previous antifungal use (p < 0.001). Parenteral nutrition was a factor that independently predicted *C. parapsilosis* candidemia (OR, 0.183; 95% CI, 0.098–0.340; p < 0.001). In short, *C. parapsilosis* as the leading non-*albicans* *Candida* spp. isolates in candidemia are posing a major threat for cancer patients. The study highlights the urgent need to evaluate the possibility of development of *C. parapsilosis* candidemia in cancer patients exposed to these risk factors and prevention strategies against this causative agent transmitted through nosocomial route should be implemented.

**Keywords:** Candidemia; malignancy; *C. parapsilosis*; *C. albicans*; non-*albicans* *Candida* spp.

**Citation:** Sun M., Chen C., Xiao W., Chang Y., Liu C., XU Q. Increase in Candida Parapsilosis Candidemia in Cancer Patients. Mediterr J Hematol Infect Dis 2019, 11(1): e2019012, DOI: http://dx.doi.org/10.4084/MJHID.2019.012

**Published:** January 1, 2019 **Received:** July 20, 2018 **Accepted:** November 26, 2018

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**Introduction.** Candida species are among the most important causes of nosocomial bloodstream infection (BSI). Candida was cited as the fourth most prevalent nosocomial BSI in the United States and seventh to tenth in population-based studies with mortality of around 40%. It is, therefore, a public health concern worldwide.

Numerous surveillance programs have focused on candidemia and have documented the prevalence of different Candida species. Until recently, *C. albicans* was the predominant Candida spp. isolated from patients with nosocomial candidemia. However, in recent years, there has been an increase in the proportion of non-*albicans* *Candida* spp. (NAC) isolates, and in some European and Latin American centers, it has overtaken *C. albicans* as the predominant cause of nosocomial candidemia. Considering the different worldwide distribution of *Candida* spp., some researchers have recommended that the epidemiology of Candida infections should be
studied at local levels rather than on a worldwide scale.\textsuperscript{10}

There is a consensus that antifungal therapy should be initiated before candidemia ensues to avoid mortality.\textsuperscript{8} Considering that the incubation time has a statistically significant impact on in-hospital mortality,\textsuperscript{1} and delaying empirical treatment for more than 12 h is associated with high mortality.\textsuperscript{11} Duration of therapy is an important point.\textsuperscript{12} What’s more, NAC is associated with stronger biofilm production than C. \textit{albicans} spp.\textsuperscript{13-15} Thus, eradication of NAC candidemia is likely to require high doses of fluconazole or other effective agents (e.g., echinocandin or amphotericin B).\textsuperscript{8,16} Epidemiological data that can help differentiate NAC from \textit{C. albicans} infections may, therefore, be important in selecting the appropriate antifungal treatment.

Although studies to date have sought to identify specific risk factors for nosocomial NAC candidemia, available data mostly come from Western countries.\textsuperscript{8} Even though several studies had reported the epidemiology of Candida infections in China, they mainly focused on adults or special groups, such as neonates.\textsuperscript{17,18} In China, investigations on \textit{C. parapsilosis} compared with Candida non-\textit{parapsilosis} and \textit{C. albicans} compared with NAC candidemia in malignancy groups are limited. We performed this retrospective study to investigate the epidemiology of candidemia among cancer patients in central China. Our findings may facilitate the application of antifungal prophylaxis to patients at greatest risk and contribute to prognosis improvement.\textsuperscript{5}

**Material and methods.** This retrospective study was carried out at Henan Cancer Hospital, a 2,991-bed special hospital located in Henan, China. From 1 March 2012 to 28 February 2018, all patients with positive blood culture for Candida species were identified.

Candidemia was defined as at least one positive blood culture for Candida spp. in patients hospitalized for more than 48 h. Those without complete case files were excluded. When a case of candidemia was identified, the following data were collected in a standardized case report form: demographics, underlying medical conditions, exposure to invasive medical procedures, immunosuppressive therapy, use of antibiotics and prophylaxis antifungal agent (fluconazole), and antifungal therapeutic duration (including the prophylaxis use of antifungal agent prior to the occurrence of candidemia and treatment during candidemia), use of H2 blockers and 30-day survival, presence of central venous catheter (CVC) and subsequent removal, the CVC was considered to be removed if this procedure was performed during the first 3 days following the first blood culture positive for Candida infection.

Catheter-related bloodstream infections were defined as 1) a colony count of blood obtained through the catheter hub that was >5-fold higher than that in blood obtained from a peripheral vein or 2) a catheter tip culture that was positive for Candida spp.\textsuperscript{19} Delayed treatment was defined when treatment was started >2 days from blood culture or when treatment was not started because the patient was dead when the diagnosis was established. All clinical data were collected within 30 days prior to the first positive blood culture, and crude mortality referred to the ratio of death within 30 days after the first positive blood culture. This study obtained permissions from the Bioethics Committee of Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital and participants (consent to participate was obtained from participants) to review patient records and use the data. Types of cancer were differentially diagnosed by pathological examination. Recurrent BSI was defined as an episode of infection occurring at least one month after the initial diagnosis. Neutropenia was defined as an absolute neutrophil count of <1.5×10\textsuperscript{9}/L.

Blood samples were cultured in the BACTEC-FX system (BD, USA). All positive cultures were manually sampled and inoculated on CHROMagar Candida medium (Autobio, Zhengzhou, China) to ensure viability and purity. An aliquot was Gram-stained for preliminary identification of the microorganism. All species were identified using the API 20C AUX system (Biomérieux, France). Antifungal susceptibility tests were performed using the broth microdilution assay according to the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS), M27-A2 document.\textsuperscript{20} Statistical analysis was performed using the SPSS 22 software (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed using Fisher exact test or Chi-squared test (as appropriate) for categorical variables. All tests were two-tailed, and a level of significance of \(p < 0.05\) was considered statistically significant. Parameters related to \textit{C. parapsilosis} candidemia and \textit{C. albicans} candidemia were analyzed by multivariate logistic regression.

**Results.** During the study period, 323 episodes of candidemia occurred in 323 patients, 58 with hematological malignancies (17.95\%), and 265 (82.04\%) with solid tumors (STs). The overall incidence rate was 1.3 episodes/1000 hospital admissions. The overall incidence rate of hematological malignancies was higher than STs (1.6 episodes/1000 hospital admissions vs. 0.6 episodes/1000 hospital admissions). \textit{C. parapsilosis} was the most frequently isolated from blood cultures (37.15\%, 120/323), followed by \textit{C. albicans} (34.37\%, 111/323), \textit{C. tropicalis} (16.10\%, 52/323), and \textit{C. glabrata} (8.98\%, 29/323). Other less common species
included *C. krusei*, *C. guilliermondii*, *C. dubliniensis*, and *C. lusitaniae*.

There were 186 males and 137 females. The average age was 52.81 ± 18.38 years. The median time from admission to the first positive blood specimen was 19 days. There were 155 patients from surgical wards (47.99%), 141 patients from medical wards (43.65%), and 27 patients from the ICU (8.36%). Common underlying diseases and risk factors 30 days prior to the first positive blood culture are listed in Table 1. Most of the cases patients with candidemia had received antibiotic therapy (91%) and had an indwelling CVC (83.3%) at the time of infection. CVCs were removed within 72hours from the onset of candidemia in 96 patients (29.7%). CVC-related candidemia was more likely to occur in non-*albicans* *Candida spp.* isolates. Advanced age, STs, abdominal surgery, and ICU stay at diagnosis were related with *C. albicans* candidemia.

### Table 1. Characteristics of 323 cancer patients with candidemia caused by Candida albicans and C. parapsilosis.

| Characteristics                          | Univariate analysis n (%) | Median (range) | Mean (range) | P     | P     |
|-----------------------------------------|---------------------------|----------------|--------------|-------|-------|
| Total (n=323)                           |                           |                |              |       |       |
| C. albicans (n = 111)                   | Total (n=212)             |                |              | <0.001| <0.001|
| Age                                     | 57(2-89)                  | 60(11-89)      | 55(2-84)     | 55.5(2-84) | 58.0(4-89) | <0.001|
| Fever                                   | 38.5(36-42)               | 38.5(36-40.2)  | 38.5(36-42)  | 38.5(36-40.2) | 38.5(36.1-42) | 0.460|
| Male                                    | 186(57.6)                 | 62(55.9)       | 124(58.5)    | 65(54.2) | 121(59.6) | 0.318|
| N° of days in hospital until candidemia | 19(1-184)                 | 20(3-184)      | 19(1-147)    | 0.543  | 21(2.5-90) | 0.163|
| Hematologic malignancy                  | 58(18.0)                  | 4(3.6)         | 54(25.5)     | <0.001 | 41(34.2) | <0.001|
| Solid tumors                            | 265(82.0)                 | 107(96.4)      | 158(74.5)    | 79(65.8) | 186(91.6) | 0.716|
| In the ICU at diagnosis                 | 27(8.4)                   | 10(9.0)        | 17(8.02)     | 6(5.0)  | 21(10.3) | 0.001|
| Mechanical ventilation                  | 114(35.3)                 | 40(36.0)       | 74(34.9)     | 0.864  | 44(36.7) | 0.716|
| Parenteral nutrition                    | 199(61.6)                 | 66(59.5)       | 133(62.7)    | 0.535  | 90(75.0) | <0.001|
| Neutropenia                             | 68(21.1)                  | 8(7.2)         | 60(28.3)     | <0.001 | 42(35.0) | 26(12.8) | <0.001|
| Previous surgery (last 3 months)        | 186(57.6)                 | 72(64.9)       | 114(53.8)    | 0.062  | 52(43.3) | 134(66.0) | <0.001|
| Abdominal surgery                       | 146(45.2)                 | 63(56.8)       | 83(39.2)     | 0.003  | 30(46.7) | 116(57.1) | <0.001|
| Receipt of dialysis                     | 19(5.9)                   | 5(4.5)         | 17(8.0)      | 0.417  | 7(5.8)  | 12(5.9)  | 0.969|
| CVC                                     | 269(83.3)                 | 96(86.5)       | 173(81.6)    | 0.162  | 107(89.2) | 162(79.8) | 0.790|
| CVC-related candidemia                  | 143(44.3)                 | 36(32.4)       | 107(50.5)    | 0.003  | 67(55.8) | 76(37.4) | 0.952|
| Receipt of corticosteroids              | 231(71.5)                 | 74(66.7)       | 157(74.1)    | 0.143  | 91(75.8) | 140(69.0) | 0.202|
| Receipt of chemotherapy^c                | 174(53.9)                 | 45(40.5)       | 129(60.8)    | <0.001 | 78(65.0) | 106(52.2) | 0.002|
| Receipt of antibiotics                  | 294(91.0)                 | 100(90.1)      | 194(91.5)    | 0.588  | 111(92.5) | 183(90.1) | 0.549|
| Antibiotic therapeutic duration (d)      | 5.48(0-14)                | 5.20(0-14)     | 5.64(0-14)   | 0.175  | 5.23(0-10) | 5.64(0-14) | 0.182|
| Receipt of H2 blocker                   | 190(58.8)                 | 59(53.2)       | 131(61.8)    | 0.122  | 76(63.3) | 114(56.2) | 0.222|
| Previous antifungal use                 | 90(27.9)                  | 16(14.4)       | 74(34.9)     | <0.001 | 53(44.2) | 37(18.2) | <0.001|
| Antifungal therapeutic duration (d)      | 0.73(0-6)                 | 0.32(0-5)      | 0.94(0-6)    | <0.001 | 1.08(0-5) | 0.52(0-6) | <0.001|
| Removal of CVC (<72h)                   | 96(29.7)                  | 32(28.8)       | 64(30.2)     | 0.671  | 39(32.5) | 57(28.1) | 0.113|
| Crude mortality                         | 47(14.6)                  | 18(16.2)       | 29(13.7)     | 0.561  | 21(17.5) | 26(12.8) | 0.257|

ICU = intensive care unit; CVC = central venous catheter; NAC = Candida non-*albicans*. 

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Table 2. Factors associated with Candida non-parapsilosis and C. parapsilosis candidemia.*

| Factors                        | OR (95% CI) | P value |
|--------------------------------|-------------|---------|
| In the ICU at diagnosis        | 2.883 (1.501-5.539) | 0.001   |
| Parenteral nutrition           | 0.183(0.098-0.340)  | <0.001  |
| Abdominal surgery              | 4.066 (1.777-9.300) | 0.004   |

*By backward stepwise multiple logistic regression.

Table 3. Factors associated with non- C. albicans and C. albicans candidemia.*

| Factors   | OR (95% CI) | P value |
|-----------|-------------|---------|
| Type of cancer | 0.164 (0.030-0.899) | 0.036   |

*By backward stepwise multiple logistic regression.

When C. parapsilosis was compared with Candida non-parapsilosis candidemia (Table 2), the cases of C. parapsilosis BSI were exposed more frequently to parenteral nutrition and CVC and less frequently to surgery. As regards the underlying diseases, both neutropenia and previous antifungal use were associated with C. parapsilosis candidemia, whereas STs and ICU stay at diagnosis were related to non-C. parapsilosis candidemia. Moreover, parenteral nutrition and receipt of chemotherapy were associated with C. parapsilosis candidemia. However, advanced age and surgery were correlated with non-C. parapsilosis candidemia. In a model of multivariate analysis, independently predicting C. parapsilosis candidemia (OR, 0.183; 95% CI, 0.098–0.340; p < 0.001). Another factor that predicted C. albicans candidemia was type of cancer (OR, 0.164; 95% CI, 0.030–0.899; p = 0.036). In other words, solid malignancy is a factor independently predicting C. albicans, and hematologic malignancy occurs more frequently with C. parapsilosis candidemia (Table 3).

As shown in Table 4, the susceptibility test of antifungal drugs was performed for four mainly isolates of Candida species. Concern need be addressed on C. albicans, C. tropicalis and C. glabrata which had higher MICs to fluconazole than C. parapsilosis.

The overall mortality among affected patients was 14.6%. C. albicans and C. parapsilosis were associated with a mortality rate of 16.2% and 17.5%, respectively. There was no significance between the two groups, C. albicans and non-albicans Candida (p = 0.561) and C. parapsilosis and non-C. parapsilosis (p = 0.257). Univariate predictors of poor outcome in candidemia of cancer patients are shown in Table 5. The variables associated with 30-day mortality were as follows: older age, in the ICU at diagnosis and mechanical ventilation. Factors associated with 30-day survival were as follows: CVC-related candidaemia and removal of CVC (<72h). As shown in Table 6, factors associated with 30-day mortality by multivariate analysis among candidemia with cancer patients

Table 4. In vitro antifungal susceptibility test results of the mainly Candida species.

| Candida species | Strains (n) | Antifungal agent | MIC Range (μg/ml) | MIC 50 (μg/ml) | MIC 90 (μg/ml) | No. (%) of susceptibility |
|-----------------|-------------|------------------|-------------------|---------------|---------------|--------------------------|
| C.albicans      | 111         | Flucytosine      | 0.125-4           | 0.125         | 0.125         | 111(100%)                |
|                 |             | Amphotericin B   | 1.25-1            | 1.25          | 1.25          | ND                       |
|                 |             | Fluconazole      | 1-64              | 1             | 2             | 110(99.1%)               |
|                 |             | Itraconazole     | 0.125-0.25        | 0.125         | 0.125         | 110(99.1%)               |
|                 |             | Voriconazole     | 0.03-0.06         | 0.03          | 0.06          | 111(100%)                |
| C.parapsilosis  | 120         | Flucytosine      | 0.125-1           | 0.125         | 0.25          | 120(100%)                |
|                 |             | Amphotericin B   | 0.5-1             | 0.5           | 0.5           | ND                       |
|                 |             | Fluconazole      | 1-8               | 1             | 1             | 120(100%)                |
|                 |             | Itraconazole     | 0.125-0.25        | 0.125         | 0.125         | 120(100%)                |
|                 |             | Voriconazole     | 0.03-0.5          | 0.03          | 0.03          | 120(100%)                |
| C.tropicalis    | 52          | Flucytosine      | 0.125-4           | 0.125         | 0.125         | 52(100%)                 |
|                 |             | Amphotericin B   | 0.125-1           | 0.125         | 0.25          | ND                       |
|                 |             | Fluconazole      | 0.25-32           | 1             | 8             | 50(96.2%)                |
|                 |             | Itraconazole     | 0.125-0.25        | 0.125         | 0.125         | 52(100%)                 |
|                 |             | Voriconazole     | 0.03-0.5          | 0.03          | 0.5           | 52(100%)                 |
| C.glabrata      | 29          | Flucytosine      | 0.125-0.5         | 0.125         | 0.125         | 29(100%)                 |
|                 |             | Amphotericin B   | 0.25-1            | 0.25          | 0.25          | ND                       |
|                 |             | Fluconazole      | 2-64              | 4             | 8             | 25(86.2%)                |
|                 |             | Itraconazole     | 0.125-1           | 0.125         | 0.25          | 21(72.4%)                |
|                 |             | Voriconazole     | 0.06-0.5          | 0.25          | 0.5           | 29(100%)                 |

ND Not Defined.
Table 5. Factors associated with 30-day mortality by univariate analysis in candidemic patients with cancer patients.

| Characteristics                                      | Survived (n = 276) | Died (n = 47) | P     |
|------------------------------------------------------|--------------------|--------------|-------|
| Age                                                  | 56(2-84)           | 58.2(4-89)   | 0.025 |
| Fever                                                | 38.5(36-40.2)      | 38.4(36.2-42)| 0.378 |
| Male                                                 | 159(57.6)          | 27(57.5)     | 0.528 |
| N° of days in hospital until candidemia              | 19(2.5-184)        | 27.3(1-147)  | 0.168 |
| Hematologic malignancy                               | 54(19.6)           | 14(29.8)     | 0.786 |
| Solid tumors                                         | 222(80.4)          | 33(70.2)     | 0.893 |
| In the ICU at diagnosis                              | 12(4.4)            | 15(31.9)     | <0.001|
| Mechanical ventilation                               | 88(31.9)           | 26(55.3)     | 0.018 |
| Parenteral nutrition                                 | 167(60.5)          | 32(68.1)     | 0.329 |
| Neutropenia                                          | 54(19.6)           | 14(29.8)     | 0.236 |
| Previous surgery (last 3 months)                    | 162(58.7)          | 24(51.1)     | 0.128 |
| Abdominal surgery                                    | 128(46.4)          | 18(38.3)     | 0.063 |
| Receipt of dialysis                                  | 16(5.8)            | 3(6.4)       | 0.763 |
| CVC                                                  | 240(86.9)          | 29(61.7)     | 0.388 |
| CVC-related candidaemia                              | 139(50.4)          | 4(8.5)       | <0.001|
| Receipt of corticosteroids                           | 199(72.1)          | 32(68.1)     | 0.265 |
| Receipt of chemotherapy                              | 149(54.0)          | 25(53.2)     | 0.819 |
| Receipt of antibiotics                               | 254(92.0)          | 40(85.1)     | 0.096 |
| Antibiotic therapeutic duration (d)                  | 6(0-14)            | 5(0-12)      | 0.353 |
| Receipt of H2 blocker                                | 156(56.5)          | 34(72.3)     | 0.080 |
| Previous antifungal use                              | 68(24.6)           | 22(46.8)     |       |
| Antifungal therapeutic duration (d)                  | 0(0-6)             | 0(0-5)       | 0.070 |
| Removal of CVC (<72h)                                | 93(33.7)           | 3(6.4)       | <0.001|
| Delayed treatment                                    | 20(7.2)            | 2(4.3)       | 0.312 |

Table 6. Factors associated with 30-day mortality by multivariate analysis.  

| Factors                          | OR (95% CI) | P value |
|----------------------------------|-------------|---------|
| Removal of CVC (<72h)            | 0.248 (0.067-0.915) | 0.036   |
| In the ICU at diagnosis          | 5.487 (1.139-6.441)  | 0.034   |

C. parapsilosis is an emerging major human pathogen that has dramatically increased in significance and prevalence over the past two decades. It causes invasive candidal disease in patients at high risk of severe infection, especially ICU patients. C. parapsilosis is frequently linked to an exogenous source, such as the hands of healthcare providers, or can be part of the normal flora of the human skin, appearing to be directly introduced into the bloodstream. High rates of candidemia due to C. parapsilosis can be attributed to nosocomial transmission. In addition, infections due to C. parapsilosis are especially associated with parenteral nutrition and indwelling catheters. Our findings are in agreement with previous epidemiological studies showing that C. parapsilosis infections are more frequent in patients with parenteral nutrition.

Girmenia et al. showed an overall decrease in isolation of C. albicans with a concomitant increase in isolation of C. parapsilosis among adult patients with cancer, which is accord with this report. In other studies, C. albicans was more frequently associated with STs of the gastrointestinal and genitourinary tracts and breast, whereas NAC was most frequently

recovered from hematologic patients. The results of our study were consistent with previous studies, wherein 12.7% of patients with C. parapsilosis and 16.7% non-albicans candidemia had a hematologic malignity. In solid cancer patients, C. albicans candidemia accounted for 32.8%. Moreover, in the present study, there was a significant difference in age between the patients with C. parapsilosis candidemia and those with other Candida spp.

The crude mortality of candidemia shows slight differences when it comes to species and not consistent in different studies. Our data show lower overall mortality in candidemia. The possible reasons are as follows: firstly, the majority of isolates were fluconazole susceptible, therefore, this antifungal drug is a reasonable alternative for the treatment of candidemia; furthermore, our study introduces an important observation of a relatively high proportion (44.3%) of CVC-related candidaemia episodes, however, the rate of removal CVC within 72h was higher than another study;31 what’s more, it is known that a delay in the treatment start has a negative impact on survival, but the incidence of delayed treatment was particularly low in the report. Finally, different study period and underlying diseases might contribute to the conflicting conclusions.

Conclusions. The emergence of C. parapsilosis as the leading NAC species is posing a major threat for cancer patients. Similarly, studies reported an increase in cases of candidemia due to C. parapsilosis. Given the incidence of disease and the unacceptably high morbidity and mortality associated with C. parapsilosis, the study highlights the urgent need to evaluate the possibility of development of C. parapsilosis candidemia in cancer patients exposed to these risk factors. Much emphasis must also be given on the early implementation of a medical intervention to reduce the incidences of candidemia in malignancy. In light of the results of this study, it can be suggested that effective prevention strategies against this causative agent transmitted through nosocomial route should be implemented. However, Candida species may vary with geographic regions, and local risk factors in cancer patients can be different. Therefore, local risk factors and epidemiological trends specific to cancer patients should be investigated.

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