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Original Article

The high rate of *Candida parapsilosis* candidemia among non-burn patients with polytrauma in the surgical intensive care units of a university hospital

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Abstract

Aim: Candidemia is a life-threatening infection that has been reported to be associated with poorer outcomes in trauma patients. The present study aimed to investigate the epidemiology of candidemia in non-burn patients with polytrauma.

Material and Methods: We conducted a retrospective, single-center, observational study of polytrauma patients with candidemia admitted to the surgical intensive care units of a university hospital in Turkey between 2013 and 2017 on.

Results: The incidence of candidemia was 127 episodes per 1000 intensive care unit admissions in polytrauma patients. Non-albicans Candida species accounted for 75.5% of all candidemia episodes. C. parapsilosis (51.05%) was the predominant species, followed by C. albicans (24.52%) and C. tropicalis (12.21%). The highest crude mortality rate (72%) was observed in patients with C. parapsilosis candidemia. In multivariate analyses, who had undergone prior gastrointestinal surgery were 7.1 times more likely to have C. parapsilosis candidemia than those with other strains.

Conclusion: Our study, remarkable, demonstrated a high incidence of Candidemia had in polytrauma patients, and non-albicans Candida species were the most frequently isolated candida species. According to our study findings, a prior history of gastrointestinal surgery may help predict C. parapsilosis, as the causative agent of candidemia in polytrauma patients. However, since our study was observational and limited to such a small number of patients, the results obtained should be applied with caution.

Keywords: Candidemia; *Candida parapsilosis*; gastrointestinal surgery; polytrauma; surgical intensive care unit

INTRODUCTION

Globally, trauma is responsible for 10% of deaths, each year and is the leading cause of mortality in the young population (1). Due to advances in intensive care unit (ICU) facilities, in surgical ICU patients, the incidence of life-threatening invasive fungal infections is increasing rapidly in association with the increased number of patients surviving polytrauma (2,3).

Trauma causes a severe systemic inflammatory response and a concomitant anti-inflammatory activity; in other words, an immunosuppressive process triggered 30 minutes after the trauma. That is a paradoxical reaction that causes a decline in the resistance against infections (4). Besides, critically ill trauma patients have more tendency to experience a longer duration of hospitalization, especially in ICUs. They frequently require aggressive therapies and several procedures. Those are included as follows: antibiotic therapies, total parenteral nutrition (TPN), invasive equipment, such as a central venous catheters (CVC), and renal replacement therapy (RRT) for acute kidney injury (AKI). Therefore, all the risk factors noted above may make these patients high risk groups for invasive fungal infections (5,6).

Candidemia, the most common invasive fungal infection in the ICU setting, is an entity in which delayed, or inappropriate antifungal therapy is associated with increased mortality (7,8). The incidence of each Candida species varies among different patient populations and geographic regions, which is essential in ensuring appropriate and timely initial antifungal agent and in designing dosage regimens (9,10). Thus, knowing the population-based candidemia epidemiology and antifungal susceptibility, especially in high-risk groups,

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may help to optimize therapies and improve outcomes that need further investigation.

The surgical units caring for trauma and burn patients have the highest rate of Candida infections (11). Although candidemia in burn patients has been studied intensely, very little is known about candidemia in non-burn trauma patients (12-15). We, therefore, aimed in this study to investigate candidemia epidemiology and antifungal susceptibility patterns of Candida species in non-burn trauma patients.

MATERIALS AND METHODS

Study design

This retrospective, single-centre, observational study was performed between January 2013 and December 2017 in the surgical ICUs of Hatay Mustafa Kemal University Hospital in Hatay, Turkey. The inclusion criteria were: patients admitted to our ICU for polytrauma; age ≥18 years; requiring at least one positive blood culture for Candida species.

The following data were collected from medical records: patient demographics, the presence of a CVC, using broad-spectrum antibiotics or steroids, receiving TPN, experiencing AKI, applied surgical procedure (abdominal surgery or the others). We recorded only the first episode of candidemia and analyzed it for each patient. All patients underwent surgery after the trauma, and none of them received prophylactic antifungal therapy. Patients with any comorbidity and burn patients were excluded.

We defined polytrauma according to the new Berlin definition: 1) an Abbreviated Injury Scale (AIS) ≥ 3 for two or more of the six body regions and 2) the presence of one or more of the five physiologic parameters (5).

Ethics approval for this study was obtained from the Ethics Committee of the Hatay Mustafa Kemal University (Decision date: 2018, Number: 170).

Organism identification and susceptibility testing

The samples, including blood culture bottles, were immediately transported to the Microbiology Laboratory of Mustafa Kemal University Hospital to be processed. BacT / Alert blood culture device (Biomerieux, France) was used for the growth of the microorganisms in these bottles. When the growth was detected, the blood sample was taken from the relevant bottles and spread on the slide to stain with Gram stain. If yeast was seen on Gram stain, the blood sample was inoculated on Sabouraud dextrose agar (Merck, Germany) with antibiotics and incubated at 37°C for two days. Ultimately, we determined the identification and antifungal susceptibilities of Candida species by the Vitek 2 Compact (Biomerieux, France) automated system.

Statistical analyses

All statistical analyses were done with the SPSS software version 23.0 (Chicago, IL, USA). We tested the normality of data using visual methods (histograms, probability plots) and the Shapiro-Wilk test. Non-normally distributed variables were compared using the Mann-Whitney U test. We analyzed the categorical variables between groups by the Pearson Chi-square or Fisher's exact test, where appropriate. Univariate analyses were performed to ascertain the effect of the presence of CVC, prior gastrointestinal surgery, penetrating trauma, receiving TPN, and the onset time of candidemia after polytrauma on the likelihood that participants have *Candida parapsilosis* (*C. parapsilosis*) candidemia. We entered the possible factors identified with univariate analyses into a logistic regression model. The logistic regression model was statistically significant (X2(4) = 9.798; p=0.020). The model explained 24.2% Negelkerke R2 of the variance in *C. parapsilosis* candidemia and correctly classified 67.3% of cases. In all of the tests, a value of $p < 0.05$ was considered to be statistically significant. The graphics were plotted using GraphPad Prism v7.0d for Mac (GraphPad Software, San Diego, CA, USA).

RESULTS

Patients' demographics

During the four years of this observational study, 385 patients with polytrauma admitted to our surgical ICUs were enrolled in the study. Among them, 49 patients were diagnosed as candidemia. The infection rate was 12.72%, and the incidence of candidemia in polytrauma patients in surgical ICUs of our institution was 127 episodes per 1000 ICU admissions.

The median age of the patients with candidemia was 28 (IQR:12.5) years, and 83.7% (n=41) of those were male. The median time interval between the trauma and the onset of candidemia was 22 days (IQR=32.5).

Head (77.5%), chest with/without fractures of upper extremities (67.3%), and pelvis with/without fractures of lower extremities (57.1%) were the most common sites of severe injury. The rate of abdominal injury was relatively low (20.4%). Most of the patients (75.5%) had penetrating trauma.

Non-albicans Candida (NAC) species accounted for most of the candidemia isolates (75.5%). *C. parapsilosis* was the most frequently isolated species (25/49, 51.05%) followed by *C. albicans* (12/49, 24.52%), *C. tropicalis* (6/49, 12.21%) and the others (6 /49, 12.22%). The distribution of all isolated Candida species was illustrated in Figure 1. Only four patients had co-existing catheter-associated candidemia with the isolation of. the same Candida species from both blood and catheter tip, and 2 of those isolates were *C. parapsilosis*. As shown in Figure 2, the proportion of *C. parapsilosis* isolates vary widely by years.

The characteristics of the patients with *C. parapsilosis* and other Candida species included in candidemia groups were shown in Table 1.

According to univariate analysis, the presence of a CVC, receiving TPN, and prior gastrointestinal surgery were significantly correlated with *C. parapsilosis* candidemia.

Table 1. Comparison of the risk factors for candidemia between the C. parapsilosis candidemia and other Candida species candidemia groups

Variables	*C. parapsilosis* group (n=25)	Other Candida species group (n=24)	P value
Age (years)	27 (14.5)	29 (13.75)	0.952
Gender (males)	21 (84)	20 (83.3)	0.652
ICU stay before issolation (days)	29 (36)	21.5 (32.5)	0.237
CVC	23 (92)	17 (70.8)	0.074
TPN	25 (100)	21(87.5)	0.110
Broad-spectrum antibiotics	25 (100)	23 (95.8)	0.490
Steroids	5 (20)	8 (33.3)	0.291
Dialysis	2 (8)	4 (16.7)	0.417
Gastrointestinal surgery	8 (32)	2 (8.3)	**0.040**
Resistance rate of antifungal agents	3 (12)	7 (29.1)	0.171
Concominant bacteriemia	2 (8.0)	6 (25)	0.138
Mortality	18 (72)	16 (66.6)	0.686

Categorical variables presented as n (%) and non-parametrik variables presented as median (IQR). P values that statistically significant are shown in bold. CVC: Central venous catheter; ICU: intensive care unit; TPN: total parenteral nutrition

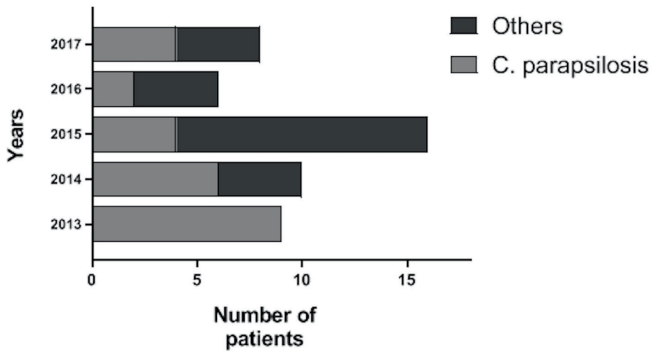

Figure 1. The distribution of Candida species.

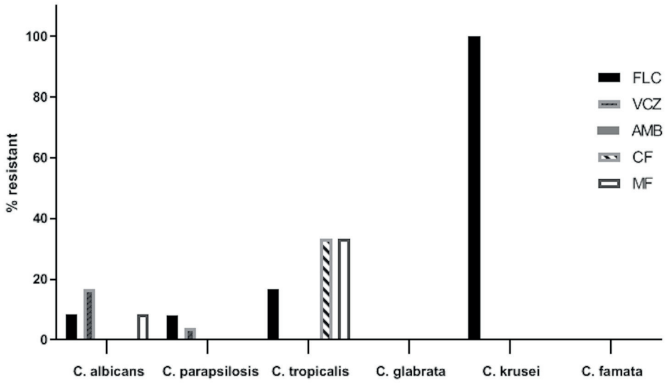

Figure 2. The proportion of C. parapsilosis isolates by years.

However, we found prior gastrointestinal surgery to be the only independent risk factor in multivariate analysis for *C. parapsilosis* candidemia (OR:7.193;95%CI:1.099-47.096).

The overall mortality rate was 69.4%. Interestingly, the highest mortality rate (72%) was seen in *C. parapsilosis* infections.

In study participants, the rates of resistance to fluconazole and voriconazole of *C. albicans* were 8.3% and 16.7%, respectively. In contrast, those rates were 8% and 4%, respectively, for *C. parapsilosis*. None of the 49 isolates was resistant to amphotericin B. The caspofungin resistance was established in only *C. tropicalis* isolates (33.3%). We encountered the micafungin resistance in 8.3% of *C. albicans* and 33.3% of *C. tropicalis*. The resistance rates for other Candida species were demonstrated in Figure 3.

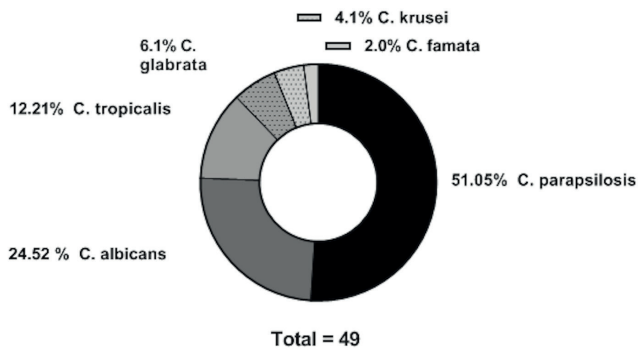

Figure 3. Antifungal resistance patterns of Candida species

DISCUSSION

Candida species have been reported to be the fifth most common pathogens responsible for ICU nosocomial bloodstream infections in trauma patients. Moreover, trauma patients with candidemia have had significantly higher mortality rates compared to those without candidemia (13). It is well known that the incidence of each Candida species varies in different geographic regions and patient populations, which is essential in choosing adequate empirical antifungal regimens and in designing dosage (9,10). Although data are available on the epidemiology of candidemia, there is a lack of knowledge on it in trauma patients in Turkey (16). So we aimed to examine the epidemiology of candidemia in non-burn polytrauma patients in our region.

The incidence of candidemia in polytrauma patients in surgical ICUs of our institution was 127/1000 ICU admissions. It is much higher than those previously reported rates of 1.76/1,000 from Turkey and 34.3 from Spain, in general, in ICU populations (16,17). However, this result is not surprising due to the longer duration of stay in the ICU for them. Polytrauma patients requiring ICU admission furthermore more frequently necessitates the use of invasive equipment, receiving parenteral nutrition or using broad-spectrum antibiotics, which are well-known predictors of candidemia compared to those without polytrauma (5,6,18).

According to our study findings, the incidence of candidemia among our study patients was also higher than the rates reported previously in trauma patients. For example, Tak et al. reported an incidence of 14.95 per 1000 ICU admission, and Singh et al. reported that as 27.6 per 1000 admission (13,14). That might have resulted from the variation in the severity of trauma across those studies. The support fort his hypothesis was shown in a previous paper by Wolf et al., reporting the rate for candidemia was 30% after a bomb blast injury (19). Due to the ability of trauma to cause immune dysfunction, more severe trauma may predict a more severe systemic inflammatory reaction and deeper immunosuppression, which leads to a significantly increased risk of infection (20).

Although *C. albicans* is the most prevalent species in candidemia, in recent years, NAC species are becoming more common both in Turkey and worldwide (9,21). The proportion of non-albicans candidemia in the present study was 75.5%. This result is similar to the study findings of Singh et al., which indicated a predominance of NAC species (over 80%) in trauma patients with candidemia (13). Besides, previous studies conducted in general surgery ICUs (60.5%) from Turkey reported similar results regarding the frequency of non-albicans candidemia (21).

The frequency of *C. parapsilosis*, the most frequently isolated species (25/49, 51.1%), was remarkably higher in our study than in recent previous studies conducted in general ICUs from Turkey (16-25.1%). However, similar to our results, the most common isolated NAC species was *C. parapsilosis* in these studies, too (21-23). To the best of our knowledge, the current study is the first report that identifies *C. parapsilosis* as being the predominant isolated species of candidemia in trauma patients (12,13,24). There are several possible explanations for this finding: Firstly, this result may be explained by the fact that Candida species varies depending on the geographical region and population (21). There have been no other studies providing information on Candida species in non-burn trauma patients in Turkey, so caution must be applied. Secondly, this unexpected result might be a consequence of the limited number of cases in our study. Lastly, our study findings may closely be associated with a local C.parapsilosis outbreak. *C. parapsilosis* is well-known to be responsible for nosocomial clusters which are spread by the healthcare workers' hands (28). The failure to implement infection control measures successfully in trauma patients during a non-elective (emergency) surgery may cause intraabdominal colonization or infection with *C. parapsilosis*. Episodes of candidemia occurring at multiple different periods and different ICUs, do however, not suggest the existence of an epidemic.

In the present study, prior gastrointestinal surgery was found to be the only independent risk factor for *C. parapsilosis* candidemia. This finding is consistent with those of Playford et al., who announced that prior gastrointestinal surgery was associated with NAC bloodstream infection while it is in contrast with that of Klingspor et al. revealing an association between prior gastrointestinal surgery and *C. glabrata* candidemia (25,26). Although receiving TPN and the presence of a CVC are well-known risk factors for *C. parapsilosis* candidemia, we determined none of them as a risk factor for *C. parapsilosis* candidemia in our multivariate analysis (27). Candida species are part of the normal gastrointestinal microbiota. Gastrointestinal surgery or perforation that disrupts the intestinal epithelial barrier plays a primary role in the transition of Candida spp. from the bowel to the bloodstream (6). Another possible explanation is that patients with gastrointestinal surgery may be more likely to experience delays in enteral feeding after surgery; this means long-term TPN, which can cause *C. parapsilosis* overgrowth in the gut. However, it should be noted that only a small number of patients enrolled; therefore, these data must be interpreted with caution.

The crude mortality rate observed in the current study (69.4%) was slightly higher than other studies performed in trauma patients with candidemia (43.31-54.1%) (13,14). This difference might be attributed to the differences in trauma severity across the studies since all patients in our study were polytrauma patients.

C. albicans is known to be the most virulent species, and infections with *C. parapsilosis* are generally associated with lower rates of mortality and morbidity than those with *C. albicans* (28). Unexpectedly, *C. parapsilosis* had the highest rate of mortality (72%) in the present study. This result may be related to the comparatively high

percentage of *C. parapsilosis* candidemia in our study compared to *C. albicans* candidemia in our study.

As NAC species are known to have higher antifungal resistance rates than *C. albicans*, increased antifungal resistance rates might be the most unwanted consequences of NAC dominance (9,23). Thus, knowing the local antifungal resistance patterns is becoming increasingly important in guiding empirical antifungal therapy of patients with candidemia.

According to the most recent reports, resistance to fluconazole was relatively low among Candida isolates ranging from 0% to 2% in Turkey (29). The fluconazole resistance in *C. parapsilosis* also determined to be much higher than those in the other Candida species (22). The rate of fluconazole resistance to *C. parapsilosis* in our study (8%) was very close to those presented by Akdaglı and colleagues. This rate seems to be higher than those previously reported, and it may be as a result of the small number of *C. albicans* candidemia (1/12, 8.3%) in our research.

To date, the echinocandin resistance among Candida isolates has described as relatively infrequent both in Turkey and worldwide (9,16, 29). In contrast to previous reports, the current study revealed five (10.2%) isolates to be resistant to echinocandins unexpectedly. The caspofungin resistance was seen in only *C. tropicalis* isolates (33.3%) while the micafungin resistance was 8.3% for *C. albicans* and 33.3% for *C. tropicalis*. Again, these results, too, need to be interpreted with caution because of the low sample size in our study.

The major limitation of this study is the low number of polytrauma patients with candidemia as well as no control group, and retrospective study design. Our study was also limited by the small proportions of candidemia caused by Candida species other than *C. parapsilosis*, which may affect the results of the antifungal resistance rates we observed.

CONCLUSION

In conclusion, compared with the general population, polytrauma patients had a higher risk for candidemia caused by NAC spp., the most common of which was *C. parapsilosis*. Prior gastrointestinal surgery was detected to be the only independent risk factor for *C. parapsilosis* candidemia. Based on our study findings, we suggested that resistance rates to many antifungal agents were high among polytrauma patients. These suggestions, Hhowever, were limited by the low number of cases. Further work is, therefore, required to improve outcomes in non-burn polytrauma patients with candidemia.

Conflict of interest: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Ethics approval for this study was obtained from the Ethics Committee of the Mustafa Kemal University (Decision date: 2018 Number: 170).

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