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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factors' analysis associated with adverse outcome of the treatment of patients with invasive candidiasis

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SUMMARY

Introduction/Objective Invasive candidiasis (IC) is the most common invasive fungal infection in humans. It manifests as candidemia, and can affect internal organs and lead to sepsis and septic shock. A good knowledge of the factors that lead to the morbidity and mortality of these patients is necessary. We aimed to investigate the factors associated with the unfavorable outcome of patients with IC treated at our institution.

Methods The research was conducted at the Military Medical Academy in Belgrade, Serbia. The retrospective cohort study included 145 patients of both sexes, aged over 18, with a proven diagnosis of IC. Demographics, comorbidities, use of therapeutic procedures, antibiotics, antifungal treatment and outcome were compared between deceased and surviving patients with IC. The results were analyzed using Student's t-test, Mann–Whitney U test, multivariate statistical analysis.

Results The results showed that the predictors of death were diabetes mellitus (adjusted OR 6.886; CI: 2.608–18.178; p = 0.000) and chemotherapy (adjusted OR 6.826; 95% CI: 2.037–22.866; p = 0.002), which increase the risk of death seven times compared to the basal risk and mechanical ventilation, which increases the risk of death about three times (adjusted OR: 3.056; 95% CI: 1.132–8.253; p = 0.012).

Conclusion Optimal treatment is necessary in terms of early detection and identification of the causative agent of IC. In susceptible patients, such as immunocompromised patients, appropriate treatment should be initiated as soon as possible.

Keywords: fungal infection; invasive candidiasis; diabetes mellitus; death

INTRODUCTION

Candida species are normal commensals of humans, residing in the gastrointestinal tract, the female genital tract, and the anterior urethra. However, these fungi can cause a severe and life-threatening conditions, if *Candida* enters the bloodstream [1].

Invasive candidiasis (IC) is an infection caused by yeasts of the genus *Candida* that can affect different internal organs, such as the heart, brain, eyes, or bones and can lead to the development of sepsis and/or septic shock. IC is the most common fungal infection in hospitals, accounting for more than 85% of all invasive fungal infections in hospitals; approximately 45% of candidemia cases are treated in intensive care units (ICUs) [2, 3]. In Europe, IC is the fourth leading cause of nosocomial blood infections, with mortality ranging from 42% to 70%, and more than half of patients are diagnosed with septic shock [4, 5].

Risk factors for IC include: more than four days of ICU treatment, mechanical ventilation (MV), APACHE > 20, surgical procedures, total parenteral nutrition (TPN), renal and/or cardiac failure, and aminoglycoside administration [3, 6, 7]. Recent studies have shown that the number of patients with IC is increasing in the group of young intravenous opiate users without other risk factors [8]. During the COVID-19 pandemic, an increased number of patients with IC was recorded as a result of the administration of immunosuppressive and immunomodulatory drugs and prolonged treatment in the ICU [9, 10].

IC is one of the causes of morbidity and mortality in patients with HIV/AIDS immunodeficiency, in individuals with solid organ and stem cell transplants, in patients undergoing chemotherapy (CHT), in persistent neutropenia, in individuals with central venous catheters (CVC), in dialysis patients, and in patients receiving therapy with broad-spectrum antibiotics [7, 11]. Other studies confirmed diabetes mellitus (DM) and immunosuppression as significant risk factors for the occurrence of IC and emphasized the importance of the presence of a CVC, prolonged use of glycopeptide antibiotics, quinolones, and aminoglycosides [12, 13], and gastrointestinal tract surgery and prolonged ICU stay [4, 14].

The aim of this study was to analyze factors associated with death in hospitalized patients who were admitted with IC or developed it during hospitalization.

METHODS

The study was designed as an observational, retrospective cohort study of a random sample

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of 145 patients from the Military Medical Academy in Belgrade (MMA), Serbia, hospitalized between 2008 and 2021. Patients were enrolled based on the following inclusion criteria: hospitalization in one of the clinics of surgery / internal medicine or at the ICU of the MMA, aged over 18 years, both sexes, patients with a confirmed diagnosis of IC – proven isolate of any fungal species of the genus *Candida* in a blood culture or in sterile areas or tissues, or patients with a probable diagnosis of IK – positive results of radiological tests and markers of invasive fungal infection (*Candida* mannan). The BACT/ALERT® system (bioMérieux, Marcy-l'Étoile, France) was used to isolate fungi from blood cultures and peritoneal fluid. Microorganisms were differentiated using the Matrix Assisted Laser Desorption Ionization – Time of Mass Spectrometer and Video Artificial Intelligence Technology. Serum samples for *Candida*-specific antibodies and *Candida*-specific antigen – mannan were analyzed by enzyme-linked immunosorbent assay. All microbiological analyzes were performed in the microbiology laboratory of the MMA. Exclusion criteria were incomplete medical documentation, combined invasive fungal infections with *Candida* and other fungi, and late initiation of antifungal therapy. The study was approved by the Ethics Committee of the MMA (resolution number 56/2019, date 06/24/2019) before initiation.

Data were obtained from the MMA's information system. Primary study outcome was in-hospital mortality, and secondary outcomes were relapse of IC (new diagnosis of IC within 30 days of initiation of treatment for the first episode of disease) and occurrence of subsequent complications in patients previously diagnosed with IC, such as vital organ failure or surgical intervention. Putative predictors of study outcomes were DM, previous surgery, previous peritoneal or hemodialysis, TPN, administration of antibiotics for more than four days, administration of more than three antibiotics, administration of a CVC, invasive and noninvasive MV, corticosteroids, immunosuppressive therapy, biological therapy, CHT, radiotherapy, neutropenia, bacterial sepsis, solid organ transplantation, and bone marrow transplantation, while confounding factors considered were: sex, age, body temperature, hospital department where the patient was treated, comorbidities, concomitant therapy, and the underlying disease that was the reason for hospitalization.

The minimum sample size sufficient to find factors significantly associated with mortality as a study outcome was calculated based on the Schlesselman method. The inputs for this calculation were: Probability of type 1 error of 0.05, power of the study 0.8, incidence of the primary outcome 20%, prevalence of DM as a risk factor of 62%, and a meaningful adjusted odds ratio of two for the risk factor. The minimum sample size sufficient for the inputs was 66 patients per study group, for a total of 132 patients.

Data collected from the MMA information system were first numerically coded, tabulated, and checked for errors. Data were then described by measures of central tendency and variability (for continuous data) or frequencies and relative numbers (percentages) (for categorical data). Normally distributed continuous data were described by mean and standard deviation, and not-normally distributed data were described by median and interquartile range. The effects of putative predictors and confounders on the study results were analyzed using multivariate binary logistic regression. Before using this multivariate technique, we checked that the assumptions were met (binary outcome, independence of observations, no multicollinearity, no extreme outliers, and sufficiently large sample). The quality of the regression model was tested using the Hosmer–Lemeshow test, Cox & Snell's R-squared, and Nagelkerke's R-squared. Results were considered statistically significant if the probability of the null hypothesis was 0.05. Survival curves were constructed for significant categorical predictors, and the equality of survival distributions for different levels of such predictors was tested with the log-rank test. All calculations were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 18.0.

RESULTS

This study included 145 patients (70 men and 75 women) with a mean age of 52.8 ± 17.5 years who were hospitalized at MMA Belgrade between 2008 and 2021. In total, 60 patients (41.1%) died during hospitalization, 85 recovered (58.2%), and only one patient (0.7%) had a relapse of IC. Age, sex, length of hospital stay, and other characteristics of the study sample related to the primary outcome are shown in Table 1.

The association of independent and confounding variables with death during hospitalization was tested using multivariate binary logistic regression. The model was built using the backward conditional deletion method, starting from a complete set of potential predictors and confounders: DM, previous surgery, previous peritoneal or hemodialysis, TPN, administration of antibiotics for more than four days, administration of more than three antibiotics, administration of a CVC, invasive and noninvasive ventilation, corticosteroids, immunosuppressive therapy, biological therapy, CHT, radiotherapy, neutropenia, bacterial sepsis, solid organ transplantation, bone marrow transplantation, sex, age, body temperature, hospital unit in which the patient was treated, comorbidities, concomitant therapy, and the underlying disease that was the reason for hospitalization. The assumptions of a binary outcome (death during hospitalization or not), independence of observations, absence of multicollinearity, absence of extreme outliers, and a sufficiently large sample were all met. The linear relationship between the explanatory variables and the logit of the outcome was tested for all continuous variables with the Box-Tidwell test, but none of these variables was included in the final model. The final binary logistic regression model included the variables listed in Table 2, and fit the data satisfactorily: Hosmer–Lemeshow test was 6.476 (df = 6, p = 0.372), Cox & Snell's square was 0.180, and Nagelkerke's square was 0.244.

Survival curves for patients with and without DM are shown in Figure 1. The logrank test (Mantel–Cox) showed a significant difference in survival distributions: $\chi^2 = 17.456$, df = 1, p = 0.000.

Table 1. Characteristics of the study sample; the data are presented as mean ± SD; the differences among the groups were tested by Mann–Whitney U test for continuous variables and by χ^2 test (or Fisher's exact test where appropriate) for categorical variables; p – probability of null hypothesis

Variable		Died (n = 60)	Survived (n = 85)	p
Age (years)		56.7 ± 17.6, 56 [25]	50.7 ± 16.8, 53 [27]	0.042
Sex (m/f)		30/30	40/45	0.727
Length of stay (days)		55.2 ± 66.2, 37 [59]	48.8 ± 34.1, 40 [28]	0.224
Treatment in intensive care unit (yes/no)		15/45	21/64	0.968
Number of antibiotics administered		3.7 ± 1.8, 4 [1]	3.8 ± 1.7, 4 [2]	0.715
Length of antibiotic therapy (days)		46.5 ± 52.6, 30 [47]	40.1 ± 28.3, 30 [31]	0.564
Length of antifungal therapy (days)		19.1 ± 11.9, 20 [15]	19.3 ± 14, 17.5 [6]	0.662
Time delay from diagnosis to antifungal therapy onset (hours)		22.6 ± 46.9, 17 [24]	18.6 ± 24.8, 24 [24]	0.886
Time delay from symptoms to antifungal therapy onset (hours)		25.5 ± 31.4, 24 [48]	41.1 ± 97.8, 24 [48]	0.473
Day of death since hospitalization		55.1 ± 62.5	-	
Day of death since initiation of antimicrobial therapy		44.0 ± 41.7	-	
Full/reduced dose of antifungals		52/8	80/5	0.168
Wide spectrum antibiotic used (yes/no)		59/1	83/2	0.313
Urinary catheter (yes/no)		60/0	81/4	0.115
Place of isolation of the causative agent (blood / pleural punctate / abdominal fluid)		58/1/1	83/2/0	0.748
Antifungal prophylaxis (yes/no)		39/21	50/35	0.452
Intravenously immunoglobulins (yes/no)		60/0	85/0	cannot be calculated
Blood culture from central venous catheters / peripheral vein		30/27	45/36	0.857
Isolated Candida type	Candida species	14	18	0.025
	Candida albicans	18	40	
	Candida glabrata	7	1	
	Candida parapsylosis	17	22	
	Candida kefiri	1	0	
	Candida lusitanie	0	2	
	Candida sake	0	1	
	Candida guillermondi	0	1	
Candida antibodies measured (yes/no)		0/60	2/83	0.342
Mannan measured (yes/no)		0/60	1/84	0.586
Type of antimycotic prescribed (azole / echinocandin / amphotericin B / unknown)		48/6/1/5	76/8/0/1	0.334
Oral / parenteral / unknown route of administration of antimycotics		3/52/5	6/78/1	0.484
Invasive fungal infection proven/probable		60/0	84/1	1,000
Supportive therapy (yes/no)		5/55	2/83	0.126
Hemodialysis (yes/no)		8/52	5/80	0.122
Peritonitis (yes/no)		5/55	7/78	0.625
Sepsis (yes/no)		12/48	14/71	0.585
Solid organ transplantation (yes/no)		2/58	1/84	0.570
Bone marrow transplantation (yes/no)		4/56	10/75	0.398
Pancreatitis (yes/no)		4/56	8/77	0.761
COVID-19 (yes/no)		0/60	1/84	1,000
Diabetes mellitus (yes/no)		28/32	14/71	0.000
Mechanical ventilation (yes/no)		34/26	37/48	0.119
Therapy with potential to suppress the immune system	No	29	51	0.319
	Biological drugs	0	2	
	Immunosuppressant drug	13	11	
	Radiation therapy	2	1	
	Chemotherapy	16	20	
Central venous catheter (yes/no)		39/21	62/23	0.306
Central venous catheter removed after diagnosis of fungal infection with delay of more than 24 hours (yes/no/unknown)		13/8/18	27/16/19	0.945
Abdominal surgery (yes/no)		27/33	43/42	0.507
Neutropenia (yes/no)		15/45	18/67	0.589

Table 2. Risk factors for death during hospitalization of patients with invasive candidiasis

Risk factors	Raw OR (95% CI)	p	Adjusted OR (95% CI)	p
Diabetes mellitus	4.437 (2.064–9.539)	0.000	6.886 (2.608–18.178)	0.000
Mechanical ventilation	1.696 (0.871–3.305)	0.120	3.056 (1.132–8.253)	0.028
Chemotherapy	1.407 (0.632–3.131)	0.403	6.826 (2.037–22.866)	0.002
Radiotherapy	3.517 (0.306–40,489)	0.313	3.788 (0.271–52.844)	0.322
Immunosuppressants	2.078 (0.826–5.233)	0.120	3.094 (0.980–9.770)	0.054

OR – odds ratio; CI – confidence interval

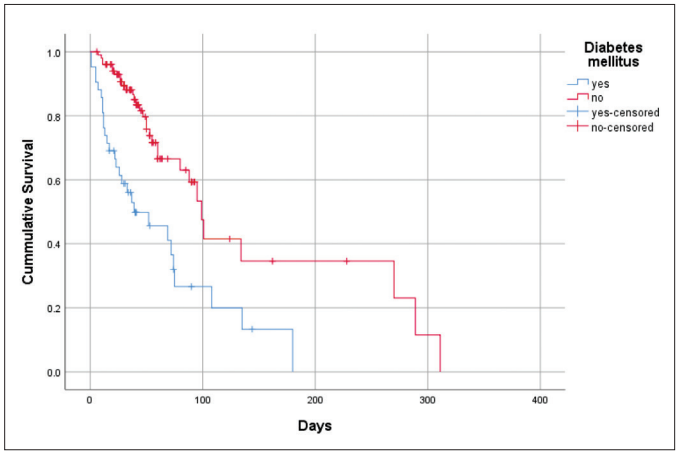

Figure 1. Survival curves for patients with and without diabetes mellitus

DISCUSSION

The prevalence of infection IC is increasing [1]. The use of antineoplastic and immunosuppressive agents, broad-spectrum antibiotics, DM, neutropenia, and more aggressive surgical procedures are potential risks for the increasing number of IC patients worldwide [11, 13, 15].

Our study showed that there are three independent predictors of death in hospitalized patients with IC: DM and CHT, which increase the risk of death almost sevenfold compared to baseline risk, while MV increases the risk of death threefold. Among other factors tested, age and isolation of *Candida glabrata* and *Candida parapsylosis* appeared to have a tendency to negatively affect hospital mortality, but this was lost after adjustment for other factors in multivariate analysis.

Candida albicans remains the most common cause of IC. In recent decades an increase in non-albicans candidemia has been observed. *Candida glabrata* is responsible for 15–25% of invasive fungal infections and is second only to *Candida albicans* in the United States and northwestern Europe, and that predisposing factors include older age and frequent use of medical devices [16]. Some authors emphasized the growing medical importance of *Candida glabrata* in the population of patients with immunodeficiency syndrome, DM, and malignant diseases, as well as in the elderly [16, 17]. IC caused by *Candida glabrata* causes significant morbidity and mortality of 40–60%, mainly due to low sensitivity to the most commonly used azoles [18]. Indeed, it was reported that *Nakaseomyces glabrata* (formerly *Candida glabrata*) was isolated in 14% of patients with IC, with an average age of 55 years, and what is more significant, 6% of isolates were resistant to echinocandins [19]. Also, in a study in Turkey, results obtained from six different medical centers the presence of *Candida glabrata* was found to be the causative agent of IC in ICUs in 10% of patients [20].

In our study, *Candida glabrata* was found to be isolated in 11.6% of patients in the observed group and in 1.17% of patients who recovered, which is in accordance with data from the literature. On the basis of a multifactorial regression analysis adjusting for other factors, *Candida glabrata* isolate had no significance in the outcome of our patients.

In our hospital, DM was registered in 29% of patients with IC, which is a lower frequency compared with data from other studies (62.5% and 50%) [21, 22]. Here, we have shown that there was a statistically significant difference in the outcome of patients with IC in relation to the presence of DM. DM is an independent factor that increased the risk of death sevenfold. The mortality was 41.4%, consistent with the results of other studies in which it ranged from 28% to 45% [23].

DM is a multifactorial, chronic metabolic disease and is a major health problem worldwide. Patients with DM often have other comorbidities that further worsen the outcome of IC. In an analysis of numerous studies on DM and IC, Rodrigues et al. [12] showed the importance of DM as an independent factor in the development of IC and the fatal outcome of these patients. Numerous studies have shown an association between *Candida* sp. infection and DM, related to oral, vulvovaginal candidiasis or IC [18].

In patient with persistent candidemia, isolates responsible for biofilm formation, including *Candida albicans, Candida tropicalis,* and *Candida glabrata* were significantly more common [18, 24]. *Candida glabrata* was more frequent in DM patients (52.9% *vs*. 32%) than in patients without DM and in infections originating from the abdomen, which is explained by the greater pathogenicity of the pathogen [24]. A retrospective study in China showed that candidiasis was the most common fungal infection in the elderly patients with DM (46.8%) [17]. In patients with DM and IC, treatment is even more difficult because of reduced sensitivity to antifungal agents, up to 47% to ketoconazole, while other authors show significant resistance to five antifungal agents in diabetics [18].

Given the increasing resistance of *Candida albicans* [25] to fluconazole and *Candida glabrate*, as well as to echinocandins [19] found in a large percentage of DM patients, the treatment of these patients is difficult both in terms of choice and dose of drugs used. In addition, the

pharmacokinetics and pharmacodynamics of antifungal drugs are impaired in patients with DM. The absorption of the drug is poor, which is due to the structural alteration of albumin and the decreased binding of the drug, which increases the concentration of free drug in the serum. Due to the damage of microcirculation and vascular permeability, the penetration of the drug to the site of infection is weak [18]. Adequate treatment is of great importance for this group of patients.

Long-term MV in the ICU exposes patients to fungal colonization and leads to candidemia. This is due to the presence of medical devices (peripherals, cannulas, CVC, urinary catheters, Hickman catheters, tubes, oxygen masks, etc.), the use of broad-spectrum antibiotics and immunosuppressive therapy. The association of TPN and MV with candidemia increases mortality by up to 77% [26]. Chakraborti et al. [27] showed that there is a significant increase in fungal colonization in endotracheal aspirates between the first and seventh day after intubation. New strategies for the use of protective MV showed a lower incidence of complications compared with the use of conventional MV (8.7% *vs*. 14.7%), which should also lead to lung injury reduction [28]. Also, increased colonization with *Candida glabrata* during the use of MV, which tends to form biofilms with the development of resistance to existing azoles, leads to treatment failure and death [13, 16, 19]. Our results show that in patients with IC MV was applied in 56.7% of cases in the observed group and in 43.5% of cases in the control group of surviving patients. Multivariate regression analysis revealed that the use of MV in patients with IC was associated with three times higher risk of death or significantly increased the probability of death. Our results are consistent with the findings of other studies [22].

In our study, 44% of patients with IC received some type of therapy affecting the immune system. In the observed patient group, 26.67% received CHT, and in the survivor group, 23.53% did. In our CHT-receiving patients, the risk of death was seven times higher compared to patients without CHT. Such a high risk of death can be explained by the nonspecific effect of CHT on cells, the occurrence of immunosuppression and the development of opportunistic infections, among which *Candida* infections take the first place. IC is very common in patients with malignant diseases, has a high incidence of morbidity and mortality, which significantly increases the cost of treatment.

CHT leads to disruption of epithelial barriers and alters the host immune response, allowing the development of IC. Following CHT, *Candida* sp. overgrowth occurs due to decreased production of antimicrobial peptides by epithelial cells or decreased levels of bacterial metabolites that normally inhibit *Candida albicans* growth, as well as direct effects of CHT on *Candida albicans* itself [29].

In our study, neutropenia as an independent factor did not increase the probability of death in patients with IC, there was no difference in the prevalence of neutropenia in the deceased and survivor groups, which may be explained by the lack of damage to the gastrointestinal barrier, insufficient degree of mucosal colonization, or colonization with less virulent *Candida* strains.

Surgical intervention in the upper abdomen was recorded in 48.27% of our patients and did not affect the outcome, while other authors presented this intervention as a risk factor for the occurrence and outcome of IC due to increased antibiotic consumption, secondary infections, and the use of MV [14].

Among the other comorbidities, sepsis, peritonitis, and pancreatitis did not affect the outcome of patients with IC. Solid organs transplantation, bone marrow transplantation, use of hemodialysis, presence of urinary catheter, and placed CVC were not significant for death outcome of patients with IC.

The presence and extraction of CVC 24 hours or more after the diagnosis of IC was not a risk factor for the unfavorable outcome of our patients, while previous studies describe CVC as an independent risk factor [13]. The results of recent studies suggest that CVC is a significant predictor of candidemia in internal medicine departments with prior use of cephalosporins and inadequate body weight. Poissy et al. [7] show that CVC is still a risk factor for candidemia in all patients and an independent risk factor for candidemia in non-ICU patients received glycopeptides and TPN.

A broad-spectrum antibiotic was used equally frequently in both groups and the average number of antibiotics was used in patients with IC in the observation and control groups. Poissy et al. [7] described the use of multiple antibiotics as a risk factor for death, which was not demonstrated in our results. Considering the duration of antifungal use in the studied groups, there was no statistical significance in relation to the outcome.

In our study, the length of hospital stay did not significantly affect the outcome of death, as the studied and control groups did not differ significantly on this parameter, as did ICU treatment. One meta-analysis has shown that ICU stay is a significant risk factor for the occurrence of IC and death [4].

Our study has several limitations. First, the sample size was limited, so the study may not be sufficiently powered to identify other putative factors because of the low prevalence in this population. Second, this was a unicenter study, so some local practices not captured by the study data may have influenced the outcome and amplified or neutralized the effects of some true predictors.

CONCLUSION

In conclusion, patients with DM or patients receiving CHT, especially if mechanically ventilated, are several times at a greater risk of dying in the hospital and therefore require special attention and timely administration of appropriate antifungal and other supportive measures.

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Анализа фактора удружених са неповољним исходом лечења болесника са инвазивном кандидијазом

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САЖЕТАК

Увод/Циљ Инвазивна кандидијаза (ИК) најчешћа је инвазивна гљивична инфекција код људи. Манифестује се као кандидемија, а може захватити унутрашње органе и довести до сепсе и септичног шока. Неопходно је добро познавање фактора који доводе до морбидитета и морталитета ових болесника.

Циљ рада је био да истражимо факторе повезане са неповољним исходом лечења болесника са ИК у нашој установи.

Методе Истраживање је спроведено на Војномедицинској академији у Београду, у Србији. Ретроспективном кохортном студијом обухваћено је 145 болесника оба пола, старости преко 18 година, са доказаном дијагнозом ИК. Демографија, коморбидитети, примена терапијских процедура, антибиотици, антифунгални третман и исход упоређени су између умрлих и преживелих болесника са ИК. За анализу резултата коришћени су Студентов т-тест, Ман–Витнијев *U* test, мултиваријантна статистичка анализа.

Резултати Показано је да су предиктори смртног исхода дијабетес мелитус (кориговани *OR* 6,886; *CI*: 2,608–18,178; *p* = 0,000) и хемотерапија (кориговани *OR* 6,826; 95% *CI*: 2,037–22,866; *p* = 0,002), који повећавају ризик за смртни исход седам пута у поређењу са базалним ризиком, и механичка вентилација, која повећава ризик за смртни исход око три пута (кориговани *OR*: 3,056; 95% *CI*: 1,132–8,253; *p* = 0,012).

Закључак Неопходан је оптималан третман у смислу раног откривања и идентификације узрочника ИК. Код осетљивих болесника, као што су болесници са ослабљеним имунитетом, одговарајући третман треба започети што је пре могуће.

Кључне речи: гљивична инфекција; инвазивна кандидоза; дијабетес мелитус; смрт