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The Prevalence of Cardiac and Ocular Findings in Patients with Invasive Candida Infection in Intensive Care Unit

Yoğun Bakımda Invazif Kandida Enfeksiyonu Tanılı Hastalarda Kalp ve Göz Bulgularının Prevalansı

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ABSTRACT

Introduction: Invasive candidiasis (IC) is a common opportunistic infection in intensive care units (ICUs). IC may cause endocarditis by spreading hematogenously to the heart valves and endocardium or may spread to intraocular tissues and cause endophthalmitis and chorioretinitis. Therefore, echocardiography and an ocular examination should be performed in patients with IC. These complications increase morbidity and mortality. The early diagnosis and treatment of IC are important to reduce these complications. The aim of this study was to determine the prevalence of cardiac and ocular involvement in patients with IC in the ICU.

Materials and Methods: This study was performed retrospectively between January 2015 and December 2017 in the 20-bed ICU. The archive files of patients diagnosed with IC were analyzed. By reviewing the consultation reports of Cardiology and Ophthalmology clinics, cardiac and ocular findings were reported.

Results: Invasive Candidiasis was detected in 44 of 1746 patients who were admitted to the ICU. While the ratio of IC was 25.2 in 1000 patients, the IC rate was 2.02 in 1000 patient days. Of these patients, 41 (93.2%) had central venous catheter-related bloodstream infection, and three (6.8%) of them had urinary tract infection. The most common agents were C. albicans (n = 20, 42.6%) and C. parapsilosis (n = 20, 42.6%). The others were C. tropicalis (n = 4, 8.5%), unspecified Candida spp. (n = 2, 4.2%), and C. glabrata (n = 1, 2.1%). None of the patients had signs of cardiac involvement, such as endocardial vegetation, and signs of ocular involvement, such as chorioretinitis, endophthalmitis, and vitritis.

Conclusion: In our study, we did not detect cardiac and ocular involvement in patients with IC. We believe that larger-scale prospective studies are needed to determine the prevalence of these complications in the ICU.

Keywords: Invasive Candidiasis, chorioretinitis, endophthalmitis, endocarditis, intensive care unit.

ÖZ

Giriş: İnvazif Kandida enfeksiyonu (İKE) yoğun bakım ünitelerinde (YBÜ) sık rastlanan fırsatçı enfeksiyonlardandır. Vücutta herhangi bir kaynakta saptanan İKE, hematojen yolla kalp kapaklarına ve endokarda yayılarak endokardite, göz içi dokulara yayılarak endoftalmit ve koryoretinite neden olabilmektedir. Bu nedenle İKE tanılı hastalarda mutlaka ekokardiyografi ve göz muayenesi yapılmalıdır. Bu komplikasyonlar morbidite ve mortaliteyi artırmaktadır. İKE'nin erken teşhisi ve tedavisi bu komplikasyonları azaltabilmek için önemlidir. Bu çalışmada, YBÜ'de İKE tanısı alan hastalardaki kalp ve göz tutulumlarının prevalansını saptamak amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışma, 20 yataklı YBÜ'de Ocak 2015 - Aralık 2017 tarihleri arasında yatan hastaları kapsamaktadır. İKE tanısı konan hastaların arşiv dosyaları tarandı. Kardiyoloji ve Göz hastalıkları kliniklerinin konsültasyon raporları incelenerek kalp ve göz tutulum bulguları kayıt altına alındı.

Bulgular: YBÜ'ye yatışı yapılan 1746 hastadan 44'ünde İKE tespit edildi. İKE sıklığı 1000 hastada 25.2 iken, İKE hızı 1000 hasta gününde 2.02 olarak saptandı. Bu hastaların 41 (%93.2)'inde santral venöz kateter ilişkili kan dolaşımı enfeksiyonu, 3 (%6.8)'ünde üriner sistem enfeksiyonu tespit edildi. En sık üretilen etkenler C. albicans (n=20, %42.6) ve C. parapsilosis (n=20, %42.6) idi. Diğerleri sırasıyla C. tropicalis (n=4, %8,5), tiplendirilemeyen Candida türleri (n=2, %4,2) ve C. glabrata (n=1, %2,1) idi. Kardiyak tutuluma işaret eden endokardiyal vejetasyon ve göz tutulumuna işaret eden koryoretinit, endoftalmit ve vitrit hastaların hiçbirinde saptanmadı.

Sonuç: Çalışmamızda İKE tanılı hastalarda kalp ve göz tutulumu saptamadık. YBÜ'de bu komplikasyonların prevalansını bulmada daha büyük ölçekli prospektif çalışmalara ihtiyaç olduğu kanaatindeyiz.

Anahtar Kelimeler: İnvazif Kandida enfeksiyonu, koryoretinit, endoftalmit, endokardit, yoğun bakım ünitesi

Introduction

Intensive care units (ICUs) are hospital units in which patients who need multiple invasive procedures are followed up while receiving intensive drug treatment due to multiple organ dysfunction and the prevalence of hospital-acquired infection is high (1). Medical or invasive medical procedures performed at the diagnosis and treatment stages to facilitate the development of nosocomial infections in critically ill patients admitted to the ICU. In ICUs, opportunistic fungal infections may occur due to risk factors such as the intensive use of broad-spectrum antibiotics, parenteral nutrition and central venous catheterization (2).

Invasive Candidiasis (IC) is among the most common opportunistic fungal infections. IC is commonly known as healthcare-associated bloodstream infection (BSI), and incidence is increasing with each passing day in ICUs. Mechanical ventilation day and length of ICU stay become prolonged, and the prognosis is adversely affected in patients with IC. IC increases morbidity and mortality and is even considered as the major cause of infection-related morbidity and mortality in ICUs (3,4).

Candida species can cause infection in many parts of the body but in ICU patients mainly observed in blood or urine. If any of the Candida species is isolated in the culture taken from a patient with signs of infection, it should be considered as an infection, infection the source should be investigated, treatment and control measures should be taken. In the presence of IC, endocarditis as an indicator the cardiac involvement and chorioretinitis and endophthalmitis as indicators of ocular involvement were reported (5,6). It was stated that morbidity and mortality increase when these complications develop, and therefore, echocardiography and fundus examinations should be performed in patients diagnosed with IC (4,5).

In this study, we aimed to determine the prevalence of cardiac and ocular involvement in patients hospitalized in the ICU.

Materials and Methods

Study design

This study was conducted after receiving the approval of the Local Ethics Committee (2018-E.1470) by retrospectively reviewing the archive records of patients in the 20-bed Anesthesiology ICU between January 2015 and December 2017.

IC was diagnosed according to the surveillance diagnostic criteria determined by the Centers for Disease Control and Prevention (7). Archive records of patients and Infection Control Committee reports were screened for demographic patient data and reproducing organism types. Consultation reports prepared by cardiology and ophthalmology clinics were examined, and findings were recorded.

Definitions

The detection of at least one Candida species in the blood culture of the patients and the presence of infection symptoms such as fever, shivering, or hypotension were considered as candidemia. In the presence of central venous catheter (CVC), the isolation of the same Candida species in the blood culture taken from the peripheral blood and CVC at the same time without any other focus of infection in a patient and at least two hours early growth in the catheter blood compared to the venous blood were defined as a central venous catheter-related bloodstream infection (CRBSI). In the presence of at least one of the signs and symptoms of a urinary tract infection (UTI) (fever > 38°C, urinary burning, frequent urination, and suprapubic sensitivity), if Candida species grew in the urine culture, it was considered as candiduria and diagnosed as symptomatic UTI.

Appropriate antifungal therapy was initiated immediately according to the culture of patients diagnosed with IC. During the treatment, cultures were repeated at intervals determined by the Infection Control Committee. The fundus examination and echocardiography were performed at least once per week or every two weeks until the cultures were negative.

The IC ratio and rate in patients were calculated using the following formulae.

Infection ratio = Number of patients diagnosed with IC / Total number of inpatients x 1000

Infection rate = Number of IC diagnoses / Total patient days x 1000

Ventilator utilization rate = Ventilator days / Patient days x 100.

Number of Inpatients: The number of patients treated in the ICU within a certain period (days, months, three months, or one year).

Number of Patient Days: The total number of days a patient stays in the ICU. In the calculation, only the day on which the patient is admitted to the ICU is counted while the discharge day is not counted among admission and discharge days. It is obtained by subtracting the admission date from the patient's discharge date. The patient day of the patient who is admitted and discharged on the same day is accepted as 1 day.

Ventilator Day: The total number of days a patient stays connected to the ventilator. The day he/she is connected to the ventilator is recorded as the first day of intubation, and the day of extubation is not included in the ventilator day.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 24 program. Data were presented as mean, standard deviation, percentage distribution, minimum and maximum values. Pearson's chi-square and Fisher's exact tests were used for the comparison of the ratios. The statistical significance level was accepted as $p<0.05$.

Results

Of the 1746 patients admitted to the ICU during the study period, IC was detected in 44 patients. While the ratio of IC in ICU

patients was 25.2 in 1000 patients, the IC rate was 2.02 in 1000 patient days. Forty-one (93.2%) patients had CRBSI, and three (6.8%) patients had UTI. Candidemia was detected in 43 different cultures and was defined as CRBSI. UTI was defined as catheter-related UTI in 4 cultures.

The demographic data of the patients are presented in Table 1. Accordingly, 26 (59.1%) of the patients were male, and 18 (40.9%) were female, and their mean age was 54.36 ± 21.9 years. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores were 22.9 ± 7, while the mean Glasgow Coma Score (GCS) at ICU admission was 5.22 ± 2.7. The total ICU hospitalization days were 3534, and the mean length of ICU stay was 82 ± 77 days, while the total ventilator days were 2605, and the mean length of stay in mechanical ventilation was 59.2 ± 64 days. The ventilator utilization rate of all patients hospitalized in the ICU in the same process was 64.7%, while the ventilator utilization rate of 44 patients diagnosed with IC was 73.7%, and this difference was significantly high (p=0.024). Furthermore, the ICU mortality rate was 32.5%, while the mortality rate in patients diagnosed with IC was 54.5% and this difference was significantly high (p=0.024).

The ICU admission diagnosis and comorbidities of the patients are presented in Table 2.

The most common organisms were C. *albicans* (n=20, 42.6%) and C. *parapsilosis* (n=20, 42.6%), and the others were C. *tropicalis* (n=4, 8.5%), unspecified *Candida* species (n=2, 4.2%) and C. *glabrata* (n=1, 2.1%), respectively.

In the ocular consultation reports examined, none of the patients had any signs of chorioretinitis, endophthalmitis, or vitritis. In the cardiology consultations including the bedside echocardiography report, none of the patients had endocardial vegetation.

Discussion

Invasive Candidiasis is one of the most common nosocomial bloodstream infections and is in the first place in ICU patients (8-10). IC leads to the prolonged length of stay in hospital and ICU and an increase in costs (10-12). Moreover, it is the most important cause of infection-related morbidity and mortality (8). While the survival rate increases with the correct antifungal therapy initiated within the first 12-24 hours, the delay in appropriate antifungal therapy for any reason leads to mortality (10). Therefore, prophylactic or empirical antifungal therapy strategies are being developed to reduce morbidity and mortality in groups with risk factors, especially in ICU patients. Despite efforts to develop new treatments, there is a significant increase in the incidence of IC and its effect on mortality in ICUs (13). Mortality rates in IC patients in ICUs were reported to be between 20% and 60%, and it was stated that this change might result from the variability in societies and Candida species (12-16). Furthermore, the prolonged length of ICU stay and prolonged mechanical ventilation support were reported in patients diagnosed with IC (12-15). In our study, in accordance with the literature, the prolongation of length of ICU stay and mechanical ventilation, and especially the increase in the ventilator utilization rate and mortality rate were found to be significant in patients diagnosed with IC.

Candida species are colonized in the gastrointestinal tract and skin in approximately 80% of ICU patients, and about 10% of them develop IC (10). The incidence of IC in ICU patients is between 0.5 and 32 per 1000 patients, while the IC rate is between 0.74 and 2.2 per 1000 patient days (17-19). In our study, the IC ratio

Table 2. Admission diagnosis and comorbidities

	n (%)
Admission diagnosis	
Respiratory Failure	9 (20.5)
Cerebrovascular Disease	8 (18.2)
Cardiac Arrest	8 (18.2)
Head Trauma	6 (13.6)
Myocardial Infarction	4 (9.1)
Multiple Trauma	4 (9.1)
Acute Abdomen	3 (6.8)
Other	2 (4.5)
Comorbidities	
Hypertension	19 (26.8)
Coronary Artery Disease / Heart Failure	13 (18.3)
Cerebrovascular Disease	11 (15.5)
Diabetes Mellitus	11 (15.5)
Malignancy	4 (5.6)
Chronic Obstructive Pulmonary Disease	3 (4.2)
Chronic Renal Failure	3 (4.2)
Other	7 (9.9)

n: Number of patients, **%:** percentage

Table 1. Demographic data of patients

		Minimum-Maximum	Mean±SD
Age (years)		17 - 87	54.36±21.9
Length of ICU stay (days)		16 - 470	82±77
Ventilation day		3 - 396	59.2±64
APACHE II		8 - 35	22.9±7
Glasgow Coma Score		3 - 12	5.22±2.27
		n	%
Gender	**Female**	18	40.9
	Male	26	59.1

APACHE: Acute Physiology and Chronic Health Evaluation, **ICU:** Intensive care unit, **SD:** Standard deviation value, **n:** number of patients, **%:** percentage value

was found to be 25.2 per 1000 patients, while the IC rate was found to be 2.02 per 1000 patient days in consistency with the literature.

IC detected at any source in the body invades the intraocular tissues hematogenously, resulting in the formation of endogenous chorioretinitis, endophthalmitis, and vitritis. Chorioretinal inflammation is defined as chorioretinitis, intraocular inflammation is defined as endophthalmitis, and vitreal inflammation is defined as vitritis. The majority of Candida endophthalmitis is endogenous endophthalmitis, which develops as a result of candidemia (8). It was reported that ocular involvement might develop in the presence of candidemia at the rates ranging from 2% to 78% (6,20). While 50-62% of endogenous endophthalmitis results from fungal causes, the first organism of fungal endophthalmitis is reported to be Candida species (21,22). Unlike previous studies considering endophthalmitis as ocular involvement during IC, recent studies have found that chorioretinitis develops more commonly (6,20,23-26). *Candida albicans* was the most common cause of ocular involvement in both endophthalmitis and chorioretinitis (6,20,23-27). *Candida parapsilosis, glabrata*, and *tropicalis* are the other causes of ocular involvement (6,24-27).

Candida endocarditis occurs as a result of the hematogenous invasion of the cardiac valves or endocardium by IC, which is located anywhere in the body. Candida endocarditis constitutes the majority of fungal endocarditis but constitutes less than 2% of all infective endocarditis (5,28). However, the mortality rate in Candida endocarditis reaches approximately 70% (5,29,30). *Candida albicans* is the most common pathogen in Candida endocarditis, followed by *Candida parapsilosis, glabrata*, and *tropicalis* (5,28-30).

Risk factors for ocular and cardiac involvement due to invasive Candida infections include diseases leading to immunodeficiency [diabetes mellitus (DM), renal failure, malignancy], intravenous drug dependence, long-term use of multiple broad-spectrum antibiotics, long-term central venous catheterization, parenteral nutrition, previous major abdominal or cardiovascular surgery, presence of a prosthetic cardiac valve, long-term steroid or immunosuppressive therapy (6,21,25,26,31,32). However, the correct antifungal therapy at an appropriate time can prevent the development of complications such as endophthalmitis and endocarditis in patients with candidemia (33,34). Although there were comorbidities such as DM, renal failure and malignancy, and risk factors such as long-term hospitalization, central venous catheterization, parenteral nutrition, previous aortic surgery and substance dependence, ocular and cardiac involvement were not observed in our patients. We believe that the absence of these complications results from taking cultures as soon as possible in suspected patients in cooperation with the Infectious Diseases Clinic and the correct targeted antifungal therapy in the shortest period of time according to the results of the cultures. However, since our study was retrospective and single-centered, the small number of patients diagnosed with IC in our study may have been a factor in the absence of complications, which is the limitation of this study.

Cardiac invasion such as endocardial vegetation and ocular invasion such as endophthalmitis and chorioretinitis may be regarded as complications in the presence of risk factors in patients diagnosed with IC in the ICU. The early diagnosis of IC and correct antifungal therapy are the most important factors in preventing such complications. In conclusion, although there was no cardiac and ocular involvement in patients with IC in our study, we believe that larger-scale prospective studies are needed to determine the prevalence of these complications.

AUTHOR CONTRIBUTIONS:

Concept: YT, OP; **Design:** YT, OP; **Supervision:** YT, OP, OK; **Fundings:** YT, OP, MO, OK; **Materials:** YT, OP, MO, OK; **Data Collection and/or Processing:** OP, MO, OK; **Analysis and/or Interpretation**: YT, OP, OK; **Literature Search:** OP, MO; **Writing Manuscript**: YT, OP, OK; **Critical Review:** YT, OP, OK.

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References

1. Palabıyık O, Öğütlü A, Toptaş Y. Yoğun bakım ünitesinde ventilatör ilişkili pnömoni ve etken mikroorganizmalar: 2 yıllık retrospektif analiz. Türk Yoğun Bakım Derneği Dergisi 2016; 14:80-85. [CrossRef]
2. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med 2005; 142: 451-66. [CrossRef]
3. Tragiannidis A, Tsoulas C, Kerl K, et al. Invasive candidiasis: update on current pharmacotherapy options and future perspectives. Expert Opin Pharmacother 2013; 14: 1515-28. [CrossRef]
4. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62: 1-50. [CrossRef]
5. Arnold CJ, Johnson M, Bayer AS, et al. Candida infective endocarditis: an observational cohort study with a focus on therapy. Antimicrob Agents Chemother 2015; 59: 2365-73. [CrossRef]
6. Kannangara S, Shindler D, Kunimoto DY, et al. Candidemia complicated by endophthalmitis: a prospective analysis. Eur J Clin Microbiol Infect Dis 2007; 26; 839-41. [CrossRef]
7. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008; 36: 309-32. [CrossRef]
8. Todd P, McCarty MD, Peter G, Pappas MD. Invasive Candidiasis. Infect Dis Clin N Am 2016; 30: 103-24. [CrossRef]
9. Epalbaum O, Chasan R. Candidemia in the intensive care unit. Clin Chest Med 2017; 38: 493-509. [CrossRef]
10. Ostrosky-Zeichner L, Al-Obaidi M. Invasive fungal infections in the intensive care unit. Infect Dis Clin N Am 2017; 31: 475-87. [CrossRef]
11. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med 2015; 373: 1445-56. [CrossRef]
12. Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol 2005; 26: 540-7. [CrossRef]
13. Lortholary O, Renaudat C, Sitbon K, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002–2010). Intensive Care Med 2014; 40: 1303-12. [CrossRef]
14. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and Outcomes of Candidemia in 2019 Patients: Data from the Prospective Antifungal Therapy Alliance Registry. Clinical Infectious Diseases 2009; 48: 1695-703. [CrossRef]
15. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004; 39: 309-17. [CrossRef]
16. Leroy O, Gangneux JP, Montravers P, et al. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: A multicenter, prospective, observational study in France (2005–2006). Crit Care Med 2009; 37: 1612-8. [CrossRef]
17. Tortorano AM, Caspani L, Rigoni AL, et al. Candidosis in the intensive care unit: a 20-year survey. J Hosp Infect 2004; 57: 8-13. [CrossRef]
18. Bouza E, Munoz P. Epidemiology of candidemia in intensive care units. Int J Antimicrob Agents 2008; 32(Suppl 2): S87-S91. [CrossRef]
19. Yapar N. Epidemiology and risk factors for invasive candidiasis. Ther Clin Risk Manag 2014; 10: 95-105. [CrossRef]
20. Henderson DK, Edwards JE, Montgomerie JZ. Hematogenous candida endophthalmitis in patients receiving parenteral hyperalimentation fluids. J Infect Dis 1981; 143: 655-61. [CrossRef]
21. Schiedler V, Scott IU, Flynn Jr HW, et al. Culture-proven endogenous endophthalmitis: clinical features and visual acuity outcomes. Am J Ophthalmol 2004; 137: 725-31. [CrossRef]
22. Kernt M, Kampik A. Endophthalmitis: Pathogenesis, clinical presentation, management, and perspectives. Clinical Ophthalmology 2010; 4: 121-35. [CrossRef]
23. Parke DW, Jones DB, Gentry LO. Endogenous endophthalmitis among patients with candidemia. Ophthalmology 1982; 89: 789-96. [CrossRef]
24. Brooks RG. Prospective study of Candida endophthalmitis in hospitalized patients with candidemia. Arch Intern Med 1989; 149: 2226-8. [CrossRef]
25. Shah CP, McKey J, Spirn MJ, et al. Ocular candidiasis: a review. Br J Ophthalmol 2008; 92: 466-8. [CrossRef]
26. Krishna R, Amuh D, Lowder CY, et al. Should all patients with candidaemia have an ophthalmic examination to rule out ocular candidiasis? Eye 2000; 14: 30-4. [CrossRef]
27. Donahue SP, Greven CM, Zuravleff JJ, et al. Intraocular candidiasis in patients with candidemia. Ophthalmology 1994; 101: 1302-9. [CrossRef]
28. Lefort A, Chartier L, Sendid B, et al. Diagnosis, management and outcome of Candida endocarditis. Clin Microbiol Infect 2012; 18: 99-109. [CrossRef]
29. Baddley JW, Benjamin Jr DK, Patel M, et al. Candida infective endocarditis. Eur J Clin Microbiol Infect Dis 2008; 27: 519-29. [CrossRef]
30. Ellis ME, Al-Abdely H, Sandridge A, et al. Fungal endocarditis: evidence in the world literature, 1965-1995. Clin Infect Dis 2001; 32: 50-62. [CrossRef]
31. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995-2000. Chest 2002; 122: 302-10. [CrossRef]
32. Yuan SM. Fungal endocarditis. Braz J Cardiovasc Surg 2016; 31: 252-5. [CrossRef]
33. Avkan Oğuz V. Kandidemi ve göz tutulumu [Candidemia and ocular involvement]. Bamçağ Bülteni 2011; 2: 43-6.
34. Düzgün E, Çakır A, Ünal MH, et al. Endojen Kandida Endoftalmisi: Tedavi seçenekleri [Endogenous Candida Endophthalmitis: Treatment Options] Ret-Vit 2014; 22: 159-67.