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Original Article

## Candidemia after cardiac surgery in Tehran, Iran: A retrospective analysis of 424 cases at two medical centers

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### ABSTRACT

**Background:** Candidaemia is an emerging problem and one of the most important nosocomial infections in many hospitals. The aim of this study was to characterize the epidemiology and patient outcomes of candidemia after cardiac surgery at two medical centers in Iran over a nine-year period.

**Methods:** A retrospective analysis was conducted reviewing the medical records of all patients who underwent surgical treatment of cardiac disease at two medical centers. Demographic data, comorbidities, surgical procedure, length of hospital stay, odds ratio and annual trend for candidemia in cardiosurgical cases were collected and analyzed.

**Results:** Candidemia was responsible for 1.78% cases of total cardiac surgeries (23,849) in two hospitals. Data showed an overall declining trend for the incidence of candidemia during the study period, so that decreased from 3.81% in 2003–2004 to 0.52% in 2011–2012 ( $P < .01$ ). The odds ratio was significantly downward (from 1 to 0.14,  $P < .01$ ). Candidemia had a direct relationship with patient age, and the mean age was 64.2 years. A remarkable gender difference skewed towards males was observed, and the male/female ratio among candidemia cases  $<60$  and  $\geq 65$  years old was 0.82 and 1.79, respectively. Housewives had the highest rate of infection (34.91%). Coronary Artery Bypass Graft was the most common type of surgical intervention. Majority of candidemia patients (89.2%) had risk factor and the most common comorbidities were diabetes. Mean total hospital stay was  $17.34 \pm 4.69$  days.

**Conclusions:** This study expands the knowledge of the epidemiology and trend of incidence of candidemia in cardiosurgical cases. The survey provides preliminary baseline data for the future monitoring of candidemia, and effective programs for controlling and preventive strategies against the disease in hospitals.

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### 1. Introduction

Candidemia are important nosocomial infection and is associated with high morbidity and mortality resulting in significant increase in the duration of hospitalizations and healthcare costs.<sup>1,2</sup> The incidence of nosocomial bloodstream infections caused by *Candida* spp. has risen in the past 20 years.<sup>1,3,4</sup> The second agents of infective endocarditis are the fungi,<sup>5,6</sup> and two-thirds of cases of fungal endocarditis are caused by *Candida* spp.<sup>6,7</sup> Among the causative agents of nosocomial bloodstream infections, *Candida* spp. ranks fourth in the United States and seventh in Europe.<sup>1,4,8</sup>

Mortality rates have been reported to range from 29% to 76%, with an attributable mortality as high as 49%.<sup>1–3</sup>

The epidemiology of candidemia varies between regions and countries, For example, an increasing incidence of candidemia in Iceland was reported<sup>9</sup> but the same was not observed in Switzerland, where that the incidence of candidemia had remained unchanged.<sup>10</sup> Risk factors such as prolonged use of intravenous catheters, increased use of intracardiac prosthetic devices, long term use of antibiotics, intravenous drug use or narcotic addiction, diabetes mellitus, immunosuppressive therapies as well as open-heart surgery, abdominal surgery, and suffering from haematological malignancies are recognized, however data on the intra-hospital epidemiology of candidemia is scarce.<sup>5,11,12</sup> Therefore, it is justifiable to find reliable data for monitoring epidemiologic aspects of disease and prepare a baseline data for future comparison. Although retrospective hospital surveys have limitations, but

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careful study of them are a useful tool and an economical way of gathering information on human disease.<sup>13,14</sup>

Without information about the prevalence of nosocomial infections, the control hospital-acquired infections and effective programming for nosocomial infections is almost impossible.<sup>15,16</sup> There were limited studies about nosocomial infections in Iran, which supposed 8–10% prevalence rate,<sup>17,18</sup> however additional information is needed to determine the country-wide presence of nosocomial infections, including candidemia.

Considering the lack of data on the status of *Candida* infection after heart surgery in Iran, the present study was conducted to determine: (i) the prevalence, odds ratios (ORs) and trend of candidemia from 2003 to 2012; (ii) the associations of demographic features (such as age, sex and the occupation) with candidemia in operated cases; and (iii) relationship of the comorbidities or predisposing factors on infections and on the in-hospital epidemiology of candidemia at two medical centers in Iran.

## 2. Patients and methods

A retrospective analysis was conducted reviewing the medical records of all patients who underwent surgical treatment of cardiac disease, between 2003 and 2012 at Lavasani hospital and between 2007 and 2012 at Milad hospital in Tehran, capital of Iran. People from different parts of the country are referred to these hospitals for heart surgery. Patients were included if they had at least one positive blood culture for *Candida* spp. and signs or symptoms of infection. No informed consent was obtained because of the retrospective nature of this study.

Demographic data, comorbidities or predisposing factors (if any), surgical procedure, and length of hospital stay were collected for each confirmed case of candidemia and then analyzed. Patient information was anonymized and de-identified prior to analysis. The ratios between male and female cases were calculated. Data was collected on an annually basis for indicating any annual trend of candidemia after heart surgery. Odds ratios (odds of candidemia in patient with cardiac surgery during successive years) were calculated.

The mean and standard deviation (SD) were used to describe quantitative data. Frequency was used to describe categorical data. The statistical significance of each difference seen between hospital stay, and between two proportions was evaluated in  $\chi^2$  tests, and by calculating the Z statistic, respectively. Frequency of surgical procedures was statistically evaluated in Student's *t*-tests. The level of significance for all statistical tests was 2-sided, with *P*-value of <.05. All statistical analyses were done with SPSS software (version 16).

## 3. Results

The total number of cardiac surgeries recorded in two large medical centers registries in the study period were 23,849 cases (15,964 cases belonged to Lavasani hospital and 7885 to Milad hospital). Among these medical records, 424 (1.78%) patients with confirmed candidemia infection were identified after heart surgery over a 9-year period (Table 1). The mean prevalence of the disease in Lavasani and Milad hospitals was 1.87% (298 cases) and 1.60% (126), respectively (Table 1).

The odds ratios (ORs) were calculated, assuming the first year's OR equal to 1.00 as the basis for comparison, and the results are shown in Table 1. As it is seen, the overall declining trend was still observed (from 1 to 0.14), and was statistically significant (*P* < .01).

Data showed an overall downward trend for candidemia in all cases operated during the study period (from 3.81% to 0.52%, *P* < .01). Thus, the incidence of post-cardiac surgery candidemia

decreased from 3.81% in 2003–2004 to 0.51% in 2011–2012 for Lavasani hospital; and also the disease declined from 3.72% in 2007–2008 (first year study) to 0.53% in 2011–2012 for Milad hospital (Table 1).

Age and gender distribution pertaining to 424 confirmed cases of candidemia after cardiac surgery and the male/female ratio by age groups are shown in Table 2. In the current survey, majority of the candidemia cases were old age. Age group  $\geq 65$  was the most affected and represented 40.10% of the total number of candidemia cases. An overall analysis of gender and age of the candidemia cases revealed that the number of males infected was higher than that of females (57.08% vs. 42.92%) with a 1.33 male to female ratio (Table 2), while the gender ratio in the general population is about 1.00. The variation in the male: female ratio with age group was not, however, statistically significant. The males/females rate of postoperative candidemia cases showed a direct relationship with patient age.

As depicted in Fig. 1, a significantly (*P* < .05) higher post-cardiac surgery candidemia was recorded in the housewife occupation (34.91%) than each other occupations groups.

Coronary Artery Bypass Graft (CABG) was the most common type of surgical intervention and was performed in 381 (89.86%) out of candidemic patients (*p* < .001). Mitral Valve Repair (MVR) was performed in thirty-seven patients (8.73%), and only 1.41% of cases underwent Atrial Septal Defect (ASD) closure. There was no statistical difference in the mean hospital stays for type of the surgical procedures (*p* > .35), as shown in Table 3.

Mean total hospital stay of cases with candidemia after cardiac surgery was  $17.34 \pm 4.69$  days. Most (65.6%) of the candidemic patients required that stay in hospitals from 10 to 19 days following surgery (*p* < .05). In contrast, only 5.2% of them estimated hospitalization of 25 or more days of hospital stay. The postoperative hospital stay for candidemia patients according to sex is given in Table 4.

Underlying diseases or predisposing factors of the candidemia in cardiac surgery patients have listed in Table 5. The most common predisposing factor included underlying diabetes (38.2% alone, 11.3% diabetes + addiction, 4.5% diabetes + hypertension), and followed by hypertension (18.9% alone and/or with concomitant hyperlipidemia 6.4%). Other underlying diseases or predisposing factors were less frequently seen, and 97 (22.88) patients had more than one underlying diseases. Forty-six patients (10.8%) had no underlying diseases or predisposing factor identified. Postoperative hospital stay among candidemic cases according to predisposing conditions had fluctuations, but there was no statistical difference (Table 5).

## 4. Discussion

Several studies have shown incidence rates of candidemia have increased significantly in recent years, resulting in a growing number of patients at risk for this disease.<sup>19–21</sup> A better understanding of the epidemiology, associated risk factors or underlying diseases for candidemia after cardiac surgery, and postoperative hospital stay is needed but difficult to obtain because of the rarity and lack of large prospective cohorts. Hence, we studied after cardiac surgery patients in order to highlight differences in epidemiology and mentioned outcomes.

In the present study, candidemia was responsible for 424 (1.78%) of total cases (23,849) after cardiac surgeries in two medical centers, and the highest prevalence (3.81%) was recorded in 2003–2004 and lowest the (0.52%) in 2011–2012. Our results were close to some previous reports, for instance, Baddley et al.<sup>20</sup> in 2008 and Pasero et al.<sup>22</sup> in 2011 reported 1.2% and 1.3% developed candidemia respectively. Previous studies indicated that contami-

**Table 1**  
Annual incidence and odds ratios of candidemia among patients with cardiac surgeries at two hospitals in Tehran, Iran.

Year	Lavasani hospital		Milad hospital		% of Total	Odds Ratios
	Operated N	Candidemia	Operated N	Candidemia		
2003–2004	1180	45 (3.81)	–	–	3.81	1.00 <sup>a</sup>
2004–2005	1475	44 (2.98)	–	–	2.98	0.78
2005–2006	1493	42 (2.81)	–	–	2.81	0.74
2006–2007	1741	39 (2.24)	–	–	2.24	0.59
2007–2008	1776	36 (2.03)	995	37 (3.72)	2.63	0.69
2008–2009	1791	32 (1.79)	1380	31 (2.25)	1.99	0.52
2009–2010	2065	29 (1.40)	1675	26 (1.55)	1.47	0.39
2010–2011	2083	19 (0.91)	1770	21 (1.19)	1.04	0.27
2011–2012	2360	12 (0.51)	2065	11 (0.53)	0.52	0.14
All	15964	298 (1.87)	7885	126 (1.60)	1.78	

No.: Number; Figures in parentheses represent percentage.

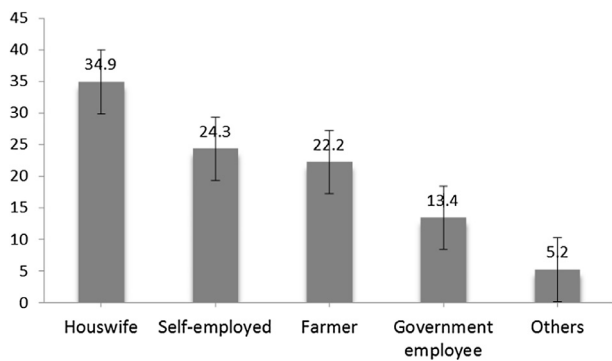
<sup>a</sup> Assuming the 2003–2004 year OR equal to 1.00 as the basis for comparison.

**Table 2**  
Age and gender distributions of the 424 confirmed cases of post-cardiac surgery candidemia at two medical centers in Tehran, Iran.

Age (years)	Number (%) of candidemia cases in:			Male/female Ratio <sup>a</sup>
	Male	Female	Overall	
<60	54 (12.74)	66 (15.56)	120 (28.30)	0.82
60–64	79 (18.63)	55 (12.97)	134 (31.60)	1.44
≥65	109 (25.71)	61 (14.39)	170 (40.10)	1.79
Total	242 (57.08)	182 (42.92)	424 (100.0)	1.33

Figures in parentheses represent percentage.

<sup>a</sup> The gender ratio in the general population was about 1.00.



**Fig. 1.** The prevalence of candidemia after cardiac surgery in different occupations at two hospitals in Tehran, Iran.

nation of operating room especially during reconstruction procedures might play a role. In addition, blood stream infections and candidemia varies with the type of population studied, the type of ward and its location, and the length of the patient’s stay in the hospital.<sup>1,2,23</sup>

The incidence was collected on an annually basis. This time interval was chosen as being likely to indicate any annual trends. The overall trend was a significant decline in the incidence of

Candidemia after cardiac surgery over the study period ( $P < .01$ ) in both medical centers. The incidence of candidemia decreased from 3.81 and 3.72% per years at the beginning of the study period to 0.51 and 0.53% at the end of the period for Lavasani and Milad hospitals, respectively, (Table 1). This may partly be attributed to greater awareness among medical teams, possibly as a result of improvements in surgical technique, prevention of contamination of operating room especially during reconstruction procedures. Another explanation is the implementation of a program which undertook in recent years in order to control infections in operating room, such as the improvement of the clean-air operating theater environment.<sup>24,25</sup>

In contrast with our findings, a number of previous studies have reported that rate of *Candida* blood stream infections increased in US,<sup>1</sup> Europe<sup>10,26,27</sup> and some other region<sup>28,29</sup> during the last years. Of course, the epidemiology of candidemia remained stable in some parts of the world.<sup>10,12,23</sup> In this study, odds ratios (odds of candidemia in patient with cardiac surgery during successive years) showed the overall declining trend was still observed, which was decreased from 1 in the first year (2003–2004) to 0.14 at the end of the study period ( $P < .01$ ).

Several studies have reported a variation within the rate of candidemia obtained from patients with blood stream infections related to patient age that are in concordance with our observations.<sup>12,21,30,31</sup> In the current survey, majority of candidemia cases

**Table 3**  
Surgical procedures and hospitalization in confirmed cases of post-cardiac surgery candidemia at two hospitals in Tehran, Iran.

Surgical procedures	Number and (%) of candidemia	Hospitalization (day):				Mean ± SD <sup>*</sup>
		10–14	15–19	20–24	≥25	
CABG	381 (89.86)	118 (27.8)	130 (30.7)	113 (26.6)	20 (4.7)	17.54 ± 4.77
MVR	37 (8.73)	19 (4.5)	8 (1.9)	8 (1.9)	2 (0.5)	17.94 ± 4.47
ASD	6 (1.41)	2 (0.5)	1 (0.2)	3 (0.7)	–	17.84 ± 5.12
Overall	424 (100.0)	139 (32.8)	139 (32.8)	124 (29.2)	22 (5.2)	17.34 ± 4.69

CABG: Coronary Artery By-pass Graft, MVR: Mitral Valve Repair, ASD: Atrial Septal Defect.

<sup>\*</sup> SD = standard deviation.

**Table 4**

Distribution of candidemia in cardiac surgery cases according to hospital stay categories and gender at two hospitals in Tehran, Iran.

Hospital Stay (day)	Female (%)	Male (%)	Both (%)	Mean hospital Stay (day) ± SD*
<15	59 (13.9)	80 (18.9)	139 (32.8)	12.13 ± 1.33
15–19	58 (13.7)	81 (19.1)	139 (32.8)	16.93 ± 1.39
20–24	57 (13.4)	67 (15.8)	124 (29.2)	21.94 ± 1.41
≥25	8 (1.9)	14 (3.3)	22 (5.2)	27.00 ± 1.66
Overall	182 (42.9)	242 (57.1)	424 (100.0)	17.34 ± 4.69

\* SD = standard deviation.

**Table 5**

Predisposing factors and hospital stays in post-cardiac surgery candidemia at two hospitals in Tehran, Iran.

Predisposing conditions	Number and (%) of candidemia	Hospital stay (day):				Mean ± SD*
		<15	15–19	20–24	≥25	
Diabetes	162 (38.2)	51 (12.0)	53 (12.5)	49 (11.5)	9 (2.1)	17.54 ± 4.77
Diabetes & addiction	48 (11.3)	11 (2.6)	20 (4.7)	14 (3.3)	3 (0.7)	17.94 ± 4.47
Diabetes & hypertension	19 (4.5)	6 (1.4)	7 (1.7)	4 (0.9)	2 (0.5)	17.84 ± 5.12
Hypertension	80 (18.9)	26 (6.1)	23 (5.4)	28 (6.6)	3 (0.7)	17.40 ± 4.66
Hypertension & hyperlipidemia	27 (6.4)	5 (1.2)	10 (2.4)	10 (2.4)	2 (0.5)	18.67 ± 4.39
Hyperlipidemia	16 (3.8)	7 (1.7)	6 (1.4)	2 (0.5)	1 (0.2)	15.69 ± 4.61
Congenital valvulopathy	14 (3.3)	7 (1.7)	6 (1.4)	1 (0.2)	–	15.29 ± 3.50
Others	12 (2.8)	3 (0.7)	2 (0.5)	7 (1.7)	–	18.75 ± 4.49
No specific disease	46 (10.8)	23 (5.4)	12 (2.8)	9 (2.1)	2 (0.5)	15.64 ± 4.65
Overall	424 (100.0)	139 (32.8)	139 (32.8)	124 (29.2)	22 (5.2)	17.34 ± 4.69

\* SD = standard deviation.

were old age, and the mean age of patients was about 64.2 years. Age group ≥65 was the most affected and represented 40.10% of the total number of after cardiac surgery patients developed candidemia. These findings are important since it may be inferred that in elderly patients at risk for candidemia.

An overall analysis of gender and age of candidemia cases after cardiac surgery revealed that the number of males infected was higher than that of females with a 1.33 male to female ratio (Table 2), while the gender ratio in the general population is about 1.00. The variation in the male/female ratio among cases generally increasing with age (from 0.82 for the cases aged <60 years to 1.79 among the cases aged ≥65 years), so that a remarkable gender difference skewed towards males was observed. A similar shift towards more candidemia has been reported from many parts of the world, including the review by Ericsson et al. (male-to-female ratio was 206/179 = 1.15),<sup>30</sup> Bassetti et al. (male-to-female ratio was = 1.30),<sup>21</sup> Ellis et al. (male-to-female ratio was 1.84/83 = 2.22),<sup>24</sup> and Pasero et al. (male-to-female ratio was 1.6).<sup>22</sup>

Sex predilection as a risk factor for the development of infective *Candida* is important because past studies have historically demonstrated a prevailing male predominance for the disease. This observation has been due in part to the associated male sex predilection with postoperative candidemia. Increasing age is a well-recognized risk factor associated with the development of the disease, and as populations in developing countries continue to age, an anticipated growth in the number of cases is expected.<sup>32,33</sup> We think that an aging effect has been operative in the studied regions and is reflected in the trend of increasing age among infected cases.

A comparison of the proportion of patients represented by each occupation indicated that in the study, rate of candidemia after cardiac surgery in housewives was the highest. Housewives are, of course, commonly gender-specific occupations, and housewives are presumably at increased risk. The reasons why candidemia is so frequent in housewives are not known, but could be presumably related to low rate of physical activity in women. In addition, women was probably due to the cultural habits of the area, whereby are obliged to be home more than men, and their act of moving are less or very less.

Coronary Artery Bypass Graft (CABG) was the most common type of surgical intervention among candidemic patients and was performed in 381 (89.86%) patients ( $p < .001$ ). Mitral Valve Repair (MVR) was performed in thirty-seven patients (8.73%), and only 1.41% of cases underwent Atrial Septal Defect (ASD) closure. As in the present study, Baddley et al.<sup>20</sup> also reported that CABG and prosthetic valve were significantly more common in *Candida* patients. An increase in previous CABG among *Candida* patients could be explained by CABG being performed in association with prosthetic valve surgery.<sup>20</sup> There were few differences in hospitalization among candidemia cases who had a heart surgery procedure, since the mean hospital stays for type of the surgical procedures were no statistical difference.

The increase in hospital-acquired candidemia cases in general is consistent with recent data describing *Candida* spp. as an emerging nosocomial bloodstream pathogen over the past decade.<sup>20</sup> In our study, the mean total hospital stay among candidemia cases after cardiac surgery was 17.34 ± 4.69 days. Most (65.6%) of the candidemic patients required that stay in hospitals from 10 to 19 days following cardiac surgery ( $p < .05$ ) and only 5.2% of them estimated hospitalization of 25 or more days of hospital stay, whereas was no statistical difference between male and female in hospital stay. Moreover, the length of hospital stay was shown to play a major role in colonization of fungi in critical care settings.<sup>34</sup>

Important predisposing conditions or risk factors for candidemia have been reported in recent, extensive reviews, and the most frequently reported are previous surgery, antibiotic use, underlying heart disease, prosthetic valves, and immunocompromising conditions.<sup>5,11,12</sup> We found some similar comorbidities or underlying diseases and noted several distinct differences among candidemia cases.<sup>21,23,24</sup> In the present study, there was a significant increase in incidence of postoperative candidemia cases among patients with underlying diseases (89.2%) as compared to cases without predisposing conditions (10.8%) at the time of candidemia diagnosis. Among patients who had cardiac surgery, diabetes alone and/or with concomitant underlying diseases were the most common comorbidities among patients with candidemia (Table 5), and 94 patients (22.17%) had >1 risk factor or underlying



diseases. Bassetti et al. reported 93.1% of candidemia cases had one or more predisposing conditions, 46% had undergone a surgical intervention, 30% had a solid tumor, 28.8% had cardiovascular diseases, 25.3% were diabetic, 6.3% had hematological malignancies, 3.4% received a solid organ transplantation, and 2% had human immunodeficiency virus (HIV) infection.<sup>21</sup> Ellis et al. (2001) in one review of fungal endocarditis found that fifty-six (21%) of 270 patients had 1 risk factor; 77 (29%) had 2 risk factors; 75 (28%) had 3; and 56 (21%) had 4–7.<sup>24</sup> The present data showed that confirmed candidemia cases with cardiac surgery in the region had hospital stay fluctuations due to comorbidities or underlying diseases, but there was no statistical difference between various comorbidities for mean hospital stay.

In conclusion, these data represent a significant decline trend for candidemia and Odds ratios in all cases cardiac-operated during the study period. Majority of candidemia cases were old ages, and a remarkable gender difference skewed towards males was observed. CABG was the most common type of surgical intervention in the candidemic patients, and diabetes were more common comorbidities or underlying diseases among candidemia cases after cardiac surgery. The survey provides preliminary baseline data for the future monitoring of the disease, and highlighting potentially important nosocomial candidemia for the development of fungal endocarditis. It is demonstrating possible trends of the disease, and also, effective programs for controlling and preventive strategies against the disease in hospitals.

### Conflict of interest

None declared.

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