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Research Paper

Prevalence and risk factors for endogenous fungal endophthalmitis in adult patients with candidemia at a tertiary care hospital in the Republic of Korea over 13 years

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ABSTRACT

Background. – Endogenous fungal endophthalmitis (EFE) is a critical complication of candidemia. We conducted a study to investigate the prevalence and risk factors for EFE.
Methods. – Adult candidemia patients ≥ 19 years who underwent an ophthalmological examination at a tertiary care hospital in the Republic of Korea from 2006 to 2018 were enrolled.
Results. – There was a total of 152 adult candidemia patients analyzed. EFE was found in 29 patients (19.1%). Patients were categorized into two groups (Non-endophthalmitis [NE] and endophthalmitis [E]). Between the two groups, there was no significant difference in terms of age, sex, and underlying comorbidities. However, there were more *Candida albicans* candidemia, abnormal alanine aminotransferase (ALT) at the time of candidemia diagnosis, receipt of antifungal treatment ≥ 48 hours after onset of candidemia symptoms and blood culture sample (AOCS), and candidemia clearance ≥ 5 days after initiation of antifungal treatment (AIAT) in the E group. A predictive model for the E was created, which had an area of 0.811 under the receiver operating characteristics curve. In a multivariate logistic regression analysis, *C. albicans* candidemia, ALT at the time of candidemia diagnosis, receipt of antifungal treatment ≥ 48 hours AOCS, and candidemia clearance ≥ 5 days AIAT were significantly associated with EFE.
Conclusion. – EFE occurred in 19% of adult patients with candidemia. Adult candidemia patients with *C. albicans* candidemia, abnormal ALT, receipt of antifungal treatment ≥ 48 hours AOCS, and candidemia clearance ≥ 5 days AIAT need to be closely monitored for the possibility of EFE.

1. Introduction

The rate of bloodstream infection caused by *Candida* species (candidemia) in the hospital setting has increased over recent decades [1]. Candidemia is well known to be associated with significant morbidity and mortality [2]. Also, candidemia can cause hematogenously disseminated metastatic fungal lesions in multiple organs, and the eyes are among the frequently affected sites of the metastatic infection [3], manifested as endogenous fungal endophthalmitis (EFE). EFE refers to endogenous fungal infections within the eye and includes endophthalmitis with vitritis or chorioretinitis [3]. Importantly, EFE may lead to potentially sight-threatening consequences requiring prompt identification and adequate treatment to preserve vision [4]. Based on potentially significant morbidity associated EFE, the Infectious Diseases Society of America (IDSA) candidiasis guideline currently recommends that all candidemia patients should undergo a dilated retinal ophthalmological examination to rule out EFE [5]. Previous studies reported the prevalence of EFE secondary to candidemia to be ranged from 2% to 37% [6–9]. Variable prevalence rates of EFE in candidemia patients might be due to the changing epidemiology of

Abbreviations: EFE, endogenous fungal endophthalmitis; NE, non-endophthalmitis; E, endophthalmitis; OR, odds ratio; ALT, alanine aminotransferase; AOCS, after the onset of candidemia symptoms and blood culture sample; AIAT, after initiation of antifungal treatment; IDSA, Infectious Diseases Society of America; ROK, Republic of Korea; IQR, interquartile range; CRF, case report form; TPN, total parenteral nutrition; CVC, presence of central venous catheter; ROC, receiver operating characteristics.

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Candida species in candidemia or increasing proportion of patients with risk factors for acquisition of candidemia such as indwelling catheters and comorbidities. In the Republic of Korea (ROK), there has been an increase of non-*Candida albicans* candidemia recently [10,11]. Also, an increasingly aging population with comorbidities has been reported in the ROK [12], suggesting there may be higher incidence rates of candidemia among adult patients in the hospital setting in the ROK. However, there have been little data regarding the prevalence and risk factors of EFE in hospitalized adult candidemia patients in the ROK. Therefore, the current study was designed to evaluate the prevalence of EFE and to identify clinical predictors of EFE in hospitalized adult candidemia patients in the ROK in recent years 2006–2018.

2. Material and methods

2.1. Study design and population

A retrospective study of adult patients ≥ 19 years diagnosed with candidemia at a tertiary care hospital (Korea University Anam Hospital, Seoul, ROK) from 2006 to 2018 was conducted. Patients' demographics, clinical variables including underlying comorbidities, clinical conditions at the time of candidemia diagnosis such as the presence of septic shock, receipt of recent surgery, presence of neutropenia, total parenteral nutrition, central venous catheter, urinary catheter, ventilator, dialysis, use of antibiotics, *Candida* spp. colonization, clinical course, and prognosis of in-hospital mortality were collected on a standardized case report form (CRF). Among candidemia patients, ophthalmological examinations were performed at the treating physician's discretion. Candidemia patients who did not have formal ophthalmological evaluation were excluded from the study. This study was approved by the institutional review board at the Korea University Anam Hospital (IRB Number 2018AN0440). Informed consent was not required due to the retrospective design of the study.

2.2. Definition

Candidemia was defined as having at least one positive peripheral blood culture for *Candida* spp. [13] obtained from an adult hospitalized patient ≥ 19 years. Identification of *Candida* spp. from blood culture was performed using the BacT/ALERT® 3D Microbial Detection System (bioMérieux, Inc., Durham, NC, USA) and the automated Vitek® 2 Yeast Biochemical Card (bioMérieux, Inc.). Candidemia symptoms were defined as systemic inflammatory symptoms from candidemia, which included fever and chills. After ophthalmologic examination, EFE was defined as the presence of chorioretinitis or vitritis with various degrees of inflammation ranging from minimal to severe vitiritis [14]. The Charlson comorbidity index was calculated to assess the impact of comorbidities. Neutropenia was defined as an absolute neutrophil count of < 500 cells/mm^3. *Candida* spp. colonization was defined as presence of *Candida* spp. in at least one non-sterile site including skin, urine, mouth, lung, or on rectal swab. The definition of septic shock was adapted from the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [15]. The use of immunosuppressive agents was defined as follows: use of systemic steroid (≥ 20 mg/day of prednisone equivalent), antimetabolites, or use of immunomodulatory agents such as tumor necrosis factor-alpha inhibitors or rituximab.

2.3. Statistical analysis

Data were recorded using Microsoft® Excel® 2013 version (Microsoft Corp, Redmond, WA, USA). Comparison analyses of risk conditions and clinical variables between the groups of non-endophthalmitis [NE] and endophthalmitis [E] candidemia patients were performed. The Pearson χ^2 test or Fisher's exact test was used for dichotomous variables. The Mann–Whitney *U* test was used for continuous variables. The Wilcoxon signed-rank test was used in the E prediction score between NE and E groups. The sensitivity and specificity of the E prediction model were calculated for each score value. The performance of the E prediction model was evaluated using the receiver operating characteristics (ROC) curve [16] with the calculation of the area under the ROC curve. Variables with a *P*-value < 0.2 on comparison analysis were included in a multiple logistic regression analysis to determine risk factors associated with E cases among candidemia patients. Odds ratio and 95% confidence intervals were calculated. A *P*-value < 0.05 was considered to be statistically significant. SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

3. Results

3.1. Patient population and prevalence of endogenous fungal endophthalmitis

During the study period, there were 388 adult patients diagnosed with candidemia. The incidence of candidemia increased recently (Fig. 1). However, 236 patients were excluded because they did not have an ophthalmological examination. Therefore, a total of 152 adult patients with candidemia who underwent an ophthalmological examination was included in the analysis. The median age of these 152 patients was 71 years with interquartile range (IQR) of 57–79 years. There were 88 males (57.9%). The most common *Candida* spp. of candidemia was *C. albicans* (41.4%), followed by *C. parapsilosis* (23.7%), *C. tropicalis* (19.7%), and *C. glabrata* (11.8%). The median of Charlson comorbidity index was 2 (IQR 1–5). Approximately half of the patients (48.0%) had underlying malignancies, and antibiotic exposure was noted in most of the patients (86.8%). The presence of central line, ventilator use, and septic shock were noted in 95 patients (62.5%), 43 patients (28.3%), and 38 patients (25.0%), respectively, at the time of candidemia diagnosis (Table 1). After

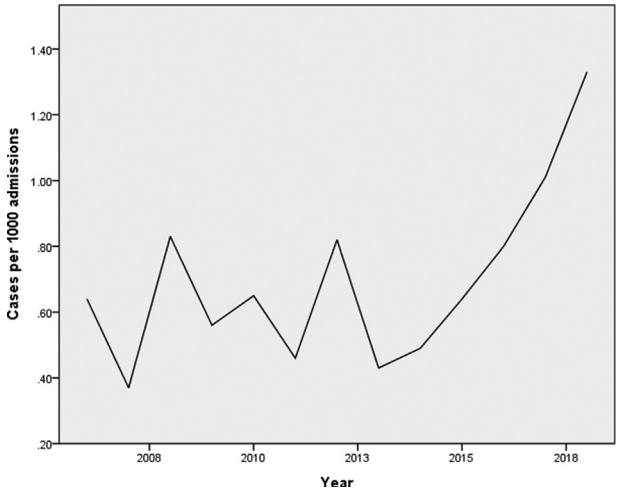

Fig. 1. Annual incidence of candidemia 2006–2018. 2006: 20 cases, 0.64 cases per 1000 admissions, 2007: 13 cases, 0.37 cases per 1000 admissions, 2008: 31 cases, 0.83 cases per 1000 admissions, 2009: 22 cases, 0.56 cases per 1000 admissions, 2010: 26 cases, 0.65 cases per 1000 admissions, 2011: 19 cases, 0.46 cases per 1000 admissions, 2012: 34 cases, 0.82 cases per 1000 admissions, 2013: 18 cases, 0.43 cases per 1000 admissions, 2014: 21 cases, 0.49 cases per 1000 admissions, 2015: 30 cases, 0.64 cases per 1000 admissions, 2016: 39 cases, 0.80 cases per 1000 admissions, 2017: 48 cases, 1.01 cases per 1000 admissions, 2018: 67 cases, 1.33 cases per 1000 admissions.

Table 1
Characteristics of adult patients with candidemia stratified according to the presence or absence of endogenous fungal endophthalmitis.

	Total $n=152$	No EFE[a] $n=123$	EFE $n=29$	*P*-value
Age years, median (IQR[b])	71 (56–79)	71 (56–79)	73 (63–81)	0.501
Male (%)	88 (57.9)	73 (59.3)	15 (51.7)	0.454
Female (%)	64 (42.1)	50 (40.7)	14 (48.3)	
Underlying disease				
Heart disease (%)	65 (42.8)	53 (43.1)	12 (41.4)	0.867
Lung disease (%)	17 (11.2)	14 (11.4)	3 (10.3)	1.000
Kidney disease (%)	46 (30.3)	35 (28.5)	11 (37.9)	0.318
Liver disease (%)	20 (13.2)	17 (13.8)	3 (10.3)	0.767
Diabetes mellitus (%)	54 (35.5)	42 (34.1)	12 (41.4)	0.464
Neurological disease (%)	46 (30.3)	36 (29.3)	10 (34.5)	0.582
Malignancy (%)	73 (48.0)	57 (46.3)	16 (55.2)	0.392
Long-term care facility residence (%)	21 (13.8)	18 (14.6)	3 (10.3)	0.766
Recent hospitalization within 3 months (%)	90 (59.2)	73 (59.3)	17 (58.6)	0.943
Clinical condition				
Charlson comorbidity index, median (IQR)	2 (1–5)	2 (1–5)	3 (2–6)	0.492
Presence of septic shock (%)	38 (25.0)	29 (23.6)	9 (31.0)	0.404
Surgery in current admission (%)	49 (32.2)	39 (31.7)	10 (34.5)	0.774
Neutropenia[c] (%)	13 (8.6)	11 (8.9)	2 (6.9)	1.000
Immunosuppressants[d] (%)	9 (5.9)	9 (7.3)	0 (0.0)	0.208
Chemotherapy (%)	36 (23.7)	27 (22.0)	9 (31.0)	0.301
Use of total parenteral nutrition (%)	141 (92.8)	112 (91.1)	29 (100.0)	0.125
Presence of central vascular catheter (%)	95 (62.5)	75 (61.0)	20 (69.0)	0.424
Presence of urinary catheter (%)	110 (72.4)	89 (72.4)	21 (72.4)	0.995
Use of ventilator (%)	43 (28.3)	36 (29.3)	7 (24.1)	0.581
Dialysis (%)	23 (15.1)	18 (14.6)	5 (17.2)	0.774
Candida colonization (%)	3 (2.0)	2 (1.6)	1 (3.4)	0.473
Use of antibiotics (%)	132 (86.8)	104 (84.6)	28 (96.6)	0.125
Abrnomal ALT[e] at the candidemia diagnosis (%)	27 (18.4)	17 (14.3)	10 (35.7)	0.008
Abnormal Tbil[f] at the candidemia diagnosis (%)	44 (31.0)	32 (28.1)	12 (42.9)	0.130
Source of candidemia				
Gastrointestinal tract (%)	22 (14.5)	16 (13.0)	6 (20.7)	0.377
Central vascular catheter (%)	83 (54.6)	66 (53.7)	17 (58.6)	0.682
Urinary tract (%)	14 (9.2)	12 (9.8)	2 (6.9)	1.000
Deep-seated abscess (%)	1 (0.7)	1 (0.8)	0 (0.0)	1.000
Others or unknown (%)	32 (21.1)	28 (22.8)	4 (13.8)	0.286
Candidemia				
C. albicans (%)	63 (41.4)	44 (35.8)	19 (65.5)	0.003
C. tropicalis (%)	30 (19.7)	25 (20.3)	5 (17.2)	0.707
C. parapsilosis (%)	36 (23.7)	34 (27.6)	2 (6.9)	0.018
C. glabrata (%)	18 (11.8)	15 (12.2)	3 (10.3)	1.000
C. krusei (%)	2 (1.3)	2 (1.6)	0 (0.0)	1.000
Others[g] (%)	3 (2.0)	3 (2.4)	0 (0.0)	1.000
Timing of initiation of antifungal treatment				
<48 hours from onset of candidemia symptoms and blood culture sample[h] (%)	77 (52.0)	69 (58.0)	8 (27.6)	0.003
≥ 48 hours from onset of candidemia symptoms and blood culture sample[h] (%)	71 (48.0)	50 (42.0)	21 (72.4)	
Receipt of antifungal treatment (%)	148 (97.4)	119 (96.7)	29 (100.0)	1.000
Candidemia clearance time after initiation of antifungal treatment in days, median (IQR)	3 (1–6)	3 (1–5)	5 (2–9)	0.030
Candidemia clearance time ≥ 5 days after initiation of antifungal treatment[i] (%)	47 (35.1)	33 (30.3)	14 (56.0)	0.015
Outcome				
In-hospital mortality (%)	58 (38.2)	43 (35.0)	15 (51.7)	0.095

[a] EFE: endogenous fungal endophthalmitis.
[b] IQR: interquartile range.
[c] Neutropenia: defined as an absolute neutrophil count of <500 cells/mm^3.
[d] Immunosuppressants: defined as use of systemic steroid (≥ 20 mg/day of prednisone equivalent), antimetabolites, or use of immunomodulatory agents such as tumor necrosis factor-alpha inhibitors or rituximab.
[e] ALT: alanine aminotransferase with calculation available for 147 cases (119 cases in the No EFE and 28 cases in the EFE).
[f] TBil, total bilirubin with calculation available for 142 cases (114 cases in the No EFE and 28 cases in the EFE).
[g] Others: *C. guilliermondii* and *C. utilis*.
[h] Calculation was available for 148 cases (119 cases in the No EFE and 29 cases in the EFE).
[i] Calculation was available for 134 cases (109 cases in the No EFE and 25 cases in the EFE).

the ophthalmological examination, EFE was diagnosed in 29 patients (19.1%). The majority of EFE was identified after the first ophthalmological examination (27/29, 93.1%) with a median 7 days following the time of positive candidemia blood culture. For candidemia patients without EFE, the majority of patients had 1 ophthalmological examination (81/123, 65.9%) or 2 ophthalmological examinations (23/123, 18.7%). The median time for the first and the second ophthalmological examination following the time of positive candidemia blood culture was 6 days and 13 days, respectively. The flow of EFE diagnosis following the ophthalmological examination is shown in Fig. 2.

3.2. Analysis of risk factors for endogenous fungal endophthalmitis

Patients were categorized into two groups (Non-endophthalmitis [NE] and endophthalmitis [E] groups). The distribution of age and sex was similar. Regarding underlying conditions, there was no significant difference between the two groups. Also, no significant

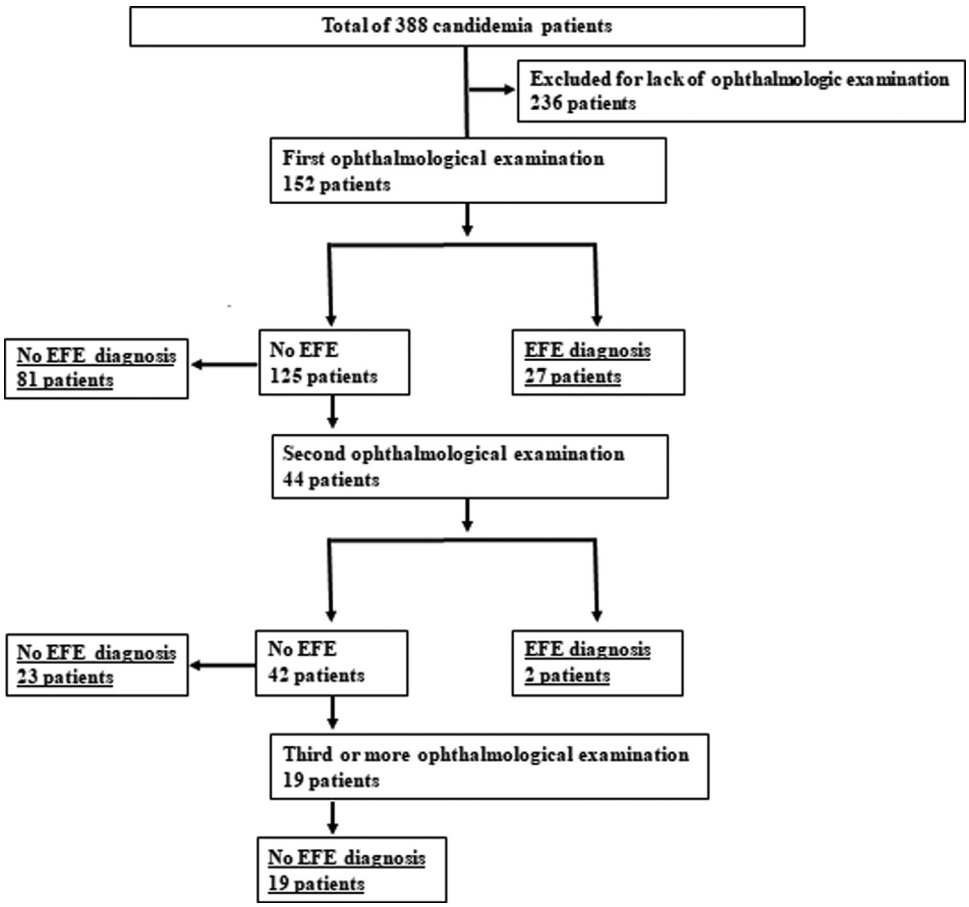

Fig. 2. The flow of endogenous fungal endophthalmitis diagnosis among adult patients with candidemia. EFE: endogenous fungal endophthalmitis.

differences in clinical conditions were noted between the two groups except for the following. There was a higher rate of alanine aminotransferase (ALT) at the time of candidemia diagnosis [ALT > 45 IU/L] in the E group (35.7%) than in the NE group (14.8%), $P = 0.008$. Moreover, the proportion of *C. albicans* candidemia was higher in the E group (65.5%) than in the NE group (35.8%), $P = 0.003$. In contrast, *C. parapsilosis* candidemia was more common in the NE group (27.6%) than in the E group (6.9%), $P = 0.018$. Most of the patients in the NE group (119 patients, 96.7%) and all patients of the E group (29 patients, 100.0%) received antifungal treatment without statistical difference. However, there were more patients who received antifungal treatment ≥ 48 hours from onset of candidemia symptoms and blood culture sample in the E group (72.4%) than in the NE group (42.0%), $P = 0.003$. Also, a higher proportion of the patients with candidemia clearance time ≥ 5 days after initiation of antifungal treatment was noted in the E group (56.0%) than in the NE group (30.3%), $P = 0.015$. Although there was a trend of a higher rate of in-hospital mortality in the E group (51.7%) than in the NE group (35.0%), no statistical significance was noted, $P = 0.095$. These are shown in Table 1. Each of the 4 significant variables between NE and E groups (abnormal ALT at the candidemia diagnosis, *C. albicans* candidemia, initiation of antifungal treatment ≥ 48 hours from onset of candidemia symptoms and blood culture sample, and candidemia clearance time ≥ 5 days after initiation of antifungal treatment) identified from the comparison analysis was given a same point score (= 1) for the creation of the E prediction model. Between NE and E groups, the patients in the E group had higher scores when tested by the Wilcoxon signed-rank test ($P < 0.001$) (Table 2). A ROC curve had an area under the curve of 0.811 for the E prediction model (95% confidence interval [CI]: 0.727–0.895, $P < 0.001$) (Fig. 3). The ideal threshold score of 2 was identified from the E prediction model with ROC curve with a sensitivity of 92.0% and a specificity of 58.1%.

Variables with a *P*-value < 0.2 on comparison analysis between NE and E groups were included in a multiple logistic regression analysis to determine risk factors associated with E cases among candidemia patients. The multivariate logistic analysis showed that *C. albicans* candidemia [odds ratio (OR): 6.192, 95% CI: 1.896–20.220, $P = 0.003$], abnormal ALT at the time of candidemia diagnosis [OR: 4.692, 95% CI: 1.452–15.161, $P = 0.010$], receipt of antifungal treatment ≥ 48 hours after onset of candidemia symptoms and blood culture sample [OR: 7.555, 95% CI: 2.251–25.357, $P = 0.001$], candidemia clearance ≥ 5 days after initiation of antifungal treatment [OR: 4.211, 95% CI: 1.384–12.810, $P = 0.011$] were significantly associated with EFE.

Table 2
Endogenous fungal endophthalmitis score among adult patients with candidemia.

Score of points	No EFE[a]	EFE[b]	*P*-value
0, (%)	23 (21.9)	0 (0.0)	0.007
1, (%)	38 (36.2)	2 (8.0)	0.006
2, (%)	38 (36.2)	14 (56.0)	0.069
3, (%)	6 (5.7)	7 (28.0)	0.003
4, (%)	0 (0.0)	2 (8.0)	0.036

[a] No EFE, no endogenous fungal endophthalmitis calculation available for 105 cases of candidemia.
[b] EFE, endogenous fungal endophthalmitis calculation available for 25 cases of candidemia. Between No EFE and EFE groups, the EFE group had higher scores when tested by the Wilcoxon signed-rank test ($P < 0.001$).

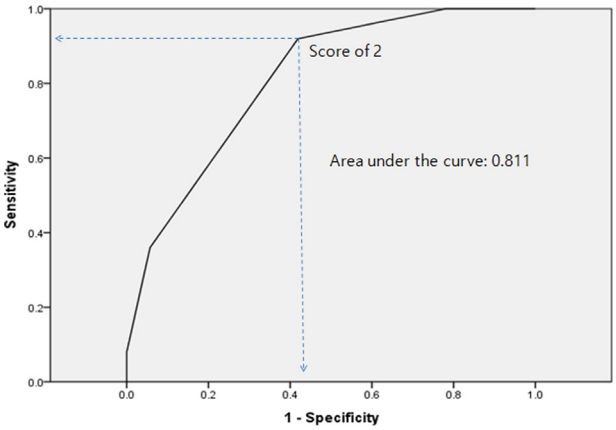

Fig. 3. The endogeneous fungal endophthalmitis prediction model among adult candidemia patients: the receiver operating characteristics curve.

4. Discussion

Our study shows that the incidence of candidemia has increased recently, which is consistent with a previous study [17] reported in the ROK. As the patient population with predisposing risk factors is expected to be increasing, the incidence of candidemia with EFE might also be expected to rise. Despite the current recommendation for patients with candidemia to have an ophthalmological examination to rule out EFE [5], more than half of the candidemia patients in our study cohort did not have an ophthalmological examination. Nonetheless, among the candidemia patients who underwent an ophthalmological examination, the prevalence of EFE was 19.1%. Our results were comparable to recent studies of EFE conducted in Japan [18,19], which reported that the prevalence of EFE ranged from 19.5% to 20.1%. However, higher (26.5%) and lower (10.8%) prevalence of EFE were reported in other recent studies [7,20]. Disparities among these studies and ours might be due to differences in patients' characteristics. For example, there was a higher prevalence of the immunosuppressed state of the patients with a higher prevalence of EFE [20], and there was a lower prevalence of EFE among the patients with younger age [7]. Therefore, the prevalence of EFE observed in our study might have been the result of multifactorial factors of characteristics of the patients in our cohort, reflecting the local epidemiology of EFE in the ROK.

In this study, several factors associated with EFE were identified. *C. albicans* candidemia was found to be an independent risk factor for EFE. This result was consistent with previous studies [7,18–20]. The differential virulence nature of the *Candida* spp. might contribute to the pathogenesis of EFE as *C. parapsilosis* is less virulent than other *Candida* spp. [21] and *C. parapsilosis* was less frequent in the E group in our study. Furthermore, significant virulence of *C. albicans* over non-*C. albicans* with enhanced capabilities of ocular invasion and recruitment of inflammatory mediators observed in the animal infection model [22] suggest a higher propensity of *C. albicans* to cause EFE. Thus, our result of significance of *C. albicans* candidemia associated with EFE reaffirms the positive correlation. Abnormal ALT at the time of candidemia diagnosis was another independent risk factor for EFE. Abnormal ALT usually indicates a hepatocellular injury, but it may represent a proinflammatory state marker [23]. Also, the degree of liver injury may be correlated with the burden of infection [24]. Taken together, abnormal ALT in the setting of candidemia may serve as an indirect marker of dissemination of candidemia, including metastatic infection such as EFE. Therefore, abnormal ALT at the time of candidemia diagnosis could be useful for one of the predictive factors for EFE. Receipt of antifungal treatment $\geq$ 48 hours after onset of candidemia symptoms and blood culture sample and candidemia clearance $\geq$ 5 days after initiation of antifungal treatment were significantly associated with EFE in our study. These results are in line with a previous study [7], which suggests that hematogenous ocular inoculation during candidemia and persistent candidemia after initiation of antifungal treatment may play a critical role in the pathogenesis of EFE. Although not being statistically significant, there was a trend of increased in-hospital mortality among candidemia patients with EFE in our study, which is in agreement with previous studies [11,19]. EFE results from fungal seeding via candidemia and persistent candidemia by delayed or inappropriate antifungal treatment is associated with increased mortality in candidemia patients [25,26]. Thus, our results illustrate that the prompt initiation of effective antifungal treatment against candidemia is essential, not only to decrease mortality but also to minimize the development of EFE complications. Furthermore, a predictive model for E with significant variables was created, which would be useful for health care providers in assessing the probability of E among adult candidemia patients. Since the rate of candidemia has been increasing [14], our predictive model might be applied to differentiate adult candidemia patients at high risk of EFE from those at low risk to provide effective screening and management for E.

Our study has some limitations, however, mainly due to retrospective study design and its relatively small sample size from a single center. Therefore, our results might not be generalizable to the clinical setting, where there is a significant difference in the patients' demographics or clinical characteristics. Furthermore, there might have been risks of unintended selection bias and confounding effects from unmeasured variable, such as evolution of serum fungal biomarkers, duration of neutropenia or duration of immunosuppressive agent use. In addition, the prevalence rate of EFE and the comparative analysis in our study may have been affected as the candidemia patients who did not have an ophthalmological examination were excluded. Also, the diagnosis of EFE might have been affected by the timing and the number of ophthalmological examinations [7,17]. However, we used consistent definitions for data collection through the careful review of the medical records to minimize the potential bias. While these limitations warrant further investigation with a larger number of adult candidemia patients, we believe that our data reflects the real-world experience of EFE as it is still common practice that an ophthalmological examination is performed at the treating physician's discretion.

5. Conclusion

Our study showed EFE occurred in 19% of the hospitalized adult patients with candidemia. Risk factors for EFE were found to be *C. albicans* candidemia, abnormal ALT at the diagnosis of candidemia, receipt of antifungal treatment $\geq$ 48 hours after onset of candidemia symptoms and blood culture sample, and candidemia clearance $\geq$ 5 days after initiation of antifungal treatment. Adult candidemia patients with these risk factors need to be closely monitored for the possibility of EFE. Further prospective studies with the involvement of larger numbers of adult patients with candidemia are required to define the exact prevalence of EFE and identify the risk factors for optimal management.

IRB approval/Research Ethics Committee

This study was approved by the institutional review board at the Korea University Anam Hospital (IRB number 2018AN0440).

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Disclosure of interest

The authors declare that they have no competing interest.

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