Clinical Infectious Diseases

MAJOR ARTICLE

Prevalence of Ocular Candidiasis and *Candida* Endophthalmitis in Patients With Candidemia: A Systematic Review and Meta-Analysis

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(See the Editorial Commentary by Adriana M. Rauseo and Andrej Spec on pages 1750–2.)

Background. Infectious diseases and ophthalmology professional societies have disagreed regarding ocular screening in patients with candidemia. We aimed to summarize the current evidence on the prevalence of ocular candidiasis (OC) and *Candida* endophthalmitis (CE) according to the standardized definitions.

Methods. A literature search was conducted from the inception date through 16 October 2022 using PubMed, Embase, and SCOPUS. Pooled prevalence of ocular complications was derived from generalized linear mixed models (PROSPERO CRD42022326610).

Results. A total of 70 and 35 studies were included in the meta-analysis for OC and concordant CE (chorioretinitis with vitreous involvement), respectively. This study represented 8599 patients with candidemia who underwent ophthalmologic examination. Pooled prevalences (95% CI) of OC, overall CE, concordant CE, and discordant CE were 10.7% (8.4–13.5%), 3.1% (2.1–4.5%), 1.8% (1.3–2.6%), and 7.4% (4.5–12%) of patients screened, respectively. Studies from Asian countries had significantly higher concordant CE prevalence (95% CI) of patients screened (3.6%; 2.9–4.6%) compared with studies from European countries (1.4%; .4–5%) and American countries (1.4%; .9–2.2%) (P <.01). Presence of total parenteral nutrition and *Candida albicans* was associated with CE, with pooled odds ratios (95% CI) of 6.92 (3.58–13.36) and 3.02 (1.67–5.46), respectively.

Conclusions. Prevalence of concordant CE overall and among Asian countries was 2 and 4 times higher than the prevalence previously reported by the American Academy of Ophthalmology (AAO) of <0.9%, respectively. There is an urgent need to study optimal screening protocols and to establish joint recommendations by the Infectious Diseases Society of America and AAO.

Keywords. candidemia; endophthalmitis; ocular candidiasis.

Candidemia is known for high mortality rates of 25–40% despite appropriate treatment [1–3]. Patients with candidemia should be evaluated for metastatic foci, particularly those with persistent candidemia [4]. The 2016 Infectious Diseases Society of America (IDSA) guidelines recommend a dilated eye exam by an ophthalmologist in all patients with candidemia, preferably within 1 week of diagnosis for nonneutropenic patients and delayed until neutrophil recovery among neutropenic patients [5]. Although these recommendations were not based on data from randomized controlled trials, it was thought that the downstream consequences of missing and not appropriately treating patients with *Candida* endophthalmitis (CE) would be substantial.

However, routine ophthalmologic examination in all patients with candidemia has been questioned, particularly with low cost-effectiveness and low quality of evidence to support this recommendation [5–8]. The American Academy of Ophthalmology (AAO) issued a statement recommending against routine screening for endogenous endophthalmitis in all patients with candidemia and only recommended screening in patients with signs or symptoms suggestive of ocular infection on 19 July 2021 [9]. Due to the disagreements in recommendations by the two professional societies, AAO and IDSA, we conducted this systematic review and meta-analysis

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to summarize the current evidence on the prevalence of *Candida* ocular involvement, both ocular candidiasis (OC) and CE, and to exploratorily investigate factors associated with CE.

METHODS

Study Definitions

Candida endophthalmitis was defined as having abnormal ocular findings, including vitritis and chorioretinitis, specifically attributed to *Candida* infection based on the direct ophthalmologic examination performed by ophthalmologists. Ocular candidiasis included any intraocular abnormalities among patients with candidemia such as vitritis, chorioretinitis, and other nonspecific abnormal retinal findings. The diagnosis of CE was classified according to previous definitions as "concordant" and "discordant" [6]. Patients with concordant CE must meet 1 of the following definitions: (1) *Candida* chorioretinitis with an extension of the surrounding inflammation into the vitreous or (2) vitreous abscess manifesting as intravitreal fluff balls [10]. Patients who did not meet 1 of the 2 concordant CE criteria, such as patients considered to have CE based on an ophthalmologist's overall impression or patients for whom diagnostic criteria for CE were not explicitly defined, were classified as having discordant CE. We *a priori* determined variables for potential risk factors associated with CE by incorporating factors that were demonstrated in at least 3 studies for our exploratory meta-analysis. Additional definitions for these parameters are described in Supplementary Methods 1.

Search Strategy

Two authors (K. P. and T. P.) performed this systematic search independently in 3 databases including PubMed, Embase, and SCOPUS from the inception date to 16 October 2022. The complete search terms for each database are available in Supplementary Methods 2. We report this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. We conducted a manual hand search from reference lists and citation tracking for eligible studies. The International Prospective Register of Systematic Reviews (PROSPERO) registration number is CRD42022326610.

Selection Criteria

The screening process was conducted in the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Two authors (T. P. and K. P.) reviewed the included studies and selected all observational studies in which the prevalence of OC or CE was provided or could be calculated. Conference abstracts, case reports, and case series were excluded due to unavailability of data required for prevalence calculation. We contacted corresponding authors of the recruited studies for methodology and definitions if needed. If more than 1 publication was based on the same cohort or population and reported the same outcomes, only the most recent or comprehensive publication was included [12]. We used the Web-based Google Translate to translate non–English-language abstracts during abstract screening. For the full-text review, non–English-language studies were translated by a professional translation agency (PoliLingua, London, UK).

Data Analysis

Our primary outcome was the prevalence of OC and CE in patients with candidemia. We extracted numbers of patients with candidemia, patients screened for ocular complications, and patients with ocular complications to calculate the pooled prevalence of CE. Crude numbers and unadjusted/adjusted odds ratio (ORs) with 95% confidence intervals (CIs) of each potential risk factor associated with CE were extracted for meta-analysis. We used the risk bias tool by Hoy et al [13] for the quality assessment of papers providing the prevalence of OC and CE. We used the Quality in Prognostic Studies (QUIPS) tool [14] for quality assessment of prognostic studies providing risk factors of concordant CE.

The prevalence of OC and CE was calculated by dividing patients with OC and CE according to the definitions above with patients with candidemia who underwent ophthalmologic screening. We performed meta-analysis using R (R language; R Foundation for Statistical Computing, Vienna, Austria) to calculate the pooled prevalence of OC and CE along with 95% CIs by using generalized linear mixed models (GLMMs) [15]. We performed subgroup analyses to better understand the differences in concordant CE prevalence based on study design, patient population, study continent, risk of bias according to criteria by Hoy et al [13], and proportion of patients with ophthalmologic screening in the study. We then used the chi-square test to determine differences in pooled prevalence between the subgroups. Sensitivity analyses of pooled OC and CE prevalence were performed by removing studies with high risk of bias.

We exploratorily investigated the risk factors associated with CE in patients with candidemia by calculating the pooled OR (pOR) with 95% CIs and using a random-effects model. We directly calculated ORs from raw numerical data provided from the study if the OR was not provided. Heterogeneity of the effect size of each study was assessed using I^2 statistics. I^2 statistics with a value less than 25% were considered low heterogeneity; a value ranging from 25% to 60% was considered moderate heterogeneity, and an I^2 value greater than 60% was considered substantial heterogeneity [16, 17].

RESULTS

Study and Patient Characteristics

We retrieved 1597 studies from the initial search; 1595 studies were retrieved from the 3 databases, whereas the other 2 studies

[3, 18] were identified from the manual search; 824 duplicates were removed, and 658 studies were excluded from title and abstract screening. We performed a full-text review on 115 studies. Thirty-nine were excluded due to incorrect study designs, including case series and case reports, conference abstracts, studies with populations with a fungal infection other than *Candida* species, studies that did not report the number of patients with ocular complications of candidemia, or those with a duplicate cohort. Six studies did not report the number of patients who underwent ophthalmologic screening. A total of 70 studies [3, 4, 8, 10, 18–83] were included in the systematic review and meta-analysis of OC, of which 35 studies [8, 10, 18, 20, 22, 27, 28, 30, 32, 34, 36, 37, 39, 41–43, 46, 49, 52, 54, 57, 58, 61, 62, 66, 68, 69, 71, 72, 74, 76–78, 80, 82] were incorporated in the meta-analysis and subgroup analysis of prevalence of concordant CE (Figure 1). A total of 5 studies [23, 43, 47, 60, 71] were incorporated in the meta-analysis of risk factors associated with CE. Characteristics of the 70 studies are reported in Supplementary Table 1. There were 8599 patients with candidemia who underwent ophthalmologic screening and were included in the study.

Prevalence of Ocular Candidiasis and *Candida* Endophthalmitis

Seventy studies [3, 4, 8, 10, 18–83] reported the number of patients with candidemia who underwent ophthalmologic screening and patients with candidemia who developed OC or CE. The pooled prevalence of OC (95% CI) was 10.70% (8.41–13.51%; $I^2 = 84\%$) of patients screened (Supplementary Figure 1). Sixty-six studies [3, 8, 10, 18, 20–54, 56–80, 82, 83] reported the number of patients with candidemia who developed CE. Among 66 studies, 35 studies [8, 10, 18, 20, 22, 27, 28, 30, 32, 34, 36, 37, 39, 41–43, 46, 49, 52, 54, 57, 58, 61, 62, 66, 68, 69, 71, 72, 74, 76–78, 80, 82] used definitions consistent with concordant CE and 31 studies [3, 21, 23–26, 29, 31, 33, 35, 38, 40, 44, 45, 47, 48, 50, 51, 53, 56, 59, 60, 63–65, 67, 70, 73, 75, 79, 83] did not (discordant CE). Characteristics of the 35 concordant CE studies are shown in Table 1. The pooled prevalence of CE (95% CI) (both concordant and discordant definitions) was 3.08% (2.08–4.54%; $I^2 = 85\%$) of patients screened (Supplementary Figure 2). The pooled prevalence of concordant CE (95% CI) was 1.83% (1.30–2.57%; $I^2 = 24\%$) of patients screened, whereas the pooled prevalence of discordant CE (95% CI) was 7.37% (4.45–11.97%; $I^2 = 82\%$) of patients screened (Figure 2 and Supplementary Figure 2). Of the 31 studies reporting discordant CE, 13 studies [3, 21, 25, 29, 31, 35, 38, 40, 45, 48, 50, 65, 79, 83] did not provide the specific criteria for CE diagnosis, 12 studies [23, 26, 33, 47, 51, 53, 56, 60, 63, 64, 67, 70] used criteria that deviated from the definition of concordant CE, and 5 studies [24, 44, 59, 73, 75] used "judgment of ophthalmologic consult service" to determine CE diagnosis.

In subgroup analyses of concordant CE prevalence, studies from Asian countries [43, 52, 54, 68, 69, 76–78, 80] showed a significantly higher concordant CE prevalence of patients screened (95% CI) of 3.64% (2.87–4.61%; $I^2 = 12\%$) compared with studies from European countries [22, 28, 36, 42, 58] of 1.40% (.38–5.02%; $I^2 = 56\%$) and American countries [8, 10, 18, 20, 27, 30, 32, 34, 37, 39, 41, 46, 49, 57, 61, 62, 66, 71, 72, 74] of 1.44% (.95–2.20%; $I^2 = 0\%$) ($P < .01$). The prevalence of concordant CE in adults [18, 19, 28, 36, 37, 39, 43, 46, 49, 61, 62, 66, 69, 71, 74, 76, 77, 82] was not significantly different compared with the prevalence in pediatric populations [27, 32, 57] (2.43% [95% CI: 1.70–3.48%; $I^2 = 29\%$] in adult vs 1.45% [95% CI: .60–3.43%; $I^2 = 0\%$] in pediatric populations; $P = .28$). In subgroup analysis of concordant CE based on the proportion of ophthalmologic examination, there was no significant difference in prevalence of concordant CE (95% CI) among the studies with a proportion of 80% or more [10, 36, 41, 54, 58, 62, 66, 68] vs less than 80% [18, 22, 28, 32, 37, 42, 43, 46, 57, 69, 74, 76–78, 80] ophthalmologic examinations (1.82 [.77–4.27; $I^2 = 39\%$] vs 2.01 [1.30–3.09; $I^2 = 37\%$], respectively; $P = .84$). Among 35 studies reporting concordant CE prevalence, 12 only included people who were screened for ocular complications and were excluded from the subgroup analysis based on the proportion of ophthalmologic examinations [8, 20, 27, 30, 34, 39, 49, 52, 61, 71, 72, 82]. Subgroup analyses did not show significant differences in concordant CE prevalence by study design and risk of bias (Figure 3, Supplementary Figure 3).

Of the 70 studies included for meta-analysis of OC and CE prevalence, there were 16 studies with high risk of bias, 37 studies with moderate risk of bias, and 17 studies with low risk of bias (Supplementary Tables 2–4). No studies included for concordant CE were considered high risk. We then performed sensitivity analyses by removing studies with high risk of bias for OC and discordant CE prevalence calculation. The pooled prevalences (95% CI) of OC and discordant CE of patients screened after removing studies with high risk of bias were 12.53% (10.03–15.55%; $I^2 = 83\%$) and 11.81% (7.76–17.58%; $I^2 = 75\%$), respectively (Supplementary Figure 4).

Factors Associated With *Candida* Endophthalmitis

Data extraction of all potential factors associated with CE and Grading of Recommendations Assessment, Development and Evaluation (GRADE) for potential factors associated with CE are available in Supplementary Tables 5 and 6. However, only 4 factors, which were *C. albicans*, non–*albicans Candida*, presence of central venous catheter (CVC), and presence of total parenteral nutrition (TPN), were reported in at least 3 studies and for which meta-analysis could be performed. We found that *C. albicans* candidemia was associated with CE with a pOR of 3.02 (95% CI: 1.67–5.46; $P < .01$; $I^2 = 52\%$) [23, 43, 47, 71], whereas patients with non–*albicans* candidemia were less likely to have CE with a pOR of .33 (95% CI: .18–.60; $P < .01$; $I^2 = 53\%$) [23, 43, 47, 71]. The presence of TPN was associated with CE with a pOR of 6.92 (95% CI: 3.58–13.36;

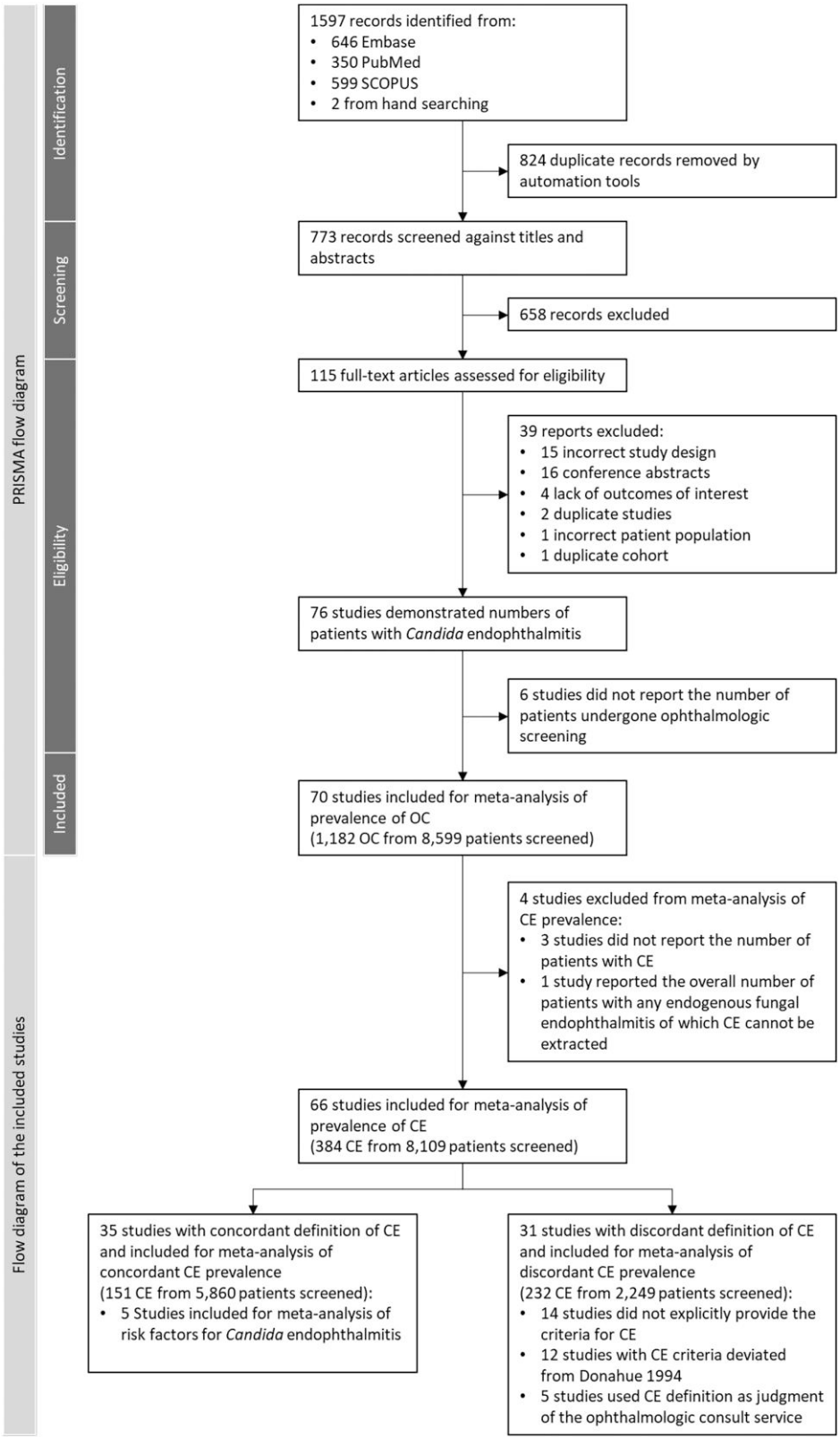

Figure 1. PRISMA diagram of the included studies for prevalence analysis. Abbreviations: CE, *Candida* endophthalmitis; OC, ocular candidiasis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Evidence Table for Studies With Concordant *Candida* Endophthalmitis

First Author, Year [Reference]	Study Design	Data Source	Source Population	Sampling Scheme	Study Population	Criteria for Candida Endophthalmitis	Patients With CBSI, n	Patients Screened, n	Patients With CE, n	Prevalence of CE, %	Risk of Bias
Adam, 2015 [20]	Retrospective cross-sectional study	Hospital-based study	Pennsylvania, USA	Full census	Patients with +BC	CCR with VE	213	213	4	1.88	Low
Blennow, 2013 [22]	Retrospective cohort	Hospital-based study	Huddinge, Sweden	Full census	Patients (≥1 year) with +BC	CCR with vitritis or white fluffy lesion with VE	144	60	0	0	Low
Donahue, 1994 [10]	Prospective observational study	Multicentered hospital-based study	Pennsylvania and North Carolina, USA	Full census	Patients with +BC	CCR with vitritis or white fluffy lesion with VE	118	118	0	0	Low
Donahue, 2003 [27]	Retrospective review of inpatient hospital consultations	Hospital-based study	Tennessee, USA	Full census	Children with ophthalmologic consultation due to disseminated candidiasis	CCR with vitritis or white fluffy lesion with VE	24	24	0	0	Low
Dozier, 2011 [8]	Retrospective case series	Hospital-based study	Tennessee, USA	Full census	Patients with +BC	Vitreous abscess manifesting as intravitreal fluff balls	211	211	1	0.47	Low
El-Abiary, 2018 [28]	Retrospective observational study	Multicentered ICU-based study	Glasgow, Scotland	Full census	Adult patients (≥17 years) with +BC	CCR with vitritis	168	80	0	0	Low
Feman, 2002 [30]	Retrospective manner, observational case series and case report	Hospital-based study	Missouri, USA	Full census	Patients whose the ophthalmologic consultation record had the words "fungal infection" and "endophthalmitis" or "retinitis"	CCR with vitritis or white fluffy lesion with VE	82[a]	82	2	2.43	Low
Fierro, 2013 [32]	Retrospective cohort	Hospital-based study	New York and Pennsylvania, USA	Full census	Children with +BC	CCR with vitritis	378	254	4	1.57	Low
Geraymovych, 2015 [34]	Retrospective review	Hospital-based study	Virginia, USA	Full census	Patients with +BC, without prior ocular surgery or ocular trauma	VE and anterior extension with fluffy vitreous balls, vitreous haze, vitreous abscess, anterior chamber cells, or hypopyon	132	132	1	0.76	Low
Ghodasra, 2014 [18]	Retrospective case series	Hospital-based study	Pennsylvania, USA	Full census	Adult patients (≥18 years) with +BC	VE with fluff balls, vitreous haze, or vitreous abscess	326	238	2	0.84	Moderate
Govindaraju, 2022 [82]	Retrospective	Hospital-based study	Michigan, USA	Full census	Adult patients with +BC or elevated beta-D-glucan level	CCR with vitritis or vitreous abscess manifesting as intravitreal fluff balls	100	100	3	3.00	Moderate
Hautala, 2021 [36]	Retrospective study	Hospital-based study	Oulu, Finland	Full census	Patients with +BC	Vitritis or fluffy lesions with VE	304	271	16	5.9	Low
Hillenbrand, 2022 [37]	Retrospective study	Hospital-based study	Ohio, USA	Full census	Adult patients with +BC	VE with fluff balls, vitreous haze or vitreous abscess	226	129	1	0.78	Low
Huynh, 2012 [39]	Retrospective review	Hospital-based study	Massachusetts, USA	Full census	Patients with +BC, sedated or	CCR with vitritis	36	36	0	0	Low

Table 1. Continued

First Author, Year [Reference]	Study Design	Data Source	Source Population	Sampling Scheme	Study Population	Criteria for Candida Endophthalmitis	Patients With CBSI, n	Patients Screened, n	Patients With CE, n	Prevalence of CE, %	Risk of Bias
					obtunded patients (unable to assess VA) were excluded						
Kannangara, 2007 [41]	Prospective study	Hospital-based study	Pennsylvania, USA	Full census	Patients with +BC	CCR with VE	46	46	0	0	Moderate
Karmisholt, 2008 [42]	Retrospective cohort	Hospital-based study	Aalborg, Denmark	Full census from Bacteremia Research Registry	Patients with +BC	CCR with vitreous inflammation	203	86	1	1.16	Moderate
Kato, 2018 [43]	Retrospective cohort	Multicentered hospital-based study	Japan	Full census	Adult patients (≥18 years) with +BC	CCR with vitritis	289	174	4	2.3	Moderate
Khalid, 2014 [46]	Retrospective review	Hospital-based study	Kansas, USA	Full census	Adult patients (>18 years) with +BC	CCR with vitritis	283	144	2	1.39	Moderate
Krishna, 2000 [49]	Prospective observational study	Hospital-based study	Ohio, USA	Full census	Patients with +BC, no prior fungemia, life expectancy >72 hours	Intravitreal fluff ball or vitreal abscess	31	31	0	0	Moderate
Mehta, 2007 [52]	Retrospective review	ICU-based study	Mumbai, India	Full census	Patients with +BC	CCR with vitritis	12[a]	12	0	0	Moderate
Nagao, 2012 [54]	Retrospective study	Multicentered hospital-based study	Kyoto, Japan	Full census	Patients with +BC	Vitritis or white fluffy lesion with VE	220	204	10	4.9	Low
Noyola, 2001 [57]	Retrospective review	NICU-based study	Texas, USA	Full census	Infants in NICU with *Candida* spp. isolated from any sterile sites or with histopathological evidence of invasive candidal dermatitis	CCR with vitreous involvement	86	67	1	1.49	Moderate
Oude Lashof, 2011 [58]	Prospective study	Hospital-based study	Maastricht, The Netherlands	Full census	Patients (≥12 years) with +BC	Vitritis or white fluffy lesion with VE	370	370	6	1.62	Moderate
Paulus, 2016 [61]	Prospective cohort study	Hospital-based study	California, USA	Full census	Adult patients (≥18 years) with +BC	CCR with vitritis	125	125	2	1.6	Moderate
Popovich, 2007 [62]	Retrospective review	Hospital-based study	Michigan, USA	Full census	Adult patients (≥18 years) with +BC, patients those died within 48 hours after candidemia were excluded	CCR with vitritis or white fluffy lesion with VE	100	80	3	3.75	Low
Rodriguez-Adrián, 2003 [66]	Prospective study	ICU-based study	Caracas, Venezuela	Full census	Patients (≥13 years) with +BC, those with ANC <500/mm^3 or major immunodeficiencies were excluded	CCR with VE	206	180	2	1.11	Moderate
Sakai, 2021 [68]	Retrospective observational study	Hospital-based study	Kobe, Japan	Full census	Patients with +BC	Vitritis or white fluffy lesion with VE	58	56	0	0	Low
Sakamoto, 2022 [69]	Retrospective cohort study	Hospital-based study	Fukuoka, Japan	Full census	Adult patients (≥18 years) with +BC	Vitritis or white fluffy lesion with VE	138	108	7	6.48	Moderate
		Multicentered		Full census		CCR with vitritis	771	771	30	3.89	Moderate

Table 1. Continued

First Author, Year [Reference]	Study Design	Data Source	Source Population	Sampling Scheme	Study Population	Criteria for Candida Endophthalmitis	Patients With CBSI, n	Patients Screened, n	Patients With CE, n	Prevalence of CE, %	Risk of Bias
Seidelman, 2021 [71]	Retrospective chart review	hospital-based study	North Carolina and Virginia, USA		Adult patients (≥18 years) with +BC						
Shah, 2008 [72]	Retrospective review	Hospital-based study	Pennsylvania, USA	Full census	Patients with +BC	CCR with vitreous cells of "fluff balls"	38	38	0	0	Low
Siddiqui, 2022 [74]	Retrospective review	Hospital-based study	Arkansas, USA	Full census	Adult patients (≥18 years) with +BC	CCR with vitritis or white fluffy lesion with VE	290	161	4	2.48	Low
Son, 2019 [76]	Retrospective review	Hospital-based study	Seoul, Korea	Full census	Patients with +BC	Vitritis or white fluffy lesion with VE	438	275	8	2.91	Moderate
Ueda, 2019 [77]	Retrospective study	Multicentered hospital-based study	Japan	Full census	Nonneutropenic adult patients (>17 years) with +BC	CCR with VE	1089	781	32	4.1	Moderate
Vena, 2017 [78]	Retrospective study	Multicentered hospital-based study	Spain	Full census	Adult patients (>16 years) with +BC	Vitritis or fluffy lesion with VE	365	168	2	1.19	Moderate
Zakhem, 2021 [80]	Retrospective review	Hospital-based study	Beirut, Lebanon	Full census	Patients with +BC	Vitreous inflammation	193	35	3	8.57	Moderate

Abbreviations: ANC, absolute neutrophil count; +BC, positive blood culture for *Candida* species; CBSI, *Candida* bloodstream infection; CCR, *Candida* chorioretinitis; CE, *Candida* endophthalmitis; ICU, intensive care unit; NICU, neonatal intensive care unit; VE, vitreal extension or extension to vitreous.

[a]Feman et al recruited patients with positive fungal culture from any of these sites: blood, bronchial wash, deep abscess, abdominal paracentesis, or thoracentesis, whereas Mehta et al recruited patients in whom *Candida* spp. can be isolated from the tracheal secretions, peritoneal fluid, the central line tip, urine cultures, or blood cultures.

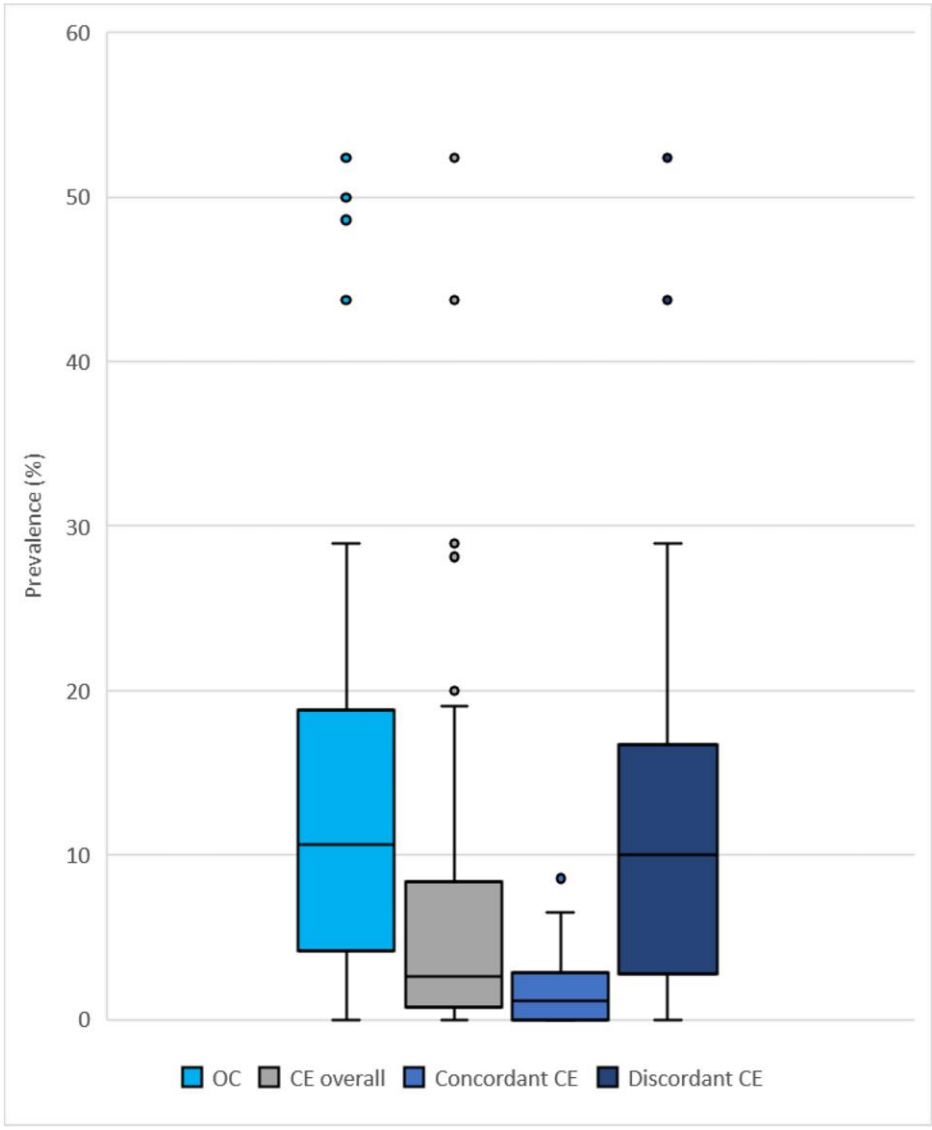

Figure 2. Prevalence of ocular involvement/complications in patients with candidemia who underwent ophthalmologic screening: OC, CE, concordant CE, and discordant CE were retrieved from 70, 66, 35, and 31 studies, respectively. The boxed area represents the 25th to the 75th percentile of the data. The horizontal line inside each box represents the median value. Error bars show the minimum and maximum values with filled circles as outliers above the plot. Abbreviations: CE, *Candida* endophthalmitis; OC, ocular candidiasis.

$P < .01$; $I^2 = 0\%$) [23, 47, 60, 71], whereas the presence of CVCs was not significantly associated with CE (Figure 4, Supplementary Figure 5). Subgroup analysis among risk factors associated with CE could not be performed due to the small number of included studies. Risk of bias of the studies included for risk factor analysis is shown in Supplementary Table 7. Of 5 studies used in risk factor analysis, 3 studies [23, 47, 60] were low risk and 2 studies [43, 71] were moderate risk.

DISCUSSION

We conducted an updated systematic review and meta-analysis to summarize the prevalence of ocular findings in patients with candidemia, namely ocular candidiasis (OC) and *Candida* endophthalmitis (CE), and exploratorily investigated risk factors for CE. With our extensive search from multiple databases without language restrictions, we found that the pooled prevalence of concordant CE (95% CI), the most stringently defined and most concerning of *Candida* ocular complications, was 1.8% (1.3–2.6%) of patients screened, which is 2 times higher than the previously published systematic analysis [6]. Of 70 included studies included in our review, 48 studies [3, 8, 10, 18, 20, 22–24, 26, 27, 29–35, 38, 39, 41, 42, 44, 46, 48, 49, 51–62, 64–67, 70, 72, 78, 79, 81, 84, 85] were published before 2018, of which 10 [29, 31, 44, 52, 55, 57, 59, 79, 81, 84] were not included in the previous

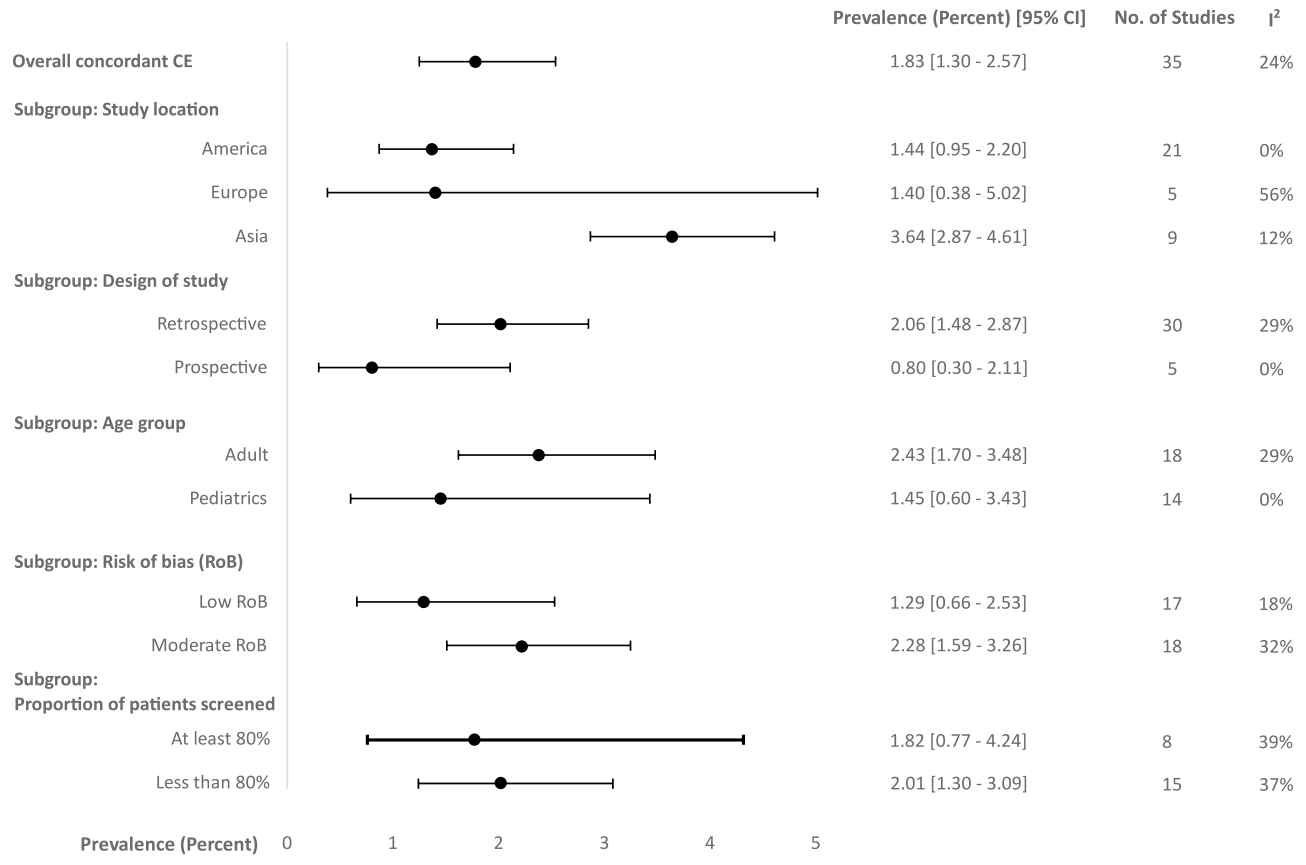

Figure 3. Subgroup analyses of prevalence of concordant *Candida* endophthalmitis among patients with candidemia who underwent ophthalmologic screening. Abbreviations: CE, *Candida* endophthalmitis; CI, confidence interval.

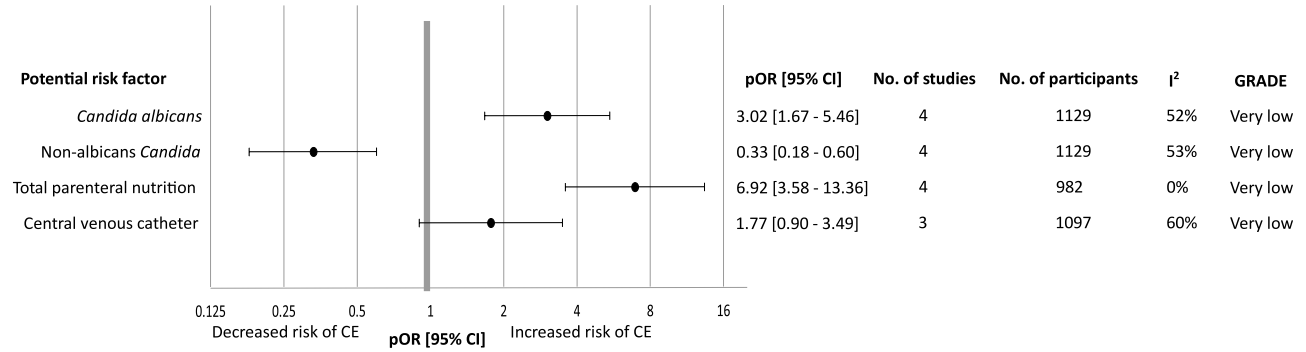

Figure 4. Pooled odd ratios of potential risk factors associated with *Candida* endophthalmitis. Abbreviations: CE, *Candida* endophthalmitis; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; pOR, pooled odds ratio.

study by Breazzano et al in 2019 [6]. If re-calculating the prevalence of concordant CE from the studies that were published before 2018 [8, 10, 18, 20, 22, 27, 30, 32, 34, 39, 41, 42, 46, 49, 52, 54, 57, 58, 61, 62, 66, 72, 78] by using generalized linear mixed models, the prevalence of concordant CE (95% CI) would be 1.3% (.9–2%), not less than 1%.

In our study, we observed a huge difference in the prevalence of ocular complications based on definitions and high heterogeneity was noted among OC and discordant CE studies, which stresses the importance of understanding terminology when applying these terms in clinical care. The prevalence of OC (any abnormal ocular findings in patients with candidemia)

was as high as 11%. However, this high prevalence of OC is possibly attributed to underlying comorbidities rather than solely from *Candida* infection. Previous prospective studies [22, 32, 66] reported that underlying diseases were confounders in the increased prevalence of abnormal ocular findings in patients with candidemia. We suspect that high heterogeneity in OC and discordant CE could possibly be explained by the nature of their wide range of definitions. Hence, clinicians should be mindful that not all abnormal ophthalmologic findings in patients with candidemia are attributed to *Candida* infection.

Among studies reporting concordant CE, we found a significantly higher prevalence of concordant CE among studies from Asian countries (3.6%), compared with studies from European countries and American countries. The cause of higher concordant CE prevalence among Asian countries is unclear, but we hypothesize that there could possibly be a component of genetic predisposition favoring more invasive fungal infections, in additional to differences in methods applied to diagnostic screening, fungal epidemiology, and antifungal prophylaxis/treatment [86–88]. Although the necessity of universal ophthalmologic screening is debated, our findings raise concerns that limiting ophthalmologic screening only in symptomatic patients, particularly in populations with a higher prevalence, may lead to underdiagnosis. Our study also identified the scarcity of CE prevalence data from Africa, South America, and Australia. Investigations on this important clinical topic should be encouraged from these continents.

In our exploratory analysis, we identified 2 risk factors associated with CE in patients with candidemia including TPN use and infection with *C. albicans*. *Candida albicans* has been well known for high virulence and more severe complications than other *Candida* species. *Candida albicans*, which is the most intrinsically virulent *Candida* species, causes more bloodstream infections, can induce inflammatory cytokines and neutrophil recruitment, and gives rise to metastatic foci such as CE [19]. Although we recognize that the identified risk factors associated with CE should be interpreted with caution due to the limited number of studies included for analysis and pORs mainly calculated from unadjusted ORs, these results highlight the importance of recommending TPN when truly indicated and achieving source control [5, 9], a practice supported by both the IDSA guidelines [5] and the AAO statement [9]. In reality, these goals are not always immediately feasible due to other clinical conditions or diagnostic uncertainty. The critical question remains whether ocular symptom screening alone is sufficient for patients with source control issues.

Limitations

We reported pooled prevalence per patient screened to be consistent with previous publications; however, this could potentially overestimate the true prevalence of *Candida* ocular complications. Although the pooled prevalence of concordant CE was only derived from studies with low to moderate risk of bias, some studies with OC and discordant CE prevalence calculations were considered high risk and should be interpreted with caution. Due to our study design and unavailability of data, we are not able to adjust for confounders related to CE among patients with candidemia and we are not able to perform a wide range of subgroup analyses to understand the differences in concordant CE prevalence based on host immune status or antifungal therapy. We do not have data from the included studies regarding duration of candidemia prior to hospitalization, treatment, specifics of treatment including dosing and susceptibility, and the presence of ocular symptoms. We recognized a lack of fully systematic screening in some studies, a lack of longitudinal screening, and differing times to ophthalmologic examination. It is also important to note that the significance of chorioretinitis in patients with candidemia is not well established. We propose that multicenter, international, prospective studies should be performed to understand the real burden of *Candida* endophthalmitis to inform guideline development and clinical practices.

Conclusions

This systematic review of 70 studies and meta-analysis of 35 studies of concordant *Candida* endophthalmitis in patients with candidemia show a higher prevalence of concordant CE compared with the prevalence cited by the recent AAO positional paper [9] (1.8% vs <0.9%), with a prevalence of 3.6% among studies from Asian countries. To develop optimal screening protocols, we must weigh the risks to the patient from a missed or delayed diagnosis against any risks associated with the evaluation, while also considering outside demands on the resources required for screening. Screening patients with candidemia for ocular involvement requires a dilated eye examination and ophthalmologists' time and expertise, resources that are limited. Neither professional group can fully address this challenge alone. There is an urgent need for more nuanced, evidence-based screening protocols to detect *Candida* ocular involvement. A joint statement from both the infectious diseases and ophthalmology professional societies is called for.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. K. P., T. P., and N. P.: study design, literature search, data extraction, quality assessment of the studies, data analysis, manuscript writing, and critical review. K. M. and A. S.: study design, data analysis, manuscript writing, and critical review. K. S.: data analysis, manuscript writing, and critical review. A. T., N. C., S. L., T. M., J. T.,

M. W., S. G., P. T., N. L., N. W., C. M., R. P., O. S. K., and S. N.: manuscript writing and critical review.

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Data sharing. K. P. and N. P. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data for our systematic review and meta-analysis are publicly available based on the study design. Study protocol and dataset can be requested at npermpa1@jhmi.edu.

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