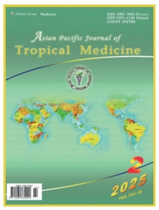

Review Article

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Trends of *Candida* species causing bloodstream infections in South-Eastern Asia: A systematic review and meta-analysis

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ABSTRACT

A reliable estimation of *Candida* bloodstream infection prevalence is increasingly important to track changes in *Candida* species distribution and define burden of ongoing candidemia. A systematic review and meta-analysis were conducted to estimate candidemia prevalence and identify patterns of *Candida* species in South-eastern Asia. Systematic electronic-databases literature search was performed on published studies recorded candidemia prevalence in South-Eastern Asia. Using meta-analysis of proportions, the overall pooled prevalences of candidemia by *Candida* (*C.*) *albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* were calculated as 28.4% (95% *CI* 24.9-31.8), 29.2% (95% *CI* 24.7-33.7), 19.1% (95% *CI* 14.8-23.4) and 14.0% (95% *CI* 10.4-17.5), respectively. Based on publication year and country, subgroup analyses were conducted on *Candida* species to determine heterogeneity source. The findings may not precisely reflect true candidemia prevalence in different countries. Therefore, it highlights continuous need to conduct prevalence studies, assess and monitor growing burden, control effect of potential risk factors and implement regional surveillance programs to prevent further rise.

KEYWORDS: *Candida* species; Candidemia; Bloodstream infections; Prevalence; South-Eastern Asia; Systematic review and meta-analysis

Summary

Question: What are the trends of *Candida* species causing bloodstream infections in South-Eastern Asia, and what is their prevalence?

Findings: This systematic review and meta-analysis of 38 studies estimates the pooled prevalence of candidemia caused by *Candida* (*C.*) *albicans* (28.4%), *C. tropicalis* (29.2%), *C. parapsilosis* (19.1%), and *C. glabrata* (14.0%) in South-Eastern Asia. The review highlights the need for continuous monitoring and surveillance programs to prevent further increases in candidemia.

Meaning: Candidemia is a significant public health concern in South-Eastern Asia, with *Candida* species being a major cause of bloodstream infections. Understanding the local trends, species distribution, and prevalence of candidemia is essential for implementing effective prevention and control strategies, especially in light of emerging drug-resistant strains.

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1. Introduction

Candida species are the causative agents of the majority of yeast infections in humans, especially bloodstream infections[1–7]. In the last two decades, they have been reported as one of the most common opportunistic pathogens and the fourth most common cause of bloodstream infections (BSIs) among hospitalized and immunocompromised patients worldwide[8–14]. *Candida* (*C.*) *albicans* has historically been the most common *Candida* species causing BSIs, recent studies have shown that *C. parapsilosis* is now the second most frequent species causing this type of infection worldwide, and its prevalence is increasing[15–17]. Therefore, this infection is now considered a significant global public health and economic concern[18–22]. In intensive care units (ICUs) around the world, most fungus-related systemic bloodstream infections are caused by the genus *Candida*, resulting in high mortality rates and high healthcare costs for governments and privately hospitalized patients[23–25]. Recently, the implementation of invasive monitoring and treatment techniques has escalated in ICUs, which eventually elevated the ratio of patients prone to fungal infections[26–29]. Although *C. albicans* is the most encountered species in invasive candidiasis, its predominance has decreased over the last two decades as the number of invasive infections caused by non-albicans *Candida* species has increased[23,30–35]. Among these, *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* complex, which consists of the three cryptic species: *C. parapsilosis* sensu stricto, *C. metapsilosis* and *C. orthopsilosis*, are of essential importance[8,23,36]. The emergence of non-albicans *Candida* species has been reported to cause a dramatic change in the spectrum of candidemia[37–40].

Candidemia is a life-threatening infection associated with high crude and attributable mortality rates[41–45], increased healthcare costs, and prolonged duration of hospitalization[46–51]. Bloodstream infections due to *Candida* cause significant mortality and morbidity worldwide, especially in ICUs and among immunocompromised patients[46,51]. Knowledge of recent local trends, species distribution and prevalence are essential for prevention and control strategies.

Despite the clinical and economic implications of fungal infections, exclusively candidemia, it is still poorly studied in some developing South-eastern Asia regions compared to European and American developed regions. Although fungal pathogens contribute a particular proportion of bloodstream infection aetiologies, they have achieved comparatively less epidemiological attention and awareness.

South-Eastern Asia is a region where the burden of fungal infections, including *Candida* species, is particularly high, and the emergence of drug-resistant strains of *Candida* has become a growing concern[52]. By identifying the risk factors associated with *C. parapsilosis* CRBSI, this systematic review will contribute to the existing knowledge on the epidemiology of *Candida* infections in South-Eastern Asia and help healthcare providers make evidence-based decisions for patient care. It will also identify any gaps in the current literature and highlight areas where further research is needed to better understand and prevent *Candida* infections in this region.

Therefore, it is of substantial significance to carry out a systematic review and meta-analysis to understand the great burden of candidemia in Southeast Asia. Accordingly, this systematic review and meta-analysis (SRMA) aim to survey the available data on the *Candida* species distribution in human bloodstream infections caused by the most common *Candida* species. This will be conducted by systematically retrieving and reviewing freely available data and generating an up-to-date comprehensive assessment of the burden of candidemia.

2. Materials and methods

2.1. Protocols and registration

Prior to conducting the systematic review, the study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and assigned the registration number CRD42023439497. To ensure the feasibility of the study and the availability of sufficient eligible studies, a formal search using specific keywords and eligibility criteria was conducted prior to registration with PROSPERO. This approach was taken to ensure that the study is conducted in accordance with established guidelines and to enhance the transparency and reproducibility of the results. A comprehensive protocol was approved before the search started, listing the databases to be searched, eligibility criteria, and other methodology details. The review was conducted according to the updated guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses[53]. Ethics approval was not required for this systematic review.

2.2. Literature review and search strategy

Prior to the study, a search was conducted in the PROSPERO[54] and database of abstracts of review of effects to ensure duplication of an existing or ongoing review project going on based on our study topic "*Candida* Bloodstream Infections (BSIs) in South-eastern Asia". The systematic review was conducted until 9th February by searching four electronic international databases comprising Google Scholar, PubMed, Scopus and ScienceDirect databases to collect studies on the prevalence of candidemia in South-eastern Asia. The search strategy was developed based on relevant keywords related to "*Candida parapsilosis*, bloodstream infections, and South-Eastern Asia". The search was limited to studies published in English. In addition, the reference lists of relevant articles, systematic reviews, and meta-analyses were screened for potential studies to be included in the review. The search was independently conducted by two reviewers, and any discrepancies were resolved by consensus or consultation with a third reviewer.

2.3. Inclusion and exclusion criteria

All observational studies whether cross-sectional or cohort studies that reported the prevalence of *Candida* bloodstream infections or candidiasis in South-eastern Asian countries (Brunei, Burma (Myanmar), Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand and Vietnam) were included in this SRMA. In addition, only articles in English language were included. There were no limits on the study period, study design, or place of publication. Studies that provided insufficient information, used a definition of candidemia that did not align with the operational definition of this study, did not report the prevalence of *Candida* bloodstream infections in Southeast Asia, or lacked access to the full text or sufficient data in the abstract, as well as studies published in languages other than English, were excluded.

2.4. Data management and study selection

In the beginning, all the references identified based on a systematic literature search are exported to Endnote X20 (Clarivate Analytics, London, UK) to be managed. Then, duplicate potential articles were removed by automatic strategy as well as manual search before the screening and assessment of the remaining articles according to title and abstract was independently done by two reviewers. After that, the full texts of potential records were downloaded and assessed for eligibility based on the inclusion and exclusion search criteria by two authors. Any disagreement or uncertainty was revealed by discussion and consensus.

2.5. Operational definitions

Candidemia was defined as at least one positive blood culture for *Candida* species isolated from patients with symptoms or signs of infection, whether isolated from the peripheral or central line.

2.6. Data extraction

The relevant data were extracted from eligible studies by two authors. This comprises screening the tittle, abstract and a full text review of the studies included to extract all the relevant data. A third author conducted an independent review of the results from the previous authors to ensure any misrepresentation of the data was identified and sorted out amicably. All the authors took precautions to minimize errors and ensure consistency in data extraction. The following data were extracted to a predesigned Excel spreadsheet: author name, year of publication, study period, study design, country, target population, sex, age range and groups (if available), setting (recruitment location), method of species detection, sample size, species identified, and their prevalence. Overall, the data of the studies recruited from various South-eastern Asian geographical locations were analysed.

2.7. Quality assessment

The risk of bias in all selected studies was independently assessed by two authors using the Joanna Briggs Institute critical appraisal checklist for prevalence studies[55]. For each article, the final score was determined as the proportion of 'yes' answers for nine items. Subsequently, the studies were categorized into "high risk of bias" (low quality) when the overall score was ≤49%, "moderate risk of bias" (moderate quality) for a score of 50%-69% and "low risk of bias" (high quality) if the score ≥70%. Disagreements between the reviewers were cleared up by discussion and verification[56,57].

2.8. Data analysis

The data entered in the Excel sheet was analysed using the *R* package and software. The proportions of the most important *Candida* species were calculated as the number of candidemia cases due to that species relative to the total number of candidemia cases using the meta prop command. Accordingly, the prevalence of candidemia due to the studied *Candida* species [at 95% confidence intervals (*CI*)] was estimated for each eligible study and subsequently for the South-eastern Asian countries by pooling the candidemia prevalence rates of all included studies using the random-effect model. Heterogeneity between the studies was evaluated by the I^2 statistics according to Cochran's *Q*-test. A cut-off value >75% of I^2 statistic indicated substantial heterogeneity[58,59], whilst a *P*-value of <0.05 was considered a significant degree of heterogeneity. Publication bias was tested graphically using a funnel plot and statistically by Egger's regression test.

2.9. Subgroup and sensitivity analysis

To explore the potential sources of heterogeneity, a subgroup analysis was conducted based on different subgroups: the publication

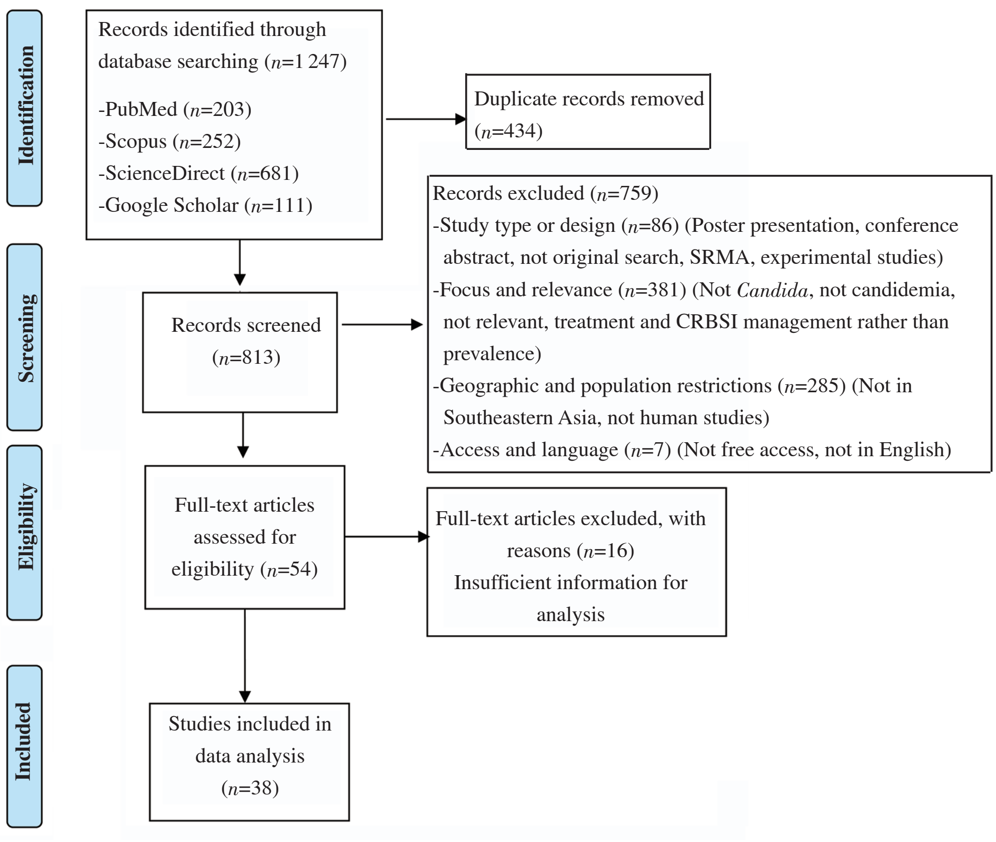

Figure 1. The PRISMA diagram showing the study selection process. SRMA: systematic review and meta-analysis.

year of study and country where the study was carried out using metaprop codes in meta and metafor packages of *R* (version 4.4.2) in *R* Studio (version 2.0). Data analysis and the creation of the plots were performed.

3. Results

3.1. Search results

We conducted an extensive and comprehensive systematic search of the electronic database and retrieved a total of 1 247 articles, of them 434 duplicate references were removed. As shown in Figure 1, the results of the complete overview of the literature search and records selection procedure were demonstrated. The title and/or abstract of the remaining 813 studies were assessed for inclusion, from which 54 were eligible for full-text screening. Finally, a total of 38 studies met the eligibility criteria and were included in this SRMA, from which 31 studies were for *C. albicans* candidemia prevalence, 28 for *C. tropicalis*, 27 for *C. parapsilosis* and 25 for *C. glabrata*.

3.2. Characteristics of included studies

The detailed characteristics of the 38 included studies are summarised in Table 1. Thirty-eight studies published between 1998 and 2022 met the inclusion criteria for candidemia prevalence. A total of 57 695 episodes of candidemia were identified and subjected to species identification. Fifteen (39.5%) of the studies were conducted in Malaysia, 10 (26.3%) in Thailand, 5 (13.1%) in Singapore, 3 (7.9%) in Indonesia, 2 (5.3%) each in the Philippines and Vietnam and 1 (2.6%) in Asia-pacific region. Based on the study designs conducted in the articles included, 44.7% (*n*=17) were cross-sectional studies, 42.1% (*n*=16) retrospective cohort and 13.2% (*n*=5) prospective cohort studies, from which two studies were laboratory-based surveillance. Of the 38 articles, 31 provided data on *C. albicans* candidemia, 28 for *C. tropicalis*, 27 for *C. parapsilosis*, 25 for *C. glabrata*, 15 for *C. krusei* and a lesser number of studies studied other less important *Candida* species. Meta-analysis was done for the four most important *Candida* species.

3.3. Prevalence of C. albicans candidemia

The pooled prevalence of candidemia due to *C. albicans* and the

Table 1. Detailed characteristics of 38 included studies.

Study ID	Reference	Study design	Country	Period of study	Inclusion age	Sample size	Species identified	Method of detection
1	Abd Aziz *et al*., 2020[60]	Cross-sectional study	Malaysia	From July 2017 to December 2018	NA	145	*Candida (C.) albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. dubliniensis*, *C. auris*, *C. krusei*, *C. orthopsilosis*, *C. duobushaemulonii*, *C. haemulonii*, *C. famata* and *C. lusitaniae*	VITEK® 2 compact automated system with VITEK® 2 card (ID-YST card) and VITEK® MS (MALDI-TOFF MS)
2	Amran *et al*., 2011[61]	Cross-sectional study	Malaysia	From January 2006 to December 2008	NA	159	*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. guilliermondii*, *C. famata*, *C. inconspicua*, *C. valida*, and *C. lusitaniae*	Conventional and commercial biochemical identification kit (API 20C AUX)
3	Bac *et al*., 2019[62]	Cross-sectional study	Vietnam	From May 2013 to May 2015	NA	93	*C. tropicalis*, *C. albicans*/dubliniensis, *C. parapsilosis*, *C. glabrata*, *C. esorugosa*, *C. krusei*	Germ tube test and PCR-RFLP
4	Batac and Denning, 2017[63]	Cross-sectional study	Philippines	In 2016	NA	1 968	*Candida* spp.	Using the methodology of the LIFE program
5	Boonsilp *et al*., 2021[64]	Cross-sectional study	Thailand	From June 2018 to July 2019	0.03-99 years	54	*C. tropicalis*, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. nivariensis*, *C. guilliermondii*, *C. caribbica*	MALDI-TOF-MS and ITS sequencing
6	Boonyasiri *et al*., 2013[65]	Retrospective (cohort) study	Thailand	From June 2006 to May 2009	Older than 15 years	147	*C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, others	Germ tube formation, Candi-select test and Rapid IDTM Yeast Plus System
7	Chai *et al*., 2007 [66]	Retrospective (cohort) study	Singapore	From January 2003 to April 2004	1-80 years	52	*C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. pelliculosa*	Carbohydrate fermentation, cornmeal morphology, appearance on CHROM-agar, assimilation patterns in the API 20C AUX and RAPD
8	Chayakulkeeree and Denning, 2017[67]	Cross-sectional study	Thailand	In 2013	All	8 650	*Candida* spp.	Using methodology by LIFE program
9	Chhabra *et al*., 2012[68]	Cross-sectional study	Malaysia	NA	NA	44	*C. albicans*, non-albicans *Candida*	Biochemical, ITS sequencing, RAPD
10	Choudhury, 2019 [69]	Cross-sectional study	Singapore	From February 2014 to August 2017	61-79 years	163	*C. glabrata*, *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. orthopsilosis*, *P. kudriavzevii*, *C. haemulonii*, *M. guilliermondii*, *C. dubliniensis*, *C. duobushaemulonii*, *C. nivariensis*, *C. metapsilosis*	NA
11	Cucunawangsih, *et al*., 2021[70]	Retrospective (cohort) study	Indonesia	From January 2011 to December 2019	0-40 days	132	*Candida* spp.	Gram stain, CHROMagar for Candida, VITEX® 2 Compact
12	Duong *et al*., 2022[71]	Cross-sectional study	Vietnam	In 2020	NA	11 291	*Candida* spp.	NA
13	Foongladda *et al*., 2004[72]	Cross-sectional study	Thailand	From 1999 to 2002	NA	202	*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei*	NA
14	Hamid *et al*., 2012[73]	Cross-sectional study	Malaysia	From January 2008 to December 2010	All	151	*C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. pelliculosa*, *C. sake*, *C. krusei*, *C. globosa*, *C. melibiosica*, *C. famata*	ID32C carbohydrate assimilation tests
15	Itable *et al*., 2014 [74]	Prospective (cohort) study	Philippines	From January 2012 to December 2012	NA	39	*C. tropicalis*, *C. parapsilosis*, *C. albicans*, others	Phenotypic identification ID-YST, VITEK, and morphology on cornmeal agar
16	Jantarabenjakul *et al*., 2021[75]	Retrospective (cohort) study	Thailand	From 2003 to 2019	Birth to 15 years of age	114	*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, other unspecified species	NA
17	Jutiamornlerd *et al*., 2011[76]	Retrospective (cohort) study	Thailand	From January 2004 to December 2009	1-98 years	206	*C. albicans*, non-albicans *Candida*	NA
18	Karunakaran *et al*., 2007[77]	Retrospective (cohort) study	Malaysia	From January to December 2004	NA	33	*C. tropicalis*, *C. albicans*, *C. parapsilosis*, others	Standard microbiological tests, the API system
19	Khumdee *et al*., 2022[78]	Cross-sectional study	Thailand	From January 2013 to March 2016	1-92 years	123	*C. tropicalis*, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. rugosa*, *C. intermedia*, *C. haemulonii*, *C. nivaniensis*	MALDI-TOF-MS
20	Mohamed *et al*., 2018[30]	Retrospective (cohort) study	Malaysia	From 1st January 2014 to 31st December 2015	All	73	*C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, *C. famata*, *C. rugosa*	Germ tube technique, inoculation on chromogenic agar and API 20C AUX biochemical identification kit
21	Naranong *et al*., 2020[79]	Prospective (cohort) study	Thailand	From January 1, 2015 to December 31, 2015	More than 15 years	52	*C. albicans*, non-albicans *Candida*	Colony morphology on chromogenic agar, carbohydrate assimilation characteristics, or a VITEK Yeast Biochemical Card

Table 1. Continued.

Study ID	Reference	Study design	Country	Period of study	Inclusion age	Sample size	Species identified	Method of detection
22	Ng *et al*., 2015[80]	Prospective (cohort) laboratory-based surveillance	Malaysia	From 2000 to 2013	NA	1 716	*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, others	Conventional (gram stain, urease, germ tube production, culture, microscopic examination and carbohydrate assimilation test, API biochemical test) and molecular (PCR amplification and ITS sequencing)
23	Ng *et al*., 1998[81]	Cross-sectional study	Malaysia	NA	NA	73	*C. parapsilosis*, *C. tropicalis*; *C. albicans*, *C. glabrata*, *C. rugosa*, *C. glabrata* and *C. krusei*	Gram stain, germ tube test, hyphal/ pseudohyphae and chlamydoconidia production, carbohydrate assimilation test using ten carbohydrates (glucose, sucrose, trehalose, cellobiose, arabinose, galactose, mannitol, raffinose, lactose and maltose)
24	Ngamchokwathana *et al*., 2021[82]	Retrospective (cohort) study	Thailand	From January 2016 to December 2017	NA	156	*C. tropicalis*, *C. albicans*, *C. glabrata*, *C. parapsilosis*	Biochemical characteristics using chromogenic medium and RapID™ Yeast Plus Panel
25	Rahman *et al*., 2008[83]	Retrospective (cohort) laboratory-based study	Malaysia	From January 2001 to June 2006	NA	788	*C. parapsilosis*, *C. albicans*, *C. tropicalis*, *C. krusei*, *C. glabrata*	Biochemical tests, sugar assimilation, germ tubes test, cornmeal tween agar and commercialized identification system, API-32C system
26	Santhanam *et al*., 2013[84]	Cross-sectional study	Malaysia	From January to July 2009	From 5 days till 86 years	56	*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*	Germ tube test, ID 32C
27	Subramaniam *et al*., 2021[85]	Retrospective (cohort) study	Malaysia	From January 2016 to December 2017	From 0 to less than 13 years old	18	*C. parapsilosis*, *C. albicans*, *C. glabrata*, *C. tropicalis*, others	Gram stain, colony characteristics, biochemical reactions, antimicrobial resistance patterns, growth requirements, and rapid latex system without using the API or VITEK systems
28	Supatharawanich *et al*., 2021[86]	Retrospective (cohort) study	Thailand	From 2009 to 2019	0.3-16.0 years	26	*C. tropicalis*, *C. albicans*, *C. krusei*, others	NA
29	Tajuddin, 2018[31]	Retrospective (cohort) study	Malaysia	From January 2010 to December 2014	age ⩾18 years old	134	*C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. albicans*, *C. krusei*, *C. guillermondii*, *C. rugosa*, *C. dubliniensis*, unspecified *Candida* spp.	Biochemical tests, sugar assimilation, germ tubes test, cornmeal tween agar and also commercialized identification system, API-32C system
30	Tan *et al*., 2016 [87]	Prospective (cohort) study	Asia-Pacific region	From 2013 to 2015	NA	661	*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. guilliermondii*, *C. pelliculosa*, *C. rugosa*, *C. krusei*, *C. dubliniensis*, others	Morphology and colony colours on CHROMagar, VITEK system, morphology studies on cornmeal agar with Tween-80, MALDI-TOF VITEK MS ID, ITS sequencing
31	Tan *et al*., 2008 [88]	Retrospective (cohort) study	Singapore	From October 2004 to December 2006	NA	279	*C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. dubliniensis*, *C. krusei*, *C. guilliermondii*, *C. rugosa*, others	API 20C AUX and morphology expression on cornmeal agar with Tween 80 and morphology on CHROMagar *Candida* media, VITEK 2 Compact
32	Teo *et al*., 2017 [89]	Retrospective (cohort) surveillance study	Singapore	From July 2012 to December 2015	at least 21 years old	261	*C. glabrata*, *C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. dubliniensis*, *C. krusei*, *C. guilliermondii*, *C. kefyr*, *C. haemulonis* and *C. pseudohaemulonii*	MALDI Biotyper, morphology studies on cornmeal Tween 80 agar, and API 20C AUX
33	Tzar *et al*., 2013 [90]	Cross-sectional study	Malaysia	NA	All	74	*Candida* spp.	CHROMagar *Candida* media, commercially-prepared carbohydrate assimilation tests, ID 32C
34	Velayuthan *et al*., 2018[91]	Cross-sectional study	Malaysia	NA	NA	1 533	*Candida* spp.	Using methodology of the Leading International Fungal Education (LIFE) program
35	Wahyuningsih *et al*., 2021[92]	Cross-sectional study	Indonesia	NA	NA	26 710	*Candida* spp.	NA
36	Wiwing and Cucunawangsih, 2020[93]	Retrospective (cohort) laboratory-based study	Indonesia	From January 2010 to December 2018	NA	72	*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, others	Using guideline from Clinical and Laboratory Standard Institute (CLSI)
37	Yamin *et al*., 2020 [94]	Retrospective (cohort) study	Malaysia	From January 2001 to December 2018	NA	1 175	*C. parapsilosis*, *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. guilliermondii*, *C. rugosa*, *C. famata*, *C. krusei*, *C. dubliniensis*, *C. lusitaniae*, *C. lipolytica*, *C. pelliculosa*, *C. haemulonii*, *C. kefyr*, *C. utilis* and *C. inconspicua*, other unidentified *Candida* spp.	Commercially available identification systems, API 20C AUX®, ID 32C® biochemical kit, VITEK® system and ITS sequencing
38	Yang *et al*., 2003 [95]	Prospective (cohort) study	Singapore	From 1 July to 30 December 2001	NA	72	*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. famata*, *C. krusei*, *C. guilliermondii*	Germ tube production, API *Candida* and API 20C AUX, morphology on cornmeal Tween 80 agar, multiplex-PCR method

Table 2. Pooled prevalence of candidemia due to main *Candida* species in different subgroups.

Subgroups		Prevalence of candidemia, % (95% *CIs*)	Number of studies analysed	Total number of subjects	Heterogeneity I^2	Heterogeneity *P*-value	Publication bias, Egger's test (*P*-value)
Candida albicans							
Total		28.4 (24.9-31.8)	31	7 337	88	<0.01	0.09
Publication year	Before 2016	31.4 (26.2-36.6)	15	4 017	91	<0.01	0.111 3
	2016-2022	25.6 (21.3-29.9)	16	3 320	84	<0.01	0.426 4
Country	Malaysia	25.9 (20.5-31.2)	13	4 565	88	<0.01	0.390 9
	Thailand	32.0 (24.0-40.0)	9	1 080	90	<0.01	NA
	Singapore	29.3 (23.4-35.2)	5	827	72	<0.01	NA
	Asia-Pacific region	33.1 (29.5-36.9)	1	661	NA	NA	NA
	Indonesia	26.4 (16.7-38.1)	1	72	NA	NA	NA
	Philippines	28.2 (15.0-44.9)	1	39	NA	NA	NA
	Vietnam	19.4 (11.9-28.9)	1	93	NA	NA	NA
Non-albicans *Candida*							
Total		71.3 (68.1-74.5)	31	7 337	86	<0.01	0.062 6
Publication year	Before 2016	68.6 (63.4-73.8)	15	4 017	91	<0.01	0.111 3
	2016-2022	73.8 (70.5-77.1)	16	3 320	77	<0.01	0.314 4
Country	Malaysia	74.4 (69.2-79.6)	13	4 565	87	<0.01	0.412 7
	Thailand	66.4 (60.6-72.2)	9	1 080	73	<0.01	NA
	Singapore	70.7 (64.8-76.6)	5	827	72	<0.01	NA
	Asia-Pacific region	66.9 (63.1-70.5)	1	661	NA	NA	NA
	Indonesia	73.6 (61.9-83.3)	1	72	NA	NA	NA
	Philippines	71.8 (55.1-85.0)	1	39	NA	NA	NA
	Vietnam	80.6 (71.1-88.1)	1	93	NA	NA	NA
Candida tropicalis							
Total		29.2 (24.7-33.7)	28	7 035	97	<0.01	0.223 7
Publication year	Before 2016	29.3 (22.2-36.5)	13	3 767	98	<0.01	0.557 0
	2016-2022	29.1 (23.3-34.9)	15	3 268	90	<0.01	0.112 2
Country	Malaysia	26.0 (18.5-33.6)	12	4 521	98	<0.01	0.661
	Thailand	33.0 (23.3-42.7)	7	822	88	<0.01	NA
	Singapore	26.3 (21.8-30.9)	5	827	52	0.08	NA
	Asia-Pacific region	33.0 (29.4-36.7)	1	661	NA	NA	NA
	Indonesia	22.2 (13.3-33.6)	1	72	NA	NA	NA
	Philippines	35.9 (21.2-52.8)	1	39	NA	NA	NA
	Vietnam	50.5 (40.0-61.1)	1	93	NA	NA	NA
Candida parapsilosis							
Total		19.1 (14.8-23.4)	27	7 009	96	<0.01	0.600 6
Publication year	Before 2016	21.1 (13.7-28.6)	13	3 767	97	<0.01	0.592 5
	2016-2022	17.2 (12.4-21.9)	14	3 242	93	<0.01	0.997 6
Country	Malaysia	25.6 (19.2-32.0)	12	4 521	90	<0.01	0.184 6
	Thailand	9.4 (3.7-15.1)	6	796	79	<0.01	NA
	Singapore	12.6 (9.6-15.7)	5	827	43	0.13	NA
	Asia-Pacific region	14.8 (12.2-17.8)	1	661	NA	NA	NA
	Indonesia	34.7 (23.9-46.9)	1	72	NA	NA	NA
	Philippines	30.8 (17.0-47.6)	1	39	NA	NA	NA
	Vietnam	17.2 (10.2-26.4)	1	93	NA	NA	NA
Candida glabrata							
Total		14.0 (10.4-17.5)	25	6 937	94	<0.01	0.000 5
Publication year	Before 2016	11.5 (7.4-15.6)	11	3 695	94	<0.01	0.043 3
	2016-2022	15.8 (10.4-21.2)	14	3 242	94	<0.01	0.016 6
Country	Malaysia	9.7 (6.0-13.4)	11	4 488	92	<0.01	0.104 4
	Thailand	14.2 (7.6-20.7)	6	796	90	<0.01	NA
	Singapore	24.5 (15.6-33.4)	5	827	89	<0.01	NA
	Asia-Pacific region	15.3 (12.6-18.3)	1	661	NA	NA	NA
	Indonesia	8.3 (3.1-17.3)	1	72	NA	NA	NA
	Vietnam	6.5 (2.4-13.5)	1	93	NA	NA	NA

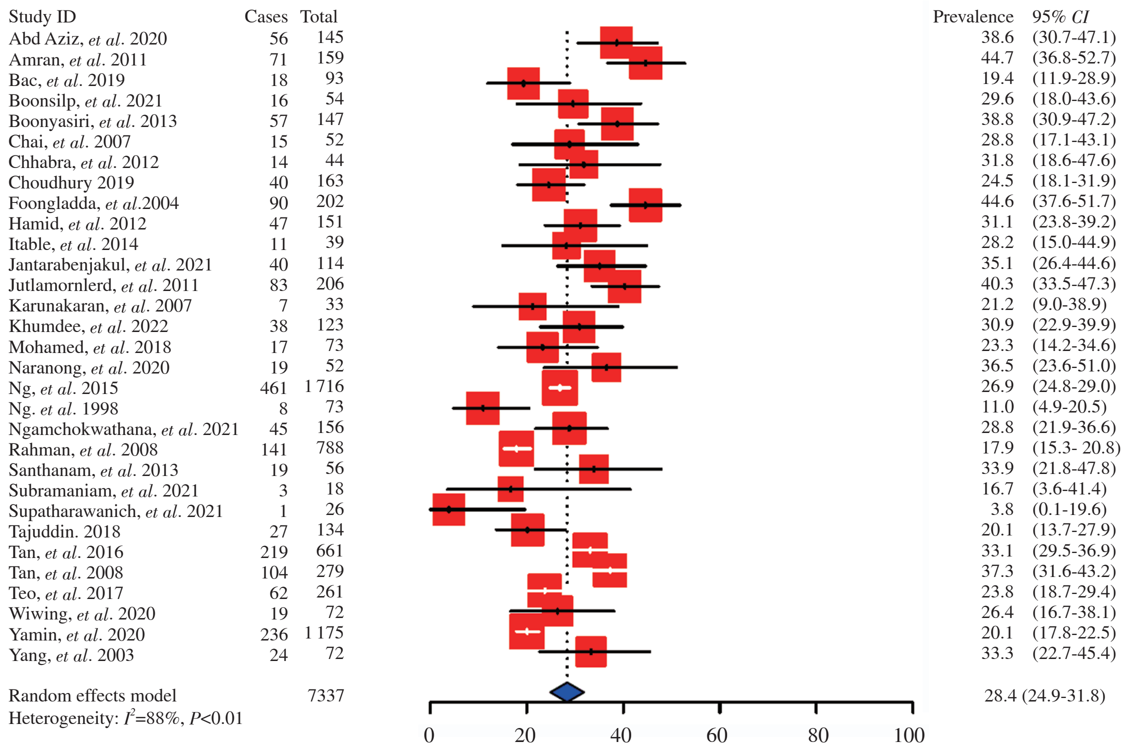

Figure 2. Forest plot representing the pooled prevalence of *Candida albicans* candidemia.

results of subgroup analysis are shown in Table 2. The results of the 31 studies included in this meta-analysis show a varied picture of *C. albicans* candidemia rates, ranging from 3.8% to 44.7%. In twenty-six (83.9%) studies, *C. albicans* candidemia rates were higher than 20%, while only in one study, the *C. albicans* candidemia rate was less than 5% of the identified candidemia episodes. The pooled candidemia rate due to *C. albicans* across the 31 observational studies was estimated to be 28.4% (95% *CI* 24.9-31.8) (Figure 2). Significant heterogeneity was observed across all the included studies (I^2=88%, P<0.01). Accordingly, subgroup analysis based on publication year and country was done to further investigate the potential sources of heterogeneity. The *C. albicans* candidemia has fallen obviously in the last seven years, from 31.4% (95% *CI* 26.2-36.6) before 2016 to 25.6% (95% *CI* 21.3-29.9) in the period between 2016 and 2022.

According to the meta-analysis, one study held in Asia-pacific regions had the highest prevalence of *C. albicans* candidemia at 33.1% (95% *CI* 29.5-36.9), followed by Thailand at 32.0% (95% *CI* 24.0-40.0), then Singapore at 29.3% (95% *CI* 23.4-35.2), while Malaysia and Vietnam had the lowest frequency of *C. albicans* candidemia at 25.9% (95% *CI* 20.5-31.2) and 19.4% (95% *CI* 11.9-28.9) respectively.

3.4. Prevalence of C. tropicalis candidemia

The pooled prevalence of candidemia due to *C. tropicalis* and the results of subgroup analysis, are shown in Table 2. The results of the 28 studies included in this meta-analysis show a different picture of *C. tropicalis* candidemia rates, ranging from 8.5% to 50.5%. In 21 (75.0%) studies, the prevalence of *C. tropicalis* candidemia were more than 20%, while one study showed the prevalence of *C. tropicalis* candidemia of less than 10% of all candidemia cases identified. The pooled candidemia rate due to *C. tropicalis* across the 28 observational studies was estimated to be 29.2% (95% *CI* 24.7-33.7) (Figure 3A). Significant heterogeneity was observed across all the included studies (I^2=97%, P<0.01). Accordingly, subgroup analysis based on publication year and country was accomplished to further investigate the potential sources of heterogeneity. The *C. tropicalis* candidemia rates of 29.3% (95% *CI* 22.2-36.5) and 29.1% (95% *CI* 23.3-34.9) have been reported before and after 2016 respectively, indicating that the publication year was not the reason behind the heterogeneity of *C. tropicalis* candidemia prevalence.

Therefore, subgrouping based on the country level was performed, as shown in Table 2. As a result, the highest prevalence of *C. tropicalis* candidemia was reported in Vietnam at 50.5% (95% *CI*

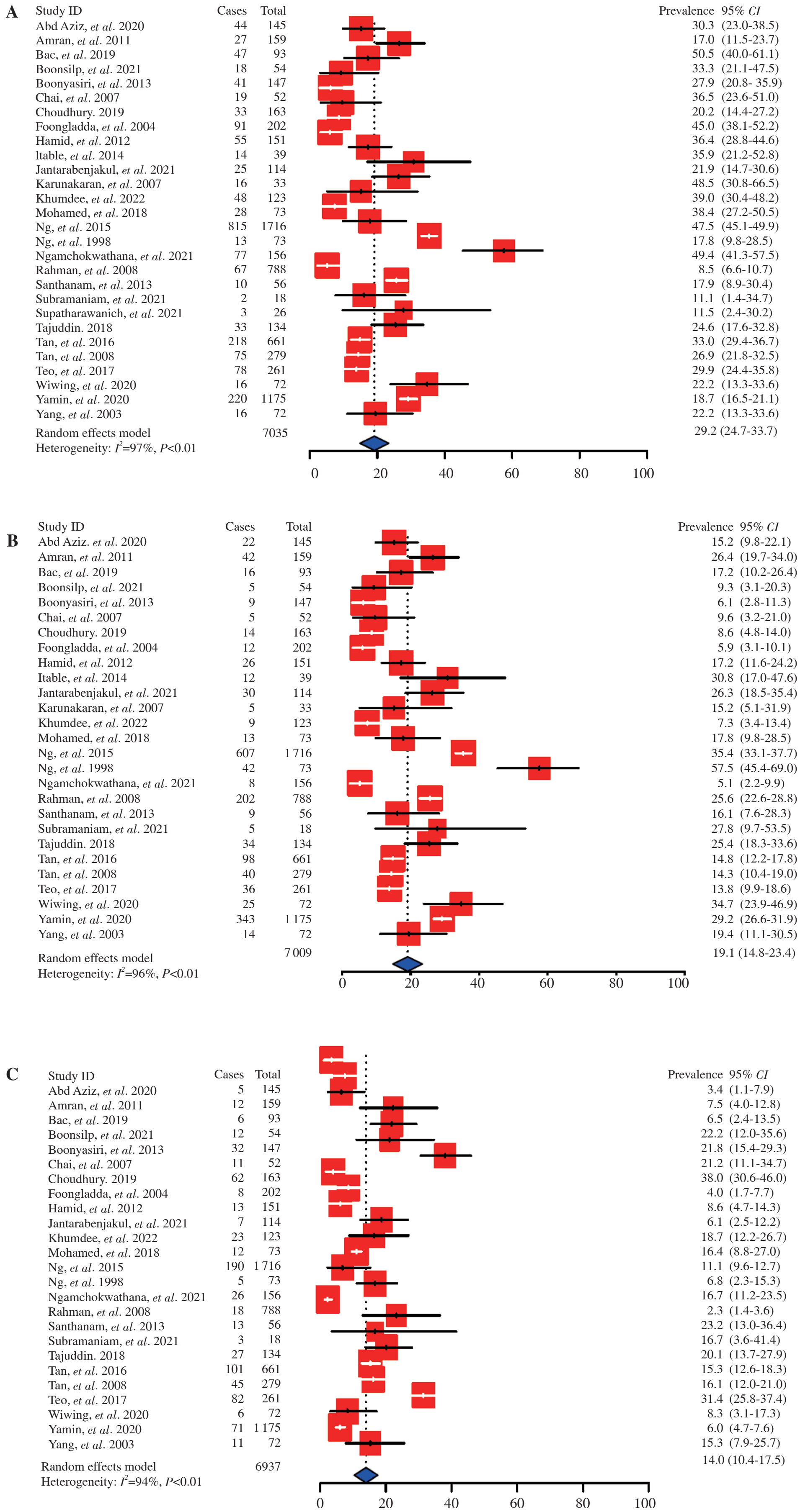

Figure 3. Forest plot representing the pooled prevalence of *Candida tropicalis* candidemia (A), *Candida parapsilosis* candidemia (B) and *Candida glabrata* candidemia (C).

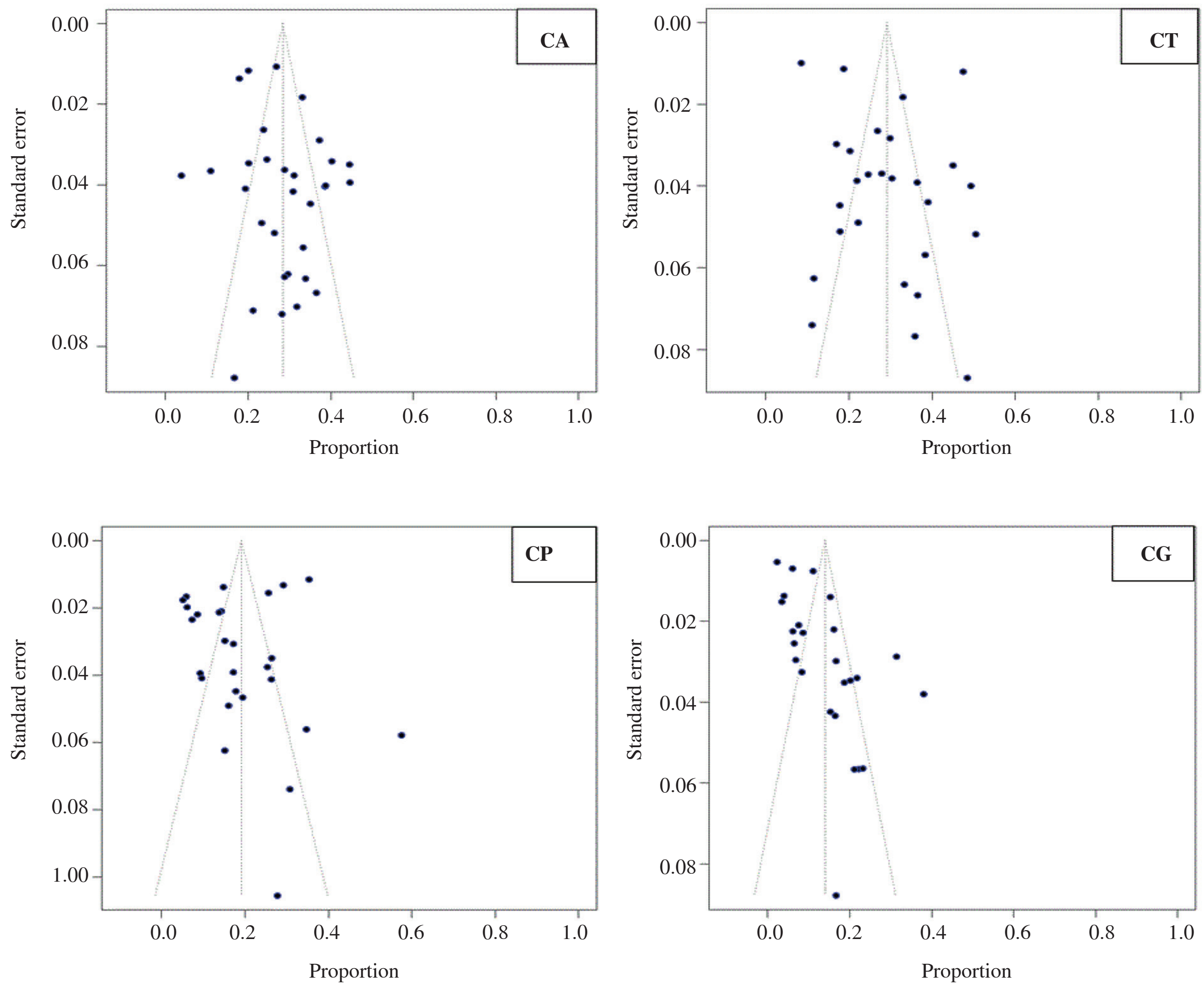

Figure 4. Funnel plots analysing publication bias among studies evaluated. CA: *Candida albicans*, CT: *Candida tropicalis*, CP: *Candida parapsilosis*, CG: *Candida glabrata*.

40.0-61.1), followed by Philippines at 35.9% (95% *CI* 21.2-52.8%), while the lowest rate of *C. tropicalis* candidemia was in Indonesia at 22.2% (95% *CI* 13.3-33.6). Interestingly, Malaysia and Singapore have almost equal *C. tropicalis* candidemia pooled prevalence (26.0% and 26.3% respectively).

3.5. Prevalence of *C. parapsilosis* candidemia

The pooled prevalence of candidemia due to *C. parapsilosis* and the results of subgroup analysis are shown in Table 2. The 27 studies included in this SRMA show remarkable differences in the prevalence of *C. parapsilosis* candidemia, ranging from 5.1% to 57.5%. In ten (37.0%) studies, the *C. parapsilosis* candidemia rates were above 20% of all candidemia cases identified. In comparison, the highest candidemia rate as a result of *C. parapsilosis* was 57.5% (95% *CI* 45.4-69.0) of the tested candidemia episodes. The pooled prevalence of *C. parapsilosis* candidemia between the 27 observational studies was estimated to be 19.1% (95% *CI* 14.8-23.4) (Figure 3B). Significant heterogeneity was observed across all the included studies (I^2=96%, P<0.01). Consequently, subgroup analysis according to the year of publication and the country where the study conducted were needed for further investigation of the potential sources of heterogeneity. The *C. parapsilosis* candidemia rate has decreased dramatically in the last seven years, from 21.1% (95% *CI* 13.7-28.6) before 2016 to 17.2% (95% *CI* 12.4-21.9) between 2016 and 2022.

Based on the meta-analysis, subgroup analysis according to country of the study revealed that Indonesia had the highest prevalence of *C. parapsilosis* candidemia at 34.7% (95% *CI* 23.9-46.9), followed by Philippines at 30.8% (95% *CI* 17.0-47.6), while Thailand had the lowest frequency of *C. parapsilosis* candidemia at 9.4% (95% *CI* 3.7-15.1). Based on the country level (Table 2), Malaysia had a midway prevalence rate of *C. parapsilosis* candidemia at 25.6% (95% *CI* 19.2-32.0), while Vietnam, Asia-pacific region and Singapore reported lower *C. parapsilosis* candidemia prevalence at 17.2% (95% *CI* 10.2-26.4), 14.8% (95% *CI* 12.2-17.8) and 12.6% (95% *CI* 9.6-15.7) respectively.

3.6. Prevalence of C. glabrata candidemia

The pooled prevalence of *C. glabrata* candidemia and the results of subgroup analysis, are shown in Table 2. The results of the 25 studies included in this SRMA present a distinctive view of *C. glabrata* candidemia rates, ranging from 2.3% to 38.0%. In seven (28.0%) studies, the prevalence of candidemia due to *C. glabrata* exceeded 20% of all candidemia cases detected, while in ten (40.0%) other studies, *C. glabrata* candidemia rates were under 10% of all candidemia episodes. The pooled candidemia rate of *C. glabrata* across the 25 observational studies was estimated to be 14.0% (95% *CI* 10.4-17.5) (Figure 3C). Significant heterogeneity was observed across all the included studies (I^2=94%, P<0.01). Due to the importance of these aforementioned findings, the subgroup analysis based on the year of publication and the country of the study was established to further investigate the potential sources of heterogeneity. The *C. glabrata* candidemia rate has risen clearly in the last seven years, from 11.5% (7.4%-15.6%) before 2016 to 15.8% (10.4%-21.2%) between (2016-2022).

Notably, there were remarkable differences in *C. glabrata* candidemia rate obtained with country subgroup analysis. A dramatically high overall estimate was observed in Singapore (24.5%; 95% *CI* 15.6-33.4) as shown in Table 2, while the lowest *C. glabrata* candidemia prevalence was reported in Vietnam and Indonesia at 6.5% and 8.3% respectively, followed by Malaysia (9.7%, 95% *CI* 6.0-13.4). Studies in Thailand reported a moderate pooled prevalence of 14.2% (95% *CI* 7.6-20.7).

3.7. Quality assessment and publication bias

In summary, 34 (89.5%) of the studies had a low risk of bias, whilst only 4 (10.5%) had a moderate risk of bias. Visual assessment of the symmetrical and asymmetrical funnel plots (Figure 4) revealed the absence and presence of publication bias, respectively. This was statistically confirmed by the Egger's test for *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* (*P* value=0.090 0, 0.223 7, 0.600 6 and 0.000 5, respectively).

4. Discussion

Bloodstream infections caused by nosocomial pathogens such as *Candida* species, including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata* and *C. krusei* have emerged worldwide[95–97]. In addition, there is gradual increase in invasive fungal infections in healthcare settings as a result of the widespread of broad-spectrum antibiotics, immunosuppressive drugs, and chemotherapy, increased organ transplantation, application of medical support technology, the extension of human life, as well as the increase in the prevalence of acquired immune deficiency syndrome[26,98–104].

Here, we conducted a SRMA to present the prevalence of candidemia caused by four main *Candida* species in South-eastern Asian countries by synthesizing data published to date on the prevalence of candidemia and species distribution and provide a point of reference for subsequent studies. The findings of this SRMA were generated by pooling eligible data on the prevalence of different *Candida* species as a causative agent of bloodstream infections reported in 38 published studies. In the present SRMA, data concerning the prevalence of *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* candidemia are available and sub-grouped based on the study publication year and country of the study. The increasing number of nosocomial *Candida* bloodstream infections has raised concerns about conducting species identification by conventional and/or molecular tests to optimize clinical treatments.

A total of 31 studies were included, from which the pooled estimate revealed that 28.4% (95% *CI* 24.9-31.8) of all candidemia cases were due to *C. albicans*, 31.4% of cases before 2016 and 25.6% of the cases from 2016 to 2022. These studies were conducted in six different countries (Malaysia, Vietnam, Thailand, Singapore, Philippines, and Indonesia) from the South-eastern Asia region. Based on the available literature, Vietnam has the lowest prevalence (19.4%; 95% *CI* 11.9-28.9). On the other hand, Thailand has the highest prevalence (32.0%; 95% *CI* 24.0-40.0). Variations could be seen between and across countries. For instance, although Thailand has the highest prevalence of *C. albicans* candidemia in most of the studies, however, one of studies showed a dramatically lower prevalence (3.8%). It is unclear whether this difference in relative prevalence is the result of different sample sizes and different geographical regions or both.

In addition, *C. tropicalis* candidemia prevalence was determined among 28 studies, in which 29.2% (95% *CI* 24.7-33.7) of candidemia cases were due to *C. tropicalis*. The pooled prevalence of *C. tropicalis* was almost the same before and after 2016. The highest *C. tropicalis* candidemia prevalence was reported in Vietnam at 50.5% (95% *CI* 40.0-61.1), while the lowest was in Indonesia at 22.2% (95% *CI* 13.3-33.6). Philippine, Thailand, Singapore and Malaysia revealed descending order of prevalence values of *C. tropicalis* candidemia between Vietnam and Indonesia prevalence values.

In this study, we also investigated the prevalence of *C. parapsilosis* candidemia from a total of 27 studies, from which the pooled estimate showed that 19.1% (95% *CI* 14.8-23.4) of candidemia cases were due to *C. parapsilosis*, 21.1% of cases before 2016 has been due to *C. parapsilosis*, while 17.2% of cases were due to *C. parapsilosis* between 2016 and 2022. The range of prevalence of *C. parapsilosis* among the six countries was from 5.1% to 57.5%. Thailand has the lowest *C. parapsilosis* candidemia prevalence (except in one study with a relatively high prevalence), while Indonesia has the highest. In Malaysia, a dramatic variation in prevalence values has been observed from different studies ranging from 15.2% to 57.5%.

Similarly, *C. glabrata* candidemia prevalence was estimated among 25 studies, in which 14.0% (95% *CI* 10.4-17.5) of candidemia cases were due to *C. glabrata*. The pooled prevalence of *C. glabrata* was not the same before and after 2016, with 11.5% of cases before 2016 and 15.8% of the cases from 2016 to 2022. The highest candidemia prevalence due to *C. glabrata* was reported in Singapore (24.5%; 95% *CI* 15.6-33.4), while the lowest was in Vietnam and Indonesia (6.5% and 8.3%, respectively). In Thailand and Malaysia, the prevalence of *C. glabrata* candidemia was interestingly variable among studies conducted in each, which may be due to different sample sizes and/or different recruitment settings.

Considering the period when the studies were conducted, for those before 2016, the prevalence of *C. albicans* was the highest, followed by *C. tropicalis*, then *C. parapsilosis*, while the prevalence of *C. glabrata* was the lowest. A slightly different pattern of *Candida* species prevalence was found in the period from 2016 to 2022, with *C. tropicalis* contributed to the highest prevalence, followed by *C. albicans*. This finding shows a steady decrease in the prevalence of *C. albicans* leading to replacing the first place with *C. tropicalis* in the last seven years compared to studies conducted before 2016, pointing fingers at the emerging importance of non-albicans *Candida* species. *C. tropicalis* is associated with significantly higher mortality rates from invasive diseases, exceeding 50%, compared to other *Candida* species such as *C. albicans*. This heightened virulence underscores its rising prominence as a major cause of invasive candidiasis. Furthermore, the emergence of azole resistance among *C. tropicalis* isolates, particularly in the Asia-Pacific region, has significantly complicated treatment regimens, contributing to the survival of resistant strains and posing a growing challenge to effective management[105]. On the other hand, despite the notable increase in *C. glabrata* prevalence and substantial decrease in *C. parapsilosis* prevalence, *C. parapsilosis* and *C. glabrata* remained the third and the fourth most encountered *Candida* species respectively all over time, a situation may be changed in coming years. However, regardless of the high rate of *C. albicans* in many countries in south-east Asia, non-albicans *Candida* species emerge as an important nosocomial pathogen that is worth our concern and should not be neglected, especially with the emergence of antifungal resistance because of the antifungal resistant precursors that might accumulate in the developing country settings.

Based on country subgrouping, in Malaysia, the pooled prevalence of *C. albicans*, *C. tropicalis* and *C. parapsilosis* were almost the same (25.9%, 26.0% and 25.6%, respectively), while *C. glabrata* was much lower (9.7%). In a single study in Vietnam, the prevalence of *C. tropicalis* was severely high (50.5%), the prevalence of *C. albicans* and *C. parapsilosis* were midway (19.4% and 17.2% respectively), and the prevalence of *C. glabrata* was the lowest (6.5%). In Thailand, the top two higher *Candida* species pooled prevalence were *C. tropicalis* and *C. albicans* (33.0% and 32.0% respectively, while the pooled prevalence of *C. parapsilosis* was very low (9.4%). In Singapore, the highest pooled prevalence was due to *C. albicans* (29.3%), followed by *C. tropicalis* (26.3%), then *C. glabrata* (24.5%), and *C. parapsilosis* was at the end (12.6%). One study in Philippines revealed that the descending order of Candidemia prevalence was *C. tropicalis*, *C. parapsilosis* then *C. albicans* at 35.9%, 30.8%, then 28.2% respectively. However, the *C. glabrata* prevalence was not reported there. Interestingly, in Indonesia, *C. parapsilosis* contributed the highest prevalence (34.7%), *C. albicans* and *C. tropicalis* in the middle (26.4 and 22.2% respectively), but *C. glabrata* was rarely encountered (8.3%). This pattern highlights how candidemia rates differ across countries, influenced by factors such as geographical location, healthcare practices, and population demographics.

Consequently, different scenarios of *Candida* species distribution and prevalence of candidemia were concluded if countries were compared. Hence, it is recommended to monitor the prevalence of bloodstream infections caused by different *Candida* species nationally in different countries to determine the most common *Candida* species for each country, because the current view might be changed if more studies are carried out locally. Therefore, we recommend extended surveillance as well as additional studies with a large and systematic sample collection from various geographical regions to be conducted across the world.

Finally, a key strength of this SRMA is to provide a comprehensive estimation of candidemia prevalence over several countries or even broader regions in Asia and enable researchers to compare results among them. However, it had several limitations. First, the included studies did not encompass all the countries of the South-eastern

Asian region such as Brunei, Burma (Myanmar), Cambodia, Timor-Leste, and Laos, and only a limited number of representative studies in the same country were analysed, so the estimated prevalence might not fully represent the prevalence for each county. Second, substantial heterogeneity was observed in the included studies, although this observation is common in meta-analyses on estimating prevalence. Finally, the potential effect of age, sex, socioeconomic status, and lifestyle of the included patients on the prevalence of candidemia could not be analysed because of the unavailability of such data in several included studies.

Conflict of interest statement

All authors declared no conflict of interest.

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Authors´ contributions

Conceptualization, D.Y., A.W., design D.Y, K.H., literature search D.Y., M.G., data acquisition, A.I., A.W., data analysis D.Y., M.G., statistical analysis, D.Y., M.G., manuscript preparation, D.Y., M.G., K.H., manuscript editing and manuscript review A.I., A.W., supervision, A.W.

References

[1] Firacative C. Invasive fungal disease in humans: Are we aware of the real impact? *Mem Inst Oswaldo Cruz* 2020; **115**: e200430. doi: 10.1590/0074-02760200430.

[2] Pfaller MA, Castanheira M, Messer SA, Moet GJ, Jones RN. Variation in *Candida* spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: Report from the SENTRY Antimicrobial Surveillance Program (2008-2009). *Diagn Microbiol Infect Dis* 2010; **68**(3): 278-283.

[3] Kauffman CA. Fungal infections. In: *Infectious disease in the aging*. Totowa: Humana Press; 2009, p. 347-66.

[4] Garber G. An overview of fungal infections. *Drugs* 2001; **61**(Suppl 1): 1-12.

[5] Sullivan D, Moran G, Coleman D. *Fungal diseases of humans.* Chichester, UK: Fungi Biol Appl Wiley; 2005, p. 171-190.

[6] Richardson MD. Changing patterns and trends in systemic fungal infections. *J Antimicrob Chemother* 2005; **56**(suppl_1): i5-i11.

[7] Morace G, Borghi E. Fungal infections in ICU patients: Epidemiology and the role of diagnostics. *Minerva Anestesiol* 2010; **76**(11): 950.

[8] Giri S, Kindo A. A review of *Candida* species causing blood stream infection. *Indian J Med Microbiol* 2012; **30**(3): 270-278.

[9] Kadosh D, Lopez-Ribot JL. *Candida albicans*: Adapting to succeed. *Cell Host Microbe* 2013; **14**(5): 483-485.

[10]Coleman DC, Sullivan DJ, Bennett DE, Moran GP, Barry HJ, Shanley DB. Candidiasis: The emergence of a novel species, *Candida dubliniensis*. *AIDS* 1997; **11**(5): 557-567.

[11]Pfaller M, Diekema D. Rare and emerging opportunistic fungal pathogens: Concern for resistance beyond *Candida albicans* and Aspergillus fumigatus. *J Clin Microbiol* 2004; **42**(10): 4419-4431.

[12]Flevari A, Theodorakopoulou M, Velegraki A, Armaganidis A, Dimopoulos G. Treatment of invasive candidiasis in the elderly: A review. *Clin Interv Aging* 2013; **8**: 1199-1208.

[13]Hajjeh R, Sofair A, Harrison L, Lyon G, Arthington-Skaggs B, Mirza S, et al. Incidence of bloodstream infections due to *Candida* species and *in vitro* susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. *J Clin Microbiol* 2004; **42**(4): 1519-1527.

[14]Huttunen R, Åttman E, Aittoniemi J, Outinen T, Syrjänen J, Kärki T, et al. Nosocomial bloodstream infections in a Finnish tertiary care hospital: A retrospective cohort study of 2175 episodes during the years 1999-2001 and 2005-2010. *Infect Dis* 2015; **47**(1): 20-26.

[15]Atiencia-Carrera MB, Cabezas-Mera FS, Tejera E, Machado A. Prevalence of biofilms in *Candida* spp. bloodstream infections: A meta-analysis. *PLoS One* 2022; **17**(2): e0263522.

[16]Reda NM, Hassan RM, Salem ST, Yousef RHA. Prevalence and species distribution of *Candida* bloodstream infection in children and adults in two teaching university hospitals in Egypt: First report of *Candida kefyr*. *Infection* 2022; **51**(2): 389-395.

[17]Branco J, Miranda IM, Rodrigues AG. *Candida parapsilosis* virulence and antifungal resistance mechanisms: A comprehensive review of key determinants. *J Fungi* 2023; **9**(1): 80.

[18]Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: A wake-up call to public health officials. *PLoS Negl Trop Dis* 2020; **14**(2): e0007964 .

[19]Bitew A, Abebaw Y. Vulvovaginal candidiasis: Species distribution of *Candida* and their antifungal susceptibility pattern. *BMC Womens Health* 2018; **18**(1): 1-10.

[20]Sabino R, Veríssimo C, Pereira ÁA, Antunes F. *Candida auris*, an agent of hospital-associated outbreaks: Which challenging issues do we need to have in mind? *Microorganisms* 2020; **8**(2): 181.

[21]Dilhari A, Weerasekera MM, Siriwardhana A, Maheshika O, Gunasekara C, Karunathilaka S, et al. *Candida* infection in oral leukoplakia: An unperceived public health problem. *Acta Odontol Scand* 2016; **74**(7): 565-

569.

[22]Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. *Ann Intensive Care* 2011; **1**: 1-7.

[23]Yamin D, Husin A, Harun A. Distribution of candidemia in Malaysian tertiary care hospital revealed predominance of *Candida parapsilosis*. *Trop Biomed* 2020; **37**(4): 903-910.

[24]Kett DH, Azoulay E, Echeverria PM, Vincent JL. *Candida* bloodstream infections in intensive care units: Analysis of the extended prevalence of infection in intensive care unit study. *Crit Care Med* 2011; **39**(4): 665-670.

[25]Wan Ismail WNA, Jasmi N, Khan TM, Hong YH, Neoh CF. The economic burden of candidemia and invasive candidiasis: A systematic review. *Value Health Reg Issues* 2020; **21**: 53-58.

[26]Yamin DH, Husin A, Harun A. Risk factors of *Candida parapsilosis* catheter-related bloodstream infection. *Front Public Health* 2021; **9**: 631865.

[27]Sipsas NV, Kontoyiannis DP. Invasive fungal infections in patients with cancer in the Intensive Care Unit. *Int J Antimicrob Agents* 2012; **39**(6): 464-471.

[28]Ostrosky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. *Crit Care Med* 2006; **34**(3): 857-863.

[29]Bassetti M, Garnacho-Montero J, Calandra T, Kullberg B, Dimopoulos G, Azoulay E, et al. Intensive care medicine research agenda on invasive fungal infection in critically ill patients. *Intensive Care Med* 2017; **43**: 1225-1238.

[30]Mohamed NA, Pathmanathan SG, Hussin H, Zaini AB. Distribution and antifungal susceptibility pattern of *Candida* species at a tertiary hospital in Malaysia. *J Infect Dev Ctries* 2018; **12**(2): 102-108.

[31]Tajuddin AHA. Epidemiology and outcomes of candidaemia among adult patients admitted at Hospital Universiti Sains Malaysia (HUSM): A 5-year review. *Int Med J Malaysia* 2018; **17**(1): 3-12.

[32]Sobel JD. The emergence of non-albicans *Candida* species as causes of invasive candidiasis and candidemia. *Curr Infect Dis Rep* 2006; **8**(6): 427-433.

[33]Chow JK, Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg D, et al. Factors associated with candidemia caused by non-albicans *Candida* species *versus Candida albicans* in the intensive care unit. *Clin Infect Dis* 2008; **46**(8): 1206-1213.

[34]Gong X, Luan T, Wu X, Li G, Qiu H, Kang Y, et al. Invasive candidiasis in intensive care units in China: Risk factors and prognoses of *Candida albicans* and non-albicans *Candida* infections. *Am J Infect Control* 2016; **44**(5): e59-e63 .

[35]Deorukhkar SC, Saini S, Mathew S. Non-albicans *Candida* infection: An emerging threat. *Interdiscip Perspect Infect Dis* 2014; **2014**: 615958. doi: 10.1155/2014/615958.

[36]Staniszewska M. Virulence factors in *Candida* species. *Curr Protein Pept Sci* 2020; **21**(3): 313-323.

[37]Juyal D, Sharma M, Pal S, Rathaur VK, Sharma N. Emergence of non-albicans *Candida* species in neonatal candidemia. *N Am J Med Sci* 2013; **5**(9): 541.

[38]Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans *Candida* spp. among candidemia isolates from inpatients in various parts of the world: A systematic review. *Int J Infect Dis* 2010; **14**(11): e954-e66 .

[39]Chander J, Singla N, Sidhu SK, Gombar S. Epidemiology of *Candida* blood stream infections: Experience of a tertiary care centre in North India. *J Infect Dev Ctries* 2013; **7**(09): 670-675.

[40]Husain S, Tollemar J, Dominguez EA, Baumgarten K, Humar A, Paterson DL, et al. Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: Prospective, multicenter, case-controlled study. *Transplantation* 2003; **75**(12): 2023-2029.

[41]Wenzel RP, Gennings C. Bloodstream infections due to *Candida* species in the intensive care unit: Identifying especially high-risk patients to determine prevention strategies. *Clin Infect Dis* 2005; **41**(Supplement_6): S389-S93 .

[42]Marchetti O, Eggimann P, Calandra T. Invasive candidiasis in critically ill patients: Does progressing knowledge improve clinical management and outcome? *Curr Opin Crit Care* 2010; **16**(5): 442-444.

[43]Gamaletsou M, Walsh T, Zaoutis T, Pagoni M, Kotsopoulou M, Voulgarelis M, et al. A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies. *Clin Microbiol Infect* 2014; **20**(1): O50-O57.

[44]González de Molina FJ, León C, Ruiz-Santana S, Saavedra P. Assessment of candidemia-attributable mortality in critically ill patients using propensity score matching analysis. *Crit Care* 2012; **16**(3): 1-8.

[45]Devrim I, Yaman Y, Demirağ B, Oymak Y, Cartı Ö, Özek G, et al. A single center's experience with *Candida parapsilosis* related long-term central venous access device infections: The port removal decision and its outcomes. *Pediatr Hematol Oncol* 2014; **31**(5): 435-441.

[46]Kutlu M, Sayın-Kutlu S, Alp-Çavuş S, Öztürk ŞB, Taşbakan M, Özhak B, et al. Mortality-associated factors of candidemia: A multi-center prospective cohort in Turkey. *Eur J Clin Microbiol Infect Dis* 2022; **41**(4): 597-607.

[47]Liu M, Huang S, Guo L, Li H, Wang F, Zhang Q, et al. Clinical features and risk factors for blood stream infections of *Candida* in neonates. *Exp Ther Med* 2015; **10**(3): 1139-1144.

[48]Dabas PS. An approach to etiology, diagnosis and management of different types of candidiasis. *J Yeast Fungal Res* 2013; **4**(6): 63-74.

[49]Deorukhkar SC, Saini S. Medical device-associated *Candida* infections in a rural tertiary care teaching hospital of India. *Interdiscip Perspect Infect Dis* 2016; **2016**: 1854673. doi: 10.1155/2016/1854673.

[50]Pristov K, Ghannoum M. Resistance of *Candida* to azoles and echinocandins worldwide. *Clin Microbiol Infect* 2019; **25**(7): 792-798.

[51]Yapar N, Akan M, Avkan-Oguz V, Ergon CM, Hancer M, Doluca M. Risk factors, incidence and outcome of candidemia in a Turkish intensive care unit: A five-year retrospective cohort study. *Anaesth Pain Intensive*

Care 2019; **18**(3): 265-271.

[52]Friedman DZ, Schwartz IS. Emerging fungal infections: New patients, new patterns, and new pathogens. *J Fungi* 2019; **5**(3): 67.

[53]Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021; **372**: n160. doi: 10.1136/bmj.n160.

[54]Schiavo JH. PROSPERO: An international register of systematic review protocols. *Med Ref Serv Q* 2019; **38**(2): 171-180.

[55]Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *JBI Evid Implement* 2015; **13**(3): 147-153.

[56]Hajissa K, Marzan M, Idriss MI, Islam MA. Prevalence of drug-resistant tuberculosis in Sudan: A systematic review and meta-analysis. *Antibiotics* 2021; **10**(8): 932.

[57]Hajissa K, Islam MA, Hassan SA, Zaidah AR, Ismail N, Mohamed Z. Seroprevalence of SARS-CoV-2 antibodies in Africa: A systematic review and meta-analysis. *Int J Environ Res Public Health* 2022; **19**(12): 7257.

[58]Yamin D, Akanmu MH, Al Mutair A, Alhumaid S, Rabaan AA, Hajissa K. Global prevalence of antifungal-resistant *Candida parapsilosis*: A systematic review and meta-analysis. *Trop Med Infect Dis* 2022; **7**(8): 188.

[59]Hajissa K, Islam MA, Sanyang AM, Mohamed Z. Prevalence of intestinal protozoan parasites among school children in africa: A systematic review and meta-analysis. *PLoS Negl Trop Dis* 2022; **16**(2): e0009971.

[60]Abd Aziz J, Atiya N, Velayuthan RD. Species distribution of *Candida* species isolated from sterile body fluids and its antifungal susceptibility pattern in UMMC. *Int J Infect Dis* 2020; **101**: 390-391.

[61]Amran F, Aziz MN, Ibrahim HM, Atiqah NH, Parameswari S, Hafiza MR, et al. *In vitro* antifungal susceptibilities of *Candida* isolates from patients with invasive candidiasis in Kuala Lumpur Hospital, Malaysia. *J Med Microbiol* 2011; **60**(Pt 9): 1312-1316.

[62]Bac ND, Anh LT, Quang LB, Luc NK, Nga TTT, Nagi M, et al. Prevalence of *Candida* bloodstream isolates from patients in two hospitals in Vietnam. *Iran J Microbiol* 2019; **11**(2): 108-113.

[63]Batac MCR, Denning D. Serious fungal infections in the Philippines. *Eur J Clin Microbiol Infect Dis* 2017; **36**(6): 937-941.

[64]Boonsilp S, Homkaew A, Phumisantiphong U, Nutalai D, Wongsuk T. Species distribution, antifungal susceptibility, and molecular epidemiology of *Candida* species causing candidemia in a tertiary care hospital in Bangkok, Thailand. *J Fungi (Basel)* 2021; **7**(7): 577.

[65]Boonyasiri A, Jearanaisilavong J, Assanasen S. Candidemia in Siriraj Hospital: Epidemiology and factors associated with mortality. *J Med Assoc Thai* 2013; **96**(Suppl 2): S91-S97.

[66]Chai YAL, Wang Y, Khoo AL, Chan FY, Chow C, Kumarasinghe G, et al. Predominance of *Candida tropicalis* bloodstream infections in a Singapore teaching hospital. *Sabouraudia* 2007; **45**(5): 435-439.

[67]Chayakulkeeree M, Denning DW. Serious fungal infections in Thailand. *Eur J Clin Microbiol Infect Dis* 2017; **36**(6): 931-935.

[68]Chhabra SS, Chong PP, Lim CSY. Genetic relatedness of *Candida albicans* clinical isolates from *Candida* bloodstream infections in a Malaysian population. *Int J Infect Dis* 2012; **16**: e320 .

[69]Choudhury S. An insight into *in vitro* susceptibility of non-albicans *Candida* species from bloodstream infections to echinocandins in a Singapore cohort. *Pathology* 2019; **51**(1): 106-108.

[70]Cucunawangsih C, Christopher PM, Lumbuun N. A high distribution of resistant pathogens among critically ill neonates from secondary referral hospital of Indonesia. *Ethiop J Health Sci* 2021; **31**(3): 495-504.

[71]Duong TN, Le MH, Beardsley J, Denning DW, Le NH, Nguyen BT. Updated estimation of the burden of fungal disease in Vietnam. *Mycoses* 2022; **66**(4): 346-353.

[72]Foongladda S, Sakulmaiwatana P, Petlum P, Vanprapar N. *Candida* species, genotypes and antifungal susceptibility of *Candida* isolates from blood samples of patients at the largest tertiary care hospital in Thailand during 1999-2002. *J Med Assoc Thai* 2004; **87**(1): 92-99.

[73]Hamid SUB, Tan S, Ridzuan SNBA, Seman MSBC, Ramli RB, Khaithir TMNB. Antifungal susceptibility patterns among *Candida* species isolated from blood at universiti kebangsaan Malaysia medical centre. *Sains Malaysiana* 2012; **41**(8): 961-967.

[74]Itable JR, Alejandria M, Mendoza M. Risk factors, species distribution and susceptibility of candidemia in the Philippines. *Int J Infect Dis* 2014; **21**: 285.

[75]Jantarabenjakul W, Yodkitudomying C, Chindamporn A, Suchartlikitwong P, Anugulruengkitt S, Pancharoen C, et al. Pediatric and neonatal invasive candidiasis: Species distribution and mortality rate in a Thai Tertiary Care Hospital. *Pediatr Infect Dis J* 2021; **40**(2): 96-102.

[76]Jutiamornlerd N, Chusri S, Siripaitoon P. Epidemiology of candidemia in Songklanagarind Hospital. *J Med Assoc Thai* 2011; **94**(8): 927-932.

[77]Karunakaran R, Raja NS, Ng KP, Navaratnam P. Etiology of blood culture isolates among patients in a multidisciplinary teaching hospital in Kuala Lumpur. *J Microbiol Immunol Infect* 2007; **40**(5): 432-437.

[78]Khumdee P, Hematulin P, Yansombat J, Mungkornkaew N, Lutful Kabir SM, Samosornsuk W, et al. Species characterization and antifungal susceptibility profile of yeast isolates from blood cultures of fungemic patients in Thammasat University Hospital, Thailand. *J Assoc Med Sci* 2022; **55**(3): 44-50.

[79]Naranong C, Anunnatsiri S, Srigulbutr S. Epidemiology and antifungal susceptibility in patients with candidemia in a University Hospital, Thailand. *J Med Assoc Thai* 2020; **103**(10): 1048-1056.

[80]Ng KP, Kuan CS, Kaur H, Na SL, Atiya N, Velayuthan RD. *Candida* species epidemiology 2000-2013: A laboratory-based report. *Trop Med Int Health* 2015; **20**(11): 1447-1453.

[81]Ng KP, Madasamy M, Saw TL, Baki A, He J, Soo-Hoo TS. *Candida* biotypes isolated from clinical specimens in Malaysia. *Mycopathologia* 1998; **144**(3): 135-140.

[82]Ngamchokwathana C, Chongtrakool P, Waesamaae A, Chayakulkeeree M. Risk factors and outcomes of non-albicans *Candida* bloodstream infection in patients with candidemia at Siriraj Hospital-Thailand's largest national tertiary referral hospital. *J Fungi (Basel)* 2021; **7**(4): 269.

[83]Rahman ZA, Noor SSM, Zahiruddin WM, Hassan H, Mohamed Z, Asma'Hassan S. Epidemiology of *Candida* species in tertiary-teaching hospital in Malaysia. *Int Med J* 2008; **15**(4): 291-294.

[84]Santhanam J, Nazmiah N, Aziz MN. Species distribution and antifungal susceptibility patterns of *Candida* species: Is low susceptibility to itraconazole a trend in Malaysia? *Med J Malays* 2013; **68**(4): 343-347.

[85]Subramaniam K, Khaithir TMN, Ding CH, Che Hussin NS. Epidemiology of bloodstream infections in the paediatric population in a Malaysian general hospital over a 2-year period. *Malays J Pathol* 2021; **43**(2): 291-301.

[86]Supatharawanich S, Narkbunnam N, Vathana N, Takpradit C, Phuakpet K, Pongtanakul B, et al. Invasive fungal diseases in children with acute leukemia and severe aplastic anemia. *Mediterr J Hematol Infect Dis* 2021; **13**(1): e2021039 .

[87]Tan TY, Hsu LY, Alejandria MM, Chaiwarith R, Chinniah T, Chayakulkeeree M, et al. Antifungal susceptibility of invasive *Candida* bloodstream isolates from the Asia-Pacific region. *Med Mycol* 2016; **54**(5): 471-477.

[88]Tan TY, Tan AL, Tee NW, Ng LS. A retrospective analysis of antifungal susceptibilities of *Candida* bloodstream isolates from Singapore hospitals. *Ann Acad Med Singap* 2008; **37**(10): 835-840.

[89]Teo JQ, Candra SR, Lee SJ, Chia SY, Leck H, Tan AL, et al. Candidemia in a major regional tertiary referral hospital-epidemiology, practice patterns and outcomes. *Antimicrob Resist Infect Control* 2017; **6**: 27.

[90]Tzar MNK, Suhaila B, Shamsul AS, Azizah M. Epidemiology of fungal infections at an infectious disease reference centre in Malaysia. *Int Med J Malaysia* 2013; **12**(1): 39-42.

[91]Velayuthan RD, Samudi C, Lakhbeer Singh HK, Ng KP, Shankar EM, Denning DW. Estimation of the burden of serious human fungal infections in Malaysia. *J Fungi (Basel)* 2018; **4**(1): 38.

[92]Wahyuningsih R, Adawiyah R, Sjam R, Prihartono J, Ayu Tri Wulandari E, Rozaliyani A, et al. Serious fungal disease incidence and prevalence in Indonesia. *Mycoses* 2021; **64**(10): 1203-1212.

[93]Wiwing V, Cucunawangsih C. Candidemia in an Indonesian teaching hospital: A 9-year observational study. *J Infect Public Health* 2020; **13**(2): 345.

[94]Yang CW, Barkham TM, Chan FY, Wang Y. Prevalence of *Candida* species, including *Candida dubliniensis*, in Singapore. *J Clin Microbiol* 2003; **41**(1): 472-474.

[95]Pfaller M, Diekema D, Jones R, Sader HS, Fluit A, Hollis R, et al. International surveillance of bloodstream infections due to *Candida* species: Frequency of occurrence and *in vitro* susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. *J Clin Microbiol* 2001; **39**(9): 3254-3259.

[96]Papon N, Courdavault V, Clastre M, Bennett RJ. Emerging and emerged pathogenic *Candida* species: Beyond the *Candida albicans* paradigm. *PLoS Pathog* 2013; **9**(9): e1003550.

[97]Dimopoulos G, Ntziora F, Rachiotis G, Armaganidis A, Falagas ME. *Candida albicans versus* non-albicans intensive care unit-acquired bloodstream infections: Differences in risk factors and outcome. *Anesth Analg* 2008; **106**(2): 523-529.

[98]Gauna TT, Oshiro E, Luzio YC, Paniago AMM, Pontes ERJC, Chang MR. Bloodstream infection in patients with end-stage renal disease in a teaching hospital in central-western Brazil. *Rev Soc Bras Med Trop* 2013; **46**: 426-432.

[99]Girmenia C, Martino P, De Bernardis F, Gentile G, Boccanera M, Monaco M, et al. Rising incidence of *Candida parapsilosis* fungemia in patients with hematologic malignancies: Clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. *Clin Infect Dis* 1996; **23**(3): 506-514.

[100]Huang YC, Lin TY, Leu HS, Peng HL, Wu JH, Chang HY. Outbreak of *Candida parapsilosis* fungemia in neonatal intensive care units: Clinical implications and genotyping analysis. *Infection* 1999; **27**(2): 97-102.

[101]Jenks JD, Cornely OA, Chen SCA, Thompson III GR, Hoenigl M. Breakthrough invasive fungal infections: Who is at risk? *Mycoses* 2020; **63**(10): 1021-1032.

[102]Bajpai VK, Khan I, Shukla S, Kumar P, Rather IA, Park YH, et al. Invasive fungal infections and their epidemiology: Measures in the clinical scenario. *Biotechnol Bioprocess Eng* 2019; **24**: 436-444.

[103]Bassetti M, Bouza E. Invasive mould infections in the ICU setting: Complexities and solutions. *J Antimicrob Chemother* 2017; **72**(suppl_1): i39-i47 .

[104]Paramythiotou E, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: How to approach, how to treat. *Molecules* 2014; **19**(1): 1085-1119.

[105]Fan X, Dai RC, Zhang S, Geng YY, Kang M, Guo DW, et al. Tandem gene duplications contributed to high-level azole resistance in a rapidly expanding *Candida tropicalis* population. *Nat Commun* 2023; **14**(1): 8369.

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