BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036452
Article Type:	Original research
Date Submitted by the Author:	11-Sep-2019
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Keywords:	ACCIDENT & EMERGENCY MEDICINE, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS

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The risk of invasive candidiasis with prolonged duration of ICU stay and broad-spectrum antibiotic use: a systematic review and meta-analysis

Running title: Duration of ICU prior to candidemia

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ABSTRACT

Objective: This study aimed to evaluate the duration of intensive care unit (ICU) stay prior to onset of invasive candidiasis (IC)/candidemia.

Design: Systematic review and meta-analysis.

Data Sources: Pubmed, Cochrane**,** Embase, and Web of Science databases were searched through June, 2019 to identify the relevant studies.

Eligibility Criteria: Adult patients who had been admitted to the ICU and developed an invasive candidiasis infection.

Data extraction and synthesis: Duplicate data extraction and quality assessment were conducted. Meta-analysis and meta-regression were conducted in Comprehensive Meta-Analysis statistical software.

Results: The mean age of patients ranged from 28.2 to 76 years across studies. The pooled mean duration of ICU stay before the onset of candidemia was 12.93 days (95% confidence interval [CI]: 11.70 – 14.15). The pooled mean duration of ICU admission prior to the onset of candidemia ranged from 4 to 47 days. IC patients had a higher proportion of broad-spectrum antibiotic use (89.13%, 95% CI: 82.68 – 93.37%) before the onset of IC, which was higher than that observed in non-IC patients (77.36%, 95% CI: 52.25 – 91.43%). The pooled mean duration of hospital stay was 36.26±5.32 days (95% CI: 25.84 – 46.67) and the pooled mean mortality rate was 49.25±2.16% (95% CI: 45.02 – 53.48%). There was no significant difference in duration of hospital stay or overall mortality between patients with or without *C. albicans,* yet a significant difference was demonstrated in mean length of ICU stay (2.82 days, $P < 0.001$). The meta-regression analysis found that South American

countries had significantly longer mean duration of ICU admission prior to candidemia onset compared with Asian, European, Australian, and North American countries.

Conclusions: The current findings demonstrate that a more proactive strategy for the diagnosis of IC should be considered in these patients, especially relevant for Asian physicians.

KEYWORDS: Invasive candidiasis, candidemia, intensive care unit, length of stay, antibiotic, mortality

Strengths and limitations of this study

- This was a systematic review to indicate that patients with IC were associated with the use of broad-spectrum antibiotics and the length of ICU stay.
- Meta-regression was used to test differences in regional subgroups, and statistical significance was found.
- Two independent reviewers performed a methodological quality assessment, with a third reviewer consulted for any uncertainties, but this systematic review lacked a pre-specified protocol and its preliminary registration.
- High heterogeneity had existed in some overall and subgroup analyses; in addition to regional differences found in this study, there may be other potential factors that may explain heterogeneity that need to be further explored.
- Due to lack of data, the possible correlation between prolonged exposure to broad-spectrum antibiotics and the time of candidemia onset after ICU admission could not be assessed.

INTRODUCTION

Candida species account for 70% to 90% of invasive fungal infections and are the most frequent cause of fungal infections in patients admitted to the intensive care unit (ICU) [1]. Invasive candidiasis (IC) is associated with a high mortality rate (range: 40% to 60%) [1, 2]. Over recent decades, the incidence of IC has been gradually increasing in most regions [3], ranging from 0.5 to 32 cases per 1,000 ICU admissions. It has been found that there is a significant difference in the incidence of IC among several countries in Latin America and North America; however, data from Asia-Pacific countries are still relatively rare [4]. Candidemia has been described as the most common manifestation of IC, and the further infection of the liver, spleen, heart valves, or eye might also occur after a bloodstream infection [5]. In the past, the main *Candida* species isolated from patients with IC was *C. albicans*. However, non-*C. albicans* species has seen a rising proportion and now account for approximately 50% of all cases of IC in the past two decades [1,6-8].

Diagnosis and management of IC remains challenging for physicians in the ICU [1, 2]. The early initiation of empiric antifungal treatment has been demonstrated to improve the prognosis of invasive candidiasis [2, 9]. However, there is difficulty in the diagnosis of IC which can delay timely antifungal treatment [2, 10]. Blood culture remains the gold standard for the diagnosis of invasive candidiasis, but its sensitivity is variable (21% to 71%) [11].

In order to improve the diagnosis of IC, and to identify the patients who may best benefit from prophylactic, preemptive, or empirical therapy prior to, or at an early stage of ICU admission several methods in predicting the development of IC based on their associated risk factors have been developed [12, 13]. The risk factors in the various predictive models include broad-spectrum antibiotic use, central venous

catheter placement, total parenteral nutrition, hemodialysis (days 1–3 in the ICU), any surgery, immunosuppressive use, pancreatitis prior to ICU admission, and steroid use. However, different risk factors are included in the different predictive models. In addition, potential risk factors such as *Candida* colonization [14] and mechanical ventilation [15] have not been included in these models.

Long-term ICU stay has been reported as a risk factor for IC [11, 14-16]. Only a few studies have examined the interval between ICU admission or initiation of broad-spectrum antibiotics and the diagnosis of IC. However, the specific duration of long-term ICU stays and the prolonged use of broad-spectrum antibiotics are often arbitrarily defined and inconsistent among studies [6, 12, 15, 17-19]. Furthermore, a large majority of severe candidiasis cases are caused by endogenous colonization. This may be the primary reason for causing a delay of 7 to 10 days between exposure to risk factors and the development of IC [20].

Thus, the objective of this systematic review was to evaluate the risk factors associated with the development of candidemia, specifically the length of ICU stay and the use of broad-spectrum antibiotics.

METHODS

Search strategy

The study was performed in accordance with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed, Cochrane, Embase, and Web of Science databases were searched through June, 2019 using the following search terms: invasive candidiasis, critical care, critical illness, candidemia, and antibiotic agents. A detailed search strategy for the Medline database is shown in Figure 1.

Randomized controlled trials (RCTs), cohort studies, case-controlled, and cross-sectional studies were included. All studies included adult patients who were critically ill, who had been admitted to the ICU, and who tested positive for *Candida* species using blood culture analyses. Studies had to have reported quantitative outcomes of interest and no author was contacted. Letters, comments, editorials, case reports, proceedings, personal communications, and case series were excluded. Studies in which patients were diagnosed with candidiasis prior to ICU admission were excluded. Studies that did not evaluate the incidence of candidiasis as a primary objective, or that were not designed to evaluate risk factors/prognostic factors of patients with candidiasis were also excluded.

Patients and/or members of the public were not involved in this study; therefore, ethical approval and informed consent were not necessary as meta-analyses do not involve human subjects and does not require institutional review board review.

Study selection and data extraction

Studies identified by the search strategy were reviewed for inclusion and data was extracted by two independent reviewers. Where there was uncertainty regarding study eligibility, a third reviewer was consulted. The following information / data was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, country, study design, type of ICU, number of participants in each group, participants' age and gender, the presence of *C. Albicans*, the presence of neutropenia, and antifungal treatment (especially the use of broad-spectrum antibiotics). The following data were also extracted from each article: length of stay in hospital/ICU, length of stay prior to ICU admission, duration of ICU stay prior to candidemia onset, antibiotic therapy prior to candidemia onset, duration of antibiotic

therapy prior to candidemia onset, and overall mortality.

Quality assessment

We used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool to assess the quality of the included studies [21]. ROBINS-I is based on the Cochrane RoB tool and is suited for evaluating non-randomized studies that compare the health effects of different interventions. ROBINS-I covers 7 different bias domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in the selection of reported results [22-23]. In this systematic review, 2 independent reviewers performed the quality assessment, with a third reviewer consulted for any uncertainties.

Statistical analysis

Study characteristics were summarized as mean ± standard deviations (SD), mean (range), median (range), or median (IQR) for age or duration of antifungal treatment; and percentage (%) for sex, rate of *C. Albicans* isolated, neutropenia, and antifungal treatment used in each study.

Clinical outcomes, including hospital stay, ICU length of stay, length of stay prior to ICU admission, duration of ICU admission prior to candidemia onset, and duration of antibiotic therapy prior to candidemia onset were represented as mean (range: [min. – max.]), median (range), or median (IQR [interquartile range: 1st – 3rd quartiles]). The rate of antibiotic therapy prior to candidemia onset and overall mortality rate were presented as a percentage (%), according to the data extracted

from the study. All the clinical outcomes were further summarized for overall studies, or subgroups of studies (with studies' number ≥2) given type of study, presence of neutropenia, type of ICU, type of *C. Albicans* isolated, presence of IC/candidemia, and region/country, and meta-regression analyses were further used to investigate statistical importance of the potential moderators. Before summarizing, studies that reported quantitative data with median (range) and/or median interquartile range (IQR) were transformed into mean ± SD according to Wan et al. [24]

The effect size for the following meta-analysis were set as length of hospital stay, ICU length of stay, duration of ICU admission prior to candidemia onset, and overall mortality compared between subgroups, *C. Albicans* and non-*C. Albicans*. The effect size was calculated as mean difference with 95% CI (Lower, Upper limit) and significance of *p*-values in length of days or rate ratio with 95%CI and p-values in overall mortality for each given study and then a pooling effect was derived thereafter. A difference in means of length days <0 (or rate ratio of overall mortality rate >1) indicated the pooling effect favored non- *C. Albicans* subgroup; difference in means of length days >0 (or rate ratio of overall mortality rate <1) indicated the pooling effect favored *C. Albicans* subgroup; difference in means of length days = 0 (or rate ratio of overall mortality rate = 1) indicated the pooling effect was similar between *C. Albicans* and non-*C. Albicans* subgroups. Heterogeneity was evaluated using a χ^2-based Cochran's Q statistic and I^2, that the random effect model (DerSimonian-Laird method) and meta-regression analyses with potential moderators were considered for the meta-analysis if either Q statistic with P values < 0.10 or I^2>50% were derived; otherwise, a fixed effect model (Mantel-Haenszel method) was considered for the meta-analysis. For the Q statistic, P values < 0.10 were considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was

assessed as follows: no heterogeneity (I^2 = 0 - 25%), moderate heterogeneity (I^2 =25 - 50%), large heterogeneity (I^2 = 50 - 75%), and extreme heterogeneity (I^2= 75 - 100%). A two-sided P value of <0.05 was considered significant.

Countries were classified according to their continent, but since the meta-analysis of this research topic from China has not yet been seen, in following discussions, research from China will be selected and specifically examined.

The publication bias was assessed by funnel plot with Egger's test and Classical fail-safe N test for all the enrolled studies (except for subgroups). The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution and a 1-tailed significance level of P > 0.05 in Egger's test.[24] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 3.3.070 (Biostat, Englewood, NJ, USA).

RESULTS

Literature search results

A total of 1875 articles were retrieved by the primary search, and 1800 articles were excluded after the title and abstract were screened based on the inclusion/exclusion criteria (Figure 1). Seventy-five articles underwent full-text review, and 34 articles were excluded due to irrelevant objectives or study designs (n=19), reporting predictor/prognostic factors for mortality (n=4), neonatal or pediatric intensive care unit (n=5), not designed for invasive candidiasis (n=4), and not reporting outcomes of interest (n=6). Thus, 41 articles were included in the systematic review.

Study characteristics

The characteristics of the 41 studies are summarized in Table 1 and Table 2 [14-16, 25, 27-29, 31-50]. A total of 10,692 patients were included across the studies, with the number of patients in each study ranging from 12 to 1,400. The mean age of the patients ranged from 28.2 to 76 years. The majority of the patients were males (range: 40% to 75.9%). These studies were conducted in different countries: 19 in Europe, 14 in Asia, 1 in the US, 4 in South America, 2 in Australia and 1 multinational study (Australia, Belgium, Greece, Brazil).

Table 1. Characteristics of studies included in this systematic review

Studies 1st Author (year)	Country	Study design	Type of ICU	Total number of patients	IC and Candidemia	No. of patients	Age (years)	Male (%)	*C.Albicans* isolated (%)	Neutropenia (%)	Antifungal treatment: Duration of treatment	Antifungal treatment: Antifungal treatment used
Zhao H (2018)	China	retrospective cohort	ICU		Candidemia	95	69.3±16.5	57.90 %	59	—	—	17.90%
Ding R (2018)	China	retrospective cohort	ICU	72	Candidemia	72	62.5 (49.8, 77.0)§	62.50 %	15	—	—	Fluconazole 30.6% Voriconazole 9.70% Echinocandin 44.4%
Yang et al. (2017) [25]	China	Retrospective cohort study (China-SCAN)	ICU	306	Early-onset IC	105	56.9 (19.94)§	64.80 %	47.7	1.90%	—	Fluconazole (39.3%) Caspofungin(21.3%) Voriconazole (19.1%) Micafungin(10.1%) Itraconazole(5.6%) Amphotericin B (3.4%) Combined therapy (1.1%)
					Late-onset IC	201	64.0 (19.67)§	70.60 %	36.1	1.50%	—	Fluconazole (36.9%) Caspofungin(25.1%) Voriconazole (17.9%) Micafungin(7.8%) Itraconazole(9.5%) Amphotericin B (1.7%) Combined therapy (1.1%)

Tukenmez Tigen E (2017)	Turkey	Case-control study	ICU	73	Candidemia	36	65 (52-73)†	52.80 %	75		17.6 ± 11.7 days	Caspofungin Posaconazole Voriconazole Itraconazole Fluconazole Amphotericin B
					Control (Non-Candidemia)	37	62 (48-72)†	48.60 %	—	—	—	—
Baldesi O (2017)	France	Case-control study	ICU	246,459	Candidemia	851	65 [54; 75]§	62.60 %	61.40	5.10%	—	—
					Control (Non-Candidemia)	245,608	65 [52; 76]§	61.70 %	—	1.60%	—	—
Rudramurthy SM (2017)	India	prospective cohort	MICU, SICU	1161	Candidemia (C. auris)	74	39 (16 – 58.5)§	62.20 %	—	—	—	fluconazole (20.3) echinocandin(9.5)
					Candidemia (non - C. auris)	1087	—	—	—	—	—	fluconazole(12.1) echinocandin(0.8)
Kawano Y (2017)	Japan	retrospective cohort	ICU	4,136	Candidemia	25	69 (24 – 88)†	56.00 %	52	0	—	antifungal treatment: 32%
OrtízRuiz et al. (2016) [16]	Colombia	Case-control study	Polyvalent, cardiovascularICU	243	Candidemia	81	64.5 (51-78) §	51.85 %	42	—	—	—
					Control	162	68 (48-77) §	59.26 %	—	—	—	—

Gong et al. (2016) [47]	China	Prospective, cohort study (China-SCAN)	MICU, SICU, Integrated ICU	306	Candidemia (*C. albicans*)	98	62.2±17.26	62.20 %	100	3.10%	12.85 days	Triazole (64.7%) Echinocandin (31.8%) Polyenes (0%)
					Candidemia (Non-*Candidaalbicans*)	146	61.4±21.36	72.60 %	—	1.40%	20.4 days	Triazole (62.8%) Echinocandin (34.1%) Polyenes (2.3%)
Playford EG (2016)	Australia	prospective cohort	MICU, SICU	6,714	ICU-aquired IC	96	—	—	66	—	—	—
					Control (no IC)	6618	—	—	—	—	—	—
Pinhati HM (2016)	Brazil	cross-sectional	ICU	40	fluconazole-resistant C. parapsilosis (FRCP)	21	70 (23 – 91)†	66.70 %	—	—	—	any: (33.3) fluconazole: (19.0)
					fluconazole-susceptible Candida species (FSC)	19	76 (35 – 90)†	57.90 %	—	—	—	any: (15.8) fluconazole: (15.8)
Aguilar et al. (2015) [15]	Spain	Prospective cohort study	SICU	22	IC	22	66 (53.7–74.2) §	72.70 %	59.1	—	10 (5.0–16.5) days	Echinocandins (86.4%) Fluconazole (13.6%)
Fochtmann et al. (2015) [27]	Austria	Retrospective cohort study	Burn ICU	174	Candidemia	20	39 (17–88) †	60%	60	—	—	Triazoles (70%)
					Control	154	58 (17–94) †	61%		—	—	Echinocandins (30%)

Klingsporet al.(2015) [28]	14 countries in Europe	Prospective cohort study	SICU	807	IC	779	63(0–91) †	62.50 %	54	—	—	Fluconazole (60%) Caspofungin (18.7%) Amphotericin B (13%) Voriconazole (4.8%)
Chakrabarti et al. (2015) [29]	India	Prospective cohort study	MICU, SICU	1400	Candidemia	1400	49.7 ± 17.7	—	20.9	1.30%	9.0 (5-15)§ days	Azoles (72.0%) Echinocandins (18.3%) Amphotericin B (14.4%)
Liao et al. (2015) [14]	China	Prospective cohort study (China-SCAN)	MICU, SICU, Mix ICU	306	Flu-S	129	62.4±19.5	68.20 %	60.5	3.10%	—	Monoantifungaltherapy (64.5%) Fungal drug adjustment (35.7%) Completely improved(34.6%)
					Flu-R	90	60.8±20.9	67.80 %	17.8	1.10%	—	Monoantifungaltherapy (48.8%) Fungal drug adjustment (61.1%) Completely improved (28.0%)
Kautzky S (2015)	Austria	prospective cohort	MICU	65	IC (invasive candida infection)	5	28.2 ± 9.7	20%	—	0%	15.40 ± 13.9	100%
					control (non-invasive candida infection)	60	52.7 ± 15.7	72%	—	8.30%	—	60.00%
Karacaer et al. (2014) [31]	Turkey	Prospective cohort study	ICU burn service	2362	IC	63	70.2 ± 19.5 (14-95)	54%	64	—	—	—

Colombo et al. (2014) [32]	Brazil	Retrospective cohort study	ICU	1,392	Candidemia	647	66 (18–97) †	50.7	44	2.50%	—	Amphotericin B (period 1:27.8%; period 2: 13.4%) Echinocandins(period 1: 5.9%; period 2: 18.0%)
Hu et al.(2014) [48]	China	Prospective cohort study (China-SCAN)	ICU	294	CRCBSI	29	69.4 ± 19.1	75.90 %	28.6	—	19.0 ± 13.3 days	Fluconazole (39.3%) Caspofungin(25.0%) Voriconazole(14.3%) Micafungin (10.70%) Itraconazole(10.7%) Amphotericin B (0%) Two-drug combination (0%)
					Non-CRCBSI	265	60.7±20.2	68.30 %	40.3	—	16.7 ± 13.3 days	Fluconazole (36.7%) Caspofungin(23.6%) Voriconazole(19.2%) Micafungin (8.7%) Itraconazole(7.9%) Amphotericin B(2.2%) Two-drugs combination(1.7%)
Lortholary O (2014)	France	prospective cohort	ICU	2507	ICU-aquired candidemia	1206	60 ± 17	62.00 %	57.10	—	—	Fluconazole(55.4 %) Echinocandins(26.2 %) Others (including combination)(12.6 %)
					non-ICU aquired candidemia	1301	60 ± 17	58.70 %	54.90	—	—	Fluconazole(59.9 %) Echinocandins(19.1 %) Others (including combination)(13.3 %)
Yapar N (2014)	Turkey	retrospective cohort	ICU	1076	Candidemia	66	54.4 ± 23.9	53%	53	—	—	9%

					Control (non-Candidemia)	1010	53.2 ± 23.0	63%	—	—	—	6.30%
Guo et al.(2013) [49]	China	Prospective cohort study (China-SCAN)	MICU SICU General Emergency Neurologic ICU	306	Candidemia	306	61.5±20.0	68.60 %	40.2	1.60%	14 (0-104)† days	Fluconazole (37.7%) Caspofungin (23.9%) Voriconazole (18.3%)
Giri S (2013)	India	prospective cohort	ICU	5,976	Candidemia	39	35.14 (3days-79y)	61.50 %	4			
Tortorano et al.(2012) [33]	Italy	Prospective cohort study	MICU, SICU	384	Candidemia	276	—	—	60.9	—	—	Fluconazole (63%) Amphotericin B (22%) Caspofungin (7%) Voriconazole (6%)
Ylipalosaari et al. (2012) [34]	Finland	Retrospective cohort study	MICU,SICU	82	ICU-acquired candidemia	38	63 (45-69) §	71%	76.3	—	Median: 22 days	Fluconazole (73%) Amphotericin B (34%) Echinocandins (31%)
					non-ICU-acquired candidemia	44	64 (56-75) §	61%	68.9	—	Median: 24 days	Fluconazole (77%) Amphotericin B (35%) Echinocandins (40%)
Pasero D et al. (2011) [35]	Italy	Prospective cohort study	SICU	349	Candidemia	26	60±21	61.50 %	73	—	—	—

					Control	323	67±16	65.30 %		—	—	—
Han SS et al. (2010) [36]	Korea	Case-control study	MICU	52	Candidemia	49	57.6±14.1	—	65	25%	11 (1-45)† days	Amphotericin B (71.4%) Fluconazole (28.6%)
					Control	147	57.4±14.0	—	—	8%		
Pratikaki M et al. (2009) [37]	Greece	Case-control study	Multi-disciplinary ICU	855	Candidemia	33	57±18	64%	33.3	0%		Amphotericin B (57.1%)
					Control	132	58±18	70%	—	0%	>14 days	Voriconazole(17.9%), Caspofungin (14.3%) Fluconazole (10.7%)
Playford et al.(2009) [38]	Australia	Prospective cohort study	MICU, SICU	615	IC	15	NA	NA	73.3	0%	—	—
Holleyetal.(2009) [39]	Australia, Belgium, Greece, Brazil	Retrospective cohort study	Multi-disciplinary ICU	189	Candidemia (*C. albicans*)	104	56.5±17.1	63.50 %	100	—	1(1-32)†days	Fluconazole (37%) Amphotericin B (31%)
					Candidemia (Non-*Candida albicans*	85	58.9±16.3	44.70 %	—	—		Fluconazole and amphotericin B (15%)
Choi et al. (2009) [40]	Korea	Retrospective cohort study	ICU	497	Candidemia (*C. albicans*)	54	49±23	44.40 %	100	13%	—	Amphotericin B (77.8%) Fluconazole (16.7%)
					Candidemia	27	48±25	44.40 %	—	19%	—	Fluconazole and amphotericin B (5.6%)

					(*C. glabrata*or, *C. krusei*)							
Yap et al (2009) [50]	China Hong Kong	Retrospective cohort study	MICU SICU	128	Candidemia	128	54 (43-68) §	63.30 %	56	11%	—	Amphotericin B (39.1%) Fluconazole (38%) Amphotericin B+fluconazole (13%) Caspofunginorvoriconazole(9.8%)
Chow et al. (2008) [41]	US	Case-control study	MICU, SICU	926	Candidemia (Non-*Candida albicans*)	67	62.3±14.5	57%	—	—	—	Fluconazole(84.8%) Amphotericin B (23.9%) Caspofungin(10.9%) Voriconazole(4.3%)
					Candidemia (*C. albicans*)	79	57±17.0	60%	100	—	—	Fluconazole (63%) Amphotericin B (33.3%) Caspofungin (11.1%) Voriconazole (0%)
					Control	780	62.3±17.4	56%	—	—	—	Fluconazole (100%) Amphotericin B (14.3%) Caspofungin (0%) Voriconazole (0%)
Bougnouxet al.(2008) [42]	France	Prospective cohort study	MICU SICU HU BU	290	Candidemia	57	56.1±18.2	67%	54.2	19.30%	13.2±10.3 days	Fluconazole(78.3%) Amphotericin B(52.2%) Flucytosine(15.2%)

Girãoet al.(2008) [43]	Brazil	Prospective cohort study	ICU	73	Candidemia (Non-*Candida albicans*)	40	51(12-86)*	60%	—	—	—	—
					Candidemia (*C. albicans*)	33	51(15-86)*	40%	100	—	—	—
Dimopoulos et al. (2008) [44]	Greece	Prospective cohort study	MICU, SICU	56	Candidemia (*C. albicans*)	36	60.5 ± 14.9	44.40 %	100	0% (excluded)	Response rate: (80.6%)	Fluconazole as prophylaxis: Amphotericin B (75%) Caspofungin (25%) No fluconazole as prophylaxis: Amphotericin B (60%) Caspofungin (40%)
					Candidemia (Non-*Candida albicans*)	20	64.5± 16.8	55%	—		Response rate: (45%)	Amphotericin B (100%)
Dimopouloset al.(2007) [45]	Greece	Prospective cohort study	MICU, SICU	24	Candidemia	24	—	—	62.5	—	16.5 (14-24)*days	C. albicans: fluconazole Non-albicans: amphotericin B
Jordà-Marcos R (2007)	Spain	prospective cohort	MICU, SICU	1765	Candidemia	63	63 (48 – 70)†	71.40 %	57.10	6.30%	—	7.90%
					Control (non-Candidemia)	1072	63 (46 – 71)†	66.50 %	—	2.80%	—	5.60%

Piazza O (2004)	Italy	retrospective cohort	ICU	478	Candidemia	12	57.58± 22.07	58.30 %	67	—	—	—
Michalopoulos et al. (2003) [46]	Greece	Prospective case-control study	CICU	150	Candidemia	30	63.2±9.7	73.30 %	70	—	—	—
					Control	120	64.3±9.9	73.30 %	—	—	—	—

Abbreviations: CICU, cardiothoracic ICU; CRCBSI, Catheter-related Candida bloodstream infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, Invasive candidiasis; MICU, medical ICU; SICU, surgical ICU.

Total number of enrolled patients: 7,982.

* Data were presented as mean (range).

† Data were presented as median (range).

§ Data were presented as median (IQR).

Dash indicates no available data.

Table 2. Length of stay, antibiotic therapy prior to candidemia onset, and overall mortality

Studies 1st Author (year)	Hospital stay (days)	ICU length of stay (days)	Length of stay prior to ICU admission (days)	Duration of ICU admission prior to candidemia onset (days)	Rate of antibiotic therapy prior to candidemia onset	Duration of antibiotic therapy prior to candidemia onset (days)	Overall mortality rate
Zhao H (2018)	N/A	24 (12-57)†	N/A	N/A	N/A	N/A	58%
Ding R (2018)	N/A	N/A	N/A	N/A	Broad-spectrum antibiotics: 98.6%	N/A	31.90%
Yang et al. (2017) [26]	(prior to IC diagnosis) Early-onset IC:4 (2, 7)§ Late-onset IC: 26 (16, 50)§	N/A	N/A	Early-onset IC: 4 (1, 7)§ Late-onset IC: 17 (10, 33)§	Early-onset IC: 62 (59.0%) Late-onset IC: 179 (89.1%)	N/A	Early-onset IC: 28.6% Late-onset IC: 40.8%
Tukenmez Tigen E (2017)	N/A	22 (18-30)† 5.5 (2.25-15.75)†	N/A	N/A	Broad-spectrum antibiotic: 100% Broad-spectrum antibiotic: 59.5%	N/A	83.30%
Baldesi O (2017)	N/A	29 (18; 49) § 7 (4; 13) §	N/A	N/A	antimicrobials: 82.2% antimicrobials: 55.1%	N/A	52.40% 17.80%
Rudramurthy SM (2017)	N/A	N/A	N/A	10 (4.7 – 22.2)§ 7 (3 – 13)§	N/A	N/A	41.90% 27%

Kawano Y (2017)	N/A	N/A	N/A	13 (1 – 73)†	Broad-spectrum antimicrobial: 84%	N/A	72%
OrtízRuiz et al. (2016) [16]	35.4±3.0	21.9±1.7	N/A	Median 25	Broad-spectrum antibiotic: 93.8 vs. 69.8% (case vs. control)	N/A	39.51%
Gong et al. (2016) [47]	*Candida albicans*: Median: 32 Non-albicans: Mediian: 44	*Candida albicans*: Median: 18 Non-albicans: Median: 29	N/A	N/A	*Candida albicans* (before diagnosis): 76 (77.6%) Non-*albicans*(before diagnosis): 121 (82.9%)	N/A	*Candida albicans* (before diagnosis): 29.6% Non-*albicans*(before diagnosis): 26.7%
Playford EG (2016)	51 (34 – 89)§ 23 (13 – 40)§	21 (14 – 32)§ 8 (5 – 12)§	N/A	10 (5 – 15.25)†	N/A	N/A	26% 18.3%
Pinhati HM (2016)	N/A	N/A	N/A	22 (0 – 83)† 25 (7 – 134)†	any: 47.6% any: 42.1%	N/A	42.9% 47.4%
Aguilar et al. (2015) [15]	N/A	N/A	N/A	20 (5, 37.5) §	Antibiotic therapy:21 (95.4 %)	10 (5.0–16.5)†	13.60%
Fochtmann et al. (2015) [27]	N/A	60 (13–176) †	N/A	16 (6–89) †	Broad-spectrum antibiotic treatment in most patients	16 (6–89)†	30%
Klingspore t al.(2015) [28]	N/A	23 (0–329) †	2 (0-744) †	12 (0–190) †	Broad-spectrum antibiotics in the last 2 weeks: 511 (78.4%)	N/A	38.80%
Chakrabart i et al. (2015) [29]	N/A	N/A	N/A	8 (4, 15) §	Candidemia patients received: antibiotics:93.0%	16.0 (7–36) days§	44.70%

Liao et al. (2015) [14]	Flu-S: 34.5 (18, 65) Flu-R: 48.0 (21, 90)	Flu-S: 22.5 (10.0, 40.0) Flu-R: 29.0 (17, 59)	N/A	Flu-S: 8.0 (3.0, 17.0)§ Flu-R: 10.5 (4.0, 27.0)§	≥5 d before diagnosis: Flu-S: 101 (78.3%) Flu-R: 73 (81.1%)	N/A	Flu-S: 31.8% Flu-R: 41.1%
Kautzky S (2015)	N/A	46 (14 – 74)† 21 (10 – 77)†	17 (1 – 21)† 3 (1 – 66)†	17.4 ± 14.5	100% 90%	N/A	80% 21.7%
Karacaer et al. (2014) [31]	46.8±36.7 (5-190)	32.9±36.9 (0-190)	N/A	N/A	N/A	15 ± 13.8	77.70%
Colombo et al. (2014) [32]	N/A	N/A	N/A	20 (0–188) †	Prior antibiotic expose: 96.1%	N/A	70.30%
Hu et al.(2014) [48]	54.0 (26.0-91.0) §	34.0 (18.0-71.0) §	N/A	11.0 (4.0, 26.0)§	CRCBSI: 100% N CRCBSI:99.5%	CRCBSI: 11.4 ± 4.2 days; N CRCBSI:10.6 ±6.5 day	44.80%
Lortholary O (2014)	N/A	N/A	N/A	N/A	N/A	N/A	51.00% 30.70%
Yapar N (2014)	N/A	30.9±33 12.9±13	N/A	N/A	96.9% 78.3%	N/A	43.9% 32.2%
Guo et al.(2013) [49]	N/A	N/A	N/A	10 (0-330)†	Treatment before diagnostic confirm: 74 (27.6%)	N/A	36.60%
Giri S (2013)	N/A	mean 26.4 (range 9-86) days	N/A	N/A	66.70%	mean 19.45 (range 4-31) days	24%

Tortorano et al.(2012) [33]	N/A	N/A	N/A	22.8 (2–190)†	broad spectrum antibiotic treatment: 85%	N/A	46.20%
Ylipalosaari et al. (2012) [34]	38.0 (22- 59) §	16.0 (11-30) §	1 (0-2) §	8.0 (1.0, 12.0) §	Previous antibacterial treatment (%): 97.4-95.5%	N/A	65.80%
Pasero D et al. (2011) [35]	N/A	21±7	N/A	20 (8, 49) §	A significantly higher administration of > 2 antibiotics for >72 hours.	N/A	47%
Han SS et al. (2010) [36]	38 (2-141)§	22 (1-141)§	8 (0-92) §	17 (0-117) †	All patients were treated with antibiotics prior to candidaemia onset	16 (1-92) †	96.00%
Pratikaki M et al. (2009) [37]	N/A	25 (14-46)§	14 (1-20) §	10 (3, 22) §	All patients received antimicrobial agents prior to candidaemia onset	N/A	60.60%
Playford et al.(2009) [38]	N/A	NA	N/A	10 (4, 16) §	Antibiotic receipt on days 1–3: 83.4%; Broad-spectrum antibiotic receipt on days 1–3: 82.0%	N/A	10.60%
Holleyetal. (2009) [39]	N/A	*C. albicans*: 29.0±18.5 non-C. albicans: 29.2 ±28.2	N/A	N/A	All patients received antimicrobial agents prior to candidaemia onset	*C. albicans*: 13 (median) non-C. albicans: 15 (median)	C. albicans: 52.9% non-C. albicans: 64.7%
Choi et al. (2009) [40]	*(prior to fungemia)* *Candida albicans*: 42±47 Non-albicans: 38±33	Candida albicans: 19±41 Non-albicans: 25±50	N/A	Candida albicans: 11±25 Non-albicans: 15±31	N/A	N/A	Candida albicans: 48% Non-albicans: 67%

Yap et al (2009) [50]	28 (17-54) §	14 (5-23) §	N/A	6 (1-13)§	Antibiotics > 48 hours before candidaemia: *C. albicans*: 70 (97.0%) *non-C. albicans*: 56 (100%)	N/A	70%
Chow et al. (2008) [41]	*Candida albicans*: 28 (20–42)§ Non-albicans: 37 (24–57)§	*Candida albicans*: 22 (15–33)§ Non-albicans: 25 (14–40)§	N/A	*Candida albicans*: 11 (9, 17) § Non-C. albicans: 10 (4, 21) §	Non-*C. albicans*: 0.75 (0–2) §	2.21 (1.4–2.7)§	*Candida albicans*: 58% Non-albicans: 57%;
Bougnouxe t al.(2008) [42]	N/A	43.1 ± 45.2	N/A	19.0 ± 2.9 or (13.0; 2-145)§	No antibiotic treatment is reported	N/A	61.80%
Girãoet al.(2008) [43]	N/A	N/A	N/A	*C. albicans*: 15 (mean) Non-C. albicans: 18 (mean)	The hospital is restricted the use of several antibiotics	N/A	*C. albicans*: 72% non-*C.albicans*: 80%
Dimopoulos et al. (2008) [44]	*C. albicans*: 22 ± 7.6 non-C. albicans: 25 ± 8.4	N/A	N/A	*C. albicans*: 12 ± 2.2 non-C. albicans: 10 ± 2.4	100% of patients received broad spectrum antibiotic treatment for>3 days during the ICU stay.	N/A	*C. albicans*: 52.8% non-*C. albicans*: 90%
Dimopoulo set al.(2007) [45]	N/A	N/A	N/A	9 (5–11) †	100% of patients received broad spectrum antibiotic treatment	N/A	N/A
Jordà-Marcos R (2007)	48 (26 – 69) 35 (22 – 57)	28 (17 – 45) 18 (12 – 28)	N/A	23.5 ± 54.7	100% 96.5%	N/A	17.2% 13.2%
Piazza O (2004)	N/A	N/A	N/A	median 13 days	N/A	N/A	67%

Michalopoulos et al. (2003) [46]	N/A	27.1 ± 7.5	N/A	15 (11-23) †	Empiric antibiotic therapy with 2 or more broad-spectrum agents for all patients	N/A	N/A

Abbreviation: ARDS, acute respiratory distress syndrome; CPB, cardiopulmonary bypass; CRCBSI, Candida catheter-related bloodstream infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, invasive candidiasis; IMV, invasive mechanical ventilation; N/A, not available; SAPS II, Simplified Acute Physiology Score II; TPN, total parenteral nutrition.

§ Data are presented as median (interquartile range; IQR).

† Data are presented as median (range).

Five studies reported the mean ICU stay prior to onset of candidemia. In 4 studies, the median ICU stay was ≤ 10 days, including the early-onset group in the study by Yang et al [25] and Flu-S group in the study by Liao et al. [14] with the overall mortality ranged from 28.6% to 70.0%. Three studies reported that the median ICU stay was >10 days prior to candidemia onset with the overall mortality ranged from 40.8% to 44.8%.

Similar to other countries, most of the patients with IC in China received antibiotic treatment prior to candidemia onset in the ICU, which was ranged from 59.0% of patients in the early-onset group [25] to 100% in the CRCBSI group and non-*C. albicans* group [49, 51]. Only one study reported the median duration of antibiotic therapy prior to candidemia onset, which was ranged from 10.6 to 11.4 days [49].

Meta-analysis

Summary of the clinical outcomes for overall studies or given subgroups

The summary of variables such as hospital length of stay, ICU length of stay, duration of ICU admission prior to candidemia onset, length of stay prior to ICU admission, and overall mortality was presented in Table 3. Five studies [14, 25, 47-49] were from China by using China-SCAN patient data, in which four studies were excluded to avoid using repeating data.

Table 3. Summary for length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset, and overall mortality for overall or given subgroups[†‡]

	Length of hospital stay, days	ICU length of stay, days	Duration of ICU admission prior to candidemia onset, days	Length of stay prior to ICU admission, days	Overall mortality
Comparison	**Mean (95%CI.)**	**Mean (95%CI.)**	**Mean (95%CI.)**	**Mean (95%CI.)**	**Rate (95%CI.)**
Overall	36.26(25.84, 46.67)	25.83(23.58, 28.07)	12.93(11.70, 14.15)	11.71(0.37, 23.05)	49.25(45.02, 53.48)
Overall optional[abcd]	[a]37.49(33.33, 41.64)	[b]25.90(23.48, 28.33)	[c]13.73(12.46, 15.00)	—	[d]50.99(46.57. 55.41)
Subgroups					
Type of study					
Prospective	41.01(32.93, 49.09)	27.43(24.59, 30.27)	12.92(11.47, 14.37)	19.21(17.15, 21.27)	42.65(37.89, 47.40)
Retrospective/ Cross-sectional	31.86(18.22, 45.50)	23.85(21.12, 26.57)	13.70(11.16, 16.24)	7.39 (-3.65, 18.44)	56.50(47.95, 65.04)
Presence of neutropenia					
Neutropenia	34.93(19.79, 50.07)	25.42(19.33, 31.50)	11.64(9.53, 13.75)	—	49.55(40.80, 58.30)
Non-neutropenia	22.94(20.88, 25.00)	—	10.00(9.26, 10.74)	—	41.32(7.94, 74.71)
Type of ICU					
ICU	37.73(21.74, 53.71)	27.28(24.89, 29.67)	14.32(5.66, 5.98)	17.17(11.90, 22.44)	49.78(44.285, 55.27)
SICU	—	21.66(19.45, 23.86)	17.31(11.93, 22.70)	—	33.12(15.16, 51.07)

MICU	—	32.74(10.25, 55.23)	17.00(16.22, 17.78)	—	88.44(72.78, 104.10)
MICU+SICU	34.64(28.17, 41.11)	22.50(18.41, 26.59)	10.93(9.55, 12.31)	—	45.71(36.42, 55.00)
C. Albicans					
C. Albicans	34.17(33.08, 35.26)	25.91(22.29, 29.53)	11.00(10.71, 11.29)	—	52.19(40.01, 64.38)
Non C. Albicans	27.01(24.25, 29.78)	24.97(18.02, 31.92)	—	—	—
Presence of IC/candidemia					
Candidemia	36.34(32.89, 39.79)	25.76(23.23, 28.28)	13.24(11.96, 14.53)	10.84(-1.96,23.64)	51.43(47.05, 55.82)
IC	33.85(-3.74, 71.43)	26.42(20.71, 32.13)	11.47(7.63, 15.31)	—	38.94(27.77, 50.10)
Region					
Asia	36.88(22.95, 50.80)	24.95(20.92, 28.98)	17.39(14.62, 20.15)	19.31(17.21, 21.42)	51.16(44.65, 57.67)
Europe/US/Australia	33.26(20.74, 45.79)	27.67(23.27, 32.07)	18.51(15.28, 21.74)	9.61 (-1.20, 20.4)	48.58(42.43, 54.73)
South America	—	—	45.76(27.84, 63.69) *	—	54.37(38.02, 70.72)

Note: Certain subgroups have only 1 study (degree of freedom = 0).

[a] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[b] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[c] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

[d] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

Dash indicates no available

[†] The range width of 95% CI is related to the accuracy of the estimation. The narrower the range, the higher the accuracy of the estimation. If both the upper and lower limits are positive, the clinical outcome estimate for this group of participants is obviously positive, if the lower limit negative and the upper limit is positive, indicating that the clinical outcome estimate for this type of participants is not significantly greater than 0.

[‡]Meta-regression is used to assess the relationship between study level covariates and effect size when obvious heterogeneity in subgroups.

[*] Meta-regression analysis illustrated the South American countries were significantly longer than the Asian, European, Australian, and North American countries in the mean of duration of ICU admission prior to candidemia onset (Asia as reference group, South America $\beta = 25.83$, $p = 0.0308$, $R^2 = 0.097$). Other meta-regression analysis in subgroups in this table did not reach statistical significance.

For overall studies, the length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset, length of stay prior to ICU admission and overall mortality rate were derived as a mean of 36.26 days (95% CI: 25.84 - 46.67), 25.83 days (95% CI: 23.58 - 28.07), 12.93 days (95% CI: 11.70 - 14.15), 11.71 days (95% CI: 0.365 - 23.05), and rate of 49.25% (95% CI: 45.02% - 53.48%), respectively. When the four China-SCANE studies were excluded from the analysis, length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset were derived as a mean of 37.49 days (95% CI: 33.33 - 41.64), 25.90 days (95% CI: 23.48 - 28.33), 13.73 days (95% CI: 12.46 - 15.00), and the overall mortality was 50.99% (95% CI: 46.57% - 55.41%), respectively (Table 3). The clinical outcomes were also summarized for subgroups of studies (with studies' number ≥2) given the type of study, presence of neutropenia, type of ICU, type of *C. Albicans* isolated, presence of IC/candidemia, and region of countries. The interval estimate showed the summarized statistics of subgroups were all significant except for

length of hospital stay of patients with IC present, length of stay prior to ICU admission of patients selected from retrospective or cross-sectional type of studies and patients with candidemia presents (95% CI included zero) (Table 3).

According to the summarized statistics, those studies with neutropenic patients had a greater length of hospital stay (mean=34.93 vs. 22.94 days), a longer duration of ICU admission prior to candidemia onset (mean=11.64 vs. 10.0 days), and a higher overall mortality rate (rate: 49.55% vs. 41.32%) compared to those with non-neutropenic patients. The duration of ICU admission prior to candidemia onset had a mean of 17.31 days, 17 days, 14.32 days, and 10.93 days for studies with patients in surgical ICU (SICU), medical ICU (MICU), ICU, and MICU+SICU, respectively. Patients with candidemia had a greater length of hospital stay (mean=36.34 vs. 33.85), longer duration of ICU admission prior to candidemia onset (mean=13.24 vs. 11.47), and a higher overall mortality rate (51.43% vs. 38.94%) compared with patients without IC. However, patients with candidemia had a shorter length of ICU stay (mean=25.76 vs. 26.42 days) and length of stay prior to ICU admission (mean=10.84 vs. 15.20 days) than patients with IC. Furthermore, patients with *C. albicans* also had a higher duration of ICU admission prior to candidemia onset compared to patients with other species of *C. albicans* (mean=11 vs. 10 days). The mean duration of ICU admission prior to candidemia onset in patients in hospitals was 18.51 days (95% CI=15.28 – 21.74 days) in Europe, 17.39 days (95% CI: 14.62 – 20.15 days) in Asia, and 45.77 days (95% CI: 27.84 – 63.69 days) in South America. Data from Giro et al.[43] and Gong et al.[47] were excluded from the summarized analysis due to a lack of standard deviations for mean values and unavailability of data ranges.

Broad-spectrum antibiotic use prior to candidemia onset, length of stay prior to ICU admission, and overall mortality

In order to compare whether there is a differences in the proportion of broad-spectrum antibiotic use between IC patients and non-IC patients, we reviewed the identified publications and excluded studies containing control groups (non-invasive candida infection) and studies with a clear number of broad-spectrum antibiotics utilized. After pooling the study data, IC patients were found to have utilized a higher proportion of broad-spectrum antibiotics (89.13%, 95% CI: 82.68%-93.37%) before IC onset, which was higher than non-IC patients (77.36%, 95% CI: 52.25%-91.43%), even if it has not yet reached statistical significance. The mean duration of antibiotic therapy prior to candidemia onset was 17.77 days (95% CI: 9.30 - 26.25), but the duration of broad-spectrum antibiotic use prior to the infection was not included due to the limitation of data. Only five studies reported length of stay prior to ICU admission and the mean was 11.71 days (95% CI: 0.37 - 23.05). The overall mortality rate was increased from 49.25% to 50.99% after excluding four China-SCAN studies (Table 3).

Comparing the effect between Candida albicans* vs. *non-Candida albicans

A meta-analysis was performed to compare the effect of length of hospital stay, ICU length of stay, and overall mortality between studies of patients infected with *C. albicans* and different strains of *Candida*. Three studies examined length of hospital stay (Choi et al 2009, Chow et al. 2008, Dimopoulos et al 2008), three studies examined ICU length of stay (Holley et al 2009, Choi et al 2009, Chow et al. 2008), and six studies examined overall mortality (Gong et al 2016, Holley et al 2009, Choi et al 2009, Chow et al. 2008, Giral et al 2008, Dimopoulos et al 2008) and were

selected for the meta-analysis. According to the heterogeneity test, a random effect model was applied for length of hospital stay (Q value=25.47, I-squared value = 92.1%, p<0.001) and overall mortality rate (Q-value=399, I-squared value=98.7%, p<0.001) and a fixed effect model for ICU length of stay (Q value = 1.56, I-squared value = 0%, p=0.458). The pooled effect demonstrated that there was no significant difference in length of stay and overall mortality between patients with and without *C. albicans* (Figure 2A, 2C; both p>0.05). However, there was a significant difference in mean length of ICU stay between patients with and without *C. albicans* (difference in means = 2.82 days, Figure 2B, P<0.001).

Quality assessment

The results of the quality assessment are shown in Table 4. For the results of ROBINS-I, 9 studies had serious bias due to confounding because no baseline confounding or appropriate analysis methods were used to adjust for important baseline confounding. Five studies had serious bias in the selection of participants due to unclear inclusion and exclusion criteria. Most of studies had low or moderate bias in classification of interventions. No studies provided the information of systematic differences between experimental intervention and comparator groups due to lack of comparison of two intervention groups. All studies had low or moderate bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Overall, 28 studies had moderate risk of bias, thirteen had serious risk of bias, and one had unclear information regarding the risk of bias.

Meta-regression of clinical outcomes

A meta-regression analysis demonstrated that South American countries were significantly longer than the Asian, European, Australian, and North American

countries for mean duration of ICU admission prior to candidemia onset (Asia as reference group, South America $\beta = 25.83$, $p = 0.0308$, $R^2 = 0.097$). Other meta-regression analysis in subgroups did not reach statistical significance (Table 3). The level of risk of bias (moderate/serious or no information) was also included in the meta-regression analysis and the coefficient was not found to achieve statistically significant results.

Table 4. Quality assessment of included studies using ROBINS-I

1st Author (year)	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ding et al. (2018)	low	moderate	low	no information	moderate	low	low	moderate
Zhao et al. (2018)	low	low	no information	no information	low	low	low	moderate
Baldesi et al. (2017)	low	moderate	no information	no information	low	low	low	moderate
Kawano et al. (2017)	serious	moderate	low	no information	low	low	low	serious
Rudramurthy et al. (2017)	low	low	low	no information	low	low	low	moderate
Tukenmez Tigen et al. (2017)	serious	moderate	low	no information	low	low	low	serious
Yang et al. (2017)	low	low	low	no information	low	low	moderate	moderate
Gong et al. (2016)	serious	moderate	low	no information	low	low	low	serious
OrtízRuiz et al. (2016)	low	low	low	no information	low	low	low	moderate
Pinhati et al. (2016)	moderate	moderate	low	no information	low	low	low	moderate
Playford et al. (2016)	low	moderate	no information	no information	low	low	low	moderate
Aguilar et al. (2015)	no information	moderate	low	no information	low	low	low	moderate
Chakrabarti et al. (2015)	serious	low	low	no information	low	low	low	serious

Fochtmann et al. (2015)	low	moderate	low	no information	low	low	low	moderate
Kautzky et al. (2015)	serious	low	no information	no information	low	low	low	serious
Klingspor et al.(2015)	low	moderate	low	no information	low	low	low	moderate
Liao et al. (2015)	low	moderate	low	no information	low	low	low	moderate
Karacaer et al. (2014)	moderate	moderate	low	no information	low	low	low	moderate
Colombo et al. (2014)	low	moderate	low	no information	low	low	low	moderate
Hu et al.(2014)	low	moderate	low	no information	low	low	low	moderate
Lortholary et al. (2014)	low	serious	low	no information	low	low	moderate	serious
Yapar et al. (2014)	moderate	moderate	low	no information	low	low	low	moderate
Giri et al. (2013)	serious	moderate	low	no information	low	low	low	serious
Guo et al.(2013)	low	low	low	no information	low	low	low	moderate
Tortorano et al.(2012)	serious	moderate	low	no information	low	low	low	serious
Ylipalosaari et al. (2012)	moderate	moderate	low	no information	low	low	low	moderate
Pasero et al. (2011)	low	low	low	no information	low	low	low	moderate
Han et al. (2010)	low	serious	no information	no information	low	low	low	serious
Pratikaki et al. (2009)	moderate	low	low	no information	low	low	low	moderate

Playford et al.(2009)	no information	low	no information	no information	low	low	low	no information
Holley et al.(2009)	low	serious	low	no information	low	low	low	serious
Choi et al. (2009)	low	serious	low	no information	low	low	low	serious
Yap et al. (2009)	no information	moderate	low	no information	low	low	low	moderate
Chow et al. (2008)[a]	low	low	low	no information	low	low	low	moderate
Chow et al. (2008)[b]	low	moderate	low	no information	low	low	low	moderate
Bougnoux et al. (2008)	no information	low	low	no information	low	low	low	moderate
Girãoet al. (2008)	no information	serious	low	no information	low	low	low	moderate
Dimopoulos et al. (2008)	low	low	low	no information	low	low	low	moderate
Dimopoulos et al. (2007)	serious	low	low	no information	low	low	low	serious
Jordà-Marcos et al. (2007)	low	moderate	low	no information	low	low	low	moderate
Piazza et al. (2004)	serious	low	moderate	no information	moderate	low	low	serious
Michalopoulos et al. (2003)	low	low	no information	no information	low	low	low	moderate

[a], Chow JK[1], Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg D, Chawla V, Young J, Hadley S. Factors associated with candidemia caused by non-albicans Candida species versus Candida albicans in the intensive care unit. Clin Infect Dis. 2008 Apr 15;46(8):1206-13. doi: 10.1086/529435.

[b], Chow JK[1], Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg DA, Chawla V, Young JA, Hadley S. Risk factors for albicans and non-albicans candidemia in the intensive care unit. Crit Care Med. 2008 Jul;36(7):1993-8. doi: 10.1097/CCM.0b013e31816fc4cd.

Publication bias

Egger's test showed potential publication bias for length of hospital stay (1-tailed P < 0.001) and duration of ICU admission prior to candidemia onset (1-tailed P = 0.004), and no significant publication bias for length of ICU stay (1-tailed P = 0.37) and overall mortality (1-tailed P = 0.38). The classic fail-safe N tests indicated that the number of missing studies which would be needed to make the P-values of the summary effect become insignificant was 65,685 for length of stay, 2,304 for ICU length of stay, 89,242 for duration of ICU admission prior to candidemia onset, and 34,263 for overall mortality. These results indicated that the significance of the observed effects of the meta-analyses would not be influenced by the inclusion of additional studies (Figure 3A-C).

DISCUSSION

The current meta-analysis demonstrated that the pooled mean of duration of ICU admission prior to candidemia varied from approximately 17 days within hospital settings in Asia, to 19 days in Europe, to 46 days in South America. Most of the IC patients had received broad-spectrum antibiotics (89%), and the mean duration of antibiotic therapy prior to candidemia onset was nearly 18 days. The pooled mean mortality rate was approximately 49%. There was no significant difference in length of stay or overall mortality between patients with and without *C. albicans,* but the mean length of ICU stay was greater for patients with *C. albicans* compared to those patients without *C. albicans*.

Seven studies were performed in hospitals in China (Table 1). Two studies evaluated patients with *Candida albicans* vs. non-*Candida albicans* candidemia. One study compared patients with catheter-related *Candida* bloodstream infection

(CRCBSI) vs. non-CRCBSI, and the other study compared patients with a fluconazole-resistant vs. fluconazole-sensitive (Flu-S) infection. The mean length of hospital stay ranged from 4 (early-onset group) to 54 days, and the mean length of ICU stay ranged from 14 to 34 days. The majority of studies (n=29) were performed in countries other than China [14, 25, 48-51]. Of these, 7 were case-control or cross-sectional studies, and 34 were retrospective or prospective cohort studies. Eleven were designed to compare patients with and without candidemia. Five studies compared patients with candidemia based on *C. Albicans* vs. another *Candida* strain, and only 1 study compared ICU-acquired candidemia vs. non-ICU acquired candidemia [34]. Most of the studies (n=24) were conducted in general ICUs, and the others in SICUs or in cardio-surgical/cardiothoracic ICUs (CICU) [47], or medical ICUs [36], suggesting that invasive candidiasis is a common problem in critically ill patients regardless of the type of ICU. The mean length of hospital stay ranged from 22 to 51 days, and the mean length of ICU stay ranged from 7 days to 60 days (Table 2). In 9 studies, the median length of ICU stay was ≤ 10 days prior to onset of IC, and the overall mortality in ICU patients with candidemia in those studies ranged from 10.6% to 65.8%. In the other studies with a median ICU length of stay > 10 days prior to onset of IC, the overall mortality ranged from 13.6% to 96.0%.

The duration of ICU stay varied widely prior to candidemia onset which indicated that the onset of IC may be initiated by distinct risk factors in the ICU, and the time point to encounter these risk factors was different among critically ill patients. As we have mentioned previously, the major cause of severe candidiasis has been the endogenous colonization of *Candida* species that requires a 7 to 10-day period for the development of IC after exposure to risk factors [20]. In addition, the median time for obtaining positive blood cultures was 2–3 days (possibly up to ≥7

days) [2]. Therefore, for patients with a confirmed diagnosis of candidemia onset at 8 days after ICU admission, the endogenous colonization of *Candida* species may have occurred in patients on the first day of ICU admission. Similarly, for the patients with a confirmed diagnosis of candidemia at 12-13 days after ICU admission, the endogenous colonization of *Candida* species may have also occurred 3-5 days after ICU admission.

The main risk factor for candidemia was systemic antibiotic use [16]. In a previously reported study in pediatric ICUs, it was reported that treatment with vancomycin or anti-anaerobic antibiotics for >3 days were independently associated with the development of candidemia [2], but only in an unadjusted analysis [16]. Overuse and prolonged exposure to broad-spectrum antibiotics have been found that closely associates them with candidemia in both China and India [52, 53]. Therefore, it may be suggested that overuse of broad-spectrum antibiotics may be associated with early-onset of candidemia after ICU admission in China. A study in Hong Kong found that candidemia occurred in patients within 6 days of being admitted to the ICU, and more than 97.0% of patients infected with fungi of *Candida* species had received >48 hours of antibiotic treatment [51]. Regardless of geographical differences, most patients with IC received broad-spectrum antibiotic treatment prior to candidemia onset in the ICU. However, due to a lack of sufficient data, any potential correlation between prolonged exposure to broad-spectrum antibiotics and the time of candidemia onset after ICU admission and the further explanation of the longer duration of ICU admission prior to candidemia onset in South America than in Asia/Europe/US/Australia could not be assessed in this systematic review.

The current results demonstrated that there was no significant difference in length of hospital stay prior to the development of IC or overall mortality between patients

with and without *C. albicans* IC. This may be due to the clinical presentation and the treatment of patients with candidemia caused by *C. albicans* and non-*C.albicans* were indistinguishable [54]. Although it was found that the mortality rates in patients with *C. albicans* and non-*C. albicans* was similar, the susceptibilities of these strains to anti-fungal agents were different [21, 55, 56]..

This systematic review had several limitations. This systematic review was lacking a pre-specified protocol and its preliminary registration, the biased post hoc decisions in review methods may occur. A number of the trials reported outcomes using median (range) and/or median (IQR). In order to combine results, the sample mean and standard deviation for such trials was estimated using a method proposed by Wan et al. [24]. This method was based under the assumption that the data were normally distributed. Across the meta-analysis, however, medians and quartiles were often reported when data did not follow a normal distribution [23]. This possibility may have confounded the results. The results of the quality assessment indicated that potential biases from confounders may be present. High heterogeneity had existed in the overall and subgroup analyses, suggesting the complexity of the risk factors causing IC and candidemia (Supplementary Table S1).

Although meta-regression analysis in different design, country, and risk of bias et al, which may be find the heterogeneity between groups were assessed in this study, there may still be other potential factors that explain heterogeneity that requires further study. Besides the factors analyzed in the subgroup analyses, there may be other factors influencing heterogeneity such as comorbidities, severity of illness, and invasive procedures (e.g., hemodialysis, invasive mechanical ventilation, total parenteral nutrition, surgery, and immunosuppression), which were not taken into account in this analysis. Publication bias may have also possibly existed in some

analyzed outcomes.

This systematic review indicated that patients who received broad-spectrum antibiotics and who were admitted to the ICU were associated with the development of candidemia. Patients with *C. albicans* infection had longer ICU stays. In this setting, the choice of early detection and therapeutic intervention strategies for IC should strengthen implementation to optimize patients' management to reduce the risk of infection and potentially save the excessive consumption of medical resources.

Acknowledgements

The medical writing and editorial assistance were provided by Elizabeth Goodwin and Prof. Jerry Tseng of MedCom Asia Inc., China. This assistance was funded by MSD China. The authors initiated the concept for this systematic review and are responsible for the content of the manuscript.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' contributions:

ZDZ: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

RZ: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

ZGL: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

XCM: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

Data sharing statement: No unpublished data are available.

Patient consent for publication: Not required.

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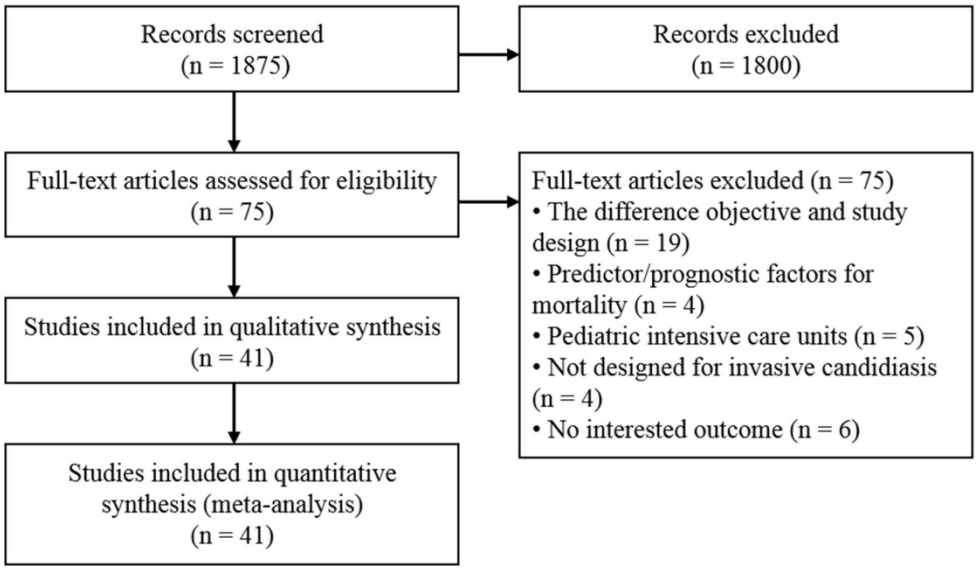
Figure legends

Figure 1. PRISMA flow diagram of study selection

Figure 2. Meta-analysis of *C. albicans* vs. non-*C. albicans* for A) length of hospital stay; B) ICU length of stay; and C) Overall mortality

Figure 3. Funnel plot for A) length of hospital stay; B) ICU length of stay; C) duration of ICU admission prior to candidemia onset



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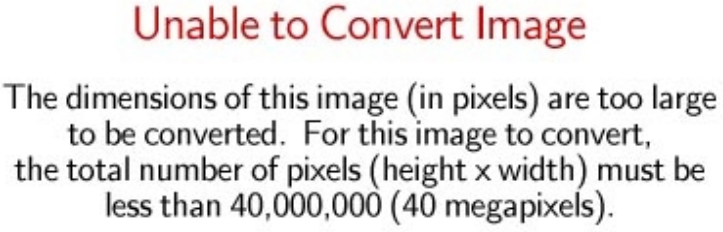
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Figure 3A

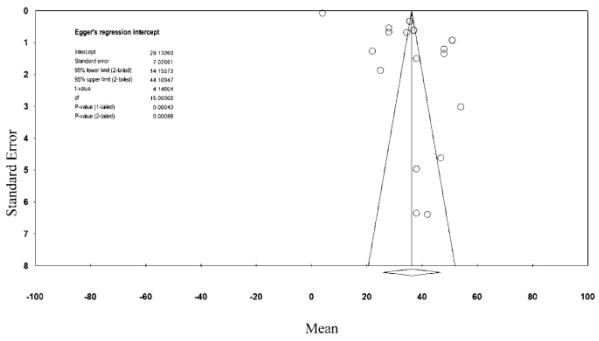


Figure 3B

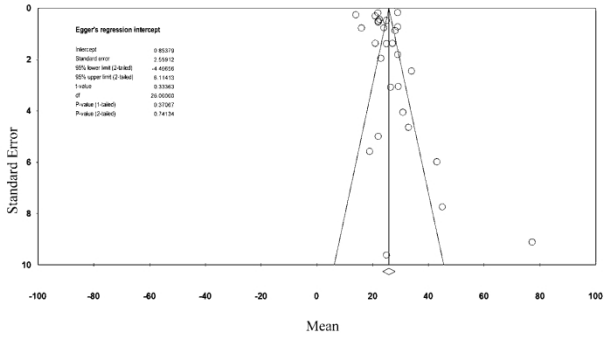
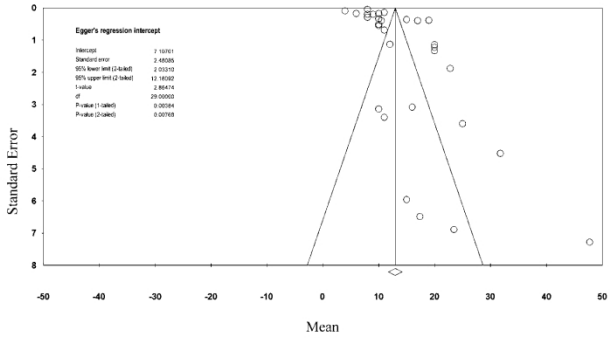


Figure 3C



Supplementary Table S1. A supplementary information of heterogeneity test for overall studies or given subgroup for Table 3.

Comparison	Length of hospital stay, days				ICU length of stay, days				Duration of ICU admission prior to candidemia onset, days				Length of stay prior to ICU admission, days				Overall mortality rate			
	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value
Overall	16	20197.0	99.92	<0.001	27	2690.9	99.00	<0.001	30	4686.2	99.36	<0.001	4	311.2	98.71	<0.001	39	26981.1	99.86	<0.001
Overall optional[abcd]	[a]13	850.7	98.47	<0.001	[b]25	2626.7	99.05	<0.001	[c]26	2649.8	99.02	<0.001					[d]35	24273.9	99.86	<0.001
Subgroups																				
Type of study																				
Prospective	7	568.3	98.77	<0.001	12	662.2	98.19	<0.001	16	1572.3	98.98	<0.001	1	0.9	0.35	<0.001	20	13805.2	99.86	<0.001
Retrospective	8	14000.4	99.94	<0.001	14	893.2	98.43	<0.001	13	2670.7	99.51	<0.001	2	28.39	92.95	<0.001	18	9479.2	99.81	<0.001
Presence of neutropenia																				
Neutropenia	7	6119.9	99.89	<0.001	8	2297.7	99.65	<0.001	11	3099.9	99.65	<0.001	0	-	-	-	11	15935.0	99.93	<0.001
Non-neutropenia	1	1.8	42.97	0.185	0			-	1	0	0	1	0	-	-	-	2	1388.4	99.86	<0.001
Type of ICU																				
ICU	7	11712.8	99.94	<0.001	16	930.6	98.28	<0.001	13	1589.8	99.18	<0.001	1	4.14	75.86	0.042	23	13807.9	99.83	<0.001
SICU				-	1	0.7	0.00	0.404	2	31.2	93.60	<0.001	0	-	-	-	2	1005.5	99.80	<0.001
MICU	0			-	1	6.2	83.92	0.013-	1	0	0	1-	0	-	-	-	1	14.3	92.99	<0.001
MICU+SICU	7	776.9	99.10	<0.001	6	713.7	99.16	<0.001	11	1539.5	99.29	<0.001	0	-	-	-	10	8098.2	99.88	<0.001

C. Albicans																		
C. Albicans	2	114.7	98.26	<0.001	2	5.79	65.45	0.055	1	0	0	1				5	1558.5	99.68	<0.001
Non C. Albicans	1	2.262	55.78	0.133	1	5.4	81.37	0.021	0	-	-	-				-	-	-	-
Presence of IC/candidemia																		
Candidemia	13	651.6	98.01	<0.001	23	2620.0	99.12	<0.001	24	2517.8	99.05	<0.001	3	302.3	99.01	<0.001	32	18755.6	99.83	<0.001
IC	2	2588.9	99.92	<0.001	3	17.0	82.33	0.001	5	1169.4	99.57	<0.001	0	-	-	-	6	3922.9	99.85	<0.001
Region																		
Asia	8	5464.6	99.85	<0.001	11	738.6	98.51	<0.001	11	2189.9	99.50	<0.001	1	1.4	26.82	0.242	16	8966.6	99.82	<0.001
Europe	3	226.5	98.68	<0.001	8	346.7	97.69	<0.001	10	907.3	98.90	<0.001	2	37.9	94.72	<0.001	13	7933.8	99.84	<0.001
South America	0	-	-	-	0	-	-	-	2	19.6	89.80	<0.001	-	-	-	-	4	1960.7	99.80	<0.001

Note: Certain subgroups have only 1 study (degree of freedom = 0).

[a] Excluded Yang et al. (2017),Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[b] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015),and Guo et al. (2013).

[c] Excluded Yang et al. (2017),Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

[d] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015),and Hu et al. (2014).

Dash indicates no available.

ZMR060116

Date of Issue: **December 2, 2019**

CERTIFICATION

This is to certify that a medical editor who is a native English speaker associated with MedCom Asia, Inc., has edited the manuscript entitled

"The risk of invasive candidiasis with prolonged duration of ICU stay and broad-spectrum antibiotic use: a systematic review and meta-analysis"

This manuscript has been sent back to the author on **December 2, 2019**. If there is any change on the manuscript by the author after the above-mentioned date, this certificate is invalid. The medical editor who edited the manuscript has been a professional editor and writer for several years and is a member of American Medical Writers Association.

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PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	34
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	33
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	28
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	38
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	38
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	41
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	41
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	42

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

The risk of invasive candidiasis with prolonged duration of ICU stay and broad-spectrum antibiotic use: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036452.R1
Article Type:	Original research
Date Submitted by the Author:	17-Feb-2020
Complete List of Authors:	Zhang, Zhidan; the First Hospital of China Medical University, Department of Critical Care Medicine Zhu, Ran; the First Hospital of China Medical University, Department of Critical Care Medicine Luan, Zhenggang; the First Hospital of China Medical University, Department of Critical Care Medicine Ma, Xiaochun; the First Hospital of China Medical University, Department of Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	ACCIDENT & EMERGENCY MEDICINE, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS

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The risk of invasive candidiasis with prolonged duration of ICU stay and broad-spectrum antibiotic use: a systematic review and meta-analysis

Running title: Duration of ICU prior to candidemia

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ABSTRACT

Objective: This study aimed to evaluate the duration of intensive care unit (ICU) stay prior to onset of invasive candidiasis (IC)/candidemia.

Design: Systematic review and meta-analysis.

Data Sources: Pubmed, Cochrane**,** Embase, and Web of Science databases were searched through June, 2019 to identify the relevant studies.

Eligibility Criteria: Adult patients who had been admitted to the ICU and developed an invasive candidiasis infection.

Data extraction and synthesis: The following data were extracted from each article: ICU length of stay in hospital, length of stay prior to ICU admission, duration of ICU stay prior to candidemia onset, antibiotic therapy prior to candidemia onset, duration of antibiotic therapy prior to candidemia onset, and overall mortality. In addition to traditional meta-analyses, meta-regression was also used to explore possible mediators that might further explain heterogeneity.

Results: The mean age of patients ranged from 28 to 76 years across studies. The pooled mean duration of ICU stay before the onset of candidemia was 12.9 days (95% confidence interval [CI]: 11.7 – 14.2). The pooled mean duration of ICU admission prior to the onset of candidemia ranged from 4 to 47 days. The pooled mean duration of hospital stay was 36.3±5.3 days (95% CI: 25.8 – 46.7) and the pooled mean mortality rate was 49.3±2.2% (95% CI: 45.0% – 53.5%). There was no significant difference in duration of hospital stay (P = 0.528) or overall mortality (P=0.111) between patients with or without *C. albicans,* yet a significant difference was demonstrated in mean length of ICU stay (2.8 days, P < 0.001). The meta-regression

analysis found that South American countries had significantly longer mean duration of ICU admission prior to candidemia onset compared with Asian, European, Australian, and North American countries.

Conclusions: Patients with IC are possibly associated with the use of broad-spectrum antibiotics and length of ICU stay, with the shortest duration of IC onset in Asia. Thus, the current findings demonstrate that a more proactive strategy for the diagnosis of IC should be considered in these patients, especially relevant for Asian physicians.

KEYWORDS: Invasive candidiasis, candidemia, intensive care unit, length of stay, antibiotic, mortality

Strengths and limitations of this study

- This meta-analysis is one of few that investigated the association of IC with the length of ICU stay, using data published worldwide and adhering to the PRISMA guideline.
- Extensive subgroup analyses were performed and meta-regression was made to examine possible causes of heterogeneity in the results.
- Although this meta-analysis was performed methodically, it lacked a pre-specified protocol and preliminary registration.
- Heterogeneity exists in some subgroup and overall analyses.
- Due to a lack of sufficient published data, relationship between prolonged exposure to broad-spectrum antibiotics and ICU-acquired candidemia could not be assessed.

INTRODUCTION

Candida species account for 70% to 90% of invasive fungal infections and are the most frequent cause of fungal infections in patients admitted to the intensive care unit (ICU) [1]. Invasive candidiasis (IC) is associated with a high mortality rate (range: 40% to 60%) [1, 2]. Over recent decades, the incidence of IC has been gradually increasing in most regions [3], ranging from 0.5 to 32 cases per 1,000 ICU admissions. It has been found that there is a significant difference in the incidence of IC among several countries in Latin America and North America; however, data from Asia-Pacific countries are still relatively rare [4]. Candidemia has been described as the most common manifestation of IC, and the further infection of the liver, spleen, heart valves, or eye might also occur after a bloodstream infection [5]. In the past, the main *Candida* species isolated from patients with IC was *C. albicans*. However, non-*C. albicans* species has seen a rising proportion and now account for approximately 50% of all cases of IC in the past two decades [1,6-8].

Diagnosis and management of IC remains challenging for physicians in the ICU [1, 2]. The early initiation of empiric antifungal treatment has been demonstrated to improve the prognosis of invasive candidiasis [2, 9]. However, there is difficulty in the diagnosis of IC which can delay timely antifungal treatment [2, 10]. Blood culture remains the gold standard for the diagnosis of invasive candidiasis, but its sensitivity is variable (21% to 71%) [11].

In order to improve the diagnosis of IC, and to identify the patients who may best benefit from prophylactic, preemptive, or empirical therapy prior to, or at an early stage of ICU admission several methods in predicting the development of IC based on their associated risk factors have been developed [12, 13]. The risk factors in the

various predictive models include broad-spectrum antibiotic use, central venous catheter placement, total parenteral nutrition, hemodialysis (days 1–3 in the ICU), any surgery, immunosuppressive use, pancreatitis prior to ICU admission, and steroid use. However, different risk factors are included in the different predictive models. In addition, potential risk factors such as *Candida* colonization [14] and mechanical ventilation [15] have not been included in these models.

Long-term ICU stay has been reported as a risk factor for IC [11, 14-16]. Only a few studies have examined the interval between ICU admission or initiation of broad-spectrum antibiotics and the diagnosis of IC. However, the specific duration of long-term ICU stays and the prolonged use of broad-spectrum antibiotics are often arbitrarily defined and inconsistent among studies [6, 12, 15, 17-19]. Furthermore, a large majority of severe candidiasis cases are caused by endogenous colonization. This may be the primary reason for causing a delay of 7 to 10 days between exposure to risk factors and the development of IC [20].

Thus, the objective of this systematic review was to evaluate the risk factors associated with the development of candidemia, specifically the length of ICU stay and the use of broad-spectrum antibiotics.

METHODS

Search strategy

The study was performed in accordance with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed, Cochrane, Embase, and Web of Science databases were searched through June, 2019 using the following terms: invasive candidiasis, critical care, critical illness, risk factors, candidemia, and antibiotic agents. Studies identified by the search strategy

were reviewed for inclusion and data were extracted by two independent reviewers. Where there was uncertainty regarding study eligibility, a third reviewer was consulted. A flow chart of the study selection is shown in Figure 1.

Study selection criteria and data extraction

Randomized controlled trials (RCTs), cohort studies, case-controlled, and cross-sectional studies were included. All studies included adult patients who were critically ill, who had been admitted to the ICU, and who were tested positive for *Candida* species using blood culture analyses. Studies had to have reported quantitative outcomes of interest and no author was contacted. Letters, comments, editorials, case reports, proceedings, personal communications, and case series were excluded. Studies in which patients were diagnosed with candidiasis prior to ICU admission were excluded. Studies that did not evaluate the incidence of candidiasis as a primary objective, or that were not designed to evaluate risk factors/prognostic factors of patients with candidiasis were also excluded.

The following information / data was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, country, study design, type of ICU, number of participants in each group, participants' age and gender, the presence of *C. albicans*, the presence of neutropenia, and antifungal treatment (especially the use of broad-spectrum antibiotics). The following data were also extracted from each article: length of stay in hospital/ICU, length of stay prior to ICU admission, duration of ICU stay prior to candidemia onset, antibiotic therapy prior to candidemia onset, duration of antibiotic therapy prior to candidemia onset, and overall mortality.

Quality assessment

We used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool to assess the quality of the included studies [21]. ROBINS-I is based on the Cochrane RoB tool and is suited for evaluating non-randomized studies that compare the health effects of different interventions. ROBINS-I covers 7 different bias domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in the selection of reported results [22-23]. In this systematic review, 2 independent reviewers performed the quality assessment, with a third reviewer consulted for any uncertainties.

Patient and public involvement

Since no patients and/or members of the public were involved in the process of designing, planning and completing this study, ethical approval, informed consent, and institutional review board's review were not required.

Statistical analysis

Study characteristics were summarized as mean±standard deviations (SD), mean (range), median (range), or median (IQR) for age or duration of antifungal treatment; and percentage (%) for sex, rate of *C. albicans* isolated, neutropenia, and antifungal treatment used in each study.

Clinical outcomes, including hospital stay, ICU length of stay, length of stay prior to ICU admission, duration of ICU admission prior to candidemia onset, and duration of antibiotic therapy prior to candidemia onset were represented as mean

(range: [min. – max.]), median (range), or median (IQR [interquartile range: 1st – 3rd quartiles]). The rate of antibiotic therapy prior to candidemia onset and overall mortality rate were presented as a percentage (%), according to the data extracted from the study. All the clinical outcomes were further summarized for overall studies, or subgroups of studies (with studies' number ≥2) given type of study, presence of neutropenia, type of ICU, type of *Candida* isolated, presence of IC/candidemia, and region/country, and meta-regression analyses were further used to investigate statistical importance of the potential moderators. Before summarizing, studies that reported quantitative data with median (range) and/or median interquartile range (IQR) were transformed into mean ± SD according to Wan et al. [24]

The outcomes selected for the analysis were length of hospital stay, ICU length of stay, duration of ICU admission prior to candidemia onset, and overall mortality compared between subgroups, *C. albicans* and non-*C. albicans*. The effect size was calculated as mean difference with 95% CI (Lower, Upper limit) and significance of *p*-values in length of days, or rate ratio with 95% CI and p-values in overall mortality for each given study, and then a pooling effect was derived thereafter. A difference in means of length days <0 (or rate ratio of overall mortality rate >1) indicated the pooling effect favored non- *C. albicans* subgroup, whereas difference in means of length days >0 (or rate ratio of overall mortality rate <1) indicated the pooling effect favored *C. albicans* subgroup. A difference in means of length days = 0 (or rate ratio of overall mortality rate = 1) indicated the pooling effect was similar between *C. albicans* and non-*C. albicans* subgroups. Heterogeneity was evaluated using a χ^2-based Cochran's Q statistic and I^2, that the random effect model (DerSimonian-Laird method) and meta-regression analyses with potential moderators were considered for the meta-analysis if either Q statistic with P values < 0.10 or

I^2>50% were derived; otherwise, a fixed effect model (Mantel-Haenszel method) was considered for the meta-analysis. For the Q statistic, P values < 0.10 were considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was assessed as follows: no heterogeneity (I^2 = 0 - 25%), moderate heterogeneity (I^2 =25 - 50%), large heterogeneity (I^2 = 50 - 75%), and extreme heterogeneity (I^2= 75 - 100%). A two-sided P value of <0.05 was considered significant.

Countries were grouped based on their continents, but since meta-analysis of this particular topic has not yet been seen in China, research from China will be separately examined and discussed.

The publication bias was assessed using the funnel plot with Egger's test and Classical fail-safe N test for all enrolled studies (except for subgroups). The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution and a 1-tailed significance level of P > 0.05 in an Egger's test.[25] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 3.3.070 (Biostat, Englewood, NJ, USA).

RESULTS

Literature search results

A total of 1875 articles were retrieved by the primary search, and 1800 articles were excluded after the title and abstract were screened based on the inclusion/exclusion criteria (Figure 1). Seventy-five articles underwent full-text review, and 34 articles were excluded for having irrelevant objectives or study designs (n=19), containing patients in neonatal or pediatric intensive care unit (n=5), not designed for invasive candidiasis (n=4), and not reporting outcomes of interest (n=6). Thus, 41 articles were included in the systematic review and meta-analysis.

Study characteristics

The characteristics of the 41 studies are summarized in Table 1 and Table 2 [14-16, 26, 27-29, 30-63]. A total of 10,692 patients were included across the studies, with the number of patients in each study ranging from 12 to 1,400. The mean age of the patients ranged from 28 to 76 years. Majority of the patients were males (range: 20% to 75.9%). These studies were conducted in different countries: 19 in Europe, 14 in Asia, 1 in the US, 4 in South America, 2 in Australia and 1 multinational study (Australia, Belgium, Greece, Brazil).

Table 1. Characteristics of studies included in this systematic review

Studies 1st Author (year)	Country	Study design	Type of ICU	Total number of patients	IC and Candidemia	No. of patients	Age (years)	Male (%)	*C.Albicans* isolated (%)	Neutropenia (%)	Antifungal treatment	
											Duration of treatment	Antifungal treatment used
Zhao H (2018) [51]	China	retrospective cohort	ICU		Candidemia	95	69.3±16.5	57.9 %	59	—	—	17.90%
Ding R (2018) [52]	China	retrospective cohort	ICU	72	Candidemia	72	62.5 (49.8, 77.0)§	62.5 %	15	—	—	Fluconazole 30.6% Voriconazole 9.7% Echinocandin 44.4%
Yang et al. (2017) [26]	China	Retrospective cohort study (China-SCAN)	ICU	306	Early-onset IC	105	56.9 (19.9)§	64.8 %	47.7	1.9%	—	Fluconazole (39.3%) Caspofungin(21.3%) Voriconazole (19.1%) Micafungin(10.1%) Itraconazole(5.6%) Amphotericin B (3.4%) Combined therapy (1.1%)
					Late-onset IC	201	64.0 (19.7)§	70.6 %	36.1	1.5%	—	Fluconazole (36.9%) Caspofungin(25.1%) Voriconazole (17.9%) Micafungin(7.8%) Itraconazole(9.5%) Amphotericin B (1.7%) Combined therapy (1.1%)

Tigen E (2017) [53]	Turkey	Case-control study	ICU	73	Candidemia	36	65 (52-73)†	52.8 %	75		17.6 ± 117 days	Caspofungin Posaconazole Voriconazole Itraconazole Fluconazole Amphotericin B
					Control (Non-Candidemia)	37	62 (48-72)†	48.6 %	—	—	—	—
Baldesi O (2017) [54]	France	Case-control study	ICU	246,459	Candidemia	851	65 [54; 75]§	62.6 %	61.40	5.1%	—	—
					Control (Non-Candidemia)	245,608	65 [52; 76]§	61.7 %	—	1.6%	—	—
Rudramurthy SM (2017) [55]	India	prospective cohort	MICU, SICU	1161	Candidemia (C. auris)	74	39 (16 – 58.5)§	62.2 %	—	—	—	fluconazole (20.3) echinocandin(9.5)
					Candidemia (non - C. auris)	1087	—	—	—	—	—	fluconazole(12.1) echinocandin(0.8)
Kawano Y (2017) [56]	Japan	retrospective cohort	ICU	4,136	Candidemia	25	69 (24 – 88)†	56.0 %	52	0	—	antifungal treatment: 32%
OrtízRuiz et al. (2016) [16]	Colombia	Case-control study	Polyvalent, cardiovascularICU	243	Candidemia	81	64.5 (51-78) §	51.9 %	42	—	—	—
					Control	162	68 (48-77) §	59.3 %	—	—	—	—

Gong et al. (2016) [47]	China	Prospective, cohort study (China-SCAN)	MICU, SICU, Integrated ICU	306	Candidemia (*C. albicans*)	98	62.2±17.3	62.2 %	100	3.1%	12.85 days	Triazole (64.7%) Echinocandin (31.8%) Polyenes (0%)
					Candidemia (Non-*C. albicans*)	146	61.4±21.4	72.6 %	—	1.4%	20.4 days	Triazole (62.8%) Echinocandin (34.1%) Polyenes (2.3%)
Playford EG (2016) [57]	Australia	prospective cohort	MICU, SICU	6,714	ICU-aquired IC	96	—	—	66	—	—	—
					Control (no IC)	6618	—	—	—	—	—	—
Pinhati HM (2016) [58]	Brazil	cross-sectional	ICU	40	fluconazole-resistant *C. parapsilosis* (FRCP)	21	70 (23 – 91)†	66.7 %	—	—	—	any: (33.3) fluconazole: (19.0)
					fluconazole-susceptible *Candida* species (FSC)	19	76 (35 – 90)†	57.9 %	—	—	—	any: (15.8) fluconazole: (15.8)
Aguilar et al. (2015) [15]	Spain	Prospective cohort study	SICU	22	IC	22	66 (53.7–74.2) §	72.7 %	59.1	—	10 (5.0–16.5) days	Echinocandins (86.4%) Fluconazole (13.6%)
Fochtmann et al. (2015) [27]	Austria	Retrospective cohort study	Burn ICU	174	Candidemia	20	39 (17–88) †	60%	60	—	—	Triazoles (70%)
					Control	154	58 (17–94) †	61%		—	—	Echinocandins (30%)

Klingsporet al.(2015) [28]	14 countries in Europe	Prospective cohort study	SICU	807	IC	779	63(0–91) †	62.5 %	54	—	—	Fluconazole (60%) Caspofungin (18.7%) Amphotericin B (13%) Voriconazole (4.8%)
Chakrabarti et al. (2015) [29]	India	Prospective cohort study	MICU, SICU	1400	Candidemia	1400	49.7 ± 17.7	—	20.9	1.3%	9.0 (5-15)§ days	Azoles (72.0%) Echinocandins (18.3%) Amphotericin B (14.4%)
Liao et al. (2015) [14]	China	Prospective cohort study (China-SCAN)	MICU, SICU, Mix ICU	306	Flu-S	129	62.4±19.5	68.2 %	60.5	3.1%	—	Monoantifungaltherapy (64.5%) Fungal drug adjustment (35.7%) Completely improved(34.6%)
					Flu-R	90	60.8±20.9	67.8 %	17.8	1.1%	—	Monoantifungaltherapy (48.8%) Fungal drug adjustment (61.1%) Completely improved (28.0%)
Kautzky S (2015) [59]	Austria	prospective cohort	MICU	65	IC (invasive *Candida* infection)	5	28.2 ± 97	20%	—	0%	15.40 ± 13.9	100%
					control (non-invasive *Candida* infection)	60	52.7 ± 15.7	72%	—	8.3%	—	60.00%
Karacaer et al. (2014) [31]	Turkey	Prospective cohort study	ICU service	burn 2362	IC	63	70.2 ± 19.5	54%	64	—	—	—

							(14-95)					
Colombo et al. (2014) [32]	Brazil	Retrospective cohort study	ICU	1,392	Candidemia	647	66 (18–97) †	50.7	44	2.5%	—	Amphotericin B (period 1:27.8%; period 2: 13.4%) Echinocandins(period 1: 5.9%; period 2: 18.0%)
Hu et al.(2014) [48]	China	Prospective cohort study (China-SCAN)	ICU	294	CRCBSI	29	69.4 ± 19.1	75.9 %	28.6	—	19.0 ± 13.3 days	Fluconazole (39.3%) Caspofungin(25.0%) Voriconazole(14.3%) Micafungin (10.70%) Itraconazole(10.7%) Amphotericin B (0%) Two-drug combination (0%)
					Non-CRCBSI	265	60.7±20.2	68.3 %	40.3	—	16.7 ± 13.3 days	Fluconazole (36.7%) Caspofungin(23.6%) Voriconazole(19.2%) Micafungin (8.7%) Itraconazole(7.9%) Amphotericin B(2.2%) Two-drugs combination(1.7%)
Lortholary O (2014) [60]	France	prospective cohort	ICU	2507	ICU-aquired candidemia	1206	60 ± 17	62.0 %	57.10	—	—	Fluconazole(55.4 %) Echinocandins(26.2 %) Others (including combination)(12.6 %)
					non-ICU aquired candidemia	1301	60 ± 17	58.7 %	54.90	—	—	Fluconazole(59.9 %) Echinocandins(19.1 %) Others (including combination)(13.3 %)

Yapar N (2014) [61]	Turkey	retrospective cohort	ICU	1076	Candidemia	66	54.4 ± 23.9	53%	53	—	—	9%
					Control (non-Candidemia)	1010	53.2 ± 23.0	63%	—	—	—	6.30%
Guo et al.(2013) [49]	China	Prospective cohort study (China-SCAN)	MICU SICU General Emergency Neurologic ICU	306	Candidemia	306	61.5±20.0	68.6 %	40.2	1.6%	14 (0-104)† days	Fluconazole (37.7%) Caspofungin (23.9%) Voriconazole (18.3%)
Giri S (2013) [30]	India	prospective cohort	ICU	5,976	Candidemia	39	35.14 (3days-79 y)	61.5 %	4			
Tortorano et al.(2012) [33]	Italy	Prospective cohort study	MICU, SICU	384	Candidemia	276	—	—	60.9	—	—	Fluconazole (63%) Amphotericin B (22%) Caspofungin (7%) Voriconazole (6%)
Ylipalosaari et al. (2012) [34]	Finland	Retrospective cohort study	MICU,SICU	82	ICU-acquired candidemia	38	63 (45-69) §	71%	76.3	—	Median: 22 days	Fluconazole (73%) Amphotericin B (34%) Echinocandins (31%)
					non-ICU-acquired candidemia	44	64 (56-75) §	61%	68.9	—	Median: 24 days	Fluconazole (77%) Amphotericin B (35%) Echinocandins (40%)
Pasero D et al. (2011) [35]	Italy	Prospective cohort study	SICU	349	Candidemia	26	60±21	61.5 %	73	—	—	—

					Control	323	67±16	65.3 %		—	—	—
Han SS et al. (2010) [36]	Korea	Case-control study	MICU	52	Candidemia	49	57.6±14.1	—	65	25%	11 (1-45)† days	Amphotericin B (71.4%) Fluconazole (28.6%)
					Control	147	57.4±14.0	—	—	8%		
Pratikaki M et al. (2009) [37]	Greece	Case-control study	Multi-disciplinary ICU	855	Candidemia	33	57±18	64%	33.3	0%		Amphotericin B (57.1%)
					Control	132	58±18	70%	—	0%	>14 days	Voriconazole(17.9%), Caspofungin (14.3%) Fluconazole (10.7%)
Playford et al.(2009) [38]	Australia	Prospective cohort study	MICU, SICU	615	IC	15	NA	NA	73.3	0%	—	—
Holleyetal.(2009) [39]	Australia, Belgium, Greece, Brazil	Retrospective cohort study	Multi-disciplinary ICU	189	Candidemia (*C. albicans*)	104	56.5±17.1	63.5 %	100	—	1(1-32)†days	Fluconazole (37%) Amphotericin B (31%)
					Candidemia (Non-*Candida albicans*	85	58.9±16.3	44.7 %	—	—		Fluconazole and amphotericin B (15%)
Choi et al. (2009) [40]	Korea	Retrospective cohort study	ICU	497	Candidemia (*C. albicans*)	54	49±23	44.4 %	100	13%	—	Amphotericin B (77.8%) Fluconazole (16.7%)
					Candidemia	27	48±25	44.4 %	—	19%	—	Fluconazole and amphotericin B (5.6%)

					(*C. glabrata*or, *C. krusei*)							
Yap et al (2009) [50]	China Hong Kong	Retrospective cohort study	MICU SICU	128	Candidemia	128	54 (43-68) §	63.3 %	56	11%	—	Amphotericin B (39.1%) Fluconazole (38%) Amphotericin B+fluconazole (13%) Caspofunginorvoriconazole(9 .8%)
Chow et al. (2008) [41]	US	Case-control study	MICU, SICU	926	Candidemia (Non-*Candida albicans*)	67	62.3±14.5	57%	—	—	—	Fluconazole(84.8%) Amphotericin B (23.9%) Caspofungin(10.9%) Voriconazole(4.3%)
					Candidemia (*C. albicans*)	79	57±17.0	60%	100	—	—	Fluconazole (63%) Amphotericin B (33.3%) Caspofungin (11.1%) Voriconazole (0%)
					Control	780	62.3±17.4	56%	—	—	—	Fluconazole (100%) Amphotericin B (14.3%) Caspofungin (0%) Voriconazole (0%)
Bougnouxet al.(2008) [42]	France	Prospective cohort study	MICU SICU HU BU	290	Candidemia	57	56.1±18.2	67%	54.2	19.3%	13.2±10.3 days	Fluconazole(78.3%) Amphotericin B(52.2%) Flucytosine(15.2%)
Girão et al.(2008) [43]	Brazil	Prospective cohort study	ICU	73	Candidemia (Non-*Candida*	40	51(12-86) *	60%	—	—	—	—

					albicans)							
					Candidemia (*C. albicans*)	33	51(15-86) *	40%	100	—	—	—
Dimopoulos et al. (2008) [44]	Greece	Prospective cohort study	MICU, SICU	56	Candidemia (*C. albicans*)	36	60.5 ± 14.9	44.4 %	100	0% (excluded)	Response rate: (80.6%)	Fluconazole as prophylaxis: Amphotericin B (75%) Caspofungin (25%) No fluconazole as prophylaxis: Amphotericin B (60%) Caspofungin (40%)
					Candidemia (Non-*Candida albicans*)	20	64.5± 16.8	55%	—		Response rate: (45%)	Amphotericin B (100%)
Dimopouloset al.(2007) [45]	Greece	Prospective cohort study	MICU, SICU	24	Candidemia	24	—	—	62.5	—	16.5 (14-24)*days	C. albicans: fluconazole Non-albicans: amphotericin B
Jordà-Marcos R (2007) [62]	Spain	prospective cohort	MICU, SICU	1765	Candidemia	63	63 (48 – 70)†	71.4 %	57.10	6.3%	—	7.90%
					Control (non-Candidemia)	1072	63 (46 – 71)†	66.5 %	—	2.8%	—	5.60%
Piazza O (2004) [63]	Italy	retrospective cohort	ICU	478	Candidemia	12	57.58± 22.07	58.3 %	67	—	—	—

Michalopoulos et al. (2003) [46]	Greece	Prospective case- control study	CICU	150	Candidemia	30	63.2±9.7	73.3 %	70	—	—	—
					Control	120	64.3±9.9	73.3 %	—	—	—	—

Abbreviations: CICU, cardiothoracic ICU; CRCBSI, Catheter-related Candida bloodstream infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, Invasive candidiasis; MICU, medical ICU; SICU, surgical ICU.

Total number of enrolled patients: 7,982.

* Data were presented as mean (range).

† Data were presented as median (range).

§ Data were presented as median (IQR).

Dash indicates no available data.

Table 2. Length of stay, antibiotic therapy prior to candidemia onset, and overall mortality

Studies 1st Author (year)	Hospital stay (days)	ICU length of stay (days)	Length of stay prior to ICU admission (days)	Duration of ICU admission prior to candidemia onset (days)	Rate of antibiotic therapy prior to candidemia onset	Duration of antibiotic therapy prior to candidemia onset (days)	Overall mortality rate
Zhao H (2018) [51]	N/A	24 (12-57)†	N/A	N/A	N/A	N/A	58%
Ding R (2018) [52]	N/A	N/A	N/A	N/A	Broad-spectrum antibiotics: 98.6%	N/A	31.90%
Yang et al. (2017) [26]	(prior to IC diagnosis) Early-onset IC:4 (2, 7)§ Late-onset IC: 26 (16, 50)§	N/A	N/A	Early-onset IC: 4 (1, 7)§ Late-onset IC: 17 (10, 33)§	Early-onset IC: 62 (59.0%) Late-onset IC: 179 (89.1%)	N/A	Early-onset IC: 28.6% Late-onset IC: 40.8%
Tigen E (2017) [53]	N/A	22 (18-30)† 5.5 (2.25-15.75)†	N/A	N/A	Broad-spectrum antibiotic: 100% Broad-spectrum antibiotic: 59.5%	N/A	83.30%
Baldesi O (2017) [54]	N/A	29 (18; 49) § 7 (4; 13) §	N/A	N/A	antimicrobials: 82.2% antimicrobials: 55.1%	N/A	52.40% 17.80%
Rudramurthy SM (2017) [55]	N/A	N/A	N/A	10 (4.7 – 22.2)§ 7 (3 – 13)§	N/A	N/A	41.90% 27%

Kawano Y (2017) [56]	N/A	N/A	N/A	13 (1 – 73)†	Broad-spectrum antimicrobial: 84%	N/A	72%
OrtízRuiz et al. (2016) [16]	35.4±3.0	21.9±1.7	N/A	Median 25	Broad-spectrum antibiotic: 93.8 vs. 69.8% (case vs. control)	N/A	39.51%
Gong et al. (2016) [47]	*Candida albicans*: Median: 32 Non-*C. albicans*: Mediian: 44	*Candida albicans*: Median: 18 Non-*C. albicans*: Median: 29	N/A	N/A	*Candida albicans* (before diagnosis): 76 (77.6%) Non-*albicans*(before diagnosis): 121 (82.9%)	N/A	*Candida albicans* (before diagnosis): 29.6% Non-*albicans*(before diagnosis): 26.7%
Playford EG (2016) [57]	51 (34 – 89)§ 23 (13 – 40)§	21 (14 – 32)§ 8 (5 – 12)§	N/A	10 (5 – 15.25)†	N/A	N/A	26% 18.3%
Pinhati HM (2016) [58]	N/A	N/A	N/A	22 (0 – 83)† 25 (7 – 134)†	any: 47.6% any: 42.1%	N/A	42.9% 47.4%
Aguilar et al. (2015) [15]	N/A	N/A	N/A	20 (5, 37.5) §	Antibiotic therapy:21 (95.4 %)	10 (5.0–16.5)†	13.60%
Fochtmann et al. (2015) [27]	N/A	60 (13–176) †	N/A	16 (6–89) †	Broad-spectrum antibiotic treatment in most patients	16 (6–89)†	30%
Klingspore t al.(2015) [28]	N/A	23 (0–329) †	2 (0-744) †	12 (0–190) †	Broad-spectrum antibiotics in the last 2 weeks: 511 (78.4%)	N/A	38.80%
Chakrabarti et al.	N/A	N/A	N/A	8 (4, 15) §	Candidemia patients received: antibiotics:93.0%	16.0 (7–36) days§	44.70%

(2015) [29]							
Liao et al. (2015) [14]	Flu-S: 34.5 (18, 65) Flu-R: 48.0 (21, 90)	Flu-S: 22.5 (10.0, 40.0) Flu-R: 29.0 (17, 59)	N/A	Flu-S: 8.0 (3.0, 17.0)§ Flu-R: 10.5 (4.0, 27.0)§	≥5 d before diagnosis: Flu-S: 101 (78.3%) Flu-R: 73 (81.1%)	N/A	Flu-S: 31.8% Flu-R: 41.1%
Kautzky S (2015) [59]	N/A	46 (14 – 74)† 21 (10 – 77)†	17 (1 – 21)† 3 (1 – 66)†	17.4 ± 14.5	100% 90%	N/A	80% 21.7%
Karacaer et al. (2014) [31]	46.8±36.7 (5-190)	32.9±36.9 (0-190)	N/A	N/A	N/A	15 ± 13.8	77.70%
Colombo et al. (2014) [32]	N/A	N/A	N/A	20 (0–188) †	Prior antibiotic expose: 96.1%	N/A	70.30%
Hu et al.(2014) [48]	54.0 (26.0-91.0) §	34.0 (18.0-71.0) §	N/A	11.0 (4.0, 26.0)§	CRCBSI: 100% N CRCBSI:99.5%	CRCBSI: 11.4 ± 4.2 days; N CRCBSI:10.6 ±6.5 day	44.80%
Lortholary O (2014) [60]	N/A	N/A	N/A	N/A	N/A	N/A	51.00% 30.70%
Yapar N (2014) [61]	N/A	30.9±33 12.9±13	N/A	N/A	96.9% 78.3%	N/A	43.9% 32.2%
Guo et al.(2013) [49]	N/A	N/A	N/A	10 (0-330)†	Treatment before diagnostic confirm: 74 (27.6%)	N/A	36.60%
Giri S (2013) [30]	N/A	mean 26.4 (range 9-86) days	N/A	N/A	66.70%	mean 19.45 (range 4-31) days	24%

Tortorano et al.(2012) [33]	N/A	N/A	N/A	22.8 (2–190)†	broad spectrum antibiotic treatment: 85%	N/A	46.20%
Ylipalosaari et al. (2012) [34]	38.0 (22- 59) §	16.0 (11-30) §	1 (0-2) §	8.0 (1.0, 12.0) §	Previous antibacterial treatment (%): 97.4-95.5%	N/A	65.80%
Pasero D et al. (2011) [35]	N/A	21±7	N/A	20 (8, 49) §	A significantly higher administration of > 2 antibiotics for >72 hours.	N/A	47%
Han SS et al. (2010) [36]	38 (2-141)§	22 (1-141)§	8 (0-92) §	17 (0-117) †	All patients were treated with antibiotics prior to candidaemia onset	16 (1-92) †	96.00%
Pratikaki M et al. (2009) [37]	N/A	25 (14-46)§	14 (1-20) §	10 (3, 22) §	All patients received antimicrobial agents prior to candidaemia onset	N/A	60.60%
Playford et al.(2009) [38]	N/A	NA	N/A	10 (4, 16) §	Antibiotic receipt on days 1–3: 83.4%; Broad-spectrum antibiotic receipt on days 1–3: 82.0%	N/A	10.60%
Holleyetal. (2009) [39]	N/A	*C. albicans*: 29.0±18.5 non-*C. albicans*: 29.2 ±28.2	N/A	N/A	All patients received antimicrobial agents prior to candidaemia onset	*C. albicans*: 13 (median) non-*C. albicans*: 15 (median)	*C. albicans*: 52.9% non-*C. albicans*: 64.7%
Choi et al. (2009) [40]	*(prior to fungemia)* *Candida albicans*: 42±47 Non-*C. albicans*: 38±33	*Candida albicans*: 19±41 Non-*C. albicans*: 25±50	N/A	*Candida albicans*: 11±25 Non-*C. albicans*: 15±31	N/A	N/A	*Candida albicans:* 48% Non-C. *albicans*: 67%

Yap et al (2009) [50]	28 (17-54) §	14 (5-23) §	N/A	6 (1-13)§	Antibiotics > 48 hours before candidaemia: *C. albicans*: 70 (97.0%) *non-C. albicans*: 56 (100%)	N/A	70%
Chow et al. (2008) [41]	*Candida albicans*: 28 (20–42)§ Non-*C. albicans*: 37 (24–57)§	*Candida albicans*: 22 (15–33)§ Non-*C. albicans:* 25 (14–40)§	N/A	*Candida albicans*: 11 (9, 17) § Non-*C. albicans*: 10 (4, 21) §	Non-*C. albicans*: 0.75 (0–2) §	2.21 (1.4–2.7)§	*Candida albicans*: 58% Non-albicans: 57%;
Bougnouxe t al.(2008) [42]	N/A	43.1 ± 45.2	N/A	19.0 ± 2.9 or (13.0; 2-145)§	No antibiotic treatment is reported	N/A	61.80%
Girão et al.(2008) [43]	N/A	N/A	N/A	*C. albicans*: 15 (mean) Non-*C. albicans*: 18 (mean)	The hospital is restricted the use of several antibiotics	N/A	*C. albicans*: 72% non-*C.albicans*: 80%
Dimopoulo s et al. (2008) [44]	*C. albicans*: 22 ± 7.6 non-*C. albicans*: 25 ± 8.4	N/A	N/A	*C. albicans*: 12 ± 2.2 non-*C. albicans*: 10 ± 2.4	100% of patients received broad spectrum antibiotic treatment for>3 days during the ICU stay.	N/A	*C. albicans*: 52.8% non-*C. albicans*: 90%
Dimopoulo set al.(2007) [45]	N/A	N/A	N/A	9 (5–11) †	100% of patients received broad spectrum antibiotic treatment	N/A	N/A
Jordà-Marc os R (2007) [62]	48 (26 – 69) 35 (22 – 57)	28 (17 – 45) 18 (12 – 28)	N/A	23.5 ± 54.7	100% 96.5%	N/A	17.2% 13.2%
Piazza O (2004) [63]	N/A	N/A	N/A	median 13 days	N/A	N/A	67%

Michalopoulos et al. (2003) [46]	N/A	27.1 ± 7.5	N/A	15 (11-23) †	Empiric antibiotic therapy with 2 or more broad-spectrum agents for all patients	N/A	N/A

Abbreviation: ARDS, acute respiratory distress syndrome; CPB, cardiopulmonary bypass; CRCBSI, Candida catheter-related bloodstream infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, invasive candidiasis; IMV, invasive mechanical ventilation; N/A, not available; SAPS II, Simplified Acute Physiology Score II; TPN, total parenteral nutrition.

§ Data are presented as median (interquartile range; IQR).

† Data are presented as median (range).

Five studies reported the mean ICU stay prior to onset of candidemia. In 4 studies, the median ICU stay was ≤ 10 days, including the early-onset group in the study by Yang et al [26] and Flu-S group in the study by Liao et al. [14] with the overall mortality ranged from 28.6% to 70.0%. Three studies reported that the median ICU stay was >10 days prior to candidemia onset with the overall mortality ranged from 40.8% to 44.8%.

Similar to other countries, most of the patients with IC in China received antibiotic treatment prior to candidemia onset in the ICU, which was ranged from 59.0% of patients in the early-onset group [26] to 100% in the CRCBSI group and non-*C. albicans* group [49, 51]. Only one study reported the median duration of antibiotic therapy prior to candidemia onset, which was ranged from 10.6 to 11.4 days [49].

Meta-analysis

Summary of the clinical outcomes for overall studies or given subgroups

The summary of variables such as hospital length of stay, ICU length of stay, duration of ICU admission prior to candidemia onset, length of stay prior to ICU admission, and overall mortality was presented in Table 3. Five studies [14, 26, 47-49] were from China by using China-SCAN patient data, in which four studies were excluded to avoid using repeating data.

Table 3. Summary for length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset, and overall mortality for overall or given subgroups[†‡]

	Length of hospital stay, days	ICU length of stay, days	Duration of ICU admission prior to candidemia onset, days	Length of stay prior to ICU admission, days	Overall mortality
Comparison	**Mean (95%CI.)**	**Mean (95%CI.)**	**Mean (95%CI.)**	**Mean (95%CI.)**	**Rate (95%CI.)**
Overall	36.3(25.8, 46.7)	25.8(23.6, 28.1)	12.9(11.7, 14.2)	11.7(0.4, 23.1)	49.3(45.0, 53.5)
Overall optional[abcd]	[a]37.5(33.3, 41.6)	[b]25.9(23.5, 28.3)	[c]13.7(12.5, 15.0)	—	[d]51.0(46.6. 55.4)
Subgroups					
Type of study					
Prospective	41.0(32.9, 49.1)	27.4(24.6, 30.3)	12.9(11.5, 14.4)	19.2(17.2, 21.3)	42.7(37.9, 47.4)
Retrospective/ Cross-sectional	31.9(18.2, 45.5)	23.9(21.1, 26.6)	13.7(11.2, 16.2)	7.4 (-3.7, 18.4)	56.5(48.0, 65.0)
Presence of neutropenia					
Neutropenia	34.9(19.8, 50.1)	25.42(19.33, 31.50)	11.64(9.53, 13.75)	—	49.6(40.8, 58.3)
Non-neutropenia	22.9(20.9, 25.0)	—	10.0(9.3, 10.7)	—	41.3(7.9, 74.7)
Type of ICU					
ICU	37.7(21.7, 53.7)	27.3(24.9, 29.7)	14.3(5.7, 6.0)	17.2(11.9, 22.4)	49.8(44.3, 55.3)
SICU	—	21.7(19.5, 23.9)	17.3(11.9, 22.7)	—	33.1(15.2, 51.1)

MICU	—	32.7(10.3, 55.2)	17.0(16.2, 17.8)	—	88.4(72.8, 104.1)
MICU+SICU	34.6(28.2, 41.1)	22.5(18.4, 26.6)	10.9(9.6, 12.3)	—	45.7(36.4, 55.0)
C. Albicans					
C. Albicans	34.2(33.1, 35.3)	25.9(22.3, 29.5)	11.0(10.7, 11.3)	—	52.2(40.0, 64.4)
Non *C. Albicans*	27.0(24.3, 29.8)	25.0(18.0, 31.9)	—	—	—
Presence of IC/candidemia					
Candidemia	36.3(32.9, 39.8)	25.8(23.2, 28.3)	13.2(12.0, 14.5)	10.8(-2.0,23.6)	51.4(47.1, 55.8)
IC	33.9(-3.7, 71.4)	26.4(20.7, 32.1)	11.5(7.7, 15.3)	—	38.9(27.8, 50.1)
Region					
Asia	36.9(23.0, 50.8)	25.0(20.9, 29.0)	17.4(14.6, 20.2)	19.3(17.2, 21.4)	51.2(44.7, 57.7)
Europe/US/Australia	33.3(20.8, 45.8)	27.7(23.3, 32.1)	18.5(15.3, 21.7)	9.6 (-1.2, 20.4)	48.6(42.4, 54.7)
South America	—	—	45.8(27.8, 63.7) *	—	54.4(38.0, 70.7)

Note: Certain subgroups have only 1 study (degree of freedom = 0).

[a] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[b] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[c] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

[d] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

Dash indicates no available

[†] The range width of 95% CI is related to the accuracy of the estimation. The narrower the range, the higher the accuracy of the estimation. If both the upper and lower limits are positive, the clinical outcome estimate for this group of participants is obviously positive, if the lower limit negative and the upper limit is positive, indicating that the clinical outcome estimate for this type of participants is not significantly greater than 0.

[‡]Meta-regression is used to assess the relationship between study level covariates and effect size when obvious heterogeneity in subgroups.

[*] Meta-regression analysis illustrated the South American countries were significantly longer than the Asian, European, Australian, and North American countries in the mean of duration of ICU admission prior to candidemia onset (Asia as reference group, South America $\beta = 25.83$, $p = 0.0308$, $R^2 = 0.097$). Other meta-regression analysis in subgroups in this table did not reach statistical significance.

For overall studies, the length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset, length of stay prior to ICU admission and overall mortality rate were derived as a mean of 36.3 days (95% CI: 25.8 - 46.7), 25.8 days (95% CI: 23.6 - 28.1), 12.9 days (95% CI: 11.7 - 14.2), 11.7 days (95% CI: 0.37 - 23.1), and rate of 49.3% (95% CI: 45.0% - 53.5%), respectively. When the four China-SCANE studies were excluded from the analysis, length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset were derived as a mean of 37.5 days (95% CI: 33.3 - 41.6), 25.9 days (95% CI: 23.5 - 28.3), 13.7 days (95% CI: 12.5 - 15.0), and the overall mortality was 50.99% (95% CI: 46.6% - 55.4%), respectively (Table 3).

The clinical outcomes were also summarized for subgroups of studies (with studies' number ≥2) given the type of study, presence of neutropenia, type of ICU, type of *C. Albicans* isolated, presence of IC/candidemia, and region of countries. The interval

estimate showed the summarized statistics of subgroups were all significant except for length of hospital stay of patients with IC present, length of stay prior to ICU admission of patients selected from retrospective or cross-sectional type of studies and patients with candidemia presents (95% CI included zero) (Table 3).

According to the summarized statistics, those studies with neutropenic patients had a greater length of hospital stay (mean=34.9 vs. 22.9 days), a longer duration of ICU admission prior to candidemia onset (mean=11.6 vs. 10.0 days), and a higher overall mortality rate (rate: 49.6% vs. 41.3%) compared to those with non-neutropenic patients. The duration of ICU admission prior to candidemia onset had a mean of 17.3 days, 17 days, 14.3 days, and 10.9 days for studies with patients in surgical ICU (SICU), medical ICU (MICU), ICU, and MICU+SICU, respectively. Patients with candidemia had a greater length of hospital stay (mean=36.3 vs. 33.9), longer duration of ICU admission prior to candidemia onset (mean=13.2 vs. 11.5), and a higher overall mortality rate (51.4% vs. 38.9%) compared with patients without IC. However, patients with candidemia had a shorter length of ICU stay (mean=25.8 vs. 26.4 days) and length of stay prior to ICU admission (mean=10.8 vs. 15.2 days) than patients with IC. Furthermore, patients with *C. albicans* also had a higher duration of ICU admission prior to candidemia onset compared to patients with other species of *C. albicans* (mean=11 vs. 10 days). The mean duration of ICU admission prior to candidemia onset in patients in hospitals was 18.5 days (95% CI=15.3 – 21.7 days) in Europe, 17.4 days (95% CI: 14.6 – 20.2 days) in Asia, and 45.8 days (95% CI: 27.8 – 63.7 days) in South America. Data from Giro et al.[43] and Gong et al.[47] were excluded from the summarized analysis due to a lack of standard deviations for mean values and unavailability of data ranges.

Broad-spectrum antibiotic use prior to candidemia onset, length of stay prior to ICU admission, and overall mortality

In order to compare whether there is a differences in the proportion of broad-spectrum antibiotic use between IC patients and non-IC patients, we reviewed the identified publications and excluded studies containing control groups (non-invasive candida infection) and studies with a clear number of broad-spectrum antibiotics utilized. After pooling the study data, there is no statistically significant difference in IC patients' use of broad-spectrum antibiotics (89.1%, 95% CI: 82.7%-93.4%) prior to IC onset vs. that of non-IC patients (77.4%, 95% CI: 52.3%-91.4%). The mean duration of antibiotic therapy prior to candidemia onset was 17.8 days (95% CI: 9.3 - 26.3), but the duration of broad-spectrum antibiotic use prior to the infection was not included due to insufficient data. Only five studies reported length of stay prior to ICU admission and the mean was 11.7 days (95% CI: 0.4 - 23.1). The overall mortality rate was increased from 49.3% to 51.0% after excluding four China-SCAN studies (Table 3).

Comparing the effect between Candida albicans* vs. *non-Candida albicans

A meta-analysis was performed to compare the effect of length of hospital stay, ICU length of stay, and overall mortality between studies of patients infected with *C. albicans* and different strains of *Candida*. Three studies examined length of hospital stay (Choi et al 2009, Chow et al. 2008, Dimopoulos et al 2008), three studies examined ICU length of stay (Holley et al 2009, Choi et al 2009, Chow et al. 2008), and six studies examined overall mortality (Gong et al 2016, Holley et al 2009, Choi et al 2009, Chow et al. 2008, Giral et al 2008, Dimopoulos et al 2008) and were selected for the meta-analysis. According to the heterogeneity test, a random effect

model was applied for length of hospital stay (Q value=25.47, I-squared value = 92.1%, p<0.001) and overall mortality rate (Q-value=399, I-squared value=98.7%, p<0.001) and a fixed effect model for ICU length of stay (Q value = 1.56, I-squared value = 0%, p=0.458). The pooled effect demonstrated that there was no significant difference in length of stay between patients with and without *C. albicans* (Figure 2A, p>0.05); however, there was a significant difference in mean length of ICU stay (difference in means = 2.8 days, Figure 2B, P<0.001). There was also no significant difference in overall mortality between patients with and without *C. albicans* (Figure 2C, p>0.05).

Quality assessment

The results of the quality assessment are shown in Table 4. For the results of ROBINS-I, 9 studies had serious bias due to confounding because no baseline confounding or appropriate analysis methods were used to adjust for important baseline confounding. Five studies had serious bias in the selection of participants due to unclear inclusion and exclusion criteria. Most of studies had low or moderate bias in classification of interventions. No studies provided the information of systematic differences between experimental intervention and comparator groups due to lack of comparison of two intervention groups. All studies had low or moderate bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Overall, 28 studies had moderate risk of bias, thirteen had serious risk of bias, and one had unclear information regarding the risk of bias.

Meta-regression of clinical outcomes

A meta-regression analysis demonstrated that South American countries were significantly longer than the Asian, European, Australian, and North American

countries for mean duration of ICU admission prior to candidemia onset (Asia as reference group, South America $\beta = 25.83$, $p = 0.0308$, $R^2 = 0.097$). Other meta-regression analysis in subgroups did not reach statistical significance (Table 3). The level of risk of bias (moderate/serious or no information) was also included in the meta-regression analysis and the coefficient was not found to achieve statistically significant results.

Table 4. Quality assessment of included studies using ROBINS-I

1st Author (year)	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ding et al. (2018) [52]	low	moderate	low	no information	moderate	low	low	moderate
Zhao et al. (2018) [51]	low	low	no information	no information	low	low	low	moderate
Baldesi et al. (2017) [54]	low	moderate	no information	no information	low	low	low	moderate
Kawano et al. (2017) [56]	serious	moderate	low	no information	low	low	low	serious
Rudramurthy et al. (2017) [55]	low	low	low	no information	low	low	low	moderate
Tigen et al. (2017) [53]	serious	moderate	low	no information	low	low	low	serious
Yang et al. (2017) [26]	low	low	low	no information	low	low	moderate	moderate
Gong et al. (2016) [47]	serious	moderate	low	no information	low	low	low	serious
OrtízRuiz et al. (2016) [16]	low	low	low	no information	low	low	low	moderate
Pinhati et al. (2016) [58]	moderate	moderate	low	no information	low	low	low	moderate
Playford et al. (2016) [57]	low	moderate	no information	no information	low	low	low	moderate
Aguilar et al. (2015) [15]	no information	moderate	low	no information	low	low	low	moderate
Chakrabarti et al. (2015) [29]	serious	low	low	no information	low	low	low	serious

Fochtmann et al. (2015) [27]	low	moderate	low	no information	low	low	low	moderate
Kautzky et al. (2015) [59]	serious	low	no information	no information	low	low	low	serious
Klingspor et al.(2015) [28]	low	moderate	low	no information	low	low	low	moderate
Liao et al. (2015) [14]	low	moderate	low	no information	low	low	low	moderate
Karacaer et al. (2014) [31]	moderate	moderate	low	no information	low	low	low	moderate
Colombo et al. (2014) [32]	low	moderate	low	no information	low	low	low	moderate
Hu et al.(2014) [48]	low	moderate	low	no information	low	low	low	moderate
Lortholary et al. (2014) [60]	low	serious	low	no information	low	low	moderate	serious
Yapar et al. (2014) [61]	moderate	moderate	low	no information	low	low	low	moderate
Giri et al. (2013) [30]	serious	moderate	low	no information	low	low	low	serious
Guo et al.(2013) [49]	low	low	low	no information	low	low	low	moderate
Tortorano et al.(2012) [33]	serious	moderate	low	no information	low	low	low	serious
Ylipalosaari et al. (2012) [34]	moderate	moderate	low	no information	low	low	low	moderate
Pasero et al. (2011) [35]	low	low	low	no information	low	low	low	moderate
Han et al. (2010) [36]	low	serious	no information	no information	low	low	low	serious
Pratikaki et al. (2009) [37]	moderate	low	low	no information	low	low	low	moderate

Playford et al.(2009) [38]	no information	low	no information	no information	low	low	low	no information
Holley et al.(2009) [39]	low	serious	low	no information	low	low	low	serious
Choi et al. (2009) [40]	low	serious	low	no information	low	low	low	serious
Yap et al. (2009) [50]	no information	moderate	low	no information	low	low	low	moderate
Chow et al. (2008)[a]	low	low	low	no information	low	low	low	moderate
Chow et al. (2008)[b]	low	moderate	low	no information	low	low	low	moderate
Bougnoux et al. (2008) [42]	no information	low	low	no information	low	low	low	moderate
Girão et al. (2008) [43]	no information	serious	low	no information	low	low	low	moderate
Dimopoulos et al. (2008) [44]	low	low	low	no information	low	low	low	moderate
Dimopoulos et al. (2007) [45]	serious	low	low	no information	low	low	low	serious
Jordà-Marcos et al. (2007) [62]	low	moderate	low	no information	low	low	low	moderate
Piazza et al. (2004) [63]	serious	low	moderate	no information	moderate	low	low	serious
Michalopoulos et al. (2003) [46]	low	low	no information	no information	low	low	low	moderate

[a], Chow JK[1], Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg D, Chawla V, Young J, Hadley S.

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[b], Chow JK[1], Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg DA, Chawla V, Young JA, Hadley S. Risk factors for albicans and non-albicans candidemia in the intensive care unit. Crit Care Med. 2008 Jul;36(7):1993-8. doi: 10.1097/CCM.0b013e31816fc4cd.

Publication bias

Egger's test showed potential publication bias for length of hospital stay (1-tailed P < 0.001) and duration of ICU admission prior to candidemia onset (1-tailed P = 0.004), and no significant publication bias for length of ICU stay (1-tailed P = 0.37) and overall mortality (1-tailed P = 0.38). The classic fail-safe N tests indicated that the number of missing studies which would be needed to make the P-values of the summary effect become insignificant was 65,685 for length of stay, 2,304 for ICU length of stay, 89,242 for duration of ICU admission prior to candidemia onset, and 34,263 for overall mortality. These results indicated that the significance of the observed effects of the meta-analyses would not be influenced by the inclusion of additional studies (Figure 3A-C).

Data sharing

No additional data is available.

DISCUSSION

The current meta-analysis demonstrated that the pooled mean of duration of ICU admission prior to candidemia varied from approximately 17 days within hospital settings in Asia, to 19 days in Europe, to 46 days in South America. Most of the IC patients had received broad-spectrum antibiotics (89%), and the mean duration of antibiotic therapy prior to candidemia onset was nearly 18 days. The pooled mean mortality rate was approximately 49%. There was no significant difference in length of stay or overall mortality between patients with and without *C. albicans,* but the mean length of ICU stay was greater for patients with *C. albicans* compared to those patients without *C. albicans*.

Seven studies were performed in hospitals in China (Table 1). Two studies evaluated patients with *Candida albicans* vs. non-*Candida albicans* candidemia. One study compared patients with catheter-related *Candida* bloodstream infection (CRCBSI) vs. non-CRCBSI, and the other study compared patients with a fluconazole-resistant vs. fluconazole-sensitive (Flu-S) infection. The mean length of hospital stay ranged from 4 (early-onset group) to 54 days, and the mean length of ICU stay ranged from 14 to 34 days. The majority of studies (n=29) were performed in countries other than China. Of these, 7 were case-control or cross-sectional studies, and 34 were retrospective or prospective cohort studies. Eleven were designed to compare patients with and without candidemia. Five studies compared patients with candidemia based on *C. Albicans* vs. another *Candida* strain, and only 1 study compared ICU-acquired candidemia vs. non-ICU acquired candidemia [34]. Most of the studies (n=24) were conducted in general ICUs, and the others in SICUs or in cardio-surgical/cardiothoracic ICUs (CICU) [47], or medical ICUs [36], suggesting that invasive candidiasis is a common problem in critically ill patients regardless of the type of ICU. The mean length of hospital stay ranged from 22 to 51 days, and the mean length of ICU stay ranged from 7 days to 60 days (Table 2). In 9 studies, the median length of ICU stay was ≤ 10 days prior to onset of IC, and the overall mortality in ICU patients with candidemia in those studies ranged from 10.6% to 65.8%. In the other studies with a median ICU length of stay > 10 days prior to onset of IC, the overall mortality ranged from 13.6% to 96.0%.

The duration of ICU stay varied widely prior to candidemia onset which indicated that the onset of IC may be initiated by distinct risk factors in the ICU, and the time point to encounter these risk factors was different among critically ill patients. As we have mentioned previously, the major cause of severe candidiasis has been the

endogenous colonization of *Candida* species that requires a 7 to 10-day period for the development of IC after exposure to risk factors [20]. In addition, the median time for obtaining positive blood cultures was 2–3 days (possibly up to ≥7 days) [2]. Therefore, for patients with a confirmed diagnosis of candidemia onset at 8 days after ICU admission, the endogenous colonization of *Candida* species may have occurred in patients on the first day of ICU admission. Similarly, for the patients with a confirmed diagnosis of candidemia at 12-13 days after ICU admission, the endogenous colonization of *Candida* species may have also occurred 3-5 days after ICU admission.

The main risk factor for candidemia was systemic antibiotic use [16]. In a previously reported study in pediatric ICUs, it was reported that treatment with vancomycin or anti-anaerobic antibiotics for >3 days were independently associated with the development of candidemia [2], but only in an unadjusted analysis [16]. A study in Hong Kong found that candidemia occurred in patients within 6 days of being admitted to the ICU, and more than 97.0% of patients infected with fungi of *Candida* species had received >48 hours of antibiotic treatment [64]. Overuse and prolonged exposure to broad-spectrum antibiotics have been found that closely associates them with candidemia in both China and India [65, 66], so it's reasonable to suspect a link between overuse of broad-spectrum antibiotics and early-onset of candidemia after ICU admission. Regardless of geographical differences, most patients with IC received broad-spectrum antibiotic treatment prior to candidemia onset in the ICU. However, due to a lack of sufficient data, potential correlation between prolonged exposure to broad-spectrum antibiotics and the time of candidemia onset after ICU admission, as well as further explanation of the longer duration of ICU admission prior to candidemia onset in South America than in

Asia/Europe/US/Australia could not be established in this systematic review.

The current results demonstrated that there was no significant difference in length of hospital stay prior to the development of IC or overall mortality between patients with and without *C. albicans* IC. This may be due to the clinical presentation and the treatment of patients with candidemia caused by *C. albicans* and non-*C.albicans* were indistinguishable [67]. Although it was found that the mortality rates in patients with *C. albicans* and non-*C. albicans* was similar, the susceptibilities of these strains to anti-fungal agents were different [21, 68, 69]..

This systematic review had several limitations. This systematic review was lacking a pre-specified protocol and its preliminary registration, the biased post hoc decisions in review methods may occur. A number of the trials reported outcomes using median (range) and/or median (IQR). In order to combine results, the sample mean and standard deviation for such trials was estimated using a method proposed by Wan et al. [24]. This method was based under the assumption that the data were normally distributed. Across the meta-analysis, however, medians and quartiles were often reported when data did not follow a normal distribution [23]. This possibility may have confounded the results. The results of the quality assessment indicated that potential biases from confounders may be present. High heterogeneity had existed in the overall and subgroup analyses, suggesting the complexity of the risk factors causing IC and candidemia (Supplementary Table S1).

Although meta-regression analysis in different design, country, and risk of bias et al, which may be find the heterogeneity between groups were assessed in this study, there may still be other potential factors that explain heterogeneity that requires further study. Besides the factors analyzed in the subgroup analyses, there may be other factors influencing heterogeneity such as comorbidities, severity of illness, and

invasive procedures (e.g., hemodialysis, invasive mechanical ventilation, total parenteral nutrition, surgery, and immunosuppression), which were not taken into account in this analysis. Publication bias may have also possibly existed in some analyzed outcomes.

This systematic review indicated that patients who received broad-spectrum antibiotics and who were admitted to the ICU were associated with the development of candidemia. Patients with *C. albicans* infection had longer ICU stays. In this setting, the choice of early detection and therapeutic intervention strategies for IC should strengthen implementation to optimize patients' management to reduce the risk of infection and potentially save the excessive consumption of medical resources.

Acknowledgements

The medical writing and editorial assistance were provided by Elizabeth Goodwin and Prof. Jerry Tseng of MedCom Asia Inc., China. This assistance was funded by MSD China. The authors initiated the concept for this systematic review and are responsible for the content of the manuscript.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' contributions:

ZDZ: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

RZ: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

ZGL: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

XCM: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

Data sharing statement: No additional data are available.

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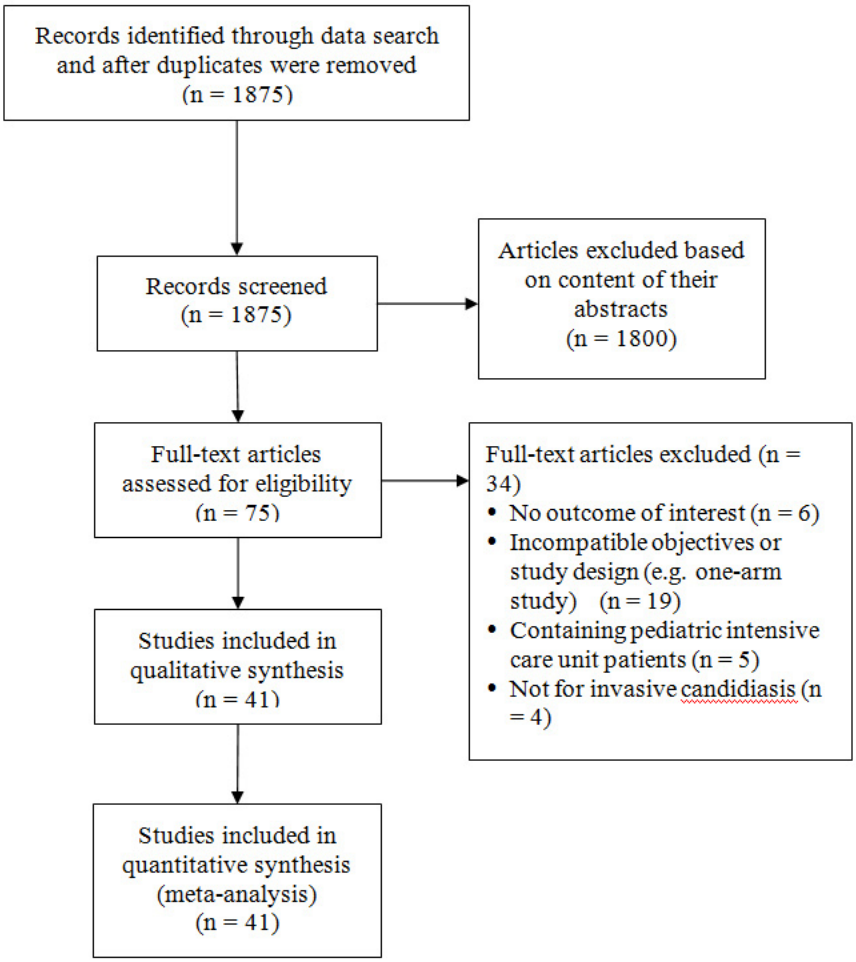
Figure legends

Figure 1. PRISMA flow diagram of study selection

Figure 2. Meta-analysis of *C. albicans* vs. non-*C. albicans* for A) length of hospital stay; B) ICU length of stay; and C) Overall mortality

Figure 3. Funnel plot for A) length of hospital stay; B) ICU length of stay; C) duration of ICU admission prior to candidemia onset



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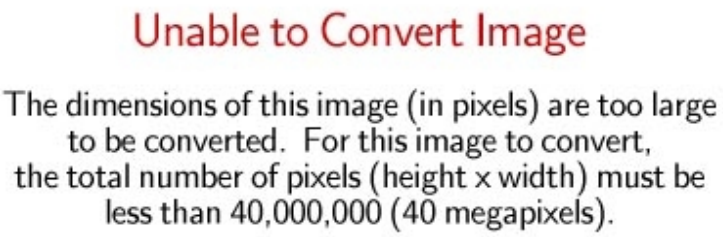
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Figure 3A

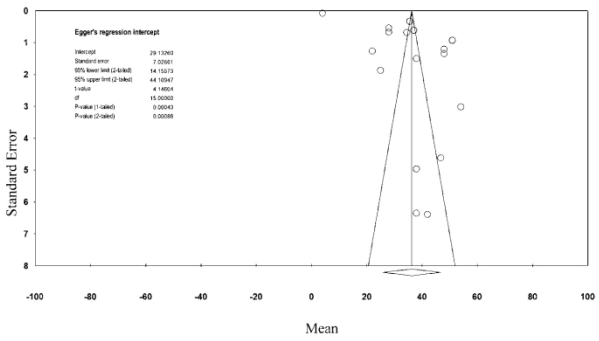


Figure 3B

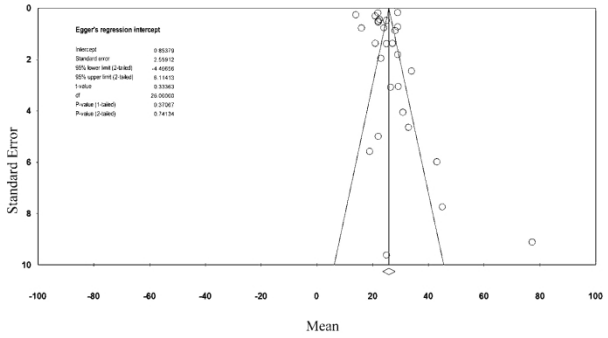
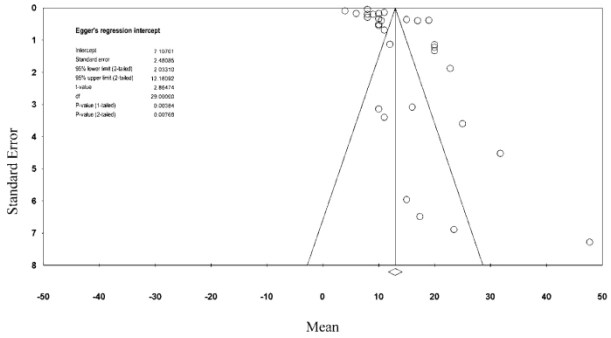


Figure 3C



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Supplementary Table S1. A supplementary information of heterogeneity test for overall studies or given subgroup for Table 3.

Comparison	Length of hospital stay, days				ICU length of stay, days				Duration of ICU admission prior to candidemia onset, days				Length of stay prior to ICU admission, days				Overall mortality rate			
	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value	Degrees of freedom	Q	I^2	P-value
Overall	16	20197.0	99.92	<0.001	27	2690.9	99.00	<0.001	30	4686.2	99.36	<0.001	4	311.2	98.71	<0.001	39	26981.1	99.86	<0.001
Overall optional[abcd]	[a]13	850.7	98.47	<0.001	[b]25	2626.7	99.05	<0.001	[c]26	2649.8	99.02	<0.001					[d]35	24273.9	99.86	<0.001
Subgroups																				
Type of study																				
Prospective	7	568.3	98.77	<0.001	12	662.2	98.19	<0.001	16	1572.3	98.98	<0.001	1	0.9	0.35	<0.001	20	13805.2	99.86	<0.001
Retrospective	8	14000.4	99.94	<0.001	14	893.2	98.43	<0.001	13	2670.7	99.51	<0.001	2	28.39	92.95	<0.001	18	9479.2	99.81	<0.001
Presence of neutropenia																				
Neutropenia	7	6119.9	99.89	<0.001	8	2297.7	99.65	<0.001	11	3099.9	99.65	<0.001	0	-	-	-	11	15935.0	99.93	<0.001
Non-neutropenia	1	1.8	42.97	0.185	0			-	1	0	0	1	0	-	-	-	2	1388.4	99.86	<0.001
Type of ICU																				
ICU	7	11712.8	99.94	<0.001	16	930.6	98.28	<0.001	13	1589.8	99.18	<0.001	1	4.14	75.86	0.042	23	13807.9	99.83	<0.001
SICU				-	1	0.7	0.00	0.404	2	31.2	93.60	<0.001	0	-	-	-	2	1005.5	99.80	<0.001
MICU	0			-	1	6.2	83.92	0.013-	1	0	0	1-	0	-	-	-	1	14.3	92.99	<0.001
MICU+SICU	7	776.9	99.10	<0.001	6	713.7	99.16	<0.001	11	1539.5	99.29	<0.001	0	-	-	-	10	8098.2	99.88	<0.001

C. Albicans																		
C. Albicans	2	114.7	98.26	<0.001	2	5.79	65.45	0.055	1	0	0	1				5	1558.5	99.68	<0.001
Non C. Albicans	1	2.262	55.78	0.133	1	5.4	81.37	0.021	0	-	-	-				-	-	-	-
Presence of IC/candidemia																		
Candidemia	13	651.6	98.01	<0.001	23	2620.0	99.12	<0.001	24	2517.8	99.05	<0.001	3	302.3	99.01	<0.001	32	18755.6	99.83	<0.001
IC	2	2588.9	99.92	<0.001	3	17.0	82.33	0.001	5	1169.4	99.57	<0.001	0	-	-	-	6	3922.9	99.85	<0.001
Region																		
Asia	8	5464.6	99.85	<0.001	11	738.6	98.51	<0.001	11	2189.9	99.50	<0.001	1	1.4	26.82	0.242	16	8966.6	99.82	<0.001
Europe	3	226.5	98.68	<0.001	8	346.7	97.69	<0.001	10	907.3	98.90	<0.001	2	37.9	94.72	<0.001	13	7933.8	99.84	<0.001
South America	0	-	-	-	0	-	-	-	2	19.6	89.80	<0.001	-	-	-	-	4	1960.7	99.80	<0.001

Note: Certain subgroups have only 1 study (degree of freedom = 0).

[a] Excluded Yang et al. (2017),Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[b] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015),and Guo et al. (2013).

[c] Excluded Yang et al. (2017),Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

[d] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015),and Hu et al. (2014).

Dash indicates no available.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	34
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	33
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	28
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	38
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	38
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	41
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	41
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	42

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The risk of invasive candidiasis with prolonged duration of ICU stay: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036452.R2
Article Type:	Original research
Date Submitted by the Author:	12-Mar-2020
Complete List of Authors:	Zhang, Zhidan; the First Hospital of China Medical University, Department of Critical Care Medicine Zhu, Ran; the First Hospital of China Medical University, Department of Critical Care Medicine Luan, Zhenggang; the First Hospital of China Medical University, Department of Critical Care Medicine Ma, Xiaochun; the First Hospital of China Medical University, Department of Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	ACCIDENT & EMERGENCY MEDICINE, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS

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The risk of invasive candidiasis with prolonged duration of ICU stay: a systematic review and meta-analysis

Running title: Duration of ICU prior to candidemia

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ABSTRACT

Objective: This study aimed to evaluate the duration of intensive care unit (ICU) stay prior to onset of invasive candidiasis (IC)/candidemia.

Design: Systematic review and meta-analysis.

Data Sources: Pubmed, Cochrane**,** Embase, and Web of Science databases were searched through June, 2019 to identify relevant studies.

Eligibility Criteria: Adult patients who had been admitted to the ICU and developed an invasive candidiasis infection.

Data extraction and synthesis: The following data were extracted from each article: the length of hospital stay, the length of ICU stay, duration of ICU admission prior to the candidemia onset, percentages of patients who received antibiotics and duration of their antibiotic therapy prior to candidemia onset, and overall mortality. In addition to the traditional meta-analyses, meta-regression was performed to explore possible mediators which might have contributed to the heterogeneity.

Results: The mean age of patients ranged from 28 to 76 years across selected studies. The pooled mean duration of ICU admission before onset of candidemia was 12.9 days (95% confidence interval [CI]: 11.7 – 14.2). The pooled mean duration of hospital stay was 36.3±5.3 days (95% CI: 25.8 – 46.7) and the pooled mean mortality rate was 49.3±2.2% (95% CI: 45.0% – 53.5%). There was no significant difference in duration of hospital stay (P = 0.528) or overall mortality (P=0.111), but a significant difference was observed in the mean length of ICU stay (2.8 days, P < 0.001) between patients with and without *C. albicans*. Meta-regression analysis found that South American patients had longer duration of ICU admission prior to candidemia onset than patients elsewhere, while those in Asia had the shortest duration.

Conclusions: Patients with IC are associated with longer ICU stay, with the shortest duration of ICU admission prior to the candidemia onset in Asia. This shows a more proactive strategy for the diagnosis of IC should be considered in caring ICU patients.

KEYWORDS: Invasive candidiasis, candidemia, intensive care unit, length of stay, antibiotic, mortality

Strengths and limitations of this study

- This meta-analysis is one of few that investigated the association of IC with the length of ICU stay, using data published worldwide and adhering to the PRISMA guideline.
- Extensive subgroup analyses were performed and meta-regression was made to examine possible causes of heterogeneity in the results.
- Although this meta-analysis was performed methodically, it lacked a pre-specified protocol and preliminary registration.
- Heterogeneity exists in some subgroup and overall analyses.
- Due to a lack of sufficient published data, relationship between prolonged exposure to broad-spectrum antibiotics and ICU-acquired candidemia could not be assessed.

INTRODUCTION

Candida species account for approximately 70% to 90% of invasive fungal infections and are the most frequent cause of fungal infections in patients admitted to the intensive care unit (ICU) [1]. Invasive candidiasis (IC) is associated with a high mortality rate (range: 40% to 60%) [1, 2]. Over recent decades, the incidence of IC has been gradually increasing in most regions [3], ranging from 0.5 to 32 cases per 1,000 ICU admissions. It has been found that there is a significant difference in the incidence of IC among several countries in Latin America and North America; however, data from Asia-Pacific countries are still relatively rare [4]. Candidemia has been described as the most common manifestation of IC, and the further infection of the liver, spleen, heart valves, or eye might also occur after a bloodstream infection [5]. In the past, the main *Candida* species isolated from patients with IC was *C. albicans*. However, non-*C. albicans* species has seen a rising proportion and now account for approximately 50% of all cases of IC in the past two decades [1,6-8].

Diagnosis and management of IC remains challenging for physicians in the ICU [1, 2]. The early initiation of empiric antifungal treatment has been demonstrated to improve the prognosis of invasive candidiasis [2, 9]. However, there is difficulty in the diagnosis of IC which can delay timely antifungal treatment [2, 10]. Blood culture remains the gold standard for the diagnosis of invasive candidiasis, but its sensitivity is variable (21% to 71%) [11].

In order to improve the diagnosis of IC, and to identify the patients who may best benefit from prophylactic, preemptive, or empirical therapy prior to, or at an early stage of ICU admission several methods in predicting the development of IC based on their associated risk factors have been developed [12, 13]. The risk factors in the

various predictive models include broad-spectrum antibiotic use, central venous catheter placement, total parenteral nutrition, hemodialysis (days 1–3 in the ICU), any surgery, immunosuppressive use, pancreatitis prior to ICU admission, and steroid use. However, different risk factors are included in different predictive models. In addition, potential risk factors such as *Candida* colonization [14] and mechanical ventilation [15] have not been included in these models.

Long-term ICU stay has been reported as a risk factor for IC [11, 14-16]. Only a few studies have examined the interval between ICU admission or initiation of broad-spectrum antibiotics and the diagnosis of IC. However, the specific duration of long-term ICU stays and the prolonged use of broad-spectrum antibiotics are often arbitrarily defined and inconsistent among studies [6, 12, 15, 17-19]. Furthermore, a large majority of severe candidiasis cases are caused by endogenous colonization. This may be the primary reason for causing a delay of 7 to 10 days between exposure to risk factors and the development of IC [20].

Thus, the objective of this systematic review was to evaluate several possible risk factors associated with the development of candidemia, including the length of hospitalization and ICU stay, as well as regional difference in those factors.

METHODS

Search strategy

The study was performed in accordance with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed, Cochrane, Embase, and Web of Science databases were searched from the inception through June, 2019 using the following terms: candidiasis, candidemia, intensive care unit or ICU, and risk factors (Supplementary table S1). Studies identified by the

search strategy were reviewed for inclusion and data were extracted by two independent reviewers. Where there was uncertainty regarding study eligibility, a third reviewer was consulted. A flow chart of the study selection is shown in Figure 1.

Study selection criteria

Randomized controlled trials (RCTs), cohort studies, case-controlled, and cross-sectional studies were included. All studies included adult patients who were critically ill, who had been admitted to the ICU, and who were tested positive for *Candida* species using blood culture analyses. Studies had to have reported quantitative outcomes of interest and no author was contacted. Letters, comments, editorials, case reports, proceedings, personal communications, and case series were excluded. Studies in which patients were diagnosed with candidiasis prior to ICU admission were excluded. Studies that did not evaluate the incidence of candidiasis as a primary objective, or that were not designed to evaluate risk factors/prognostic factors of patients with candidiasis were also excluded.

Data extraction

The following information / data was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, country, study design, type of ICU, number of participants in each group, participants' age and gender, the presence of *C. albicans*, the presence of neutropenia, and antifungal treatment (especially the use of broad-spectrum antibiotics). The following data were also extracted from each article: length of stay in hospital/ICU, length of stay prior to ICU admission, duration of ICU stay prior to candidemia onset, antibiotic therapy prior to candidemia onset, duration of antibiotic therapy prior to candidemia onset,

and overall mortality.

Quality assessment

We used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool to assess the quality of the included studies [21]. ROBINS-I is based on the Cochrane RoB tool and is suited for evaluating non-randomized studies that compare the health effects of different interventions. ROBINS-I covers 7 different bias domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in the selection of reported results [22-23]. In this systematic review, 2 independent reviewers performed the quality assessment, with a third reviewer consulted for any uncertainty.

Patient and public involvement

No patients and/or members of the public were involved in the process of designing, planning and completing this study.

Statistical analysis

Study characteristics were summarized as mean±standard deviations (SD), mean (range), median (range), or median (IQR) for age or duration of antifungal treatment, and percentage (%) for sex, rate of *C. albicans* isolated, neutropenia, and antifungal treatment used in each study.

Clinical outcomes, including the length of hospital stay, length of ICU stay, length of hospital stay prior to ICU admission, duration of ICU admission prior to

candidemia onset, and duration of antibiotic therapy prior to candidemia onset were represented as mean (range: [min. – max.]), median (range), or median (IQR [interquartile range: 1st – 3rd quartiles]). The rate of antibiotic therapy prior to candidemia onset and overall mortality rate were presented as percentages. All clinical outcomes were further summarized for subgroups of studies (with studies' number ≥2). Types of study, presence of neutropenia, types of ICU, type of *Candida* isolated, presence of IC/candidemia, and regions/countries were listed for comparison as well. Meta-regression analyses were performed to investigate statistical importance of potential moderators. Quantitative data reported with median (range) and/or median interquartile range (IQR) were converted to mean ± SD, according to the method described by Wan et al. [24]

The outcomes selected for the analysis were the length of hospital stay, the length of ICU stay, duration of ICU admission prior to candidemia onset, and overall mortality between patients who were diagnosed with *C. albicans* and those with non-*C. albicans*. The effect size was calculated as mean difference with 95% CI (Lower, Upper limit) in length of days, or rate ratio with 95% CI in overall mortality for each given study, and then a pooling effect was derived thereafter. A difference in means of length in days <0 (or rate ratio of overall mortality rate >1) indicated the pooling effect favoring non- *C. albicans* subgroup, whereas difference in means of length in days >0 (or rate ratio of overall mortality rate <1) indicated the pooling effect favoring *C. albicans* subgroup. A difference in means of length in days = 0 (or rate ratio of overall mortality rate = 1) indicated that the pooling effect was similar between *C. albicans* and non-*C. albicans* subgroups. Heterogeneity was evaluated using a χ^2-based Cochran's Q statistic and I^2. The random effect model (DerSimonian-Laird method) and meta-regression analyses with potential moderators

were used for the meta-analysis if either Q statistic with P values < 0.10 or I^2>50%; otherwise, a fixed effect model (Mantel-Haenszel method) was used instead. For the Q statistic, P values < 0.10 were considered statistically significant for heterogeneity. For the I^2 statistic, heterogeneity was assessed as follows: no heterogeneity (I^2 = 0 - 25%), moderate heterogeneity (I^2 =25 - 50%), large heterogeneity (I^2 = 50 - 75%), and extreme heterogeneity (I^2= 75 - 100%). A two-sided P value of <0.05 was considered statistically significant.

Countries were grouped based on their continents, but since meta-analysis of this particular topic has not yet been seen in China, research articles from China will be separately examined and discussed.

The publication bias was assessed using the funnel plot with Egger's test and Classical fail-safe N test for all enrolled studies (except for subgroups). The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution and a 1-tailed significance level of P > 0.05 in an Egger's test.[25] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 3.3.070 (Biostat, Englewood, NJ, USA).

RESULTS

Literature search results

A total of 1875 articles were retrieved from databases, and 1800 articles were excluded after their titles and abstracts were screened based on the inclusion/exclusion criteria (Figure 1). Seventy-five articles underwent full-text review, and 34 articles were excluded for having irrelevant objectives or study designs (n=19), containing patients in neonatal or pediatric intensive care unit (n=5), not having invasive

candidiasis (n=4), and not reporting outcomes of interest (n=6). The remaining 41 articles were included in the systematic review and meta-analysis.

Study characteristics

Characteristics of the 41 studies are summarized in Table 1 and Table 2 [14-16, 26-29, 30-63]. A total of 10,692 patients were included in those studies, with the number of patients in each study ranging from 12 to 1,400. Mean age of the patients ranged from 28 to 76 years. Majority of the patients were males (range: 20% to 75.9%). These studies were conducted in different countries, with 19 in Europe, 14 in Asia, 1 in the US, 4 in South America, 2 in Australia and one multinational study (Australia, Belgium, Greece, Brazil).

Table 1. Characteristics of studies included in this systematic review

Studies 1st Author (year)	Country	Study design	Type of ICU	Total number of patients	IC and Candidemia	No. of patients	Age (years)	Male (%)	*C.Albicans* isolated (%)	Neutropenia (%)	Antifungal treatment	
											Duration of treatment	Antifungal treatment used
Zhao H (2018) [51]	China	retrospective cohort	ICU	95	Candidemia	95	69.3±16.5	57.9 %	59	—	—	17.90%
Ding R (2018) [52]	China	retrospective cohort	ICU	72	Candidemia	72	62.5 (49.8, 77.0)§	62.5 %	15	—	—	Fluconazole 30.6% Voriconazole 9.7% Echinocandin 44.4%
Yang et al. (2017) [26]	China	Retrospective cohort study (China-SCAN)	ICU	306	Early-onset IC	105	56.9 (19.9)§	64.8 %	47.7	1.9%	—	Fluconazole (39.3%) Caspofungin(21.3%) Voriconazole (19.1%) Micafungin(10.1%) Itraconazole(5.6%) Amphotericin B (3.4%) Combined therapy (1.1%)
					Late-onset IC	201	64.0 (19.7)§	70.6 %	36.1	1.5%	—	Fluconazole (36.9%) Caspofungin(25.1%) Voriconazole (17.9%) Micafungin(7.8%) Itraconazole(9.5%) Amphotericin B (1.7%) Combined therapy (1.1%)

Tigen E (2017) [53]	Turkey	Case-control study	ICU	73	Candidemia	36	65 (52-73)†	52.8 %	75		17.6 ± 117 days	Caspofungin Posaconazole Voriconazole Itraconazole Fluconazole Amphotericin B
					Control (Non-Candidemia)	37	62 (48-72)†	48.6 %	—	—	—	—
Baldesi O (2017) [54]	France	Case-control study	ICU	246,459	Candidemia	851	65 [54; 75]§	62.6 %	61.40	5.1%	—	—
					Control (Non-Candidemia)	245,608	65 [52; 76]§	61.7 %	—	1.6%	—	—
Rudramurthy SM (2017) [55]	India	prospective cohort	MICU, SICU	1161	Candidemia (*C. auris*)	74	39 (16 – 58.5)§	62.2 %	—	—	—	fluconazole (20.3) echinocandin(9.5)
					Candidemia (non - *C. auris*)	1087	—	—	—	—	—	fluconazole(12.1) echinocandin(0.8)
Kawano Y (2017) [56]	Japan	retrospective cohort	ICU	4,136	Candidemia	25	69 (24 – 88)†	56.0 %	52	0	—	antifungal treatment: 32%
OrtízRuiz et al. (2016) [16]	Colombia	Case-control study	Polyvalent, cardiovascularICU	243	Candidemia	81	64.5 (51-78) §	51.9 %	42	—	—	—
					Control	162	68 (48-77) §	59.3 %	—	—	—	—

Gong et al. (2016) [47]	China	Prospective, cohort study (China-SCAN)	MICU, SICU, Integrated ICU	306	Candidemia (*C. albicans*)	98	62.2±17.3	62.2 %	100	3.1%	12.85 days	Triazole (64.7%) Echinocandin (31.8%) Polyenes (0%)
					Candidemia (Non-*C. albicans*)	146	61.4±21.4	72.6 %	—	1.4%	20.4 days	Triazole (62.8%) Echinocandin (34.1%) Polyenes (2.3%)
Playford EG (2016) [57]	Australia	prospective cohort	MICU, SICU	6,714	ICU-aquired IC	96	—	—	66	—	—	—
					Control (no IC)	6618	—	—	—	—	—	—
Pinhati HM (2016) [58]	Brazil	cross-sectional	ICU	40	fluconazole-resistant *C. parapsilosis* (FRCP)	21	70 (23 – 91)†	66.7 %	—	—	—	any: (33.3) fluconazole: (19.0)
					fluconazole-susceptible *Candida* species (FSC)	19	76 (35 – 90)†	57.9 %	—	—	—	any: (15.8) fluconazole: (15.8)
Aguilar et al. (2015) [15]	Spain	Prospective cohort study	SICU	22	IC	22	66 (53.7–74.2) §	72.7 %	59.1	—	10 (5.0–16.5) days	Echinocandins (86.4%) Fluconazole (13.6%)
Fochtmann et al. (2015) [27]	Austria	Retrospective cohort study	Burn ICU	174	Candidemia	20	39 (17–88) †	60%	60	—	—	Triazoles (70%)
					Control	154	58 (17–94) †	61%		—	—	Echinocandins (30%)

Klingsporet al.(2015) [28]	14 countries in Europe	Prospective cohort study	SICU	807	IC	779	63(0–91) †	62.5 %	54	—	—	Fluconazole (60%) Caspofungin (18.7%) Amphotericin B (13%) Voriconazole (4.8%)
Chakrabarti et al. (2015) [29]	India	Prospective cohort study	MICU, SICU	1400	Candidemia	1400	49.7 ± 17.7	—	20.9	1.3%	9.0 (5-15)§ days	Azoles (72.0%) Echinocandins (18.3%) Amphotericin B (14.4%)
Liao et al. (2015) [14]	China	Prospective cohort study (China-SCAN)	MICU, SICU, Mix ICU	306	Flu-S	129	62.4±19.5	68.2 %	60.5	3.1%	—	Monoantifungaltherapy (64.5%) Fungal drug adjustment (35.7%) Completely improved(34.6%)
					Flu-R	90	60.8±20.9	67.8 %	17.8	1.1%	—	Monoantifungaltherapy (48.8%) Fungal drug adjustment (61.1%) Completely improved (28.0%)
Kautzky S (2015) [59]	Austria	prospective cohort	MICU	65	IC (invasive *Candida* infection)	5	28.2 ± 97	20%	—	0%	15.40 ± 13.9	100%
					control (non-invasive *Candida* infection)	60	52.7 ± 15.7	72%	—	8.3%	—	60.00%
Karacaer et al. (2014) [31]	Turkey	Prospective cohort study	ICU service	burn 2362	IC	63	70.2 ± 19.5	54%	64	—	—	—

							(14-95)					
Colombo et al. (2014) [32]	Brazil	Retrospective cohort study	ICU	1,392	Candidemia	647	66 (18–97) †	50.7	44	2.5%	—	Amphotericin B (period 1:27.8%; period 2: 13.4%) Echinocandins(period 1: 5.9%; period 2: 18.0%)
Hu et al.(2014) [48]	China	Prospective cohort study (China-SCAN)	ICU	294	CRCBSI	29	69.4 ± 19.1	75.9 %	28.6	—	19.0 ± 13.3 days	Fluconazole (39.3%) Caspofungin(25.0%) Voriconazole(14.3%) Micafungin (10.70%) Itraconazole(10.7%) Amphotericin B (0%) Two-drug combination (0%)
					Non-CRCBSI	265	60.7±20.2	68.3 %	40.3	—	16.7 ± 13.3 days	Fluconazole (36.7%) Caspofungin(23.6%) Voriconazole(19.2%) Micafungin (8.7%) Itraconazole(7.9%) Amphotericin B(2.2%) Two-drugs combination(1.7%)
Lortholary O (2014) [60]	France	prospective cohort	ICU	2507	ICU-aquired candidemia	1206	60 ± 17	62.0 %	57.10	—	—	Fluconazole(55.4 %) Echinocandins(26.2 %) Others (including combination)(12.6 %)
					non-ICU aquired candidemia	1301	60 ± 17	58.7 %	54.90	—	—	Fluconazole(59.9 %) Echinocandins(19.1 %) Others (including combination)(13.3 %)

Yapar N (2014) [61]	Turkey	retrospective cohort	ICU	1076	Candidemia	66	54.4 ± 23.9	53%	53	—	—	9%
					Control (non-Candidemia)	1010	53.2 ± 23.0	63%	—	—	—	6.30%
Guo et al.(2013) [49]	China	Prospective cohort study (China-SCAN)	MICU SICU General Emergency Neurologic ICU	306	Candidemia	306	61.5±20.0	68.6 %	40.2	1.6%	14 (0-104)† days	Fluconazole (37.7%) Caspofungin (23.9%) Voriconazole (18.3%)
Giri S (2013) [30]	India	prospective cohort	ICU	5,976	Candidemia	39	35.14 (3days-79 y)	61.5 %	4			
Tortorano et al.(2012) [33]	Italy	Prospective cohort study	MICU, SICU	384	Candidemia	276	—	—	60.9	—	—	Fluconazole (63%) Amphotericin B (22%) Caspofungin (7%) Voriconazole (6%)
Ylipalosaari et al. (2012) [34]	Finland	Retrospective cohort study	MICU,SICU	82	ICU-acquired candidemia	38	63 (45-69) §	71%	76.3	—	Median: 22 days	Fluconazole (73%) Amphotericin B (34%) Echinocandins (31%)
					non-ICU-acquired candidemia	44	64 (56-75) §	61%	68.9	—	Median: 24 days	Fluconazole (77%) Amphotericin B (35%) Echinocandins (40%)
Pasero D et al. (2011) [35]	Italy	Prospective cohort study	SICU	349	Candidemia	26	60±21	61.5 %	73	—	—	—

					Control	323	67±16	65.3 %		—	—	—
Han SS et al. (2010) [36]	Korea	Case-control study	MICU	52	Candidemia	49	57.6±14.1	—	65	25%	11 (1-45)† days	Amphotericin B (71.4%) Fluconazole (28.6%)
					Control	147	57.4±14.0	—	—	8%		
Pratikaki M et al. (2009) [37]	Greece	Case-control study	Multi-disciplinary ICU	855	Candidemia	33	57±18	64%	33.3	0%		Amphotericin B (57.1%)
					Control	132	58±18	70%	—	0%	>14 days	Voriconazole(17.9%), Caspofungin (14.3%) Fluconazole (10.7%)
Playford et al.(2009) [38]	Australia	Prospective cohort study	MICU, SICU	615	IC	15	NA	NA	73.3	0%	—	—
Holleyetal.(2009) [39]	Australia, Belgium, Greece, Brazil	Retrospective cohort study	Multi-disciplinary ICU	189	Candidemia (*C. albicans*)	104	56.5±17.1	63.5 %	100	—	1(1-32)†days	Fluconazole (37%) Amphotericin B (31%)
					Candidemia (Non-*Candida albicans*	85	58.9±16.3	44.7 %	—	—		Fluconazole and amphotericin B (15%)
Choi et al. (2009) [40]	Korea	Retrospective cohort study	ICU	497	Candidemia (*C. albicans*)	54	49±23	44.4 %	100	13%	—	Amphotericin B (77.8%) Fluconazole (16.7%)
					Candidemia	27	48±25	44.4 %	—	19%	—	Fluconazole and amphotericin B (5.6%)

					(*C. glabrata*or, *C. krusei*)							
Yap et al (2009) [50]	China Hong Kong	Retrospective cohort study	MICU SICU	128	Candidemia	128	54 (43-68) §	63.3 %	56	11%	—	Amphotericin B (39.1%) Fluconazole (38%) Amphotericin B+fluconazole (13%) Caspofunginorvoriconazole(9 .8%)
Chow et al. (2008) [41]	US	Case-control study	MICU, SICU	926	Candidemia (Non-*Candida albicans*)	67	62.3±14.5	57%	—	—	—	Fluconazole(84.8%) Amphotericin B (23.9%) Caspofungin(10.9%) Voriconazole(4.3%)
					Candidemia (*C. albicans*)	79	57±17.0	60%	100	—	—	Fluconazole (63%) Amphotericin B (33.3%) Caspofungin (11.1%) Voriconazole (0%)
					Control	780	62.3±17.4	56%	—	—	—	Fluconazole (100%) Amphotericin B (14.3%) Caspofungin (0%) Voriconazole (0%)
Bougnouxet al.(2008) [42]	France	Prospective cohort study	MICU SICU HU BU	290	Candidemia	57	56.1±18.2	67%	54.2	19.3%	13.2±10.3 days	Fluconazole(78.3%) Amphotericin B(52.2%) Flucytosine(15.2%)
Girão et al.(2008) [43]	Brazil	Prospective cohort study	ICU	73	Candidemia (Non-*Candida*	40	51(12-86) *	60%	—	—	—	—

					albicans)							
					Candidemia (*C. albicans*)	33	51(15-86) *	40%	100	—	—	—
Dimopoulos et al. (2008) [44]	Greece	Prospective cohort study	MICU, SICU	56	Candidemia (*C. albicans*)	36	60.5 ± 14.9	44.4 %	100	0% (excluded)	Response rate: (80.6%)	Fluconazole as prophylaxis: Amphotericin B (75%) Caspofungin (25%) No fluconazole as prophylaxis: Amphotericin B (60%) Caspofungin (40%)
					Candidemia (Non-*Candida albicans*)	20	64.5± 16.8	55%	—		Response rate: (45%)	Amphotericin B (100%)
Dimopouloset al.(2007) [45]	Greece	Prospective cohort study	MICU, SICU	24	Candidemia	24	—	—	62.5	—	16.5 (14-24)*days	C. albicans: fluconazole Non-albicans: amphotericin B
Jordà-Marcos R (2007) [62]	Spain	prospective cohort	MICU, SICU	1765	Candidemia	63	63 (48 – 70)†	71.4 %	57.10	6.3%	—	7.90%
					Control (non-Candidemia)	1072	63 (46 – 71)†	66.5 %	—	2.8%	—	5.60%
Piazza O (2004) [63]	Italy	retrospective cohort	ICU	478	Candidemia	12	57.58± 22.07	58.3 %	67	—	—	—

Michalopoulos et al. (2003) [46]	Greece	Prospective case- control study	CICU	150	Candidemia	30	63.2±9.7	73.3 %	70	—	—	—
					Control	120	64.3±9.9	73.3 %	—	—	—	—

Abbreviations: CICU, cardiothoracic ICU; CRCBSI, Catheter-related Candida bloodstream infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, Invasive candidiasis; MICU, medical ICU; SICU, surgical ICU.

Total number of enrolled patients: 7,982.

* Data were presented as mean (range).

† Data were presented as median (range).

§ Data were presented as median (IQR).

Dash indicates no available data.

Table 2. Length of hospital and ICU stay, percentages of patients receiving antibiotics duration of antibiotic therapy prior to candidemia onset, and overall mortality

Studies 1st Author (year)	Length of hospital stay (days)	Length of ICU stay (days)	Length of hospital stay prior to ICU admission (days)	Duration of ICU admission prior to candidemia onset (days)	Percentages of patients receiving antibiotic therapy prior to candidemia onset	Duration of antibiotic therapy prior to candidemia onset (days)	Overall mortality rate
Zhao H (2018) [51]	N/A	24 (12-57)†	N/A	N/A	N/A	N/A	58%
Ding R (2018) [52]	N/A	N/A	N/A	N/A	Broad-spectrum antibiotics: 98.6%	N/A	31.90%
Yang et al. (2017) [26]	(prior to IC diagnosis) Early-onset IC:4 (2, 7)§ Late-onset IC: 26 (16, 50)§	N/A	N/A	Early-onset IC: 4 (1, 7)§ Late-onset IC: 17 (10, 33)§	Early-onset IC: 62 (59.0%) Late-onset IC: 179 (89.1%)	N/A	Early-onset IC: 28.6% Late-onset IC: 40.8%
Tigen E (2017) [53]	N/A	22 (18-30)† 5.5 (2.25-15.75)†	N/A	N/A	Broad-spectrum antibiotic: 100% Broad-spectrum antibiotic: 59.5%	N/A	83.30%
Baldesi O (2017) [54]	N/A	29 (18; 49) § 7 (4; 13) §	N/A	N/A	antimicrobials: 82.2% antimicrobials: 55.1%	N/A	52.40% 17.80%
Rudramurthy SM (2017) [55]	N/A	N/A	N/A	10 (4.7 – 22.2)§ 7 (3 – 13)§	N/A	N/A	41.90% 27%

Kawano Y (2017) [56]	N/A	N/A	N/A	13 (1 – 73)†	Broad-spectrum antimicrobial: 84%	N/A	72%
OrtízRuiz et al. (2016) [16]	35.4±3.0	21.9±1.7	N/A	Median 25	Broad-spectrum antibiotic: 93.8 vs. 69.8% (case vs. control)	N/A	39.51%
Gong et al. (2016) [47]	*Candida albicans*: Median: 32 Non-*C. albicans*: Mediian: 44	*Candida albicans*: Median: 18 Non-*C. albicans*: Median: 29	N/A	N/A	*Candida albicans* (before diagnosis): 76 (77.6%) Non-*albicans*(before diagnosis): 121 (82.9%)	N/A	*Candida albicans* (before diagnosis): 29.6% Non-*albicans*(before diagnosis): 26.7%
Playford EG (2016) [57]	51 (34 – 89)§ 23 (13 – 40)§	21 (14 – 32)§ 8 (5 – 12)§	N/A	10 (5 – 15.25)†	N/A	N/A	26% 18.3%
Pinhati HM (2016) [58]	N/A	N/A	N/A	22 (0 – 83)† 25 (7 – 134)†	any: 47.6% any: 42.1%	N/A	42.9% 47.4%
Aguilar et al. (2015) [15]	N/A	N/A	N/A	20 (5, 37.5) §	Antibiotic therapy:21 (95.4 %)	10 (5.0–16.5)†	13.60%
Fochtmann et al. (2015) [27]	N/A	60 (13–176) †	N/A	16 (6–89) †	Broad-spectrum antibiotic treatment in most patients	16 (6–89)†	30%
Klingspore t al.(2015) [28]	N/A	23 (0–329) †	2 (0-744) †	12 (0–190) †	Broad-spectrum antibiotics in the last 2 weeks: 511 (78.4%)	N/A	38.80%
Chakrabarti et al.	N/A	N/A	N/A	8 (4, 15) §	Candidemia patients received: antibiotics:93.0%	16.0 (7–36) days§	44.70%

(2015) [29]							
Liao et al. (2015) [14]	Flu-S: 34.5 (18, 65) Flu-R: 48.0 (21, 90)	Flu-S: 22.5 (10.0, 40.0) Flu-R: 29.0 (17, 59)	N/A	Flu-S: 8.0 (3.0, 17.0)§ Flu-R: 10.5 (4.0, 27.0)§	≥5 d before diagnosis: Flu-S: 101 (78.3%) Flu-R: 73 (81.1%)	N/A	Flu-S: 31.8% Flu-R: 41.1%
Kautzky S (2015) [59]	N/A	46 (14 – 74)† 21 (10 – 77)†	17 (1 – 21)† 3 (1 – 66)†	17.4 ± 14.5	100% 90%	N/A	80% 21.7%
Karacaer et al. (2014) [31]	46.8±36.7 (5-190)	32.9±36.9 (0-190)	N/A	N/A	N/A	15 ± 13.8	77.70%
Colombo et al. (2014) [32]	N/A	N/A	N/A	20 (0–188) †	Prior antibiotic expose: 96.1%	N/A	70.30%
Hu et al.(2014) [48]	54.0 (26.0-91.0) §	34.0 (18.0-71.0) §	N/A	11.0 (4.0, 26.0)§	CRCBSI: 100% N CRCBSI:99.5%	CRCBSI: 11.4 ± 4.2 days; N CRCBSI:10.6 ±6.5 day	44.80%
Lortholary O (2014) [60]	N/A	N/A	N/A	N/A	N/A	N/A	51.00% 30.70%
Yapar N (2014) [61]	N/A	30.9±33 12.9±13	N/A	N/A	96.9% 78.3%	N/A	43.9% 32.2%
Guo et al.(2013) [49]	N/A	N/A	N/A	10 (0-330)†	Treatment before diagnostic confirm: 74 (27.6%)	N/A	36.60%
Giri S (2013) [30]	N/A	mean 26.4 (range 9-86) days	N/A	N/A	66.70%	mean 19.45 (range 4-31) days	24%

Tortorano et al.(2012) [33]	N/A	N/A	N/A	22.8 (2–190)†	broad spectrum antibiotic treatment: 85%	N/A	46.20%
Ylipalosaari et al. (2012) [34]	38.0 (22- 59) §	16.0 (11-30) §	1 (0-2) §	8.0 (1.0, 12.0) §	Previous antibacterial treatment (%): 97.4-95.5%	N/A	65.80%
Pasero D et al. (2011) [35]	N/A	21±7	N/A	20 (8, 49) §	A significantly higher administration of > 2 antibiotics for >72 hours.	N/A	47%
Han SS et al. (2010) [36]	38 (2-141)§	22 (1-141)§	8 (0-92) §	17 (0-117) †	All patients were treated with antibiotics prior to candidaemia onset	16 (1-92) †	96.00%
Pratikaki M et al. (2009) [37]	N/A	25 (14-46)§	14 (1-20) §	10 (3, 22) §	All patients received antimicrobial agents prior to candidaemia onset	N/A	60.60%
Playford et al.(2009) [38]	N/A	NA	N/A	10 (4, 16) §	Antibiotic receipt on days 1–3: 83.4%; Broad-spectrum antibiotic receipt on days 1–3: 82.0%	N/A	10.60%
Holleyetal. (2009) [39]	N/A	*C. albicans*: 29.0±18.5 non-*C. albicans*: 29.2 ±28.2	N/A	N/A	All patients received antimicrobial agents prior to candidaemia onset	*C. albicans*: 13 (median) non-*C. albicans*: 15 (median)	*C. albicans*: 52.9% non-*C. albicans*: 64.7%
Choi et al. (2009) [40]	*(prior to fungemia)* *Candida albicans*: 42±47 Non-*C. albicans*: 38±33	*Candida albicans*: 19±41 Non-*C. albicans*: 25±50	N/A	*Candida albicans*: 11±25 Non-*C. albicans*: 15±31	N/A	N/A	*Candida albicans:* 48% Non-C. *albicans*: 67%

Yap et al (2009) [50]	28 (17-54) §	14 (5-23) §	N/A	6 (1-13)§	Antibiotics > 48 hours before candidaemia: *C. albicans*: 70 (97.0%) *non-C. albicans*: 56 (100%)	N/A	70%
Chow et al. (2008) [41]	*Candida albicans*: 28 (20–42)§ Non-*C. albicans*: 37 (24–57)§	*Candida albicans*: 22 (15–33)§ Non-*C. albicans:* 25 (14–40)§	N/A	*Candida albicans*: 11 (9, 17) § Non-*C. albicans*: 10 (4, 21) §	Non-*C. albicans*: 0.75 (0–2) §	2.21 (1.4–2.7)§	*Candida albicans*: 58% Non-albicans: 57%;
Bougnouxe t al.(2008) [42]	N/A	43.1 ± 45.2	N/A	19.0 ± 2.9 or (13.0; 2-145)§	No antibiotic treatment is reported	N/A	61.80%
Girão et al.(2008) [43]	N/A	N/A	N/A	*C. albicans*: 15 (mean) Non-*C. albicans*: 18 (mean)	The hospital is restricted the use of several antibiotics	N/A	*C. albicans*: 72% non-*C.albicans*: 80%
Dimopoulo s et al. (2008) [44]	*C. albicans*: 22 ± 7.6 non-*C. albicans*: 25 ± 8.4	N/A	N/A	*C. albicans*: 12 ± 2.2 non-*C. albicans*: 10 ± 2.4	100% of patients received broad spectrum antibiotic treatment for>3 days during the ICU stay.	N/A	*C. albicans*: 52.8% non-*C. albicans*: 90%
Dimopoulo set al.(2007) [45]	N/A	N/A	N/A	9 (5–11) †	100% of patients received broad spectrum antibiotic treatment	N/A	N/A
Jordà-Marc os R (2007) [62]	48 (26 – 69) 35 (22 – 57)	28 (17 – 45) 18 (12 – 28)	N/A	23.5 ± 54.7	100% 96.5%	N/A	17.2% 13.2%
Piazza O (2004) [63]	N/A	N/A	N/A	median 13 days	N/A	N/A	67%

Michalopoulos et al. (2003) [46]	N/A	27.1 ± 7.5	N/A	15 (11-23) †	Empiric antibiotic therapy with 2 or more broad-spectrum agents for all patients	N/A	N/A

Abbreviations: ARDS, acute respiratory distress syndrome; CPB, cardiopulmonary bypass; CRCBSI, catheter-related bloodstream *Candida* infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, invasive candidiasis; IMV, invasive mechanical ventilation; N/A, not available; SAPS II, Simplified Acute Physiology Score II; TPN, total parenteral nutrition.

§ Data are presented as median (interquartile range; IQR).

† Data are presented as median (range).

Among studies that reported mean length of ICU admission being ≤ 10 days prior to candidemia onset, including the early-onset group in the study by Yang et al [26] and Flu-S group in the study by Liao et al. [14], the overall mortality ranged from 28.6% to 70.0% (Table 2). Among studies that reported the median length of ICU admission being >10 days prior to candidemia onset, the overall mortality ranged from 40.8% to 44.8%.

Similar to other countries, most patients with IC in China received antibiotic treatment prior to candidemia onset in the ICU, which ranged from 59.0% of the early-onset group [26] to 100% in the CRCBSI and non-*C. albicans* groups [49, 51]. Only one study reported the median duration of antibiotic therapy prior to candidemia onset, which ranged from 10.6 to 11.4 days [49].

Meta-analysis

Summary of the clinical outcomes for overall studies or given subgroups

The summary of variables such as the length of hospital stay, length of ICU stay, duration of ICU admission prior to candidemia onset, length of hospital stay prior to ICU admission, and overall mortality was presented in Table 3. Five studies [14, 26, 47-49] were from China by using China-SCAN patient data, in which four studies were excluded to avoid overlapping data.

Table 3. Summary for length of hospital stay, length of ICU stay, duration of ICU admission and hospital stay prior to candidemia onset, and overall mortality for overall or given subgroups[†‡]

	Length of hospital stay, days	Length of ICU stay, days	Duration of ICU admission prior to candidemia onset, days	Length of hospital stay prior to ICU admission, days	Overall mortality
Comparison	**Mean (95%CI.)**	**Mean (95%CI.)**	**Mean (95%CI.)**	**Mean (95%CI.)**	**Rate (95%CI.)**
Overall	36.3(25.8, 46.7)	25.8(23.6, 28.1)	12.9(11.7, 14.2)	11.7(0.4, 23.1)	49.3(45.0, 53.5)
Overall optional[abcd]	[a]37.5(33.3, 41.6)	[b]25.9(23.5, 28.3)	[c]13.7(12.5, 15.0)	—	[d]51.0(46.6. 55.4)
Subgroups					
Type of study					
Prospective	41.0(32.9, 49.1)	27.4(24.6, 30.3)	12.9(11.5, 14.4)	19.2(17.2, 21.3)	42.7(37.9, 47.4)
Retrospective/ Cross-sectional	31.9(18.2, 45.5)	23.9(21.1, 26.6)	13.7(11.2, 16.2)	7.4 (-3.7, 18.4)	56.5(48.0, 65.0)
Presence of neutropenia					
Neutropenia	34.9(19.8, 50.1)	25.4(19.3, 31.5)	11.6(9.5, 13.8)	—	49.6(40.8, 58.3)
Non-neutropenia	22.9(20.9, 25.0)	—	10.0(9.3, 10.7)	—	41.3(7.9, 74.7)
Type of ICU					
ICU	37.7(21.7, 53.7)	27.3(24.9, 29.7)	14.3(5.7, 6.0)	17.2(11.9, 22.4)	49.8(44.3, 55.3)

SICU	—	21.7(19.5, 23.9)	17.3(11.9, 22.7)	—	33.1(15.2, 51.1)
MICU	—	32.7(10.3, 55.2)	17.0(16.2, 17.8)	—	88.4(72.8, 104.1)
MICU+SICU	34.6(28.2, 41.1)	22.5(18.4, 26.6)	10.9(9.6, 12.3)	—	45.7(36.4, 55.0)
C. albicans					
C. albicans	34.2(33.1, 35.3)	25.9(22.3, 29.5)	11.0(10.7, 11.3)	—	52.2(40.0, 64.4)
Non *C. albicans*	27.0(24.3, 29.8)	25.0(18.0, 31.9)	—	—	—
Presence of IC/candidemia					
Candidemia	36.3(32.9, 39.8)	25.8(23.2, 28.3)	13.2(12.0, 14.5)	10.8(-2.0,23.6)	51.4(47.1, 55.8)
IC	33.9(-3.7, 71.4)	26.4(20.7, 32.1)	11.5(7.7, 15.3)	—	38.9(27.8, 50.1)
Region(s)					
Asia	36.9(23.0, 50.8)	25.0(20.9, 29.0)	17.4(14.6, 20.2)	19.3(17.2, 21.4)	51.2(44.7, 57.7)
Europe/US/Australia	33.3(20.8, 45.8)	27.7(23.3, 32.1)	18.5(15.3, 21.7)	9.6 (-1.2, 20.4)	48.6(42.4, 54.7)
South America	—	—	45.8(27.8, 63.7) *	—	54.4(38.0, 70.7)

Note: Certain subgroups have only 1 study (degree of freedom = 0).

[a] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[b] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[c] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

[d] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

Dash indicates no available

[†] The range width of 95% CI is related to the accuracy of the estimation. The narrower the range, the higher the accuracy of the estimation. If both the upper and lower limits are positive, the clinical outcome estimate for this group of participants is positive, if the lower limit is negative and the upper limit is positive, indicating that the clinical outcome estimate for this type of participants is not significantly greater than 0.

[‡]Meta-regression is used to assess relationship between the study-level covariates and effect size when obvious heterogeneity exists in subgroups.

[*] Meta-regression analysis illustrated South American patients had significantly longer duration of ICU admission prior to candidemia onset than their counterparts in Asia, Australia, Europe and North America (using Asia as the reference group, for South America: $\beta = 25.83$, $p = 0.0308$, $R^2 = 0.097$). Other meta-regression analyses in subgroups in this table did not reach statistical significance.

Across all studies, the mean length of hospital stay, mean length of ICU stay, mean duration of ICU admission prior to candidemia onset, mean length of hospital stay prior to ICU admission and mean overall mortality rate were found to be 36.3 days (95% CI: 25.8 - 46.7), 25.8 days (95% CI: 23.6 - 28.1), 12.9 days (95% CI: 11.7 - 14.2), 11.7 days (95% CI: 0.37 - 23.1), and rate of 49.3% (95% CI: 45.0% - 53.5%), respectively. After four China-SCAN studies were excluded from the analysis, the mean length of hospital stay, mean length of ICU stay, mean duration of ICU admission prior to candidemia onset and the mean overall mortality rate were found to be 37.5 days (95% CI: 33.3 - 41.6), 25.9 days (95% CI: 23.5 - 28.3), 13.7 days (95% CI: 12.5 - 15.0) and 50.99% (95% CI: 46.6% - 55.4%), respectively (Table 3). Other outcomes including types of study, presence of neutropenia, types of ICU, types of *C. Albicans* isolated, presence of IC/candidemia, and regions/countries were also summarized for subgroups of studies (with studies' number ≥2). The interval estimate showed the summarized statistics of subgroups were all significant except for length

of hospital stay of patients with IC, length of hospital stay prior to ICU admission of patients selected from retrospective or cross-sectional type of studies, and patients with candidemia (95% CI included zero) (Table 3).

According to the summarized statistics in Table 3, neutropenic patients had a greater length of hospital stay (mean=34.9 vs. 22.9 days), a longer duration of ICU admission prior to candidemia onset (mean=11.6 vs. 10.0 days), and a higher overall mortality rate (rate: 49.6% vs. 41.3%) than non-neutropenic patients. The mean durations of ICU admission prior to candidemia onset were 17.3 days, 17 days, 14.3 days, and 10.9 days for patients in surgical ICU (SICU), medical ICU (MICU), ICU, and MICU+SICU, respectively. Patients with candidemia had a greater length of hospital stay (mean=36.3 vs. 33.9), longer duration of ICU admission prior to candidemia onset (mean=13.2 vs. 11.5), and a higher overall mortality rate (51.4% vs. 38.9%) than patients without IC. However, patients with candidemia had a shorter length of ICU stay (mean=25.8 vs. 26.4 days) and a shorter length of hospital stay prior to ICU admission (mean=10.8 vs. 15.2 days) than patients with IC. Furthermore, patients with *C. albicans* also had a higher duration of ICU admission prior to candidemia onset compared to patients with other species of *C. albicans* (mean=11 vs. 10 days). The mean durations of ICU admission prior to candidemia onset in hospitalized patients were 18.5 days (95% CI=15.3 – 21.7 days) in Europe, 17.4 days (95% CI: 14.6 – 20.2 days) in Asia, and 45.8 days (95% CI: 27.8 – 63.7 days) in South America. Data from Girão et al.[43] and Gong et al.[47] were excluded from the summarized analysis due to absence of standard deviations for mean values and data ranges.

Broad-spectrum antibiotic use prior to candidemia onset, length of hospital stay prior to ICU admission, and overall mortality

In order to compare the broad-spectrum antibiotic use between IC patients and non-IC patients, we reviewed and excluded studies containing control groups with non-invasive candida infection and/or with a clear number of broad-spectrum antibiotics use. After pooling all data, the difference in IC patients' use of broad-spectrum antibiotics (89.1%, 95% CI: 82.7%-93.4%) prior to IC onset vs. that of non-IC patients (77.4%, 95% CI: 52.3%-91.4%) did not reach statistical significance. The mean duration of antibiotic therapy prior to candidemia onset was 17.8 days (95% CI: 9.3 - 26.3), but the duration of broad-spectrum antibiotic use prior to the infection could not be determined due to insufficient data. Only five studies reported length of hospital stay prior to ICU admission and the mean was 11.7 days (95% CI: 0.4 - 23.1). The overall mortality rate increased from 49.3% to 51.0% after excluding four China-SCAN studies (Table 3).

Comparing the effect between Candida albicans* vs. *non-Candida albicans

A meta-analysis was performed to compare effect of the length of hospital stay, length of ICU stay, and overall mortality between patients infected with *C. albicans* and those infected with different strains of *Candida*. Three studies examined the length of hospital stay [40, 41, 44], three studies examined the length of ICU stay [39-41], and six studies examined overall mortality [39-41, 43, 44, 47]; these were selected for the meta-analysis. According to the heterogeneity test, a random effect model was applied for the length of hospital stay ($Q = 25.47$, $I^2 = 92.1\%$, $p < 0.001$) and overall mortality rate ($Q = 399$, $I^2 = 98.7\%$, $p < 0.001$), while a fixed effect model was applied for the length of ICU stay ($Q = 1.56$, $I^2 = 0\%$, $p= 0.458$). The pooled effect demonstrated no

significant difference in length of hospital stay between patients with and without *C. albicans* (Figure 2A, p>0.05); however, there was a significant difference in mean length of ICU stay (difference in means = 2.8 days, Figure 2B, P<0.001). There was also no significant difference in overall mortality between patients with and without *C. albicans* (Figure 2C, p>0.05).

Quality assessment

Results of the quality assessment are shown in Table 4. For the results of ROBINS-I, 9 studies had serious bias due to confounding because no baseline confounding or appropriate analysis methods were used to adjust for important baseline confounding. Five studies had serious bias in the selection of participants due to unclear inclusion and exclusion criteria. Most of studies had low or moderate bias in classification of interventions. No study provided the information of systematic difference between experimental intervention and comparator groups due to a lack of comparison of two intervention groups. All studies had low or moderate bias in missing data, in measurement of outcomes, and in selection of the reported result. Overall, 28 studies had moderate risk of bias, thirteen had serious risk of bias, and one had unclear information regarding the risk of bias.

Meta-regression of clinical outcomes

A meta-regression analysis demonstrated that South American patients had significantly longer mean duration of ICU admission prior to candidemia onset than patients in Asia, Australian, Europe and North America (using Asia as the reference group, South America had $\beta = 25.83$, $p = 0.0308$, $R^2 = 0.097$). Other subgroup meta-regression analyses did not reach statistical significance (Table 3). The level of risk of bias (moderate/serious or no information) was also included in the

meta-regression analyses and the coefficient was not found to achieve statistical significance.

Table 4. Quality assessment of included studies using ROBINS-I

1st Author (year)	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ding et al. (2018) [52]	low	moderate	low	no information	moderate	low	low	moderate
Zhao et al. (2018) [51]	low	low	no information	no information	low	low	low	moderate
Baldesi et al. (2017) [54]	low	moderate	no information	no information	low	low	low	moderate
Kawano et al. (2017) [56]	serious	moderate	low	no information	low	low	low	serious
Rudramurthy et al. (2017) [55]	low	low	low	no information	low	low	low	moderate
Tigen et al. (2017) [53]	serious	moderate	low	no information	low	low	low	serious
Yang et al. (2017) [26]	low	low	low	no information	low	low	moderate	moderate
Gong et al. (2016) [47]	serious	moderate	low	no information	low	low	low	serious
OrtízRuiz et al. (2016) [16]	low	low	low	no information	low	low	low	moderate
Pinhati et al. (2016) [58]	moderate	moderate	low	no information	low	low	low	moderate
Playford et al. (2016) [57]	low	moderate	no information	no information	low	low	low	moderate
Aguilar et al. (2015) [15]	no information	moderate	low	no information	low	low	low	moderate
Chakrabarti et al. (2015) [29]	serious	low	low	no information	low	low	low	serious

Fochtmann et al. (2015) [27]	low	moderate	low	no information	low	low	low	moderate
Kautzky et al. (2015) [59]	serious	low	no information	no information	low	low	low	serious
Klingspor et al.(2015) [28]	low	moderate	low	no information	low	low	low	moderate
Liao et al. (2015) [14]	low	moderate	low	no information	low	low	low	moderate
Karacaer et al. (2014) [31]	moderate	moderate	low	no information	low	low	low	moderate
Colombo et al. (2014) [32]	low	moderate	low	no information	low	low	low	moderate
Hu et al.(2014) [48]	low	moderate	low	no information	low	low	low	moderate
Lortholary et al. (2014) [60]	low	serious	low	no information	low	low	moderate	serious
Yapar et al. (2014) [61]	moderate	moderate	low	no information	low	low	low	moderate
Giri et al. (2013) [30]	serious	moderate	low	no information	low	low	low	serious
Guo et al.(2013) [49]	low	low	low	no information	low	low	low	moderate
Tortorano et al.(2012) [33]	serious	moderate	low	no information	low	low	low	serious
Ylipalosaari et al. (2012) [34]	moderate	moderate	low	no information	low	low	low	moderate
Pasero et al. (2011) [35]	low	low	low	no information	low	low	low	moderate
Han et al. (2010) [36]	low	serious	no information	no information	low	low	low	serious
Pratikaki et al. (2009) [37]	moderate	low	low	no information	low	low	low	moderate

Playford et al.(2009) [38]	no information	low	no information	no information	low	low	low	no information
Holley et al.(2009) [39]	low	serious	low	no information	low	low	low	serious
Choi et al. (2009) [40]	low	serious	low	no information	low	low	low	serious
Yap et al. (2009) [50]	no information	moderate	low	no information	low	low	low	moderate
Chow et al. (2008)[a]	low	low	low	no information	low	low	low	moderate
Chow et al. (2008)[b] [41]	low	moderate	low	no information	low	low	low	moderate
Bougnoux et al. (2008) [42]	no information	low	low	no information	low	low	low	moderate
Girão et al. (2008) [43]	no information	serious	low	no information	low	low	low	moderate
Dimopoulos et al. (2008) [44]	low	low	low	no information	low	low	low	moderate
Dimopoulos et al. (2007) [45]	serious	low	low	no information	low	low	low	serious
Jordà-Marcos et al. (2007) [62]	low	moderate	low	no information	low	low	low	moderate
Piazza et al. (2004) [63]	serious	low	moderate	no information	moderate	low	low	serious
Michalopoulos et al. (2003) [46]	low	low	no information	no information	low	low	low	moderate

[a], Chow JK[1], Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg D, Chawla V, Young J, Hadley S.

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Publication bias

Egger's test showed potential publication bias for length of hospital stay (1-tailed P < 0.001) and duration of ICU admission prior to candidemia onset (1-tailed P = 0.004); there was no significant publication bias for length of ICU stay (1-tailed P = 0.37) and overall mortality (1-tailed P = 0.38). The classic fail-safe N tests indicated that the number of missing studies which would be needed to make the P-values of the summary effect become insignificant, was 65,685 for length of stay, 2,304 for length of ICU stay, 89,242 for duration of ICU admission prior to candidemia onset, and 34,263 for overall mortality. These results indicated that the significance of the observed effects of the meta-analyses would not be influenced by the inclusion of additional studies (Figure 3A-C).

Data sharing

No additional data is available.

DISCUSSION

The current meta-analysis demonstrated that the pooled mean of duration of ICU admission prior to candidemia varied from approximately 17 days in Asia, to 19 days in Europe and 46 days in South America. Most of the IC patients had received broad-spectrum antibiotics (89%), and the mean duration of antibiotic therapy prior to candidemia onset was nearly 18 days. The pooled mean mortality rate was approximately 49%. There was no significant difference in the length of hospital stay or overall mortality between patients with and without *C. albicans,* but the mean length of ICU stay was greater for patients with *C. albicans* compared to those patients without *C. albicans*.

As for the study design, eight were case-control or cross-sectional studies, and the remaining 33 were retrospective or prospective cohort studies (Table 1). Eleven studies were designed to compare patients with and without candidemia. Five studies compared patients with infection of *C. albicans* vs. those infected with another *Candida* strain, and only one study compared ICU-acquired candidemia vs. non-ICU acquired candidemia [34]. Eight studies were performed in Chinese hospitals (Table 1). Two studies evaluated patients with *Candida albicans* vs. non-*Candida albicans* infection. One study compared patients with catheter-related *Candida* bloodstream infection (CRCBSI) vs. non-CRCBSI, and another study compared patients with a fluconazole-resistant vs. fluconazole-sensitive (Flu-S) infection.

Fewer than half of the studies (n=18) were conducted in general or multi-disciplinary ICUs, with the rest in SICUs, in the cardio-surgical/cardiothoracic ICUs (CICU) [46], or in medical ICUs [36]. This suggests that invasive candidiasis is a common problem in critically ill patients regardless of the ICU type . The mean length of hospital stay ranged from 4 (early-onset group) to 54 days, and the mean length of ICU stay ranged from 7 days to 60 days (Table 2). In 9 studies, median lengths of ICU stay were ≤ 10 days prior to onset of IC, and the overall mortality in ICU patients with candidemia in those studies ranged from 10.6% to 65.8%. In those studies with median lengths of ICU stay > 10 days prior to onset of IC, the overall mortality ranged from 13.6% to 96.0%.

The durations of ICU stay varied widely prior to candidemia onset which indicated the time and circumstances involved in encountering ICU-acquired risk factors might differ among critically ill patients. As we have mentioned previously, one major cause of severe candidiasis is the endogenous colonization of *Candida* species that requires a 7 to 10-day period for the development of IC after exposure to

the risk factors [20]. In addition, the median time for obtaining positive blood cultures was 2–3 days (possibly up to ≥7 days) [2]. Thus, for a patient with the confirmed diagnosis of candidemia at 8 days after ICU admission, the endogenous colonization of *Candida* species might have actually occurred on or before the first day of ICU admission. Similarly, for a patient with the confirmed diagnosis of candidemia at 12-13 days after ICU admission, the endogenous colonization of *Candida* species might have occurred 3-5 days after ICU admission.

One main risk factor for candidemia was the systemic antibiotic use [16]. In a previous study of pediatric ICUs, it was reported that treatment with vancomycin or anti-anaerobic antibiotics for >3 days was independently associated with the development of candidemia [2], but only in an unadjusted analysis [16]. A study in Hong Kong found that candidemia occurred in patients within 6 days of ICU admission, and more than 97.0% of patients infected with fungi of *Candida* species had received >48 hours of antibiotic treatment [64]. Overuse and prolonged use of broad-spectrum antibiotics have been closely associated with candidemia in China and India [65, 66], so it's reasonable to suspect a link between overuse of broad-spectrum antibiotics and early-onset of candidemia after ICU admission. Regardless of geographical differences, most patients with IC received broad-spectrum antibiotic treatment prior to candidemia onset in the ICU. However, due to a lack of sufficient data, potential correlation between prolonged exposure to broad-spectrum antibiotics and the time of candidemia onset after ICU admission could not be assessed. Further explanations of the longer duration of ICU admission prior to candidemia onset in South America than in Asia/Europe/US/Australia also could not be determined in this systematic review.

Results of this study showed no significant difference in the length of hospital stay

prior to the development of IC and in the overall mortality between patients with and without invasive infection of *C. albicans*. This may be due to the fact that clinical presentation and the treatment of patients with candidemia caused by *C. albicans* and non-*C.albicans* were indistinguishable [67]. Although it was found that the mortality rates in patients with *C. albicans* and non-*C. albicans* was similar, the susceptibilities of these strains to anti-fungal agents were different [21, 68, 69].

This systematic review had several limitations. Because this systematic review lacks a pre-specified protocol and the preliminary registration, biased post hoc decisions in the reviewing process may occur. In addition, a number of the trials reported outcomes using median (range) and/or median (IQR), and in order to combine these results, the sample means and standard deviations for those trials were estimated using a method proposed by Wan et al. [24], based under the assumption that data were normally distributed. Across the meta-analysis, however, medians and quartiles were often reported when data did not follow a normal distribution [23], which may have confounded the results. Results of the quality assessment also indicated that potential biases from confounders may be present. High heterogeneity existed in both overall and subgroup analyses, suggesting complexity of the risk factors causing IC and candidemia (Supplementary Table S2).

Although different designs, regional differences, and risks of bias may contribute to the heterogeneity between groups, there may be other potential factors that requires further study. Factors such as comorbidities, severity of illness, and invasive procedures (e.g., hemodialysis, invasive mechanical ventilation, total parenteral nutrition, surgery, and immunosuppression), were not taken into account in this analysis. Publication bias may have existed in some analyzed outcomes as well.

This meta analysis finds that patients who had longer length of ICU stay were

more likely to develop candidemia. Therefore, early detection and therapeutic intervention should be considered in the ICU to reduce potential risk of fungal infection and its complications, which will help conserving valuable medical resources and ultimately saving more lives.

Acknowledgements

The medical writing and editorial assistance were provided by Elizabeth Goodwin and Prof. Jerry Tseng of MedCom Asia Inc., China. This assistance was funded by MSD China. The authors initiated the concept for this systematic review and are responsible for the content of the manuscript.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' contributions:

ZDZ: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

RZ: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

ZGL: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

XCM: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; manuscript editing; manuscript review.

Data sharing statement: No additional data are available.

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Figure legends

Figure 1. PRISMA flow diagram of study selection

Figure 2. Meta-analysis of *C. albicans* vs. non-*C. albicans* for A) length of hospital stay; B) ICU length of stay; and C) Overall mortality

Figure 3. Funnel plot for A) length of hospital stay; B) ICU length of stay; C) duration of ICU admission prior to candidemia onset

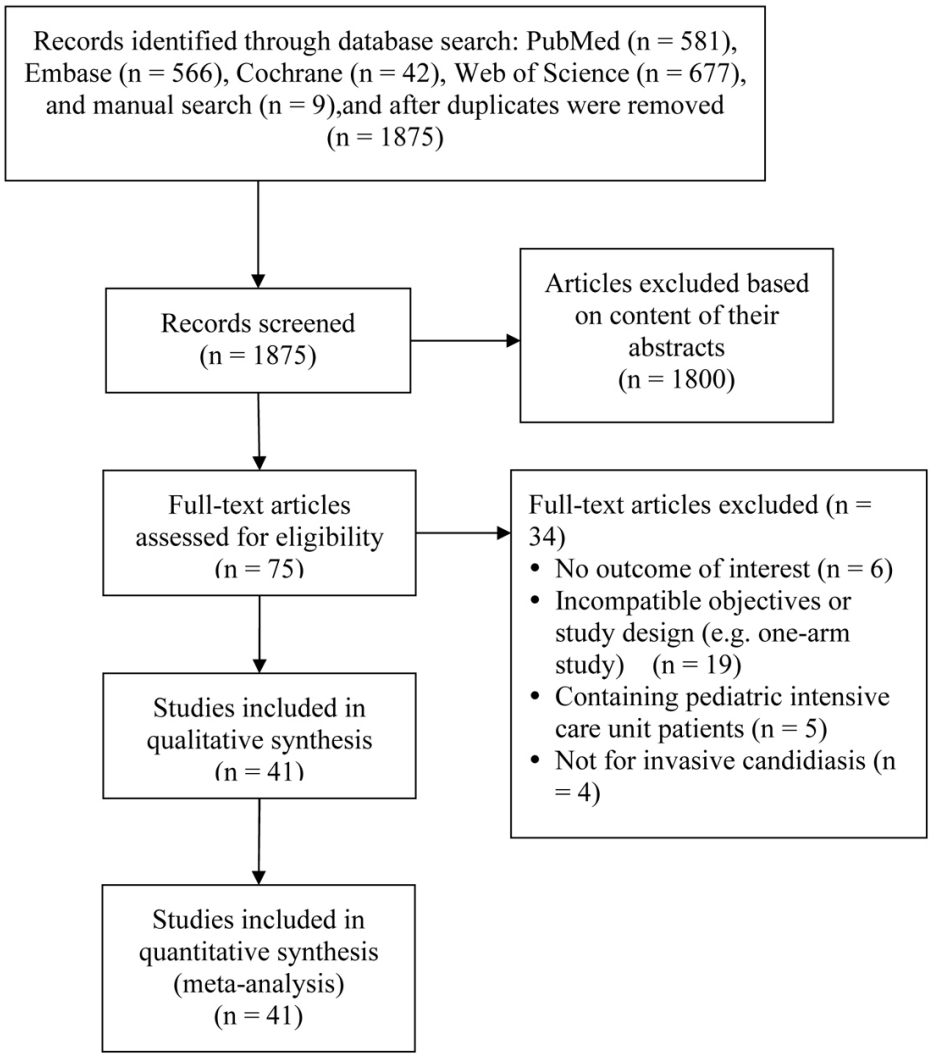

Figure 1

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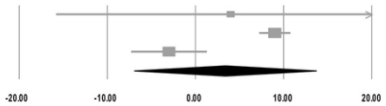
Figure 2.

A. Length of hospital stay (days)

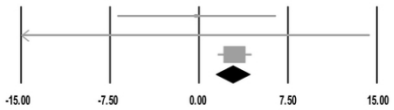
Study name	Difference in means	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Choi et al (2009)	4.00	-15.82	23.82	0.40	0.692	16.668
Chow et al. (2008)	9.00	7.21	10.79	9.85	<0.001	42.924
Dimopoulos et al.	-3.00	-7.31	1.31	-1.36	0.173	40.408
Pooled effects	**3.32**	**-6.99**	**13.62**	**0.63**	**0.528**	



Heterogeneity test:
Total
Q =25.467, df = 2, P < 0.001, I-square = 92.15%

B. ICU length of stay (days)

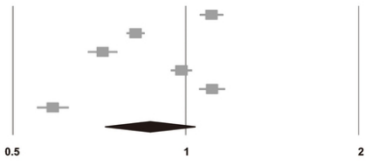
Study name	Difference in means	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Holley et al. (2009	-0.20	-6.89	6.49	-0.06	0.953	4.372
Choi et al. (2009)	-6.00	-26.40	14.40	-0.58	0.564	0.471
Chow et al. (2008)	3.00	1.56	4.44	4.10	<0.001	95.157
Pooled effects	**2.82**	**1.42**	**4.22**	**3.94**	**<0.001**	



Heterogeneity test:
Total
Q =1.560, df = 2, P = 0.458, I-square = 0%

C. Overall mortality

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Gong et al. (2016)	1.11	1.06	1.16	4.21	<0.001	16.699
Holley et al.(2009)	0.82	0.79	0.85	-10.56	<0.001	16.779
Choi et al. (2009)	0.72	0.67	0.76	-10.89	<0.001	16.587
Chow et al. (2008)	0.98	0.94	1.03	-0.79	0.427	16.740
Girao et al. (2008)	1.11	1.05	1.17	3.91	<0.001	16.657
Dimopoulos et al.	0.59	0.55	0.63	-16.22	<0.001	16.540
Pooled effects	**0.86**	**0.72**	**1.03**	**-1.59**	**0.111**	



Heterogeneity test:
Total
Q =399.000, df = 5, P < 0.001, I-square = 98.75%

Figure 2

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Figure 3A

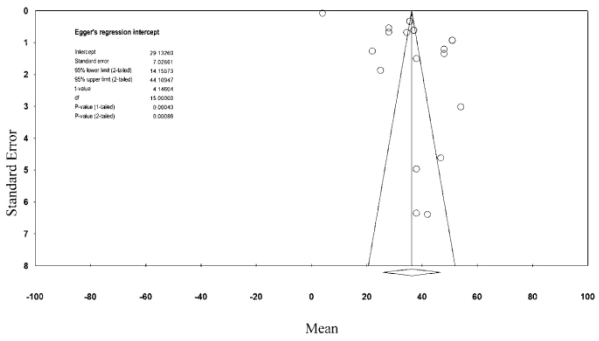


Figure 3B

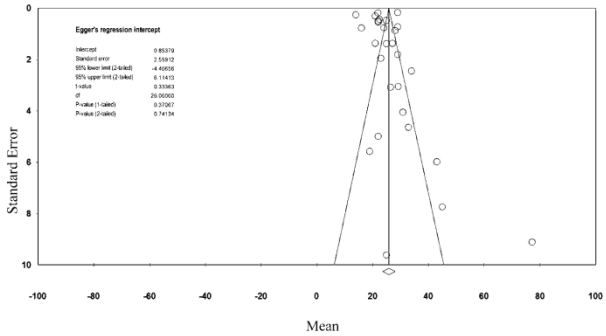
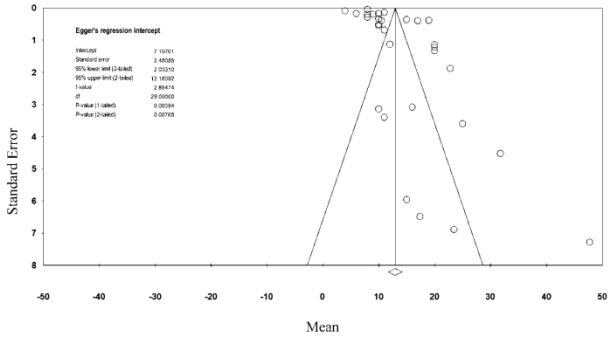


Figure 3C



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Supplementary Table S1. Literature search through several databases and the results.

Database	Key words and the combination	Articles found through initial search (N)	Articles excluded based on selection criteria or were duplicates (N)	Articles qualified for full text review (N)	Articles selected for meta-analysis (ref. no.)
PubMed*	(candidiasis OR candidemia) AND (intensive care unit OR ICU) AND risk factors	581	522	59	#14, 15, 26-29, 30-35, 37-45, 47, 48, 51, 53-58, 60, 63
Cochrane	(candidiasis OR candidemia) AND (intensive care unit OR ICU) AND risk factors	42	42	0	-
Embase **	(candidiasis OR candidemia) AND (intensive care unit OR ICU) AND risk factors	566	560	6	#36, 52, 59, 61
Web of Science***	(candidiasis OR candidemia) AND (intensive care unit OR ICU) AND risk factors	677	676	1	-
Manual search		9	0	9	#16, 46, 49, 50, 62
Total number		**1875**	**1800**	**75**	**41**

* PubMed search filters: Abstract available, English, Chinese, Human

** Embase search filters: Abstract, English, Human

*** Web of Science search filters: Articles, English, Human

Supplementary Table S2. A supplementary information of heterogeneity test for overall studies or given subgroup for Table 3.

	Length of hospital stay, days				Total length of ICU stay, days				Duration of ICU admission prior to candidemia onset, days				Length of hospital stay prior to ICU admission, days				Overall mortality rate			
Comparison	**Degrees of freedom**	**Q**	**I^2**	**P-value**	**Degrees of freedom**	**Q**	**I^2**	**P-value**	**Degrees of freedom**	**Q**	**I^2**	**P-value**	**Degrees of freedom**	**Q**	**I^2**	**P-value**	**Degrees of freedom**	**Q**	**I^2**	**P-value**
Overall	16	20197.0	99.92	<0.001	27	2690.9	99.00	<0.001	30	4686.2	99.36	<0.001	4	311.2	98.71	<0.001	39	26981.1	99.86	<0.001
Overall optional[abcd]	[a]13	850.7	98.47	<0.001	[b]25	2626.7	99.05	<0.001	[c]26	2649.8	99.02	<0.001					[d]35	24273.9	99.86	<0.001
Subgroups																				
Type of study																				
Prospective	7	568.3	98.77	<0.001	12	662.2	98.19	<0.001	16	1572.3	98.98	<0.001	1	0.9	0.35	<0.001	20	13805.2	99.86	<0.001
Retrospective	8	14000.4	99.94	<0.001	14	893.2	98.43	<0.001	13	2670.7	99.51	<0.001	2	28.39	92.95	<0.001	18	9479.2	99.81	<0.001
Presence of neutropenia																				
Neutropenia	7	6119.9	99.89	<0.001	8	2297.7	99.65	<0.001	11	3099.9	99.65	<0.001	0	-	-	-	11	15935.0	99.93	<0.001
Non-neutropenia	1	1.8	42.97	0.185	0			-	1	0	0	1	0	-	-	-	2	1388.4	99.86	<0.001
Type of ICU																				
ICU	7	11712.8	99.94	<0.001	16	930.6	98.28	<0.001	13	1589.8	99.18	<0.001	1	4.14	75.86	0.042	23	13807.9	99.83	<0.001
SICU				-	1	0.7	0.00	0.404	2	31.2	93.60	<0.001	0	-	-	-	2	1005.5	99.80	<0.001
MICU	0			-	1	6.2	83.92	0.013-	1	0	0	1-	0	-	-	-	1	14.3	92.99	<0.001
MICU+SICU	7	776.9	99.10	<0.001	6	713.7	99.16	<0.001	11	1539.5	99.29	<0.001	0	-	-	-	10	8098.2	99.88	<0.001
C. Albicans																				
C. Albicans	2	114.7	98.26	<0.001	2	5.79	65.45	0.055	1	0	0	1					5	1558.5	99.68	<0.001

Non C. Albicans	1	2.262	55.78	0.133	1	5.4	81.37	0.021	0	-	-	-				-	-	-	-
Presence of IC/candidemia																			
Candidemia	13	651.6	98.01	<0.001	23	2620.0	99.12	<0.001	24	2517.8	99.05	<0.001	3	302.3	99.01	<0.001	32	18755.6	99.83	<0.001
IC	2	2588.9	99.92	<0.001	3	17.0	82.33	0.001	5	1169.4	99.57	<0.001	0	-	-	-	6	3922.9	99.85	<0.001
Region																			
Asia	8	5464.6	99.85	<0.001	11	738.6	98.51	<0.001	11	2189.9	99.50	<0.001	1	1.4	26.82	0.242	16	8966.6	99.82	<0.001
Europe	3	226.5	98.68	<0.001	8	346.7	97.69	<0.001	10	907.3	98.90	<0.001	2	37.9	94.72	<0.001	13	7933.8	99.84	<0.001
South America	0	-	-	-	0	-	-	-	2	19.6	89.80	<0.001	-	-	-	-	4	1960.7	99.80	<0.001

Note: Certain subgroups have only 1 study (degree of freedom = 0).

[a] Excluded Yang et al. (2017),Gong et al (2016), Liao et al. (2015), and Guo et al. (2013).

[b] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015),and Guo et al. (2013).

[c] Excluded Yang et al. (2017),Gong et al (2016), Liao et al. (2015), and Hu et al. (2014).

[d] Excluded Yang et al. (2017), Gong et al (2016), Liao et al. (2015),and Hu et al. (2014).

Dash indicates no available.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	34
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	33
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	28
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	38
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	38
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	41
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	41
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	42

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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