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

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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)/candidaemia.

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 IC infection.

Data extraction and synthesis The following data were extracted from each article: length of hospital stay, length of ICU stay, duration of ICU admission prior to candidaemia onset, percentage of patients who received antibiotics and duration of their antibiotic therapy prior to candidaemia 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 candidaemia was 12.9 days (95% CI 11.7 to 14.2). The pooled mean duration of hospital stay was 36.3±5.3 days (95% CI 25.8 to 46.7), and the pooled mean mortality rate was 49.3%±2.2% (95% CI 45.0% to 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 *Candida albicans*. Meta-regression analysis found that South American patients had longer duration of ICU admission prior to candidaemia 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 candidaemia onset in Asia. This shows a more proactive strategy in the diagnosis of IC should be considered in caring for ICU patients.

Strengths and limitations of this study

- This meta-analysis is one of the few that investigated the association of invasive candidiasis with length of intensive care unit (ICU) stay, using data published worldwide and adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 prespecified 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 candidaemia could not be assessed.

INTRODUCTION

Candida species account for approximately 70%–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%–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 1000 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] Candidaemia has been described as the most common manifestation of IC, and 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 *Candida albicans*. However, non-*C. albicans* species have 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 remain challenging for physicians in the ICU.[1 2] The early initiation of empiric antifungal treatment has been demonstrated to improve the prognosis of IC.[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 IC, but its sensitivity is variable (21%–71%).[11]

To improve the diagnosis of IC and to identify the patients who may best benefit from prophylactic, pre-emptive or empiric 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, haemodialysis (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* colonisation[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 colonisation. This may be the primary reason for causing a delay of 7–10 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 candidaemia, including the length of hospitalisation and ICU stay, as well as regional differences in these factors.

METHODS

Search strategy

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

Randomised controlled trials, 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.

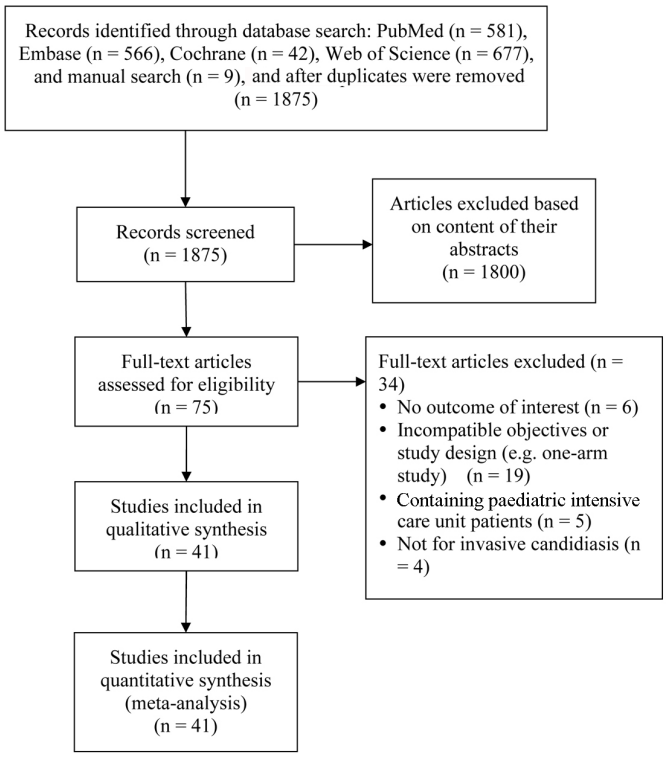

Figure 1 PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data extraction

The following information/data were extracted from studies that met the inclusion criteria: name of the first author, year of publication, country, study design, type of ICU, number of participants in each group, participants' age and gender, presence of *C. albicans*, presence of neutropaenia 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 candidaemia onset, antibiotic therapy prior to candidaemia onset, duration of antibiotic therapy prior to candidaemia 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 Risk of Bias tool and is suited for evaluating non-randomised studies that compare the health effects of different interventions. ROBINS-I covers seven 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, two 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 summarised as mean±SD, mean (range), median (range) or median (IQR) for age or duration of antifungal treatment, and percentage for sex, rate of *C. albicans* isolated, neutropaenia and antifungal treatment used in each study.

Clinical outcomes, including length of hospital stay, length of ICU stay, length of hospital stay prior to ICU admission, duration of ICU admission prior to candidaemia onset and duration of antibiotic therapy prior to candidaemia onset, were represented as mean (range: min–max), median (range) or median (IQR: first to third quartiles). The rate of antibiotic therapy prior to candidaemia onset and overall mortality rate were presented as percentages. All clinical outcomes were further summarised for subgroups of studies (with number of studies ≥2). Types of study, presence of neutropaenia, types of ICU, type of *Candida* isolated, presence of IC/candidaemia 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 IQR were converted to mean±SD, according to the method described by Wan *et al*.[24]

The outcomes selected for the analysis were length of hospital stay, length of ICU stay, duration of ICU admission prior to candidaemia onset and overall mortality between patients who were diagnosed with *C. albicans* and those with non-*C. albicans*. The effect size was calculated as the mean difference with 95% CI (lower limit, upper limit) in length of days, or rate ratio with 95% CI in overall mortality for each given study, and a pooling effect was derived thereafter. A difference in the mean of length in days <0 (or rate ratio of overall mortality rate >1) indicated the pooling effect favouring non-*C. albicans* subgroup, whereas a difference in the mean of length in days >0 (or rate ratio of overall mortality rate <1) indicated the pooling effect favouring *C. albicans* subgroup. A difference in the mean 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 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 is <0.10 or I^2 is >50%; otherwise, a fixed-effect model (Mantel-Haenszel method) was used. 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.

Publication bias was assessed using the funnel plot with Egger's test and the classic 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 one-tailed significance level of p>0.05 in an Egger's test.[25] All analyses were performed using Comprehensive Meta-Analysis V.3.3.070 statistical software (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search results

A total of 1875 articles were retrieved from the 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 paediatric ICU (n=5), not having IC (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

The characteristics of the 41 studies are summarised in (tables 1 and 2).[14–16 26–29 30–63] A total of 10 692 patients were included in these studies, with the number of patients in each study ranging from 12 to 1400. The mean age of the patients ranged from 28 to 76 years, and majority were male (range: 20%–75.9%). These studies were conducted in different countries, with 19 in Europe, 14 in Asia, 1 in the USA, 4 in South America, 2 in Australia and 1 multinational study (Australia, Belgium, Greece and Brazil).

Among studies that reported the mean length of ICU admission being ≤10 days prior to candidaemia onset, including the early-onset group in the study by Yang *et al*[26] and the 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 candidaemia 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 candidaemia

Table 1 Characteristics of studies included in this systematic review

Studies												Antifungal treatment
First author (year)	Country	Study design	Type of ICU	Total number of patients	IC and candidaemia	Patients (n)	Age (years)	Male (%)	*Candida albicans* isolated (%)	Neutropaenia (%)	Duration of treatment	Antifungal treatment used
Zhao (2018)[51]	China	Retrospective cohort	ICU	95	Candidaemia	95	69.3±16.5	57.90	59	—	—	17.90%
Ding (2018)[52]	China	Retrospective cohort	ICU	72	Candidaemia	72	62.5 (49.8–77.0)*	62.50	15	—	—	Fluconazole (30.6%) Voriconazole (9.7%) Echinocandin (44.4%)
Yang (2017)[26]	China	Retrospective cohort study (China-SCAN)	ICU	306	Early-onset IC	105	56.9 (19.9)*	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 (19.7)*	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%)
Tigen (2017)[53]	Turkey	Case–control study	ICU	73	Candidaemia	36	65 (52–73)†	52.80	75		17.6±11.7 days	Caspofungin Posaconazole Voriconazole Itraconazole Fluconazole Amphotericin B
					Control (non-candidaemia)	37	62 (48–72)†	48.60	—	—	—	—

Continued

Table 1 Continued

Antifungal treatment												
Studies												
First author (year)	**Country**	**Study design**	**Type of ICU**	**Total number of patients**	**IC and candidaemia**	**Patients (n)**	**Age (years)**	**Male (%)**	***Candida albicans* isolated (%)**	**Neutropaenia (%)**	**Duration of treatment**	**Antifungal treatment used**
Baldesi (2017)[54]	France	Case–control study	ICU	246 459	Candidaemia	851	65 (54–75)*	62.60	61.4	5.10	—	—
					Control (non-candidaemia)	245 608	65 (52–76)*	61.70	—	1.60	—	—
Rudramurthy (2017)[55]	India	Prospective cohort	MICU, SICU	1161	Candidaemia (*C. auris*)	74	39 (16–58.5)*	62.20	—	—	—	Fluconazole (20.3%) Echinocandin (9.5%)
					Candidaemia (non-*C. auris*)	1087	—	—	—	—	—	Fluconazole (12.1%) Echinocandin (0.8%)
Kawano (2017)[56]	Japan	Retrospective cohort	ICU	4136	Candidaemia	25	69 (24–88)†	56.00	52	0	—	Antifungal treatment (32%)
Ortíz Ruiz (2016)[16]	Colombia	Case–control study	Polyvalent, cardiovascular ICU	243	Candidaemia	81	64.5 (51–78)*	51.90	42	—	—	—
					Control	162	68 (48–77) *	59.30	—	—	—	—
Gong (2016)[47]	China	Prospective cohort study (China-SCAN)	MICU, SICU, integrated ICU	306	Candidaemia (*C. albicans*)	98	62.2±17.3	62.20	100	3.10	12.85 days	Triazole (64.7%) Echinocandin (31.8%) Polyenes (0%)
					Candidaemia (non-*C. albicans*)	146	61.4±21.4	72.60	—	1.40	20.4 days	Triazole (62.8%) Echinocandin (34.1%) Polyenes (2.3%)
Playford (2016)[57]	Australia	Prospective cohort	MICU, SICU	6714	ICU-acquired IC	96	—	—	66	—	—	—
					Control (no IC)	6618	—	—	—	—	—	—
Pinhati (2016)[58]	Brazil	Cross-sectional	ICU	40	Fluconazole-resistant *C. parapsilosis*	21	70 (23–91)†	66.70	—	—	—	Any (33.3%) Fluconazole (19.0%)
					Fluconazole-susceptible *Candida* species	19	76 (35–90)†	57.90	—	—	—	Any (15.8%) Fluconazole (15.8%)
Aguilar (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%)

Continued

Table 1 Continued

Antifungal treatment												
Studies												
First author (year)	Country	Study design	Type of ICU	Total number of patients	IC and candidaemia	Patients (n)	Age (years)	Male (%)	*Candida albicans* isolated (%)	Neutropaenia (%)	Duration of treatment	Antifungal treatment used
Fochtmann (2015)[27]	Austria	Retrospective cohort study	Burn ICU	174	Candidaemia	20	39 (17–88)†	60	60	—	—	Triazoles (70%)
					Control	154	58 (17–94)†	61		—	—	Echinocandins (30%)
Klingspor (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 (2015)[29]	India	Prospective cohort study	MICU, SICU	1400	Candidaemia	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 (2015)[14]	China	Prospective cohort study (China-SCAN)	MICU, SICU, mixed ICU	306	Flu-S	129	62.4±19.5	68.20	60.5	3.10	—	Monoantifungal therapy (64.5%) Fungal drug adjustment (35.7%) Completely improved (34.6%)
					Flu-R	90	60.8±20.9	67.80	17.8	1.10	—	Monoantifungal therapy (48.8%) Fungal drug adjustment (61.1%) Completely improved (28.0%)
Kautzky (2015)[59]	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 (2014)[31]	Turkey	Prospective cohort study	ICU burn service	2362	IC	63	70.2±19.5 (14–95)	54	64	—	—	—
Colombo (2014)[32]	Brazil	Retrospective cohort study	ICU	1392	Candidaemia	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%)

Continued

Table 1 Continued

Antifungal treatment												
Studies												
First author (year)	**Country**	**Study design**	**Type of ICU**	**Total number of patients**	**IC and candidaemia**	**Patients (n)**	**Age (years)**	**Male (%)**	***Candida albicans* isolated (%)**	**Neutropaenia (%)**	**Duration of treatment**	**Antifungal treatment used**
Hu (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-drug combination (1.7%)
Lortholary (2017)[60]	France	Prospective cohort	ICU	2507	ICU-acquired candidaemia	1206	60±17	62.00	57.1	—	—	Fluconazole (55.4%) Echinocandins (26.2%) Others (including combination) (12.6%)
					Non-ICU-acquired candidaemia	1301	60±17	58.70	54.9	—	—	Fluconazole (59.9%) Echinocandins (19.1%) Others (including combination) (13.3%)
Yapar (2014)[61]	Turkey	Retrospective cohort	ICU	1076	Candidaemia	66	54.4±23.9	53	53	—	—	9%
					Control (non-candidaemia)	1010	53.2±23.0	63	—	—	—	6.30%

Continued

Table 1 Continued

Antifungal treatment												
Studies												
First author (year)	Country	Study design	Type of ICU	Total number of patients	IC and candidaemia	Patients (n)	Age (years)	Male (%)	*Candida albicans* isolated (%)	Neutropaenia (%)	Duration of treatment	Antifungal treatment used
Guo (2013)[49]	China	Prospective cohort study (China-SCAN)	MICU, SICU, general emergency, neurological ICU	306	Candidaemia	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 (2013)[30]	India	Prospective cohort	ICU	5976	Candidaemia	39	35.14 (3 days–79 years)	61.50	4			
Tortorano (2012)[33]	Italy	Prospective cohort study	MICU, SICU	384	Candidaemia	276	—	—	60.9	—	—	Fluconazole (63%) Amphotericin B (22%) Caspofungin (7%) Voriconazole (6%)
Ylipalosaari (2012)[34]	Finland	Retrospective cohort study	MICU, SICU	82	ICU-acquired candidaemia	38	63 (45–69)*	71	76.3	—	Median: 22 days	Fluconazole (73%) Amphotericin B (34%) Echinocandins (31%)
					Non-ICU-acquired candidaemia	44	64 (56–75)*	61	68.9	-	Median: 24 days	Fluconazole (77%) Amphotericin B (35%) Echinocandins (40%)
Pasero (2011)[35]	Italy	Prospective cohort study	SICU	349	Candidaemia	26	60±21	61.50	73	—	—	—
					Control	323	67±16	65.30		—	—	—
Han (2010)[36]	Korea	Case–control study	MICU	52	Candidaemia	49	57.6±14.1	—	65	25	11 (1–45)† days	Amphotericin B (71.4%)
					Control	147	57.4±14.0	—	—	8		Fluconazole (28.6%)
Pratikaki (2011)[37]	Greece	Case–control study	Multidisciplinary ICU	855	Candidaemia	33	57±18	64	33.3	0	>14 days	Amphotericin B (57.1%)
					Control	132	58±18	70	—	0		Voriconazole (17.9%) Caspofungin (14.3%) Fluconazole (10.7%)
Playford (2009)[38]	Australia	Prospective cohort study	MICU, SICU	615	IC	15	NA	NA	73.3	0	—	—

Continued

Table 1 Continued

Antifungal treatment												
Studies												
First author (year)	**Country**	**Study design**	**Type of ICU**	**Total number of patients**	**IC and candidaemia**	**Patients (n)**	**Age (years)**	**Male (%)**	***Candida albicans* isolated (%)**	**Neutropaenia (%)**	**Duration of treatment**	**Antifungal treatment used**
Holley (2009)[39]	Australia, Belgium, Greece, Brazil	Retrospective cohort study	Multidisciplinary ICU	189	Candidaemia (*C. albicans*)	104	56.5±17.1	63.50	100	—	1 (1–32)† days	Fluconazole (37%) Amphotericin B (31%)
					Candidaemia (non-*C. albicans*)	85	58.9±16.3	44.70	—	—		Fluconazole and amphotericin B (15%)
Choi (2009)[40]	Korea	Retrospective cohort study	ICU	497	Candidaemia (*C. albicans*)	54	49±23	44.40	100	13	—	Amphotericin B (77.8%) Fluconazole (16.7%)
					Candidaemia (*C. glabrata* or *C. krusei*)	27	48±25	44.40	—	19	—	Fluconazole and amphotericin B (5.6%)
Yap (2009)[50]	China, Hong Kong	Retrospective cohort study	MICU, SICU	128	Candidaemia	128	54 (43–68)*	63.30	56	11	—	Amphotericin B (39.1%) Fluconazole (38%) Amphotericin B+fluconazole (13%) Caspofungin or voriconazole (9.8%)

Continued

Table 1 Continued

Antifungal treatment												
Studies												
First author (year)	**Country**	**Study design**	**Type of ICU**	**Total number of patients**	**IC and candidaemia**	**Patients (n)**	**Age (years)**	**Male (%)**	***Candida albicans* isolated (%)**	**Neutropaenia (%)**	**Duration of treatment**	**Antifungal treatment used**
Chow (2008)[41]	USA	Case–control study	MICU, SICU	926	Candidaemia (non-*C. albicans*)	67	62.3±14.5	57	—	—	—	Fluconazole (84.8%) Amphotericin B (23.9%) Caspofungin (10.9%) Voriconazole (4.3%)
					Candidaemia (*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%)
Bougnoux (2008)[42]	France	Prospective cohort study	MICU SICU	290	Candidaemia	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%)
Girão (2008)[43]	Brazil	Prospective cohort study	ICU	73	Candidaemia (non-*C. albicans*)	40	51 (12–86)‡	60	—	—	—	—
					Candidaemia (*C. albicans*)	33	51 (15–86)‡	40	100	—	—	—
Dimopoulos (2008)[44]	Greece	Prospective cohort study	MICU, SICU	56	Candidaemia (*C. albicans*)	36	60.5±14.9	44.40	100	0 (excluded)	Response rate: 80.6%	Fluconazole as prophylaxis: No fluconazole as prophylaxis: Amphotericin B (60%) Caspofungin (40%)
					Candidaemia (non-*C. albicans*)	20	64.5±16.8	55	—		Response rate: 45%	Amphotericin B (100%)

Continued

Table 1 Continued

Studies				Total number of patients	IC and candidaemia	Patients (n)	Age (years)	Male (%)	*Candida albicans* isolated (%)	Neutropaenia (%)	Duration of treatment	Antifungal treatment used
Antifungal treatment												
First author (year)	**Country**	**Study design**	**Type of ICU**									
Dimopoulos (2007)[45]	Greece	Prospective cohort study	MICU, SICU	24	Candidaemia	24	–	–	62.5	–	16.5 (14–24)‡ days	*C. albicans*: fluconazole Non-*C. albicans*: amphotericin B
Jordà-Marcos (2007)[62]	Spain	Prospective cohort	MICU, SICU	1765	Candidaemia	63	63 (48–70)†	71.40	57.1	6.30	–	7.90%
					Control (non-candidaemia)	1072	63 (46–71)†	66.50	–	2.80	–	5.60%
Piazza (2003)[63]	Italy	Retrospective cohort	ICU	478	Candidaemia	12	57.58±22.07	58.30	67	–	–	–
Michalopoulos (2003)[46]	Greece	Prospective case–control study	CICU	150	Candidaemia	30	63.2±9.7	73.30	70	–	–	–
					Control	120	64.3±9.9	73.30	–	–	–	–

Total number of enrolled patients: 7982.
Dash indicates no available data.
*Data are presented as median (IQR).
†Data are presented as median (range).
‡Data are presented as mean (range).
CICU, cardiothoracic intensive care unit; CRCBSI, catheter-related *Candida* bloodstream infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, invasive candidiasis; ICU, intensive care unit; MICU, medical intensive care unit; NA, not available; SICU, surgical intensive care unit.

onset in the ICU, which ranged from 59.0% in the early-onset group[26] to 100% in the catheter-related *Candida* bloodstream infection (CRCBSI) and non-*C. albicans* groups.[49 51] Only one study reported the median duration of antibiotic therapy prior to candidaemia 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 length of hospital stay, length of ICU stay, duration of ICU admission prior to candidaemia onset, length of hospital stay prior to ICU admission and overall mortality is presented in table 3. Five studies[14 26 47–49] were from China, using China-SCAN patient data, in which four studies were excluded to avoid overlapping data.

Across all studies, the mean length of hospital stay, mean length of ICU stay, mean duration of ICU admission prior to candidaemia 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 to 46.7), 25.8 days (95% CI 23.6 to 28.1), 12.9 days (95% CI 11.7 to 14.2), 11.7 days (95% CI 0.37 to 23.1) and 49.3% (95% CI 45.0% to 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 candidaemia onset and the mean overall mortality rate were found to be 37.5 days (95% CI 33.3 to 41.6), 25.9 days (95% CI 23.5 to 28.3), 13.7 days (95% CI 12.5 to 15.0) and 50.99% (95% CI 46.6% to 55.4%), respectively (table 3).

Other outcomes including types of study, presence of neutropaenia, types of ICU, types of *C. albicans* isolated, presence of IC/candidaemia and regions/countries were also summarised for subgroups of studies (with studies' number ≥2). The interval estimate showed the summarised 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 candidaemia (95% CI included 0) (table 3).

According to the summarised statistics in table 3, patients with neutropaenia had longer length of hospital stay (mean=34.9 vs 22.9 days), longer duration of ICU admission prior to candidaemia onset (mean=11.6 vs 10.0 days) and higher overall mortality rate (rate: 49.6% vs 41.3%) than non-neutropaenic patients. The mean durations of ICU admission prior to candidaemia 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 candidaemia had longer length of hospital stay (mean=36.3 vs 33.9), longer duration of ICU admission prior to candidaemia onset (mean=13.2 vs 11.5) and higher overall mortality rate (51.4% vs 38.9%) than patients without IC. However, patients with candidaemia had shorter length of ICU stay

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

Studies							
First 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 candidaemia onset (days)	Percentages of patients receiving antibiotic therapy prior to candidaemia onset	Duration of antibiotic therapy prior to candidaemia onset (days)	Overall mortality rate
Zhao (2018)[51]	NA	24 (12–57)*	NA	NA	NA	NA	58
Ding (2018)[52]	NA	NA	NA	NA	Broad-spectrum antibiotics: 98.6%	NA	31.90
Yang (2017)[26]	Prior to IC diagnosis	NA	NA	Early-onset IC: 4 (1–7)†	Early-onset IC: 62 (59.0%)	NA	Early-onset IC: 28.6
	Early-onset IC: 4 (2–7)†			Late-onset IC: 17 (10–33)†	Late-onset IC: 179 (89.1%)		Late-onset IC: 40.8
	Late-onset IC: 26 (16–50)†						
Tigen (2017)[53]	NA	22 (18–30)*	NA	NA	Broad-spectrum antibiotic: 100%	NA	83.30
		5.5 (2.25–15.75)*			Broad-spectrum antibiotic: 59.5%		
Baldesi (2017)[54]	NA	29 (18–49)†	NA	NA	Antimicrobials: 82.2%	NA	52.40
		7 (4–13)†			Antimicrobials: 55.1%		17.80
Rudramurthy (2017)[55]	NA	NA	NA	10 (4.7–22.2)†	NA	NA	41.90
				7 (3–13)†			27
Kawano (2017)[56]	NA	NA	NA	13 (1–73)*	Broad-spectrum antimicrobial: 84%	NA	72
Ortíz Ruiz (2016)[16]	35.4±3.0	21.9±1.7	NA	Median 25	Broad-spectrum antibiotic: 93.8% vs 69.8% (case vs control)	NA	39.51
Gong (2016)[47]	*Candida albicans*: median: 32	*C. albicans*: median: 18	NA	NA	*C. albicans* (before diagnosis): 76 (77.6%)	NA	*C. albicans* (before diagnosis): 29.6
	Non-*C. albicans*: median: 44	Non-*C. albicans*: median: 29			Non-*C. albicans* (before diagnosis): 121 (82.9%)		Non-*C. albicans* (before diagnosis): 26.7
Playford (2016)[57]	51 (34–89)†	21 (14–32)†	NA	10 (5–15.25)*	NA	NA	26
	23 (13–40)†	8 (5–12)†					18.30
Pinhati (2016)[58]	NA	NA	NA	22 (0–83)*	Any: 47.6%	NA	42.90
				25 (7–134)*	Any: 42.1%		47.40
Aguilar (2015)[15]	NA	NA	NA	20 (5–37.5)†	Antibiotic therapy: 21 (95.4%)	10 (5.0–16.5)*	13.60
Fochtmann (2015)[27]	NA	60 (13–176)*	NA	16 (6–89)*	Broad-spectrum antibiotic treatment in most patients	16 (6–89)*	30

Continued

Table 2 Continued

Studies First 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 candidaemia onset (days)	Percentages of patients receiving antibiotic therapy prior to candidaemia onset	Duration of antibiotic therapy prior to candidaemia onset (days)	Overall mortality rate
Klingspor (2015)[28]	NA	23 (0–329)*	2 (0–744)*	12 (0–190)*	Broad-spectrum antibiotics in the last 2 weeks: 511 (78.4%)	NA	38.80
Chakrabarti (2015)[29]	NA	NA	NA	8 (4–15)†	Patients with candidaemia received antibiotics: 93.0%	16.0 (7–36) days†	44.70
Liao (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)	NA	Flu-S: 8.0 (3.0–17.0)† Flu-R: 10.5 (4.0–27.0)†	≥5 days before diagnosis: Flu-S: 101 (78.3%) Flu-R: 73 (81.1%)	NA	Flu-S: 31.8 Flu-R: 41.1
Kautzky (2015)[59]	NA	46 (14–74)* 21 (10–77)*	17 (1–21)* 3 (1–66)*	17.4±14.5	100% 90%	NA	80 21.70
Karacaer (2014)[31]	46.8±36.7 (5–190)	32.9±36.9 (0–190)	NA	NA	NA	15±13.8	77.70
Colombo (2014)[32]	NA	NA	NA	20 (0–188)*	Prior antibiotic exposure: 96.1%	NA	70.30
Hu (2014)[48]	54.0 (26.0–91.0)†	34.0 (18.0–71.0)†	NA	11.0 (4.0–26.0)†	CRCBSI: 100% Non-CRCBSI: 99.5%	CRCBSI: 11.4±4.2 days Non-CRCBSI: 10.6±6.5 days	44.80
Lortholary (2017)[60]	NA	NA	NA	NA	NA	NA	51.00 30.70
Yapar (2014)[61]	NA	30.9±33 12.9±13	NA	NA	96.90% 78.30%	NA	43.90 32.20
Guo (2013)[49]	NA	NA	NA	10 (0–330)*	Treatment before diagnosis confirmation: 74 (27.6%)	NA	36.60
Giri (2013)[30]	NA	Mean 26.4 (range 9–86) days	NA	NA	66.70%	Mean 19.45 (range 4–31) days	24
Tortorano (2012)[33]	NA	NA	NA	22.8 (2–190)*	Broad-spectrum antibiotic treatment: 85%	NA	46.20
Ylipalosaari (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%	NA	65.80
Pasero (2011)[35]	NA	21±7	NA	20 (8–49)†	A significantly higher administration of >2 antibiotics for >72 hours.	NA	47

Continued

Table 2 Continued

Studies First 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 candidaemia onset (days)	Percentages of patients receiving antibiotic therapy prior to candidaemia onset	Duration of antibiotic therapy prior to candidaemia onset (days)	Overall mortality rate
Han (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 (2011)[37]	NA	25 (14–46)†	14 (1–20)†	10 (3–22)†	All patients received antimicrobial agents prior to candidaemia onset.	NA	60.60
Playford (2009)[38]	NA	NA	NA	10 (4–16)†	Antibiotic receipt on days 1–3: 83.4% Broad-spectrum antibiotic receipt on days 1–3: 82.0%	NA	10.60
Holley (2009)[39]	NA	*C. albicans*: 29.0±18.5 Non-*C. albicans*: 29.2±28.2	NA	NA	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 (2009)[40]	Prior to fungaemia *C. albicans*: 42±47 Non-*C. albicans*: 38±33	*C. albicans*: 19±41 Non-*C. albicans*: 25±50	NA	*C. albicans*: 11±25 Non-*C. albicans*: 15±31	NA	NA	*C. albicans:* 48 Non-*C. albicans*: 67
Yap (2009)[50]	28 (17–54)†	14 (5–23)†	NA	6 (1–13)†	Antibiotics >48 hours before candidaemia: *C. albicans*: 70 (97.0%) Non-*C. albicans*: 56 (100%)	NA	70
Chow (2008)[41]	*C. albicans*: 28 (20–42)† Non-*C. albicans*: 37 (24–57)†	*C. albicans*: 22 (15–33)† Non-*C. albicans:* 25 (14–40)†	NA	*C. albicans*: 11 (9–17)† Non-*C. albicans*: 10 (4–21)†	Non-*C. albicans*: 0.75 (0–2)†	2.21 (1.4–2.7)†	*C. albicans*: 58 Non-*C.* albicans: 57
Bougnoux (2008)[42]	NA	43.1±45.2	NA	19.0±2.9 or (13.0; 2–145)†	No antibiotic treatment is reported.	NA	61.80
Girão (2008)[43]	NA	NA	NA	*C. albicans*: 15 (mean) Non-*C. albicans*: 18 (mean)	The hospital restricted the use of several antibiotics.	NA	*C. albicans*: 72 Non-*C. albicans*: 80
Dimopoulos (2008)[44]	*C. albicans*: 22±7.6 Non-*C. albicans*: 25±8.4	NA	NA	*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.	NA	*C. albicans*: 52.8 Non-*C. albicans*: 90

Continued

Table 2 Continued

Studies	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 candidaemia onset (days)	Percentages of patients receiving antibiotic therapy prior to candidaemia onset	Duration of antibiotic therapy prior to candidaemia onset (days)	Overall mortality rate
First author (year)							
Dimopoulos (2007)[45]	NA	NA	NA	9 (5–11)*	100% of patients received broad-spectrum antibiotic treatment	NA	NA
Jordà-Marcos (2007)[62]	48 (26–69)	28 (17–45)	NA	23.5±54.7	100%	NA	17.20
	35 (22–57)	18 (12–28)			96.50%		13.20
Piazza (2003)[63]	NA	N/A	NA	Median 13 days	NA	NA	67
Michalopoulos (2003)[46]	NA	27.1±7.5	NA	15 (11–23)*	Empiric antibiotic therapy with two or more broad-spectrum agents for all patients.	NA	NA

*Data are presented as median (range).
†Data are presented as median (IQR).
CRCBSI, catheter-related bloodstream *Candida* infection; Flu-R, fluconazole-resistant; Flu-S, fluconazole-sensitive; IC, invasive candidiasis; ICU, intensive care unit; NA, not available.

(mean=25.8 vs 26.4 days) and 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 longer duration of ICU admission prior to candidaemia onset compared with patients with other species of *C. albicans* (mean=11 vs 10 days). The mean durations of ICU admission prior to candidaemia onset in hospitalised patients were 18.5 days (95% CI 15.3 to 21.7 days) in Europe, 17.4 days (95% CI 14.6 to 20.2 days) in Asia and 45.8 days (95% CI 27.8 to 63.7 days) in South America. Data from Girão *et al*[43] and Gong *et al*[47] were excluded from the summarised analysis due to absence of SD for mean values and data ranges.

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

To compare the broad-spectrum antibiotic use between patients with and without IC, 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 the use of broad-spectrum antibiotics among patients with IC (89.1%, 95% CI 82.7% to 93.4%) prior to IC onset versus those without IC (77.4%, 95% CI 52.3% to 91.4%) did not reach statistical significance. The mean duration of antibiotic therapy prior to candidaemia onset was 17.8 days (95% CI 9.3 to 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 to 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 *C. albicans* and non-*C. albicans*

A meta-analysis was performed to compare the effect of 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* ($p>0.05$; figure 2A); however, there was a significant difference in mean length of ICU stay (difference in means=2.8 days, $p<0.001$; figure 2B). There was also no significant difference in overall mortality between patients with and without *C. albicans* ($p>0.05$; figure 2C).

Table 3 Summary of length of hospital stay, length of ICU stay, duration of ICU admission and hospital stay prior to candidaemia onset, and overall mortality in the overall or given subgroups‡§

Comparison	Length of hospital stay (days) Mean (95% CI)	Length of ICU stay (days) Mean (95% CI)	Duration of ICU admission prior to candidaemia onset (days) Mean (95% CI)	Length of hospital stay prior to ICU admission (days) Mean (95% CI)	Overall mortality Rate (95% CI)
Overall	36.3 (25.8 to 46.7)	25.8 (23.6 to 28.1)	12.9 (11.7 to 14.2)	11.7 (0.4 to 23.1)	49.3 (45.0 to 53.5)
Overall optional*†	37.5 (33.3 to 41.6)*	25.9 (23.5 to 28.3)*	13.7 (12.5 to 15.0)†	—	51.0 (46.6 to 55.4)†
Subgroups					
Type of study					
Prospective	41.0 (32.9 to 49.1)	27.4 (24.6 to 30.3)	12.9 (11.5 to 14.4)	19.2 (17.2 to 21.3)	42.7 (37.9 to 47.4)
Retrospective/ cross-sectional	31.9 (18.2 to 45.5)	23.9 (21.1 to 26.6)	13.7 (11.2 to 16.2)	7.4 (–3.7 to 18.4)	56.5 (48.0 to 65.0)
Presence of neutropaenia					
Neutropaenia	34.9 (19.8 to 50.1)	25.4 (19.3 to 31.5)	11.6 (9.5 to 13.8)	—	49.6 (40.8 to 58.3)
Non-neutropaenia	22.9 (20.9 to 25.0)	—	10.0 (9.3 to 10.7)	—	41.3 (7.9 to 74.7)
Type of ICU					
ICU	37.7 (21.7 to 53.7)	27.3 (24.9 to 29.7)	14.3 (5.7 to 6.0)	17.2 (11.9 to 22.4)	49.8 (44.3 to 55.3)
SICU	—	21.7 (19.5 to 23.9)	17.3 (11.9 to 22.7)	—	33.1 (15.2 to 51.1)
MICU	—	32.7 (10.3 to 55.2)	17.0 (16.2 to 17.8)	—	88.4 (72.8 to 104.1)
MICU+SICU	34.6 (28.2 to 41.1)	22.5 (18.4 to 26.6)	10.9 (9.6 to 12.3)	—	45.7 (36.4 to 55.0)
Candida albicans					
C. albicans	34.2 (33.1 to 35.3)	25.9 (22.3 to 29.5)	11.0 (10.7 to 11.3)	—	52.2 (40.0 to 64.4)
Non-*C. albicans*	27.0 (24.3 to 29.8)	25.0 (18.0 to 31.9)	—	—	—
Presence of IC/ candidaemia					
Candidaemia	36.3 (32.9 to 39.8)	25.8 (23.2 to 28.3)	13.2 (12.0 to 14.5)	10.8 (–2.0 to 23.6)	51.4 (47.1 to 55.8)
IC	33.9 (–3.7 to 71.4)	26.4 (20.7 to 32.1)	11.5 (7.7 to 15.3)	—	38.9 (27.8 to 50.1)
Region(s)					
Asia	36.9 (23.0 to 50.8)	25.0 (20.9 to 29.0)	17.4 (14.6 to 20.2)	19.3 (17.2 to 21.4)	51.2 (44.7 to 57.7)
Europe/USA/ Australia	33.3 (20.8 to 45.8)	27.7 (23.3 to 32.1)	18.5 (15.3 to 21.7)	9.6 (–1.2 to 20.4)	48.6 (42.4 to 54.7)
South America	—	—	45.8 (27.8 to 63.7)¶	—	54.4 (38.0 to 70.7)

Certain subgroups have only one study (df=0).
Dash indicates no available data.
*Excluded Yang *et al*[26] (2017), Gong *et al* (2016),[47] Liao *et al*[14] (2015) and Guo *et al*[49] (2013).
†Excluded Yang *et al* [26] (2017) Gong *et al* [47] (2016), Liao *et al* (2015)[14] and Hu *et al*[48] (2014).
‡The range 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 the group of participants is positive; if the lower limit is negative and the upper limit is positive, it indicates that the clinical outcome estimate for the 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 exists in subgroups.
¶Meta-regression analysis illustrated South American patients had significantly longer duration of ICU admission prior to candidaemia onset than their counterparts in Asia, Australia, Europe and North America (using Asia as the reference group, for South America: β=25.83, p=0.0308, R^2=0.097). Other meta-regression analyses in subgroups in this table did not reach statistical significance.
IC, invasive candidiasis; ICU, intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit.

Quality assessment

The results of the quality assessment are shown in table 4. Regarding the results of ROBINS-I, nine 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

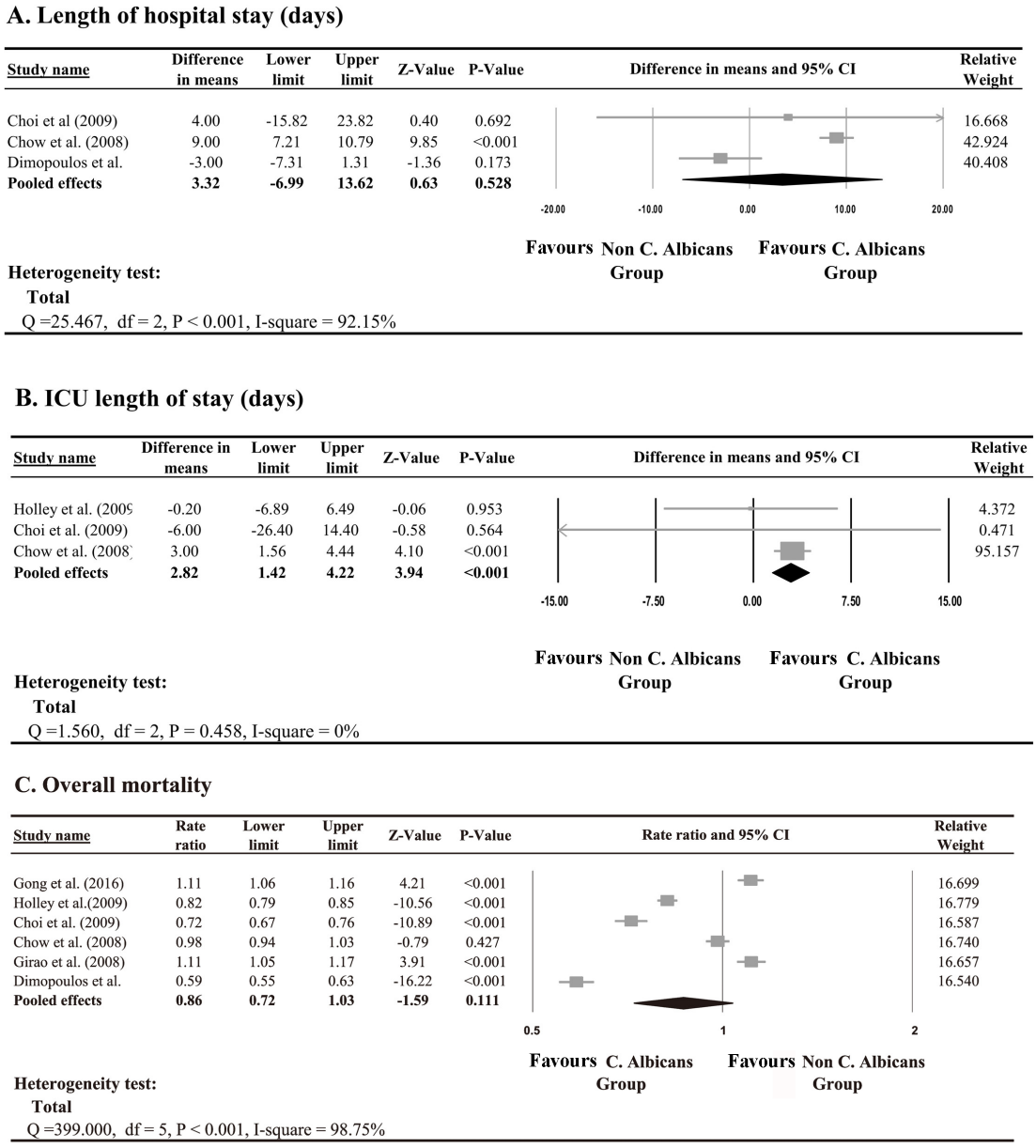

Figure 2 Meta-Analysis of *Candida albicans* vs non-*Candida albicans* for (A) length of hospital stay, (B) intensive care unit (ICU) length of stay and (C) overall mortality.

of the studies had low or moderate bias in classification of interventions. No study provided information on the 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 results. Overall, 28 studies had moderate risk of bias, 13 had serious risk of bias, and 1 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 candidaemia onset than patients in Asia, Australia, Europe and North America (using Asia as the reference group, South America had β=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.

Publication bias

Egger's test showed potential publication bias for length of hospital stay (one-tailed p<0.001) and duration of ICU admission prior to candidaemia onset (one-tailed p=0.004); there was no significant publication bias for length of ICU stay (one-tailed p=0.37) and overall mortality (one-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, 2304 for length of ICU stay, 89 242 for duration of ICU admission prior to candidaemia onset and 34 263 for

Table 4 Quality assessment of included studies using ROBINS-I

First 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 (2018)[52]	Low	Moderate	Low	No information	Moderate	Low	Low	Moderate
Zhao (2018)[51]	Low	Low	No information	No information	Low	Low	Low	Moderate
Baldesi (2017)[54]	Low	Moderate	No information	No information	Low	Low	Low	Moderate
Kawano (2017)[56]	Serious	Moderate	Low	No information	Low	Low	Low	Serious
Rudramurthy (2017)[55]	Low	Low	Low	No information	Low	Low	Low	Moderate
Tigen (2017)[53]	Serious	Moderate	Low	No information	Low	Low	Low	Serious
Yang (2017)[26]	Low	Low	Low	No information	Low	Low	Moderate	Moderate
Gong (2016)[47]	Serious	Moderate	Low	No information	Low	Low	Low	Serious
Ortíz Ruiz (2016)[16]	Low	Low	Low	No information	Low	Low	Low	Moderate
Pinhati (2016)[58]	Moderate	Moderate	Low	No information	Low	Low	Low	Moderate
Playford (2016)[57]	Low	Moderate	No information	No information	Low	Low	Low	Moderate
Aguilar (2015)[15]	No information	Moderate	Low	No information	Low	Low	Low	Moderate
Chakrabarti (2015)[29]	Serious	Low	Low	No information	Low	Low	Low	Serious
Fochtmann (2015)[27]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Kautzky (2015)[59]	Serious	Low	No information	No information	Low	Low	Low	Serious
Klingspor (2015)[28]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Liao (2015)[14]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Karacaer (2014)[31]	Moderate	Moderate	Low	No information	Low	Low	Low	Moderate
Colombo (2014)[32]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Hu (2014)[48]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Lortholary (2017)[60]	Low	Serious	Low	No information	Low	Low	Moderate	Serious
Yapar (2014)[61]	Moderate	Moderate	Low	No information	Low	Low	Low	Moderate
Giri (2013)[30]	Serious	Moderate	Low	No information	Low	Low	Low	Serious
Guo (2013)[49]	Low	Low	Low	No information	Low	Low	Low	Moderate
Tortorano (2012)[33]	Serious	Moderate	Low	No information	Low	Low	Low	Serious
Ylipalosaari (2012)[34]	Moderate	Moderate	Low	No information	Low	Low	Low	Moderate
Pasero (2011)[35]	Low	Low	Low	No information	Low	Low	Low	Moderate
Han (2010)[36]	Low	Serious	No information	No information	Low	Low	Low	Serious
Pratikaki (2011)[37]	Moderate	Low	Low	No information	Low	Low	Low	Moderate
Playford (2009)[38]	No information	Low	No information	No information	Low	Low	Low	No information

Continued

Table 4 Continued

First 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
Holley (2009)[39]	Low	Serious	Low	No information	Low	Low	Low	Serious
Choi (2009)[40]	Low	Serious	Low	No information	Low	Low	Low	Serious
Yap (2009)[50]	No information	Moderate	Low	No information	Low	Low	Low	Moderate
Chow (2008)*	Low	Low	Low	No information	Low	Low	Low	Moderate
Chow (2008)* [41]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Bougnoux (2008)[42]	No information	Low	Low	No information	Low	Low	Low	Moderate
Girão (2008)[43]	No information	Serious	Low	No information	Low	Low	Low	Moderate
Dimopoulos (2008)[44]	Low	Low	Low	No information	Low	Low	Low	Moderate
Dimopoulos (2007)[45]	Serious	Low	Low	No information	Low	Low	Low	Serious
Jordà-Marcos (2007)[62]	Low	Moderate	Low	No information	Low	Low	Low	Moderate
Piazza (2003)[63]	Serious	Low	Moderate	No information	Moderate	Low	Low	Serious
Michalopoulos (2003)[46]	Low	Low	No information	No information	Low	Low	Low	Moderate

*Adapted from Chow *et al*.[70 71]
ROBINS-I, Risk of Bias In Non-randomized Studies of Interventions.

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 candidaemia varied from approximately 17 days in Asia to 19 days in Europe and 46 days in South America. Most of the patients with IC had received broad-spectrum antibiotics (89%), and the mean duration of antibiotic therapy prior to candidaemia 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 longer for patients with *C. albicans* compared with 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 candidaemia. Five studies compared patients with infection of *C. albicans* versus those infected with another *Candida* strain, and only one study compared ICU-acquired candidaemia versus non-ICU acquired candidaemia.[34] Eight studies were performed in Chinese hospitals (table 1). Two studies evaluated patients with *C. albicans* versus non-*C. albicans* infection. One study compared patients with CRCBSI versus non-CRCBSI, and another study compared patients with a fluconazole-resistant versus fluconazole-sensitive infection.

Fewer than half of the studies (n=18) were conducted in general or multidisciplinary ICUs, with the rest in SICUs, in the cardiosurgical/cardiothoracic ICUs[46] or in MICUs.[36] This suggests that IC is a common problem in critically ill patients regardless of 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 nine studies, the median length of ICU stay was ≤10 days prior to onset of IC, and the overall mortality in ICU patients with candidaemia in these studies ranged from 10.6% to 65.8%. In studies with a median length 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 candidaemia 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 colonisation of *Candida* species, which requires a period of 7–10 days 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 candidaemia at 8 days after ICU admission, the endogenous colonisation 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 candidaemia at 12–13 days after ICU admission, the endogenous colonisation of *Candida* species might have occurred 3–5 days after ICU admission.

One main risk factor for candidaemia was systemic antibiotic use.[16] In a previous study of paediatric ICUs, it was reported that treatment with vancomycin or antianaerobic antibiotics for >3 days was independently associated with the development of candidaemia,[2] but only in an unadjusted analysis.[16] A study in Hong Kong found that candidaemia 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 candidaemia in China and India,[65 66] so it is reasonable to suspect a link between overuse of broad-spectrum antibiotics and early-onset of candidaemia after ICU admission. Regardless of geographical differences, most patients with IC received broad-spectrum antibiotic treatment prior to candidaemia 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 candidaemia onset after ICU admission could not be assessed. Further explanations on the longer duration of ICU admission prior to candidaemia onset in South America than in Asia/Europe/USA/Australia also could not be determined in this systematic review.

The 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 candidaemia 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* were similar, the susceptibilities of these strains to antifungal agents were different.[21 68 69]

This systematic review had several limitations. Because this systematic review lacks a prespecified protocol and preliminary registration, biased post-hoc decisions in the reviewing process may occur. In addition, a number of trials reported outcomes using median (range) and/or median (IQR), and in order to combine these results the sample mean and SD for those trials were estimated using a method proposed by Wan *et al*,[24] based on 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. The 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 candidaemia (online supplementary table S2).

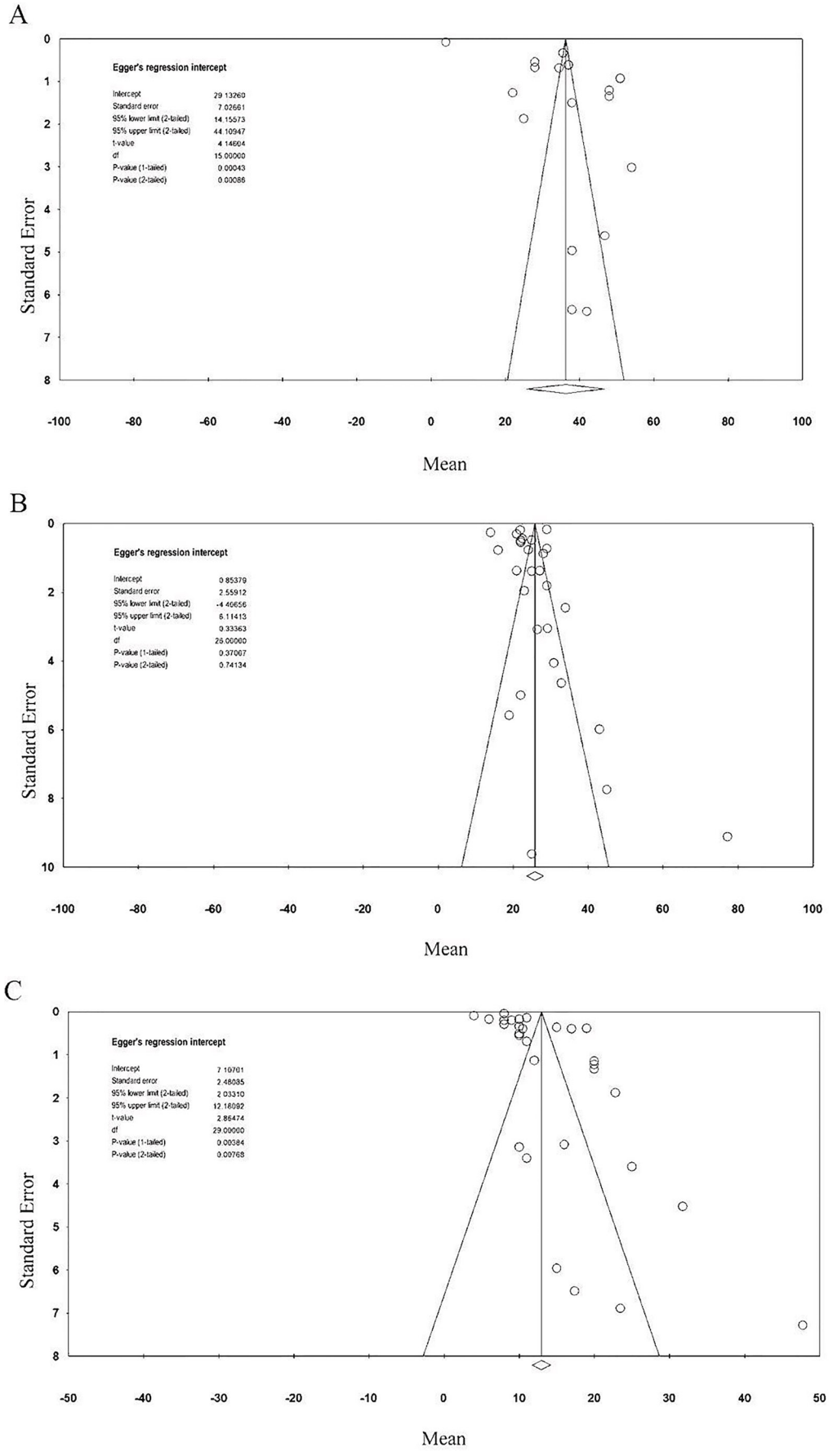

Figure 3 Funnel plot for (A) length of hospital stay, (B) ICU length of stay and (C) duration of ICU admission prior to candidaemia onset. ICU, intensive care unit.

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

This meta-analysis finds that patients who had longer length of ICU stay were more likely to develop candidaemia. 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 conserve valuable medical resources and ultimately save more lives.

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