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Diagnostic accuracy of *Candida albicans* germ tube antibody for invasive candidiasis: systematic review and meta-analysis

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ABSTRACT

Background: Candida albicans germ tube antibody (CAGTA) may be helpful as a marker for the diagnosis of invasive candidiasis (IC). However, the performance has been variable. We conducted a meta-analysis to assess the diagnostic accuracy of this assay for diagnosing IC.
Method: We searched MEDLINE, EMBASE, Cochrane Collaboration databases, reference lists of retrieved studies, and review articles. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and a summary receiver-operating characteristic curve of CAGTA for diagnosing IC were pooled using meta-analysis.
Results: A total of 976 patients (262 with proven or probable IC), included in 7 studies, were analyzed. The pooled sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios and area under the curve were 66% (95% confidence interval [95% CI], 59% to 73%), 76% (95% CI, 58% to 88%), 2.8 (95% CI, 1.5 to 5.8), 0.44 (95% CI, 0.34 to 0.57), 6 (95% CI, 3 to 5), and 0.68 (95% CI, 0.64 to 0.72), respectively. Heterogeneity of specificity was significant.
Conclusion: The diagnostic accuracy of the CAGTA assay is moderate for IC. Since the CAGTA assay is not absolutely sensitive and specific for IC, the CAGTA results should be interpreted in parallel with other biomarkers and clinical findings.

1. Introduction

Invasive candidiasis (IC) is an important infectious complication in immunocompromised patients and is associated with severe morbidity and high mortality(Andes et al., 2012; Peman and Zaragoza, 2012; Torres-Rodriguez et al., 1997). IC comprises 3 disease entities: 1) candidemia in the absence of deep-seated candidiasis; 2) candidemia associated with deep-seated candidiasis; and 3) deep-seated candidiasis in the absence of candidemia (Clancy and Nguyen, 2013). However, the insensitivity of microbiologic cultures, the gold standard diagnostic, usually results in delayed diagnosis and definitive treatment which increase the mortality and medical costs (Kullberg and Arendrup, 2015; Pappas et al., 2018). Therefore, how to improve the speed and accuracy of clinic diagnosis for IC is an important issue that must be resolved.

Several nonculture diagnostics, such as *Candida albicans* germ tube antibody (CAGTA), 1,3-β-D-glucan, polymerase chain reaction, and the T2Candida panel, are now available for use as adjuncts to cultures, but there is widespread uncertainty about their utility in clinical practice (Clancy and Nguyen, 2018a; Cortes et al., 2011). Different studies have assessed the clinical value of CAGTA assays; Vircell Kit (Grenada) and VirClia IgG Monotest (Spain) are the routine detection way with widespread use in many European centers (Clancy and Nguyen, 2018b; Peman et al., 2011). Data are less extensive for CAGTA, which detects responses against a hyphal protein (Hwp1) expressed during candidal tissue invasion and biofilm formation (Martinez-Jimenez et al., 2014; Zaragoza et al., 2009a).

The sensitivity and specificity of CAGTA for IC have ranged from 42% to 96% and 54% to 100%, respectively, in different reports (Fortun et al., 2014; Leon et al., 2016; Martinez-Jimenez et al., 2015; Parra-Sanchez et al., 2017). The objective of this paper is to conduct a meta-analysis to evaluate its overall accuracy.

2. Materials and method

2.1. Study selection

Two investigators (T.W. and W.S.Z.) searched the MEDLINE, EMBASE, and Cochrane Collaboration databases for pertinent articles published in English on human subjects up to March 2018. The search terms included "invasive candidiasis," "candidiasis," "IC," and "*Candida albicans* germ tube antibody" or "CAGTA." We screened the reference

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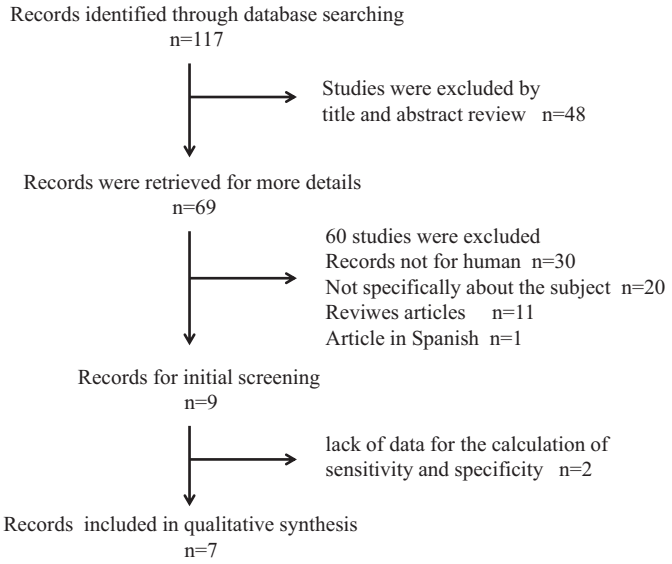

Fig. 1. Flowchart demonstrating the algorithm for identifying suitable papers for inclusion.

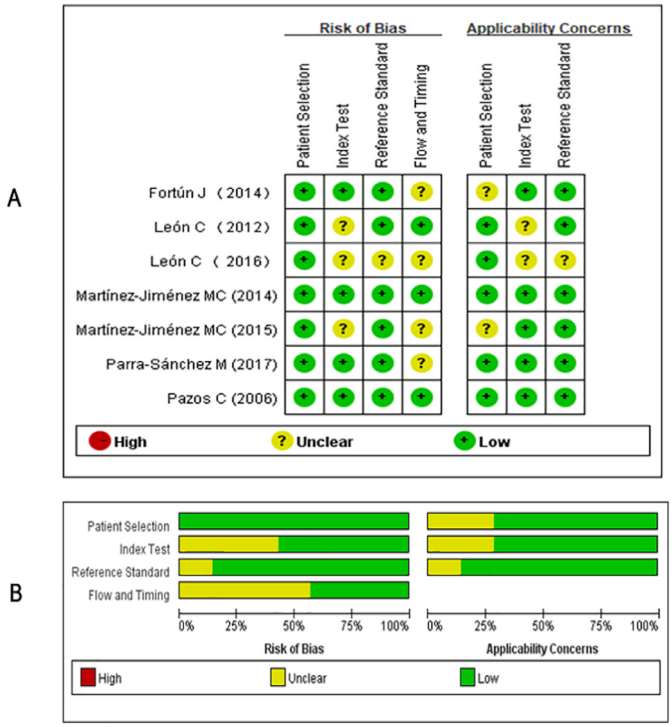

Fig. 2. The results of quality assessment of the included studies. A, Modified QUADAS-2 items used in the study to assess the quality of the eligible studies. B, Results of applicability concerns using the Modified QUADAS-2 showing the proportion of studies with low, high, or unclear risk of bias.

lists of included studies and related publications. Conference abstracts and letters to journal editors were excluded because of the limited data presented in them.

The reference standard was based on established criteria for the definition of IC in neutropenic patients, the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria, and definitions used in recent clinical trials for nonneutropenic patients (Avni et al., 2011). IC or proven *Candida* infection was defined as a) primary candidemia (C) (presence of *Candida* spp. in 1 or more blood cultures taken from peripheral veins) and b) intra-abdominal candidiasis (IAC) on the basis of macroscopic findings and direct examination or positive culture for *Candida* spp. and c) positivities of 2 biomarkers in a single sample or positivities of any biomarker in 2 consecutive samples (the BDG, CAGTA, mannan-Ag, and mannan-Ab). The following articles were excluded from the review: animal or in vitro studies, articles in languages other than English, and case reports and studies that included less than 10 patients (including cases and

Table 1
Characteristics of 7 reports included in the meta-analysis.

First author, year of population, type of study	Patients	Diagnostic criteria for *Candida* infection	Assay method	Cutoff value	No. of patients and no. of sample	No. of control patients and no. of sample	Type of control group
Parra-Sanchez et al., 2017, prospective, cohort and observational study	Adult non-neutropenic critically ill patients in medical–surgical ICU	Culture from a sterile site	Invasive candidiasis CAGTA IFA IgG Vircell SL, Granada, Spain	≥1/160	179, 361	10, 10	Healthy subjects
Leon et al., 2016, prospective, cohort and observational study	Non-neutropenic patients with SAC on ICU admission	2 Biomarkers in a single sample or positivities of any biomarker in 2 consecutive samples	Vircell kit assay, Granada, Spain	≥1/160	233, 860	None	-
Martinez-Jimenez et al., 2015, retrospective trial	Adult patients with candidemia and patients with bacteremia	Candidemia	Vircell Microbiologist S.L., Granada, Spain	≥1/80	31, 31	50, 50	patients with bacteremia
Fortun et al., 2014, prospective study	ICU patients with clinically suspected IC and no prior antifungal treatment	Culture from a sterile site		≥1/160	71, 71	40, 40	ICU patients with suspected IC in whom IC was discarded and 40 healthy individuals
Martinez-Jimenez et al., 2014, retrospective STUDY	ICU patients	Candidemia	Vircell Microbiologist S.L., Granada, Spain	≥1/160	50, 50	50, 50	Healthy individuals
Leon et al., 2012, prospective, cohort, observational, and multicenter study	Non-neutropenic patients, with SAC on ICU admission	*Candida* growth in the culture medium		≥1/160	176, 176	None	-
Pazos et al., 2006, prospective study	Neutropenic adult patients	Blood culture	*Candida* IFA IgG, Laboratorios Vircell S.A., Spain	≥1/160	154, 154	None	-

controls). When the same sample group of people was analyzed in several publications, the results were accounted for only once. All of the related articles were scrutinized to judge the eligibility of studies by 2 reviewers (T.W. and W.S.Z.). A third investigator (Y. W) made the final decision on the disagreements and examined whether any additional studies have been neglected.

2.2. Data extraction

From each included study, we extracted data regarding the following aspects: first author, year of publication, type of study, cutoff value, characteristics of the patients, diagnostic criteria for IC infection, assay method, no. of patients and no. of samples, no. of control patients and samples, and type of control group. The patient data were extracted in regard to the number of true- and false-positive results as well as true- and false-negative results acquired with the CAGTA assay. When such data were not provided definitely, we used the specific mathematical formulas to calculate them from the related data on sensitivity, specificity, and positive and negative predictive value or contacted the authors directly. We assessed the methodological quality using the quality assessment for studies of diagnostic accuracy (QUADAS-2) tool (Reitsma et al., 2012).

The QUADAS-2 form is composed of 4 domains: 1) patient selection, 2) index test, 3) reference standard, and 4) flow and timing. We supplied an additional domain to evaluate the comparator test, with the same items used for the index test. For each domain, the risk of bias and concerns about applicability (the latter not applying to the flow and timing domains) were analyzed and rated as low risk, high risk, and unclear risk. Low risk of bias means plausible bias unlikely to seriously alter the results; unclear risk of bias means plausible bias that raises some doubt about the results; high risk of bias means means plausible bias that seriously weakens confidence in the results. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity.

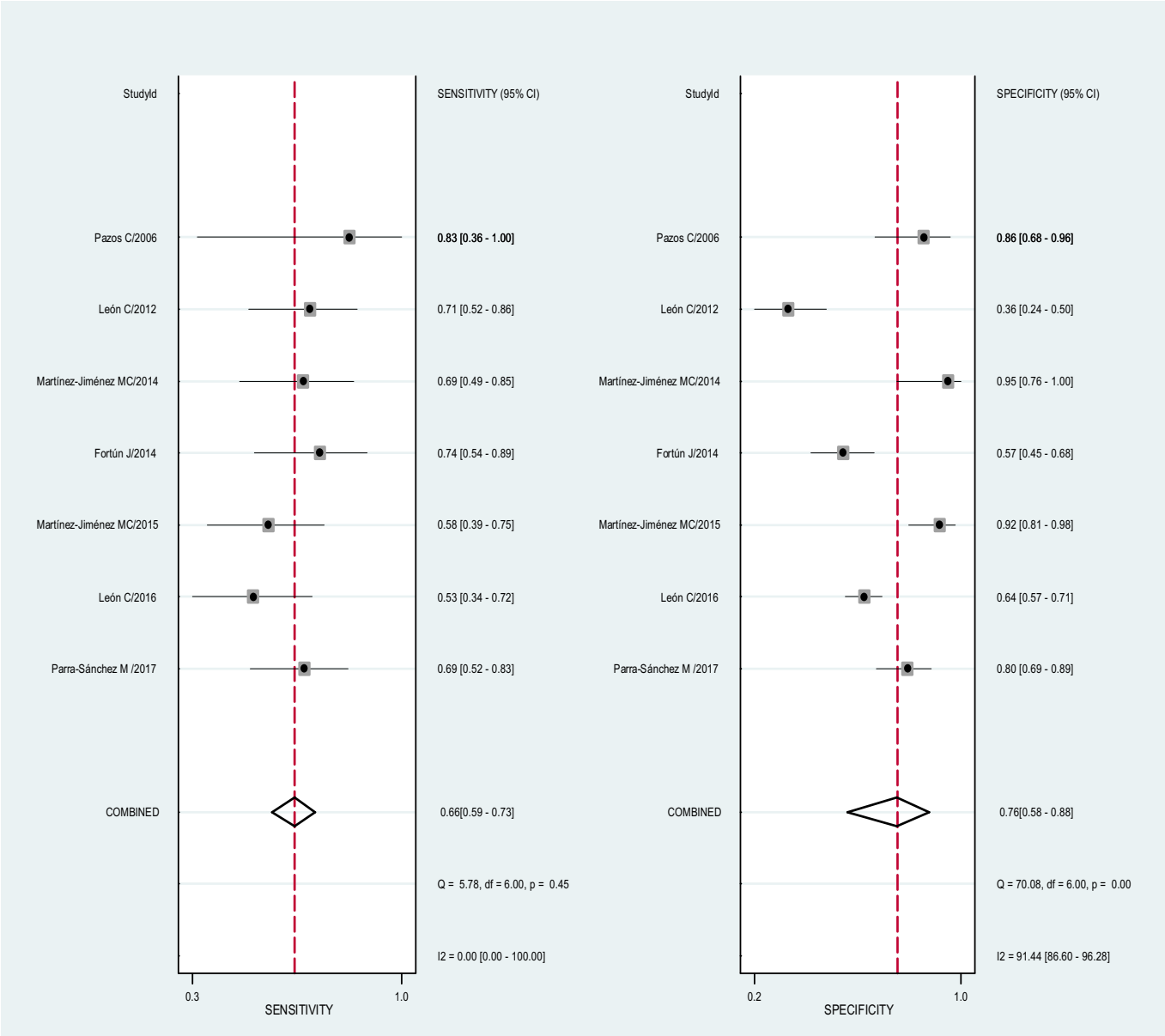

Fig. 3. Forest plot of the pooled sensitivity and specificity of CAGTA for the diagnosis of IC.

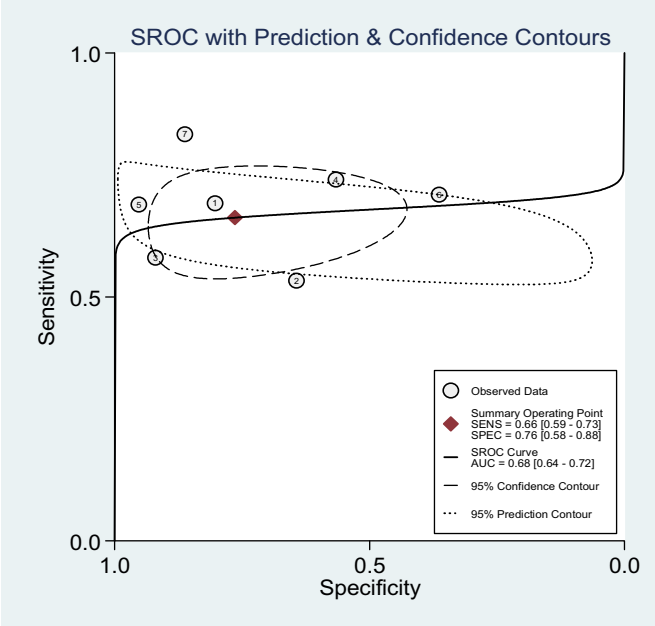

Fig. 4. SROC plots.

2.3. Data analysis

We used standard methods recommended for meta-analyses of diagnostic test evaluations (Deville et al., 2002). Analyses were performed using RevMan5 software (the Cochrane Information Management System), STATA version 12.0 (STATA Corporation, College Station, TX). All statistical tests were 2-sided, and statistical significance was defined as a *P* value of less than 0.05.

The analysis was based on a summary receiver operating characteristic (SROC) curve (Moses et al., 1993). The following measures of test accuracy were computed for each study: sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR). Sensitivity and specificity for the single test threshold identified for each study were used to plot an SROC curve (Reitsma et al., 2005). Random-effects model was used to calculate the average sensitivity, specificity, and the other measures across studies.

The term heterogeneity when used in relation to meta-analyses refers to the degree of variability in results across studies. We used the χ^2 and Fisher exact tests to detect statistically significant heterogeneity. We analyzed the effects of variable covariates on DOR (i.e., different reference standard (culture vs nonculture), intensive care unit (ICU) patients (only vs mixed/other), data collection (prospective vs retrospective), and cutoff value (1/160 vs 1/80)). We also searched for the presence of a threshold effect, a source of heterogeneity unique to diagnostic meta-analysis. We assessed the potential publication bias by using the funnel plots of Deeks et al. (2005).

3. Results

3.1. Eligible studies characteristics and quality assessment

As shown in Fig. 1, we identified 117 possible relevant articles from 3 different databases (the EMBASE, MEDLINE databases, and Cochrane Collaboration databases). Nine full-length articles were selected for details analysis on the basis of titles or abstracts. Two studies were excluded because they did not allow the calculation of sensitivity or specificity or underestimate rate (Zaragoza et al., 2009a, 2009b). We eventually pooled 7 eligible studies.

Table 1 describes the characteristics of included studies. Of the 7 included studies, 2 were retrospective studies (Martinez-Jimenez et al., 2014, 2015), and 5 were prospective studies (Fortun et al., 2014; Leon et al., 2012, 2016; Parra-Sanchez et al., 2017; Pazos et al., 2006). On the whole, 976 patients were enrolled with a mean of 139 patients per study. Data for evaluating the accuracy of CAGTA for the diagnosis of IC were extracted from these studies. The small number of IC cases in different studies and the variation due to chance mainly led to the wider range of sensitivity. The sensitivity in different studies ranged from 0.53 to 0.95, whereas the specificity ranged from 0.57 to 0.92. Diagnostic criteria for *Candida* infection were positive of *Candida* culture in 6 studies and positivities of 2 biomarkers in a single sample or positivities of any biomarker in 2 consecutive samples in only 1 study(Leon et al., 2016). The study population in the 4 papers was ICU patients (Fortun et al., 2014; Leon et al., 2016; Martinez-Jimenez et al., 2014; Parra-Sanchez et al., 2017). The populations in the other 3 studies were adult patients with candidemia or bacteremia, adult patients with candidemia, and adult patients with hematological cancer (Leon et al., 2012; Martinez-Jimenez et al., 2015; Pazos et al., 2006). Three studies were done in the adult non-neutropenic population (Leon et al., 2012, 2016; Parra-Sanchez et al., 2017); the remaining 4 articles did not mention whether the non-neutropenic population was included or not. Two studies were done in patients with severe abdominal conditions (SAC) on ICU admission (Leon et al., 2012, 2016). In 6 studies, the cutoff value was 1/160. In only 1 study, the cutoff value was 1/80 (Martinez-Jimenez et al., 2015).

QUADAS-2 was used to assess the quality of the selected studies. Fig. 2 shows the results of quality assessment of the included studies. In Fig. 2A, all of the studies, except 1 (Martinez-Jimenez et al., 2014), prospectively enrolled the study cohort with definite inclusion and exclusion criteria. In these studies, the patient selection domain was labeled low. The reference standard domain of all studies was labeled low except 1 (Deeks et al., 2005). Blood culture is considered as the gold standard for the diagnosis of *Candida* in 6 of the studies. With 1 exception, the diagnostic criteria for IC are 2 biomarkers in a single sample or positivities of any biomarker in 2 consecutive samples (Leon et al., 2016). The flow and timing domain in 4 studies was labeled unclear because of the unclear description. Most of the domains for applicability

Table 2
Summary of subgroup analysis of the included studies by different study characteristics.

Parameter	Category	No. of studies	Summary sensitivity (95% CI)	*P*	Summary specificity (95% CI)	*P*	χ^2 (*P*)
Design	Prospective	5	0.68 (0.60–0.76)	0.35	0.66 (0.51–0.80)	0.00	0.05
	Retrospective	2	0.63 (0.51–0.76)		0.94 (0.86–1.00)		
Criterion	Culture	6	0.69 (0.61–0.76)	0.64	0.78 (0.63–0.94)	0.45	0.18
	Nonculture	1	0.53 (0.34–0.72)		0.64 (0.18–1.00)		
Cutoff	1/160	6	0.68 (0.61–0.75)	0.95	0.72 (0.56–0.87)	0.17	0.26
	1/80	1	0.58 (0.41–0.75)		0.93 (0.79–1.00)		
ICU	Yes	4	0.67 (0.58–0.75)	0.18	0.63 (0.45–0.81)	0.01	0.19
	No	3	0.66 (0.55–0.77)		0.87 (0.77–0.98)		

concerns were labeled low because they matched the review question well (Fig. 2. B).

3.2. Sensitivity, specificity, PLR, NLR, DOR, and SROC curve

As shown in the forest plots (Fig. 3), the pooled sensitivity was 0.66 (95% CI, 0.59–0.73), whereas the pooled specificity was 0.76 (95% CI, 0.58–0.88). The PLR and NLR with associated 95% CI were 2.8 (1.5–5.3) and 0.44 (0.34–0.57), respectively. The diagnostic OR was 6 (95% CI, 3–5). I^2 values of specificity were larger than 25%, indicating significant heterogeneity for this index. As shown in Fig. 4, the area under the curve (AUC) was 0.68 (95% CI, 0.64–0.72), recognizing that different thresholds may have been used.

3.3. Heterogeneity assessment and meta-regression analysis

Because the heterogeneity of specificity in the pooled analysis was highly significant ($P = 0.00$), we evaluated the existence of the threshold effect. The P value for the Spearman correlation coefficient (between the logit of sensitivity and logit of specificity) was 0.03, which showed that there was threshold effect that existed in this meta-analysis. The meta-regression analysis showed that the study design (prospective vs. retrospective) ($P = 0.00$) and the population (ICU vs. not ICU) ($P = 0.01$) were the most important source of heterogeneity (Table 2).

3.4. Subgroup analysis

The results of the subgroup analysis are shown in Table 2 and Fig. 5. The subgroup with prospective study had a lower pooled specificity (0.66, 95% CI: 0.51–0.80) than the subgroup with retrospective study (0.94, 95% CI: 0.86–1.00) ($P = 0.00$). No statistically significant differences were found between the pooled sensitivities of the prospective studies with retrospective studies(Martinez-Jimenez et al., 2014, 2015).

The sensitivity of ICU patients was 0.67, which was similar to the other patients ($P = 0.18$). But the specificity of ICU patients was lower, almost with significant difference ($P = 0.04$). The other subgroups (cutoff: 1/160 or 1/80; reference: culture or nonculture) did not show significantly different sensitivities or specificities.

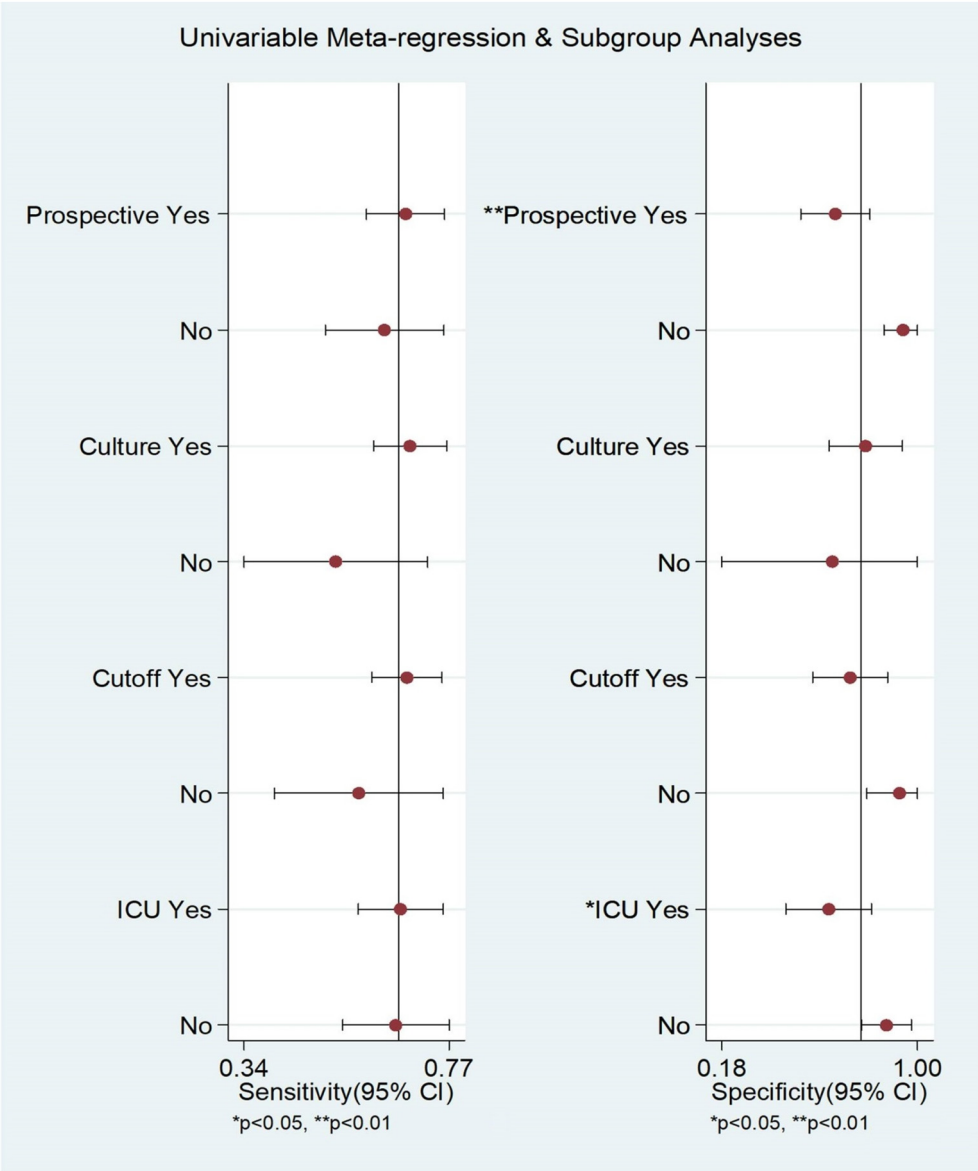

Fig. 5. Forest plots of subgroup analyses for sensitivity and specificity.

3.5. Publication bias

According to the Deeks' funnel plot asymmetry test, the statistically nonsignificant value ($P = 0.20$) for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias (Fig. 6).

4. Discussion

The main finding of our meta-analysis is that CAGTA measurement seems not to be a good diagnostic assay for IC. In our meta-analysis, when comparing patients who had proven or probable IC with patients without IC diagnosed in accordance with the EORTC/MSG or similar criteria, the AUC was 0.68, while a value between 0.80 and 0.90 has been regarded as a good diagnostic test index traditionally. Our results indicated that CAGTA detection has high specificity (0.76) and relatively moderate sensitivity (0.66). Nevertheless, the above findings should be interpreted in light of the high statistical heterogeneity.

In the present study, CAGTA shows low sensitivity and specificity with 0.66 and 0.76, respectively. There are several possible reasons related to the low accuracy of CAGTA in the diagnosis of IC. CAGTA detects antimycelium antibodies against the hpw1 antigen, which is only expressed during the invasive phase of *Candida* infection (Mayer et al., 2013; Saville et al., 2003). CAGTA could be used to determine whether candidemia originated in the catheter or in deep organs. So CAGTA can be used to identify previously exposed or high-risk patients. However, the disadvantage is that it cannot distinguish between previous infection and active infection. In patients with IC (candidemia and IAC), 2 studies (Leon et al., 2016; Parra-Sanchez et al., 2017) showed a higher sensitivity for candidemia than for IAC but similar results for specificity and predictive values. However, the number of patients was not sufficient for a reliable analysis of the differences in biomarkers accuracy between IAC and candidemia. Moreover, the raw data for source of infection are insufficient; only 3 studies were done in patients with SAC on ICU admission (Leon et al., 2012, 2016; Parra-Sanchez et al., 2017). We cannot make any conclusion based on real data. For the immunocompromised patients, the sensitivity of antibody testing is limited because the patient cannot produce antibodies against *Candida* (Mayer et al., 2013; Saville et al., 2003).

As for meta-analysis, it is an important goal to explore the causes of heterogeneity rather than the calculation of summary measures. The meta-regression in our study did not indicate any to zero. Firstly, the diagnostic criteria for invasive candidiasis in the 7 studies were different. Leon et al. (2016) reported a higher sensitivity and lower specificity compared with those in other studies. In the report, IC diagnosis required positivities of 2 biomarkers in a single sample or positivities of any biomarker in 2 consecutive samples. Secondly, the lower specificity in this study may be explained by the different study population included in this meta-analysis. Three studies were described in detail as non-neutropenic patients and 1 as neutropenic patients. The immune status of the patients was not mentioned in the 3 literatures (Fortun et al., 2014; Martinez-Jimenez et al., 2014, 2015). Thirdly, some were retrospective studies performed in a single center on heterogeneous populations and the number of candidemias analyzed was low. Finally, this meta-analysis did not show the diagnostic accuracy of CAGTA in different *Candida* species. The original data about the diagnostic value of CAGTA in different candida species mentioned in the included study are too little to be statistically analyzed. Three studies contained information for *Candida* species identification from microbial culture and analyzed the detection efficiency of CAGTA in different strains (Martinez-Jimenez et al., 2014, 2015; Parra-Sanchez et al., 2017). However, the *Candida* species identification contained in each study is not uniformly the same. Therefore, we cannot get the combined data for statistics and in-depth analysis. Moreover, in another study, the multiplex quantitative real-time PCR assay was performed to detect the 6 most frequent species of the genus *Candida* in IC, but it did not report the relation between the detection efficiency of CAGTA and *Candida* species (Fortun et al., 2014).

Clearly, positive CAGTA test cannot indicate a certain *Candida* pathogen, which placed doctors in a dilemma to make decisions. Another

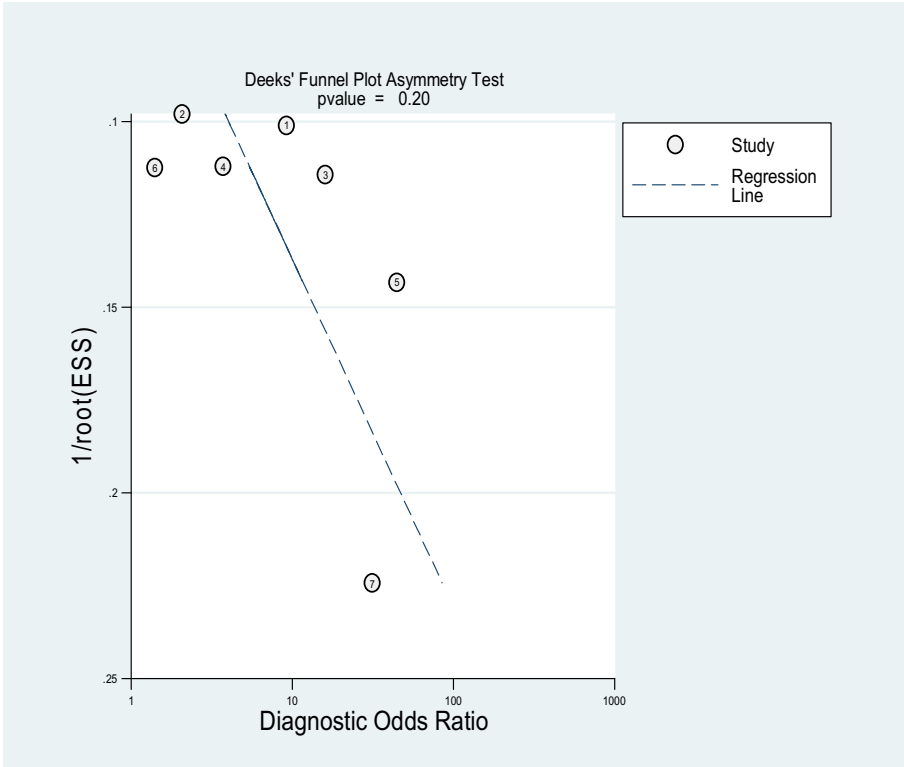

Fig. 6. Linear regression test of funnel plot asymmetry. The statistically nonsignificant value ($P = 0.20$) for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias.

much more important concern is that many patients might be missed or misdiagnosed for IC if we interpreted the result only with lower sensitivity, leading to delayed treatment, with poor specificity causing unnecessary antifungal therapy. In clinical practice, physicians tend to initiate antifungal treatment early for a positive test result that may suggest invasive disease because of the high morbidity and mortality associated with IC. As a consequence, distraction from identifying the actual cause of a patient's disease and rampant use of antifungal agents would exist.

To our knowledge, this paper is the first meta-analysis that summarizes the diagnostic value of CAGTA for the diagnosis of IC. There are still some limitations in our study. First, we acknowledged that this meta-analysis included relatively fewer eligible studies. Even though we tried our best to retrieve any related studies and obtain additional data from investigators, it seems inevitable that some missing and unpublished data may still exist. Furthermore, the exclusion of studies with fewer than 10 patients may have led to a biased result. Additionally, the eligible studies adopt different diagnostic criteria regarding accuracy of diagnosis, which can cause misclassification bias and lead to biased results. Lastly, the meta regression results showed no relationship between the characteristics and the pooled results. Further studies focused on this issue are needed.

5. Conclusion

In conclusion, the current meta-analysis suggests that the accuracy of CAGTA is marginal. Since the CAGTA assay is not absolutely specific for IC, the results of that should not be interpreted alone but could be used as a part of full assessment with clinical features, image findings, and other laboratory results for the diagnosis of IC. Furthermore, CAGTA detection does not indicate certain fungal genus, leading to limited use of targeted treatment in practice. This finding, together with the low sensitivity, makes it difficult to apply CAGTA as a diagnostic tool for early detection of IC. The combination of these biomarkers (the BDG, CAGTA, mannan-Ag, and mannan-Ab) (Bassetti et al., 2017; Leon et al., 2016) for the diagnosis of IC could be used as a complementary decision-support tool in antifungal stewardship programs.

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