Diagnostic accuracy of serum 1,3-β-D-glucan for pneumocystis jiroveci pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis

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Diagnostic accuracy of serum 1,3-β-D-glucan for pneumocystis jiroveci pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis.

ニューモシスチスイロヴェチ肺炎、深在性カンジダ症、侵襲性アスペルギルス症における血清 1,3-β-D グルカンの診断真度:
システマティックレビューとメタアナリシス

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Diagnostic Accuracy of Serum 1,3-β-D-Glucan for *Pneumocystis jiroveci* Pneumonia, Invasive Candidiasis, and Invasive Aspergillosis: Systematic Review and Meta-Analysis

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Serum 1,3-β-D-glucan (BG) assay may be helpful as a marker for the diagnosis of *Pneumocystis jiroveci* pneumonia (PJP) and invasive fungal infection (IFI). We conducted a systematic review to assess the diagnostic accuracy of this assay. We searched MEDLINE, Web of Science, Cochrane Collaboration databases, Ichushi-Web, reference lists of retrieved studies, and review articles. Our search included studies of serum BG assay that used (i) positive cytological or direct microscopic examination of sputum or bronchoalveolar lavage fluid for PJP and (ii) European Organization for Research and Treatment of Cancer or similar criteria for IFI as a reference standard and provided data to calculate sensitivity and specificity. Only major fungal infections such as invasive candidiasis and invasive aspergillosis were included in the IFI group. Twelve studies for PJP and 31 studies for IFI were included from January 1966 to November 2010. The pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curve (AUC-SROC) for PJP were 96% (95% confidence interval [95% CI], 92% to 98%), 84% (95% CI, 83% to 86%), 102.3 (95% CI, 59.2 to 176.6) and 0.96 (95% CI, 0.94 to 0.99), respectively. No heterogeneity was found. For IFI, the values were 80% (95% CI, 77% to 82%), 82% (95% CI, 81% to 83%), 25.7 (95% CI, 15.0 to 44.1), and 0.88 (95% CI, 0.82 to 0.93). Heterogeneity was significant. The diagnostic accuracy of the BG assay is high for PJP and moderate for IFI. Because the sensitivity for PJP is particularly high, the BG assay can be used as a screening tool for PJP.

Pneumocystis jiroveci pneumonia (PJP) continues to be a serious problem among immunocompromised patients despite the decreased number of cases among human immunodeficiency virus (HIV)-infected patients over the past decade with the widespread use of prophylaxis. The high mortality of patients requiring mechanical ventilation has remained unchanged, ranging from 50 to 60% (35). Although the gold standard for diagnosis is microscopic visualization of the organism, the methods are not sensitive, particularly in HIV-negative patients (31).

The incidence of invasive fungal infection (IFI) has been increasing, especially among immunocompromised patients undergoing aggressive chemotherapy for cancer, bone marrow and organ transplantation, and advanced critical care. Despite advances in therapy, IFI is associated with considerable morbidity and a mortality rate of 30 to 70% for aspergillosis and 40 to 50% for candidiasis (15). Diagnosis of IFI is challenging because clinical and radiological signs and conventional microbiological and histological techniques are not sensitive enough (25). For these reasons, intensive research currently aims at the development of new diagnostic methods for PJP and IFI.

One of these new diagnostic techniques is the assay for the serum 1,3-β-D-glucan (BG) derived from major cell wall components of various medically important fungi. The Fungitell test (Associates of Cape Cod, Inc., East Falmouth, MA) is a chromogenic kinetic test that was approved in 2003 by the U.S. Food and Drug Administration for the presumptive diagnosis of IFI. The BG assay has been used frequently, and the results are included in the revised IFI diagnosis criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria (11). However, the results of test performances have varied, as Nakamura and colleagues (42) suggested that the detection rate of BG in HIV-negative patients was lower than that in HIV patients.

One systematic review (23) on the accuracy of BG assay only for diagnosing IFI has recently been published. The review did not assess the diagnostic accuracy for PJP. The article included 2 of 16 evaluated studies using inappropriate reference standards; such inappropriate reference standards, according to the EORTC/MSG, consisted of only mycological criteria (22, 39). The review also used language restrictions and did not investigate possible explanations for the observed heterogeneity. We report a new systematic review of the accuracy of the BG assay for diagnosing PJP and IFI. We also focus on study design, reference standard, and assay as explanations for between-study variability in diagnostic accuracy.

MATERIALS AND METHODS

Data sources and searches. We developed a protocol for the review by following standard reporting guidelines (7, 21). The search was carried out using four different databases (MEDLINE, Web of Science, Cochrane Collaboration databases, and Ichushi-Web) from January 1966 until No-

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vember 2010. Ichushi-Web, which is a major Japanese database, was included because the BG assay was first developed in Japan. The term "diagnosis" and the medical subject heading terms "fungi," "mycoses," and "beta-glucans" were used for searching MEDLINE, the terms "glucan" and "diagnosis" for searching the Web of Science and Cochrane Collaboration databases, and the terms "fungi," "mycoses," "*Pneumocystis*," "*carinii*," "*jiroveci*," "aspergillosis," "*Aspergillus*," "*Candida*," "candidiasis," "glucan," and "diagnosis" for searching Ichushi-Web. Reference lists of retrieved studies and review articles were also reviewed. Only papers published in full text were selected, while no language restrictions were applied to the search.

Study selection. Studies relevant for determining the diagnostic validity of serum BG assay for PJP and IFI in humans were included if two sets of criteria were met. First, positive findings for cytological or direct microscopic examination of sputum or bronchoalveolar lavage fluid for PJP and the proven or probable presence of IFI according to the EORTC/MSG criteria (5) or similar criteria for IFI as a reference standard. If a study used both positive findings for cytological or microscopic examination and positive PCR as a reference standard for PJP, we excluded participants who had been diagnosed with positive PCR. Second, absolute numbers of true-positive, false-negative, true-negative, and false-positive observations were available or could be derived from the reported data. Only major fungi such as invasive candidiasis and invasive aspergillosis were included in the IFI group because the number of the other fungi was small in included studies and certain zygomycetes (*Mucor* and *Rhizopus* species) and because *Cryptococcus* species had no BG cell wall. Case reports and review articles were excluded. If a study appeared to meet selection criteria but had a patient population that appeared to be the same as or to overlap with the patient population of a similar study, we included the larger of the studies.

Data extraction and study quality assessment. We wanted to extract the following variables: publication year; name(s) and institution(s) of the author(s); information on the original sample source; study design; patient demographics and comorbidities; type of invasive fungal infection; characteristics of control subjects; numbers of true-positive, false-negative, true-negative, and false-positive observations; type and manufacturer of the BG assay; reference standard; cutoff values for definition of a positive BG test result; and blinding of investigators to results.

Two investigators independently rated the quality of the findings by using a modified version of the Quality Assessment for Diagnostic Accuracy Studies (QUADAS) tool (58), which contains 11 items specifically developed to assess the quality of systematic reviews of primary studies of diagnostic tests, and is recommended by the *Cochrane Diagnostic Reviewers' Handbook* (52). As recommended by the designers of the QUADAS tool, we did not apply weights to the QUADAS item or use a summary score in the analysis. Instead, we used subgroup analyses to explore whether scores on the following quality items explained variation in diagnostic performance: representative spectrum, acceptable reference standard, differential verification avoided, and index test results blinded. These items have been shown to result in biased estimates of the diagnostic performance (30, 53). We resolved discrepancies about any item through discussion.

Data synthesis and analysis. For main outcomes, we evaluated the diagnostic accuracy of the serum BG assay for PJP and for IFI. Subgroup analyses were performed only when each subgroup included data of at least three diagnostic studies. If several cutoffs were reported in one study, we used the cutoff that offered the best test performance. A random-effects model was used to combine estimates of sensitivity, specificity, diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curve (AUC-SROC) with 95% confidence interval (95% CI) (10, 37). We also assessed heterogeneity by means of the Cochran *Q* method and the test of inconsistency (I^2)(9, 18). Sensitivity analysis was based on control participants, exclusion of possible IFI in control patients, language, and prophylactic antifungal therapy. We conducted a stratified analysis for study design, the brand-name assay, the reference standard, the kind of mycosis, and the QUADAS item and used metaregression to identify the possible sources of heterogeneity among studies (41). We explored the possibility of publication bias by means of funnel plots and the Egger test for diagnostic odds ratios (13, 55). For all analyses, we used MetaDiSc, version 1.4 (Hospital Universitario Ramón y Cajal, Madrid, Spain) and Comprehensive Meta Analysis version 2 (Biostat Inc., Englewood, CA).

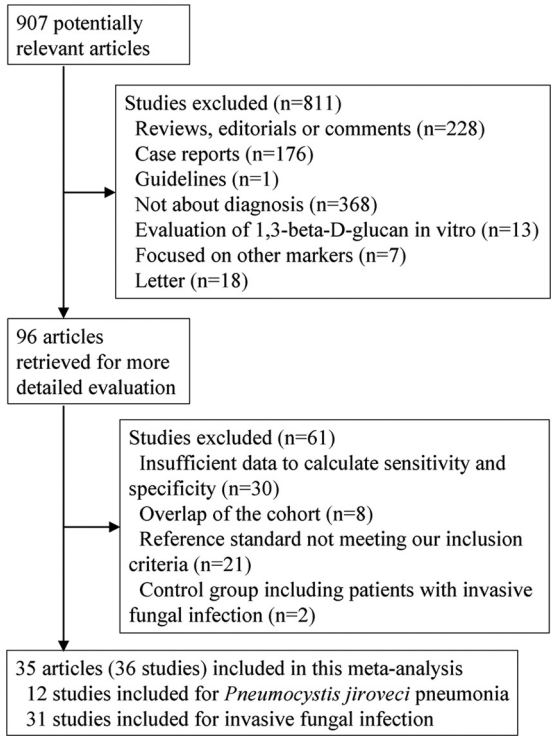

FIG 1 Flow diagram for the selection of studies.

RESULTS

Search results and characteristics of studies. We identified 907 possibly relevant articles from four different databases (MEDLINE, Web of Science, Cochrane Collaboration databases, and Ichushi-Web), and 96 full-length articles were selected for detailed analysis on the basis of title or abstract. Retrieval and inclusion flow is shown in Fig. 1. Eventually, 35 articles met the inclusion criteria (1–4, 12, 14, 16, 17, 19, 20, 24, 26, 27, 29, 32–34, 38, 40, 43–51, 54, 56, 57, 59–62), but since the article by Odabasi et al. (45) included two studies, a case-control study and a retrospective cohort study, 36 studies in all were included. Twelve studies were included for PJP and 31 studies for IFI. The characteristics of these studies are outlined in Tables 1, 2, and 3. A total of 5,453 participants were covered by the studies, with women accounting for a median of 43.3%, and the median of the mean or median age was 55.1 years (interquartile range, 47.0 to 58.3 years). Hematological disorders constituted the underlying diseases of most patients. Characteristics of control groups varied, with most studies using patients with hematological disorders. The two studies published by Obayashi and colleagues included different patient cohorts, one study analyzing 50 patients who were enrolled in 1992 and 1993 at nine hospitals in Japan (43) and the other study 58 patients who had been enrolled from 2000 to 2005 and who had undergone autopsy after death (44).

TABLE 1 Characteristics of studies included in the meta-analysis[b]

Author (reference)	Year	Region	Language	Assay	Cutoff (pg/ml)	Mean or median age (yr)	Sex (female)	Patient population	Study design	Prophylactic antifungal therapy
Obayashi et al. (43)	1995	Japan	English	Fungitec G	20	NA	NA	Patients with various underlying diseases	Case-control study	Not reported
Yasuoka et al. (59)	1996	Japan	English	Fungitec G	20	NA	NA	Patients with HIV	Case-control study	Not reported
Mitsutake et al. (38)	1996	Japan	English	Fungal index	60	NA	NA	Patients with various underlying diseases	Case-control study	Not reported
Moro et al. (40)	2003	Japan	Japanese	Wako	11	58.5	0.412	Patients with various underlying diseases	Case-control study	Not reported
Odabasi-1 et al.[a] (45)	2004	USA	English	Fungitell	60	NA	NA	NA	Case-control study	Not reported
Odabasi-2 et al.[a] (45)	2004	USA	English	Fungitell	60	NA	NA	Patients with HM	Retrospective cohort	Yes
Kondori et al. (26)	2004	Sweden	English	Fungitec G	20	52.9	0.636	Patients who are immunocompromised	Case-control study	Yes
Kawazu et al. (24)	2004	Japan	English	Wako	11	45.1	0.338	Patients with HM	Prospective cohort	Yes
Horiguchi (20)	2004	Japan	Japanese	Fungitec G	20	61.5	0.397	Patients with HM	Prospective cohort	Not reported
Pickering et al. (49)	2005	USA	English	Fungitell	60	NA	NA	NA	Case-control study	Not reported
Pazos et al. (47)	2005	Spain	English	Fungitell	120	44.0	0.432	Patients with HM	Prospective cohort	Yes
Ostrosky-Zeichner et al. (46)	2005	USA	English	Fungitell	60	46.0	0.583	Patients with various underlying diseases	Case-control study	Yes
Yoshida et al. (60)	2006	Japan	Japanese	Fungitec G	20	62.8	0.347	NA	Case-control study	Not reported
Fujita et al. (14)	2006	Japan	English	Wako	11	52.8	0.648	Patients with various underlying diseases	Case-control study	Yes
Tasaka et al. (56)	2007	Japan	English	Wako	31.1	NA	0.452	Patients with various underlying diseases	Case-control study	Not reported
Akamatsu et al. (2)	2007	Japan	English	Fungitec G	40	51.0	0.461	Solid-organ transplant recipients	Prospective cohort	Not reported
Alam et al. (3)	2007	Kuwait	English	Fungitell	80	NA	NA	Patients with various underlying diseases	Case-control study	Not reported
Lu et al. (33)	2007	China	Chinese	Fungitec G	20	43.8	0.376	NA	Case-control study	Not reported
Persat et al. (48)	2008	France	English	Fungitell	80	NA	NA	Patients with various underlying diseases	Case-control study	Not reported
Senn et al. (54)	2008	Switzerland	English	Wako	7	57.0	0.389	Patients with HM	Prospective cohort	Yes
Obayashi et al. (44)	2008	Japan	English	Fungitec G	30	NA	NA	Patients with various underlying diseases	Case-control study	Not reported
Watanabe et al. (57)	2009	Japan	English	Fungitec G	23.2	39.4	NA	Patients with HIV	Case-control study	Not reported
Desmet et al. (12)	2009	Belgium	English	Fungitell	100	42.4	0.267	Patients with HIV and HM	Case-control study	Not reported
Presterl et al. (50)	2009	Austria	English	Fungitell	40	NA	0.317	Patients who were admitted to ICU	Retrospective cohort	Not reported
Koo et al. (27)	2009	USA	English	Fungitell	80	54.0	0.436	Patients who were admitted to hospital	Case-control study	Yes
Hachem et al. (16)	2009	USA	English	Fungitell	80	NA	NA	Patients with HM and solid tumor	Prospective cohort	Not reported
Lunel et al. (34)	2009	The Netherlands	English	Fungitell	60	NA	0.373	Patients with various underlying diseases	Retrospective cohort	No
Zhao et al. (62)	2009	China	Chinese	GKT-25 M	10	6.2	0.315	Patients with various underlying diseases	Prospective cohort	Not reported
Racil et al. (51)	2009	Czech Republic	Czech	Fungitell	80	NA	0.374	Patients with HM	Retrospective cohort	Yes
Leon et al. (29)	2009	Spain, Argentina, and France	English	Fungitell	75	60.0	0.327	Patients with various underlying diseases	Prospective cohort	No
Liu et al. (32)	2009	China	Chinese	GKT-25 M	20	26.0	0.457	Patients with HM	Retrospective cohort	Not reported
Yu et al. (61)	2010	China	Chinese	GKT-25 M	20	54.0	0.365	Patients who were admitted to hospital	Retrospective cohort	Not reported
Hirata et al. (19)	2010	Japan	English	Wako	8.9	57.3	0.433	Patients with HM	Retrospective cohort	Yes
Held et al. (17)	2010	Germany	English	Fungitell	85	53.8	0.420	Patients with various underlying diseases	Case-control study	Not reported
Acosta et al. (1)	2011	Spain	English	Fungitell	80	57.5	0.667	Patients with various underlying diseases	Prospective cohort	Yes
Alexander et al. (4)	2010	USA	English	Fungitell	60	52.0	0.452	Lung transplant patients	Prospective cohort	Yes

[a] Since the article by Odabasi et al. included two studies, Odabasi-1 indicates a case-control study and Odabasi-2 indicates a retrospective cohort study.
[b] NA, not available; HIV, human immunodeficiency virus; HM, hematological malignancy; ICU, intensive care unit.

The 36 studies included six assays: 17 used Fungitell (1, 3, 4, 12, 16, 17, 27, 29, 34, 45–51), 9 used the Fungitec G test (2, 20, 26, 33, 43, 44, 57, 59, 60), 6 used the Wako β-glucan test (14, 19, 24, 40, 54, 56), 3 used the GKT-25 M set (32, 61, 62), and 1 used the fungal index (38). All studies but one were based in 1 of 13 countries, with the majority of assays in Japan ($n = 13$), as well as in the United States ($n = 7$), China ($n = 4$), Spain ($n = 2$), Austria ($n = 1$), Belgium ($n = 1$), Czech Republic ($n = 1$), France ($n = 1$), Germany ($n = 1$), Kuwait ($n = 1$), The Netherlands ($n = 1$), Sweden ($n = 1$), and Switzerland ($n = 1$); one study that performed assays in multiple countries (Spain, Argentina, and France) was also included. Prophylactic antifungal therapy was used in 12 studies.

TABLE 2 Diagnostic performance for *Pneumocystis jiroveci* pneumonia according to data extracted from different studies

Author (reference)	HIV status of patient population (no.)[a]	True positive	False negative	False positive	True negative
Yasuoka et al. (59)	HIV positive (7)	6	1	0	23
Moro et al. (40)	HIV negative (4)	4	0	13	82
Tasaka et al. (56)	Not available	53	4	14	87
Akamatsu et al. (2)	HIV negative (2)	2	0	26	130
Persat et al. (48)	HIV positive (16), HIV negative (4)	20	0	39	123
Obayashi et al. (44)	Not available	6	0	9	98
Watanabe et al. (57)	HIV positive (111)	105	6	51	371
Desmet et al. (12)	HIV positive (8), HIV negative (6)	14	0	3	25
Koo et al. (27)	HIV negative (14)	13	1	124	635
Yu et al. (61)	Not available	2	0	32	72
Held et al. (17)	Not available	45	1	3	47
Acosta et al. (1)	HIV positive (3)	3	0	7	31

[a] HIV, human immunodeficiency virus.

Assessment of study quality. Table 4 presents the results of the quality assessment. All studies used acceptable reference standard and avoided differential verification bias. Incorporation bias was avoided in 97% (35 of 36) of the studies. Most studies did not report whether the interpreters of BG results were blinded to the final diagnosis and vice versa. We therefore conducted stratification based only on the representative spectrum item among pre-planned subgroup analyses. A cohort design rather than a case-control design was used by 47% (17 of 36) of the studies (1, 2, 4, 16, 19, 20, 24, 29, 32, 34, 45, 47, 50, 51, 54, 61, 62). Characteristics of enrolled patients were fully described in 64% (23 of 36) of the studies (1, 2, 4, 12, 14, 16, 17, 19, 20, 24, 26, 27, 29, 32–34, 40, 46, 47, 54, 56, 61, 62). While 55% (17 of 31) of the studies used the EORTC/MSG criteria as the reference standard for IFI, 12 studies

TABLE 3 Diagnostic performance for invasive fungal infection according to data extracted from different studies

Author (reference)	Reference standard[b]	True positive	False negative	False positive	True negative
Obayashi et al. (43)	Autopsy, microbiologically documented	37	4	0	153
Mitsutake et al. (38)	Microbiological culture from blood or sterile material or autopsy	32	5	0	30
Moro et al. (40)	Similar criteria (Japanese guideline)	7	0	13	82
Odabasi-1 et al.[a] (45)	Microbiological culture from blood	29	1	2	28
Odabasi-2 et al.[a] (45)	EORTC/MSG	15	0	10	220
Kondori et al. (26)	Microbiological culture from blood or sterile material	14	0	0	19
Kawazu et al. (24)	EORTC/MSG	6	5	2	123
Horiguchi (20)	EORTC/MSG	7	1	9	52
Pickering et al. (49)	Histopathologic examination or blood culture	15	1	16	44
Pazos et al. (47)	EORTC/MSG	7	1	3	26
Ostrosky-Zeichner et al. (46)	EORTC/MSG	95	22	22	148
Yoshida et al. (60)	Similar criteria (Japanese guideline)	11	1	14	81
Fujita et al. (14)	Microbiological culture from blood	72	4	28	147
Akamatsu et al. (2)	EORTC/MSG	12	7	26	130
Alam et al. (3)	Microbiological culture from blood	14	13	0	26
Lu et al. (33)	Histopathologic examination or blood culture	25	3	5	50
Persat et al. (48)	EORTC/MSG	70	26	39	123
Senn et al. (54)	EORTC/MSG	20	10	28	85
Obayashi et al. (44)	Autopsy	39	2	9	98
Presterl et al. (50)	Microbiological culture from blood or sterile material	12	11	14	44
Koo et al. (27)	EORTC/MSG	50	23	124	635
Hachem et al. (16)	EORTC/MSG	29	16	2	18
Lunel et al. (34)	Microbiological culture from blood or sterile material	16	5	12	18
Zhao et al. (62)	EORTC/MSG	18	4	19	89
Racil et al. (51)	EORTC/MSG	8	1	51	35
Leon et al. (29)	Histopathologic examination or microbiological culture from blood or sterile material	14	4	105	117
Liu et al. (32)	EORTC/MSG	15	5	6	61
Yu et al. (61)	EORTC/MSG	5	3	32	72
Hirata et al. (19)	EORTC/MSG	8	2	2	196
Acosta et al. (1)	EORTC/MSG	7	2	7	31
Alexander et al. (4)	EORTC/MSG	8	3	54	5

[a] Since the article by Odabasi included two studies, Odabasi-1 indicates a case-control study and Odabasi-2 indicates a retrospective cohort study.
[b] EORTC/MSG, the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.

TABLE 4 Results of the risk of bias assessment per study[a]

Author (reference)	Representative spectrum	Acceptable reference standard	Acceptable delay between tests	Partial verification avoided	Differential verification avoided	Incorporation avoided	Index test results blinded	Reference standard results blinded	Relevant clinical information	Uninterpretable results reported	Withdrawals reported
Obayashi et al. (43)	No	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear
Yasuoka et al. (59)	No	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Mitsutake et al. (38)	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Moro et al. (40)	No	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Odabasi-1 et al. (45)	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Yes
Odabasi-2 et al. (45)	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes
Kondori et al. (26)	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Kawazu et al. (24)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Horiguchi (20)	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Pickering et al. (49)	No	Yes	Unclear	No	Yes	Yes	Unclear	Unclear	No	Yes	No
Pazos et al. (47)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Ostrosky-Zeichner et al. (46)	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes
Yoshida et al. (60)	No	Yes	Unclear	No	Yes	Yes	Yes	Unclear	No	Yes	Yes
Fujita et al. (14)	No	Yes	Unclear	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	No
Tasaka et al. (56)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	No
Akamatsu et al. (2)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Alam et al. (3)	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Unclear
Lu et al. (33)	No	Yes	Unclear	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Persat et al. (48)	No	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Senn et al. (54)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Obayashi et al. (44)	No	Yes	Yes	No	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Watanabe et al. (57)	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Desmet et al. (12)	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Presterl et al. (50)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	No	No
Koo et al. (27)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Hachem et al. (16)	Yes	Yes	Yes	UNclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Lunel et al. (34)	Yes	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Zhao et al. (62)	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Racil et al. (51)	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear
Leon et al. (29)	Yes	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes
Liu et al. (32)	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Yu et al. (61)	Yes	Yes	Unclear	Unclear	Yes	No	Unclear	Unclear	Yes	Unclear	Unclear
Hirata et al. (19)	Yes	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes
Held et al. (17)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Unclear	Yes
Acosta et al. (1)	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes
Alexander et al. (4)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes

[a] Yes indicates no bias; No indicates potential bias; Unclear indicates bias unclear.

used microbiological culture from blood or sterile material, autopsy, or histopathological examination which consisted of the proven presence of IFI according to the EORTC/MSG criteria. Enrollment was prospective in 28% (10 of 36) of the studies (1, 2, 4, 16, 20, 24, 29, 47, 54, 62).

Diagnostic accuracy for PJP. Table 5 shows the pooled analysis findings for sensitivity, specificity, DOR, and AUC-SROC of the BG assay for PJP and IFI. The pooled findings for PJP showed sensitivity of 96% (95% CI, 92% to 98%), specificity of 84% (95% CI, 83% to 86%), DOR of 102.3 (95% CI, 59.2 to 176.6), and AUC-SROC of 0.96 (95% CI, 0.94 to 0.99). The DOR was not heterogeneous ($Q = 7.24$; $P = 0.77$; $I^2 = 0\%$). The SROC curve is shown in Fig. 2.

Of the 12 included studies for PJP, 5 studies for patients with HIV (1, 12, 48, 57, 59) and 5 studies for HIV-negative patients (2, 12, 27, 40, 48) provided specific data for the diagnostic accuracy of the BG assay. The diagnostic accuracy was not significantly different between HIV patients and HIV-negative patients (Table 5).

Stratification based on findings of the brand-name assay, study design, or QUADAS item (representative spectrum) did not produce statistically significant differences in the accuracy of the BG assay, either. When we excluded studies including healthy controls or blood donors, no statistically significant differences in the accuracy of the BG assay were noted. Even after the exclusion of studies written in languages other than English, the results did not change significantly. In the result of multivariable metaregression, DOR was not significantly influenced by language, the brand-name assay, study design, age, or sex.

Diagnostic accuracy for IFI. The pooled findings for IFI showed sensitivity of 80% (95% CI, 77% to 82%), specificity of 82% (95% CI, 81% to 83%), DOR of 25.7 (95% CI, 15.0 to 44.1), and AUC-SROC of 0.88 (95% CI, 0.82 to 0.93) (Table 5). The DOR was significantly heterogeneous ($Q = 144.33$; $P < 0.001$; $I^2 = 79\%$). The SROC curve is shown in Fig. 2.

In 17 cohort studies (1, 2, 4, 16, 19, 20, 24, 29, 30, 34, 45, 47, 50, 51, 54, 61, 62), the pooled sensitivity, specificity, DOR, and AUC-SROC were 72% (95% CI, 67% to 77%), 78% (95% CI, 76% to 80%), 12.3 (95% CI, 6.0 to 25.1), and 0.79 (95% CI, 0.73 to 0.85), respectively. In 14 case-control studies (3, 14, 26, 27, 33, 38, 40, 43–46, 48, 49, 60), the pooled sensitivity, specificity, DOR, and AUC-SROC for IFI were 83% (95% CI, 80% to 86%), 86% (95% CI, 84% to 88%), 68.3 (95% CI, 30.7 to 151.8), and 0.95 (95% CI, 0.92 to 0.98), respectively. AUC-SROC was significantly lower in cohort studies than in case-control studies ($P < 0.001$) (Table 5).

TABLE 5 Results of meta-analyses for diagnostic accuracy of PJP and IFI[a] with serum 1,3-β-D-glucan

Test	No. of studies	% sensitivity (95% CI)	% specificity (95% CI) %	Diagnostic odds ratio (95% CI)	AUC-SROC (95% CI)
PJP					
All data	12	96 (92–98)	84 (83–86)	102.3 (59.2–176.6)	0.96 (0.94–0.99)
Healthy control excluded	12	96 (92–98)	84 (82–86)	99.8 (57.8–172.4)	0.96 (0.94–0.99)
Effect of HIV status					
HIV-positive patients	5	95 (90–98)	85 (82–88)	117.3 (55.0–250.4)	0.97 (0.95–0.99)
HIV-negative patients	5	97 (83–100)	83 (81–85)	50.3 (15.0–169.4)	0.93 (0.80–1.00)
Effect of study design					
Cohort study	3	100 (59–100)	78 (73–83)	20.1 (3.4–117.8)	0.91 (0.74–1.00)
Case-control study	9	95 (92–98)	85 (84–87)	121.4 (68.4–215.6)	0.97 (0.95–0.99)
Effect of assay type					
Fungitell	5	98 (93–100)	83 (81–85)	139.2 (44.5–435.5)	0.96 (0.88–1.00)
Fungitec G test	4	94 (89–98)	88 (85–90)	117.8 (53.8–258.3)	0.97 (0.94–0.99)
Only paper in English included	10	95 (92–98)	85 (83–87)	112.8 (64.1–198.4)	0.96 (0.94–0.99)
Effect of methodological quality (representative spectrum)					
Yes (no bias)	8	95 (92–98)	84 (83–86)	100.5 (55.9–180.6)	0.86 (0.61–1.00)
No (potential bias)	4	97 (86–100)	84 (80–88)	115.2 (25.6–517.0)	0.97 (0.93–1.00)
IFI					
All data	31	80 (77–82)	82 (81–83)	25.7 (15.0–44.1)	0.88 (0.82–0.93)
Healthy control excluded	28	78 (75–81)	80 (79–82)	19.2 (11.0–33.7)	0.86 (0.81–0.92)
Per event excluded	26	80 (77–83)	82 (80–83)	25.3 (14.0–45.8)	0.90 (0.86–0.95)
Possible IFI in control excluded	28	81 (78–83)	82 (81–84)	30.7 (16.4–57.5)	0.89 (0.83–0.94)
Effect of study design					
Cohort study	17	72 (67–77)	78 (76–80)	12.3 (6.0–25.1)	0.79 (0.73–0.85)
Case-control study	14	83 (80–86)	86 (84–88)	68.3 (30.7–151.8)	0.95 (0.92–0.98)
Effect of reference standard					
EORTC/MSG	17	77 (70–78)	83 (81–84)	15.2 (8.5–27.3)	0.80 (0.73–0.86)
Similar criteria	14	86 (82–90)	81 (79–83)	61.4 (20.3–185.5)	0.95 (0.90–0.99)
Effect of assay type					
Fungitell	15	75 (71–79)	77 (75–79)	12.0 (6.1–23.7)	0.86 (0.79–0.93)
Fungitec G test	7	89 (83–93)	90 (88–92)	100.7 (23.2–437.6)	0.96 (0.96–1.00)
Wako	5	84 (77–90)	90 (87–92)	60.1 (11.2–321.3)	0.94 (0.86–1.00)
Effect of kind of mycosis					
Candidiasis	19	81 (77–85)	81 (80–83)	25.7 (12.9–51.2)	0.90 (0.85–0.95)
Aspergillosis	17	77 (71–82)	83 (82–85)	23.2 (9.9–54.4)	0.86 (0.77–0.94)
Effect of antifungal therapy	12	81 (77–85)	84 (82–85)	25.9 (10.0–66.8)	0.87 (0.78–0.96)
Only papers in English included	23	79 (76–82)	83 (82–84)	26.8 (13.9–51.5)	0.87 (0.80–0.95)
Effect of methodological quality (representative spectrum)					
Yes (no bias)	18	71 (66–76)	80 (78–81)	11.8 (6.4–21.9)	0.78 (0.71–0.85)
No (potential bias)	13	85 (82–88)	87 (85–89)	89.3 (36.4–219.1)	0.96 (0.93–0.98)

[a] PJP, *Pneumocystis jiroveci* pneumonia; HIV, human immunodeficiency virus; IFI, invasive fungal infection; EORTC/MSG, the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.

This difference was attributable to both significantly low sensitivity and significantly low specificity in the cohort study. When we conducted subgroup analysis for a reference standard, AUC-SROC of EORTC/MSG criteria and similar criteria were 0.80 (95% CI, 0.73 to 0.86) and 0.95 (95% CI, 0.90 to 0.99). The diagnostic accuracy was significantly lower in EORTC/MSG criteria than in similar criteria. Because the pooled specificity was similar, the lower diagnostic accuracy of EORTC/MSG criteria was mainly attributable to lower sensitivity. When stratified analysis was conducted based on findings of the brand-name assay, AUC-SROC of Fungitell, Fungitec G test, and Wako were 0.86 (95% CI, 0.79 to 0.93), 0.96 (95% CI, 9.96 to 1.00), and 0.94 (95% CI, 0.86 to 1.00). Fungitell had an accuracy statistically lower than that of the Fungitec G test or Wako. Fungitell was lower in both sensitivity and specificity. Subgroup analysis within the QUADAS item (representative spectrum) showed lower accuracy in the no-bias group than in the potential-bias group.

Of the 31 included studies for IFI, 19 studies for invasive candidiasis (2–4, 14, 16, 19, 26, 27, 29, 34, 38, 40, 44–46, 48, 49, 61) and 17 studies for invasive aspergillosis (1, 2, 4, 16, 19, 20, 24, 27, 38, 40, 44–48, 51, 61) provided specific data for the diagnostic accuracy of the BG assay. When we conducted subgroup analysis for underlying disease, the pooled findings for invasive candidiasis showed sensitivity of 81% (95% CI, 77% to 85%), specificity of 81% (95% CI, 80% to 83%), DOR of 25.7 (95% CI, 12.9 to 51.2), and AUC-SROC of 0.90 (95% CI, 0.85 to 0.95). The pooled findings for invasive aspergillosis showed sensitivity of 77% (95% CI, 71% to 82%), specificity of 83% (95% CI, 82% to 85%), DOR of 23.2 (95% CI, 9.9 to 54.4), and AUC-SROC of 0.86 (95% CI, 0.77 to 0.94) (Table 5). The diagnostic accuracies for invasive candidiasis and invasive aspergillosis were not significantly different.

When we excluded studies including healthy controls, studies in which diagnostic performance was analyzed per episode and not per patient, or studies including possible IFI in control popu-

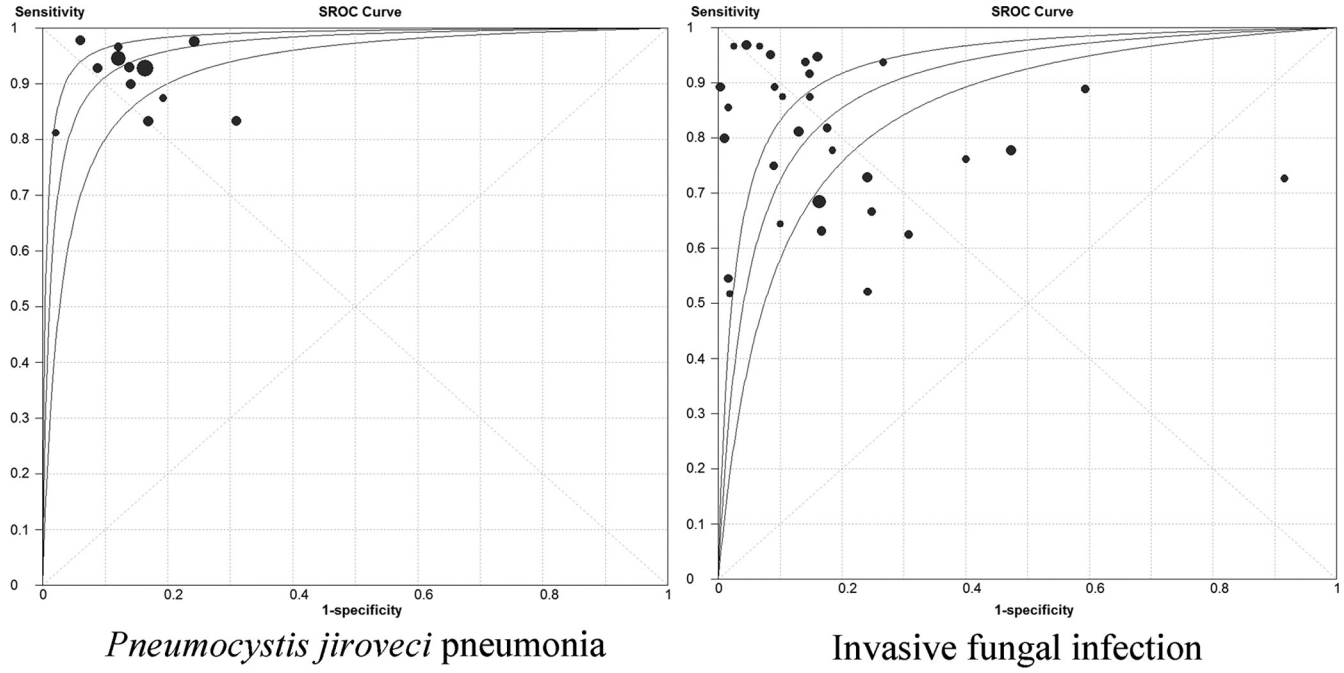

FIG 2 Summary receiver operating characteristic (SROC) curves for *Pneumocystis jiroveci* pneumonia and invasive fungal infection. Individual study estimates of sensitivity and 1 − specificity are represented by the circles. Circle sizes are proportional to study weights; however, sizes are not to scale. The lateral lines represent 95% confidence intervals.

lation, no statistically significant differences in the accuracy of the BG assay were noted. Even after the exclusion of studies written in languages other than English and studies in which prophylactic antifungal therapy was not reported or used, the results did not change significantly. In the multivariable metaregression results, DOR was not significantly influenced by language, reference standard, age, or sex. Although we performed sensitivity analysis, stratified analysis, and metaregression based on various factors to determine the source of this majority of heterogeneity among the studies, heterogeneity was still significant.

Publication bias. The appearance of funnel plots was asymmetrical, and Egger's test results were significant ($P = 0.01$). This suggested that publication bias may be present. After exclusion of the four studies that included 50 or fewer participants, differences in the accuracy of the BG assay findings were not statistically significant.

DISCUSSION

Our meta-analysis to examine the diagnostic accuracy of the serum BG assay for PJP and IFI has resulted in several significant findings.

First, the BG assay showed the high AUC-SROC for PJP with no heterogeneity. Moreover, the BG assay is not an invasive test. The gold standard for diagnosis is microscopic visualization of the organism, and bronchoalveolar lavage fluid, sputum, or tissue is necessary for diagnosis. Because patients with PJP tend to present with nonproductive or minimally productive cough, sputum is often insufficient for diagnosis and an invasive procedure such as bronchoscopy is needed. Noninvasive BG assay is useful as a screen to avoid unnecessary invasive procedures.

Second, we showed that the BG assays have high sensitivity for PJP. The BG assay can therefore be used as a screening tool. If any of the BG assays are negative, PJP can be ruled out and unnecessary procedures or treatments for PJP can be avoided.

Third, the pooled specificity was moderate for PJP because the BG assay could be positive for various fungal infections and the presence of factors such as use of intravenous amoxicillin-clavulanic acid, treatment of patients with immunological preparations (albumins or globulins), use of cellulose membranes and filters made from cellulose in hemodialysis, and use of cotton gauze swabs/packs/pads and sponges during surgery (8). If the BG assay is positive, it is important to consider the factor associated with false-positive results and exclude IFI by other modalities or invasive procedures such as computed tomography scan and bronchoscopy.

Fourth, the diagnostic accuracies for HIV patients and HIV-negative patients were not significantly different. Nakamura and colleagues (42) suggested that the detection rate of BG in HIV-negative patients was lower than that in HIV patients. HIV-negative patients usually have significantly fewer organisms in bronchoalveolar lavage fluid than do HIV patients. This can lead to false-negative results, particularly in HIV-negative patients (8). However, our results showed that the BG assay was useful not only in HIV patients but also in HIV-negative patients.

Fifth, the diagnostic accuracy for IFI of the BG assay was moderate, with high statistical heterogeneity. While there are several molecular and serological assays for the diagnosis of specific types of IFI, which can be detected by means of galactomannan, mannan, and DNA sequences (36), only the BG assay can be used for various fungal infections. For instance, the diagnostic accuracy of the galactomannan assay for invasive aspergillosis is similar to that of BG for IFI. Leeflang and colleagues (28) used a meta-analysis to demonstrate that the galactomannan assay had an overall sensitivity of 78% (95% CI, 61% to 89%) and an overall specificity of

81% (95% CI, 72% to 88%) for proven or probable cases of invasive aspergillosis. However, patients at risk for one type of IFI are often at risk for one or more other types of IFI. Because both the sensitivity and the specificity of the BG assay are moderate for IFI, combination with other modalities and procedures is necessary to either rule out or rule in IFI. Therefore, it is reasonable that the BG assay positivity is used only as a mycological criterion in the revised EORTC/MSG criteria.

The summary results from our overall analysis for IFI are similar to those of the earlier review of Karageorgopoulos and colleagues (sensitivity, 80% vs. 77%; specificity, 82% vs. 85%; AUC-SROC, 0.88 vs. 0.89) (23). However, Karageorgopoulos and colleagues included only 23 studies because of language restrictions and did not stratify their final analysis by study design or reference standard. Our meta-analysis showed that the substantial between-study heterogeneity for IFI resulted from differences in study design, reference standard, brand-name assay, and QUADAS item. We observed that case-control studies seemed to overestimate both sensitivity and specificity (3, 14, 26, 27, 33, 38, 40, 43–46, 48, 49, 60). We also observed that the sensitivity of the EORTC/MSG criteria was lower than that of similar criteria (1, 2, 4, 16, 19, 20, 24, 27, 32, 45–48, 51, 54, 61, 62). Fungitell was statistically lower in accuracy than Fungitec G test or Wako. Subgroup analysis within the QUADAS item (representative spectrum) showed lower accuracy in the no-bias group than in the potential-bias group. Well-designed, high-quality prospective cohort studies on the BG assay for IFI are needed.

Only one study, that by Alexander and colleagues (4), reported low diagnostic accuracy for IFI in lung transplants. These authors suggested that the BG assay might have limited utility as a screening tool for lung transplants. However, further studies are needed to confirm these findings of this study, because the sample size was small.

Our review has several limitations. First, there was evidence of publication bias, so it is possible that our results constitute an overestimation of the performance of the test. However, when we excluded small studies that have a greater tendency to overestimate diagnostic performance, differences in the accuracy of the BG assay still were not statistically significant. It is thus reasonable to conclude that the effect of publication bias was only minor (6).

Second, the quality of our included studies was moderate. The bias in which low-quality studies overestimate test performance has been seen previously in studies of diagnostic tests (30, 53). Although this relationship was found for diagnostic accuracy for IFI, stratification based on findings of the QUADAS item (representative spectrum) for PJP did not produce statistically significant differences in the accuracy of the BG assay.

In conclusion, the diagnostic accuracy of the BG assay is high for PJP and moderate for IFI. Because the sensitivity for PJP is particularly high, the BG assay can be used as a screening tool for PJP.

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