Research Article

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Diagnostic efficacy of serum 1,3-β-D-glucan for invasive fungal infection: An update meta-analysis based on 37 case or cohort studies

Abstract: Objective The aim of this study was to investigate the diagnostic performance of serum 1,3-β-D-glucan as biomarker for invasive fungal infection through meta-analysis.

Methods The electronic databases of Medline, Cochrane, Embase, Web of Science, OVID and CNKI were systematic searched to identified the case-control or Cohort studies relevant to diagnostic efficacy of serum 1,3-β-D-glucan for invasive fungal infection. The data of true positive (tp), false positive (fp), false negative (fn) and true negative (tn) patients number were extracted from each of the original included studies. The diagnostic sensitivity, specificity and systematic receiver operating characteristic (SROC) curve were calculated and pooled through random or fixed effect method. The publication bias was evaluated by the Deek's funnel plot.

Results Thirty-seven relevant studies were fulfilled the inclusion criteria and included in our present meta-analysis. The combined sensitivity, specificity, positive likely hood ratio (+lr), negative likely hood ratio (-lr) and diagnostic odds ratio(dor) for 1,3-β-D-glucan in diagnosis of invasive fungal infectionwere 0.83 (95%CI:0.38-0.61), 0.81 (95%CI:0.80-0.82), 5.13 (95%CI:3.98-6.62), 0.23 (95%CI:0.18-0.30), and 29.68 (95%CI:18.94-46.52) respectively. The pooled area under the ROC curve (AUC) was 0.91.The Deek's funnel plot asymmetry test showed there was no publication bias for 1,3-β-D-glucan in diagnosis of invasive fungal infection of the included 37 studies.

Conclusion Serum 1,3-β-D-glucan assay was a promising biomarker for invasive fungal infection diagnosis.

Keywords: 1,3-β-D-glucan; invasive fungal infection; meta-analysis; diagnosis

1 Introduction

Invasive fungal infections (IFIs) are serious kinds of fungal diseases that invade the body, grow and reproduce in body tissues, organs and blood, and cause inflammation and tissue damage [1]. Due to the application of high strength, immunosuppressive agents and high-dose chemotherapy for organ transplantation, hematopoietic stem cell transplantation, a variety of catheter in interventional, indwelling intubation ventilator have been widely carried out and the increase of AIDS infection, the incidence of IFI increased significantly [2]. However, the diagnosis of invasive fungal infection was not easy in clinical practice [3]. Generally, invasive fungal infection often requires fungal culture or histopathological examination to confirm the diagnosis. However, fungal culture usually takes 2 to 4 days to obtain results, while histological examination is difficult to achieve in most cases. Therefore, it is important to make a rapid and accurate diagnosis of IFI with a simple and convenient method. 1,3-β-D-glucan is a fungal-cell-wall polysaccharide that can released into the peripheral blood in patients with IFIs. And serum 1,3-β-D-glucan were used as serum biomarker for IFIs diagnosis. However, the diagnostic performance of 1,3-β-D-glucan was quite different according to the previously published studies because of different 1,3-β-D-glucan assays and cutoff value [4]. Therefore, we performed this meta-analysis and pooled the diagnostic efficacy to further assess it clinical value.

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2 Methods

2.1 Publication search strategy

The electronic databases of Medline, Cochrane, Embase, Web of Science, OVID and CNKI were systematic searched to identified the case-control or Cohort studies relevant to diagnostic efficacy of serum 1,3-β-D-glucan for invasive fungal infection. The below terms were used for electronic databases searching. (1) invasive fungal infection/IFI; (2) invasive fungal disease/IFD; (3) 1,3-β-D-glucan/BG/BDG. The language was limited to English and Chinese. In order to identify additional relevant publications, the reference of the included studies were also screened to find potential suitable studies. For studies without enough data to make the meta-analysis, the corresponding authors were contacted by e-mail to obtain further information, if necessary.

2.2 Data and information extraction

Hu Caibao and Zhao Tian independently read the whole paper and extracted the data and information. Any disagreement was consulted to another investigator (Chen Changqin) for consensus. The extracted data and information included (1) The study type (case-control or Cohort); (2) The language of the publication (English or Chinese); (3) The journal name of the paper published; (4) The year of the paper published; (5) The first and the corresponding authors; (6) The diagnosis of invasive fungal infectionreference standard; (7) The cutoff value of serum 1,3-β-D-glucan in each study; (8) The number of true positive, false positive, false negative and true negative; (9) Invasive fungal infection detection methods; (10) The region the study performed. And the above detail information and data were by Zhao Tian and Chen Changqin respectively and cross checked.

2.3 Publication quality evaluation

The general method quality of the included 37 studies was evaluated through the QUADAS tool byTingyu and Hu Caibao independently with eight questionnaires [5, 6]. For each of the question, there was 3 status "yes", "no" and "unclear". "yes" represents high quality, "no" represents low quality and "unclear" represents moderate quality.

## 3 Statistical analysis

The diagnostic efficacy for 1,3-β-D-glucan for invasive fungal infection was pooled by MetaDiSc 1.4 software by the equation of sensitivity=true positive/(true positive+ false negative), specificity=true negative/(true negative+ false positive). Subgroup analysis was performed according to different serum 1,3-β-D-glucan cutoff value. The diagnostic parameters were pooled by mixed or random effect model according to the statistical heterogeneity across theincluded studies. The SROC curve was drawn by Stata12.0SE software and the AUC was calculated through sensitivity vs specificity for 1,3-β-D-glucan in diagnosis of invasive fungal infection. P< 0.05 was considered statistical significant.

4 Results

4.1 Main characteristic of the individual 37 publications

As a result of the related electronic databases systematic searching, finally 37 relevant studies were fulfilled the inclusion criteria and included in our present meta-analysis (Figure 1). Among the 37 publications, 15 studies were Cohort designed prospective study and other 22 are case-control publications. The cutoff value for 1,3-β-D-glu-
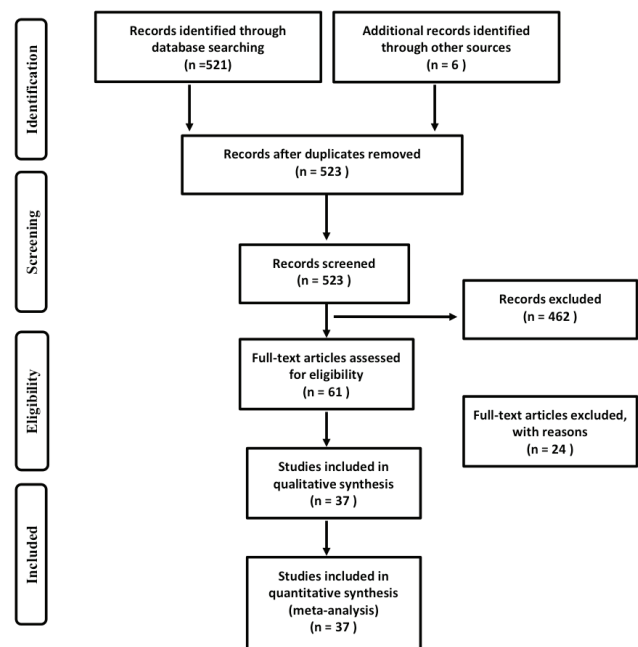
Figure 1: The flowchart of publication searching and studies inclusion

Table 1: The main characters of the recruited 37 publications

Study	Year	Country	Study type	Method	Cutoff value (pg/mL)	Reference	tp	fp	fn	tn
Miyazaki [7]	1997	Japan	Case-control	Fungitec G-test	10	Micobiological culture	17	0	7	36
Obayashi [8]	1995	Japan	Case-control	Fungitec G-test	20	Autopsy	37	0	4	153
Kawazu [9]	2004	Japan	Cohort	Wako	11	EORTC/MSG	6	2	5	123
Kondori [10]	2004	Sweden	Case-control	Fungitec G-test	20	Micobiological culture	14	0	0	19
Odabasi [11]	2004	U.S	Cohort	Fungitell	80	EORTC/MSG	18	15	2	248
Ostrosky-Zeichner [12]	2005	U.S	Case-control	Fungitell	60	EORTC/MSG	95	22	22	148
Pazos [13]	2005	Spain	Cohort	Fungitell	120	EORTC/MSG	7	3	1	26
Pickering [14]	2005	U.S	Case-control	Fungitell	60	Histopathologic examination	31	10	1	22
Fujita [15]	2006	Japan	Case-control	Wako	11	Micobiological culture	72	28	4	147
Alam [16]	2007	Kuwait	Case-control	Fungitell	80	EORTC/MSG	14	0	13	26
Akamatsu [17]	2007	Japan	Cohort	Fungitec G-test	40	EORTC/MSG	12	26	7	130
Obayashi [18]	2008	Japan	Case-control	Fungitec G-test	30	Autopsy	39	9	2	98
Senn [19]	2008	Switzerland	Cohort	Wako	7	EORTC/MSG	20	28	10	85
Persat [20]	2008	France	Case-control	Fungitell	80	EORTC/MSG	70	39	26	123
Ellis [21]	2008	UAE	Cohort	Fungitell	80	EORTC/MSG	36	23	2	19
Leon [22]	2009	Europe	Cohort	Fungitell	75	Histopathologic examination	14	105	4	117
Lunel [23]	2009	Netherlands	Cohort	Fungitell	60	Micobiological culture	16	12	5	18
Hachem [24]	2009	U.S	Cohort	Fungitell	80	EORTC/MSG	29	2	16	18
Koo [25]	2009	U.S	Case-control	Fungitell	80	EORTC/MSG	50	124	23	635
Presterl [26]	2009	Austria	Cohort	Fungitell	40	Micobiological culture	12	14	11	44
Racil [27]	2010	Czech Republic	Case-control	Fungitell	80	EORTC/MSG	8	55	1	27
Alexander [28]	2010	U.S	Cohort	Fungitell	60	EORTC/MSG	8	54	3	5
Hirata [29]	2010	Japan	Cohort	Wako	8.9	EORTC/MSG	8	2	2	196
Li J [30]	2010	China	Case-control	Fungitec G-test	20	Micobiological culture	37	16	1	26
Zuo XH (1)[31]	2010	China	Case-control	Fungitec G-test	20	EORTC/MSG	35	4	5	31
Zuo XH (2) [31]	2010	China	Case-control	Fungitec G-test	50	EORTC/MSG	29	3	11	32
De Vlieger [32]	2011	Belgium	Cohort	Fungitell	140	EORTC/MSG	12	10	2	33
Posteraro [33]	2011	Italy	Cohort	Fungitell	80	EORTC/MSG	15	5	1	74
Acosta [34]	2011	Spain	Cohort	Fungitell	80	EORTC/MSG	7	7	2	31
Jiang ZM [35]	2011	China	Case-control	Fungitec G-test	20	Micobiological culture	44	21	2	45
Yang HQ [36]	2011	China	Case-control	Fungitec G-test	20	Micobiological culture	423	355	34	1027
Jin X [37]	2011	China	Case-control	Fungitec G-test	10	EORTC/MSG	40	1	5	39
Metan [38]	2012	Turkery	Case-control	Fungitell	80	EORTC/MSG	33	19	17	59
Liu CH [39]	2012	China	Case-control	Fungitec G-test	20	EORTC/MSG	36	6	7	51
Ding C [40]	2012	China	Case-control	Fungitec G-test	20	Micobiological culture	42	1	6	29
Wang QF [41]	2012	China	Case-control	Fungitec G-test	20	Micobiological culture	47	7	2	75
Yang D [42]	2013	China	Case-control	Fungitec G-test	20	Micobiological culture	26	16	9	87
Zeng WX [43]	2016	China	Case-control	Fungitec G-test	20	Micobiological culture	38	3	39	478

can in diagnosis of invasive fungal infection ranged from 7 (pg/mL) to 140 (pg/mL). The general characteristics of the 37 publications were demonstrated in Table 1.

4.2 Quality assessment of the included studies

Eight items (questions) original from QUADAS (Quality Assessment of Diagnostic Accuracy Studies) were used to assessed the general quality of the included studies. For the QUADAS quality assessment, most of the 37 studies fulfilled the items of "Clear description of study selection criteria "and" acceptable reference standard". However, most of the included studies didn't clearly addressed the item of " withdraw reports". The generally quality of the included 37 publications were showed in Figure 2.

4.3 The pooled diagnostic sensitivity

The I^2 test of the 37-publication indicated significant heterogeneity (I^2=83.5%). The diagnostic sensitivity was pooled by random effect model. The combined sensitivity for 1,3-β-D-glucan in diagnosis of invasive fungal infection was 0.83 (95%CI:0.38-0.61), Figure 3.

4.4 The pooled diagnostic specificity

Significant statistical heterogeneity was found in the aspect of pooling the specificity through the I^2 test (I^2=95.5%). The pooled diagnostic specificity was 0.81 (95%CI:0.80-0.82) by random effect model, Figure 4.
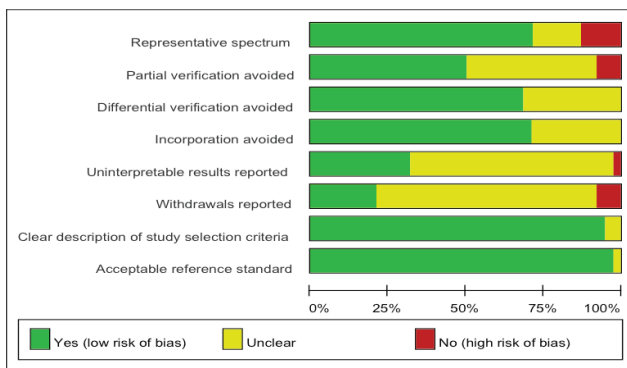

	Sensitivity (95% CI)
Miyazaki	0.71 (0.49 - 0.87)
Obayashi	0.90 (0.77 - 0.97)
Kawazu	0.55 (0.23 - 0.83)
Kondori	1.00 (0.77 - 1.00)
Odabasi	0.90 (0.68 - 0.99)
Ostrosky-Zeichner	0.81 (0.73 - 0.88)
Pazos	0.88 (0.47 - 1.00)
Pickering	0.97 (0.84 - 1.00)
Fujita	0.95 (0.87 - 0.99)
Alam	0.52 (0.32 - 0.71)
Akamatsu	0.63 (0.38 - 0.84)
Obayashi	0.95 (0.83 - 0.99)
Senn	0.67 (0.47 - 0.83)
Persat	0.73 (0.63 - 0.81)
Ellis	0.95 (0.82 - 0.99)
Leon	0.78 (0.52 - 0.94)
Lunel	0.76 (0.53 - 0.92)
Hachem	0.64 (0.49 - 0.78)
Koo	0.68 (0.57 - 0.79)
Presterl	0.52 (0.31 - 0.73)
Racil	0.89 (0.52 - 1.00)
Alexander	0.73 (0.39 - 0.94)
Hirata	0.80 (0.44 - 0.97)
Li J	0.97 (0.86 - 1.00)
Zuo XH(1)	0.88 (0.73 - 0.96)
Zuo XH(2)	0.73 (0.56 - 0.85)
De Vlieger	0.86 (0.57 - 0.98)
Posteraro	0.94 (0.70 - 1.00)
Acosta	0.78 (0.40 - 0.97)
Jiang ZM	0.96 (0.85 - 0.99)
Yang HQ	0.93 (0.90 - 0.95)
Jin X	0.89 (0.76 - 0.96)
Metan	0.66 (0.51 - 0.79)
Liu CH	0.84 (0.69 - 0.93)
Ding C	0.88 (0.75 - 0.95)
Wang QF	0.96 (0.86 - 1.00)
Yang D	0.74 (0.57 - 0.88)
Zeng WX	0.49 (0.38 - 0.61)

Pooled Sensitivity = 0.83 (0.81 to 0.84)
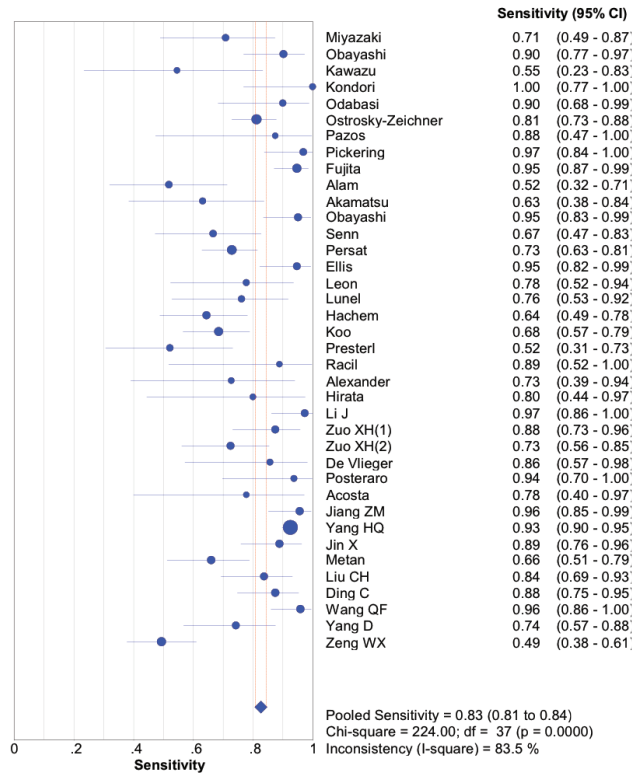Chi-square = 224.00; df = 37 (p = 0.0000)
Inconsistency (I-square) = 83.5 %

Figure 3: Pooled forest plot of sensitivity of 1,3-β-D-glucan in diagnosis of invasive fungal infection.

4.5 The pooled +lr and −lr

The statistical heterogeneity for effect size +lr and −lr were evaluated through I^2 test. And the results indicated statistical significant heterogeneity (P=0.000). Therefore, the data was pooled through random effect. The pooled +lr and −lr were 5.13 (95%CI:3.98-6.62), Figure 5 and 0.23 (95%CI:0.18-0.30), Figure 6.

4.6 Pooled diagnostic odds ratio(dor)

Because of significant statistical heterogeneity across the included 37 studies (I^2=80.9%), the dor was calculated through random effect model. The combined dor was 29.68 (95%CI:18.94-46.52), Figure 7.

4.7 The pooled summary ROC and AUC

The combined receiver operating characteristic (ROC) curve was calculated by Stata12.0SE software (Figure 8). The area under the ROC curve was 0.91.
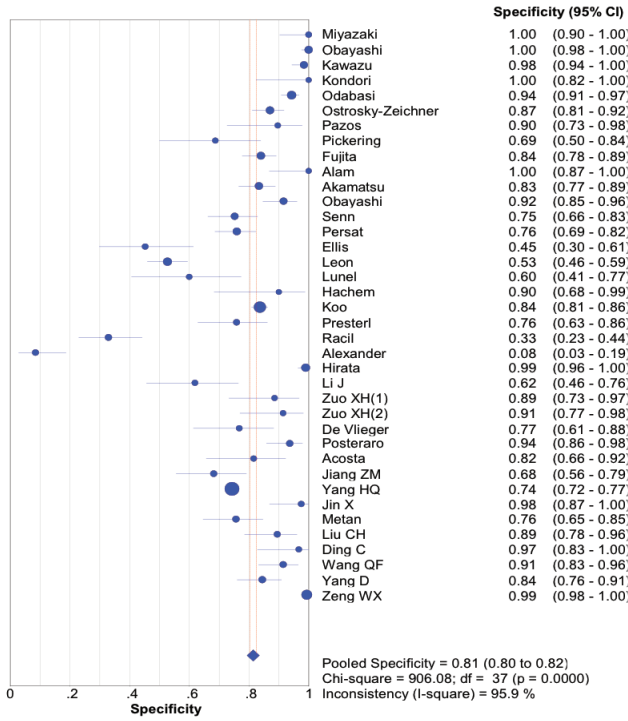

Figure 2: The general quality of the included 37 studies evaluated by QUADAS

Figure 4: Pooled forest plot of specificity of 1,3-β-D-glucan in diagnosis of invasive fungal infection
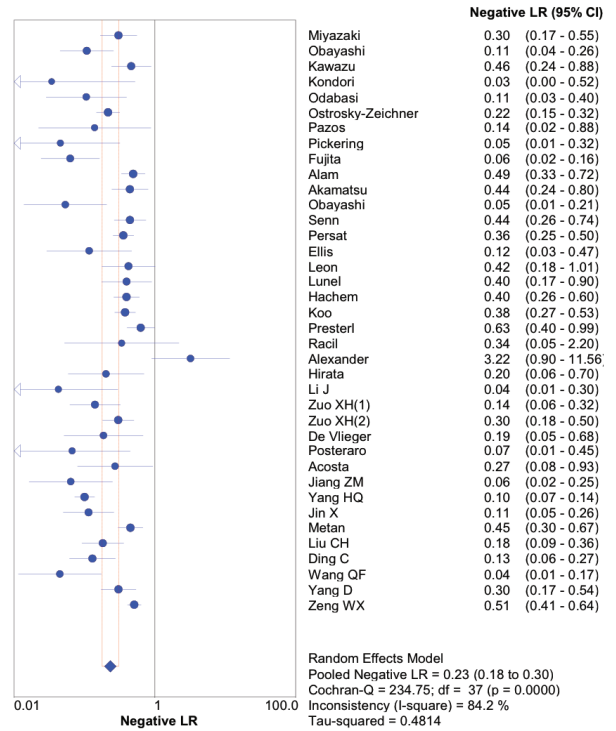

Figure 6: Pooled forest plot of -lr for 1,3-β-D-glucan in diagnosis of invasive fungal infection
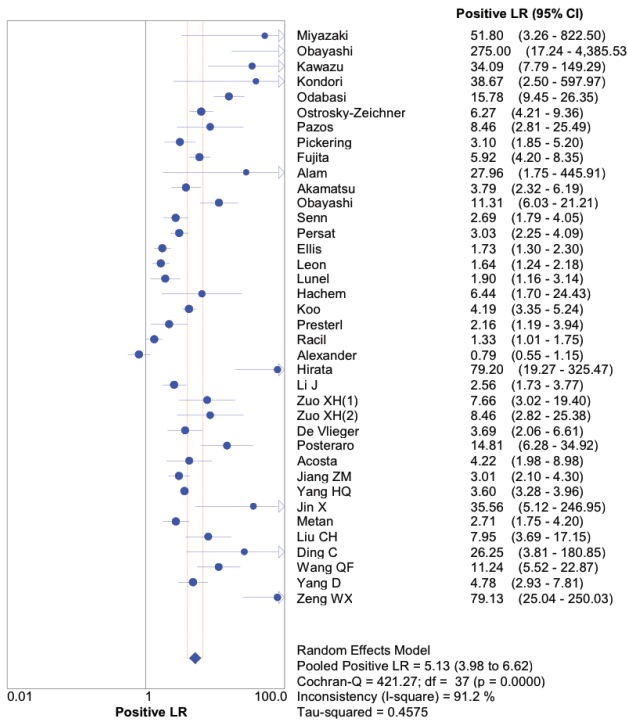

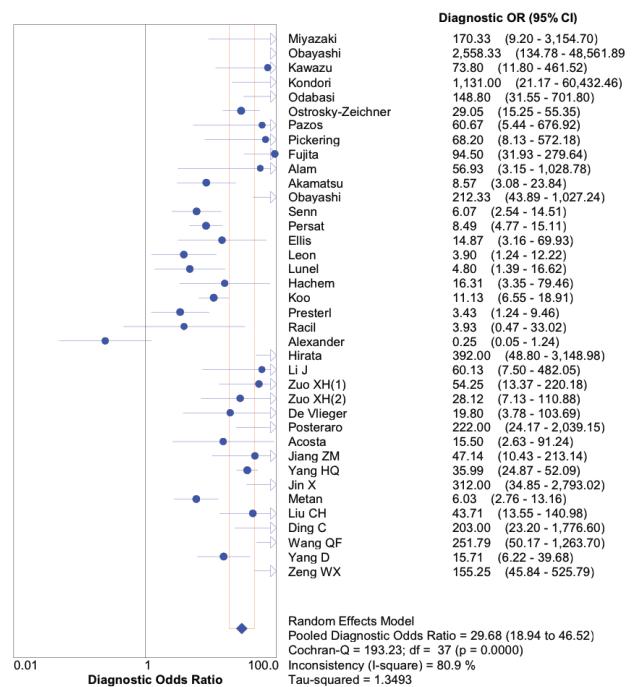**Figure 5:** Pooled forest plot of +lr for 1,3-β-D-glucan in diagnosis of invasive fungal infection

Figure 7: Pooled forest plot of dor for 1,3-β-D-glucan in diagnosis of invasive fungal infection

4.8 Diagnostic efficacy changes according to cutoff value

The diagnostic sensitivity, specificity, +lr, -lr and odds ratio changes according to cutoff value were demonstrated in Figure 9. The diagnostic sensitivity, specificity and −lrdid not change a lot for different cutoff value of serum 1,3-β-D-glucan (Figure 9a, Figure 9b, Figure 9d).
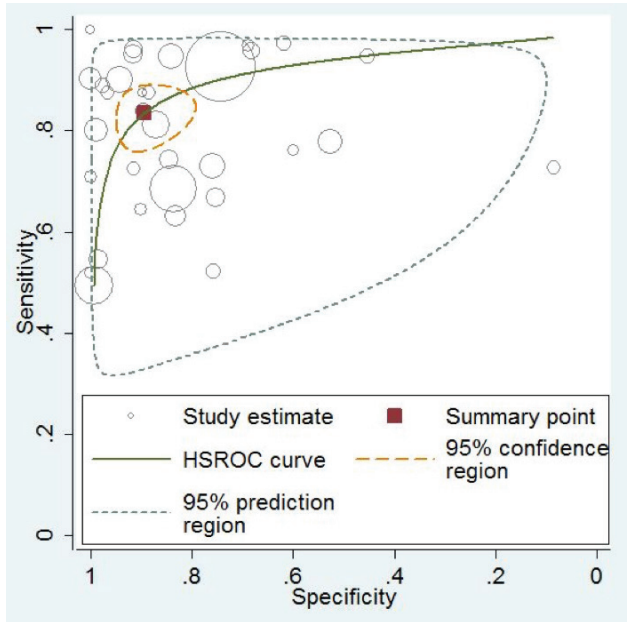
Figure 8: The AUC of the SROC for 1,3-β-D-glucan in diagnosis of invasive fungal infection

However, the +lr and dor changed significantly for different cutoff value especially for <20 (pg/mL) group (Figure 9c and Figure 9e).

4.9 Subgroup analysis

In order to minimize the clinical heterogeneity, we performed subgroup analysis according to invasive fungal infection detection method, study type and gold diagnostic reference. However, the diagnostic efficacy didn't significant changed for different subgroups (Table 2).

4.10 Publication bias evaluation

The publication bias was evaluate by the Deek's funnel plot (Figure 10) and line regression test. The Deek's funnel plot asymmetry test showed there was no publication bias for 1,3-β-D-glucan in diagnosis of invasive fungal infection of the included 37 studies.

5 Discussion

Statistical studies demonstrated that invasive fungal infection(IFI) has significantly increased because of the extensive application of high-dose chemotherapy, glucocorticoids, broad-spectrum antibiotics and immunosup-
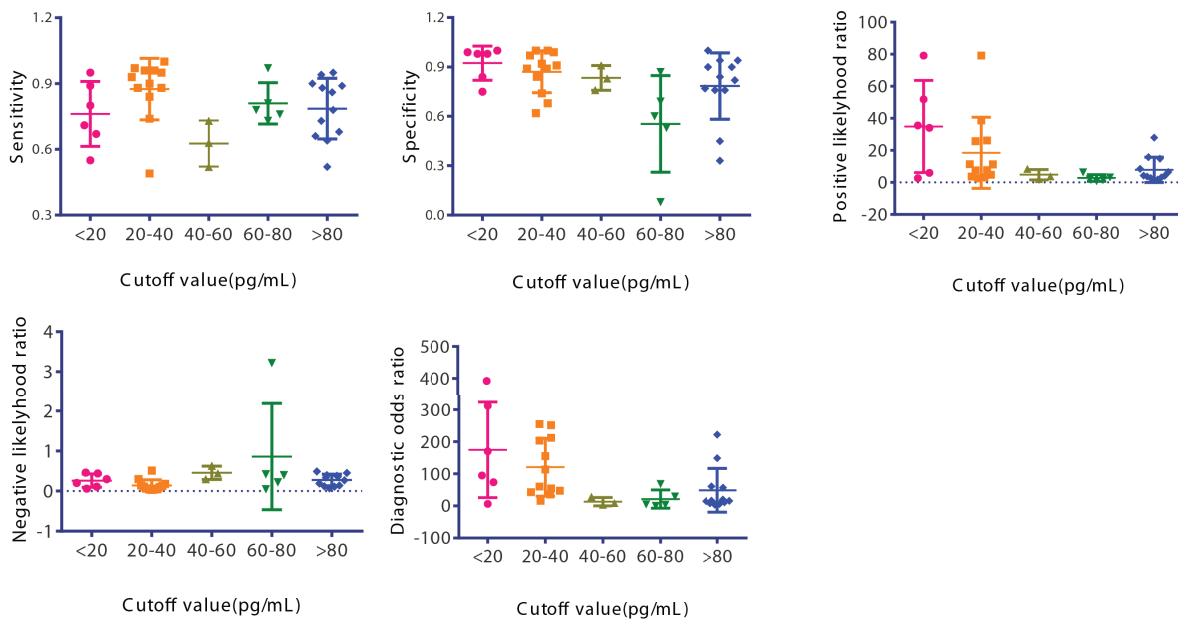

Figure 9: The scatter plot of diagnostic efficacy changes according to cutoff value

pressive agents, as well as the extensive development of solid organ transplantation and hematopoietic stem cell transplantation [44, 45].Generally, appropriate clinical antifungal treatment is often not timely, which leading to deterioration of the patient's condition, thereafter resulting in high mortality. Therefore, rapid and accurate diagnosis of IFI is particularly important for patients with IFI.

1,3-β-D-glucan is a polysaccharide component of fungal cell wall, which is fungi specific and can't find in other microorganisms infection disease such as bacteria, viruses and mycoplasma.1,3-β-D-glucan assay was widely used clinically for IFI diagnosis with good clinical practice value. Previously studies showed 1,3-β-D-glucan was continuously released into the peripheral blood in

Figure 10: The funnel plot of publication bias for 1,3-β-D-glucan in diagnosis of invasive fungal infection

patients with IFI. Generally, 1,3-β-D-glucan concentration was very low in serum of healthy people, usually less than 10 pg /mL. However, it serum level elevated significant when invasive fungal infection occurred in patients, which was generally greater than 20 pg /mL. Theoretically, 1,3-β-D-glucan detection may be the ideal method for rapid diagnosis of invasive fungal infections in early stage. However, the sensitivity and specificity of these findings are not completely consistent according to the previously published studies. In order to explicated its diagnostic efficacy, we performed this meta-analysis with 37 case-control or cohort studies and pooled the diagnostic efficacy. In our present, meta-analysis, we included 37 relevant studies with the combined sensitivity, specificity, positive likelihood ratio(+lr), negative likelyhood ratio(-lr) and diagnostic odds ratio(dor) of 0.83 (95%CI:0.38-0.61), 0.81 (95%CI:0.80-0.82), 5.13 (95%CI:3.98-6.62), 0.23 (95%CI:0.18-0.30), and 29.68 (95%CI:18.94-46.52). And the pooled AUC was 0.91. The results indicated that serum 1,3-β-D-glucan assay was a promising biomarker for invasive fungal infection diagnosis.

ROC curve is an accurate and comprehensive method for evaluation diagnostic tests. According to the results of Swets [46], if the area under the ROC curve (AUC) less than 0.5, there is no diagnostic value. The diagnostic value of low with limited clinical value when the AUC between 0.5 ~ 0.7. However, the diagnostic accuracy is high when the AUC is more than 0.7. In this present meta-analysis, we found the pooled AUC was 0.91 which indicated that the diagnostic accuracy is high for serum 1,3-β-D-glucan assay in diagnosis of IFIs.

However, there are several limitations in this study. Firstly, there are some clinical heterogeneity which can lead to unstable results. Secondly, statistical heteroge-
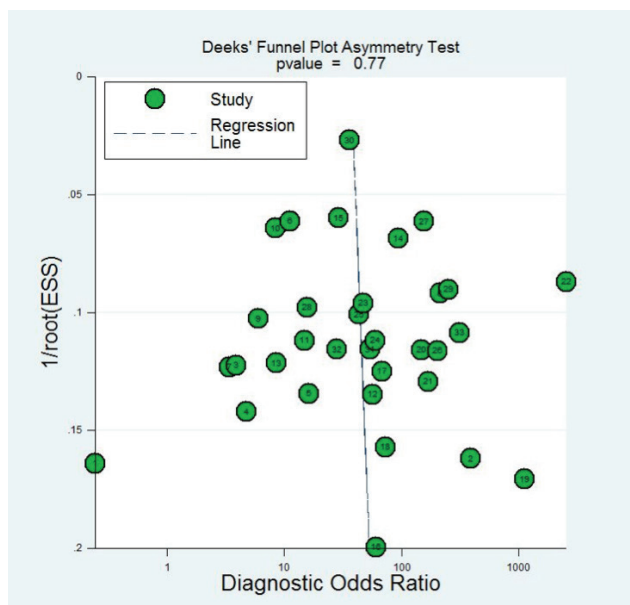
Table 2: The subgroup analysis of 1,3-β-D-glucan for invasive fungal infection

Subgroup	No. of study	Sensitivity	Specificity	AUC
Method				
Fungitell	18	0.76(0.72-0.79)	0.76(0.74-0.78)	0.86
Fungitec G-test	16	0.87(0.84-0.89)	0.83(0.82-0.85)	0.95
Wako	3	0.83(0.76-0.89)	0.90(0.88-0.92)	0.93
Study type				
Cohort	14	0.75(0.70-0.80)	0.79(0.77-0.81)	0.85
Case-control	23	0.84(0.82-0.86)	0.82(0.81-0.83)	0.93
Reference				
EORTC/MSG	21	0.76(0.73-0.79)	0.83(0.81-0.84)	0.87
Micobiological culture	12	0.87(0.84-0.89)	0.81(0.80-0.83)	0.94
Others	4	0.92(0.86-0.96)	0.76(0.82-0.80)	0.97

neity was also existed in pooling the data, which may decrease the statistical power. Thirdly, BDG is present in numerous fungi and is therefore non-specific. However, it could probably be a helpful tool for ruling out an IFI.

6 Conclusion

Serum 1,3-β-D-glucan assay was a promising biomarker for invasive fungal infection diagnosis. However, because of the non-specificity and heterogeneity across the included studies, it should be further evaluated by high quality multicenter prospective diagnostic studies which can provided more strong evidence.

Conflict of interest: The authors report no conflicts of interest in this work.

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