Differential Diagnostic Value of Bilateral Inferior Petrosal Sinus Sampling (BIPSS) in ACTH-Dependent Cushing Syndrome: a Systematic Review and Meta-Analysis

Hao Wang (wanghaodl@126.com)
First Affiliated Hospital of Dalian Medical University https://orcid.org/0000-0002-0795-2181
Ying Ba
First Affiliated Hospital of Dalian Medical University
Qian Xing
First Affiliated Hospital of Dalian Medical University
Run-Ce Cai
First Affiliated Hospital of Dalian Medical University

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Abstract

Background: Previous studies have shown inconsistent results in the differential diagnosis obtained from bilateral inferior petrosal sinus sampling (BIPSS) in adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome. This meta-analysis evaluated the diagnostic value of BIPSS via the published literature.

Methods: This study searched PubMed, Embase, Web of Science, the Cochrane library, and the Wanfang database for published data on the differential diagnosis obtained using BIPSS in Cushing syndrome as of October 2019. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and receiver operating characteristic (ROC) curves were calculated based on the relevant data.

Results: This meta-analysis included a total of 23 studies with 1,617 patients. The calculated sensitivity, specificity, PLR, and NLR were 0.94 (95% confidence interval, CI: 0.91–0.96), 0.89 (95% CI: 0.79–0.95), 8.8 (95% CI: 4.3–17.9), and 0.07 (95% CI: 0.04–0.11), respectively. The pooled DOR and area under the ROC curve were 129 (95% CI: 48–345) and 0.97 (95% CI: 0.95–0.98), respectively.

Conclusion: This meta-analysis indicated that BIPSS had a highly diagnostic value for ACTH originally in patients with ACTH-dependent Cushing syndrome, and BIPSS should be used as a routine method to identify ACTH sources.

Keywords: Bilateral inferior petrosal sinus sampling, ACTH-dependent Cushing syndrome, Differential diagnosis , Diagnostic meta-analysis

Background

Adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome is caused by excessive secretion of ACTH in pituitary or pituitary tumors, causing bilateral adrenal hyperplasia and excessive cortisol secretion with clinical manifestations such as moon-shaped face, buffalo hump, and hypertension. The majority of ACTH-dependent Cushing syndrome is caused by ACTH tumors, (i.e., the Cushing disease, CD). Other cases have ectopic sources (i.e., ectopic ACTH syndrome, EAS). These have different therapeutic principles and prognoses. Based only on clinical manifestations, detection of cortisol levels and ACTH, high- and low-dose dexamethasone suppression tests, and imaging, these conditions are not completely distinguishable, especially in the case of EAS that progresses slowly. Studies have shown that non-functional pituitary tumors are common [1–3], suggesting that even if a pituitary tumor is revealed by magnetic resonance imaging (MRI), the tumor is not necessarily the source of the ACTH. Some ACTH-secreting tumors are small in size, and may not be revealed by MRI. Only 50–70% of them are diagnosed [4, 5]. Therefore, negative MRI does not completely exclude ACTH-secreting tumors. In high-dose dexamethasone suppression test (HDDST), most of the ACTH-secreting tumors are suppressed, and most of the EASs are unrepressed. However, a small number of patients have unpredicted presentations on HDDST [6, 7]. HDDST cannot effectively distinguish between ACTH-secreting tumors and EAS. For these reasons, more effective diagnostic approaches are needed to distinguish the two diseases.

Bilateral inferior petrosal sinus sampling (BIPSS) has been considered to be the gold standard for differential diagnosis of the above two diseases. BIPSS is an interventional method in which a blood sample from the bilateral inferior petrosal sinus and a peripheral blood sample are used to measure ACTH by calculating the lower sinus/peripheral (IPS/P) ACTH ratio and left and right inferior petrosal sinus (IPS/IPS) ACTH ratio. The IPS/P ACTH ratio is used to distinguish between CD and EAS. In general, an IPS/P ACTH ratio of ≥ 2 before a corticotrophin-releasing hormone (CRH) stimulation test and an IPS/P ACTH ratio of ≥ 3 after the CRH test are criteria for diagnosing CD [6]. The ratio of ACTH between the two sides of the IPS was used to determine the location of

pituitary microadenomas, with IPS/IPS > 1.4 indicating a tumor located at the side with higher ACTH, and IPS/IPS ≤ 1.4 indicating a tumor locating near the midline. Studies have shown that vasopressin receptor is present on the surface of ACTH-secreting tumors, and administration of vasopressin stimulates the release of ACTH [8]. Application of desmopressin (DDAVP) during BIPSS enhances diagnostic accuracy [9]. Generally speaking, although BIPSS is a mildly invasive examination, it is relatively safe. It has occasional complications including groin hematoma, cerebral hemorrhage, and vasovagal reactions (VVRs) [10–12]. However, meta-analysis of BIPSS is currently unavailable. This study performed a meta-analysis of BIPSS for the differential diagnosis of ACTH-dependent Cushing syndrome and evaluated the differential diagnostic value of BIPSS in ACTH-dependent Cushing syndrome.

Methods

Data Sources, Search Strategy, and Selection Criteria

This study strictly followed the Preferred Reporting Items for Systematic reviews and Meta- Analyses (PRISMA) guidelines [13] and used PubMed, Embase, Web of Science, Cochrane Library, and the Wanfang databases to search for studies using BIPSS for the differential diagnosis of ACTH-dependent Cushing syndrome as of October 2019. The following search terms were used: petrosal sinus sampling, bilateral inferior petrosal sinus sampling, Cushing's syndrome, Cushing disease, and ectopic Cushing syndrome. The search strategies in the various databases were as follows: PubMed: ("petrosal sinus sampling" [Mesh]) AND "Cushing's syndrome" [Mesh]); Embase: (Emtree term-exploded = Cushing's syndrome AND Abstract = petrosal sinus sampling); Web of Science: TS = (petrosal sinus sampling AND Cushing's syndrome); and Cochrane Library and WanFang: keyword = (petrosal sinus sampling AND Cushing's syndrome). During searching, keywords and free words were used simultaneously. Manual searches were also used, and relevant references included in the extracted papers were also searched.

Literature was searched by two of the authors(Hao Wang, Run Ce-Cai) independently. If there was a disagreement for inclusion or exclusion, another author(Ying Ba) became involved in resolution following discussion. The inclusion criteria of this meta-analysis were as follows: (1) patients confirmed with Cushing syndrome (CS) and unclear ACTH source; (2) CS caused by ACTH-secreting tumor or EAS confirmed by postoperative pathology or by clinical manifestations, biochemical tests, and surgery; (3) the study provided true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) or the data for the calculation of TP, FP, FN, and TN. The exclusion criteria were: (1) studies with incomplete data or data which could not be used to calculate the contingency table; (2) non-original studies; (3) repeated studies; (4) animal studies; and (5) studies with less than 20 patients included.

Data Collection and Quality Assessment

Literature search of this meta-analysis was conducted by two of the authors(Qian Xing, Ying Ba) and the extraction of relevant data was performed after discussion by these two authors. In case of disagreement, another author(Hao Wang) was involved in further discussion. Contents of data extraction in the literature included: name of the first author, year of publication, country of the study, study design (prospective and retrospective), the application of CRH or DDAVP stimulation, the application of prolactin (PRL) correction, TP, FP, FN, and TN. The quality of the included studies was evaluated by two of the authors independently using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [14, 15] according to the four aspects as follows: selection of cases, trials to be assessed, gold standard, and flowchart and progress of cases. Each of the assessments contained

seven items which were answered as “yes,” “no,” or “uncertain.” An answer of “yes” indicated that the risk offset of the study was low, and the answers of “no” and “uncertainty” indicated high risk offset of the study.

Statistical Analysis

This study used Revman 5.3 for quality evaluation and Stata 14.0 statistical software for data analysis. The TP, FP, FN, TN, sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and corresponding 95% confidence intervals (CIs) of each included study were extracted, or else we calculated the integrated sensitivity, specificity, PLR, and NLR using the bivariate random effects model [16]. The receiver operating characteristic (SROC) curve and the area under the ROC were calculated using a hierarchical regression model [17]. The Q statistic and I-square were used for heterogeneity tests. $P > 0.10$ indicated no significant heterogeneity, while $P < 0.10$ indicated significant heterogeneity for the Q statistic [18, 19]. The fixed effect model was used when the heterogeneity was low ($P > 0.05$, I-square < 50%), while the random effect model was used when the heterogeneity was high ($P < 0.05$, I-square > 50%). A meta-regression analysis of the diagnostic odds ratio (DOR) was performed according to the study design, year of publication, country of publication, application of CRH or DDAVP, application of PRL correction, and the numbers of patients included in the studies. Deek’s asymmetry test was used to evaluate whether a publication bias existed. All reported P values were two-sided, and $P < 0.05$ was considered statistically significant for pooled diagnostic parameters.

Results

As shown in Fig. 1 describing the literature searches and the workflow for study inclusion, there were 822 articles in the initial search, but 256 of them were found to be duplicated and were removed from further analysis. In addition, a total of 472 articles included irrelevant research articles, reviews, commentaries, editorials, and letters, which were further removed. Of the remaining 94 articles, those that contained incomplete data, replicated research, no gold standard, incomplete research descriptions, or less than 20 patients were also removed. Thus, a total of 23 studies were included in this meta-analysis [3, 6, 10, 22–41].

Table 1 shows the characteristics of the included studies which were published in 1991–2019, including 11 studies conducted in Europe, nine studies conducted in the United States or Brazil, and 3 studies conducted in China or India. There were 3 prospective studies and 20 retrospective studies included in this meta-analysis. Figure 2 shows the quality of the included studies in this meta-analysis.

The summary results for sensitivity and specificity are presented in Fig. 3. The pooled sensitivity was 0.94 (95% CI: 0.91–0.96), the specificity was 0.89 (95% CI: 0.79–0.95), the PLR was 8.8 (95% CI: 4.3–17.9), and the NLR was 0.07 (95% CI: 0.04–0.11). The DOR of further integration of BIPSS on ACTH–dependent Cushing syndrome was 129 (95% CI: 48–345; Fig. 4). Lastly, the summary area under the ROC curve was 0.97 (95% CI: 0.95–0.98; Fig. 5), and the results of the DOR forest map for heterogeneity testing were $P = 0.00$, I-square = 99.35. A meta-regression analysis was performed based on the study design (prospective or retrospective), year of publication, country of publication, size(patients enrolled 21–100,100–200,≥200),ethnic, application of CRH or DDAVP, and application of PRL correction (Fig. 6). The results suggested that the research design was the main cause of heterogeneity. Deek’s asymmetry test was used to detect the presence of publication bias, and the results indicated a publication bias ($P = 0.01$; Fig. 7).

Table 1
Characteristics of the included studies

author	year	country	design	Method (stimulation)	PRL adjust	Gold Standard	TP	FP	FN	TN
Oldfield EH	1991	USA	pro	CRH	No	Pathology	203	0	0	17
Findling JW	1991	USA	pro	CRH	No	Pathology	18	3	2	6
Kaltsas GA	1999	UK	retro	CRH	No	Pathology	50	0	19	6
Invitti C	1999	Italy	retro	DDAVP	No	Pathology	65	0	11	9
Bonelli FS	2000	USA	retro	CRH	No	Pathology	71	1	6	9
Wiggam MI	2000	Northen Ireland	retro	CRH	No	Pathology	36	0	8	1
Colao A	2001	Italy	retro	CRH	No	Pathology	60	0	8	10
Lefournier V	2003	France	retro	CRH	No	Pathology	65	2	4	6
Swearingen B	2004	USA	retro	CRH	Yes	Pathology	70	2	9	2
Liu C	2004	USA	retro	CRH	No	Pathology	39	0	3	9
Kaskarelis LS	2006	Greece	retro	CRH	No	Pathology	40	3	6	5
Machado MC	2006	Brazil	retro	CRH	No	Pathology	46	0	1	5
Castinetti F	2007	France	retro	DDAVP	Yes	Pathology	32	0	4	7
Tsagarakis S	2007	Greece	retro	CRH	No	Pathology	46	0	1	7
Shi XH	2011	China	retro	No	No	Pathology	58	1	10	4
Mulligan GB	2011	USA	retro	CRH	No	Pathology	33	1	2	1
Andereggen L	2011	Switzerland	retro	CRH	No	Pathology	19	1	1	2
Sharma ST	2011	USA	retro	No	No	Pathology	16	1	1	7
Shetch SA	2012	USA	retro	CRH	Yes	Pathology	195	5	12	5
Grant P	2012	UK	retro	DDAVP	No	Pathology	72	1	0	10
Zhou WW	2016	China	pro	No	No	Pathology	84	1	3	5
Jarial KDS	2018	India	pro	CRH	No	Pathology	26	0	0	2
Pereria CA	2019	Portugal	retro	No	No	Pathology	27	0	1	2

Discussion

This study was the first meta-analysis to evaluate the differential diagnostic value of BIPSS in ACTH-dependent Cushing syndrome. It included a total of 23 studies and 1,617 patients. Our results suggested that the sensitivity and specificity of BIPSS to pituitary or ectopic ACTH were 94% and 89%, respectively, indicating a high value of BIPSS for the differential diagnosis of ACTH-dependent Cushing syndrome. In addition, the DOR value was high, suggesting that BIPSS could effectively identify the ACTH source. The area under the SROC curve was 0.97, suggesting that the overall diagnostic performance of BIPSS was good.

BIPSS has typical clinical and biochemical performances in CS but unclear value in the differential diagnosis of ACTH source. Because BIPSS does not identify ACTH source from a morphological perspective but from a functional perspective, this diagnostic approach is accurate, with relatively high sensitivity and specificity. CD accounts for a large proportion of ACTH-dependent Cushing syndrome, and BIPSS is particularly suitable for patients with negative MRI results. BIPSS provides an important basis for guiding the surgical treatment of the disease.

BIPSS has a high differential diagnostic value for CD and EAS. Application of CRH or DDVAP stimulation enhances the sensitivity and specificity of BIPSS. However, BIPSS should still be combined with other diagnostic methods, such as imaging, HDDST, and low-dose dexamethasone suppression test (LDDST) for comprehensive diagnosis.

False negative results can occur in BIPSS, which have been reported to be approximately 10% [28] and may be related to operational failure or abnormal venous drainage from the inferior petrosal sinus. BIPSS is not ideal for identifying the diseased side [27, 42], which may be due to the presence of branches joined to the cavernous sinus and frequent contralateral venous return. A previous study used cavernous sinus sampling instead of BIPSS to obtain a good differential diagnosis for CD and EAS [43]. For BIPSS, the success rate is closely related to the operator's technique and experience, and accurate catheterization is very important. Results of a previous study suggest that PRL for correction improves the success rate of catheterization [44].

This meta-analysis provides implications for future studies as follows: PRL can be used as a reference to improve the accuracy of catheterization during BIPSS. CRH or DDAVP stimulation should be used during BIPSS to improve the sensitivity and specificity.

The strengths of this study were that we followed a standard protocol and used a comprehensive search strategy. Furthermore, the bivariate random effects model and hierarchical summary ROC analyses were used. Finally, the meta-regression analysis suggested that the source of heterogeneity was mainly in the experimental design.

However, our meta-analysis also had some limitations. First, some details of patient characteristics were not available, which might affect the diagnostic value of BIPSS. Second, the analysis used summarized data, which restricted us from conducting more detailed analysis. Finally, the publication bias of this meta-analysis was $P < 0.05$, suggesting the presence of publication bias. The possible reasons for this were that (1) BIPSS had high diagnostic accuracy of TP and TN for the ACTH source and might likely show the ideal statistical results in the software, leading to the calculation of publication bias; (2) authors might have submitted studies only with positive results to increase the chance of being published; and (3) this meta-analysis included studies published only in Chinese and English but no other languages.

This study was the first meta-analysis to evaluate BIPSS effects on determination of the etiology of ACTH-dependent Cushing syndrome, suggesting that BIPSS had a great differential diagnostic value for the ACTH source.

Results of this study require further large-scale prospective studies to validate the differential diagnostic value of BIPSS for ACTH sources in different patients.

Conclusion:

This meta-analysis indicated that BIPSS had a highly diagnostic value for patients with ACTH-dependent Cushing syndrome, and BIPSS should be used as a routine method to identify ACTH sources. CRH or DDAVP stimulation should be used during BIPSS to improve the sensitivity and specificity.

Declarations

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Availability of data and materials

Not applicable. This study is a systematic review and we used primary data, which are already publicly available.

Authors' contributions

HW conceived and designed the study and approved the final draft of the manuscript submitted for review and publication; YB, QX and RCC searched databases, data extracted and study selection. HW performed data analysis. HW,YB,QX,RCC wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

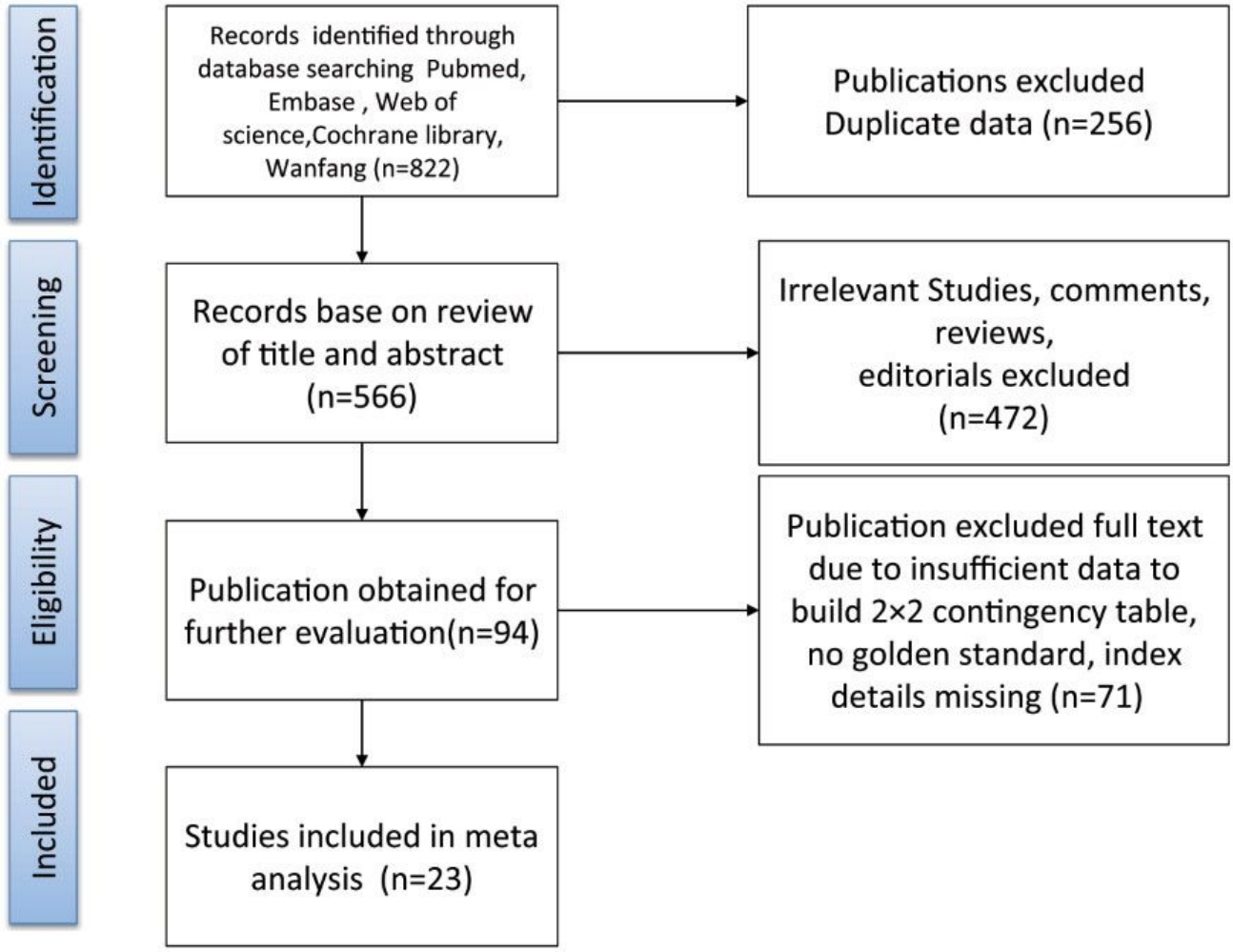

Figure 1

Retrieval flowchart to obtain study data for meta-analysis

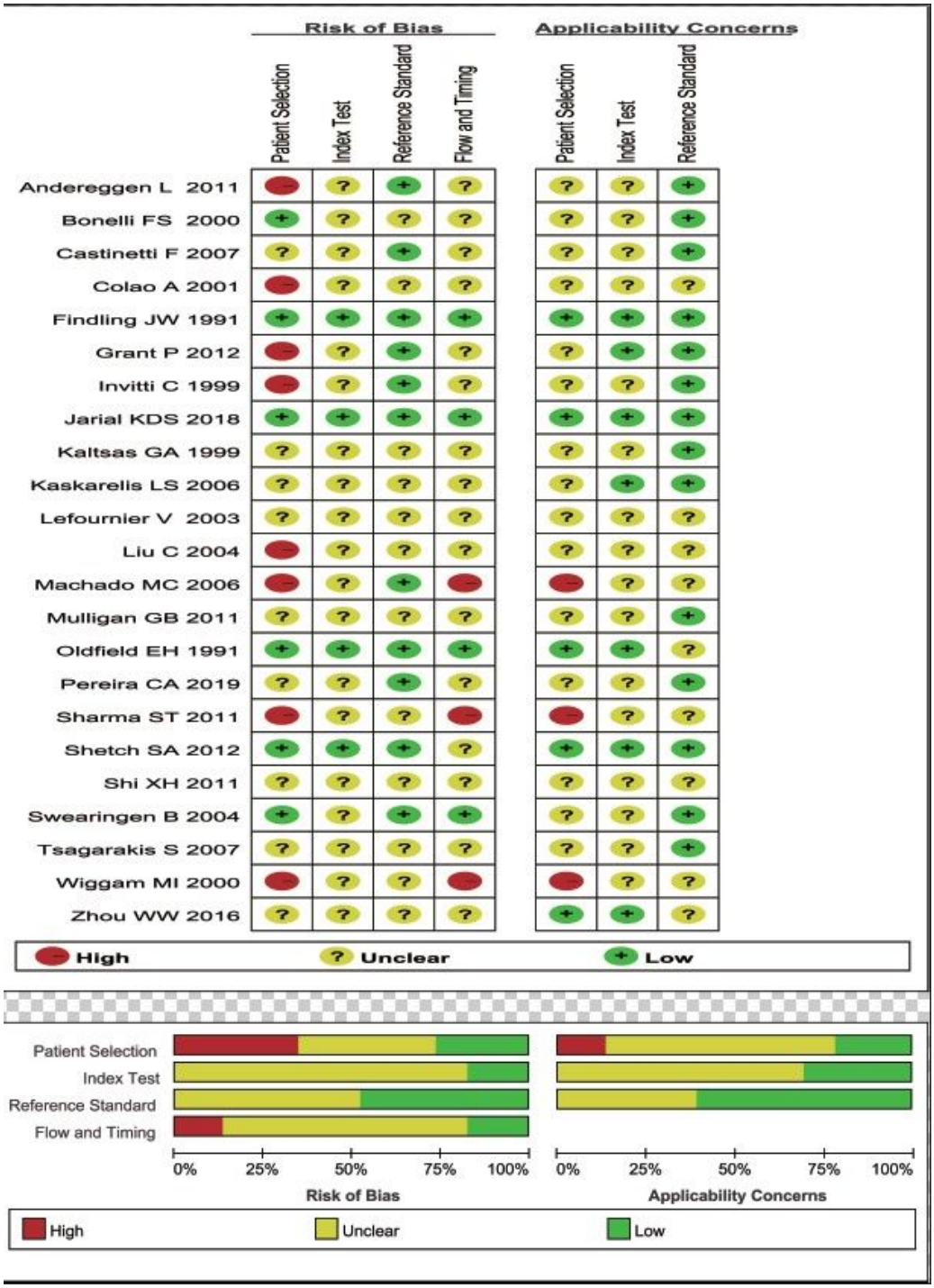

Figure 2

Quality assessments for the included studies

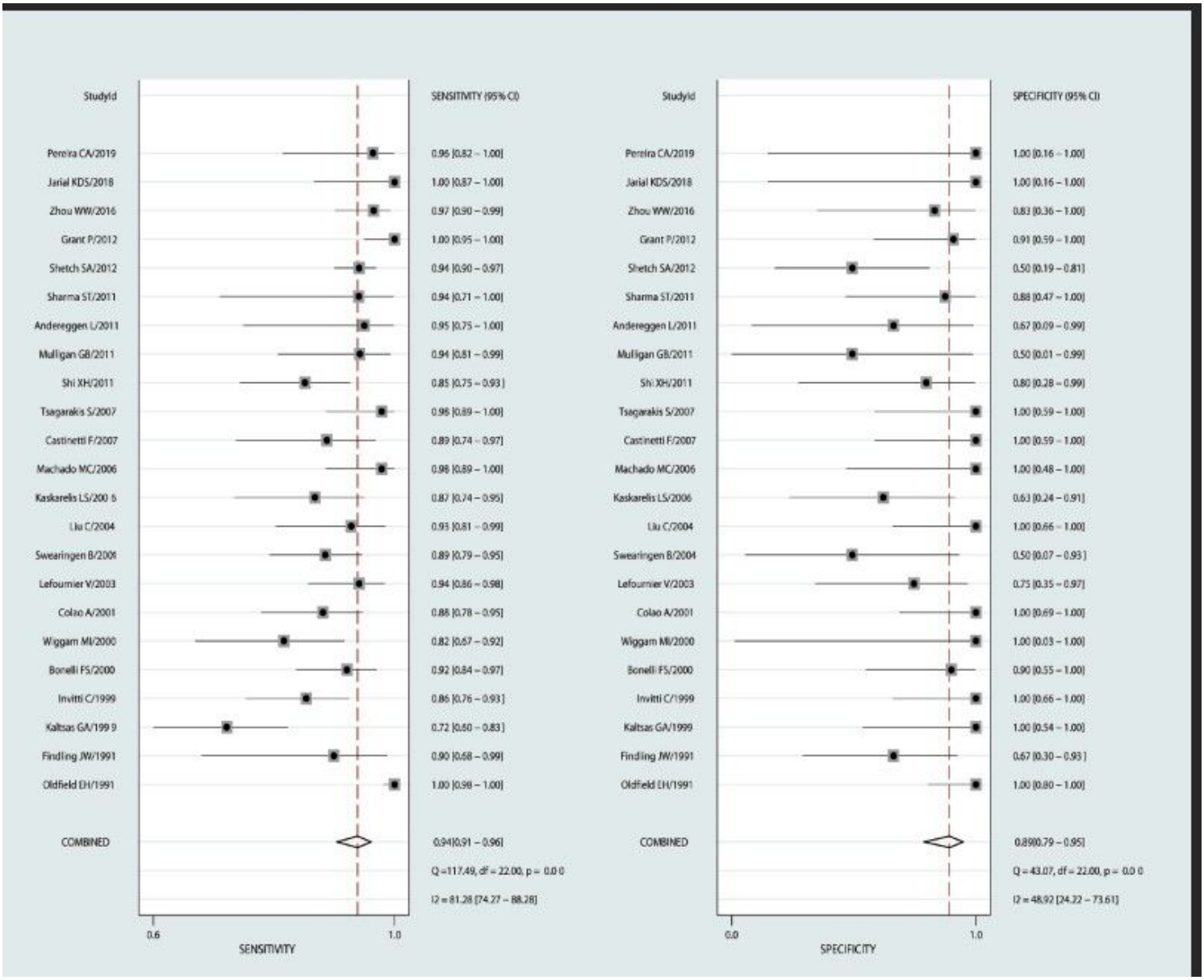

Figure 3

Forest plot for sensitivity and specificity

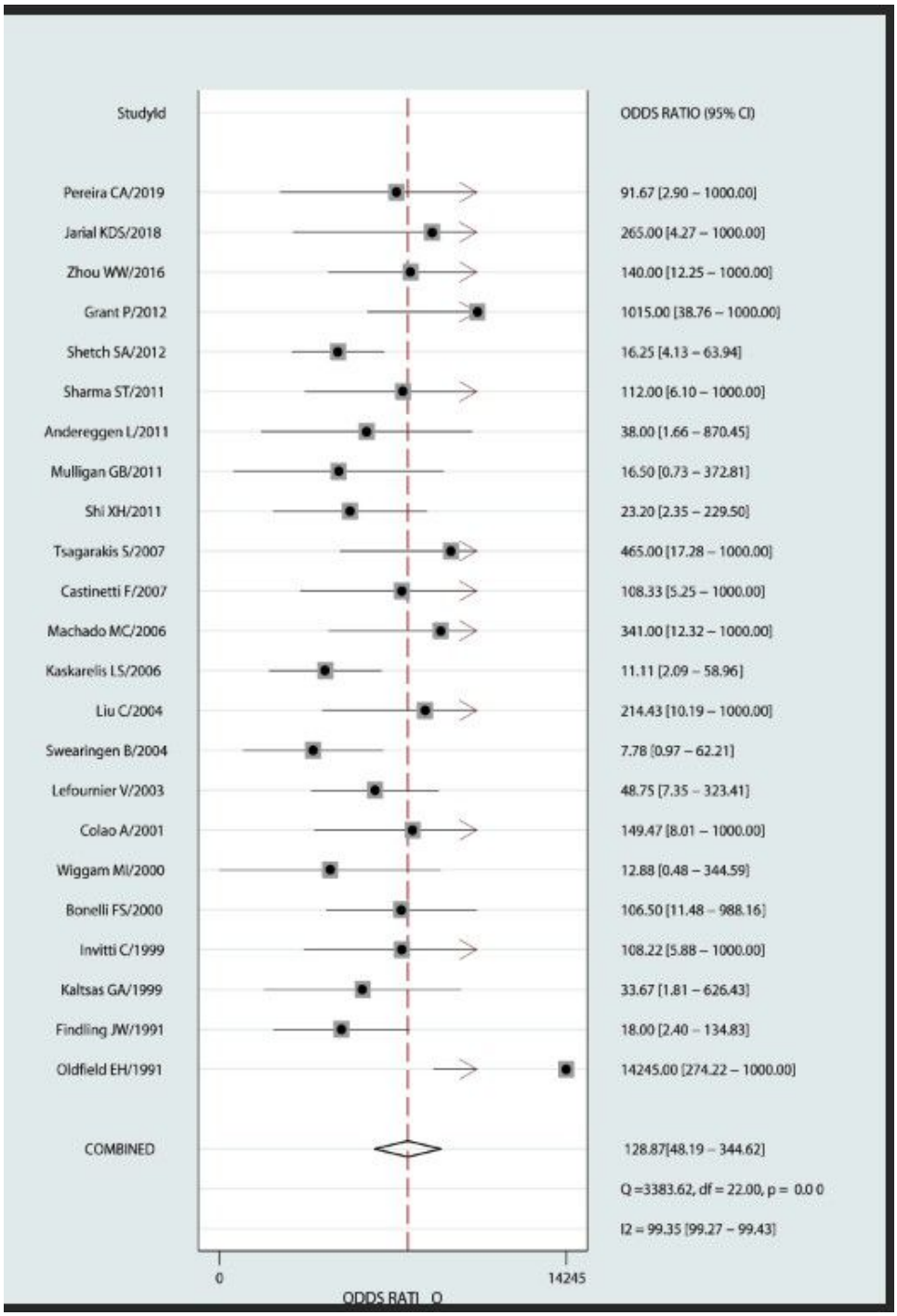

Figure 4

Forest plot for DOR

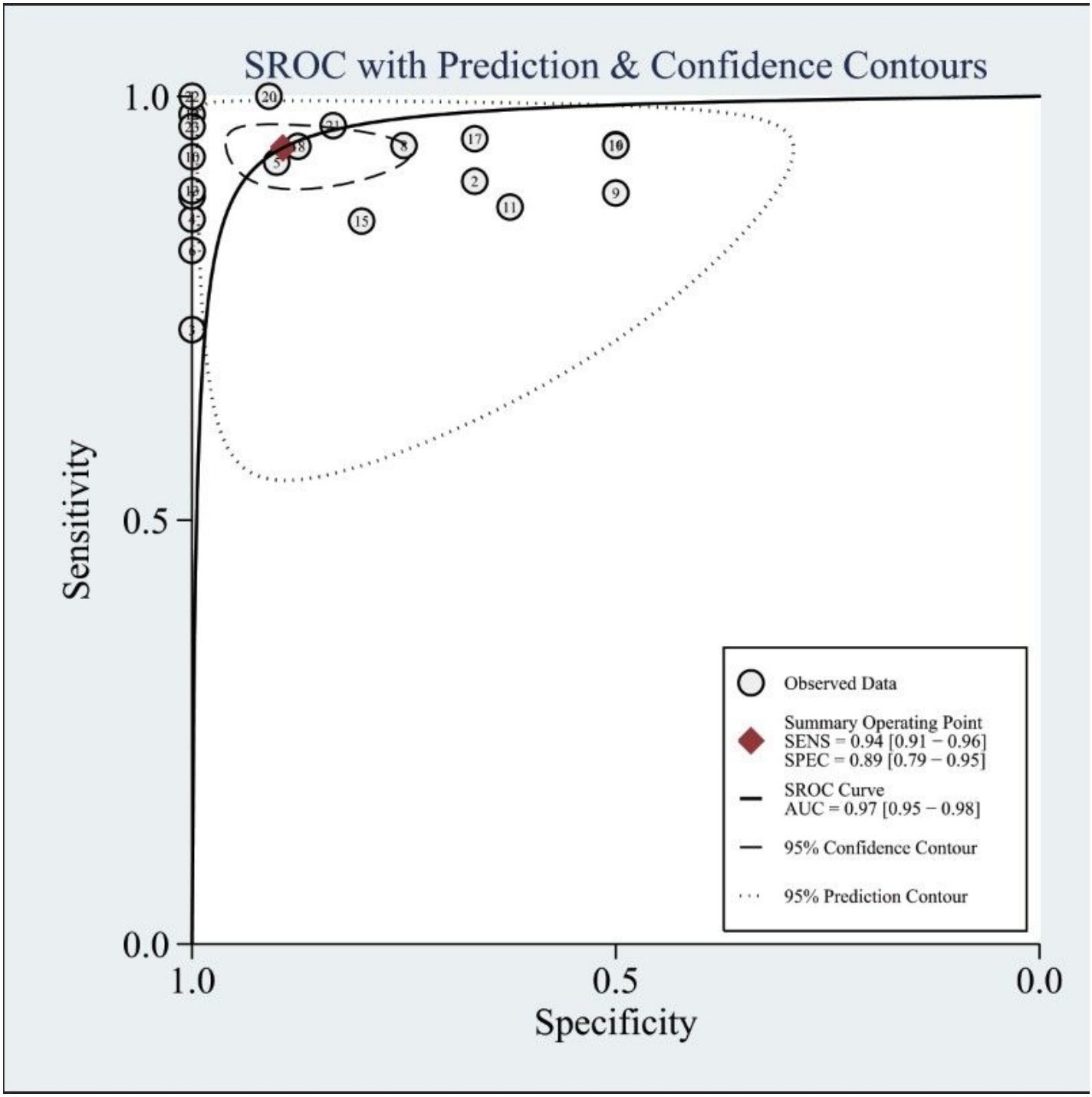

Figure 5

Area under the ROC curve

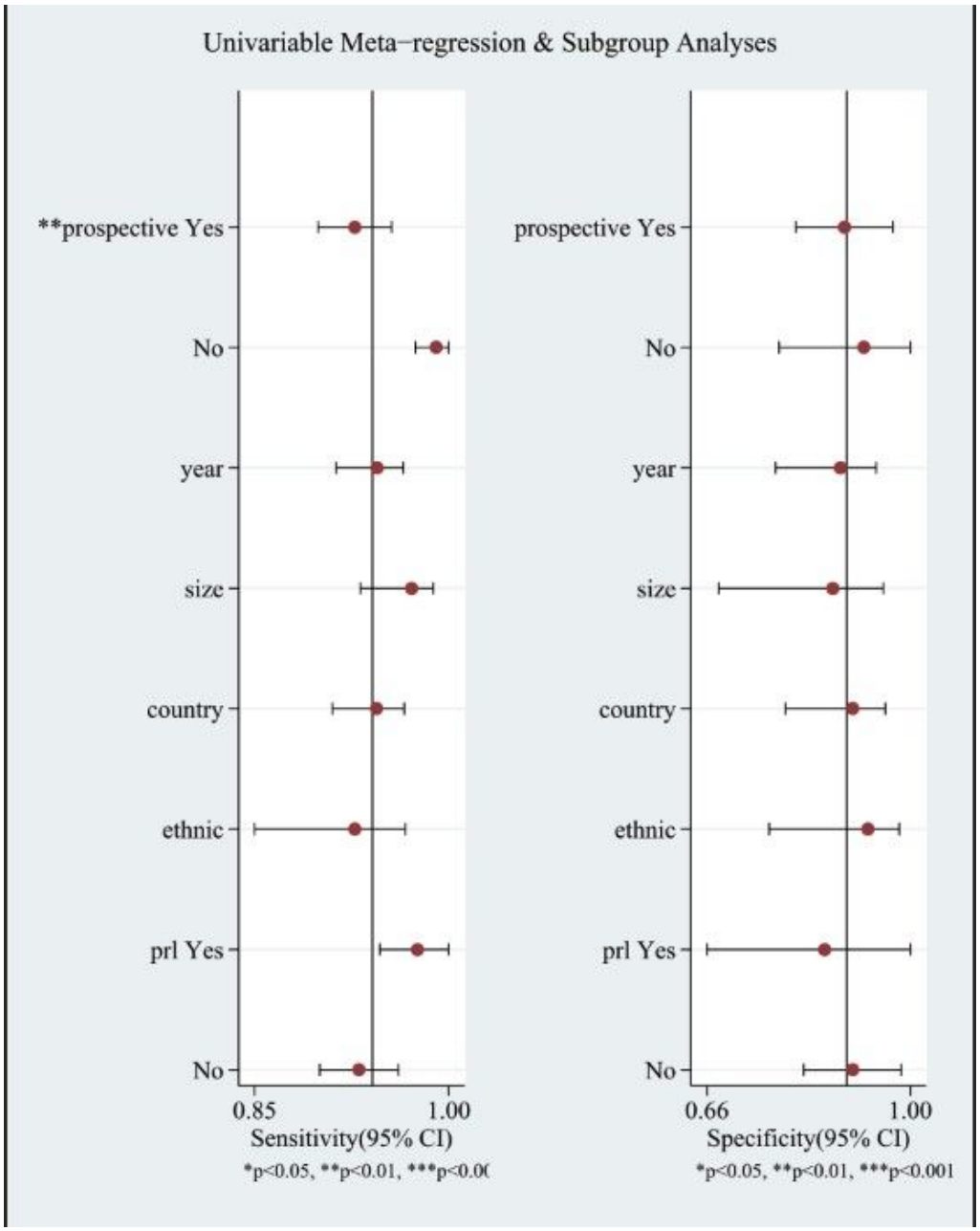

Figure 6

Meta-regression analysis for DOR

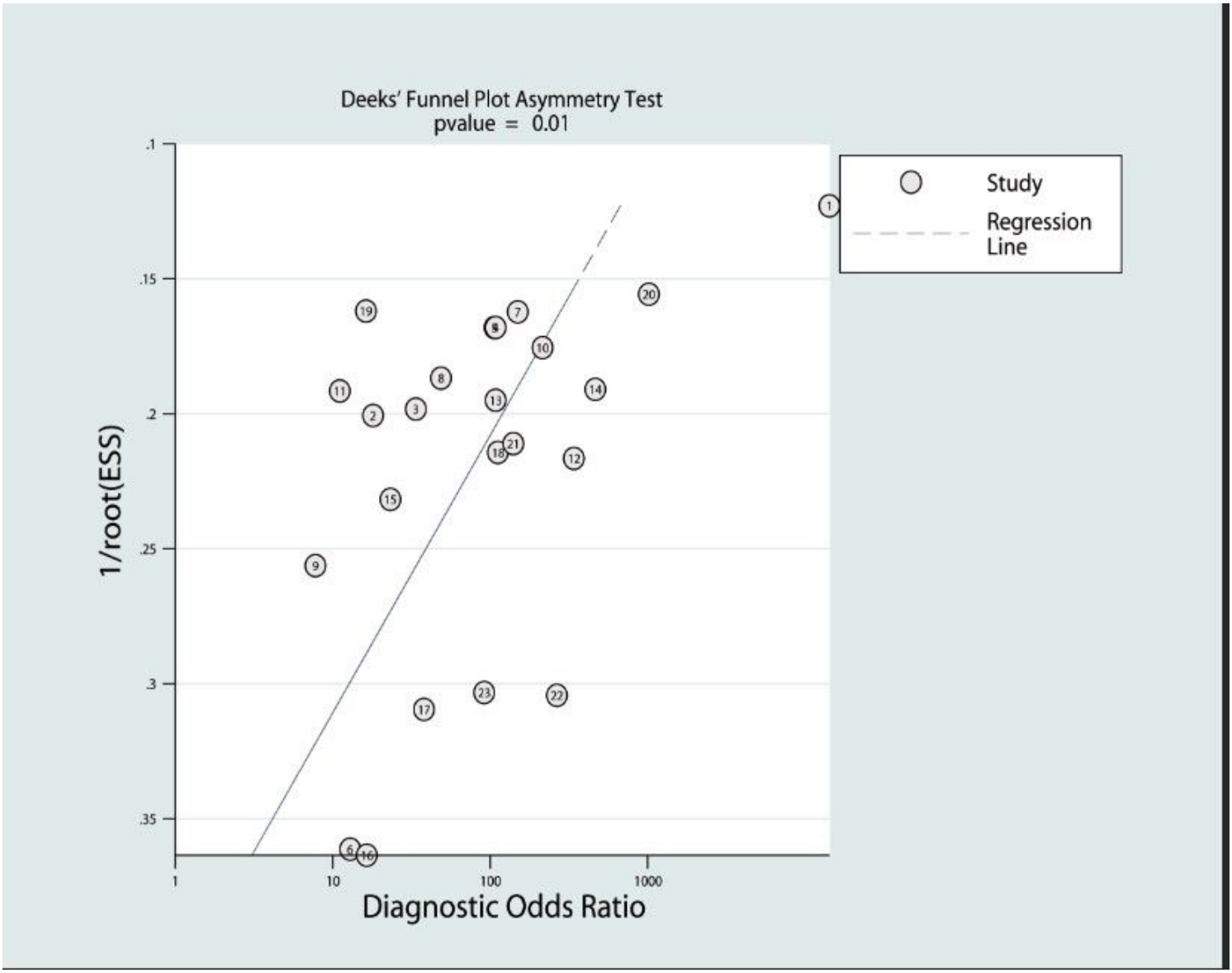

Figure 7

Deek's plot for BIPSS in the differential diagnosis of ACTH-dependent CS

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009Checklist.doc