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Diagnostic accuracy of serum human epididymis protein 4 in ovarian cancer patients with different ethnic groups and menopausal status: a meta-analysis and systematic evaluation

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ABSTRACT

Objectives: We aimed to analyze and evaluate the diagnostic value of serum human epididymis protein 4 (HE4) in ovarian cancer (OC) of patients with different menopausal status.

Material and methods: A comprehensive electronic and manual search of the relevant literature was performed through several databases such as CNKI, Wanfang database, VIP database, Chinese biomedical database, web of science, PubMed, EMBASE, and Cochrane database. We collected Chinese and English articles to

assess the diagnostic value of HE4 for ovarian cancer in female with different menopausal status. The quality of the studies included in the systematic review was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

Results: A total of 14 publications were included in this study and we didn't find publication bias in them. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of HE4 for the diagnosis of ovarian cancer in postmenopausal vs. premenopausal female were 0.71 (95% CI, 0.63–0.78) vs 0.78 (95% CI, 0.74–0.81); 0.91 (95% CI, 0.85–0.95) vs 0.90 (95% CI, 0.86–0.93); 11.90 (95% CI, 6.42–22.07) vs 11.03 (95% CI, 6.44–18.89); and 0.30 (95% CI, 0.22–0.39) vs 0.24 (95% CI, 0.20–0.29), respectively.

Conclusions: Serum HE4 has greater diagnostic value in detecting ovarian cancer, especially in Asian postmenopausal female.

Key words: ovarian cancer; meta-analysis; HE4; tumor markers; diagnosis

INTRODUCTION

Ovarian cancer (OC) is one of the most common malignant tumors in female. Its mortality rate accounts for 5% in female cancers. The five-year survival rate for patients with advanced ovarian cancer is only 22-30%. Over the past 30 years, the survival rate of ovarian cancer patients has not been significantly improved and accompanied with ethnic difference [1]. At the same time, there were significant racial differences in incidence, 5-year survival, mortality, early diagnosis and susceptibility of OC [2]. Thus, the diagnosis of ovarian cancer cannot be generalized, and the strategy with the best sensitivity should be selected according to different ethnic and population distributions.

Unlike other biomarkers, the expression of human epididymal protein 4 (HE4) is tissue-specific due to the specific expression of WAP four-disulfide core domain 2

(WFDC2) in ovarian carcinoma , especially in serous and endometrioid cancers [3]. HE4 is a serine protease inhibitor containing 124 amino acids (20–25 kDa) of the WFDC domain protein family [4]. It can interact with a variety of proteins, including MUC16 (CA-125) and other WFDC members, such as SPINT4 (Serine peptidase inhibitor, Kunitz type 4). Importantly, HE4 overexpression has been found to be associated with ovarian cancer [5]. EOC is driven by ERK/mitogen-activated protein kinase (MAPK), hypoxia-inducible factor 1α (HIF1α) and matrix metalloproteinases [6].

Several studies have shown that HE4 has high sensitivity and specificity for diagnosing ovarian cancer, and that HE4 shows greater advantages over other biomarkers in diagnosing ovarian cancer alone. However HE4 level is greatly affected by age, and the age of menopause in female of different countries or ethnic groups is also greatly affected by many aspects such as parity, hormones, living environment and lifestyle [7]. Although many studies have included HE4 as a promising tumor marker in the detection of ovarian cancer, NCCN and ESMO/ESGO practice guidelines do not recommend the use of HE4 due to conflicting results from studies across countries [8]. Therefore, it is necessary to explore the applicability of race and menopausal status to HE4 in order to maximize the feasibility of it in the diagnosis of ovarian cancer.

MATERIAL AND METHODS

We performed a meta-analysis of data from multiple studies in the present study to systematically offer a comprehensive update on the feasibility of serum HE4 in the diagnosis of ovarian cancer female of different ethnic groups and menopausal status.

Search Strategy

In this study, two researchers independently searched all Chinese and English articles published from January 2011 to August 2021 on ovarian cancer with serum HE4 diagnosis. The databases were as follows: CNKI, Wanfang database, VIP database, Chinese biomedical database, web of science, PubMed, EMBASE, Cochrane. Index words were as follows: Ovarian Neoplasms, Ovarian Cancer, Human epididymal protein 4, Human epididymal protein secreted 4, HE4, and WFDC2. The search strategy is as follows: [Human epididymal protein 4 (Title/Abstract)] or [Human epididymal protein 4 (Title/Abstract)] or [WFDC2 (Title/Abstract)] or [HE4 (Title/Abstract)] and [Neoplasm, Ovarian (Title/Abstract)] or [Ovarian Neoplasms (Title/Abstract)] or [Ovarian Neoplasms (Title/abstract)] or [Neoplasm, Ovarian (Title/Abstract)] or [Neoplasm, Ovary (Title/Abstract)] or [Ovary Neoplasm (Title/Abstract)] or [Neoplasm, Ovarian (Title/Abstract)] or [Ovary Cancer (Title/Abstract)] or [Cancer, Ovary (Title/Abstract)] or [Cancers, Ovary (Title/Abstract)] or [Ovarian Cancers (Title/Abstract)] or [Ovarian Cancer (Title/Abstract)] or [Cancer, Ovary (Title/Abstract)] or [Cancers, Ovarian (Title/Abstract)] or [Ovarian Cancers (Title/Abstract)] or [Cancer of Ovarian (Title/Abstract)] or [cancer of the Ovarian (Title/Abstract)] or [Ovarian NeoplasmsTerms (Mesh)] and [predictive value *(Title/Abstract) or sensitivity and specificity (MeSH)] or [title (predictive/Abstract) and value* (Term/Abstract) accuracy* (Title/Abstract)].

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) a case group of patients with definitive pathological diagnosis of primary ovarian cancer and a control group of women with pathologically confirmed benign gynaecological disease and/or healthy women. This pathological examination of biopsy specimens represents the diagnostic gold standard

in accordance with the International Federation of Gynecology and Obstetrics guidelines; (2) Clinical diagnostic tests for serum HE4 and ovarian cancer included all study types (retrospective studies were not excluded); (3) The study subjects included patients with ovarian cancer, benign pelvic diseases or healthy female; (4) Specimen collection was collected from the investigators before surgery or cytotoxic therapy; (5) The statistical method was correct, the study data were reliable, and four key clinical parameters (the number of true positive, false positive, true negative and false negative cases) could be extracted; (6) The diagnostic cutoff value was described; (7) The source and detection method of the reagent were clear; (8) The article was published in Chinese and English; (9) The study population was greater than or equal to 20 patients.

Exclusion criteria were as follows: (1) editorials, case reports, letter, reviews or studies without complete data; (2) sensitivity and specificity were not reported or could not be calculated; (3) duplicate publications; (4) no description of histopathological diagnosis in all or part of the study population; (5) the study population had recurrent ovarian cancer or had received cytotoxic therapy; (6) the study objectives were not consistent with this experiment.

Data extraction

All of the literature was independently selected by two reviewers based on the inclusion and exclusion criteria. They then extracted the following information from the related studies: year of publication, author, country of origin, sample size, assay methods, cut-off values, and data regarding true positive (TP), false positive (FP), false negative (FN) and true negative (TN) rates with histology as the gold standard.

The disagreements of study's eligibility were resolved by full-text review and discussion. And if the two reviewers could not reach a consensus, a third reviewer would be consulted.

Quality evaluation of included studies

The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of all studies and the potential for bias. The tool consists of two parts: the risks of bias and concerns regarding applicability. The risks of bias were evaluated from four parts: patient selection, reference standard, index test, flow and timing. The concerns of applicability were assessed in three domains: patient selection, index test, and reference standard. If a study was judged as"low" on all domains, it meant an overall judgement of "low risk of bias" or "low concern regarding applicability". Else, if it was evaluated as "high" or "unclear" in one or more domains, it would be judged as having be judge regarding applicability" or "risk of bias". This process was performed using Review Manager 5 (http://ims.cochrane.org/revman/download). As is shown in Figure 1.

Statistical Analysis

The statistical analysis was performed using STATA 16.0 software (STATA Corp LCC, College Station, TX, USA). We extracted the number of participants with a TP, FP, FN or TN from each study and then calculated the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and corresponding 95% confidence intervals (95% CI). Also, we constructed the forest plots of accuracy indexes. In order to describe the relationship between specificity and test sensitivity, we constructed a summary receiver operating characteristic (SROC) curve based on the TP and FP rates. The closer the area under the curve (AUC) close to 1, the better diagnostic performance of urine HE4 was.

The threshold effect was an important cause of heterogeneity in diagnostic testing which could be confirmed by the Spearman correlation coefficient and probability (P) value between the logistic regression of sensitivity and 1–specificity. Q and I^2 tests were used to assess the heterogeneity caused by non-threshold effects. $P < 0.10$ for the Q test or an I^2 value greater than 50% indicated a substantial heterogeneity. Then the random effects model could be applied. Else, we would use a fixed effects model. The function of potential sources of between-study heterogeneity was to explore the subgroup and sensitivity analyses. Deeks' funnel plots were used to assess potential publication bias with STATA 16.0 software. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

Screening results

The results of the study selection process are shown in Table 1. We obtained 4343 articles from the initial electronic search. After excluding 1457 duplicates, we excluded 135 articles published due to publishing before 2011. Based on the article title and abstract, researchers removed 1336 articles in the categories of conference, review, and case reports, 39 in the categories of animal experiments, and 1315 articles incompatible with this study. Subsequently, the remaining 61 articles were read in full, and 41 articles in total were excluded, including inconsistent content, incorrect experimental statistical methods, incomplete data and failure to obtain the full text. Finally, a total of 14 studies were included in the final analysis.

Characteristics and quality assessment of included studies

In this meta-analysis, 14 diagnostic studies consisted of a total of 1191 patients with ovarian cancer and 3148 patients in the control group (patients with non-malignant

gynecological tumors or healthy female). In addition, eight Asian studies (China, Korea, Vietnam, Iran) [7, 9–14] and six non-Asian studies (Italy, Sweden, Poland, Ireland, Brazil) were included (Tab. 2) [15–21]. All patients with ovarian cancer were diagnosed with postoperative histopathology. All studies were published between 2011 and 2021, with sample sizes ranging from 92 to 832 individuals. Serum HE4 levels were measured in these studies using different assays, such as: chemiluminescent microparticle immunoassay (CMIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA). We assessed the quality of 14 articles by using the QUADAS-2 tool. According to the results of methodological assessment, the quality of all included articles was acceptable. Characteristics of the included studies and details of the methodological assessment are shown in Table 3.

Diagnostic accuracy

The between-study variability (i.e., heterogeneity) was high for both sensitivity (I^2 = 72.07%) and specificity (I^2 = 90.07%). It suggested a high levels of heterogeneity in the 14 studies. So, we applied the random effects model. The major cause of heterogeneity was the threshold effect. In the meta-analysis, the SROC curve showed the distribution of each study was not “shoulder-arm”, revealing that the heterogeneity was caused by other factors and the threshold effect was not significant. In conclusion, the pooled sensitivity and specificity were 0.76 (95% CI, 0.71–0.80) and 0.92 (95% CI, 0.88–0.94), respectively (Fig. 3a) after employing the random-effects model. Moreover, the pooled PLR was 11.59 (95% CI, 7.12–18.87), the NLR was 0.25 (95% CI, 0.20–0.31) (Fig. 3b), the DOR was 46.88 (95% CI, 24.86–88.42) (Fig. 3c), and the AUC of the SROC was 0.90 (95% CI, 0.87–0.92) (Fig. 3d). These results showed that serum HE4 may serve as an effective marker for the diagnosis of ovarian cancer.

Analysis

Considering the difference in the distribution of ovarian cancer and the change of serum HE4 level in different populations, we performed analysis according to the patient's ethnicity and menopausal status to further explore its clinical value in the diagnosis of ovarian cancer and the best applicable population (Tab. 1). The results of the analysis of pre-menopausal female showed that the pooled sensitivity of serum HE4 for the diagnosis of ovarian cancer was 0.71 (95% CI, 0.63–0.78) and the specificity was 0.91 (95% CI, 0.85–0.95) (Fig. 4a). Pooled sensitivity in postmenopausal female was 0.78 (95% CI, 0.74–0.81) and specificity was 0.90 (95% CI, 0.86–0.93) (Fig. 4b). The sensitivity of HE4 in diagnosing premenopausal ovarian cancer patients was slightly lower than that in postmenopausal patients, while the specificity was slightly higher. As is shown in the Figure 5, the results of analysis in different geographical populations showed that the pooled sensitivity was 0.76 (95% CI, 0.68–0.83) and the specificity was 0.93 (95% CI, 0.91–0.95) in Asian populations. The pooled sensitivity was 0.77 (95% CI, 0.72–0.81) and the specificity was 0.90 (95% CI, 0.83–0.95) in the non-Asian population. Compared with European and American patients, Asian patients had slightly lower sensitivity and slightly higher specificity.

Sensitivity analysis and publication bias

A single study included in this meta-analysis was evaluated each time to determine the effect of the individual data set on the specificity and sensitivity. The results showed that the study by Bandiera, Zhang, Lycke, Kim, McKendry et al. had a vital impact on the results of this experiment (Fig. 6). Subsequently, the above six articles were excluded and tested for diagnostic accuracy again. The sensitivity and specificity of HE4 in the diagnosis of ovarian cancer were 0.76 (95% CI, 0.71–0.80) and 0.92 (95% CI, 0.88–0.94), respectively. Compared with the precious results, the

sensitivity and specificity of HE4 in the diagnosis of ovarian cancer were slightly increased. We conducted Deeks' funnel plot asymmetry test regarding publication bias. A significant publication bias ($p = 0.29$) was found in the pooled analysis of these studies (Fig. 7).

DISCUSSION

In this study, we conducted a systematic review to evaluate the accuracy and feasibility of serum HE4 as a biomarker for the diagnosis of ovarian cancer in populations of different ethnicities and menopausal status and to explore the best applicable population. At present, there are few studies on the ethnic aspects of OC, and to our knowledge, the first meta-analysis discusses the diagnostic value of HE4 for OC considering both the menopausal status of patients and ethnic factors. Serum HE4 expression was elevated in 76% of patients with ovarian cancer and was not abnormal in 92% of patients without ovarian cancer. Based on DOR (46.88), PLR (11.59), NLR (0.25) and other indicators, the probability of preoperative diagnosis of ovarian cancer is greatly increased if serum HE4 detection exceeds the normal level. After compared sensitivity (0.71 vs 0.78), specificity (0.91 vs 0.90), DOR (40.32 vs 46.14), PLR (11.90 vs 11.03), NLR (0.3 vs 0.24) between premenopausal and postmenopausal HE4 in the diagnosis of ovarian cancer, we found that HE4 is more helpful to the diagnosis of ovarian cancer in postmenopausal women but more sensitive to premenopausal women. Meanwhile, by further exploring the ethnicity, we discovered that serum HE4 may be more suitable for the diagnosis and screening of ovarian cancer in Asian female and the effect is close to the gold standard. Therefore, serum HE4 seems to be more suitable for the diagnosis of ovarian cancer in Asian postmenopausal female, and the conclusion was confirmed by Yu et al.'s study, which fully demonstrated that although serum HE4 has a high diagnostic value in the diagnosis of OC, it varies because of ethnicity and menopausal status [22].

Among the risk factors for ovarian cancer, parity, tubal ligation, and talc use are significantly and well recognized among ethnic differences, but the risk of hysterectomy is controversial. A meta-analysis showed an inverse association between hysterectomy and EOC risk in studies conducted before 2000, while a positive association was observed after 2000, suggesting that temporal transfer may have occurred for this association [23]. Peres et al. found that part of the reason for this shift may be a change in the pattern of hormone therapy usage [24]. Subsequently, their findings were supported in a study based on big data. It showed that differences in risk factors among ethnic groups do not fully explain ethnic differences in OC incidence. In the studies on high-permeability susceptibility genes, ethnic differences in *BRCA1* or *BRCA2* mutations have been found with a probability of 7% in white European female and 5% in Asian female [25]. In terms of genetic polymorphisms, the NFKB1-94 ins/delATTG polymorphism was significantly associated with the reduced risk of Asian populations(including OC), but with an increased risk of cancer in Caucasian populations [26]. At the same time, there are also ethnic differences in MTHFR gene polymorphisms, and they are strongly associated with the development of ovarian cancer [27]. Although the Kras3'-untranslated region Rs 61764370 polymorphism cannot be used to assess ovarian cancer in whites, it is unknown whether it can be used in other populations [28]. It is concluded that environmental and ethnic differences in gene expression may be one of the reasons for the differential expression of HE4 in ovarian cancer in different populations.

However, in OC patients with different age status and different regions, the selection of cut-off value of HE4 is affected. Bolster et al found in a NOBIDA Biobank sample that age was the main determinant of HE4 in healthy subjects, up 37% at 60 (compared with 20) and 101% at 80 [29]. In the study of Mokhtar, it was identified that in addition to age factors, there were significant differences in HE4 concentration between different ethnic groups (Malay and Indian), and the HE4 level of Indian was higher than that of Malay ($p < 0.05$) [30]. However, Gasiorowska

obtained the cut-off value of Post-menopausal HE4 in Polish population (93 pmol/L) significantly higher than Asian population (69 pmol/L) [30, 31]. According to well established methods, Lowe et al. [32] found an increased risk of ovarian cancer in healthy post-menopausal female by measuring their serum HE4 levels. In addition, several studies had demonstrated that HE4 was influenced by many factors, such as age, ethnicity, menstrual cycle, body mass index, tobacco, hormones, and coffee [35]. HE4 levels also appeared to increase with age, and this dependence is nonlinear. At the same time, the division of age at menopause varies greatly between ethnicities [29, 34]. In view of the above factors, it is very necessary to adjust the level of HE4 diagnosis according to age and ethnicity in order to be more accurately applied to the detection of ovarian cancer.

Recent studies have found that HE4 may be enriched through MAPK, steroid biosynthesis, cell cycle, p53 hypoxia pathway, focal adhesion, ECM receptor interaction, and cell adhesion molecule (CAM) pathways [35]. Overexpression of recruited HE4 enhances ovarian cancer proliferation, invasion, and metastasis in part through the interaction of annexin A2 [36], or participates in cell adhesion, migration, and tumor growth by activating the EGFR-MAPK signaling pathway in ovarian cancer cells [18]. Vitro studies have shown that HE4 promotes proliferation by participating in cell cycle regulation [37]. In addition, compared with the control group, HE4 gene knockout had a significant inhibitory effect on ovarian tumor growth in nude mice [38]. Thus, HE4 may play a role in the whole course of ovarian cancer disease progression, providing a reliable basis for its use as a biomarker for the diagnosis of ovarian cancer. The high expression of HE4 in patients with early ovarian cancer provides the possibility for it to become a sentinel biomarker for early warning of ovarian cancer. It is expected to be one of the indicators for screening ovarian cancer in the general population, improve the viability, fertility and life value of patients and reduce economic and psychological pressure.

Heterogeneity is a potential problem when interpreting the results of any meta-analysis. In this study, we found considerable heterogeneity among the included studies, and the Cochran-Q test for DOR yielded $p < 0.05$ showed that heterogeneity could not be explained by a threshold effect. Therefore, we explored potential sources of heterogeneity while performing stratified analyses according to patient ethnicity and menopausal status. Serum HE4 has a higher diagnostic accuracy for Asian ovarian cancer patients than non-Asian patients, but the heterogeneity remains high. We speculated that different disease stages of ovarian cancer patients, different cut-off values, types of instruments, and reagent sources may cause heterogeneity. Because of the limited amounts of eligible studies, we could not further prove the source of the heterogeneity. Therefore, prospective studies with large samples were needed to confirm this result in the future.

There were also some limitations except heterogeneity. First, we included studies that enrolled healthy women in the control group, which may cause the increase of false in the pooled specificity for differentiating benign disease. Second, this study did not consider the age at menarche, BMI, smoking and other related factors that may affect serum HE4 levels in the study subjects, which may lead to bias in the inference results. Third, our study did not investigate the stage of ovarian cancer, and most of the patients with clinically confirmed ovarian cancer were currently in the advanced stage of the disease, from which the conclusion of this study may overestimate the diagnostic value of HE4. Fourth, the heterogeneity in our included studies might indicate the presence of confounding factors that caused bias. Last, we only included articles published in Chinese or English in our meta-analysis, that could introduce inevitable bias.

In conclusion, the current evidence suggested that serum HE4 was a potential biomarker for the diagnosis of ovarian cancer, which could greatly increase the accuracy of preoperative diagnosis of ovarian cancer for Asian post-menopausal

female. But the quality of the included studies and patients who were suspected to have ovarian cancer were not included. According to such reasons, additional studies were needed to verify the results of this study and the accuracy of this method regarding to a high-quality diagnosis.

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Author contributions

Qing Guo contributed to the conception of the study; Rui Sun, Lin Liu contributed significantly to analysis and manuscript preparation; Rui Sun performed the data analyses and wrote the manuscript; Zhengli Feng helped perform the analysis with constructive discussions; Ao Ni searched and selected the publications.

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Availability of data and materials

All data generated or analyzed during this study are included in this article and its tables and figures.

Conflict of interest

The authors declare that they have no competing interests.

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Table 1.

Variables	SEN (95% CI)	I^2 (%)	SPE (95% CI)	I^2 (%)	PLR (95% CI)	NLP (95% CI)	DOR (95% CI)	AUC
Total	0.76 0.71–0.80	72.07	0.92 0.88–0.94	90.07	11.59 7.12–18.87	0.25 0.20–0.31	46.88 24.86-88.42	0.90 0.87–0.92
Subgroup analysis								
Pre	0.71 0.63–0.78	62.46	0.91 0.85–0.95	91.61	11.90 6.42–22.07	0.30 0.22–0.39	40.32 20.36–79.84	0.88 0.85–0.90
Pro	0.78 0.74–0.81	37.61	0.90 0.86–0.93	76.23	11.03 6.44–18.89	0.24 0.20–0.29	46.14 23.25–91.56	0.87 0.83–0.89
Asian	0.76 0.68–0.83	83.35	0.93 0.91–0.95	76.07	14.93 8.33–26.77	0.24 0.16–0.35	63.27 26.25–152.52	0.95 0.93–0.97
	0.77	45.52	0.90	92.01	8.30	0.26	32.31	0.84

Non-Asian	0.72–0.81		0.83–0.95			4.37–15.79	0.21–0.32	14.47–22.16	0.80–0.87					
Study Area			OC				Control							
Asian	Non-Asian	Asian	Non-Asian	Pre	Post	Undetermined	Asian	Non-asian	Pre	Post				
8	6	642	649	393	797	1	1858	1290	1991	1157				

AUC — area under the SROC curve; CI — confidence interval; DOR — diagnostic odds ratio; NLR — negative likelihood ratio; PLR — positive likelihood ratio; SEN — sensitivity; SPE — specificity

Table 2.

Table 3.

Author	Year	Country	Simple Size		Cut-off Values (pmol/L)			TP(a)			FP(b)			FN(c)			TN(d)			Test Methords
			Case	Con-trol	All	Pre	Post	All	Pre	Post	All	Pre	Post	All	Pre	Post	All	Pre	Post	
Bandiera	2011	**Italy**	114	305	70	70	140	91	22	68	8	6	2	23	4	19	297	102	195	CMIA
Zhang	2019	**China**	181	175	140	140	140	120	36	84	9	0	9	61	27	34	166	115	51	ECLIA

Lycke	2018	**Sweden**	135	476	70	70	140	100	19	81	41	22	19	35	4	31	435	218	217	ECLIA
Farzaneh	2014	**Iran**	43	56	73	75	100	30	12	16	3	2	0	15	9	6	51	45	9	EIA
Anton	2012	**Brazil**	37	83	87	68	104	28	9	19	19	7	12	9	3	6	64	28	36	EIA
Horała	2018	**Poland**	35	57	87.6	59.7	104.9	30	6	24	2	9	2	5	2	3	55	32	14	ECLIA
Shin	2020	**Korea**	39	227	/	92.1	121	21	6	15	10	4	6	18	13	5	217	154	63	ECLIA
Wang	2019	**China**	35	95	/	69.8	114.9	32	11	21	0	0	0	3	3	0	95	69	26	ECLIA
Chen	2015	**China**	60	70	87.6	72.3	97.5	53	18	35	2	1	2	7	2	5	68	21	46	ECLIA
Kim	2019	**Korea**	70	762	79.6	83	85.5	56	10	45	55	15	22	14	4	11	707	552	173	ECLIA
Huy	2018	**Vietnam**	30	247	55.4	55.4	59.3	24	10	13	21	13	4	6	3	4	226	204	26	ECLIA
Terlikowska	2016	**Poland**	96	128	72.3	70.3	109.1	81	28	53	18	9	1	15	5	10	110	78	40	ECLIA
McKendry	2021	**Ireland**	89	185	/	51.8	94.3	62	14	48	43	25	18	27	7	20	142	43	99	ECLIA
Shen	2021	**China**	227	282	70	49.5	64.5	168	73	95	28	23	5	59	33	26	254	194	60	ECLIA

CMIA — chemiluminescent microparticle immunoassay; ECLIA — enzyme-linked immunosorbent assay; EIA — enzyme immunoassay; ELASA — Enzyme Linked Immunosorbent Assay; FN — falsenegative rate; FP — false-positive rate; NR — not reported; TN — true negative rate; TP — true positive rate

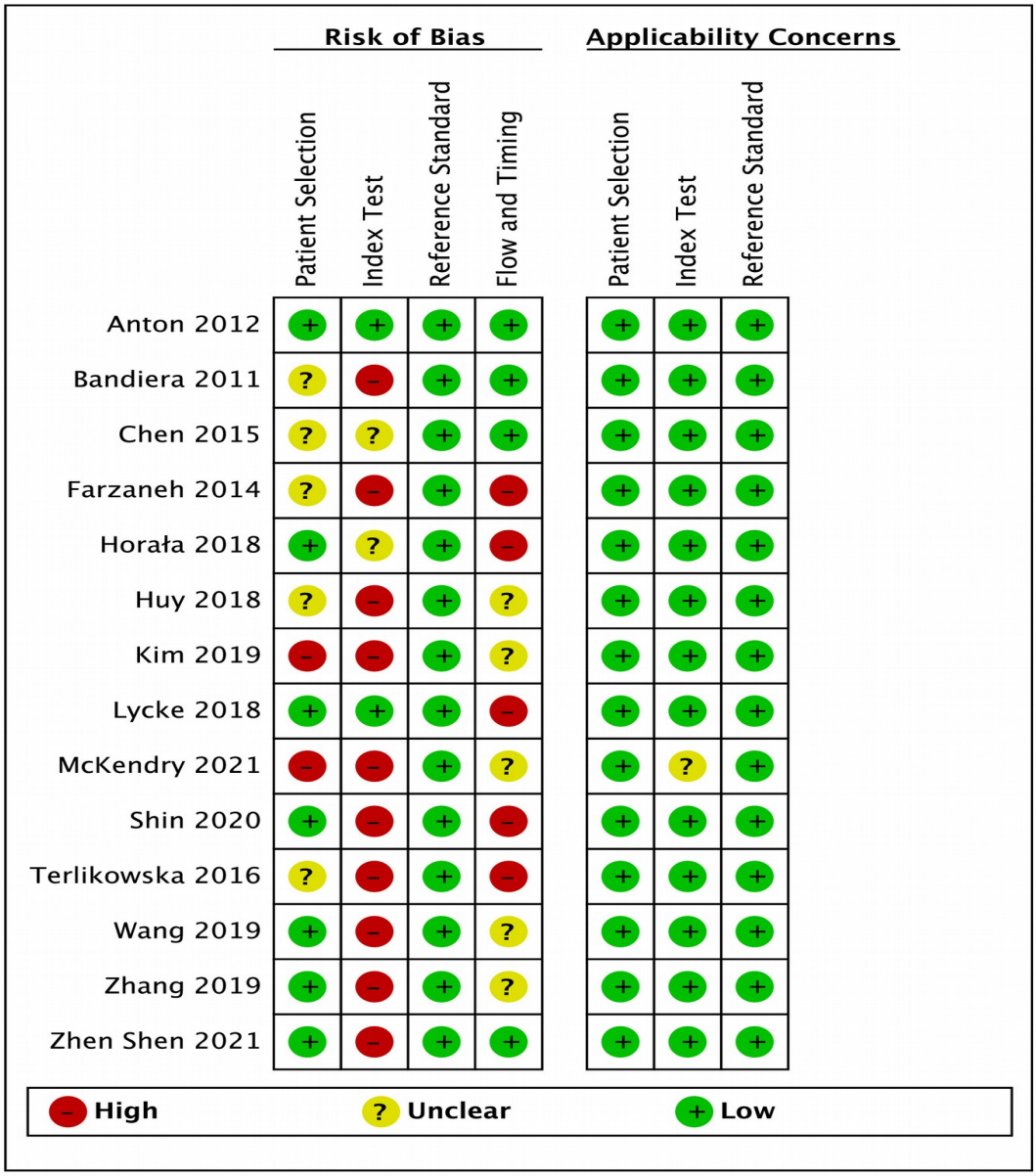


Figure 1. Summary the assessment of methodological quality of included studies by QUADAS-2 tool

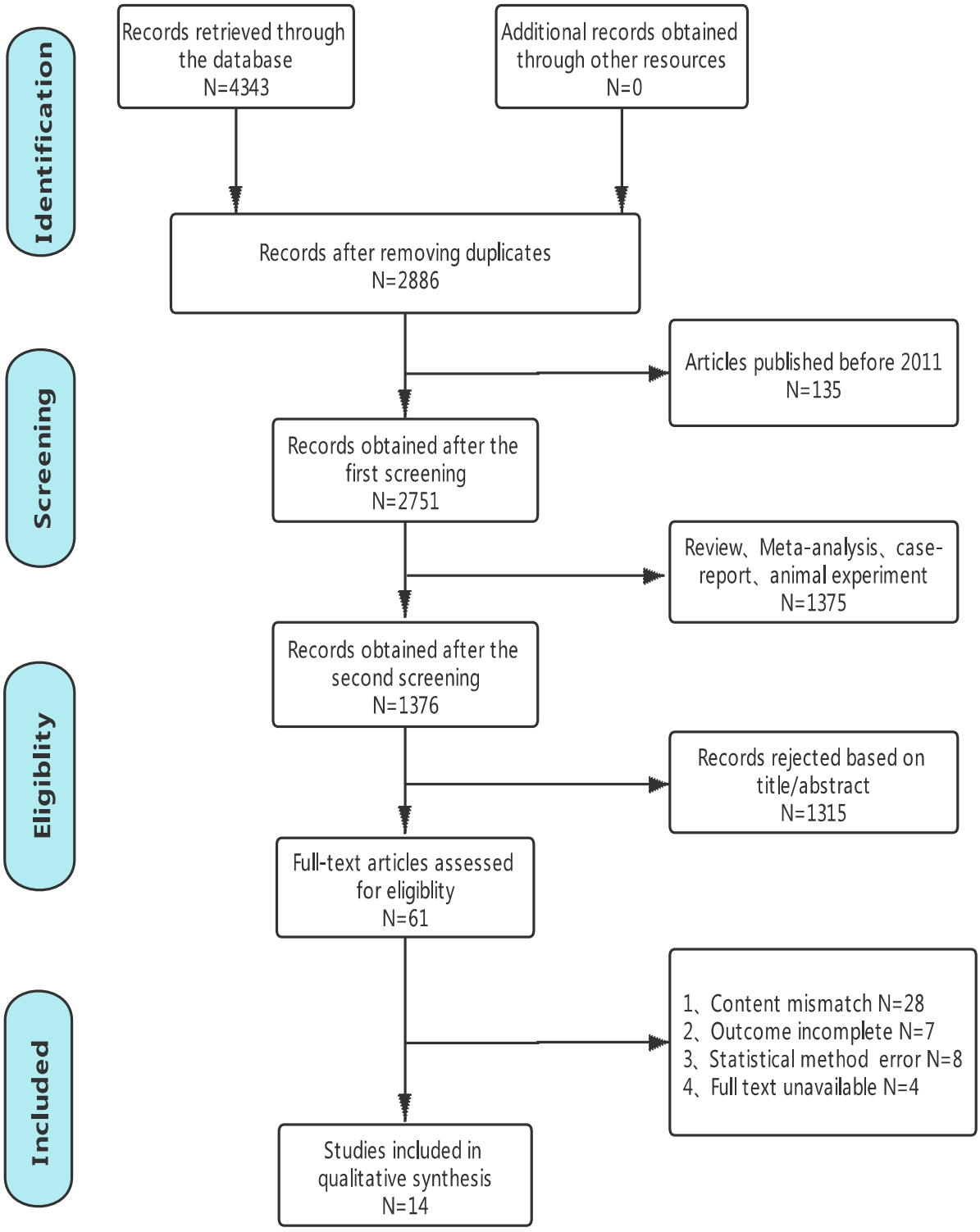
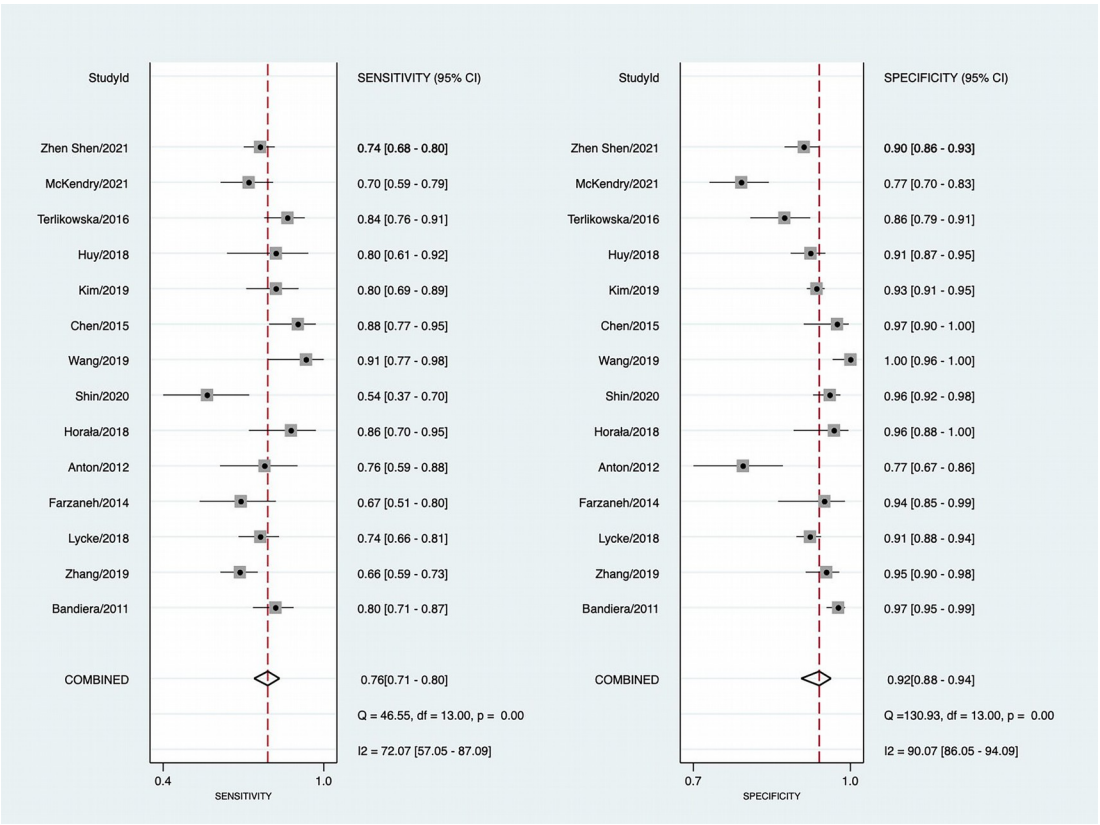
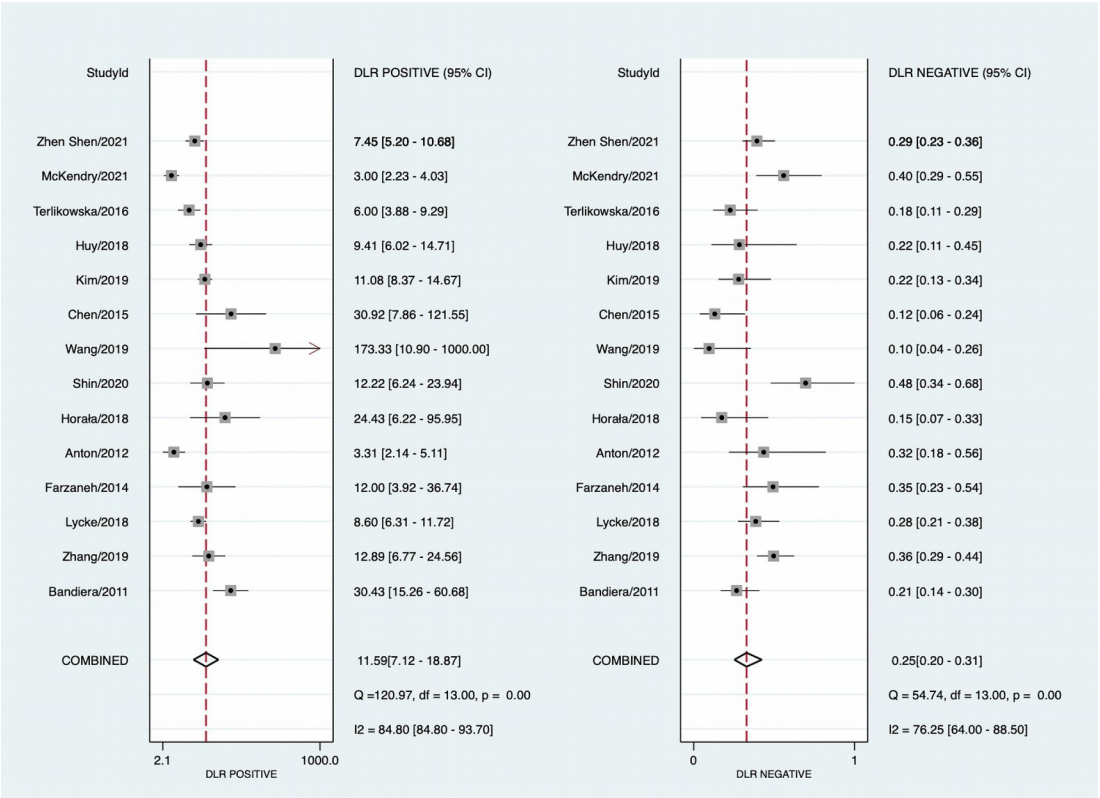


Figure 2. Flowchart depicting the study selection process for this systematic review and meta-analysis

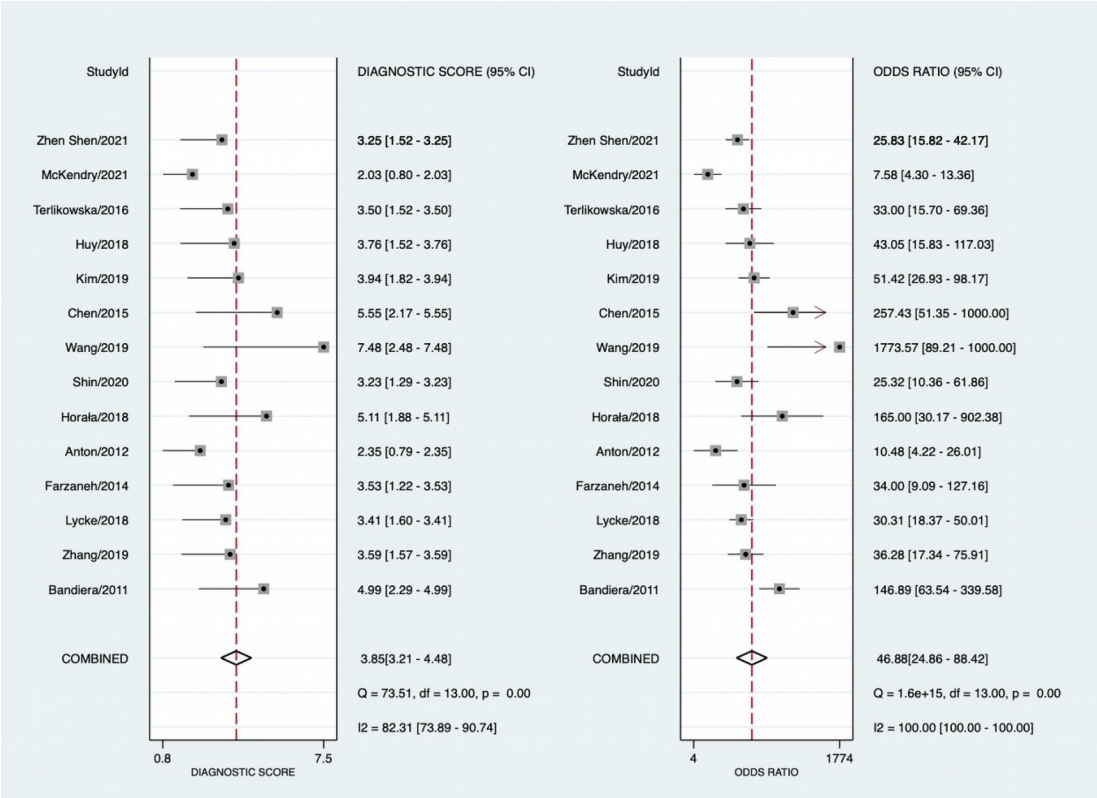
a


StudyId
SENSITIVITY (95% CI)
Zhen Shen/2021 0.74 [0.68 - 0.80]
McKendry/2021 0.70 [0.59 - 0.79]
Terlikowska/2016 0.84 [0.76 - 0.91]
Huy/2018 0.80 [0.61 - 0.92]
Kim/2019 0.80 [0.69 - 0.89]
Chen/2015 0.88 [0.77 - 0.95]
Wang/2019 0.91 [0.77 - 0.98]
Shin/2020 0.54 [0.37 - 0.70]
Horała/2018 0.86 [0.70 - 0.95]
Anton/2012 0.76 [0.59 - 0.88]
Farzaneh/2014 0.67 [0.51 - 0.80]
Lycke/2018 0.74 [0.66 - 0.81]
Zhang/2019 0.66 [0.59 - 0.73]
Bandiera/2011 0.80 [0.71 - 0.87]
COMBINED 0.76[0.71 - 0.80]
Q = 46.55, df = 13.00, p = 0.00
I2 = 72.07 [57.05 - 87.09]
0.4
1.0
SENSITIVITY
StudyId
SPECIFICITY (95% CI)
Zhen Shen/2021 0.90 [0.86 - 0.93]
McKendry/2021 0.77 [0.70 - 0.83]
Terlikowska/2016 0.86 [0.79 - 0.91]
Huy/2018 0.91 [0.87 - 0.95]
Kim/2019 0.93 [0.91 - 0.95]
Chen/2015 0.97 [0.90 - 1.00]
Wang/2019 1.00 [0.96 - 1.00]
Shin/2020 0.96 [0.92 - 0.98]
Horała/2018 0.96 [0.88 - 1.00]
Anton/2012 0.77 [0.67 - 0.86]
Farzaneh/2014 0.94 [0.85 - 0.99]
Lycke/2018 0.91 [0.88 - 0.94]
Zhang/2019 0.95 [0.90 - 0.98]
Bandiera/2011 0.97 [0.95 - 0.99]
COMBINED 0.92[0.88 - 0.94]
Q =130.93, df = 13.00, p = 0.00
I2 = 90.07 [86.05 - 94.09]
0.7
1.0
SPECIFICITY

b


StudyId
DLR POSITIVE (95% CI)
Zhen Shen/2021 7.45 [5.20 - 10.68]
McKendry/2021 3.00 [2.23 - 4.03]
Terlikowska/2016 6.00 [3.88 - 9.29]
Huy/2018 9.41 [6.02 - 14.71]
Kim/2019 11.08 [8.37 - 14.67]
Chen/2015 30.92 [7.86 - 121.55]
Wang/2019 173.33 [10.90 - 1000.00]
Shin/2020 12.22 [6.24 - 23.94]
Horała/2018 24.43 [6.22 - 95.95]
Anton/2012 3.31 [2.14 - 5.11]
Farzaneh/2014 12.00 [3.92 - 36.74]
Lycke/2018 8.60 [6.31 - 11.72]
Zhang/2019 12.89 [6.77 - 24.56]
Bandiera/2011 30.43 [15.26 - 60.68]
COMBINED 11.59[7.12 - 18.87]
Q =120.97, df = 13.00, p = 0.00
I2 = 84.80 [84.80 - 93.70]
2.1
1000.0
DLR POSITIVE
StudyId
DLR NEGATIVE (95% CI)
Zhen Shen/2021 0.29 [0.23 - 0.36]
McKendry/2021 0.40 [0.29 - 0.55]
Terlikowska/2016 0.18 [0.11 - 0.29]
Huy/2018 0.22 [0.11 - 0.45]
Kim/2019 0.22 [0.13 - 0.34]
Chen/2015 0.12 [0.06 - 0.24]
Wang/2019 0.10 [0.04 - 0.26]
Shin/2020 0.48 [0.34 - 0.68]
Horała/2018 0.15 [0.07 - 0.33]
Anton/2012 0.32 [0.18 - 0.56]
Farzaneh/2014 0.35 [0.23 - 0.54]
Lycke/2018 0.28 [0.21 - 0.38]
Zhang/2019 0.36 [0.29 - 0.44]
Bandiera/2011 0.21 [0.14 - 0.30]
COMBINED 0.25[0.20 - 0.31]
Q = 54.74, df = 13.00, p = 0.00
I2 = 76.25 [64.00 - 88.50]
0
1
DLR NEGATIVE

c


Studyld
DIAGNOSTIC SCORE (95% CI)
Zhen Shen/2021 3.25 [1.52 - 3.25]
McKendry/2021 2.03 [0.80 - 2.03]
Terlikowska/2016 3.50 [1.52 - 3.50]
Huy/2018 3.76 [1.52 - 3.76]
Kim/2019 3.94 [1.82 - 3.94]
Chen/2015 5.55 [2.17 - 5.55]
Wang/2019 7.48 [2.48 - 7.48]
Shin/2020 3.23 [1.29 - 3.23]
Horała/2018 5.11 [1.88 - 5.11]
Anton/2012 2.35 [0.79 - 2.35]
Farzaneh/2014 3.53 [1.22 - 3.53]
Lycke/2018 3.41 [1.60 - 3.41]
Zhang/2019 3.59 [1.57 - 3.59]
Bandiera/2011 4.99 [2.29 - 4.99]
COMBINED 3.85[3.21 - 4.48]
Q = 73.51, df = 13.00, p = 0.00
I2 = 82.31 [73.89 - 90.74]
0.8
7.5
DIAGNOSTIC SCORE
Studyld
ODDS RATIO (95% CI)
Zhen Shen/2021 25.83 [15.82 - 42.17]
McKendry/2021 7.58 [4.30 - 13.36]
Terlikowska/2016 33.00 [15.70 - 69.36]
Huy/2018 43.05 [15.83 - 117.03]
Kim/2019 51.42 [26.93 - 98.17]
Chen/2015 257.43 [51.35 - 1000.00]
Wang/2019 1773.57 [89.21 - 1000.00]
Shin/2020 25.32 [10.36 - 61.86]
Horała/2018 165.00 [30.17 - 902.38]
Anton/2012 10.48 [4.22 - 26.01]
Farzaneh/2014 34.00 [9.09 - 127.16]
Lycke/2018 30.31 [18.37 - 50.01]
Zhang/2019 36.28 [17.34 - 75.91]
Bandiera/2011 146.89 [63.54 - 339.58]
COMBINED 46.88[24.86 - 88.42]
Q = 1.6e+15, df = 13.00, p = 0.00
I2 = 100.00 [100.00 - 100.00]
4
1774
ODDS RATIO

d

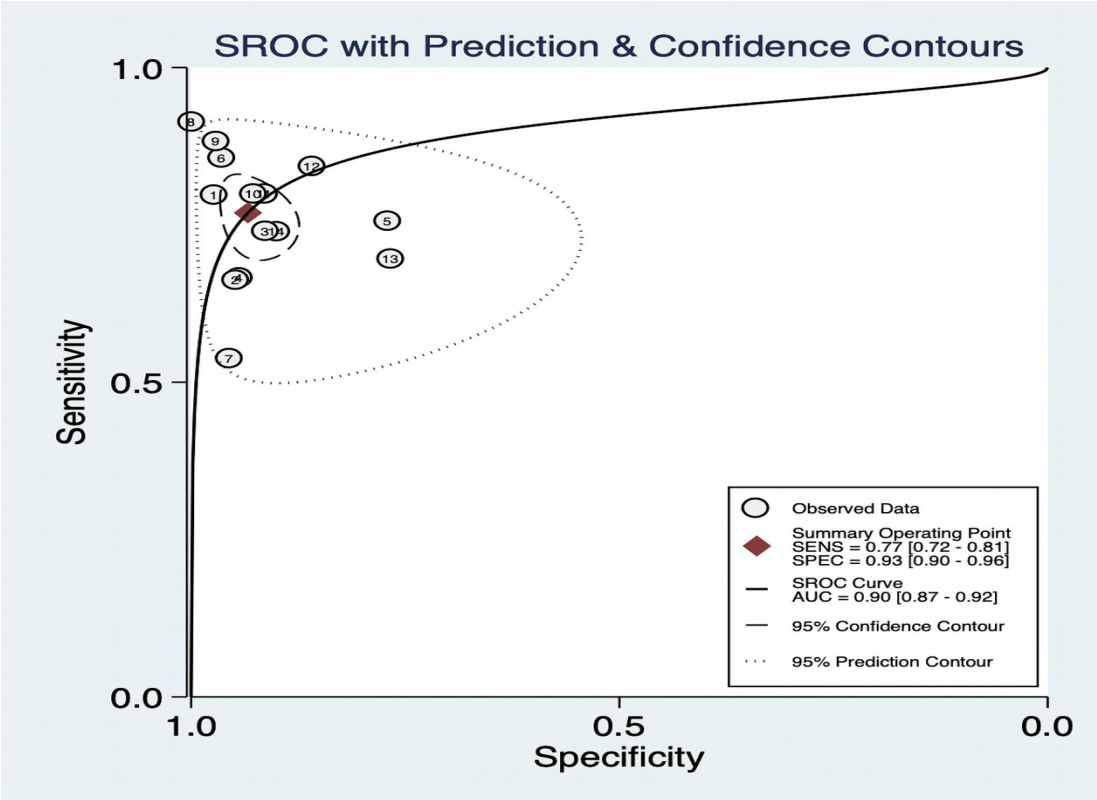
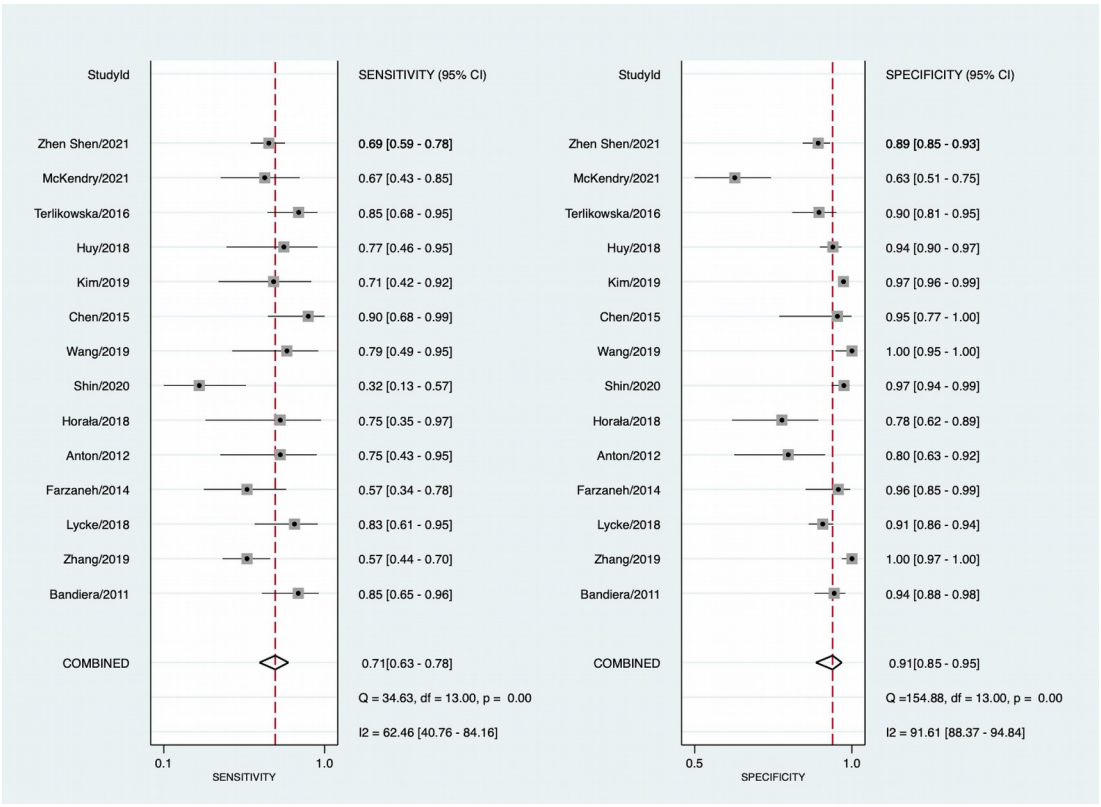
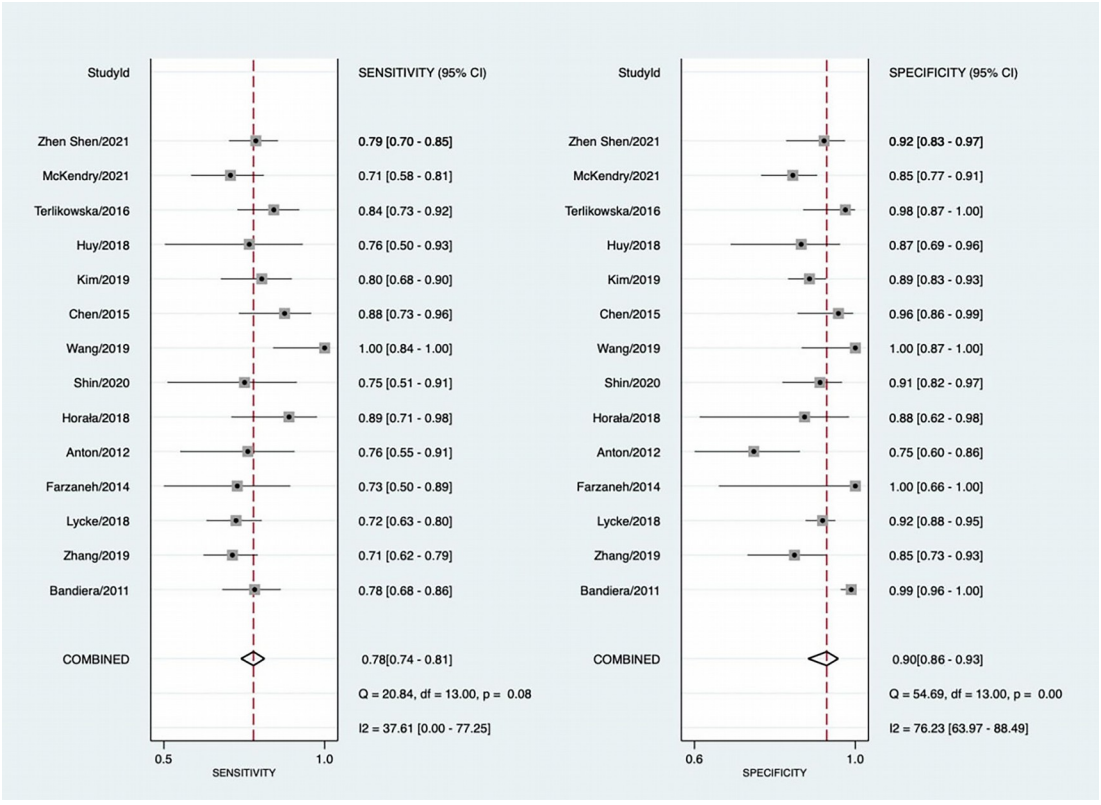

SROC with Prediction & Confidence Contours
1.0
0.5
0.0
Sensitivity
1.0
0.5
0.0
Specificity
Observed Data
Summary Operating Point
SENS = 0.77 [0.72 - 0.81]
SPEC = 0.93 [0.90 - 0.96]
SROC Curve
AUC = 0.90 [0.87 - 0.92]
95% Confidence Contour
95% Prediction Contour

Figure 3 Forest plots of estimated efficacy for serum HE4 in the diagnosis of ovarian cancer. (a) sensitivity (left) versus specificity (right); b, positive likelihood ratio (left) versus negative likelihood ratio (right) (NLR); c, diagnostic odds ratio (DOR); d, SROC curve.

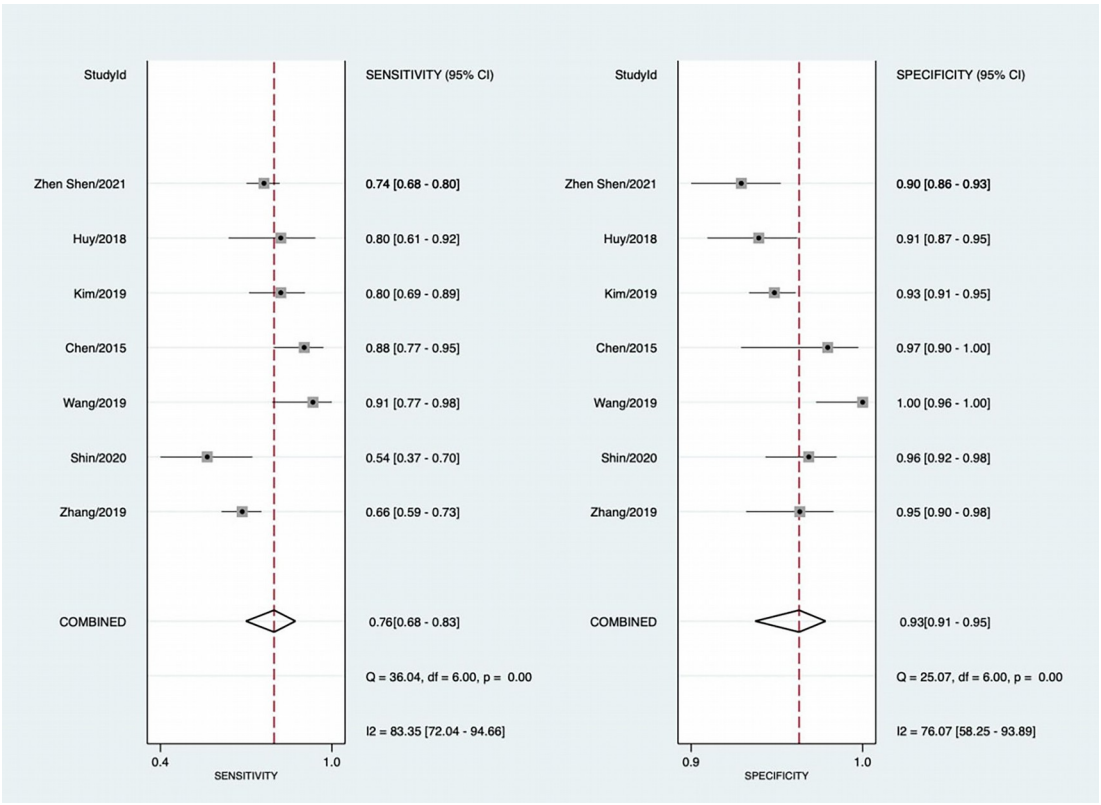
a


Studyld
SENSITIVITY (95% CI)
Zhen Shen/2021 0.69 [0.59 - 0.78]
McKendry/2021 0.67 [0.43 - 0.85]
Terlikowska/2016 0.85 [0.68 - 0.95]
Huy/2018 0.77 [0.46 - 0.95]
Kim/2019 0.71 [0.42 - 0.92]
Chen/2015 0.90 [0.68 - 0.99]
Wang/2019 0.79 [0.49 - 0.95]
Shin/2020 0.32 [0.13 - 0.57]
Horała/2018 0.75 [0.35 - 0.97]
Anton/2012 0.75 [0.43 - 0.95]
Farzaneh/2014 0.57 [0.34 - 0.78]
Lycke/2018 0.83 [0.61 - 0.95]
Zhang/2019 0.57 [0.44 - 0.70]
Bandiera/2011 0.85 [0.65 - 0.96]
COMBINED 0.71[0.63 - 0.78]
Q = 34.63, df = 13.00, p = 0.00
I2 = 62.46 [40.76 - 84.16]
0.1
1.0
SENSITIVITY
Studyld
SPECIFICITY (95% CI)
Zhen Shen/2021 0.89 [0.85 - 0.93]
McKendry/2021 0.63 [0.51 - 0.75]
Terlikowska/2016 0.90 [0.81 - 0.95]
Huy/2018 0.94 [0.90 - 0.97]
Kim/2019 0.97 [0.96 - 0.99]
Chen/2015 0.95 [0.77 - 1.00]
Wang/2019 1.00 [0.95 - 1.00]
Shin/2020 0.97 [0.94 - 0.99]
Horała/2018 0.78 [0.62 - 0.89]
Anton/2012 0.80 [0.63 - 0.92]
Farzaneh/2014 0.96 [0.85 - 0.99]
Lycke/2018 0.91 [0.86 - 0.94]
Zhang/2019 1.00 [0.97 - 1.00]
Bandiera/2011 0.94 [0.88 - 0.98]
COMBINED 0.91[0.85 - 0.95]
Q =154.88, df = 13.00, p = 0.00
I2 = 91.61 [88.37 - 94.84]
0.5
1.0
SPECIFICITY

b


Studyld
SENSITIVITY (95% CI)
Zhen Shen/2021 0.79 [0.70 - 0.85]
McKendry/2021 0.71 [0.58 - 0.81]
Terlikowska/2016 0.84 [0.73 - 0.92]
Huy/2018 0.76 [0.50 - 0.93]
Kim/2019 0.80 [0.68 - 0.90]
Chen/2015 0.88 [0.73 - 0.96]
Wang/2019 1.00 [0.84 - 1.00]
Shin/2020 0.75 [0.51 - 0.91]
Horała/2018 0.89 [0.71 - 0.98]
Anton/2012 0.76 [0.55 - 0.91]
Farzaneh/2014 0.73 [0.50 - 0.89]
Lycke/2018 0.72 [0.63 - 0.80]
Zhang/2019 0.71 [0.62 - 0.79]
Bandiera/2011 0.78 [0.68 - 0.86]
COMBINED 0.78[0.74 - 0.81]
Q = 20.84, df = 13.00, p = 0.08
I2 = 37.61 [0.00 - 77.25]
0.5
1.0
SENSITIVITY
Studyld
SPECIFICITY (95% CI)
Zhen Shen/2021 0.92 [0.83 - 0.97]
McKendry/2021 0.85 [0.77 - 0.91]
Terlikowska/2016 0.98 [0.87 - 1.00]
Huy/2018 0.87 [0.69 - 0.96]
Kim/2019 0.89 [0.83 - 0.93]
Chen/2015 0.96 [0.86 - 0.99]
Wang/2019 1.00 [0.87 - 1.00]
Shin/2020 0.91 [0.82 - 0.97]
Horała/2018 0.88 [0.62 - 0.98]
Anton/2012 0.75 [0.60 - 0.86]
Farzaneh/2014 1.00 [0.66 - 1.00]
Lycke/2018 0.92 [0.88 - 0.95]
Zhang/2019 0.85 [0.73 - 0.93]
Bandiera/2011 0.99 [0.96 - 1.00]
COMBINED 0.90[0.86 - 0.93]
Q = 54.69, df = 13.00, p = 0.00
I2 = 76.23 [63.97 - 88.49]
0.6
1.0
SPECIFICITY

c


StudyId
SENSITIVITY (95% CI)
Zhen Shen/2021
0.74 [0.68 - 0.80]
Huy/2018
0.80 [0.61 - 0.92]
Kim/2019
0.80 [0.69 - 0.89]
Chen/2015
0.88 [0.77 - 0.95]
Wang/2019
0.91 [0.77 - 0.98]
Shin/2020
0.54 [0.37 - 0.70]
Zhang/2019
0.66 [0.59 - 0.73]
COMBINED
0.76[0.68 - 0.83]
Q = 36.04, df = 6.00, p = 0.00
I2 = 83.35 [72.04 - 94.66]
0.4
1.0
SENSITIVITY
StudyId
SPECIFICITY (95% CI)
Zhen Shen/2021
0.90 [0.86 - 0.93]
Huy/2018
0.91 [0.87 - 0.95]
Kim/2019
0.93 [0.91 - 0.95]
Chen/2015
0.97 [0.90 - 1.00]
Wang/2019
1.00 [0.96 - 1.00]
Shin/2020
0.96 [0.92 - 0.98]
Zhang/2019
0.95 [0.90 - 0.98]
COMBINED
0.93[0.91 - 0.95]
Q = 25.07, df = 6.00, p = 0.00
I2 = 76.07 [58.25 - 93.89]
0.9
1.0
SPECIFICITY

d

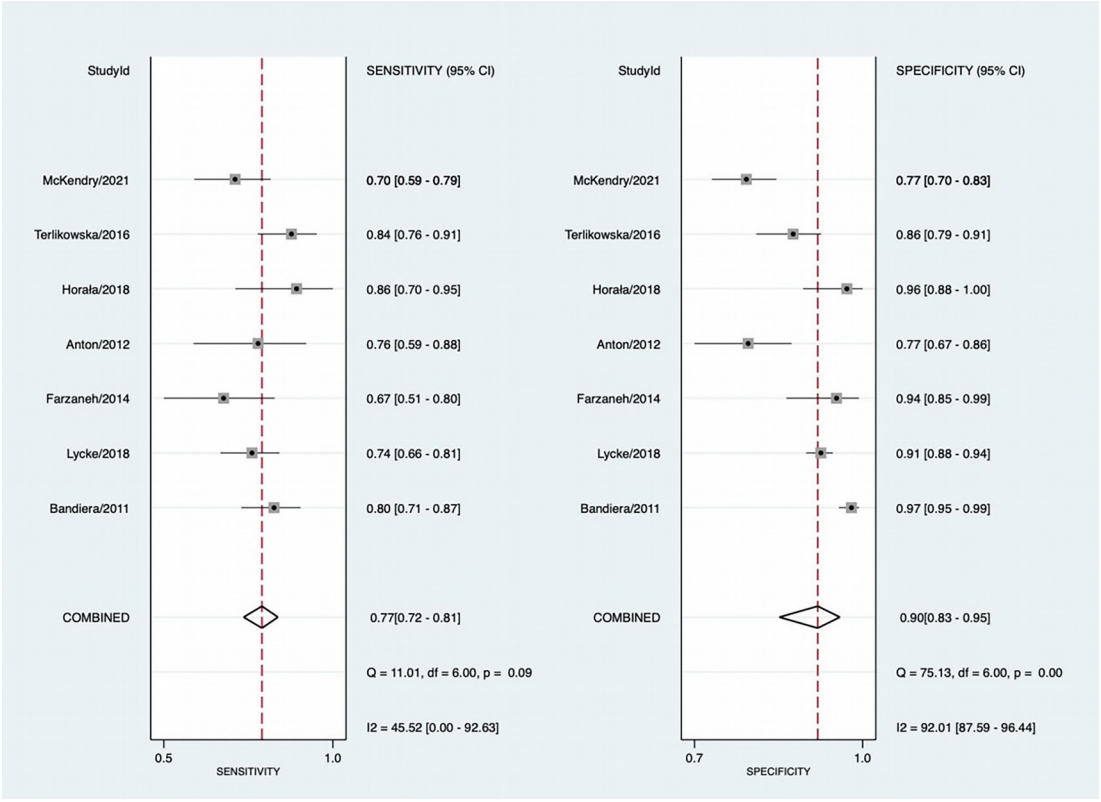
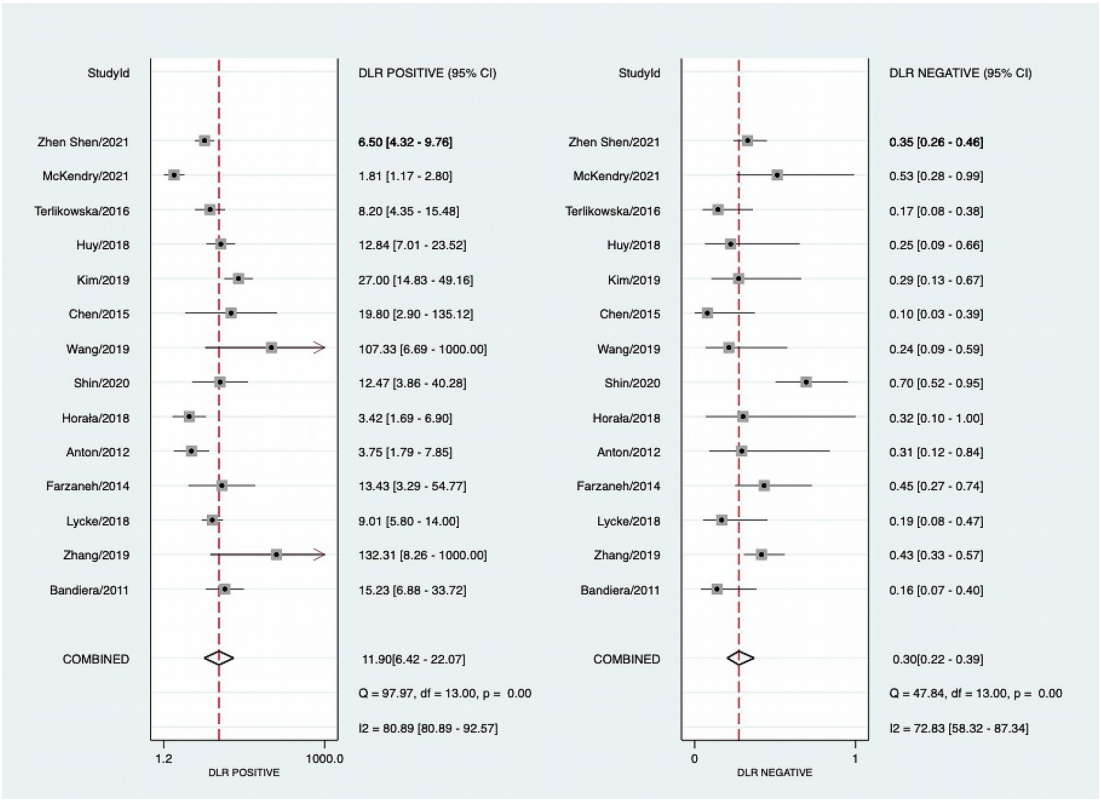
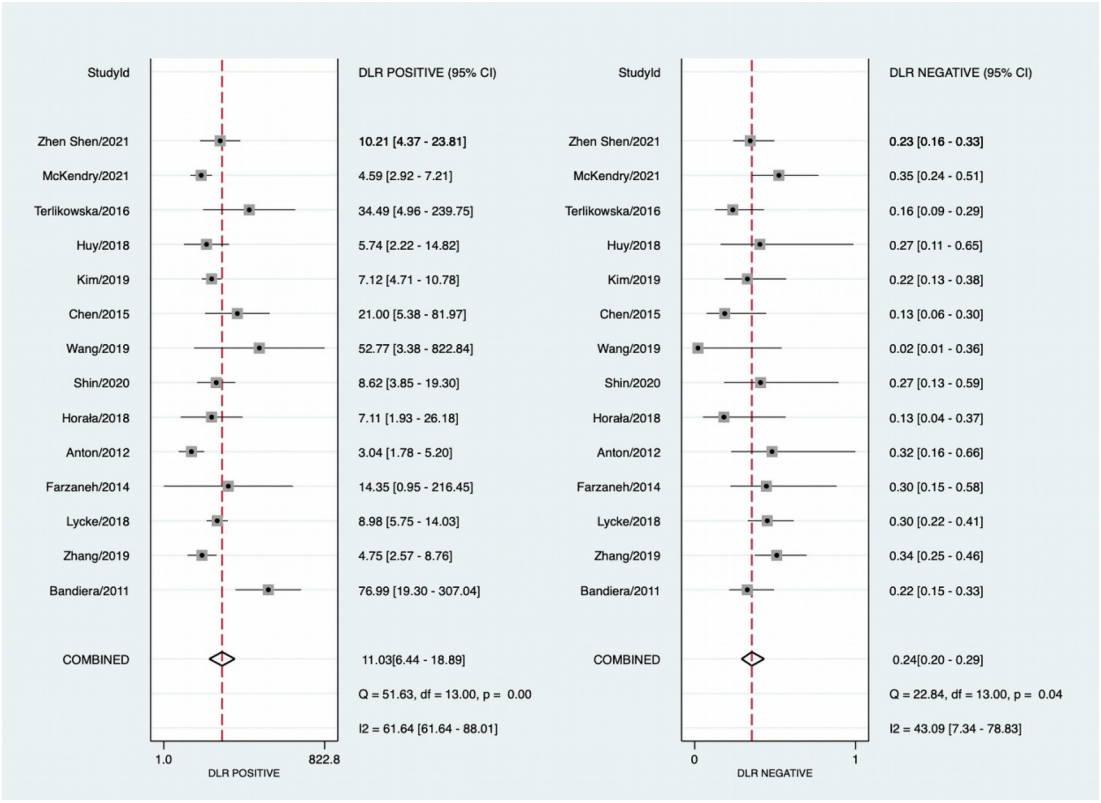

StudyId
SENSITIVITY (95% CI)
McKendry/2021
0.70 [0.59 - 0.79]
Terlikowska/2016
0.84 [0.76 - 0.91]
Horała/2018
0.86 [0.70 - 0.95]
Anton/2012
0.76 [0.59 - 0.88]
Farzaneh/2014
0.67 [0.51 - 0.80]
Lycke/2018
0.74 [0.66 - 0.81]
Bandiera/2011
0.80 [0.71 - 0.87]
COMBINED
0.77[0.72 - 0.81]
Q = 11.01, df = 6.00, p = 0.09
I2 = 45.52 [0.00 - 92.63]
0.5
1.0
SENSITIVITY
StudyId
SPECIFICITY (95% CI)
McKendry/2021
0.77 [0.70 - 0.83]
Terlikowska/2016
0.86 [0.79 - 0.91]
Horała/2018
0.96 [0.88 - 1.00]
Anton/2012
0.77 [0.67 - 0.86]
Farzaneh/2014
0.94 [0.85 - 0.99]
Lycke/2018
0.91 [0.88 - 0.94]
Bandiera/2011
0.97 [0.95 - 0.99]
COMBINED
0.90[0.83 - 0.95]
Q = 75.13, df = 6.00, p = 0.00
I2 = 92.01 [87.59 - 96.44]
0.7
1.0
SPECIFICITY

Figure 4: Forest plot of the estimated effect size of serum HE4 for the diagnosis of ovarian cancer in different women. a, (premenopausal women) sensitivity (left) versus specificity (right); b, (postmenopausal women) sensitivity (left) versus specificity (right); c, (Asian female) sensitivity (left) versus specificity (right); d, (non-Asian female) sensitivity (left) versus specificity (right);

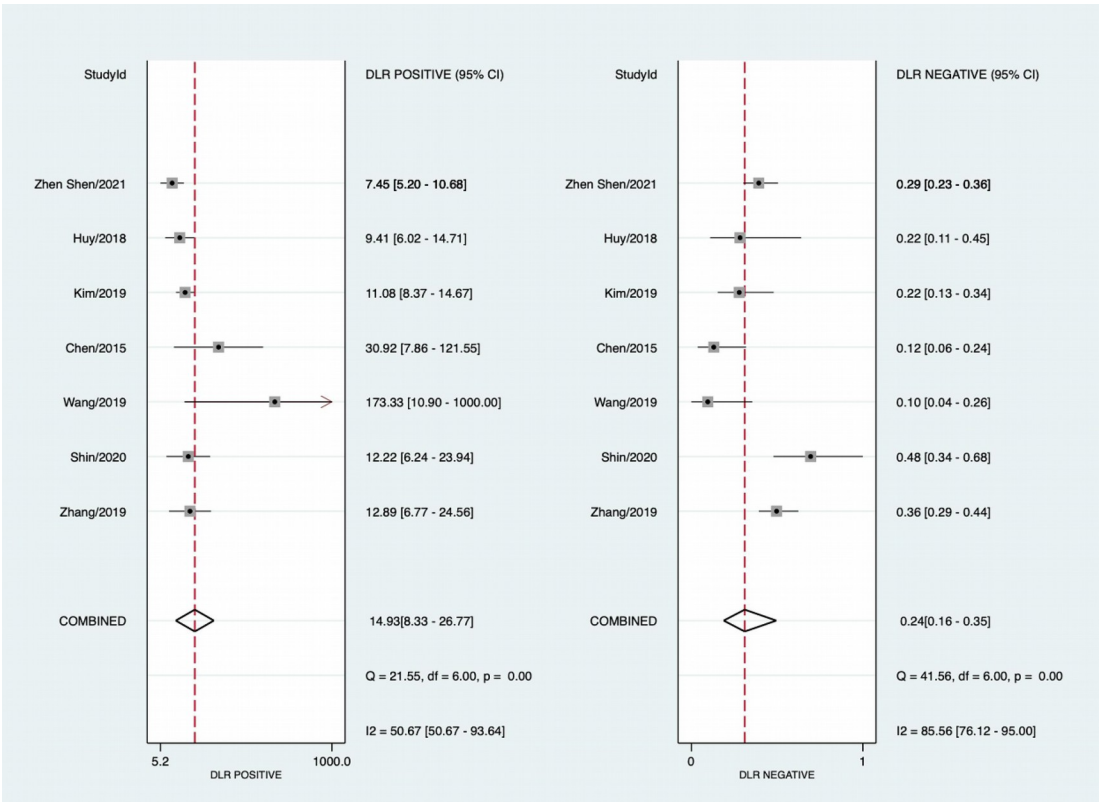
a


StudyId
DLR POSITIVE (95% CI)
Zhen Shen/2021 6.50 [4.32 - 9.76]
McKendry/2021 1.81 [1.17 - 2.80]
Terlikowska/2016 8.20 [4.35 - 15.48]
Huy/2018 12.84 [7.01 - 23.52]
Kim/2019 27.00 [14.83 - 49.16]
Chen/2015 19.80 [2.90 - 135.12]
Wang/2019 107.33 [6.69 - 1000.00]
Shin/2020 12.47 [3.86 - 40.28]
Horała/2018 3.42 [1.69 - 6.90]
Anton/2012 3.75 [1.79 - 7.85]
Farzaneh/2014 13.43 [3.29 - 54.77]
Lycke/2018 9.01 [5.80 - 14.00]
Zhang/2019 132.31 [8.26 - 1000.00]
Bandiera/2011 15.23 [6.88 - 33.72]
COMBINED 11.90[6.42 - 22.07]
Q = 97.97, df = 13.00, p = 0.00
I2 = 80.89 [80.89 - 92.57]
1.2
1000.0
DLR POSITIVE
StudyId
DLR NEGATIVE (95% CI)
Zhen Shen/2021 0.35 [0.26 - 0.46]
McKendry/2021 0.53 [0.28 - 0.99]
Terlikowska/2016 0.17 [0.08 - 0.38]
Huy/2018 0.25 [0.09 - 0.66]
Kim/2019 0.29 [0.13 - 0.67]
Chen/2015 0.10 [0.03 - 0.39]
Wang/2019 0.24 [0.09 - 0.59]
Shin/2020 0.70 [0.52 - 0.95]
Horała/2018 0.32 [0.10 - 1.00]
Anton/2012 0.31 [0.12 - 0.84]
Farzaneh/2014 0.45 [0.27 - 0.74]
Lycke/2018 0.19 [0.08 - 0.47]
Zhang/2019 0.43 [0.33 - 0.57]
Bandiera/2011 0.16 [0.07 - 0.40]
COMBINED 0.30[0.22 - 0.39]
Q = 47.84, df = 13.00, p = 0.00
I2 = 72.83 [58.32 - 87.34]
0
1
DLR NEGATIVE

b


StudyId
DLR POSITIVE (95% CI)
Zhen Shen/2021 10.21 [4.37 - 23.81]
McKendry/2021 4.59 [2.92 - 7.21]
Terlikowska/2016 34.49 [4.96 - 239.75]
Huy/2018 5.74 [2.22 - 14.82]
Kim/2019 7.12 [4.71 - 10.78]
Chen/2015 21.00 [5.38 - 81.97]
Wang/2019 52.77 [3.38 - 822.84]
Shin/2020 8.62 [3.85 - 19.30]
Horała/2018 7.11 [1.93 - 26.18]
Anton/2012 3.04 [1.78 - 5.20]
Farzaneh/2014 14.35 [0.95 - 216.45]
Lycke/2018 8.98 [5.75 - 14.03]
Zhang/2019 4.75 [2.57 - 8.76]
Bandiera/2011 76.99 [19.30 - 307.04]
COMBINED 11.03[6.44 - 18.89]
Q = 51.63, df = 13.00, p = 0.00
I2 = 61.64 [61.64 - 88.01]
1.0
822.8
DLR POSITIVE
StudyId
DLR NEGATIVE (95% CI)
Zhen Shen/2021 0.23 [0.16 - 0.33]
McKendry/2021 0.35 [0.24 - 0.51]
Terlikowska/2016 0.16 [0.09 - 0.29]
Huy/2018 0.27 [0.11 - 0.65]
Kim/2019 0.22 [0.13 - 0.38]
Chen/2015 0.13 [0.06 - 0.30]
Wang/2019 0.02 [0.01 - 0.36]
Shin/2020 0.27 [0.13 - 0.59]
Horała/2018 0.13 [0.04 - 0.37]
Anton/2012 0.32 [0.16 - 0.66]
Farzaneh/2014 0.30 [0.15 - 0.58]
Lycke/2018 0.30 [0.22 - 0.41]
Zhang/2019 0.34 [0.25 - 0.46]
Bandiera/2011 0.22 [0.15 - 0.33]
COMBINED 0.24[0.20 - 0.29]
Q = 22.84, df = 13.00, p = 0.04
I2 = 43.09 [7.34 - 78.83]
0
1
DLR NEGATIVE

c


StudyId
DLR POSITIVE (95% CI)
Zhen Shen/2021
7.45 [5.20 - 10.68]
Huy/2018
9.41 [6.02 - 14.71]
Kim/2019
11.08 [8.37 - 14.67]
Chen/2015
30.92 [7.86 - 121.55]
Wang/2019
173.33 [10.90 - 1000.00]
Shin/2020
12.22 [6.24 - 23.94]
Zhang/2019
12.89 [6.77 - 24.56]
COMBINED
14.93[8.33 - 26.77]
Q = 21.55, df = 6.00, p = 0.00
I2 = 50.67 [50.67 - 93.64]
5.2
1000.0
DLR POSITIVE
StudyId
DLR NEGATIVE (95% CI)
Zhen Shen/2021
0.29 [0.23 - 0.36]
Huy/2018
0.22 [0.11 - 0.45]
Kim/2019
0.22 [0.13 - 0.34]
Chen/2015
0.12 [0.06 - 0.24]
Wang/2019
0.10 [0.04 - 0.26]
Shin/2020
0.48 [0.34 - 0.68]
Zhang/2019
0.36 [0.29 - 0.44]
COMBINED
0.24[0.16 - 0.35]
Q = 41.56, df = 6.00, p = 0.00
I2 = 85.56 [76.12 - 95.00]
0
1
DLR NEGATIVE

d

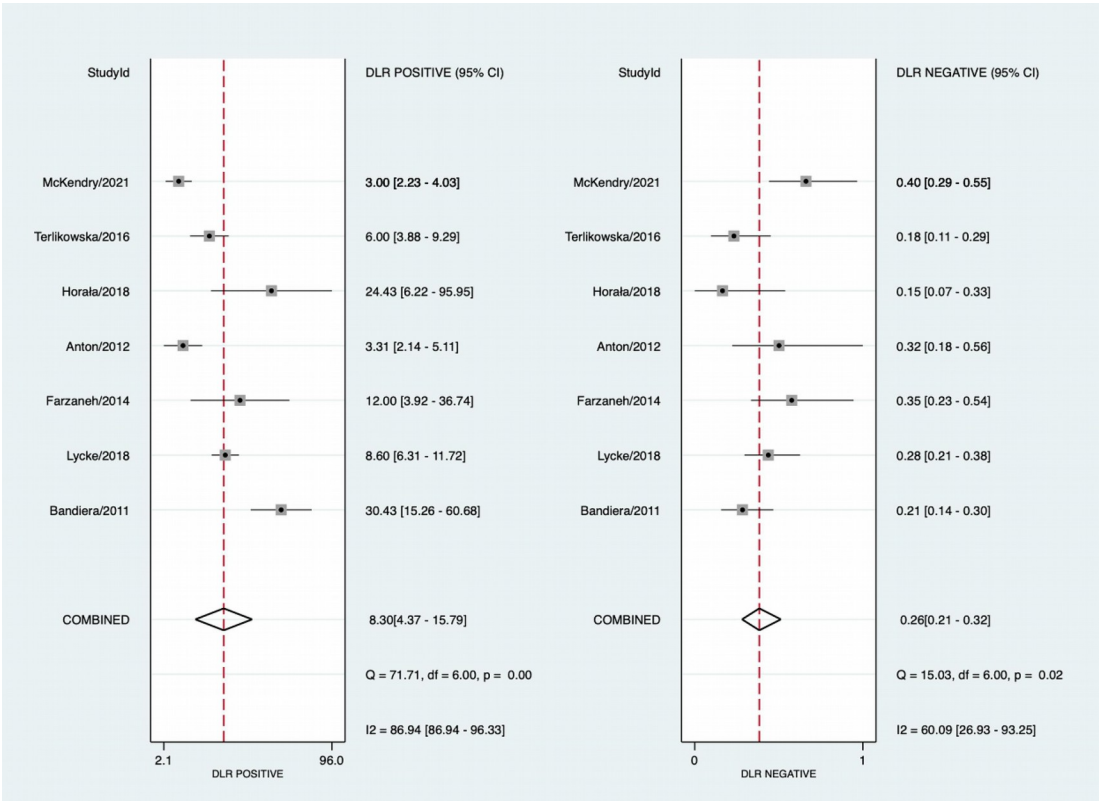

StudyId
DLR POSITIVE (95% CI)
McKendry/2021
3.00 [2.23 - 4.03]
Terlikowska/2016
6.00 [3.88 - 9.29]
Horała/2018
24.43 [6.22 - 95.95]
Anton/2012
3.31 [2.14 - 5.11]
Farzaneh/2014
12.00 [3.92 - 36.74]
Lycke/2018
8.60 [6.31 - 11.72]
Bandiera/2011
30.43 [15.26 - 60.68]
COMBINED
8.30[4.37 - 15.79]
Q = 71.71, df = 6.00, p = 0.00
I2 = 86.94 [86.94 - 96.33]
2.1
96.0
DLR POSITIVE
StudyId
DLR NEGATIVE (95% CI)
McKendry/2021
0.40 [0.29 - 0.55]
Terlikowska/2016
0.18 [0.11 - 0.29]
Horała/2018
0.15 [0.07 - 0.33]
Anton/2012
0.32 [0.18 - 0.56]
Farzaneh/2014
0.35 [0.23 - 0.54]
Lycke/2018
0.28 [0.21 - 0.38]
Bandiera/2011
0.21 [0.14 - 0.30]
COMBINED
0.26[0.21 - 0.32]
Q = 15.03, df = 6.00, p = 0.02
I2 = 60.09 [26.93 - 93.25]
0
1
DLR NEGATIVE

Figure 5: Forest plot of the estimated effect size of serum HE4 for the diagnosis of ovarian cancer in different women. a, (premenopausal women) positive likelihood ratio (PLR) (left) versus negative likelihood ratio (NLR) (right); b, (postmenopausal women) positive likelihood ratio (PLR) (left) versus negative likelihood ratio (NLR) (right); c, (Asian female) positive likelihood ratio (PLR) (left) versus negative likelihood ratio (NLR) (right); d, (non-Asian female) positive likelihood ratio (PLR) (left) versus negative likelihood ratio (NLR) (right).

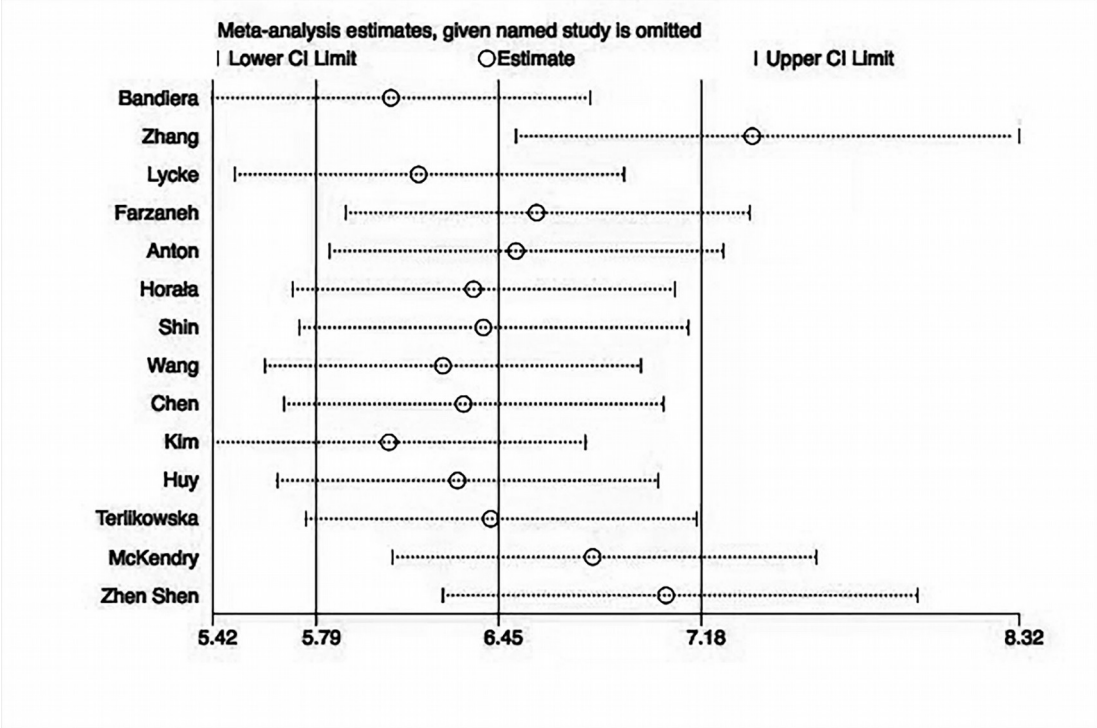


Figure 6: Sensitivity analysis to assess articles with high impact on the results of this study

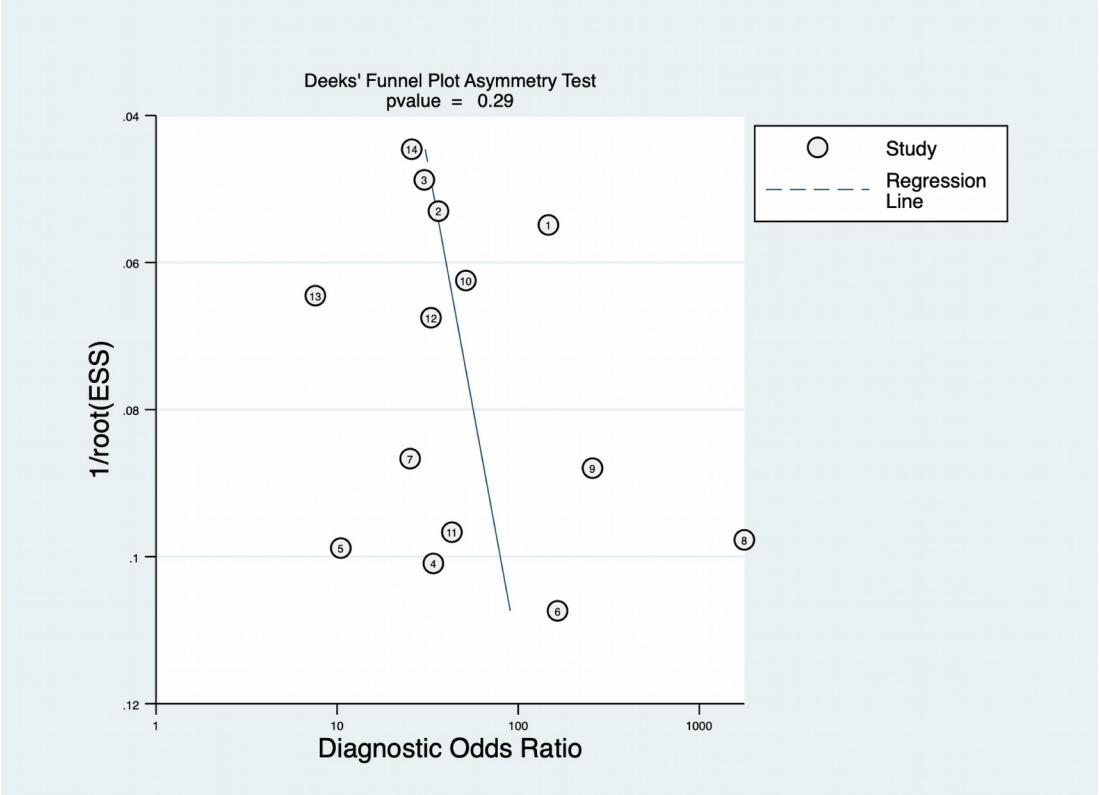


Figure 7: Deek's Funnel Plot Asymmetry Test for the assessment of potential publication bias.

Study		OC					Control			
Asian	Non-Asian	Asian	Non-Asian	Pre	Post	Undetermined	Asian	Non-asian	Pre	Post
8	6	642	649	393	797	1	1858	1290	1991	1157

Table 2: