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Diagnostic value of the Risk of Ovarian Malignancy Algorithm (ROMA) index in the detection of ovarian cancer in postmenopausal women: a systematic review and meta-analysis

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Abstract

Objective Given the significance of ovarian cancer and the importance of early diagnosis, this meta-analysis aimed to assess the diagnostic value of the ROMA index in predicting ovarian cancer in postmenopausal women.

Methods This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant articles were retrieved from databases, including Web of Science, PubMed (MEDLINE), Google Scholar, Scopus, and Embase. The quality of the included studies was assessed using QUADAS-2. The GRADEPRO tool was used to evaluate and grade the quality of the evidence obtained from the meta-analysis. The diagnostic performance of the ROMA index in postmenopausal women was evaluated and comparisons were made using sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and inverse negative likelihood ratio (1/LR-). Data were analyzed in STATA software using the "midas" and "metandi" commands.

Results In this study, 34 out of the 99 identified studies were included in the meta-analysis. Analysis of the ROMA index in postmenopausal Asian women revealed a sensitivity of 88%, specificity of 93%, diagnostic odds ratio (DOR) of 99, positive likelihood ratio (LR+) of 13, negative likelihood ratio (LR-) of 0.131, and inverse negative likelihood ratio (1/LR-) of 8. Furthermore, in cross-sectional studies conducted on postmenopausal women, the ROMA index demonstrated a sensitivity of 90%, specificity of 93%, DOR of 129, LR+ of 14, LR- of 0.106, and 1/LR- of 9. Finally, with a cut-off range of 25.1–40, the ROMA index showed a sensitivity of 90%, specificity of 90%, DOR of 76, LR+ of 9, LR- of 0.115, and 1/LR- of 9. No significant publication bias was detected in this study ($P > 0.05$).

Conclusion The ROMA index showed greater efficacy in postmenopausal Asian women than in their European counterparts. Cross-sectional studies produced larger estimates than cohort studies. Furthermore, the highest estimate of the ROMA index was obtained with a cutoff of (25.1–40) as opposed to (10–25).

Keywords ROMA, Meta-analysis, Ovarian cancer, Diagnostic value, Systematic review

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Introduction

Ovarian cancer is the eighth most common cancer in women, the fifth leading cause of cancer-related death among women, and the second most prevalent malignancy in Europe and the United States [1–3]. Notably, it is recognized as the deadliest cancer of the female



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reproductive system [4, 5]. The early stage symptoms are non-specific [6, 7], and many patients experience gastrointestinal symptoms [8]. As a result, more than 60% of cases are diagnosed when the disease has advanced significantly [8–10].

Diagnosing ovarian cancer at an advanced stage leads to high mortality [6, 11], and is often referred to as the silent killer of women worldwide [12]. Owing to its poor prognosis, the 5-year survival rate is less than 30% [13, 14], and it is estimated that this disease will lead to the death of eight million patients with ovarian cancer between 2022 and 2050 [15]. This cancer primarily affects women during menopause, with the majority of cases occurring between the ages of 55 and 65 years [2]. Early diagnosis is crucial to improve patient survival rates [7, 14, 16] and leads to improved survival rates [17]. Various methods are available for diagnosing ovarian cancer, including clinical examination, pelvic imaging techniques, and serum biomarkers such as CA125 and HE4 [2, 18]. The most commonly used biomarker for diagnosing ovarian cancer is CA125 [6, 19].

This serum biomarker has several limitations, including elevated levels in various benign conditions in women, such as endometriosis, myoma, ovarian cysts, and pelvic inflammatory disease, as well as in non-female malignancies, including colon, pancreatic, breast, bladder, and lung cancers, and physiological conditions such as pregnancy and menstruation [19–21]. Additionally, the sensitivity and specificity of this biomarker are relatively low in the early stages of the disease, and its performance is better in postmenopausal than in premenopausal women [19, 22]. Another biomarker, HE4, has been clinically utilized since 2003 and has demonstrated higher sensitivity (90% vs. 83%) and specificity (95% vs. 85%) than CA125 in identifying ovarian cancer, particularly in the early stages of the disease in premenopausal women [8, 19]. This biomarker was approved by the US FDA for the diagnosis of ovarian cancer [10, 23].

However, HE4 also has several limitations, including the fact that its levels gradually increase with age, which complicates the establishment of a reliable reference range, as well as an increase in cases of lung cancer and kidney failure [8, 22]. In 2009, Moro et al. introduced a new index, ROMA, designed to enhance the diagnostic process by combining existing diagnostic methods [9, 13, 22, 23]. The ROMA index is a composite of CA125 and HE4 levels along with menopausal status [8, 9].

The ROMA index has a significant ability to differentiate ovarian cancer from benign ovarian tumors [5]. Women with a higher ROMA index are at an increased risk of ovarian cancer and should be referred to an oncology specialist for effective treatment [7, 8, 12].

Given the importance of early diagnosis of ovarian cancer, the heterogeneity in the results of primary studies, and the methodological limitations of some published meta-analyses on this topic, the present study utilized the most accurate statistical tools and controlled for confounders through subgroup analysis to assess the diagnostic value of the ROMA index in predicting ovarian cancer in postmenopausal women.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol for this systematic review and meta-analysis has been registered in PROSPERO under ID: CRD42024599579, which is available at: https://www.crd.york.ac.uk/prosp/ero/display_record.php?ID=CRD42024599579. The study was approved by the Ethical Committee of the Urmia University of Medical Sciences (Approval No: IR.UMSU.REC.1403.385).

Retrieval strategy

A comprehensive search of the scientific literature was conducted on December 5, 2024, covering all years of the Web of Science, PubMed (MEDLINE), Google Scholar, Scopus, and Embase databases. To ensure comprehensive coverage, the references cited in the identified articles were also reviewed. The search strategies are available in the Additional file 1.

Literature selection criteria

Inclusion criteria

- 1) full-text publications; 2) the study must involve human subjects; 3) the results of the ROMA index in postmenopausal women must be reported; 4) no language restrictions; 5) studies in which the values of the 2 × 2 table can be calculated; 6) studies in which the patient group included ovarian cancer cases, and the control group included borderline cases and healthy individuals. This study was conducted based on all published articles available in specified databases. Therefore, no geographical restrictions were applied to the study locations or populations. In addition, a literature search was performed without any time restrictions. Data related to postmenopausal women were extracted from studies that included only postmenopausal women, or both premenopausal and postmenopausal women.

Exclusion criteria

- 1) animal studies; 2) Articles without full-text availability; 3) Articles lacking ROMA index data in postmenopausal women; 4) studies in which the values of the 2×2 table could not be extracted.

Quality evaluation

Quality assessment of the articles was performed using the QUADAS-2 tool, which is specifically designed to evaluate the quality of meta-analyses involving diagnostic tests. This tool assesses articles in terms of risk of bias across four domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing. Additionally, it evaluates applicability concerns in three domains, including Patient Selection, Index Test, and Reference Standard [24].

Grading of the evidence

The GRADEPRO tool (<https://gradepro.org/>) was used to evaluate and grade the quality of the evidence obtained from the meta-analysis. This tool is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, which enables researchers to assess the quality of evidence in a systematic and transparent manner. Overall, the quality of evidence was rated moderate, indicating a moderate level of confidence in the effect estimates. This suggests that the true effect is likely to be close to the estimated effect, but there is a possibility that it may be substantially different. The primary reason for downgrading the certainty of the evidence was the high heterogeneity among the studies included in the meta-analysis. This heterogeneity resulted in a downgrade owing to serious inconsistencies, as defined within the GRADE framework. Considerable variability in the results of the primary studies, differences in study populations, measurement tools, and intervention methods were identified as factors contributing to the reduced consistency of the findings. Comprehensive details of the evidence grading based on the five GRADE domains (study limitations, inconsistency, imprecision, indirectness, and publication bias) are presented in the corresponding table in Additional File 2.

Data extraction

The extracted information included the first author, country, continent, year of publication, study design, and values for True Positive (TP), False Positive (FP), False Negative (FN), True Negative (TN), sensitivity, specificity, Positive Likelihood Ratio (LR +), Negative Likelihood

Ratio (LR -), Diagnostic Odds Ratio (DOR), and inverse LR - for postmenopausal women based on the optimal cut-off. These values were extracted from all the articles.

Statistical analysis

The Midas and Metandi packages [25, 26] in Stata 18.0 (Stata Corporation, TX, USA) were used for statistical analysis of the indicators related to the study, including sensitivity, specificity, DOR, LR +, LR -, and 1/LR -. The positive likelihood ratio (LR⁺) is the true-positive rate divided by the false-positive rate, while the negative likelihood ratio (LR⁻) is the false-negative rate divided by the true-negative rate. Likelihood ratios ranged from zero to infinity, with values further from 1.0, providing stronger diagnostic evidence. An LR⁺ value greater than 10 strongly supports ruling in a diagnosis, whereas an LR value close to zero helps rule out disease. An LR⁺ of 1.0, is uninformative, as it means that the test does not distinguish between diseased and healthy individuals. The diagnostic odds ratio (DOR), defined as LR⁺ divided by LR⁻, quantified the overall test performance. It ranges from 0 to infinity, with higher values indicating better discrimination between patients and healthy individuals. A DOR of 1 implies no diagnostic value, whereas values below 1 suggest misleading test interpretation.

Subgroup analysis was also performed based on continent, study method, and cutoff value. The DOR value ranges from zero to infinity, with higher values indicating a greater discriminatory power of the ROMA index in diagnosing ovarian cancer. The SROC curve was constructed using sensitivity and specificity, and the closer the area under the curve (AUC) was to one, the higher the diagnostic validity of the ROMA index. The I² test was used to assess heterogeneity, and Fagan's nomogram was used to examine the relationship between prior and posterior probabilities.

Results

Literature retrieval and characteristics of eligible studies

According to the PRISMA flowchart presented in (Fig. 1), a total of 99 articles were identified through the search strategy. Of these, 21 articles were duplicates, 25 articles contained unrelated data, and nine articles were not relevant to postmenopausal women; thus, they were excluded from the study. After a thorough full-text review and assessment of data consistency, 34 studies were finally included in the analysis.

Following the QUADAS-2 criteria

The quality of the studies included in the analysis was assessed using the QUADAS-2 tool (Table 1). As shown in (Fig. 2), the highest scores for both the "risk of

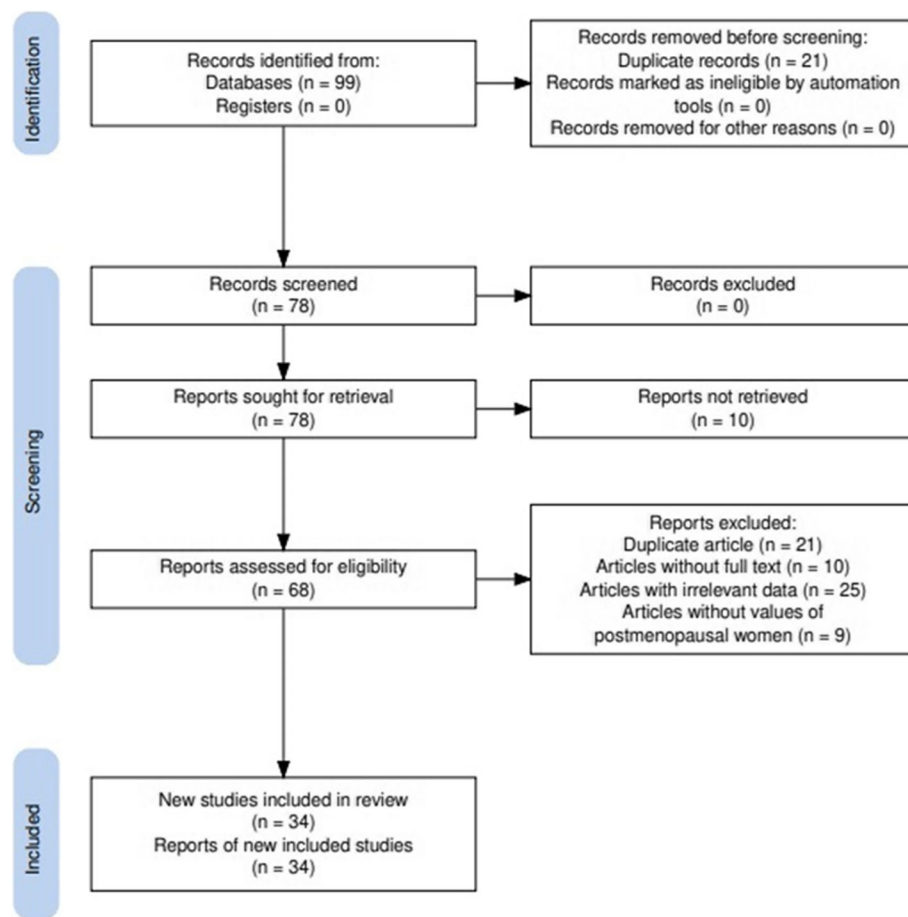


Fig. 1 A flowchart of the study selection process (PRISMA)

bias" and "concerns regarding applicability" domains were attributed to patient selection.

The main characteristics of the included studies in the meta-analysis

Table 2 presents the general information of all studies, including the country where the study was conducted, continent, study design, and validation parameters (sensitivity, specificity, LR +, LR-, DOR, and 1/LR-).

The geographic distribution of studies

As shown in (Fig. 3), The geographic distribution of the studies is depicted on the map. No studies were found in Africa or the Americas; however, the distribution of studies across Asia and Europe includes a considerable number of countries, which may serve as representative samples of these two continents. Therefore, when comparing continents, Europe and Asia received more attention. The map indicates that the majority of studies conducted in Asia on the ROMA index are from China,

Iran, and Vietnam, whereas in Europe, most studies are focused on Italy, the Netherlands, and Spain.

Meta-analysis results and heterogeneity analysis of diagnostic accuracy

The SROC diagram and Forest plot presented in (Fig. 4) illustrate the diagnostic accuracy of the ROMA index in postmenopausal women. The results (Fig. 4A) show that the highest sensitivity, 98%, was reported in the study by Aarenstrup (2012, Denmark), while the lowest sensitivity, 49%, was observed in the study by A. Stiekema (2014, Netherlands). The pooled sensitivity across studies was 90%, which aligns with the value reported in a study by Behnamfar (2023, Iran). Regarding specificity, the highest value of 100% was observed in studies by Farzaneh (2014, Iran), Abha Hada (2020, China), Shoichiro Yamanaka (2022, Japan), and Fariba Behnamfar (2023, Iran). The lowest specificity (59%) was found in the study by Toon Van Gorp (2012, Belgium). The pooled specificity was 89%, which is consistent with the value calculated by Karen K.L. Chan (2012, Asia). The heterogeneity values

Table 1 The quality of included articles according to the QUADAS-2 guidelines

ID	STUDY	Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
1	GONG Shipeng2019 [27]	LOW	LOW	LOW	LOW	LOW	LOW	LOW
2	Laisheng Li2016 [28]	UNCLEAR	LOW	UNCLEAR	UNCLEAR	HIGH	LOW	HIGH
3	Srinivas Kondal-samy2013 [29]	HIGH	UNCLEAR	HIGH	UNCLEAR	HIGH	UNCLEAR	HIGH
4	A. Stiekema2014 [30]	HIGH	LOW	UNCLEAR	HIGH	HIGH	LOW	LOW
5	Elisabetta Bandiera2011 [31]	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW
6	Maria Lycke2018 [32]	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	LOW	LOW
7	Giuseppina Rug-geri2011 [33]	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	LOW	UNCLEAR
8	Nguyen Vu Quoc Huy2018 [14]	HIGH	LOW	LOW	UNCLEAR	LOW	LOW	LOW
9	Khawla Al Musalhi2016 [34]	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	HIGH	UNCLEAR
10	Mona Aarenstrup Karlsen2012 [35]	UNCLEAR	HIGH	UNCLEAR	UNCLEAR	LOW	LOW	HIGH
11	Z.G. Dikmen2014 [2]	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW
12	Toon Van Gorp2012 [36]	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH	HIGH
13	Shoichiro Yamanaka2022 [1]	UNCLEAR	UNCLEAR	LOW	UNCLEAR	HIGH	UNCLEAR	HIGH
14	Lei Zhang2018 [6]	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	LOW	UNCLEAR
15	Zvezdana Špacir Prskalo2018 [37]	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
16	SU WEI2016 [38]	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW
17	Doan Tu Tran2021 [39]	UNCLEAR	LOW	UNCLEAR	UNCLEAR	HIGH	LOW	UNCLEAR
18	Yong-ning CHEN2020 [40]	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	HIGH	LOW
19	Abha Hada2020 [41]	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
20	Fariba Behnamfar2023 [42]	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
21	Zhen Shen2021 [43]	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
22	ANITA CHUDECKA-GLAZ2016 [44]	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW
23	Elisabetta Bandiera2011 [31]	LOW	LOW	UNCLEAR	LOW	UNCLEAR	LOW	LOW
24	Blanca Ortiz-Muñoz2014 [45]	LOW	LOW	UNCLEAR	UNCLEAR	HIGH	LOW	UNCLEAR
25	Karen K.L. Chan2012 [46]	UNCLEAR	LOW	LOW	LOW	HIGH	UNCLEAR	LOW
26	Farah Farzaneh2014 [47]	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
27	Katarzyna M. Terlikowska2016 [48]	UNCLEAR	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW
28	Rafael Molina2011 [49]	UNCLEAR	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR
29	Wen-Ting Chen2014 [50]	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	UNCLEAR	LOW
30	Xinliang Chen2014 [51]	HIGH	UNCLEAR	UNCLEAR	HIGH	HIGH	UNCLEAR	UNCLEAR
31	Ying Xu2015 [52]	LOW	LOW	UNCLEAR	LOW	LOW	LOW	UNCLEAR
32	Ângela Melo2018 [53]	UNCLEAR	HIGH	LOW	UNCLEAR	HIGH	UNCLEAR	LOW
33	Hyun-Jin Choi2019 [54]	HIGH	LOW	LOW	UNCLEAR	HIGH	LOW	LOW
34	ZDENEK NOVOTNY2012 [23]	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	LOW	LOW

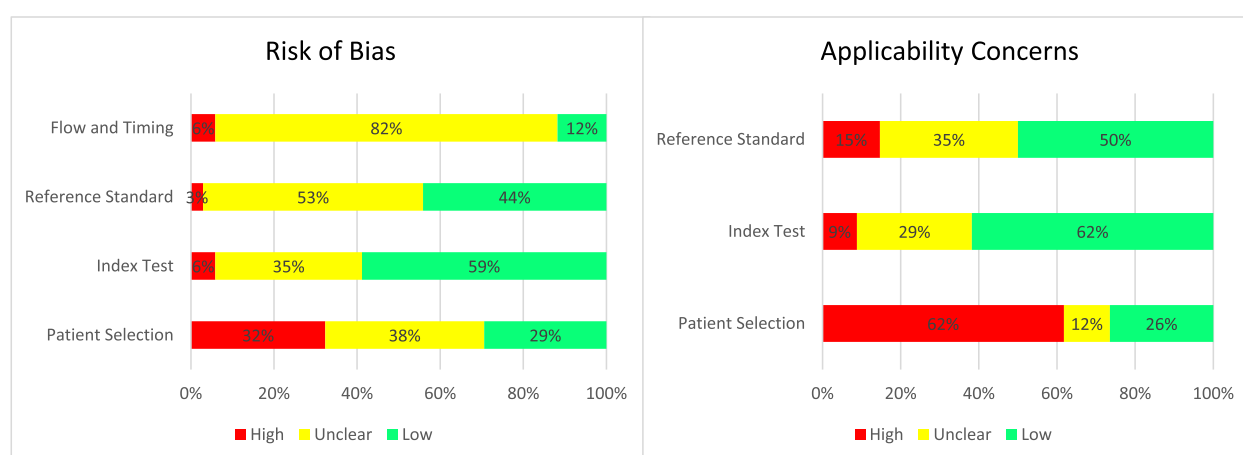


Fig. 2 Risk of bias summary and Applicability Concerns graph(QUADAS-2)

for sensitivity and specificity were $I^2 = 93.06$, $p = 0.00$, and $I^2 = 81.67$, $p = 0.00$, respectively. These results suggest a high degree of heterogeneity in the sensitivity and specificity across the included studies. The SROC plot (Fig. 4B) displays the intersection points of sensitivity and specificity for the ROMA index based on the studies reviewed. This plot includes a summary point representing the combined sensitivity and specificity of all studies. The number of circles in the SROC diagram represents the number of included studies. The dashed line around this summary point denotes the confidence interval (CI) within which the true values are expected to fall with a 95% probability. Two studies, Lei Zhang (2018, China) and Zvezdana Špacir Prskalo (2018, Croatia), were within this confidence interval. The dotted line in the plot represents the prediction region, indicating that, if the ROMA index is applied to new individuals, there is a 95% probability that the values will fall within this region. Furthermore, the SROC chart showed an AUC of 0.95, indicating high diagnostic accuracy of the ROMA index for detecting ovarian cancer. Fagan's nomogram (Fig. 4C) illustrates that with a pre-test probability of 25% and PLR of 9, the post-test probability (PPV) increased to 74%. This finding suggests that a positive ROMA index result significantly increases the likelihood of the disease being present.

Subgroup analyses

The diagnostic performance of the ROMA index varies depending on factors such as the continent where the study was conducted, type of study design, and cut-off value used. These factors contributed to the observed heterogeneity (Table 3), and understanding their impact is crucial for interpreting the overall findings of this meta-analysis. Investigating these variations

will help optimize the application of the ROMA index in different clinical settings and populations.

Analysis of the SROC curves for postmenopausal women of Asian and European descent revealed that the summary point for Asian women was closer to the top-left corner (0,1) of the curve. This indicates the superior diagnostic performance of the ROMA index in this population compared to that in European women (18 studies vs. 15 studies) (Fig. 5A, B). This observation was further supported by a comparison of the Diagnostic Odds Ratio (DOR), which was 99 for Asian women and 57 for European women. A higher DOR reflects better discriminatory ability between diseased and non-diseased individuals. The difference in diagnostic performance may be attributed to genetic variations, biological differences, or regional differences in diagnostic procedures and healthcare practices.

When comparing SROC curves based on study design, cross-sectional studies showed a smaller distance from the top-left corner (0,1) than cohort studies. This suggests that cross-sectional studies provide higher estimates of the diagnostic accuracy of the ROMA index (4 studies vs. 27 studies) (Fig. 6A, B). This finding was further validated by the DOR comparison, where cross-sectional studies reported a DOR of 129 compared to 77 in cohort studies. This variation may be due to methodological differences between study designs. Cross-sectional studies assess subjects at a single point in time, which can lead to inflated estimates of sensitivity and specificity. In contrast, cohort studies follow participants over time, which may introduce variability and lower the diagnostic estimates. These results highlight the importance of considering study design when interpreting the diagnostic accuracy of the ROMA index.

Table 2 The main characteristics of the included studies in the meta-analysis

ID	Author	Country	Cancer Type	Time Frame	Continent	Design	N	TP	FP	FN	TN	Sensitivity	Specificity	LR +	LR-	DOR	1/LR-
1	GONG Shihong 2019 [27]	China	EOC, BOT	Sep 2014_ Nov 2016	Asia	Cross-sectional	719	68	10	6	48	0.918919	0.827586	5.32973	0.097973	54.4	10.2069
2	Laisheng Li 2016 [28]	China	OC	Sep 2012_ Apr 2014	Asia	Cohort	1189	70	5	12	85	0.853659	0.944444	15.36585	0.15495	99.16667	6.453704
3	Srinivas Kondalsamy 2013 [29]	Australia	EOC	NA	Australia	Case control	158	27	13	11	34	0.710526	0.723404	2.568826	0.400155	6.41958	2.499033
4	A. Stiekema 2014 [30]	Netherlands	EOC	Feb 1994_ Nov 2008	Europe	Cohort	361	106	18	111	59	0.488479	0.766234	2.089606	0.667578	3.13013	1.497952
5	Elisabetta Bandiera 2011 [31]	Italy	EOC	2003_2010	Europe	Cohort	419	81	15	6	81	0.931034	0.84375	5.958621	0.081737	72.9	12.23438
6	Maria Lycke 2018 [32]	Sweden	EOC, BOT	Sep 2013_ Feb 2016	Europe	Clinical trial	638	102	2	10	8	0.910714	0.8	4.553571	0.111607	40.8	8.96
7	Giuseppina Ruggeri 2011 [33]	Italy	EOC	2006	Europe	Cohort	259	72	7	3	22	0.96	0.758621	3.977143	0.052727	75.42857	18.96552
8	Nguyen Vu Quoc Huy 2018 [14]	Vietnam	EOC	Jan 2016_ Nov 2017	Asia	Cross-sectional	277	14	1	3	29	0.823529	0.966667	24.70588	0.182556	135.3333	5.477778
9	Khawla Al Musalhi 2016 [34]	Oman	EOC	Mar 2014_ Apr 2015	Asia	Cross-sectional	213	25	5	2	19	0.925926	0.791667	4.444444	0.093567	47.5	10.6875
10	Mona Aarestrup Karlsson 2012 [35]	Denmark	EOC, BOT	Sep 2004_ Jan 2010	Europe	Cohort	1218	198	70	5	209	0.975369	0.749104	3.887544	0.03288	118.2343	30.41362
11	Z.G. Dikmen 2014 [2]	Turkey	OC	NA	Europe	Cohort	249	32	1	1	12	0.969697	0.923077	12.60606	0.032828	384	30.46154
12	Toon Van Gorp 2012 [36]	Belgium	EOC	Aug 2005_ Mar 2009	Europe	Cohort	432	101	35	10	50	0.90991	0.588235	2.209781	0.153153	14.42857	6.529412
13	Shoichiro Yamanaka 2022 [1]	Japan	EOC, BOT	Jan 2007_ Jul 2021	Asia	Cohort	171	45	0	6	5	0.882353	1	N/A	0.117647	N/A	8.5
14	Lei Zhang 2018 [6]	China	EOC, BOT	Jul 2016_ Jul 2017	Asia	Cohort	373	103	5	15	55	0.872881	0.916667	10.47458	0.138675	75.53333	7.211111
15	Zvezdana Špacir Prskalo 2018 [37]	Croatia	EOC, BOT	May 2015_ May 2017	Europe	Cohort	159	32	5	4	53	0.888889	0.913793	10.31111	0.121593	84.8	8.224138

Table 2 (continued)

Id	Author	Country	Cancer Type	Time Frame	Continent	Design	N	TP	FP	FN	TN	Sensitivity	Specificity	LR +	LR-	DOR	1/LR-
16	SUWEI 2016 [38]	China	OC,BOT	Sep 2013_ May 2015	Asia	Cohort	158	34	1	3	32	0.918919	0.969697	30.32432	0.083615	362.6667	11.9596
17	Doan Tu Tran 2021 [39]	Vietnam	EOC	Jan 2018_ Jun 2020	Asia	Cohort	475	28	1	9	67	0.756757	0.985294	51.45946	0.246874	208.4444	4.050654
18	Yong-ning CHEN 2020 [40]	China	EOC,BOT	Sep 2014_ Nov 2016	Asia	Cohort	719	68	10	6	48	0.918919	0.827586	5.32973	0.097973	54.4	10.2069
19	Abha Hada 2020 [41]	China	EOC,BOT	Jan 2014_ Dec 2014	Asia	Cohort	155	15	0	4	23	0.789474	1	N/A	0.210526	N/A	4.75
20	Fariba Behnamfar 2023 [42]	Iran	EOC,BOT	2020_2021	Asia	Cross-sectional	203	19	0	2	42	0.904762	1	N/A	0.095238	N/A	10.5
21	Zhen Shen 2021 [43]	China	EOC	Jul 2005_ Jun 2018	Asia	Cohort	509	113	8	8	42	0.933884	0.84	5.836777	0.078709	74.15625	12.705
22	ANITA CHUDECKA-GŁAZ 2016 [44]	Poland	OC,BOT	Nov 2012_ Dec 2014	Europe	Cohort	619	116	15	8	71	0.935484	0.825581	5.363441	0.078146	68.63333	12.79651
23	Elisabetta Bandiera 2011 [31]	Italy	EOC	2003–2010	Europe	Cohort	419	81	15	6	81	0.931034	0.84375	5.958621	0.081737	72.9	12.23438
24	Blanca Ortiz-Muñoz 2014 [45]	Spain	EOC	Jan 2014_ Apr 2014	Europe	Cohort	218	18	5	1	80	0.947368	0.941176	16.10526	0.055921	288	17.88235
25	Karen K.L. Chan 2012 [46]	Asia	EOC	2009–2010	Asia	Cohort	414	40	6	3	47	0.930233	0.886792	8.217054	0.078674	104.4444	12.71069
26	Farah Farzaneh 2014 [47]	Iran	EOC	Mar 2012_ Mar 2013	Asia	Clinical trial	99	18	0	4	9	0.818182	1	N/A	0.181818	N/A	5.5
27	Katarzyna M. Terlikowska 2016 [48]	Poland	EOC	2012_2016	Europe	Cohort	224	56	2	7	39	0.888889	0.95122	18.22222	0.116809	156	8.560976
28	Rafael Molina 2011 [49]	Spain	OC	NA	Europe	Cohort	527	80	10	4	49	0.952381	0.830508	5.619048	0.057337	98	17.44068
29	Wen-Ting Chen 2014 [50]	China	EOC	Jun 2010_ Mar 2013	Asia	Cohort	297	63	3	6	12	0.913043	0.8	4.565217	0.108696	42	9.2

Table 2 (continued)

Id	Author	Country	Cancer Type	Time Frame	Continent	Design	N	TP	FP	FN	TN	Sensitivity	Specificity	LR +	LR-	DOR	1/LR-
30	Xinliang Chen 2014 [51]	China	OC	Mar 2012_ Mar 2014	Asia	Cohort	232	37	1	3	21	0.925	0.954545	20.35	0.078571	259	12.72727
31	Ying Xu 2015 [52]	China	EOC,BOT	Jul 2013_ Now 2014	Asia	Cohort	1021	81	4	22	43	0.786408	0.914894	9.240291	0.233461	39.57955	4.283366
32	Ângela Melo 2018 [53]	Portugal	EOC,BOT	Jan 2013_ Dec 2016	Europe	Cohort	247	20	4	5	60	0.8	0.9375	12.8	0.213333	60	4.6875
33	Hyun-Jin Choi 2019 [54]	Korea	EOC,BOT	Mar 2010_ Apr 2014	Asia	Cohort	649	215	2	37	76	0.853175	0.974359	33.27381	0.150689	220.8108	6.636175
34	ZDENEK NOVOTNY 2012 [23]	Czech	OC	2010_2011	Europe	Cohort	277	20	31	1	225	0.952381	0.878906	7.864823	0.05418	145.1613	18.45703

N/A not applicable, NA not available in study, N Sample Size, OC Ovarian Cancer, EOC Epithelial Ovarian Cancer, BOT Borderline Ovarian Tumors

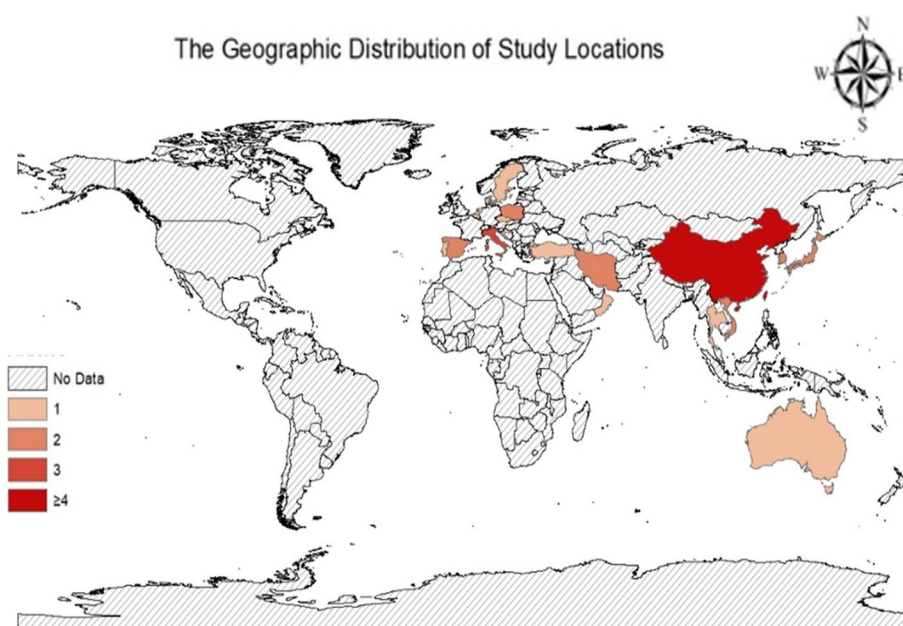


Fig. 3 The geographic distribution of studies

A comparison of SROC curves based on different ROMA index cut off values showed that the summary point for the 25.1–40 range was closer to the top left corner (0,1) than that for the 10–25 range. This indicates superior diagnostic performance within the 25.1–40 range (4 studies vs. 27 studies) (Fig. 7A, B). The DOR analysis supported this finding, with a DOR of 75 for the 25.1–40 range compared to 41 for the 10–25 range. The choice of an optimal cut off value is crucial in clinical applications of the ROMA index, as inappropriate thresholds may lead to increased false-positive or false-negative results, affecting patient management and treatment decisions.

Analysis based on likelihood ratio scattergram

In this study, the diagnostic value of the ROMA index was evaluated based on a likelihood ratio scattergram. According to this chart, for the application of the ROMA index in postmenopausal Asian women, the summary point was located in the second quartile (Fig. 8A) because $LR+ > 10$ and $LR- < 0.1$. Therefore, based on this chart, the ROMA index is useful only for confirming the diagnosis of ovarian cancer in postmenopausal Asian women and not for excluding this disease. For postmenopausal European women, the summary point was in the fourth quartile, indicating that the ROMA index is not useful for confirming or excluding the disease. Based on the study design (cross-sectional and cohort studies), the summary point in cross-sectional studies also fell into the second quartile (Fig. 8B), suggesting that the ROMA index is

useful only for confirming the diagnosis of ovarian cancer in postmenopausal women. In cohort studies, the summary point was located in the fourth quartile, indicating that the ROMA index was not useful for confirming or excluding the disease.

Detection of the publication bias

In the Deeks' Funnel Plot Asymmetry Test, the p -value was 0.30, indicating the absence of publication bias in this study (Additional file 3).

Discussion

Ovarian cancer is a malignant and aggressive cancer often referred to as the "silent killer" of women worldwide [11]. The risk of ovarian malignancy algorithm (ROMA) index is an innovative approach for diagnosing ovarian cancer that combines CA125 and HE4 levels with menopausal status [8, 9]. Numerous studies have been conducted to evaluate the diagnostic value of the ROMA index; however, these studies often yield debatable results owing to variations in study designs and heterogeneous findings. Therefore, we conducted this meta-analysis to estimate the diagnostic performance of the ROMA index for ovarian cancer.

In this meta-analysis, the ROMA index demonstrated a sensitivity of 0.89, specificity of 0.89, diagnostic odds ratio (DOR) of 68, positive likelihood ratio ($LR+$) of 8, and negative likelihood ratio ($LR-$) of 0.119, with the inverse of $LR-$ ($1/LR-$) equal to 8. These values indicate that the ROMA index is highly effective in diagnosing

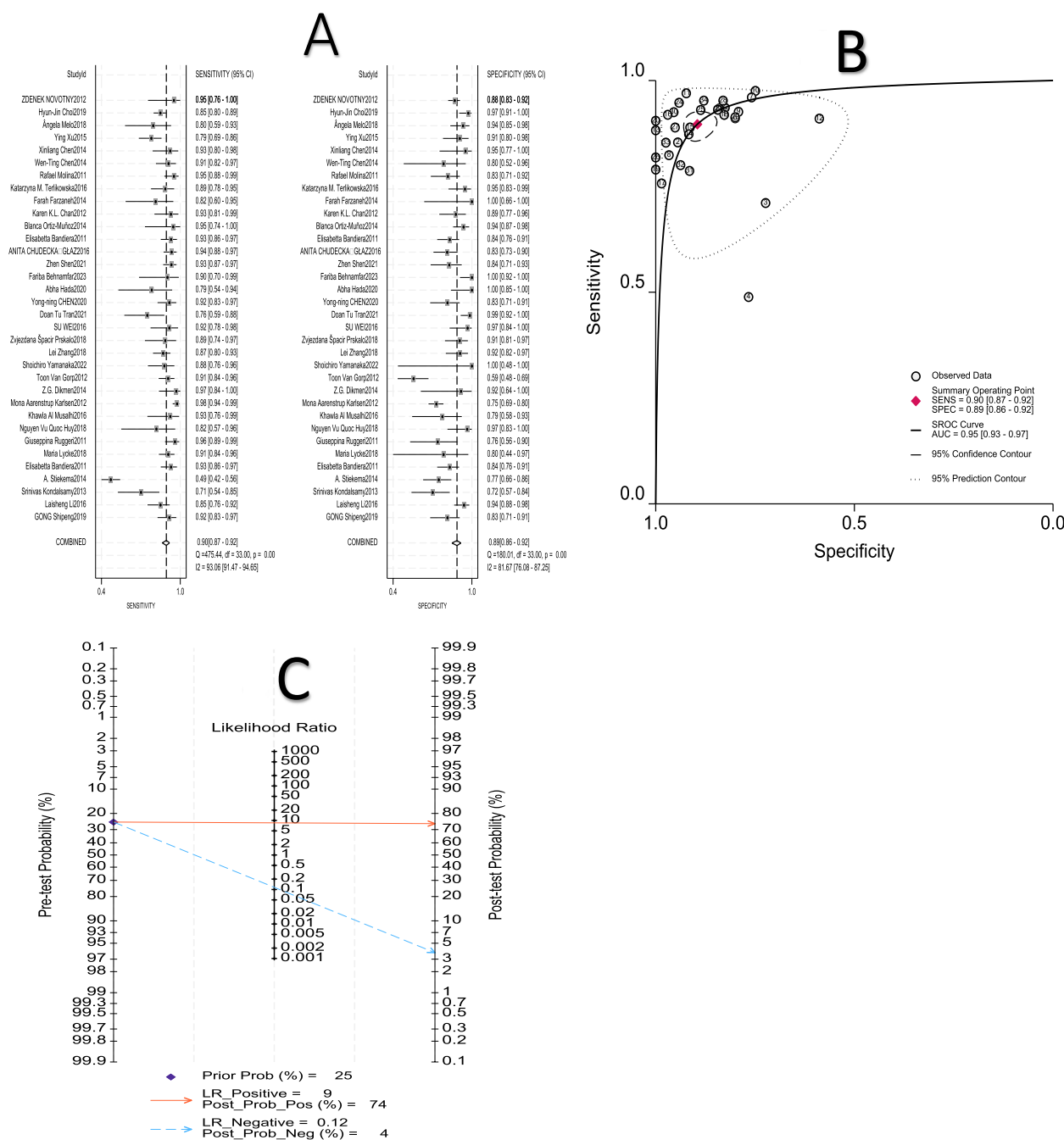


Fig. 4 A = forest plot B = SROC models C = Fagan's plot for postmenopausal woman

ovarian cancer. Owing to significant heterogeneity across the included studies, we applied a bivariate random effects model to minimize potential bias arising from this variability. To further investigate the sources of heterogeneity, subgroup analyses were conducted based on continent (Asia and Europe), study design (cohort and cross-sectional), and cutoff value ranges (cutoff: 10–25 vs. cutoff: 25.1–40). The results indicated that the ROMA

index exhibited higher diagnostic accuracy in postmenopausal Asian women than in postmenopausal European women (DOR = 13 vs. DOR = 6). Additionally, cross-sectional studies provided higher estimates of the diagnostic value compared than cohort studies (DOR = 129 vs. DOR = 77). Regarding cutoff values, the 25.1–40 range showed better diagnostic performance than the 10–25 range (DOR = 76 vs. DOR = 42).

Table 3 Summary of Total and subgroup analysis of ROMA index for postmenopausal women

		Postmenopausal woman					
		Total	Continent		Study design		Cut-offs
			Asia	Europe	Cross sectional	Cohort	
							Cut-off = (10–25) Cut-off = (25.1–40)
Optimal cut off	Sensitivity	0.89	0.878	0.914	0.901	0.902	0.922
	Specificity	0.89	0.932	0.843	0.934	0.894	0.779
	DOR	68	98.972	57.085	128.658	77.331	41.621
	LR +	8	12.992	5.81	13.609	8.497	4.177
	LR-	0.119	0.131	0.102	0.106	0.11	0.1
	1/LR-	8	7.618	9.826	9.454	9.101	9.965

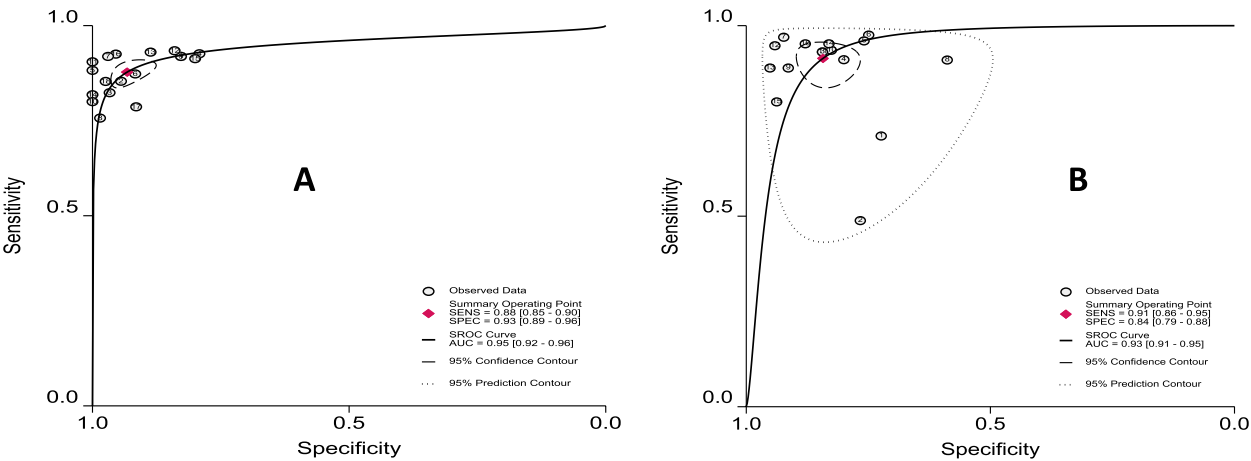


Fig. 5 A: SROC for postmenopausal Asian women B: SROC for postmenopausal European women

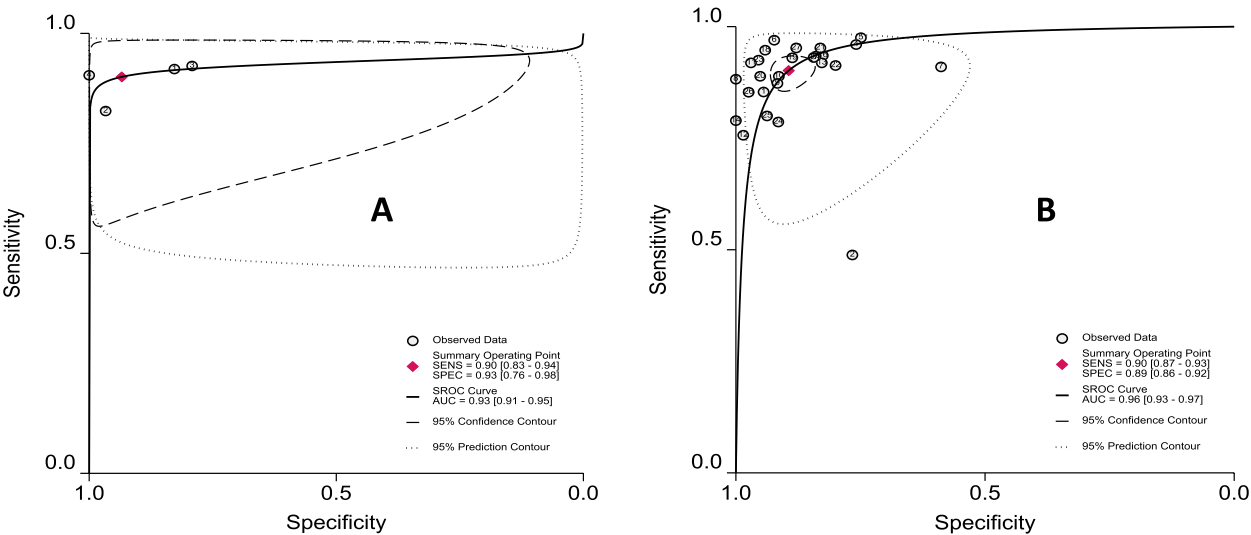


Fig. 6 A: SROC for cross-sectional studies B: SROC for cohort studies

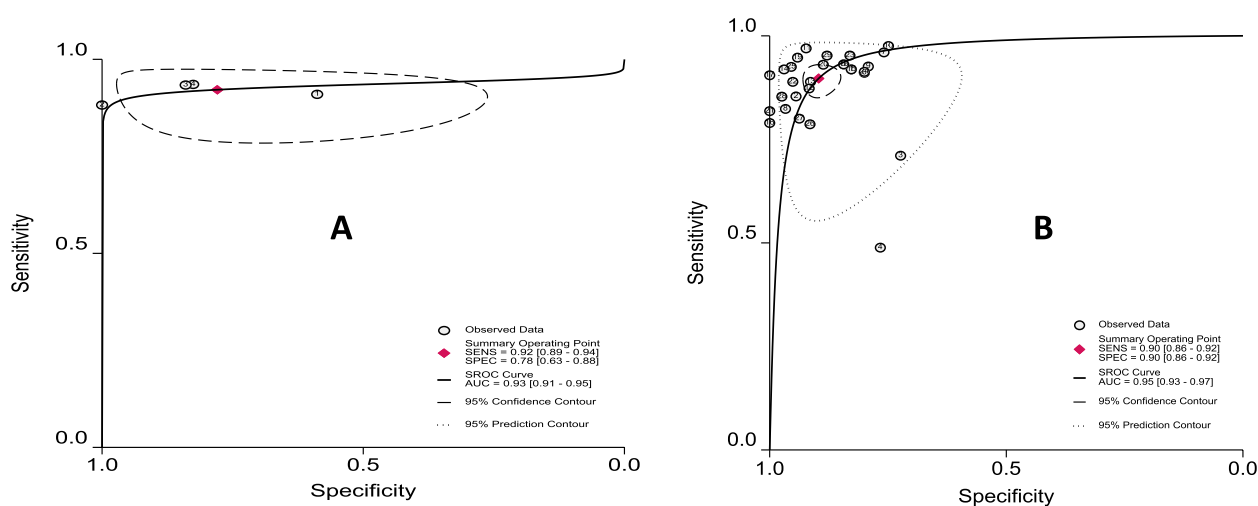


Fig. 7 A: SROC based on cut-off (10–25) B: SROC based on cut-off (25.1–40)

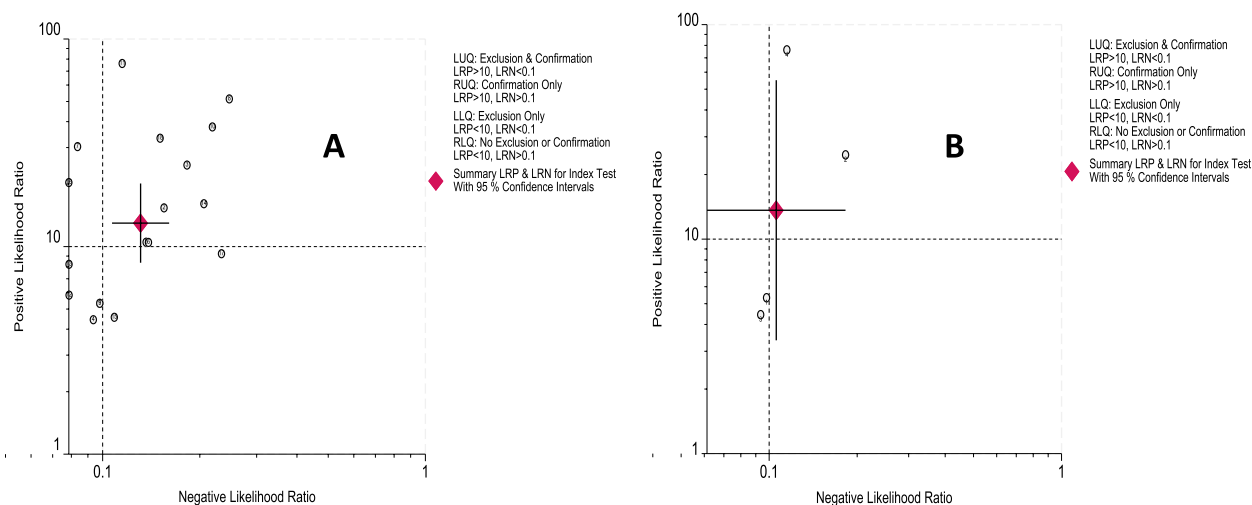


Fig. 8 A: likelihood ratio scattergram for postmenopausal Asian women B: likelihood ratio scattergram for cross-sectional studies

Our analysis was based on the results of studies conducted in China, Vietnam, Oman, Iran, Korea, Singapore, Taiwan, Malaysia, Japan, Thailand, Turkey, the Netherlands, Italy, Sweden, Denmark, Belgium, Poland, Croatia, Spain, Portugal, the Czech Republic, and Australia. However, the majority of studies from Asia have focused on China and Iran, which could potentially influence the results of our analysis. However, these two countries are geographically large and represent both distant and nearby Asia. Despite these limitations, this meta-analysis included all the available evidence. Moreover, the number of studies included in this meta-analysis was higher than that in previous meta-analyses. According to the findings, which suggest that the ROMA index is more

effective in postmenopausal Asian women than in postmenopausal European women, the best explanation is that the effectiveness and positive predictive value (PPV) of screening tests are enhanced when the incidence of the disease increases [55, 56]. The overall incidence of cancer in Asian countries, including China [57] and Iran [58–60], is increasing. Given the issue of underreporting, the actual prevalence is likely higher than that reflected in the official statistics [61]. Consequently, the performance and utility of diagnostic tests are expected to be higher in such populations. As the incidence of ovarian cancer is higher in Asian countries than in European countries [62], this may explain why the ROMA index shows better performance in postmenopausal Asian women. The

5-year survival rate in countries like China, which is the focus of most studies in this analysis, ranges from 40 to 49% [62]. This increase in survival rates compared with other regions has led to an increase in the prevalence of ovarian cancer, ultimately increasing the positive predictive value of the test [63, 64]. Additionally, other factors, such as improved diagnostic capabilities within the healthcare systems of these countries, may contribute to increased detection rates of ovarian cancer, ultimately leading to an increase in the reported incidence. Social Determinants of Health encompass non-medical factors that play a crucial role in shaping health outcomes and directly impact health equity [65]. Among these, socioeconomic status is considered a key indicator of SDH, encompassing factors such as financial resources, education level, and access to healthcare services. Disparities in SES can contribute to inequalities in cancer diagnosis and prognosis, influencing both the accessibility of early detection and the effectiveness of treatment interventions [66]. Postmenopausal Asian women with a lower socioeconomic status may have limited access to routine screening programs, leading to the diagnosis of ovarian cancer at more advanced stages. At these stages, the Risk of Ovarian Malignancy Algorithm (ROMA) index may have a higher diagnostic value owing to the larger tumor burden and increased detectability. In contrast, postmenopausal European women with a higher socioeconomic status are more likely to have access to regular screening programs, resulting in earlier detection of malignancies. In such cases, the sensitivity of the ROMA index may be reduced because of the detection of tumors at earlier stages with lower biomarker expression [67]. Genetic factors, particularly mutations in the BRCA1 and BRCA2 genes, are associated with ovarian cancer susceptibility [68]. These mutations may vary across populations in different continents, potentially contributing to differences in the diagnostic performance of the ROMA index. Further extensive studies are required to explore this variability and its clinical implications.

The strengths of this meta-analysis include the inclusion of 34 studies, which provided greater diversity than previous studies. Additionally, subgroup analyses based on continent, study design, and cutoff values, which were not performed in any prior meta-analysis of the ROMA index, provide valuable insights. Moreover, this study utilized the "midas" and "metandi" commands, tools commonly used to assess diagnostic test accuracy, whereas earlier meta-analyses conducted in 2012 [69], 2014 [70], 2016 [71], 2019 [72] and 2021 [73] employed the "metaDisc" command. The commands used in earlier studies were less robust and yielded more limited outputs, whereas those applied in the current study allowed for the analysis of multiple dimensions of the problem, providing

more accurate results. In previous studies, the highest reported estimate of the ROMA index was obtained in a 2021 study (DOR = 44), whereas in the present study, a higher estimate of the ROMA index was obtained, particularly in cross-sectional studies (DOR = 129).

Limitation and conclusion

However, this study had several limitations that must be considered when interpreting the results. A primary challenge was limited access to full-text articles, which restricted comprehensive subgroup analyses for more precise evaluation of ROMA's diagnostic performance across key variables such as different study methodologies, disease stages (early vs. advanced), and histological tumor types (e.g., serous, endometrioid, mucinous, and clear cell carcinomas). Additionally, limitations in the available data within the included studies restricted further subgroup analyses in areas such as lifestyle factors and precise age classification. In this meta-analysis, the researchers utilized all available scientific evidence from reputable databases to assess ROMA's diagnostic accuracy with maximal precision. Nevertheless, a concerning finding was the paucity of adequate research on this index's diagnostic value in many countries worldwide. This data gap may prevent a comprehensive understanding of ROMA's actual performance across diverse populations. For instance, in the subgroup analysis by continent (Asia vs. Europe), more studies originated from Asia (18 vs. 15). Similarly, in the subgroup analysis based on study design, the majority were cohort studies (27 vs. 4 cross-sectional studies). In terms of cutoff values, more studies used a cutoff range of 25.1–40 than 10–25 (27 vs. 4). This imbalance in the number of studies within the subgroups may affect the accuracy of the results because a smaller number of studies leads to reduced sample sizes and decreased precision of estimates, which in turn may limit the generalizability of the findings to global populations. To address these limitations, future multicenter prospective studies involving medical centers in various countries with racial, ethnic, and geographic diversity are essential. Such studies would not only provide more comprehensive data on ROMA's diagnostic accuracy across populations but also enable evaluation of potential confounding factors, including genetic variations, lifestyle factors, and healthcare access disparities. Expanding this research could advance clinical knowledge in several ways. First, it significantly enhanced the external validity of the findings. Second, it would facilitate a more accurate identification of patient subgroups that would benefit most from this diagnostic index. Third, the resulting data can provide a robust scientific foundation for refining and optimizing

current diagnostic algorithms, including the ROMA index. Ultimately, these advancements could lead to the development of more precise and personalized clinical guidelines that improve diagnostic and therapeutic decision-making globally, thereby significantly enhancing the quality of care for patients with ovarian cancer. This achievement would be particularly valuable for developing countries facing greater diagnostic challenges.

Based on analyses conducted using studies on the ROMA index and employing subgroup analysis and likelihood ratio scattergrams, it was concluded that the ROMA index demonstrates higher diagnostic performance in postmenopausal Asian women than in postmenopausal European women. Furthermore, the ROMA index with a cut-off (25.1–40) showed better performance than the cut-off (10–25). In addition, cross-sectional studies have provided higher estimates than cohort studies.

Abbreviations

DOR	Diagnostic odds ratio
LR +	Positive likelihood ratio
LR-	Negative likelihood ratio
CA125	Carbohydrate antigen 125
HE4	Human epididymis protein 4
ROMA	Risk of Ovarian Malignancy Algorithm;
GRADE	Grading of Recommendations Assessment, Development and Evaluation
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
SROC	Summary receiver operating character
OC	Ovarian Cancer
EOC	Epithelial Ovarian Cancer
BOT	Borderline Ovarian Tumors

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12905-025-03766-4>.

Additional file 1. Search strategy.

Additional file 2. The Grading of Recommendations, Assessment, Development and Evaluation approach was applied based on the characteristics of the studies included in meta-analysis.

Additional file 3: Fig. 1. Deeks' Funnel Plot Asymmetry Test to Assess Publication Bias.

Acknowledgements

The authors would like to express their gratitude to the Clinical Researches. Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran, for English editing and other improvement process.

Authors' contributions

A.F, J.R, and H.G designed the study. A.F conducted the literature review, screening and selection of studies, and data collection. A.F and M.H assessed the risk of bias. A.F and M.H performed the statistical analyses. A.F, M.H, and J.R completed the final manuscript.

Funding

No funding.

Data availability

The data supporting the findings of this study are provided in tabular format within the manuscript itself.

Declarations

Ethics approval and consent to participate

Not applicable.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 19 February 2025 Accepted: 2 May 2025

Published online: 05 June 2025

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