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Review Article

Sentinel lymph node biopsy in apparently early-stage epithelial ovarian cancer: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the detection rate, sensitivity, and negative predictive value (NPV) of sentinel lymph node (SLN) biopsy in patients with apparently early-stage epithelial ovarian cancer (EOC).

Methods: A systematic search of multiple electronic databases was conducted from inception to October 31, 2025. Studies reporting detection rate, sensitivity, and NPV of SLN biopsy in apparently early-stage EOC, with completion pelvic and para-aortic lymphadenectomy as reference standard, were included. Study selection, risk-of-bias assessment, and data extraction were independently performed by four reviewers. Pooled estimates with 95 % confidence intervals (CI) were calculated using random-effects models on a per-patient basis and by anatomical site. Heterogeneity was assessed using the I^2 statistic.

Results: Fourteen studies comprising 365 patients were included. Most studies used indocyanine green injected into the infundibulopelvic ligament for para-aortic mapping and the utero-ovarian ligament for pelvic mapping. The pooled para-aortic detection rate was 79.9 % (95 %CI 66.1–91.4 %; $I^2 = 74$ %), while the pelvic detection rate was 42.7 % (95 %CI 28.5–57.3 %; $I^2 = 71$ %). Pooled NPV was 100 % in both para-aortic and pelvic regions ($I^2 = 0$ %). Sensitivity was 97.8 % (95 %CI 84.0–100 %) in the para-aortic area and 100 % (95 %CI 75.3–100 %) in the pelvis.

Conclusions: In apparently early-stage EOC, SLN biopsy shows acceptable para-aortic detection but limited pelvic detection. Nonetheless, sensitivity and NPV indicate high diagnostic accuracy. Further studies are needed to optimize pelvic mapping strategies and confirm these findings. At present, sentinel lymph node mapping in apparently early-stage epithelial ovarian cancer should be regarded as investigational and not as standard of care.

1. Introduction

Ovarian cancer is the seventh most common malignancy among women and accounts for more deaths than any other cancer of the female genital tract in developed countries. Early detection offers the potential for a favorable prognosis and effective treatments, benefiting approximately 10–20 % of patients [1,2].

The comprehensive surgical staging in apparently early-stage epithelial ovarian cancer (EOC) involves systematic pelvic and para-aortic lymphadenectomy due to the possibility of upstaging. Histological examination finds nodal metastases in about 15 % of patients with apparent early-stage disease, who may greatly benefit from targeted adjuvant chemotherapy and maintenance treatment [3,4]. In this context, sentinel lymph node (SLN) mapping is an appealing alternative to systematic lymphadenectomy, as it may reduce morbidity while ensuring adequate staging [5].

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Nevertheless, despite endorsements by various researchers [6], challenges remain in adopting an SLN mapping algorithm for early-stage EOC [7]. Notably, the SELLY Trial, the most extensive prospective study to date on SLN mapping in early-stage EOC, failed to meet expectations, showing low detection rates and sensitivity [8]. However, due to the wide variation in results and ongoing practical issues with the SLN mapping technique, further research is necessary.

Well-established knowledge regarding endometrial and cervical cancer demonstrated that the effectiveness of an SLN algorithm is greater when each node area is considered a separate unit and a completion lymphadenectomy is carried out where mapping is unsuccessful [3,6,7]. Considering these fundamental aspects of SLN biopsy in gynecologic oncology, we aimed to identify the limitations of current evidence and explore ways to improve further the investigation of the SLN biopsy technique in EOC. So far, no comprehensive systematic review has included both the SELLY trial and all other smaller studies available. Due to the limited number of cases reported in the literature, it is crucial to gather and analyze all available data, including those from smaller case series, to prevent losing valuable information [8]. On this basis, we conducted a systematic review and meta-analysis to reevaluate existing evidence on SLN biopsy in apparently early-stage EOC, and in particular, to estimate the detection rate, sensitivity, and negative predictive value (NPV) for the pelvic and para-aortic areas separately.

2. Materials and methods

2.1. Eligibility criteria, information sources, search strategy

The systematic review and meta-analysis was planned before starting the online search, considering the population of interest, test and reference standard, outcome measures, study eligibility criteria, and statistical analyses, including subgroup analyses. This study was deemed exempt from Institutional Review Board approval. The review and meta-analysis were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [9] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) [10]. The protocol was registered on PROSPERO in accordance with the registration policy (ID: CRD420251167753).

All authors participated in the design of the search strategy and the definition of inclusion and exclusion criteria. We included all studies that met the following inclusion criteria. Population: patient with apparently early-stage EOC defined as preoperative clinical or radiological apparent FIGO stage I or II EOC; Index test: pelvic and para-aortic SLN mapping; Reference test: completion pelvic and para-aortic lymphadenectomy; Outcomes: overall (per patient) detection rate, sensitivity, and negative predictive value; site-specific pelvic and para-aortic detection rate, sensitivity, and negative predictive value. Outcomes eligibility required reporting enough data to estimate at least one of the outcomes. We excluded studies that included only patients with borderline or benign adnexal tumors, as well as those with non-primary ovarian malignancies. We excluded review articles and any records that did not present study data. No language exclusion criterion was applied. For non-English titles, abstracts, or full-text records obtained through the literature search, translation using Google Translator was planned, a validated method for conducting systematic reviews [11].

An expert and certified professional librarian (Biblioteca Meneghetti, University of Verona) performed a literature search of records from January 1, 1989, up to October 31, 2025, in the electronic databases EMBASE, Scopus, PubMed/MEDLINE, Web of Science, and the Cochrane Library. The literature search was made in conjunction with a gynecologist and included the combinations of the following keywords and MeSH terms: "ovarian cancer," "early stage," "Indocyanine green," "Methylene blue," "Technetium 99," "Lymph Node Metastasis," "sentinel lymph node," "lymphadenectomy," "(para-/lumbo-) aortic," "pelvic," "dissection," "sentinel node," "ultra-staging," "tracer," and "injection." The detailed search strategy is available as Supplementary Material. The references of all included records were systematically revised to identify other eligible publications.

2.2. Study selection and data extraction

Three reviewers (PCZ, SG, RV) independently screened the titles and abstracts of records obtained by the literature search after duplicate removal and assessed the full text of potentially eligible records for inclusion. In cases of disagreement, the record was reexamined with a further reviewer (SU). Two reviewers extracted the data using a standardized form (PCZ, RV). The dataset comprised the following information: first author, publication year, research setting, study design, patient population, details of SLN biopsy technique, adverse events, outcome measures with details regarding their assessment and the definitions used, and items for quality evaluation.

We gathered information regarding the SLN technique, including the surgical approach, the injection site of the tracer, the tracer used, and the type of histological evaluation of the SLN. Ultra-staging was defined as any procedure beyond the routine assessment of sentinel lymph nodes. We extracted data regarding SLN mapping overall by patient and site-specific by pelvic and para-aortic area. From each included study, we extracted the absolute number of total patients, pelvic areas (hemipelvis), and para-aortic areas who underwent SLN mapping, as well as the absolute number of patients, hemipelvis, and para-aortic areas in which at least one SLN was mapped. Among mapped SLNs, we extracted the absolute number of true positive and false negative SLNs, comparing them with completion pelvic and para-aortic lymphadenectomy, overall and stratified by anatomic region. False-positive findings and specificity were not considered, as per the definition of SLN methodology.

2.3. Assessment of risk of bias

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used to assess the quality of the studies [12]. Using the QUADAS-2 instrument, two reviewers (RV, PCZ) independently evaluated the risk of bias in the included studies. The risk of bias for sensitivity and NPV outcomes was assessed together. Any disagreement was resolved by reexamining the article with a further reviewer (SG).

2.4. Data synthesis

Proportion meta-analyses were used to estimate pooled proportions with 95 % confidence intervals (CIs) for the outcomes of interest. The overall per-patient detection rate was defined as the proportion of patients undergoing SLN procedures in which at least one SLN was detected, out of the total number of patients who underwent the SLN mapping procedure. SLN mapping was not systematically attempted bilaterally but was targeted to the anatomical region corresponding to the affected or previously removed ovary; this was subsequently followed by a bilateral completion pelvic and para-aortic lymphadenectomy. The site-specific detection rate was calculated as the proportion of hemipelvis or para-aortic regions in which at least one SLN was detected out of the total number of hemipelvis and para-aortic regions that underwent SLN mapping. Sensitivity and NPV were calculated according to their definitions, overall, per patient, and site-specific by anatomic region. In accordance with the SLN algorithm applied in all included studies, failure to map a pelvic or para-aortic region was systematically managed by mandatory completion lymphadenectomy of the unmapped region, which served as the reference standard. Therefore, unmapped regions were excluded from the denominator for sensitivity and negative predictive value calculations and were not classified as false-negative SLNs. The proportion meta-analyses were conducted using the random-effects model because the assumption of a common diagnostic performance for all included studies, required by the fixed-effects model, was considered absent. However, the result under the fixed effect model is provided. The included studies did not have the exact composition of the study populations, interventions (i.e., injection site, tracer used), or surgeon expertise. Therefore, we did not expect the same diagnostic performance for all included studies, but rather that the variation of the diagnostic performance across studies follows the same distribution [13]. This assumption was particularly expected for the detection rate. Therefore, a subgroup analysis was planned to investigate heterogeneity, stratifying by the tracer used for the per-patient analysis and the site of injection for the site-specific analysis.

The Freeman-Tukey double arcsine transformation method was implemented to address issues of zero-range limits and the inflated weight of studies with extreme data. In cases where estimates are too extreme, near 0 or 1, estimates based on raw data have been provided. The Wilson-Score method was used to estimate 95 % CIs. Heterogeneity was quantified using the I^2 test; an I^2 value less than 25 % was considered low, and an I^2 value greater than 75 % was considered high. Publication bias was assessed by the Funnel plot inspection when at least ten studies were identified. All analyses were two-tailed with a statistical significance threshold of $p = .05$. The meta-analysis was performed with R Statistical Software (v4.1.2; R Core Team 2024).

3. Results

3.1. Study selection

The initial literature search yielded 151 records. After removing duplicates and screening titles and abstracts, 17 records underwent full-text assessment for eligibility. Three records were excluded because they did not present study data [14–16]. Finally, 14 records were included and provided data, 7 retrospective and 7 prospective (Table 1) [8, 17–28]. The PRISMA Flowchart depicts the reference selection process (Fig. 1).

3.2. Study characteristics

The 14 included studies (encompassing 365 patients) investigated the use of SLN biopsy in apparently early-stage EOC, employing various injection techniques and dyes (Table 1).

Three studies tested a single injection site for mapping both the pelvic and para-aortic regions: in three patients, the dye was injected under the ovarian cortex (3/365; 0.8 %) [24]; in two studies, the injection site was the mesovarium for a total of 7 patients (1.9 %) [25,27]. Two different injection sites for the pelvic and para-aortic mapping were tested in the other 355 patients (97.2 %) [8,17–22,24,26,28–30]. In these 355 cases, all investigations used the infundibulo-pelvic ligament (IPL) injection for mapping the para-aortic area [8,17–19,21,22,24,26, 28–31]. Except for one case by Uccella et al. and five cases of Lago et al. in which the dye was injected in the cervix [19,30], all studies mapped the pelvic area injecting the utero-ovarian ligament (UOL) (349/365 cases; 95.6 %) [8,17–19,21,22,24,26,28,29,31]. Additional minor variations in the tracer injection technique were noted, including administration at both the dorsal and ventral surfaces of the UOL or a single injection at the UOL stump.

The 14 included studies variably implemented the Blue dye, indocyanine green (ICG), and technetium-99 (Tc99) as tracers. After injection, a gamma probe was used to identify the Tc99, the Blue dye was observed visually, and a real-time fluorescent infrared light camera was used to trace the ICG. Nine studies used a single dye. Hassandez et al. used only Tc99 in all 9 patients (2.4 %; 9/365) [24]. The Blue dye was used as a unique tracer in 32 patients (8,7) [21,22], and ICG in 242 (66,3 %) [8, 18,19,25,30]. In four studies with a double tracer (22 patients; 6.2 %) [17,24,26,27], Tc99 was administered in combination with the Blue dye; the Tc99 was combined with ICG in two studies (50 patients; 13.6 %) [28,31]. The authors adopted a lag time between the tracer injection and the start of the SLN search of 15 min in 6 studies [10,17,22,25,26, 28,31] 10 min in six [8,18,21,24,27,30], and 30 min in two studies [19, 29]. Hassanzadeh et al. presented the data regarding three different

Table 1
Characteristics of included studies.

	Study/Main record (year)	Country	Study design	Number of patients	Tracer used	Injection site	Total SLN detected	Surgical approach
1	Kleppe et al., 2014	The Netherlands	Case series	5	Tc^{99} + Blue dye	UOL and IPL	5	Open
2	Angelucci et al., 2016	Italy	Case series	5	ICG	Mesovarium	5	LPS
3	Hassanzadeh et al., 2016[a]	Iran	Case series	3	Tc^{99}	Ovarian cortex	2	Open
		Iran	Case series	6	Tc^{99}	UOL and IPL	6	Open
		Iran	Case series	4	Tc^{99} + Blue dye	UOL and IPL	4	Open
4	Nyberg et al., 2017	Finland	Case series	2	Tc^{99} + Blue dye	Mesovarium	2	Open
5	Uccella et al., 2017	Italy	Case report	1	ICG	Cervix and IPL	1	LPS
6	Lago et al., 2018	Spain	Prospective trial	10	ICG + Tc99	UOL and IPL	10	LPS/Open
7	Lago et al., 2020	Spain	Prospective trial	20	ICG + Tc100	UOL and IPL	20	LPS/Open
8	Guerra et al., 2021	Venezuela	Case series	11	Blue dye	UOL and IPL	10	Open
9	Laven et al., 2021	The Netherlands	Prospective trial	11	Tc^{99} + Blue dye	UOL and IPL	3	Open
10	Agustì et al., 2023	Spain	Prospective trial	30	ICG + Tc99	UOL and IPL	27	LPS/Open
11	Nero et al., 2024[b]	Italy	Prospective trial	169	ICG	UOL and IPL	99	LPS/Open
12	Heda et al., 2025	India	Prospective trial	21	Tc^{99} + Blue dye	UOL and IPL	20	LPS/Open
13	Lago et al., 2025	Spain	Case series	31	ICG	UOL/Cervix and IPL	28	LPS/Open
14	Uccella et al., 2025	Italy	Prospective trial	36	ICG	UOL and IPL	31	LPS/Open

SLN, Sentinel lymph node; UOL, Utero-ovarian ligament; IPL, infundibulo-pelvic ligament.
[a] Hassanzadeh et al., 2016 present the data regarding three different injection sites and tracers, and the three groups were included separately in the meta-analysis.
[b] Nero et al., 2024 report the results of the SELLY trial, of which some cases were already presented by Uccella S, Nero C et al., 2019 and Uccella S, Fagotti A et al., 2019.

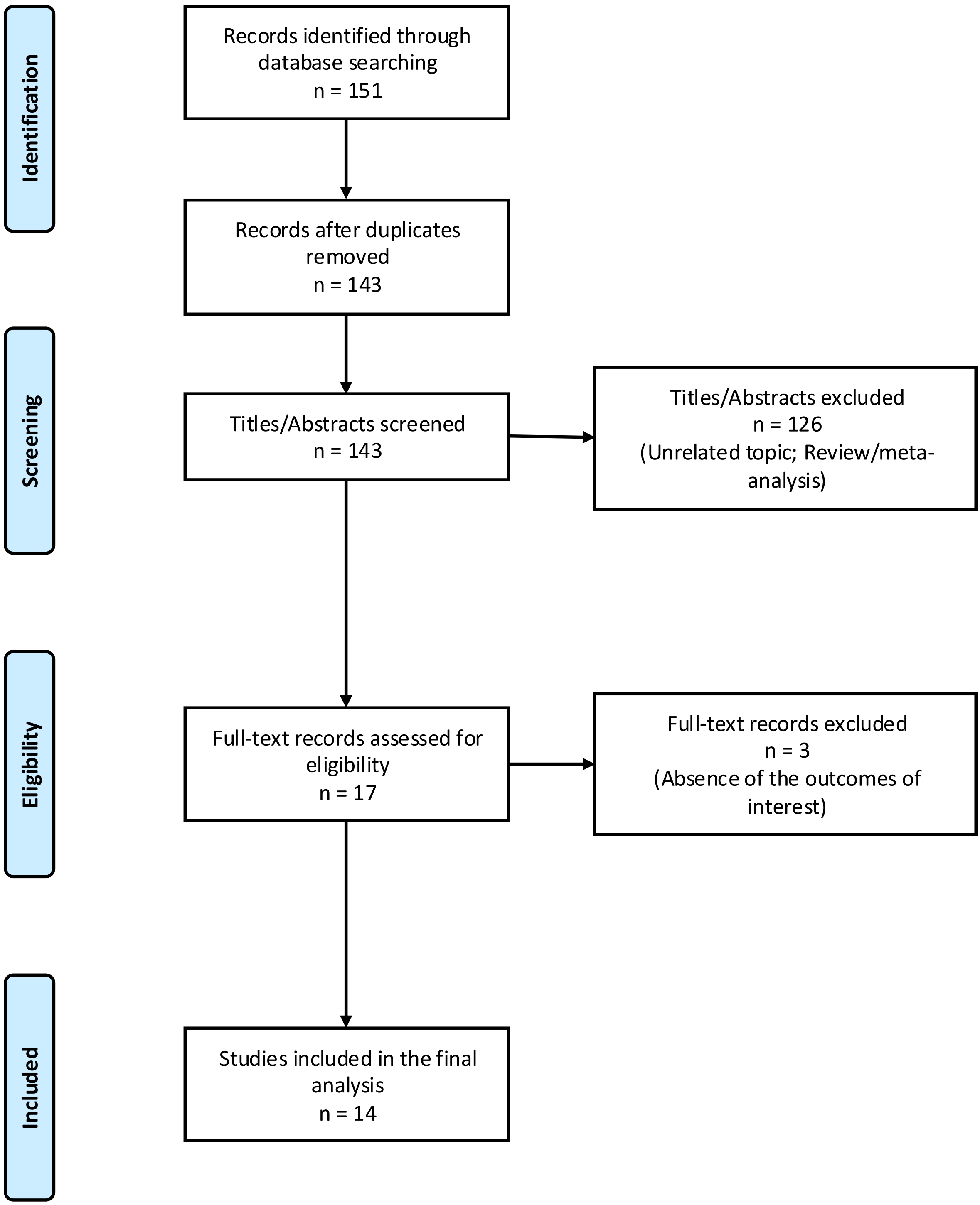

Fig. 1. PRISMA flowchart of study selection.

injection sites and tracers, and the three groups were included separately in the meta-analysis [24].

Regarding the timing of injection related to the surgical staging process, in most cases, the dye injection was performed after adnexectomy and frozen section confirmation of malignancy, with the tracer injected at the UOL and IPL stumps [8,17–19,21,28–31]. In only a few studies, dye injection was performed before adnexectomy with the adnexal mass in situ [22,24–27]. In four studies, involving a total of 79 patients, SLN mapping was performed during surgical restaging after the incidental diagnosis of EOC [18,30–32].

None of the 14 included studies reported adverse effects or surgical complications related to the SLN biopsy procedure; instead, three investigations reported vascular injuries during the comprehensive surgical staging by pelvic and para-aortic completion lymphadenectomy.

SLN ultra-staging was implemented in six studies [8,18,20,21,28,29]. Out of 45 positive SLNs, 28 SLNs were identified as positive for macro-metastasis, 3 for micro-metastasis, and 14 for isolated tumor cells (ITCs). All these cases were considered positive SLNs.

3.3. *Risk of bias of included studies*

The bias assessment findings according to QUADAS-2 are presented in Fig. 2. Among the fourteen studies, 13 were considered to have a low risk of bias in the patient selection and index test domain for all outcomes [8,17–22,24,26–30]. Only one study was considered to be at high risk of bias due to its failure to provide details regarding the patient recruitment method or anticipated outcomes [25]. All studies were considered at low risk of bias in the reference standard domain and applicability for sensitivity and NPV analysis. For the detection rate outcome, the reference standard domain was not applicable. Four studies were considered for both outcomes to be at high risk of bias in flow and timing tests due to discrepancies between the SLN technique proposed and that actually used [22,24,26,28]. Despite sharing the same study protocol, the cohorts reported by Nero et al. (SELLY trial) [8] and Uccella et al. [18]. were independent and enrolled during different time periods; therefore, no patient overlap occurred in the present meta-analysis.

3.4. Quantitative synthesis of results

3.4.1. Overall (per patient) detection rate, sensitivity, and negative predictive value

At least one SLN was identified in either the pelvic or para-aortic areas in 273 out of 365 patients. The overall detection rate reported in the 14 studies ranged from 58.6 % to 100 %; the pooled overall detection rate was 92.6 % (95 % CI: 80.2–99.8 %; $I^2 = 81$ %; Chi^2 p-value <0.01) (Fig. 3a). The funnel plot reported an asymmetrical pattern. (Supplementary Fig. 1). Of 273 patients with at least one mapped SLN, 45 (16.4 %) had at least one positive SLN, and 228 had negative SLNs. Out of 228 patients with negative SLNs, 6 had positive lymph node status at the definitive pathology of the completion pelvic and para-aortic lymphadenectomy. The pooled overall NPV was 100 % (95 % CI: 99.92–100 %; $I^2 = 0$ %; Chi^2 p-value = 0.99, raw NPV: 98.3 %; 95 % CI: 96.0–100 %), and the pooled overall sensitivity was 93.8 % (95 %CI: 83.399.8 %; $I^2 = 0$ %; Chi^2 p-value = 0.7) (Fig. 3b and c).

3.4.2. Site-specific (per pelvic and para-aortic area) detection rate, sensitivity, and negative predictive value

The pooled detection rate in the para-aortic region was 79.9 % (95 % CI: 66.1–91.4 %; $I^2 = 74$ %; Chi^2 p-value <0.01) (Fig. 4a). The funnel plot provided a symmetrical pattern (Supplementary Fig. 2). Para-aortic lymph node metastases were reported in 36 patients; four patients with positive para-aortic lymph nodes had a negative para-aortic SLN. The pooled NPV for the para-aortic area was 100 % (95 %CI 100–100 %; $I^2 =$ 0 %; Chi^2 p-value = 1.00; raw NPV: 97.8 %; 95 %CI: 84.0–100 %). The pooled para-aortic sensitivity of SLN biopsy was 97.8 % (95 %CI 84.0–100 %; $I^2 = 0$ %; Chi^2 p-value = 1.00) (Fig. 4b and c).

The pooled detection rate observed in the pelvic region was 42.7 % (95 %CI: 28.5–57.3 %; $I^2 = 71$ %; Chi^2 p-value <0.01) (Fig. 5a). The funnel plot had a symmetrical pattern (Supplementary Fig. 3). The presence of metastases in the pelvic lymph nodes was documented in 8 cases; however, no one with positive pelvic lymph nodes had a negative SLN. The pooled pelvic NPV was 100 % (95 %CI 100–100 %; $I^2 = 0$ %; Chi^2 p-value = 1.00) and the pooled pelvic sensitivity was 100 % (95 % CI 75.3–100 %; $I^2 = 0$ %; Chi^2 p-value = 1.00) (Fig. 5b and c).

3.4.3. Subgroup analyses for the detection rate

The pooled overall detection rate (per patient) stratified by the used tracer was feasible for ICG, Tc99, and Tc99 combined with ICG or Blue dye (Supplementary Fig. 4). Only two studies used the Blue dye alone, and two subgroups of the study by Hassanzadeh et al. implemented the Tc99 alone. The pooled overall detection rate for ICG alone (242 patients) was 88.5 % (95 %CI 64.5–100 %; $I^2 =84$ %; Chi^2 p-value <0.01). Pooled overall detection rate for Tc99 combined with ICG (60 patients) was 97.5 % (95 %CI 88.4–100 %; $I^2 =32$ %; Chi^2 p-value = 0.23), and combined with Blue dye (22 patients) was 86.4 % (95 %CI

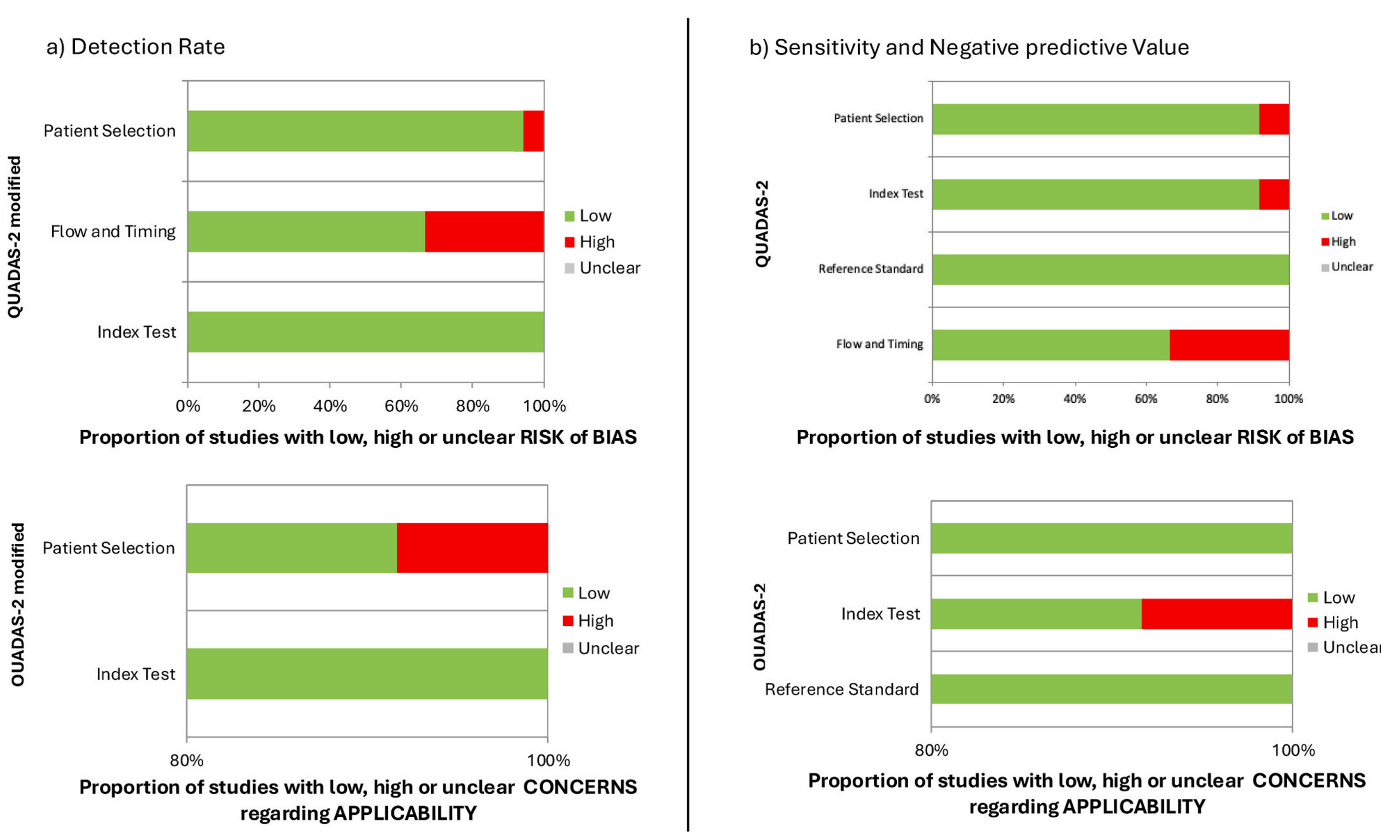

Fig. 2. Risk of Bias assessment with the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) for a) detection rate and b) sensitivity and negative predictive value. The reference standard domain was not applicable for the detection rate.

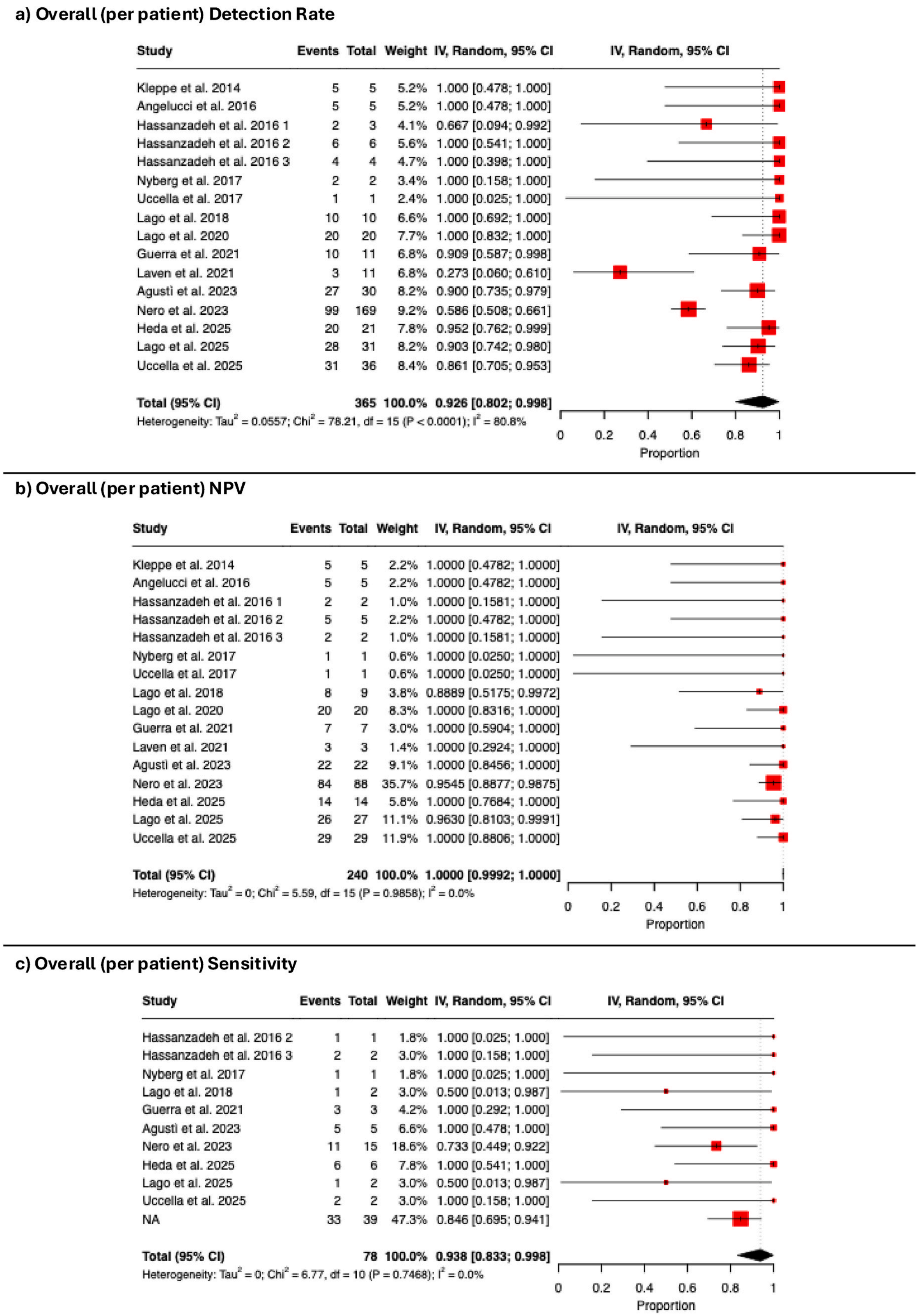

Fig. 3. Forest plot of proportional meta-analysis for a) Overall (per patient) Detection Rate, b) Overall (per patient) Negative predictive value (NPV), and c) Overall (per patient) sensitivity.

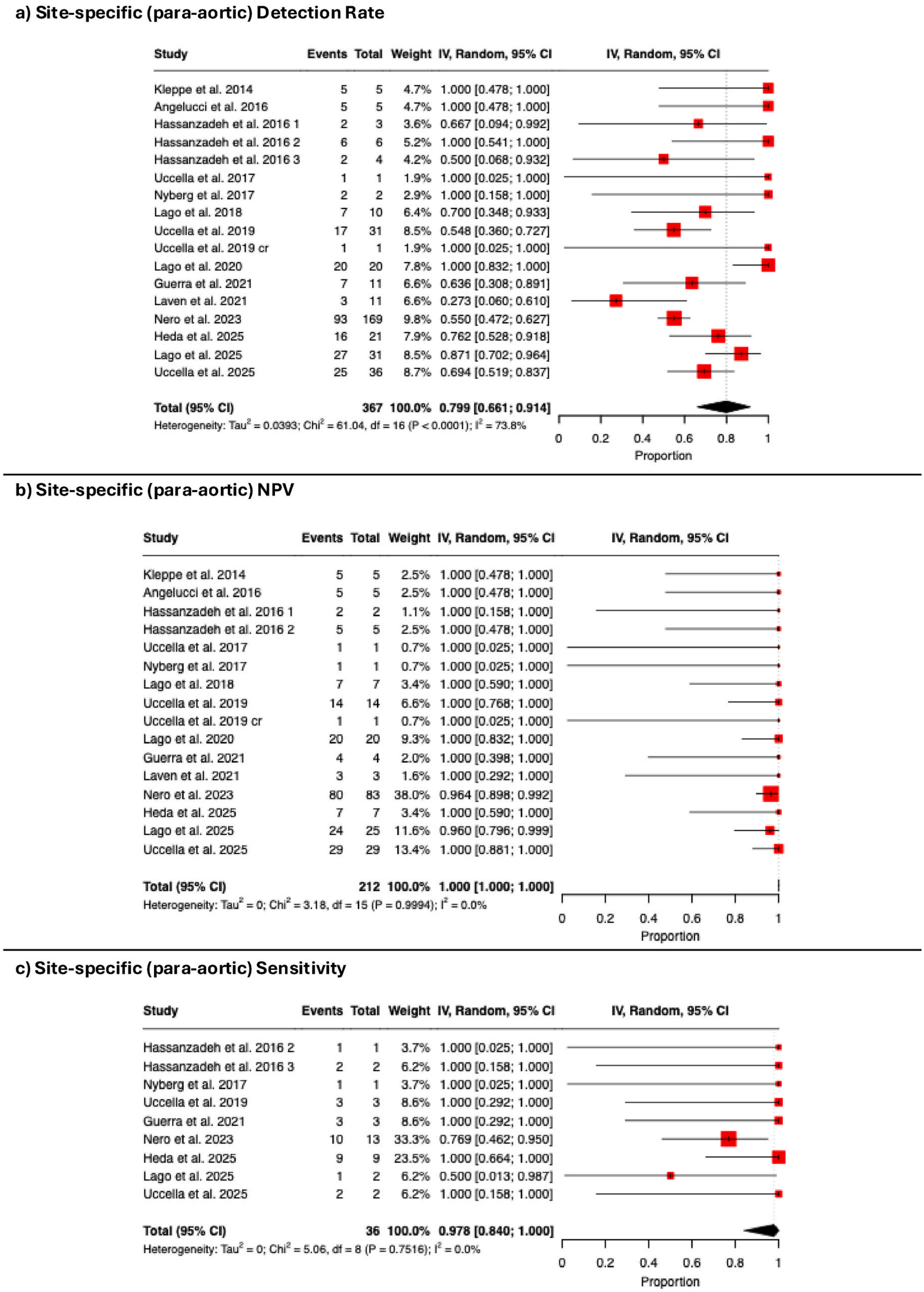

Fig. 4. Forest plot of proportional meta-analysis for a) Site-specific (para-aortic) Detection Rate, b) Site-specific (para-aortic) Negative predictive value (NPV), and c) Site-specific (para-aortic) sensitivity.

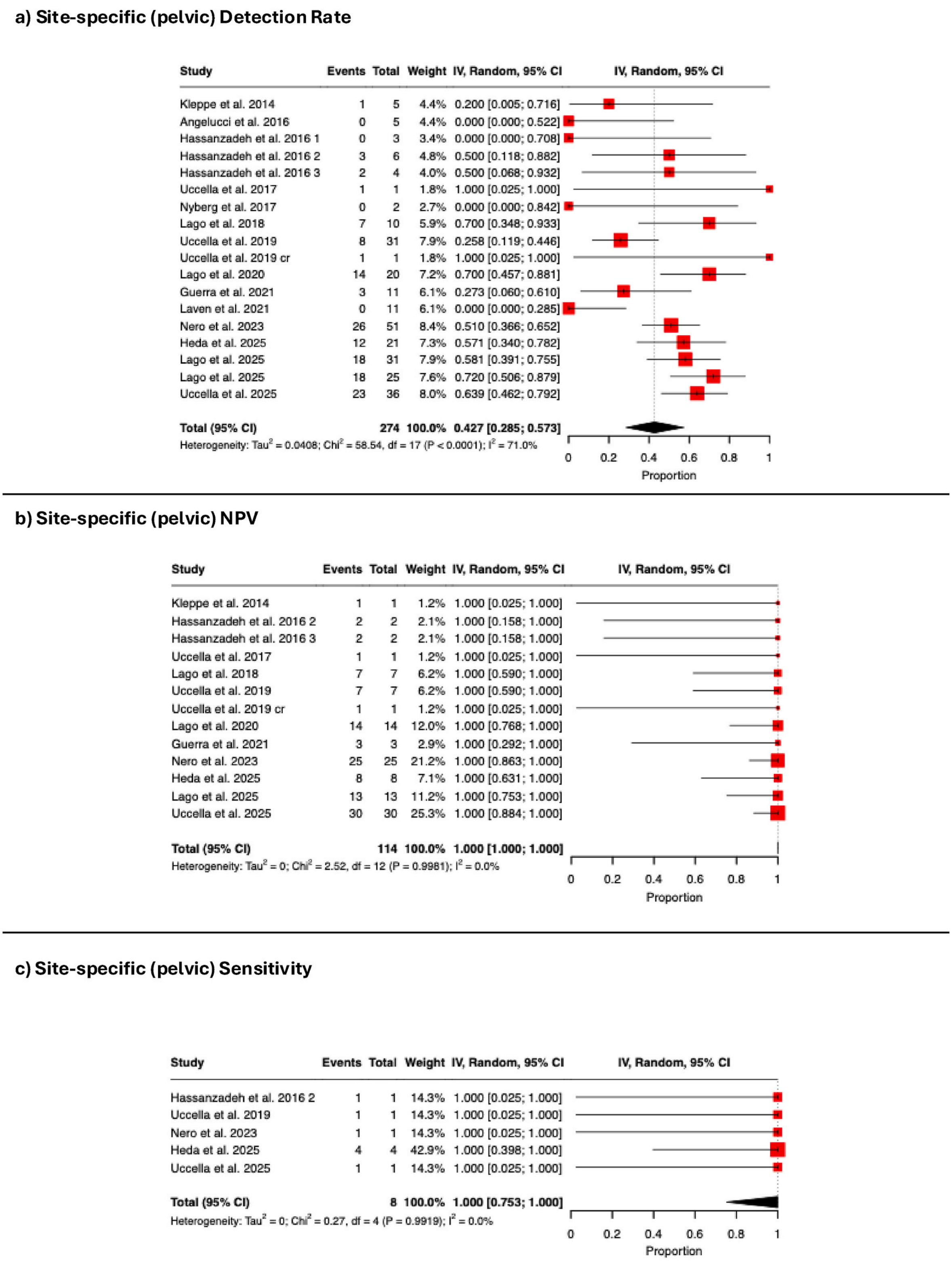

Fig. 5. Forest plot of proportional meta-analysis for a) Site-specific (pelvic) Detection Rate, b) Site-specific (pelvic) Negative predictive value (NPV), and c) Site-specific (pelvic) sensitivity.

32.7–100 %; $I^2 = 79$ %; Chi^2 p-value <0.01).

The pooled detection rate in the para-aortic region stratified by the injection site was feasible for the IPL and mesovarium (Supplementary Fig. 5). Only one study injected the ovarian cortex [24]. The pooled detection rate in the para-aortic region for the tracer injection in the IPL (357 patients) was 77.5 % (95 %CI 62.7–90.1 %; I^2 =77 %; Chi^2 p-value <0.01). The pooled detection rate in the para-aortic region for the tracer injection in the mesovarium (7 patients) was 100 % (95 %CI 75–100 %; $I^2 = 0$ %; Chi^2 p-value = 0.8).

The pooled detection rate in the pelvic region stratified by the site of injection was feasible for the UOL and mesovarium (Supplementary Fig. 6). Only two studies injected the cervix [19,30], and one injected the ovarian cortex [24]. The pooled detection rate in the pelvic area for the tracer injection in the UOL (207 patients) was 44.5 % (95 %CI 29–60.5 %; $I^2 = 71$ %; Chi^2 p-value <0.01). The pooled detection rate in the pelvic region for the tracer injection in the mesovarium (7 patients) was 0.0 % (95 %CI 0–25 %; $I^2 = 0$ %; Chi^2 p-value = 0.8).

Finally, in 79 patients, injections were conducted in the UOL stumps during restaging surgery. The pooled detection rate in this case was 74.9 % (95 %CI; 43.8–97.6 %; $I^2 = 70$ %; Chi^2 p-value =0.02) (Supplementary Fig. 7).

4. Discussion

4.1. Main results

The SLN biopsy technique in apparent EOC has been investigated in a limited number of studies, mostly with small sample sizes. The pooled detection rate appears acceptable in the para-aortic area but insufficient in the pelvis. As expected, heterogeneity in detection rates was high but not fully explained by injection site or tracer type. Instead, sensitivity and NPV when the SLN was detected were high and consistent across all anatomical regions, supporting further research.

4.2. Comparison with existing literature

A SLN biopsy algorithm is evaluated using two parameters: detection rate and diagnostic accuracy [6,7]. The detection rate reflects a technique's ability to identify the SLN. In daily surgical practice, clinical efficiency of an SLN algorithm is primarily determined by its diagnostic accuracy (sensitivity and negative predictive value), whereas the detection rate reflects a technique's ability to identify the SLN and mainly reflects the proportion of patients who will still require completion lymphadenectomy.

In endometrial and cervical cancers, pelvic SLN detection rates of approximately 80–90 %—specifically 81 % (95 % CI, 77–84 %) and 89.2 % (95 % CI, 86.3–91.6 %), respectively—have been widely accepted as satisfactory performance thresholds and originate from the pivotal studies that ultimately supported and led to the clinical adoption of SLN mapping in these tumor [6,33,34].

Using these established benchmarks as a reference for EOC, the site-specific detection rates observed in our review—79.9 % (95 % CI, 66.1–91.4 %) in the para-aortic region and 42.7 % (95 % CI, 28.5–57.3 %) in the pelvis—indicate that the para-aortic mapping achieves an acceptable level of performance, whereas pelvic mapping remains markedly suboptimal. These substantial differences in detection rate performance between the pelvic and para-aortic regions highlight the need to assess SLN identification by anatomical site [34].

Furthermore, the pooled detection rate estimate was associated with moderate or high heterogeneity. This observation suggests the presence of factors that differ across studies and likely affect the detection rate, such as the injection site and the tracer used. Consistent with available evidence, our results suggest a lower overall performance for the Blue dye in mapping the SLN. ICG and Tc99, or their combination, appear to have a higher performance in mapping at least one SLN per patient, as previously reported in experiences with endometrial and cervical cancers [35–39]. Although our data do not allow definitive conclusions on the best tracer, none of the most recent studies included in this review compare different tracers, as indocyanine green has effectively become the standard in current clinical practice. Regarding the injection site, almost all studies implemented the IPL as the injection site for mapping the para-aortic region [8,17–22,24,26,28–30]. Similarly, most investigators used the UOL to map the pelvis, and the subgroup analysis showed a low detection rate [8,17–22,24,26,28,29]. Notably, although we conducted subgroup analyses for expected factors potentially affecting the detection rate, observed heterogeneity remained high or moderate. This observation suggests the presence of other factors, such as the entire injection technique, regardless of the injection site. For instance, many protocol breaches were reported in the included studies, likely due to significant challenges in obtaining the mapping, driven by technical and anatomical constraints. In the SELLY trial, the center with the highest number of enrolled patients had a higher-than-expected overall number of failed procedures, particularly in the pelvis [8]. Therefore, training and experience that mitigate the failure in SLN mapping likely contribute to the observed heterogeneity [40–43]. The predominance of small, single-center studies may have contributed to some heterogeneity in the pooled estimates, which should be interpreted accordingly.

The most relevant factors determining the feasibility of SLN mapping are sensitivity and NPV [10,11]. Confirming that the detected lymph node represents the first lymphatic station along a defined lymphatic drainage pathway for a tumor metastasizing through that pathway provides the conceptual foundation for the SLN procedure [33]. In this context, our findings confirm the high sensitivity and NPV of SLN in EOC, with no heterogeneity across studies. Our results are promising and align with the NPV observed in endometrial and cervical cancers [33,43]. For instance, the SENTIREC-endo study considered an NPV above 94 % acceptable for the clinical implementation of SLN mapping [44]; in the SENTICOL trial [45], an NPV of 98.2 % supported the adoption of SLN mapping in cervical cancer; and in the FIRES study, the SLN mapping demonstrated feasibility even in high-risk endometrial cancer, reaching an NPV of 99.6 % [46]. In our systematic review, only two studies differed from the pooled analysis. Nero et al. reported three false negatives out of 88 patients with negative SLNs [8], and Lago et al., in 2025 identified a false-negative case [19]. However, these findings were based exclusively on per-patient analyses. When applying the recommended site-specific approach, which separates the pelvic and para-aortic regions, all included studies consistently showed high sensitivity and NPV. This analytical method provides a more accurate assessment of diagnostic performance because unmapped areas are excluded from the NPV denominator. Importantly, in all studies included in this review, any pelvic or para-aortic region where no SLN was identified was systematically evaluated through the reference completion lymphadenectomy. Therefore, unmapped regions were always surgically examined and could not be classified as false negatives. This is especially relevant for the two patients reported in the studies by Lago et al. and in the SELLY trial [8,29]. In these trials, an SLN was mapped only in the para-aortic region, with no pelvic SLN identified. In both cases, the metastatic lymph node was located in the pelvis and was detected only through the completion pelvic lymphadenectomy, not via SLN mapping. Accordingly, these cases do not represent false negatives for the para-aortic SLN (since the para-aortic SLN was correctly identified and negative); they cannot be considered false negatives for the pelvic SLN because no pelvic SLN was mapped, and the pelvic region was properly evaluated through completion lymphadenectomy, in line with SLN algorithm principles [3,6,7]. This methodological approach, site-specific analysis combined with mandatory completion lymphadenectomy in unmapped regions, mirrors validated SLN algorithms in endometrial and cervical cancers, where regions without detected SLNs are also surgically verified and therefore excluded from false-negative calculations [47,48].

4.3. Strengths and limitations

The rigorous and systematic approach strengthened the systematic review and subsequent meta-analysis. The research team followed established procedures for systematic review reporting under certified methodology. The selection process was conducted with strict adherence to predetermined criteria, only considering patients diagnosed with apparently early-stage EOC. Furthermore, a reliable reference standard was used, along with stratification of outcomes by pelvic and para-aortic areas. This allows a better understanding of the technical aspects and the corresponding elements for improvement.

Nevertheless, this review is not lacking constraints. The broad range of research designs and the small sample size observed in most included studies restrict the ability to draw definitive conclusions. Furthermore, the moderate to high heterogeneity observed in the detection rate highlights additional, less-defined factors that may potentially affect the performance of the technique, surgeon experience, institutional volume, and protocol adherence should be considered unmeasured confounders that may have contributed to heterogeneity and could not be formally analyzed in this meta-analysis. Another significant drawback is the absence of full awareness of protocol infractions. A more comprehensive understanding of these violations, particularly in the context of prospective studies, would enhance the design of future research and mitigate potential setbacks.

Moreover, delayed staging was only considered in depth in two studies, suggesting a lack of awareness of pelvic anatomy variation in delayed surgery, which may affect SLN mapping. The lack of a precise examination and comprehension of factors contributing to protocol breaches may undermine the credibility and dependability of the results, thereby impacting the review's overarching findings. The absence of site-specific analysis was a final issue that affected some investigations. Site-specific analysis is crucial for a comprehensive understanding of metastatic sites and ovarian lymphatic drainage channels; however, such research findings were often overlooked in the included literature.

5. Conclusions and implications

Well-established knowledge regarding endometrial and cervical cancer indicates that the effectiveness of an SLN algorithm is higher when each node area is treated as a distinct unit, and a completion lymphadenectomy is performed when mapping is unsuccessful [3,6,7]. To address false negatives and inefficient mapping in endometrial cancer, algorithms were developed to manage these failures [3]. The Memorial Sloan Kettering Cancer Center (MSKCC) protocol for SLN mapping in endometrial cancer, which includes lymphadenectomy, further emphasizes the importance of NPV. According to MSKCC's protocol, even with a lower detection rate, SLN mapping remains beneficial because of its high NPV. Even if the sentinel node detection rate is suboptimal, the high NPV ensures that patients with negative sentinel nodes avoid a completion lymphadenectomy [49,50].

Therefore, the detection rate indicates the proportion of patients expected to undergo an completion systematic lymphadenectomy who would not benefit from the SLN biopsy. Instead, sensitivity and NPV are the parameters that determine whether the SLN biopsy is feasible [49,50]. Based on this, the results of our systematic review 1) support the potential use of SLN mapping in apparent early-stage EOC (high NPV), 2) highlight the need for further investigation of the SLN mapping technique, especially for the pelvis (moderate/poor detection rate), and 3) emphasize the importance of distinguishing the detection rate from diagnostic accuracy by focusing on the entire algorithm and constantly analyzing pelvic and para-aortic regions separately.

In the restaging subgroup, tracer injection into the utero-ovarian ligament stump yielded a pooled pelvic detection rate of 74.9 % (Supplementary Fig. 7), although with substantial heterogeneity, indicating that pelvic SLN mapping may still be feasible after prior adnexal surgery. However, previous resection and altered pelvic anatomy/lymphatic drainage likely drive this variability; therefore, these data should be interpreted cautiously and support the need for prospective, standardized restaging-specific mapping protocols.

Regarding the SLN mapping technique, the pelvic area needs specific investigation. Some of the well-known difficulties that could have contributed to the scarcity of pelvic SLN mapping include the absence of a uterus due to prior surgery, problematic mapping in patients undergoing restaging surgery, and the lack of appropriate timing and injection method for the tracer in the UOL. Notably, in the SELLY trial, only 30.2 % of participants received UOL injections [8]. In the MELISA Trial, a prospective study, the pelvic mapping did not exceed 44 %. Only Lago et al. observed a 93 % successful SLN mapping in the pelvic area after injecting the UOL [20]. This high detection rate could be attributed to the deep injection near the dorsal-lateral parametria rather than the UOL stem. This probably enabled the identification of uterine rather than ovarian lymphatic pathways, resulting in a high detection rate. Although pelvic SLNs show high sensitivity and negative predictive value when successfully mapped, the low pelvic detection rate observed in this meta-analysis implies that completion pelvic lymphadenectomy remains an essential component of a safe SLN algorithm in early-stage EOC until pelvic mapping techniques are further optimized. The idea that the pelvic SLN in apparently early-stage EOC could be identified through an extra-ovarian injection instead of injecting the UOL paved the way to define new SLN mapping protocols. In this regard, the concordance between two theoretically different lymphatic pathways by performing a cervical and UOL injection with two different tracers has been shown [51], suggesting that the two injection sites might be equivalent in the identified pelvic SLN and that the well-standardized technique of cervical injection for the pelvic SLN mapping may be an alternative approach in EOC [51]. This hypothesis is consistent with studies comparing different uterine injection sites for the SLN mapping in endometrial cancer [34,43,52].

In conclusion, the results of this systematic review and meta-analysis support the need for further research on the SLN mapping technique in early-stage EOC. The initial high NPV indicates that the technique is promising. Future studies could use these findings to standardize the SLN mapping procedure, define outcomes and reporting methods, and clarify additional details such as SLN ultra-staging.

Ethical approval

Not applicable.

Systematic review registration

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The Authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2026.111449.

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