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A Comprehensive Review of the Ovarian Cancer Score (OCS): Advances in Early Detection and Diagnostic Accuracy

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Abstract
Ovarian cancer remains the most lethal gynecologic malignancy worldwide, largely due to the absence of reliable methods for early detection and accurate diagnosis. Conventional diagnostic tools, including serum biomarkers such as CA125 and HE4, the Risk of Ovarian Malignancy Algorithm (ROMA), and imaging techniques, demonstrate limited sensitivity and specificity, particularly in early-stage disease and in distinguishing benign from malignant adnexal masses. These limitations highlight the urgent need for more precise and non-invasive diagnostic approaches. Recent advances in liquid biopsy have identified small extracellular vesicles (sEVs) as promising carriers of tumor-derived molecular biomarkers. sEVs contain proteins, nucleic acids, and other bioactive molecules that reflect the biological characteristics of their cells of origin, making them valuable tools for cancer detection. This review focuses on the Ovarian Cancer Score (OCS), a novel diagnostic algorithm that integrates sEV-derived biomarkers, specifically CA125, HE4, and complement component C5a. We summarize the biological basis of sEV-associated biomarkers and evaluate the diagnostic performance of OCS in comparison with conventional serum markers and multivariate indices. Evidence from multicenter studies indicates that OCS demonstrates superior sensitivity and specificity, including in early-stage ovarian cancer, younger patient populations, and cases with normal CA125 levels. Furthermore, this review discusses the clinical applicability of OCS, its potential advantages over existing diagnostic methods, and current limitations, including the need for large-scale validation and standardization. Overall, OCS represents a significant advancement in non-invasive ovarian cancer diagnostics and holds strong potential to improve early detection, risk stratification, and patient outcomes.

Keywords: Ovarian cancer; Ovarian Cancer Score (OCS); Small extracellular vesicles (sEVs); Liquid biopsy; Diagnostic biomarkers; Early detection

1. Introduction

Ovarian cancer (OC) is one of the most deadly cancers that affects the female reproductive system around the world [1]. Every year, about 314,000 new ovarian cancer cases are diagnosed, with nearly 213,000 related deaths. Epithelial ovarian cancer (EOC) accounts for more than 90% of all ovarian cancer cases [2]. Ovarian cancer typically presents with few symptoms in early stages and mild symptoms later on. Common signs include persistent bloating, nausea, reduced appetite, back pain, and increased urinary frequency [3]. Ovarian cancer frequently goes undetected in its early stages. About 13–27% of patients survive five years after diagnosis [4]. The high mortality rate is largely due to challenges in early detection with current diagnostic biomarkers [5]. Early detection, particularly distinguishing

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benign from malignant masses, is therefore crucial for improving outcomes [2]. However, nearly 66% of patients are diagnosed at advanced FIGO stage III–IV, underscoring the urgent need for earlier identification and intervention [6, 7]. This highlights the importance of diagnostic tools for identifying ovarian masses because early diagnosis are still lacking [8].

CA125 is a blood biomarker for ovarian cancer and was initially introduced for monitoring patients during therapy [9]. Studies show that using CA125 alone or together with pelvic ultrasound can help in large-scale screening. However, it is not very effective in finding early-stage ovarian cancer because its sensitivity and specificity are low [10, 11]. Also, CA125 levels can rise in non-cancerous conditions such as endometriosis and other gynecologic diseases [12, 13]. To improve the accuracy for ovarian cancer detection, other biomarkers have been developed, such as Human Epididymis Protein 4 (HE4). This biomarker is known to be highly expressed in ovarian cancer. Although these markers are quite specific, their sensitivity is still low [14]. A combined test called ROMA, which includes both CA125 and HE4, was created to better tell the difference between benign and cancerous ovarian tumors [15, 16]. However, some studies have shown that ROMA does not provide much improvement compared to using CA125 or HE4 alone. These limitations highlight that new biomarkers are needed to improve early detection and to better distinguish between malignant and benign ovarian masses [17]. Studies suggest OCS show better results than traditional markers such as CA125, HE4 and ROMA index.

Small extracellular vesicles (sEV) are surrounded by a membrane that carry proteins and genetic material [18]. The substances inside them can help in detect ovarian cancer. Scientists discovered that sEV-derived CA125, HE4, and C5a might be useful biomarkers and created an Ovarian Cancer Score (OCS) using these markers to better tell the difference between ovarian cancer and non-cancerous diseases [19, 20]. This study examines whether the Ovarian Cancer Score (OCS) can detect ovarian cancer more effectively than CA125, HE4, or the ROMA index. It includes patients with adnexal masses from several hospitals. The study also looks at how well OCS performs in different groups, such as pre and post-menopause women, patients with different cancer stages, younger patients, and those who have normal CA125 level [2].

To date, no review has specifically synthesized the evidence on OCS, compared its diagnostic value against existing tools, or evaluated its applicability across diverse patient populations. Therefore, this review aims to critically assess current data on the Ovarian Cancer Score (OCS), examine its diagnostic advantages relative to conventional biomarkers and algorithms, and discuss future implications for clinical integration, research development, and implementation challenges.

2. Ovarian Cancer: Clinical Background

2.1 Epidemiology and Global Burden

Ovarian cancer remains the most lethal gynecologic malignancy worldwide, despite being only the second most common cancer of the female reproductive tract [21, 22]. The highest incidence rates of ovarian cancer are reported in Eastern and Central Europe, reaching approximately 11.4 per 100,000 and 6.0 per 100,000 women, respectively. In contrast, China has a comparatively lower incidence of about 4.1 per 100,000, yet its large population results in a substantial disease burden, with an estimated 52,100 new cases and 22,500 deaths reported in 2015. For comparison, the United States recorded approximately 21,290 new cases and 14,180 deaths during the same period [23, 24, 25]. Although ovarian cancer incidence and mortality have declined over the past decade, it remains the deadliest gynecologic malignancy, with a 5-year survival rate of only 50%. Most cases are diagnosed at advanced stages due to the absence of early specific symptoms [21]. The prognosis of advanced-stage ovarian cancer is poor, with a five-year survival rate of about 17% [26].

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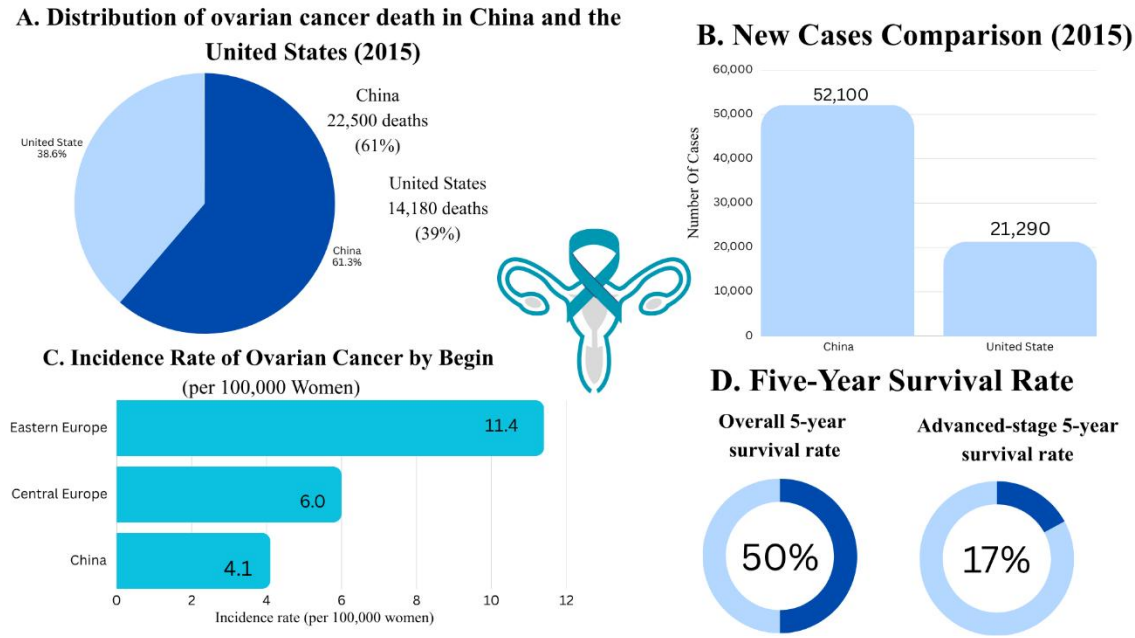


Figure 1: Global Burden and Survival Status of Ovarian Cancer: (A) Distribution of ovarian cancer deaths (2015) shows a higher proportion in China (~61%) compared to the United States (~39%). (B) Comparison of new cases indicates that China reported more than twice the number of cases than the United States. (C) Incidence rates per 100,000 women are highest in Eastern Europe (11.4), followed by Central Europe (6.0) and China (4.1). (D) Survival outcomes reveal an overall 5-year survival of ~50%, which declines to ~17% in advanced-stage disease.

Most ovarian cancers develop from the epithelial cells of the ovary. Based on how these epithelial cells look under a microscope, ovarian cancers are divided into five main types: high-grade serous carcinoma, which makes up about 68% of the cases; clear cell carcinoma (12%); endometrioid carcinoma (11%); mucinous carcinoma (3%); and low-grade serous carcinoma (3%) [27,28].

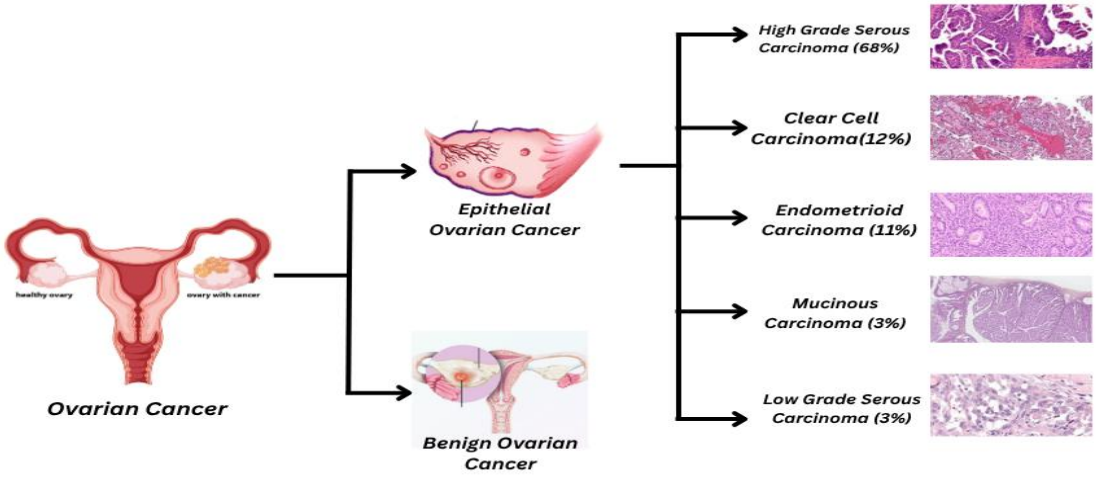


Figure 2: Classification and histopathological subtypes of ovarian cancer: The diagram categorizes ovarian cancer into benign tumors and epithelial ovarian cancer, the most common malignant form. Epithelial ovarian cancer is further classified into major histological subtypes: high-grade serous (68%), clear cell (12%), endometriosis (11%), mucinous (3%), and low-grade serous carcinoma (3%). Representative micrographs highlight their distinct morphological features, emphasizing tumor heterogeneity and the predominance of high-grade serous carcinoma.

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Ovarian cancer is difficult to detect at an early stage, and most cases are diagnosed only after the disease has progressed, limiting effective management. Current screening modalities, including transvaginal ultrasound and the CA-125 biomarker, lack sufficient sensitivity and specificity for early detection and have therefore not succeeded in reducing the high mortality associated with this cancer [29, 30].

3. Pathophysiology and Clinical Overview of Ovarian Cancer

Ovarian cancer (OC) arises through multifactorial mechanisms involving genetic, epigenetic, and cellular alterations. Although defined by malignant proliferation within the ovary, increasing evidence indicates that many OCs do not originate in the ovary itself. A substantial proportion, particularly high-grade serous tumors, arise from malignant transformation within the fallopian tube epithelium, with subsequent spread to the ovary and peritoneum. Molecular profiling further supports this shared origin, as tumors from the fallopian tube, ovary, and peritoneum display highly similar signatures. In contrast, endometrioid and clear cell ovarian cancers are generally associated with endometriosis-related pathways of development [31, 32, and 29]. Epithelial ovarian cancer (EOC) is the major type of ovarian malignancy and includes several histological subtypes, such as serous, endometrioid, clear cell, and mucinous carcinoma. These subtypes vary in their origins and molecular features, contributing to the disease's heterogeneity [33, 34]. Although the pathogenesis of epithelial ovarian cancer is not fully defined, molecular and gene expression evidence supports the fallopian tubal fimbria as the primary site of origin for most high-grade serous ovarian cancers, which later metastasize to the ovary and peritoneal cavity [35]. Approximately half of all high-grade serous ovarian cancers (HGSOC) carry genetic alterations in homologous recombination repair genes—divided equally between germline and somatic variants—leading to homologous recombination deficiency (HRD) and impaired repair of DNA double-strand breaks. BRCA1 and BRCA2 mutations account for about half of HRD-associated tumors and are present in roughly 25% of all HGSOC cases. The remaining HRD cases result from defects in other homologous recombination genes, including CHEK2, RAD51, BRIP1, and PALB2 [36]. Dysregulation of the PI3K/AKT/mTOR signaling cascade is common in ovarian cancer and plays a key role in tumor growth and resistance to chemotherapy. Accordingly, this pathway is being actively explored as a promising target for novel therapeutic strategies [37, 31]

4. Limitations of Current Diagnostic Approaches

4.1 CA125

Cancer antigen 125 (CA125), identified in 1981, has been extensively studied for its association with ovarian cancer. However, it is well established that CA125 alone is not a fully reliable marker for accurate diagnosis [38]. CA125 is an epitope located on mucin 16 (MUC16), a cell-surface glycoprotein. It is normally expressed in tissues derived from coelomic epithelium, including the ovary, fallopian tube, peritoneum, pleura, pericardium, colon, kidney, and stomach. Currently, three antibody groups are used to detect the CA125 antigen, each recognizing a distinct, non-overlapping epitope. These include OC125-like, M11-like, and OV197-like antibodies [39,40]. Early studies reported that serum CA125 levels above 35 U/mL were elevated in approximately 80% of patients with ovarian cancer [41]. However, clinical trials have not shown significant benefit from CA125-based screening, mainly because its sensitivity is low in early-stage disease. In preoperative evaluation, CA125 also offers limited value in distinguishing benign from malignant ovarian masses, even when used as part of multimodal diagnostic approaches [42,43]. The diagnostic accuracy of CA125 for early-stage ovarian cancer is limited, as only about 50% of early-stage patients show elevated levels. This results in a relatively low sensitivity (50–62%) for detecting early-stage disease. CA125 is more effective in distinguishing advanced-stage ovarian cancer from healthy controls than early-stage cases. In a retrospective study, Funston et al. found that women with normal CA125 levels before diagnosis were more likely to be diagnosed at an early stage than those with elevated levels. These findings indicate that relying solely on CA125 for screening may delay diagnosis and negatively affect patient outcomes [44,45]. Additional limitations of CA125 arise from its wide biological variability. Serum levels can be influenced by age, menopausal status, race, pregnancy, and the menstrual cycle, which raises concerns about relying on a fixed diagnostic cut-off. Age-specific thresholds may offer improved accuracy and help reduce false-positive results, although their effect on overall sensitivity and specificity still requires further investigation. Moreover, the positive predictive value of CA125 remains low, at approximately 5%, indicating that many women with elevated levels do not have ovarian cancer [38]. Emerging biomarkers such as HE4 are being explored to address the limitations of CA-125, which has reduced specificity. HE4 shows better performance than CA-

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125 in predicting tumor malignancy and recurrence. To improve diagnostic accuracy, multiparametric tests such as ROMA combine CA-125, HE4, and additional indicators. A triple-screen approach using CA-125, HE4, and a symptom index has also shown promising results [6]

4.2 HE4

In 2008, the FDA approved HE4 as a glycoprotein biomarker for monitoring disease recurrence or progression. HE4 is overexpressed in most, though not all, epithelial ovarian cancers [46,47]. HE4 is considered one of the most promising biomarkers for ovarian cancer [48]. It was first identified in the epithelium of the distal epididymis, where it may play a role in sperm maturation. HE4 is also known as WFDC2, a name that reflects its structure, which includes two whey acidic protein domains and a core stabilized by four disulfide bonds formed by eight cysteine residues [49]. In females, HE4 is mainly expressed in the fallopian tubes, endometrium, and endocervix, while normal ovarian surface epithelium does not express HE4. In contrast, malignant ovarian carcinomas frequently overexpress HE4, often at much higher levels than many other tumor types [50,51].

As mentioned earlier, HE4 expression in ovarian tumors varies by histological subtype. It is primarily expressed in serous and endometrioid ovarian cancers, which account for most ovarian cancer cases, and is seldom detected in mucinous or germ cell tumors. Elevated serum HE4 levels in nearly 92% of patients with ovarian cancer, showing sensitivity comparable to CA125 but with higher specificity [52,53]. HE4 has been shown to have higher sensitivity and specificity than CA125 in the early stages of epithelial ovarian cancer. It is expressed at significantly higher levels in malignant ovarian tissues compared to benign tumors and is widely regarded as a serum tumor marker for detection and staging of ovarian cancer [54]. The relative merits of CA125 and HE4 remain a topic of ongoing debate. While several meta-analyses report similar sensitivity for the two biomarkers (approximately 0.75), most studies indicate that HE4 has superior specificity [46]. Studies using multimarker panels that include HE4 have demonstrated improved sensitivity and specificity for early-stage ovarian cancer detection, as well as better discrimination between benign and malignant cases [55,56].

4.3 ROMA Algorithm

In 2009, Moore et al. proposed the Risk of Ovarian Malignancy Algorithm (ROMA), which combines serum levels of CA125 and HE4 with menopausal status to objectively assess the likelihood of ovarian cancer in women with an adnexal mass. This model relies solely on quantitative biomarkers and provides a standardized, reproducible approach for risk evaluation [57]. The ROMA has been proposed to differentiate benign adnexal masses from epithelial ovarian cancer. Several studies have demonstrated that, due to its high sensitivity and specificity, ROMA can serve as a superior marker for predicting malignant ovarian masses [58,59,60]. ROMA is a quantitative test that measures serum concentrations of CA125 and HE4, combined with menopausal status. Cut-off values vary depending on laboratory methods, hormonal status, and whether the patient is pre- or post-menopausal. The test, approved by the FDA in June 2012, is intended for patients meeting the following criteria:

- Age over 18 years.
- Presence of an adnexal lesion eligible for surgery, not yet referred to a specialized center.
- ROMA results should be interpreted alongside clinical evaluation and independent radiological findings.
- The algorithm is not suitable as a screening tool, as a standalone diagnostic test, in pregnant women, in patients previously treated for neoplasms, or during chemotherapy.
- High serum concentrations of rheumatoid factor (>250 IU/mL) may interfere with the calculated ROMA value [61].

ROMA calculates the predicted probability of epithelial ovarian cancer (EOC) using serum CA125 and HE4 levels, combined with menopausal status. The algorithm uses a predictive index (PI) to classify patients into high- or low-risk groups: [62]

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4.4 Predicted probability (ROMA)

$$\text{ROMA \%} = \frac{\exp(PI)}{[1+\exp(PI)]} \times 100$$

Using manufacturer-specified cut-offs for 75% specificity:

- High-risk: ROMA ≥ 12.5% (pre-menopausal) or ≥ 14.4% (post-menopausal)
- Low-risk: ROMA < 12.5% (pre-menopausal) or < 14.4% (post-menopausal) [62]

ROMA demonstrates good overall diagnostic accuracy for detecting epithelial ovarian cancer; however, its performance varies across studies, suggesting dependence on specific populations or clinical settings [58]. Multiple meta-analyses have compared ROMA with individual biomarkers. Although ROMA shows slightly lower specificity than HE4, it performs better than CA125 and demonstrates superior overall diagnostic value [14]. The ROMA index has strong ability to distinguish ovarian cancer from benign ovarian tumors. Women with an elevated ROMA value are considered at higher risk for malignancy and should be referred to a gynecologic oncology specialist for appropriate management [63].

4.5 Imaging Tools

4.5.1 Transvaginal Ultrasound (TVU)

Ultrasound is the principal imaging modality used in ovarian cancer evaluation. Over recent years, substantial technological advancements have improved its diagnostic capability. When performed by a skilled sonographer, ultrasound plays a critical role in the initial detection and assessment of ovarian malignancy [64]. Ovarian sonography can effectively identify changes in ovarian size and adnexal structure before symptoms appear or abnormalities become detectable on pelvic examination [65,66]. Current clinical approaches for ovarian cancer (OC) screening mainly rely on physical examination and adnexal imaging using transvaginal ultrasound (TVU). TVU is the most commonly applied imaging method for early evaluation of ovarian abnormalities and helps clinicians identify changes in ovarian size, shape, and internal structure [42]. Image interpretation follows the International Ovarian Tumor Analysis (IOTA) simple rules, which classify lesions based on specific benign and malignant features. Key ultrasound indicators include papillary projections, ascites, solid components, and internal blood flow, which assist in estimating the likelihood of malignancy and determining appropriate clinical management [67]. Although ultrasound demonstrates high sensitivity in detecting ovarian lesions, it has limited specificity and positive predictive value. Even in postmenopausal women, false-positive findings remain common due to the high prevalence of benign ovarian masses in this population [68].

4.5.2 MRI/CT

In addition to ultrasound, anatomical imaging using computed tomography (CT) and magnetic resonance imaging (MRI) is routinely applied in clinical practice to evaluate disease extent and detect peritoneal spread in patients with ovarian cancer [65]. Computed tomography (CT) is primarily used for staging, monitoring treatment response, and detecting disease recurrence. It is particularly effective in assessing the extent of hematogenous, peritoneal, and lymphatic spread, and can visualize metastatic involvement of the liver, para-aortic region, omentum, and mesentery more accurately than ultrasound [69,70]. Although CT is widely used in the follow-up of patients treated for ovarian cancer, it has limited sensitivity in accurately determining the extent of residual disease [71,72]. Magnetic resonance imaging (MRI) is commonly used as a secondary imaging modality and provides high-contrast visualization of internal tissues. Pelvic MRI offers improved resolution, allowing clearer assessment of fine structural features within ovarian masses, including papillary projections that are often associated with epithelial tumors [73]. Diffusion-weighted MRI provides improved contrast between tumor and normal tissue, supporting disease staging and treatment evaluation. Its superior soft-tissue resolution also enhances the distinction between benign, malignant, and borderline adnexal masses [74,75]. Conventional imaging modalities such as ultrasonography, computed tomography, and MRI may produce false-negative findings when normal anatomical structures are altered or absent following surgical intervention or radiation therapy. These techniques may also result in false-positive interpretations due to the difficulty in differentiating viable tumor tissue from necrotic or fibrotic post-treatment changes. [76].

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5. Emerging Role of sEVs in Ovarian Cancer Detection

5.1 Biology of Small Extracellular Vesicles

Extracellular vesicles (EVs) are small membrane-bound particles released by cells and found in body fluids such as blood, saliva, and urine. They facilitate cell-to-cell communication by transferring biomolecules to target cells. Because they reflect the molecular status of their cells of origin, EVs are considered promising liquid biopsy markers for early disease detection [77,78]. EVs were first identified in 1983 by Johnstone and colleagues during studies on sheep erythrocytes [79,80]. Cancer cells release more EVs than normal cells, likely due to the altered conditions of the tumor microenvironment [81]. These EVs contribute to tumor progression by facilitating communication between cancer cells and surrounding stromal cells and carry molecular information that reflects their cells of origin, highlighting their potential as cancer biomarkers [82,83,84].

EVs are generally classified into three main groups based on their size, density, morphology, content, and biogenesis: microvesicles (also called ectosomes or microparticles), apoptotic bodies, and small extracellular vesicles (sEVs). The boundaries between these categories can sometimes overlap. Typically, sEVs range from 30 to 150 nm, microvesicles from 100 to 1000 nm, and apoptotic bodies from 50 to 5000 nm [85,86]. The cargo of EVs includes a wide range of biomolecules, such as non-coding RNAs, mRNAs, DNA, lipids, glycans, and proteins [87,88]. This cargo reflects the molecular characteristics of the cells from which the EVs originate, often carrying cell type- or tissue-specific markers [89]. Therefore, comparing EV components across different cancer histotypes, stages, and grades could provide valuable candidate biomarkers [90]. However, the small size of sEVs limits their cargo capacity and makes them difficult to detect with standard microscopy and sorting techniques. Moreover, the overlapping size and properties among EV subclasses, along with the lack of unique identifying markers, complicate the accurate characterization of their contents, including RNA [91,92,93].

EVs represent promising biomarkers because they carry molecular signatures of their cells of origin, thereby reflecting the biological state of cancer cells more accurately than many conventional markers [94]. sEV have shown significant diagnostic potential in distinguishing malignant from benign adnexal masses and in predicting prognosis in epithelial ovarian cancer (EOC). A serum sEV model was developed and validated across training and testing cohorts, demonstrating strong diagnostic performance [95].

5.2 sEV Biomarkers in Ovarian Cancer

Ascites and serum from ovarian cancer patients contain numerous tumor-derived factors that promote disease progression, and their elevated levels are associated with poor prognosis, even in early-stage disease [96]. In advanced EOC (stage III/IV), the presence of ascites strongly correlates with reduced 5-year survival rates [97]. This association suggests that ascites-derived extracellular vesicles (EVs) may serve as a rich source of prognostic biomarkers. Ovarian cancer cells release large quantities of EVs—including microvesicles and exosomes—that transport diverse biological molecules to surrounding cells. Experimental studies show that ovarian cancer–derived exosomes can be readily taken up by non-tumor cells, altering gene expression and promoting a more aggressive tumor phenotype [98]. These tumor-enriched small EVs therefore represent a promising platform for identifying sensitive and specific biomarkers for ovarian cancer detection [99].

Elevated levels of ovarian cancer–derived EVs have been associated with metastasis and advanced-stage disease. Malignant fluids such as ascites, serum, and other tumor-associated effusions contain significantly higher concentrations of EVs compared with fluids from benign conditions [100,101,102]. Moreover, key EV cargo components—including proteins, glycans, and microRNAs—show distinct expression patterns between benign and malignant phenotypes, further supporting their utility as diagnostic and prognostic biomarkers [103]. Despite advances in treatment, the overall survival rate for ovarian cancer has shown little improvement over the past decades, underscoring the urgent need for more reliable biomarkers for early diagnosis. The challenge is heightened by the early dissemination of ovarian cancer cells from the fallopian tube into the peritoneal cavity, making early detection particularly difficult. Currently, CA125 (MUC16), HE4 and C5a are widely used biomarkers for monitoring disease recurrence, but their sensitivity for early-stage detection remains limited [104,105]. Increasing evidence indicates that several sEV-associated proteins—especially CA125, HE4, and C5a—exhibit strong diagnostic performance and are emerging as promising biomarkers for early detection and accurate classification of epithelial ovarian cancer (EOC) [90].

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5.2.1 sEV-CA125

Cancer Antigen 125 (CA125) is one of the most widely used biomarkers for the detection and management of ovarian cancer. CA125 is a high–molecular weight mucinous glycoprotein expressed on the surface of ovarian cancer cells and subsequently released into the bloodstream. Serum CA125 levels are elevated in a substantial proportion of patients—approximately 50% of early-stage cases and over 90% of advanced-stage disease [106,107]. However, because ovarian cancer is relatively uncommon and serum CA125 can also rise in several benign conditions, its use in population-level screening results in a high rate of false positives [108]. Recent studies demonstrate that sEV-derived CA125 protein levels as potential biomarkers for epithelial ovarian cancer, with particular consideration of their value in early-stage disease, based on evidence from larger and clinically diverse cohorts. Recent studies have demonstrated that CA125 can also be detected in sEVs with notably higher analytical sensitivity [109,110,111]. Importantly, increases in EV concentrations, particularly microvesicles, have been observed several months before rises in serum CA125 levels, indicating their potential value as early detection biomarkers. A combined sEV marker model incorporating CA125 achieved an AUC of 0.912, which was superior to the serum-based model (0.809), further supporting its diagnostic strength [20]. In addition to early detection, sEV-associated CA125 has shown improved performance over serum CA125 and total EV levels in predicting tumour recurrence, chemoresistance, residual disease, and overall patient survival. Collectively, these findings suggest that sEV-derived CA125 represents a promising biomarker with greater clinical utility than conventional serum-based markers [94].

5.2.2 sEV-HE4

Human epididdymal protein 4 (HE4) is a member of the whey acidic protein (WAP) four-disulfide core family and is encoded by the WFDC2 gene. It was initially identified in epithelial cells of the human epididymis, but later studies showed that HE4 is highly overexpressed in ovarian cancer tissues [112,113] while exhibiting minimal or no expression in normal ovarian tissue [114]. Due to this differential expression, serum HE4 has emerged as a valuable biomarker for ovarian cancer, demonstrating a specificity of approximately 96% and a sensitivity of around 67% [115]. Although HE4 offers relatively strong specificity, its sensitivity—especially for early-stage detection—remains limited [14]. This limitation has led to increasing interest in evaluating HE4 within small extracellular vesicles (sEV-HE4), which may provide improved diagnostic performance.

Recent studies have developed diagnostic models based on HE4 levels in serum-derived sEVs to distinguish EOC, including early-stage disease, from benign ovarian conditions and other non-malignant disorders. Compared with conventional serum HE4, sEV-based HE4 models demonstrate superior diagnostic performance, particularly for early-stage detection. Although serum HE4 is an established biomarker for monitoring disease progression and treatment response, its sensitivity for early diagnosis remains limited [116,117]. In contrast, sEV-encapsulated HE4 shows a stronger ability to discriminate EOC from non-EOC cases, consistent with previous proteomic evidence demonstrating enrichment of HE4 within tumor-derived vesicles. These findings support the potential value of serum sEV-HE4 as a more sensitive and reliable biomarker for early detection and clinical stratification of EOC [118].

5.2.3 sEV-C5a

Complement component 5a (C5a) is a key effector of the complement cascade and has recently gained attention for its potential role in ovarian cancer biology. Emerging evidence shows that C5a and its receptor C5aR1 can influence tumor progression by stabilizing β-catenin [119] and activating ERK1/2-mediated signaling pathways, which are known to promote cancer cell invasion and metastasis. Elevated C5a levels have been associated with the pathological status of epithelial ovarian cancer, suggesting a functional link between complement activation and tumor development [120]. C5a has also been identified in sEV-based proteomic studies, prompting the hypothesis that sEV-derived C5a may serve as a more sensitive biomarker than serum C5a alone. In line with this, several recent investigations have evaluated sEV-C5a levels in larger and more clinically diverse cohorts to determine its potential diagnostic value, particularly in early-stage EOC [121]. Recent research has examined C5a and related indicators within serum-derived sEVs to evaluate their potential diagnostic value in ovarian tumors. Across multiple studies, sEV-associated C5a has shown a stronger ability to differentiate benign from malignant ovarian conditions when compared with traditional serum tumor markers [122,123]. This improved discriminatory performance suggests that incorporating sEV-derived

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proteins—particularly sEV-C5a—may enhance both the sensitivity and specificity of ovarian tumor detection. Collectively, these findings highlight sEV-C5a as a promising biomarker for early screening, differential diagnosis, and clinical monitoring of ovarian malignancies [124].

6. The Ovarian Cancer Score (OCS)

6.1 Concept and Component of OCS

The Ovarian Cancer Score (OCS) is a recently developed diagnostic tool that integrates three small extracellular vesicle (sEV)-derived proteins—CA125, HE4, and C5a—to improve the detection of epithelial ovarian cancer (EOC) [2]. Small extracellular vesicles (sEVs) are bilayer membrane vesicles that carry proteins and nucleic acids [18], and their molecular cargo has been identified as a promising source of cancer-specific biomarkers [125] (see Section 4.2). Previous studies have highlighted the diagnostic potential of sEV-derived CA125, HE4, and C5a in distinguishing EOC from benign ovarian conditions [20].

Building on these findings, an algorithm was developed that quantitatively integrates the concentrations of sEV-derived CA125, HE4, and C5a to generate the OCS. This scoring system provides a comprehensive assessment of tumor-associated signals, improving the differentiation between EOC and benign ovarian masses [2]. By combining these three sEV-derived markers, the OCS leverages complementary molecular information: CA125 and HE4 reflect tumor-specific antigen expression [126], while C5a represents immune-related or tumor-microenvironment changes [127]. The multicenter study reported that the OCS was evaluated in women presenting with adnexal masses and to compared its accuracy with that of serum CA125, HE4, and the ROMA index [128,129]. Additionally, diagnostic outcomes were analyzed across subgroups stratified by menopausal status, FIGO stage, age under 45 years, and CA125-negative EOC patients. The OCS thus represents a novel, integrative approach to early detection and accurate classification of ovarian cancer, with the potential to overcome limitations associated with conventional serum biomarkers [2].

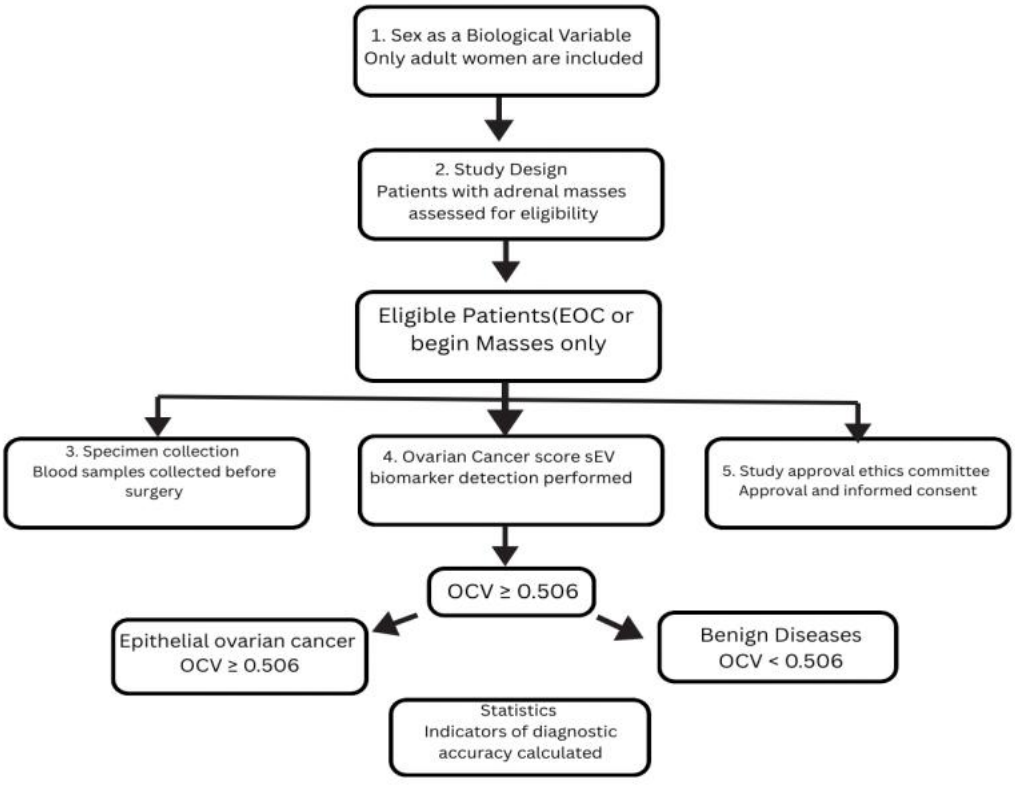


Figure 3: The methodology Flow Diagram

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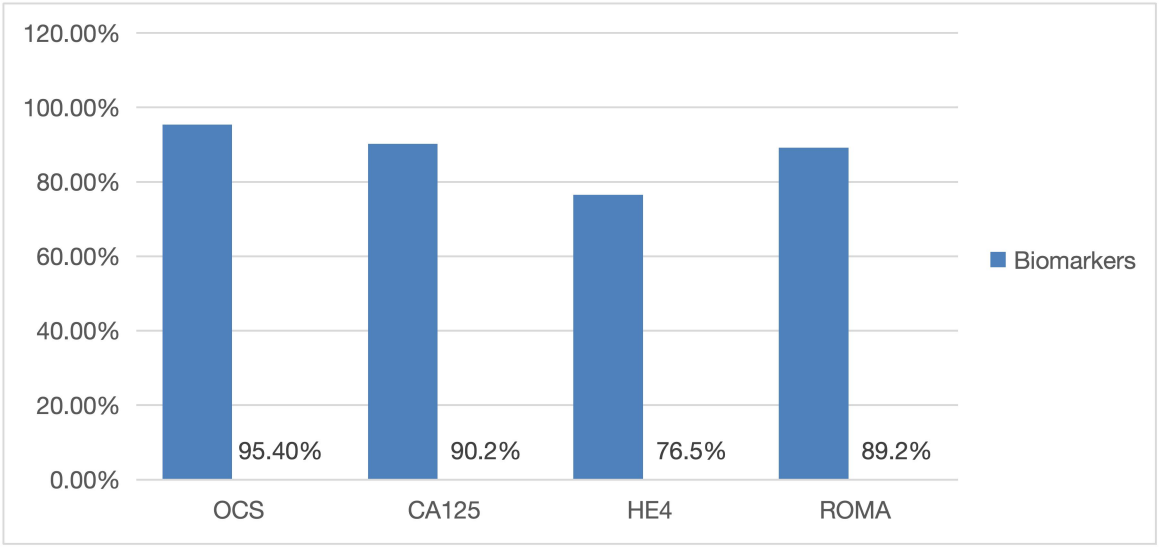
6.2 Search Strategy and Selection Criteria

This multicenter study was conducted across four hospitals in China from October 2019 to April 2023 to evaluate the diagnostic performance of the Ovarian Cancer Score (OCS) in patients with adnexal masses. Adult women presenting with radiologically confirmed adnexal masses and clinically indicated for surgery were assessed for eligibility. Inclusion criteria comprised epithelial ovarian cancer (EOC) or benign ovarian masses classified according to WHO standards, while patients with metastatic or non-epithelial ovarian tumors, borderline tumors, prior chemotherapy or radiation, other malignancies, or pregnancy were excluded. clinicopathological classification and staging were performed using WHO (2014) and FIGO (2013) guidelines, with all pathological diagnoses confirmed by at least two senior pathologists.

Blood samples were collected 24–48 hours prior to surgery, and serum was processed to isolate small extracellular vesicles (sEVs). Concentrations of sEV-derived CA125, HE4, and C5a were quantified using standardized immunoassays, and the OCS was calculated via a pre-established algorithm integrating these biomarkers. A pre-specified cut-off value was applied to distinguish malignant from benign adnexal masses. Diagnostic performance was compared with serum CA125, HE4, and the ROMA index, and subgroup analyses were conducted based on menopausal status, FIGO stage, patient age, and CA125-negative cases. All analyses were performed with clinical information blinded to laboratory personnel, ensuring unbiased assessment, and statistical evaluation included sensitivity, specificity, and accuracy metrics. The study was approved by the institutional ethics committees of all participating centers, and written informed consent was obtained from all participants.

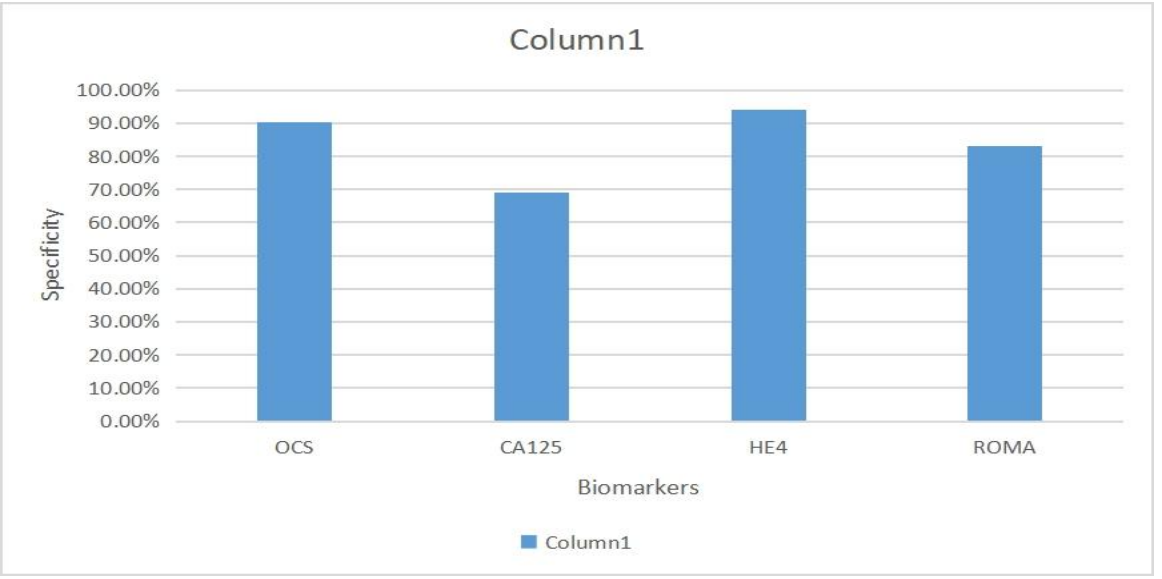
7. Diagnostic Performance of OCS

The Ovarian Cancer Score (OCS) demonstrated superior diagnostic performance in differentiating epithelial ovarian cancer (EOC) from benign ovarian conditions. In the prospective cohort, the OCS achieved a sensitivity of 95.4% and specificity of 90.4%, which were significantly higher than those of serum CA125 (sensitivity: 90.2%, specificity: 69.2%). Across all cases, the overall sensitivity and specificity of OCS were 95.5% and 90.2%, respectively. Compared head-to-head with other biomarkers in a subset of participants, OCS showed significantly higher sensitivity than serum HE4 (95.1% vs. 76.5%) while slightly lower specificity (90.6 % vs. 94.0 %). Compared to ROMA, OCS and slightly higher sensitivity than ROMA (95.1% vs. 89.2%), while maintaining greater specificity than ROMA (90.6% vs. 83.1%). The false-positive rate of OCS was 9.4%, lower than that of CA125 (34.4%) and ROMA (16.9%), but slightly higher than HE4 (6%).



Graph 1: OCS sensitivity with other biomarkers

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Graph 2: OCS specificity with other biomarkers

Subgroup analyses indicated that the OCS performance was robust across different clinical settings. Sensitivity and specificity were consistent regardless of menopausal status, with premenopausal and postmenopausal women showing sensitivities of 95.2% and 95.5%, and specificities of 90.0% and 91.4%, respectively. OCS also maintained high sensitivity across FIGO stages, including early-stage disease (stage I: 89.1%, stage II: 92.5%, stage I + II: 91.4%), outperforming serum CA125, which showed markedly reduced sensitivity in early-stage patients (stage I: 66.7%, stage I + II: 77.7%). Among younger women under 45 years of age, OCS demonstrated higher sensitivity (92.7%) and specificity (89.9%) compared with CA125 (sensitivity: 80.0%, specificity: 62.1%), including improved performance in early-stage subgroups.

Table 1. Diagnostic performance of OCS in different groups

	Biomarker	***Sensitivity%***	***Specificity%***	***PPV%***	***NPV%***
EOC vs Benign	OCS	95.4	90.4	72.5	98.7
EOC vs Benign	CA125	90.2	69.2	44.1	96.3
EOC vs Benign (Pre-M)	OCS	95.2	90.0	56.7	99.3
EOC vs Benign (Pre-M)	CA125	89.3	64.5	26.0	97.7
EOC vs Benign (Post-M)	OCS	95.5	91.4	88.1	96.8
EOC vs Benign (Post-M)	CA125	90.8	83.6	78.7	93.1

Table 2. Diagnostic performance of OCS in different stages

	Biomarkers%	***Sensitivity%***	***Specificity%***	***PPV%***	***NPV%***
FIGO 1 vs. Benign	OCS	89.1	90.4	34.5	99.3
FIGO 1 vs. Benign	CA125	66.7	69.2	10.9	97.4
FIGO 2 vs. Benign	OCS	92.5	90.4	32.2	99.6
FIGO 2 vs. Benign	CA125	90.0	69.2	12.8	99.3
FIGO 3 vs. Benign	OCS	97.9	90.4	53.9	99.7
FIGO 3 vs. Benign	CA125	98.9	69.2	27.1	99.8
FIGO 4 vs. Benign	OCS	100.0	90.4	29.7	100.0
FIGO 4 vs. Benign	CA125	100.0	69.2	11.9	100.0

The OCS also exhibited consistent performance across histological subtypes of EOC. Sensitivity was highest for serous carcinomas (98.2%) and high-grade serous ovarian cancer (HGSOC, 98.5%), and remained high in endometrioid (96.2%), mucinous (90.0%), and clear cell carcinomas (84.4%). These findings highlight the strengths of OCS,

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including higher overall accuracy, improved diagnostic stability due to its sEV-based design, and reduced false-positive rates compared with conventional serum biomarkers. Collectively, the OCS represents a promising tool for early and reliable detection of ovarian cancer across diverse patient populations [2].

8. Limitations

Despite the promising diagnostic performance of the Ovarian Cancer Score (OCS), several limitations should be acknowledged. First, although the multicenter findings support the accuracy of OCS in distinguishing epithelial ovarian cancer from benign adnexal disease, broader validation in larger and more diverse populations is still required, particularly for less common histological subtypes such as mucinous, endometrioid, and clear cell carcinoma. Second, borderline ovarian tumors and non-epithelial malignancies were excluded to minimize confounding effects; therefore, the applicability of OCS to these categories remains uncertain and warrants further investigation. Finally, while the OCS demonstrated strong sensitivity in early-stage disease, additional evidence from longitudinal and screening-based studies is needed to confirm its role in early detection within asymptomatic or general-risk populations.

9. Future Directions

Future studies should focus on large, prospective multicenter cohorts to validate the Ovarian Cancer Score (OCS) across diverse populations and ovarian cancer subtypes. Further evaluation is needed in borderline tumors, non-epithelial malignancies, and screening contexts involving asymptomatic or high-risk women. Integrating sEV-based diagnostics with imaging modalities and current risk algorithms may improve diagnostic accuracy while reducing dependence on single serum markers. Finally, progress in assay standardization, automation, and cost-effectiveness will be critical for incorporating OCS into routine clinical practice and advancing personalized early detection strategies.

10. Conclusion

Ovarian cancer remains the most lethal gynecologic malignancy, primarily due to the lack of reliable methods for early detection. Conventional diagnostic tools, including imaging and serum CA125, have important clinical value but demonstrate limited sensitivity and specificity, particularly in early-stage disease. The incorporation of HE4 and algorithms such as ROMA has improved diagnostic performance; however, their clinical utility remains variable across populations and tumor subtypes. Recent advances in proteomics and liquid biopsy technologies, particularly small extracellular vesicles (sEVs), offer promising opportunities for non-invasive ovarian cancer diagnostics. sEVs provide a stable source of tumor-derived biomarkers that reflect tumor heterogeneity and disease progression. Emerging evidence suggests that integrating sEV-based biomarkers with established serum markers and imaging modalities, including multivariate models such as the Ovarian Cancer Score (OCS), may substantially enhance diagnostic accuracy and risk stratification. Future efforts should focus on standardization, large-scale validation, and clinical translation of these multimodal diagnostic approaches to improve early detection and patient outcomes.

References

[1]. Qian, L., Zhu, J., Xue, Z., Zhou, Y., Xiang, N., Xu, H., ... & Guo, T. (2024). Proteomic landscape of epithelial ovarian cancer. *Nature Communications*, *15*(1), 6462.

[2]. Wang, H., Zhu, J., Zou, D., Rao, Q., Han, L., Lu, H., ... & Zhou, Q. (2025). Multicenter study of ovarian cancer score for diagnosing ovarian cancer. *Gynecologic Oncology*, *193*, 58-64.

[3]. De La Franier, B., & Thompson, M. (2019). Early stage detection and screening of ovarian cancer: A research opportunity and significant challenge for biosensor technology. *Biosensors and Bioelectronics*, *135*, 71-81.

[4]. Aggarwal, R., Sheikh, A., Akhtar, M., Ghazwani, M., Hani, U., Sahebkar, A., & Kesharwani, P. (2025). Understanding gold nanoparticles and their attributes in ovarian cancer therapy. *Molecular Cancer*, *24*(1), 88.

[5]. Qian, L., Sun, R., Xue, Z., & Guo, T. (2023). Mass spectrometry–based proteomics of epithelial ovarian cancers: A clinical perspective. *Molecular & Cellular Proteomics*, *22*(7).

[6]. Hong, M. K., & Ding, D. C. (2025). Early diagnosis of ovarian cancer: A comprehensive review of the advances, challenges, and future directions. *Diagnostics*, *15*(4), 406.

[7]. Torre, L. A., Trabert, B., DeSantis, C. E., Miller, K. D., Samimi, G., Runowicz, C. D., ... & Siegel, R. L. (2018). Ovarian cancer statistics,

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https://creativecommons.org/licenses/by/4.0

2018. *CA: a cancer journal for clinicians*, *68*(4), 284-296.

[8]. Sahu, S. A., & Shrivastava, D. (2023). A comprehensive review of screening methods for ovarian masses: towards earlier detection. *Cureus*, *15*(11).

[9]. Cviič, D., Jagarlamudi, K., Meglič, L., Škof, E., Zore, A., Lukanović, D., Eriksson, S., & Osredkar, J. (2023). A Dual Biomarker TK1 Protein and CA125 or HE4-Based Algorithm as a Better Diagnostic Tool than ROMA Index in Early Detection of Ovarian Cancer. Cancers, 15(5), 1593.

[10]. Urban, N., McIntosh, M. W., Andersen, M. R., & Karlan, B. Y. (2003). Ovarian cancer screening. *Hematology/Oncology Clinics*, *17*(4), 989-1005.

[11]. Buamah, P. (2000). Benign conditions associated with raised serum CA-125 concentration. *Journal of surgical oncology*, *75*(4), 264-265.

[12]. Hellstrom, I., Raycraft, J., Hayden-Ledbetter, M., Ledbetter, J. A., Schummer, M., McIntosh, M., ... & Hellström, K. E. (2003). The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. *Cancer research*, *63*(13), 3695-3700.

[13]. Drapkin, R., Von Horsten, H. H., Lin, Y., Mok, S. C., Crum, C. P., Welch, W. R., & Hecht, J. L. (2005). Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer research*, *65*(6), 2162-2169.

[14]. Dochez, V., Caillon, H., Vaucel, E., Dimet, J., Winer, N., & Ducarme, G. (2019). Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *Journal of ovarian research*, *12*(1), 28.

[15]. Li, F., Tie, R., Chang, K., Wang, F., Deng, S., Lu, W., ... & Chen, M. (2012). Does risk for ovarian malignancy algorithm excel human epididymis protein 4 and CA125 in predicting epithelial ovarian cancer: a meta-analysis. *BMC cancer*, *12*(1), 258.

[16]. Hada, A., Han, L. P., Chen, Y., Hu, Q. H., Yuan, Y., & Liu, L. (2020). Comparison of the predictive performance of risk of malignancy indexes 1–4, HE4 and risk of malignancy algorithm in the triage of adnexal masses. *Journal of ovarian research*, *13*(1), 46.

[17]. Jacob, F., Meier, M., Caduff, R., Goldstein, D., Pochechueva, T., Hacker, N., ... & Heinzelmann-Schwarz, V. (2011). No benefit from combining HE4 and CA125 as ovarian tumor markers in a clinical setting. *Gynecologic oncology*, *121*(3), 487-491.

[18]. Ariston Gabriel, A. N., Wang, F., Jiao, Q., Yvette, U., Yang, X., Al-Ameri, S. A., ... & Wang, C. (2020). The involvement of exosomes in the diagnosis and treatment of pancreatic cancer. *Molecular cancer*, *19*(1), 132.

[19]. Zhu, Y., Wang, C., Ma, Z., Li, F., Xu, C., Pan, W., & Liu, A. (2023). Role of exosomes in the invasion and metastasis of ovarian cancer and application potential of clinical diagnosis and treatment. *Journal of Cancer*, *14*(7), 1141.

[20]. Li, P., Bai, Y., Shan, B., Zhang, W., Liu, Z., Zhu, Y., ... & Hu, Y. (2021). Exploration of potential diagnostic value of protein content in serum small extracellular vesicles for early-stage epithelial ovarian carcinoma. *Frontiers in Oncology*, *11*, 707658.

[21]. Wentzensen, N., Ring, K., Erickson, B. K., Reid, B., O'Donnell, T., Check, D., ... & Choudhury, P. P. (2025). Ovarian cancer risk prediction: a clinical epidemiology perspective. *American journal of epidemiology*, *194*(5), 1182-1191.

[22]. Smolarz, B., Biernacka, K., Łukasiewicz, H., Samulak, D., Piekarska, E., Romanowicz, H., & Makowska, M. (2025). Ovarian Cancer—Epidemiology, Classification, Pathogenesis, Treatment, and Estrogen Receptors' Molecular Backgrounds. *International Journal of Molecular Sciences*, *26*(10), 4611.

[23]. Reid, B. M., Permuth, J. B., & Sellers, T. A. (2017). Epidemiology of ovarian cancer: a review. *Cancer biology & medicine*, *14*(1), 9-32.

[24]. Chen, W., Zheng, R., Baade, P. D., Zhang, S., Zeng, H., Bray, F., ... & He, J. (2016). Cancer statistics in China, 2015. *CA: a cancer journal for clinicians*, *66*(2), 115-132.

[25]. American Cancer Society. (2020). Cancer Facts & Figures 2020. Atlanta: American Cancer Society.

[26]. Huang, J., Chan, W. C., Ngai, C. H., Lok, V., Zhang, L., Lucero-Prisno III, D. E., ... & NCD Global Health Research Group of Association of Pacific Rim Universities (APRU). (2022). Worldwide burden, risk factors, and temporal trends of ovarian cancer: a global study. *Cancers*, *14*(9), 2230.

[27]. Ali, A. T., Al-Ani, O., & Al-Ani, F. (2023). Epidemiology and risk factors for ovarian cancer. *Menopause Review/Przegląd Menopauzalny*, *22*(2), 93-104.

[28]. Köbel, M., Kalloger, S. E., Lee, S., Duggan, M. A., Kelemen, L. E., Prentice, L., ... & Goode, E. L. (2013). Biomarker-based ovarian carcinoma typing: a histologic investigation in the ovarian tumor tissue analysis consortium. *Cancer epidemiology, biomarkers & prevention*, *22*(10), 1677-1686.

[29]. Zamwar, U. M., Anjankar, A. P., & Anjankar, A. (2022). Aetiology, epidemiology, histopathology, classification, detailed evaluation, and treatment of ovarian cancer. *Cureus*, *14*(10).

[30]. Mancari, R., Cutillo, G., Bruno, V., Vincenzoni, C., Mancini, E., Baiocco, E., ... & Vizza, E. (2020). Development of new medical treatment for epithelial ovarian cancer recurrence. *Gland surgery*, *9*(4), 1149.

[31]. Nair, M., Samidurai, A., Das, A., Kakar, S. S., & Kukreja, R. C. (2025). Ovarian cancer and the heart: pathophysiology, chemotherapy-induced cardiotoxicity, and new therapeutic strategies. *Journal of Ovarian Research*, *18*(1), 72.

[32]. Stewart, C., Ralyea, C., & Lockwood, S. (2019, April). Ovarian cancer: an integrated review. In *Seminars in oncology nursing* (Vol. 35, No. 2, pp. 151-156). WB Saunders.

[33]. Tossetta, G., & Inversetti, A. (2023). Ovarian cancer: advances in pathophysiology and therapies. *International Journal of Molecular Sciences*, *24*(10), 8930.

[34]. Tossetta, G., Fantone, S., Montanari, E., Marzioni, D., & Goteri, G. (2022). Role of NRF2 in ovarian cancer. *Antioxidants*, *11*(4), 663.

[35]. Karnezis, A. N., Cho, K. R., Gilks, C. B., Pearce, C. L., & Huntsman, D. G. (2017). The disparate origins of ovarian cancers: pathogenesis and prevention strategies. *Nature Reviews Cancer*, *17*(1), 65-74.

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https://creativecommons.org/licenses/by/4.0

[36]. Caruso, G., Weroha, S. J., & Cliby, W. (2025). Ovarian cancer: a review. *Jama*.

[37]. Panagopoulou, M., Panou, T., Gkountakos, A., Tarapatzi, G., Karaglani, M., Tsamardinos, I., & Chatzaki, E. (2024). BRCA1 & BRCA2 methylation as a prognostic and predictive biomarker in cancer: Implementation in liquid biopsy in the era of precision medicine. *Clinical epigenetics*, *16*(1), 178.

[38]. Gupta, K. K., Gupta, V. K., & Naumann, R. W. (2019). Ovarian cancer: screening and future directions. *International Journal of Gynecological Cancer*, *29*(1), 195-200.

[39]. Gandhi, T., Zubair, M., & Bhatt, H. (2024). Cancer antigen 125. In *StatPearls [Internet]*. StatPearls Publishing.

[40]. Charkhchi, P., Cybulski, C., Gronwald, J., Wong, F. O., Narod, S. A., & Akbari, M. R. (2020). CA125 and ovarian cancer: a comprehensive review. *Cancers*, *12*(12), 3730.

[41]. Bast Jr, R. C., Klug, T. L., John, E. S., Jenison, E., Niloff, J. M., Lazarus, H., ... & Knapp, R. C. (1983). A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *New England journal of medicine*, *309*(15), 883-887.

[42]. Liberto, J. M., Chen, S. Y., Shih, I. M., Wang, T. H., Wang, T. L., & Pisanic, T. R. (2022). Current and emerging methods for ovarian cancer screening and diagnostics: a comprehensive review. *Cancers*, *14*(12), 2885.

[43]. Timmerman, D., Van Calster, B., Jurkovic, D., Valentin, L., Testa, A. C., Bernard, J. P., ... & Bourne, T. (2007). Inclusion of CA-125 does not improve mathematical models developed to distinguish between benign and malignant adnexal tumors. *Journal of clinical oncology*, *25*(27), 4194-4200.

[44]. Zhang, R., Siu, M. K., Ngan, H. Y., & Chan, K. K. (2022). Molecular biomarkers for the early detection of ovarian cancer. *International journal of molecular sciences*, *23*(19), 12041.

[45]. Funston, G., Mounce, L. T., Price, S., Rous, B., Crosbie, E. J., Hamilton, W., & Walter, F. M. (2021). CA125 test result, test-to-diagnosis interval, and stage in ovarian cancer at diagnosis: A retrospective cohort study using electronic health records. *British Journal of General Practice*.

[46]. Ghose, A., McCann, L., Makker, S., Mukherjee, U., Gullapalli, S. V. N., Erekkath, J., ... & Boussios, S. (2024). Diagnostic biomarkers in ovarian cancer: advances beyond CA125 and HE4. *Therapeutic advances in medical oncology*, *16*, 17588359241233225.

[47]. Bouchard, D., Morisset, D., Bourbonnais, Y., & Tremblay, G. M. (2006). Proteins with whey-acidic-protein motifs and cancer. *The lancet oncology*, *7*(2), 167-174.

[48]. Anastasi, E., Giovanna Marchei, G., Viggiani, V., Gennarini, G., Frati, L., & Reale, M. G. (2010). HE4: a new potential early biomarker for the recurrence of ovarian cancer. *Tumor Biology*, *31*(2), 113-119.

[49]. Piovano, E., Attamante, L., Macchi, C., Cavallero, C., Romagnolo, C., Maggino, T., ... & Zola, P. (2014). The role of HE4 in ovarian cancer follow-up: a review. *International Journal of Gynecological Cancer*, *24*(8), 1359-1365.

[50]. Steffensen, K. D., Waldstrøm, M., Brandslund, I., & Jakobsen, A. (2011). Prognostic impact of prechemotherapy serum levels of HER2, CA125, and HE4 in ovarian cancer patients. *International Journal of Gynecological Cancer*, *21*(6), 1040-1047.

[51]. Galgano, M. T., Hampton, G. M., & Frierson Jr, H. F. (2006). Comprehensive analysis of HE4 expression in normal and malignant human tissues. *Modern Pathology*, *19*(6), 847-853

[52]. Anastasi, E., Farina, A., Granato, T., Colaiacovo, F., Pucci, B., Tartaglione, S., & Angeloni, A. (2023). Recent insight about HE4 role in ovarian cancer oncogenesis. *International journal of molecular sciences*, *24*(13), 10479.

[53]. Chudecka-Głaz, A., Strojna, A., Michalczyk, K., Wieder-Huszla, S., Safranow, K., Skwirczyńska, E., & Jurczak, A. (2023). Evaluation of he4 use in the diagnosis of ovarian cancer: first and second recurrence, and an analysis of HE4 concentration during second-and third-line chemotherapy. *Diagnostics*, *13*(3), 452.

[54]. Huang, J., Chen, J., & Huang, Q. (2018). Diagnostic value of HE4 in ovarian cancer: A meta-analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *231*, 35-42.

[55]. Gao, L., Cheng, H. Y., Dong, L., Ye, X., Liu, Y. N., Chang, X. H., ... & Cui, H. (2011). The role of HE4 in ovarian cancer: inhibiting tumour cell proliferation and metastasis. *Journal of International Medical Research*, *39*(5), 1645-1660.

[56]. Yurkovetsky, Z., Skates, S., Lomakin, A., Nolen, B., Pulsipher, T., Modugno, F., ... & Lokshin, A. E. (2010). Development of a multimarker assay for early detection of ovarian cancer. *Journal of Clinical Oncology*, *28*(13), 2159-2166.

[57]. Anton, C., Carvalho, F. M., Oliveira, E. I., Maciel, G. A. R., Baracat, E. C., & Carvalho, J. P. (2012). A comparison of CA125, HE4, risk ovarian malignancy algorithm (ROMA), and risk malignancy index (RMI) for the classification of ovarian masses. *Clinics*, *67*, 437-441.

[58]. Singh, A. K., Yadav, P., Shukla, M., Samaiya, S., Singh, S., Sorout, S., & SAMAIYA, S. (2025). Comparative Meta-Analysis of Carbohydrate Antigen 125 (CA125), Human Epididymis Protein 4 (HE4), and Diagnostic Indices (Risk of Malignancy Index (RMI) and Risk of Ovarian Malignancy Algorithm (ROMA)) for Pre-operative Detection of Ovarian Carcinoma. *Cureus*, *17*(4).

[59]. Moore, R. G., McMeekin, D. S., Brown, A. K., DiSilvestro, P., Miller, M. C., Allard, W. J., ... & Skates, S. J. (2009). A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecologic oncology*, *112*(1), 40-46.

[60]. Sandri, M. T., Bottari, F., Franchi, D., Boveri, S., Candiani, M., Ronzoni, S., ... & Sideri, M. (2013). Comparison of HE4, CA125 and ROMA algorithm in women with a pelvic mass: correlation with pathological outcome. *Gynecologic oncology*, *128*(2), 233-238.

[61]. Chudecka-Głaz, A. M. (2015). ROMA, an algorithm for ovarian cancer. *Clinica Chimica Acta*, *440*, 143-151.

[62]. Montagnana, M., Danese, E., Ruzzenente, O., Bresciani, V., Nuzzo, T., Gelati, M., ... & Guidi, G. C. (2011). The ROMA (Risk of Ovarian Malignancy Algorithm) for estimating the risk of epithelial ovarian cancer in women presenting with pelvic mass: is it really useful?. *Clinical chemistry and laboratory medicine*, *49*(3), 521-525

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https://creativecommons.org/licenses/by/4.0

[63]. Fathi, A., Heidari, M., Rasouli, J., & Ghasemnejad-Berenji, H. (2025). 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. *BMC Women's Health*, *25*(1), 280.

[64]. Fischerova, D., & Burgetova, A. (2014). Imaging techniques for the evaluation of ovarian cancer. *Best practice & research Clinical obstetrics & gynaecology*, *28*(5), 697-720.

[65]. Di Lorenzo, G., Ricci, G., Severini, G. M., Romano, F., & Biffi, S. (2018). Imaging and therapy of ovarian cancer: clinical application of nanoparticles and future perspectives. *Theranostics*, *8*(16), 4279.

[66]. Clarke-Pearson, D. L. (2009). Screening for ovarian cancer. *New England Journal of Medicine*, *361*(2), 170-177.

[67]. Kaijser, J., Bourne, T., Valentin, L., Sayasneh, A., Van Holsbeke, C., Vergote, I., ... & Timmerman, D. (2013). Improving strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. *Ultrasound in obstetrics & gynecology*, *41*(1), 9-20.

[68]. Rauh-Hain, J. A., Krivak, T. C., Del Carmen, M. G., & Olawaiye, A. B. (2011). Ovarian cancer screening and early detection in the general population. *Reviews in obstetrics and gynecology*, *4*(1), 15.

[69]. Khiewvan, B., Torigian, D. A., Emamzadehfard, S., Paydary, K., Salavati, A., Houshmand, S., ... & Alavi, A. (2017). An update on the role of PET/CT and PET/MRI in ovarian cancer. *European journal of nuclear medicine and molecular imaging*, *44*(6), 1079-1091.

[70]. Grab, D., Flock, F., Stöhr, I., Nüssle, K., Rieber, A., Fenchel, S., ... & Kreienberg, R. (2000). Classification of asymptomatic adnexal masses by ultrasound, magnetic resonance imaging, and positron emission tomography. *Gynecologic oncology*, *77*(3), 454-459.

[71]. Buist, M. R., Golding, R. P., Burger, C. W., Vermorken, J. B., Kenemans, P., Schutter, E. M., ... & Falke, T. H. (1994). Comparative evaluation of diagnostic methods in ovarian carcinoma with emphasis on CT and MRI. *Gynecologic oncology*, *52*(2), 191-198.

[72]. Buy, J. N., Ghossain, M. A., Sciot, C., Bazot, M., Guinet, C., Prevot, S., ... & Poitout, P. (1991). Epithelial tumors of the ovary: CT findings and correlation with US. *Radiology*, *178*(3), 811-818.

[73]. Sohaib, S. A. A., & Reznek, R. H. (2007). MR imaging in ovarian cancer. *Cancer Imaging*, *7*(Special issue A), S119.

[74]. Gagliardi, T., Adejolu, M., & DeSouza, N. M. (2022). Diffusion-weighted magnetic resonance imaging in ovarian cancer: exploiting strengths and understanding limitations. *Journal of Clinical Medicine*, *11*(6), 1524.

[75]. Bourgioti, C., Konidari, M., & Moulopoulos, L. A. (2023). Manifestations of ovarian cancer in relation to other pelvic diseases by MRI. *Cancers*, *15*(7), 2106.

[76]. Yoshida, Y., Kurokawa, T., Tsujikawa, T., Okazawa, H., & Kotsuji, F. (2009). Positron emission tomography in ovarian cancer: 18F-deoxy-glucose and 16α-18F-fluoro-17β-estradiol PET. *Journal of Ovarian Research*, *2*(1), 7.

[77]. Zhou, X., Huang, J., Zhang, D., Qian, Z., Zuo, X., & Sun, Y. (2025). Small extracellular vesicles: the origins, current status, future prospects, and applications. *Stem Cell Research & Therapy*, *16*(1), 184.

[78]. Welsh, J. A., Goberdhan, D. C., O'Driscoll, L., Buzas, E. I., Blenkiron, C., Bussolati, B., ... & Benedikter, B. J. (2024). Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches. *Journal of extracellular vesicles*, *13*(2), e12404.

[79]. Peng, L., Lai, Y., & Cao, B. (2025). Advances in small extracellular vesicles: roles in the tumor microenvironment and epithelial ovarian cancer diagnosis and treatment. *Frontiers in Oncology*, *15*, 1526944.

[80]. Liang, J., & Yin, H. (2023). STAM transports STING oligomers into extracellular vesicles, down-regulating the innate immune response. *Journal of Extracellular Vesicles*, *12*(3), 12316.

[81]. King, H. W., Michael, M. Z., & Gleadle, J. M. (2012). Hypoxic enhancement of exosome release by breast cancer cells. *BMC cancer*, *12*(1), 421.

[82]. Lucidi, A., Buca, D., Ronsini, C., Tinari, S., Bologna, G., Buca, D., ... & Petrillo, M. (2020). Role of extracellular vesicles in epithelial ovarian cancer: a systematic review. *International Journal of Molecular Sciences*, *21*(22), 8762.

[83]. Théry, C., Boussac, M., Véron, P., Ricciardi-Castagnoli, P., Raposo, G., Garin, J., & Amigorena, S. (2001). Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles. *The Journal of Immunology*, *166*(12), 7309-7318.

[84]. Ekström, K., Valadi, H., Sjöstrand, M., Malmhäll, C., Bossios, A., Eldh, M., & Lötvall, J. (2012). Characterization of mRNA and microRNA in human mast cell-derived exosomes and their transfer to other mast cells and blood CD34 progenitor cells. *Journal of extracellular vesicles*, *1*(1), 18389.

[85]. Negahdaripour, M., Owji, H., Eskandari, S., Zamani, M., Vakili, B., & Nezafat, N. (2021). Small extracellular vesicles (sEVs): Discovery, functions, applications, detection methods and various engineered forms. *Expert opinion on biological therapy*, *21*(3), 371-394.

[86]. Russell, A. E., Sneider, A., Witwer, K. W., Bergese, P., Bhattacharyya, S. N., Cocks, A., ... & Vader, P. (2019). Biological membranes in EV biogenesis, stability, uptake, and cargo transfer: an ISEV position paper arising from the ISEV membranes and EVs workshop. *Journal of extracellular vesicles*, *8*(1), 1684862.

[87]. Melo, S. A., Sugimoto, H., O'Connell, J. T., Kato, N., Villanueva, A., Vidal, A., ... & Kalluri, R. (2014). Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. *Cancer cell*, *26*(5), 707-721.

[88]. Valadi, H., Ekström, K., Bossios, A., Sjöstrand, M., Lee, J. J., & Lötvall, J. O. (2007). Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nature cell biology*, *9*(6), 654-659.

[89]. Gomes, J., Gomes-Alves, P., Carvalho, S. B., Peixoto, C., Alves, P. M., Altevogt, P., & Costa, J. (2015). Extracellular vesicles from ovarian carcinoma cells display specific glycosignatures. *Biomolecules*, *5*(3), 1741-1761.

[90]. Nawaz, M., Fatima, F., Nazarenko, I., Ekström, K., Murtaza, I., Anees, M., ... & Kislinger, T. (2016). Extracellular vesicles in ovarian

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https://creativecommons.org/licenses/by/4.0

cancer: applications to tumor biology, immunotherapy and biomarker discovery. *Expert review of proteomics*, *13*(4), 395-409.

[91]. Das, A. (2024). Extracellular Vesicles: Tiny messengers for mighty rna delivery. *Biologics*, *4*(1), 88-104.

[92]. De Sousa, K. P., Rossi, I., Abdullahi, M., Ramirez, M. I., Stratton, D., & Inal, J. M. (2023). Isolation and characterization of extracellular vesicles and future directions in diagnosis and therapy. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *15*(1), e1835.

[93]. Liangsupree, T., Multia, E., & Riekkola, M. L. (2021). Modern isolation and separation techniques for extracellular vesicles. *Journal of Chromatography A*, *1636*, 461773.

[94]. Asare-Werehene, M., Hunter, R. A., Gerber, E., Reunov, A., Brine, I., Chang, C. Y., ... & Tsang, B. K. (2023). The application of an extracellular vesicle-based biosensor in early diagnosis and prediction of chemoresponsiveness in ovarian cancer. *Cancers*, *15*(9), 2566.

[95]. Li, L., Zhang, F., Zhang, J., Shi, X., Wu, H., Chao, X., ... & Liang, Z. (2023). Identifying serum small extracellular vesicle microRNA as a noninvasive diagnostic and prognostic biomarker for ovarian cancer. *ACS nano*, *17*(19), 19197-19210.

[96]. DEMBO, A. J., DAVY, M., STENWIG, A. E., BERLE, E. J., BUSH, R. S., & KJORSTAD, K. (1990). Prognostic factors in patients with stage I epithelial ovarian cancer. *Obstetrics & Gynecology*, *75*(2), 263-273.

[97]. Puls, L. E., Duniho, T., Hunter IV, J. E., Kryscio, R., Blackhurst, D., & Gallion, H. (1996). The prognostic implication of ascites in advanced-stage ovarian cancer. *Gynecologic oncology*, *61*(1), 109-112.

[98]. Enriquez, V. A., Cleys, E. R., Da Silveira, J. C., Spillman, M. A., Winger, Q. A., & Bouma, G. J. (2015). High LIN28A expressing ovarian cancer cells secrete exosomes that induce invasion and migration in HEK293 cells. *BioMed research international*, *2015*(1), 701390.

[99]. Vaksman, O., Tropé, C., Davidson, B., & Reich, R. (2014). Exosome-derived miRNAs and ovarian carcinoma progression. *Carcinogenesis*, *35*(9), 2113-2120.

[100]. Graves, L. E., Ariztia, E. V., Navari, J. R., Matzel, H. J., Stack, M. S., & Fishman, D. A. (2004). Proinvasive properties of ovarian cancer ascites-derived membrane vesicles. *Cancer research*, *64*(19), 7045-7049.

[101]. Taylor, D. D., & Gercel-Taylor, C. (2008). RETRACTED: MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer.

[102]. Kobayashi, M., Salomon, C., Tapia, J., Illanes, S. E., Mitchell, M. D., & Rice, G. E. (2014). Ovarian cancer cell invasiveness is associated with discordant exosomal sequestration of Let-7 miRNA and miR-200. *Journal of translational medicine*, *12*(1), 4.

[103]. Sinha, A., Ignatchenko, V., Ignatchenko, A., Mejia-Guerrero, S., & Kislinger, T. (2014). In-depth proteomic analyses of ovarian cancer cell line exosomes reveals differential enrichment of functional categories compared to the NCI 60 proteome. *Biochemical and biophysical research communications*, *445*(4), 694-701.

[104]. Sankey MD, H. (2009). PROLOG: Gynecology and surgery.

[105]. Guidi, G. C., Plebani, M., & Lippi, G. (2011). HE4 in ovarian cancer: from discovery to clinical application. *Advances in clinical chemistry*, *55*, 1.

[106]. van Haaften-Day, C., Shen, Y. U., Xu, F., Yu, Y., Berchuck, A., Havrilesky, L. J., ... & Hacker, N. F. (2001). OVX1, macrophage-colony stimulating factor, and CA-125-II as tumor markers for epithelial ovarian carcinoma: A critical appraisal. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *92*(11), 2837-2844.

[107]. Nustad, K., Bast, Jr, R. C., O'brien, T. J., Nilsson, O., Seguin, P., Suresh, M. R., ... & Hilgers, J. (1996). Specificity and affinity of 26 monoclonal antibodies against the CA 125 antigen: first report from the ISOBM TD-1 workshop. *Tumor Biology*, *17*(4), 196-219.

[108]. Henderson, J. T., Webber, E. M., & Sawaya, G. F. (2018). Screening for ovarian cancer: updated evidence report and systematic review for the US preventive services task force. *Jama*, *319*(6), 595-606.

[109]. Li, J., Sherman-Baust, C. A., Tsai-Turton, M., Bristow, R. E., Roden, R. B., & Morin, P. J. (2009). Claudin-containing exosomes in the peripheral circulation of women with ovarian cancer. *BMC cancer*, *9*(1), 244.

[110]. Peng, P., Yan, Y., & Keng, S. (2011). Exosomes in the ascites of ovarian cancer patients: origin and effects on anti-tumor immunity. *Oncology reports*, *25*(3), 749-762.

[111]. Taylor, D. D., Gercel-Taylor, C., & Parker, L. P. (2009). RETRACTED: Patient-derived tumor-reactive antibodies as diagnostic markers for ovarian cancer.

[112]. Li, K., Pei, Y., Wu, Y., Guo, Y., & Cui, W. (2020). Performance of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) in diagnosis of ovarian cancer: a systematic review and meta-analysis. *Journal of Ovarian Research*, *13*(1), 6.

[113]. Tiss, A., Timms, J. F., Smith, C., Devetyarov, D., Gentry-Maharaj, A., Camuzeaux, S., ... & Cramer, R. (2010). Highly accurate detection of ovarian cancer using CA125 but limited improvement with serum matrix-assisted laser desorption/ionization time-of-flight mass spectrometry profiling. *International Journal of Gynecological Cancer*, *20*(9), 1518-1524.

[114]. Yu, C., Dou, T., Liu, Y., & Liu, R. (2020). Clinical value of TV-CDS combined with serum tumor markers in diagnosis of ovarian cancer. *Oncology Letters*, *20*(2), 2028-2034.

[115]. Wang, H., Liu, P., Xu, H., & Dai, H. (2021). Early diagonosis of ovarian cancer: serum HE4, CA125 and ROMA model. *American Journal of Translational Research*, *13*(12), 14141.

[116]. Giannopoulou, L., Zavridou, M., Kasimir-Bauer, S., & Lianidou, E. S. (2019). Liquid biopsy in ovarian cancer: the potential of circulating miRNAs and exosomes. *Translational Research*, *205*, 77-91.

[117]. Sharma, S., Zuñiga, F., Rice, G. E., Perrin, L. C., Hooper, J. D., & Salomon, C. (2017). Tumor-derived exosomes in ovarian cancer–liquid biopsies for early detection and real-time monitoring of cancer progression. *Oncotarget*, *8*(61), 104687.

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[118]. Shender, V. O., Pavlyukov, M. S., Ziganshin, R. H., Arapidi, G. P., Kovalchuk, S. I., Anikanov, N. A., ... & Govorun, V. M. (2014). Proteome–metabolome profiling of ovarian cancer ascites reveals novel components involved in intercellular communication. *Molecular & Cellular Proteomics*, *13*(12), 3558-3571.

[119]. Ding, P., Xu, Y., Li, L., Lv, X., Li, L., Chen, J., ... & Hu, W. (2022). Intracellular complement C5a/C5aR1 stabilizes β-catenin to promote colorectal tumorigenesis. *Cell reports*, *39*(9).

[120]. Zhang, C., Cao, K., Yang, M., Wang, Y., He, M., Lu, J., ... & Liu, H. (2023). C5aR1 blockade reshapes immunosuppressive tumor microenvironment and synergizes with immune checkpoint blockade therapy in high-grade serous ovarian cancer. *Oncoimmunology*, *12*(1), 2261242.

[121]. Zhang, W., Ou, X., & Wu, X. (2019). Proteomics profiling of plasma exosomes in epithelial ovarian cancer: A potential role in the coagulation cascade, diagnosis and prognosis. *International journal of oncology*, *54*(5), 1719-1733.

[122]. Chen, Z., Liang, Q., Zeng, H., Zhao, Q., Guo, Z., Zhong, R., ... & Zhao, K. (2020). Exosomal CA125 as a promising biomarker for ovarian cancer diagnosis. *Journal of Cancer*, *11*(21), 6445.

[123]. Zhao, Z., Yang, Y., Zeng, Y., & He, M. (2016). A microfluidic ExoSearch chip for multiplexed exosome detection towards blood-based ovarian cancer diagnosis. *Lab on a Chip*, *16*(3), 489-496.

[124]. Shi, H., Liu, L., Deng, X., Xing, X., Zhang, Y., Djouda Rebecca, Y., & Han, L. (2024). Exosomal biomarkers in the differential diagnosis of ovarian tumors: the emerging roles of CA125, HE4, and C5a. *Journal of Ovarian Research*, *17*(1), 4.

[125]. Baghban, N., Ullah, M., & Nabipour, I. (2023). The current trend of exosome in epithelial ovarian cancer studies: A bibliometric review. *Frontiers in Pharmacology*, *14*, 1082066.

[126]. Gentry-Maharaj, A., Blyuss, O., Ryan, A., Burnell, M., Karpinskyj, C., Gunu, R., ... & Menon, U. (2020). Multi-marker longitudinal algorithms incorporating HE4 and CA125 in ovarian cancer screening of postmenopausal women. *Cancers*, *12*(7), 1931.

[127]. Bareke, H., & Akbuga, J. (2018). Complement system's role in cancer and its therapeutic potential in ovarian cancer. *Scandinavian Journal of Immunology*, *88*(1), e12672.

[128]. Suri, A., Perumal, V., Ammalli, P., Suryan, V., & Bansal, S. K. (2021). Diagnostic measures comparison for ovarian malignancy risk in Epithelial ovarian cancer patients: a meta-analysis. *Scientific reports*, *11*(1), 17308.

[129]. Moore, R. G., Miller, M. C., Disilvestro, P., Landrum, L. M., Gajewski, W., Ball, J. J., & Skates, S. J. (2011). Evaluation of the diagnostic accuracy of the risk of ovarian malignancy algorithm in women with a pelvic mass. *Obstetrics & Gynecology*, *118*(2 Part 1), 280-288.

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