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REVIEW

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Developments in ovarian cancer markers and algorithms

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Abstract

Ovarian carcinoma contributes significantly to cancer-associated mortality in women, highlighting the urgent need for effective early detection strategies. Despite CA-125 (Cancer antigen 125) being widely used, it lacks reliable biomarkers for early diagnosis, requiring the exploration of alternative biomarkers such as miRNA, lncRNA and DNA methylation. As well, algorithms such as ROMA (Risk of Ovarian Malignancy Algorithm), RMI (Risk of Malignancy Index) and OVA1 (Ovarian Cancer Risk Assessment Algorithm 1) aim to enhance early detection accuracy. With an emphasis on epigenetic changes, this review synthesizes recent advances in molecular biomarkers and algorithms for early ovarian cancer diagnosis, providing insights into improving detection accuracy and managing disease.

Keywords

Molecular markers; Cancer antigen 125; Human epididymis protein 4; RMI; ROMA; Ovarian cancer

1. Introduction

Ovarian cancer is one of the most aggressive and lethal gynecological malignancies, ranking fifth in cancer-related mortality among women [1]. Although treatment modalities have advanced over the past few decades, survival rates have been limited [2]. Due to insidious symptoms and an absence of practical diagnostic tools, early ovarian cancer is often misdiagnosed and poorly treated. A five-year survival rate of less than 30% is common for patients with advanced ovarian cancer despite aggressive treatment [3].

The critical need for effective early detection biomarkers in ovarian carcinoma is underscored by their potential to significantly improve prognosis with early detection correlating with five-year survival rates ranging from 70% to 90% [3]. Moreover, early intervention not only improves survival rates while preserving fertility and enhancing quality of life for patients [4]. The gold standard of diagnosis remains histopathological analysis; however, its invasiveness poses certain limitations, particularly in early detection scenarios where symptoms are absent. Therefore, biomarkers play an essential role in facilitating early ovarian carcinoma diagnosis.

In evaluating the clinical utility of biomarkers for ovarian cancer diagnosis or screening, specificity and sensitivity are paramount. High specificity prevents false positives, while high sensitivity prevents delayed diagnosis and adverse outcomes associated with delayed diagnosis [5]. To accurately detect ovarian cancer, screening tests must be highly specific to meet epidemiological standards, further emphasizing the need for robust biomarkers.

2. Traditional biomarkers for ovarian cancer detection

2.1 Limitations of CA-125 in ovarian cancer screening

In 1981, Bast and colleagues reported the use of CA-125 protein in epithelial ovarian cancer (EOC) screening. However, CA-125 has recently come under increased scrutiny as a screening tool. Factors such as inflammation, menstrual cycle, pregnancy and liver function can impact CA-125 levels, leading to decreased specificity and increased false positives [6]. CA-125's 0.74 sensitivity and 0.83 specificity in diagnosing ovarian carcinoma were revealed by Zhen *et al*. [7], underlining its inadequacy as a single diagnostic marker. In addition, CA-125 only identifies around half of the early cases [8], highlighting its limitations in early detection. Therefore, ovarian cancer early indicators need to be more accurate.

2.2 HE4

Ovarian cancers, especially serous and endometrioid tumors, exhibit elevated *WFDC2* (*Whey Acidic Protein Four-Disulfide Core Domain 2*)-encoded protein HE4 (Human Epididymis Protein 4) expression [9]. According to a meta-analysis, HE4 has 84.1% specificity and 79.4% sensitivity for ovarian carcinoma [10]. Compared to CA-125, HE4 offers higher specificity but lower sensitivity [11]. Notably, HE4 exhibits superior sensitivity (92.61%) than CA-125 (63.41%) in detecting early-stage ovarian cancer [12]. Furthermore, HE4 can be used to distinguish epithelial ovarian cancer (EOC) from endometriosis [13], gastrointestinal-origin ovarian metastases

[14], as well as differentiating low-grade and high-grade serous ovarian cancer [15].

The utility of HE4 in distinguishing benign from malignant non-epithelial ovarian carcinomas appears limited [16]. Several factors, including age, smoking, kidney function, infection or inflammation, menopause, breast cancer, lung cancer and hormone levels, among others, affect HE4 levels [17, 18].

3. Potential biomarkers for ovarian cancer detection

3.1 Non-coding RNAs

Approximately 98% of the human genome comprises non-coding RNA (ncRNA), categorized into housekeeping ncRNAs and regulatory ncRNAs, including short-chain ncRNA and long non-coding RNA (lncRNA) based on length. Short-chain ncRNA, including microRNA (miRNA) and small interfering RNA (siRNA), is composed of less than 200 nucleotides, while lncRNA usually exceeds 200 nucleotides.

3.1.1 MicroRNAs (miRNA)

MiRNAs are short RNA molecules with an average length of 22 nucleotides. Interacting with the 3′untranslated regions of target mRNAs, they control target gene activity [19]. Since miRNAs are detectable, stable, and tumor-specific, circulating miRNAs have emerged as promising, non-invasive and highly sensitive diagnostic indicator. Based on a meta-analysis, circulating miRNAs are useful for diagnosing ovarian cancer, with a sensitivity and specificity of 0.78 [20].

As potential diagnostic markers for ovarian cancer, the MIR200 family of miR-200a, miR-200b, miR-200c, miR-429 and miR-141 has been extensively studied [21, 22]. Among these, miR-200c and miR-141 have a high diagnostic efficacy in early-stage ovarian cancer [21, 23].

Further, the let-7 miRNA family shows promise in diagnosing ovarian cancer [24, 25]. There is a diagnostic value of 82.0 for Let-7f in early ovarian cancer and an 87.9 for advanced ovarian cancer. When combined with microRNA-34a and miR-31, the overall diagnostic efficacy in early and late serum samples was 96.9 and 95.5, respectively, showing its effectiveness in diagnosing ovarian cancer [24].

In ovarian cancer, miR-21 and miR-125b have been investigated for their diagnostic potential [26, 27]. Ovarian carcinoma patients have elevated serum expression of miR-21, which correlates with the histological subtype of EOC and the FIGO (International Federation of Gynecology and Obstetrics) stage but has lower diagnostic significance than CA-125 [26, 28]. Similarly, elevated serum level of miR-125b is strongly associated with FIGO staging and lymph node metastasis in EOC patients [29].

Moreover, combining miRNAs with other biomarkers or utilizing specific miRNA models has shown promising results in improving diagnostic accuracy. Among the models developed by Lei Li and colleagues in 2023, the sEVmiR-EOC model uses miRNA in small extracellular vesicles derived from serum. This model is capable of distinguishing between benign and malignant ovarian tumors and outperforms CA-125 in separating people with benign illnesses from those with early-stage EOC [30]. In 2021, Raju Kandimalla *et al*. [31] proposed a logistic regression model named OCaMIR (Ovarian Cancer MicroRNA-based Integrated Risk Model), which can distinguish between cancer patients and healthy individuals in a prospective cohort with 0.92 AUC, 82% sensitivity and 86% specificity. Compared to the commonly used CA-125 marker, the OCaMIR model demonstrated higher diagnostic efficacy and accuracy.

3.1.2 LncRNAs

Ovarian cancer may be detected by a wide range of lncRNAs. For example, *LEMD1-AS1* (*LEMD1 antisense RNA 1*), *RBAT1* (*retinoblastoma associated transcript-1*), *LINC01554* (*Long Intergenic Non-Protein Coding RNA 01554*) and *ROR* (*regulator of reprogramming*) demonstrate diagnostic value in distinguishing ovarian cancer from normal tissues [32–35]. Notably, *lncRNA RP5-837J1.2* exhibits extremely high diagnostic efficacy in ovarian cancer diagnosis, with a 0.996 AUC (Area Under The Curve), 97.30% sensitivity and 94.60% specificity [36].

3.1.3 Circular RNAs (circRNAs)

CircRNAs, a subclass of lengthy non-coding RNAs with closed-loop structures of hundreds to thousands of nucleotides, have shown increased stability and diagnostic potential in ovarian cancer [37]. Meta-analyses demonstrated the high accuracy and reliability of circRNA in ovarian cancer diagnosis [38]. Specific circRNAs, such as *hsa_circ_0003972*, *hsa_circ_0007288*, *CircRAB11FIP1*, *circN4BP2L2* and *CiRS-7*, show promise as diagnostic biomarkers, with diagnostic accuracy validated in various studies [39–42]. Additionally, circRNA contained in exosomes has emerged as a potential diagnostic tool for ovarian cancer, such as *circ-0001068*, *Foxo3* and *circATP2B4* [43–45].

3.2 DNA methylation

DNA methylation changes in promoter regions alter the activity of genes that suppress tumor growth at an early stage of tumorigenesis [46]. The presence of this alteration in circulating tumor DNA (ctDNA) can predict ovarian carcinoma diagnosis by up to a year, underlining DNA methylation's potential as an early detection method [47].

Advances in liquid biopsy have facilitated research into DNA methylation for early cancer detection. Specific gene methylation signatures, including *SOX1* (*SRY-box 1*), *PAX1* (*paired box gene 1*), *SFRP1* (*secreted frizzled receptor proteins 1*), *CDH13* (*Cadherin 13*), *HNF1B* (*Hepatocyte Nuclear Factor 1 Beta*), *PCDH17* (*Protocadherin 17*), *GATA4* (*GATA Binding Protein 4*), *HOXA9* (*homeobox A9*) and other panels of genes, effectively differentiate between ovarian cancer and benign tumors [48–50]. Based on methylation profiles, support vector machine classifiers have been developed to enhance diagnostic accuracy [51]. It has shown promising sensitivity and specificity in the context of cell-free DNA (cfDNA), particularly in diagnosing early-stage ovarian cancers [52, 53]. Combining DNA methylation analysis with other diagnostic methods, such as CA-125 testing, has shown improved sensitivity for detecting high-risk ovarian cancer

[47]. Overall, these findings suggest that DNA methylation patterns hold considerable promise as biomarkers for ovarian cancer early detection. Recent research has explored the integration of DNA methylation biomarkers into cervical scraping tests for ovarian carcinoma diagnosis [54, 55]. Notably, the combination of methylation in *AMPD3*, *NRN1* and *TBX15* genes showed promising sensitivity, specificity and diagnostic accuracy in cervical smear tests [55].

DNA methylation patterns can vary as ovarian cancer progresses, resulting in variations in cfDNA methylation biomarkers among patients at various disease stages. Consequently, it is critical to identify indicators directly from plasma samples of early-stage OC (ovarian cancer) patients to accurately detect the early stages of ovarian carcinoma, rather than a mix of indicators from different stages, which emphasizes the need to examine DMRs (differentially methylated regions) from a larger group of early-stage OC patient [56].

3.3 ctDNA

ctDNA is cancer cell-released cfDNA that harbors cancer-related genetic and epigenetic alterations, serving as a precise marker for cancer research and therapy. In contrast to protein biomarkers, ctDNA's half-life of less than two hours makes it a highly accurate measure of tumor burden [57]. Research has shown that ctDNA's diagnostic accuracy is promising, with 84% sensitivity, 91% specificity and 0.94 AUC in detecting ovarian cancer, outperforming other biomarkers like miRNA and lncRNA [20]. However, ctDNA detection in blood remains challenging due to its low concentration, particularly in early-stage tumors [58]. Despite this challenge, advancements in digital PCR (Polymerase Chain Reaction) and targeted error sequences (TEC-Seq) have improved ctDNA detection rates in cancer patients, providing the potential for cancer detection and monitoring [59, 60].

3.4 Tumor-educated platelets (TEP)

Platelets, beyond their role in blood clotting, play a crucial role in cancer genesis and progression, including facilitating tumor growth, immune evasion and metastasis [61]. Tumor-educated platelets (TEP) are platelets that have undergone physical (such as size and quantity) and compositional (such as RNA and protein) modifications as a result of direct or indirect interactions with tumor cells [62], making them potential candidates for liquid biopsy.

3.4.1 Proteins in platelets

In 2018, Lomnytska *et al*. [63] demonstrated that platelet proteins can distinguish between benign adnexal lesions and ovarian cancer. They successfully predicted early-stage ovarian cancer cases using platelet protein expression profiles.

3.4.2 RNA in platelets

Platelets' RNA profiles differ between cancer patients and healthy individuals, suggesting their potential as ovarian cancer markers [64]. TEPs contain seven mRNAs related to various cellular activities, suggesting their utility in cancer detection [65]. The study by Gao *et al*. [66] in 2022 employed 102 platelet RNAs to develop a tumor-educated platelet-derived gene panel for ovarian cancer (TEPOC) classifier. It demonstrated promising diagnostic capabilities across a wide range of ovarian cancer subtypes and ethnic backgrounds, showing that it could be a robust diagnostic tool for early-stage, borderline and non-epithelial cancers [66].

3.5 Autoantibody

Tumor-associated antigens (TAA) can trigger an autoimmune reaction in cancer patients, resulting in unique autoantibody production. As early cancer biomarkers, these autoantibodies hold promise due to their detectability, presence in blood, high levels and long-term nature [67].

Human malignancies often feature genetic alterations in the *TP53* (*Tumor Protein 53*) gene, which codes for the p53 tumor suppression protein. *TP53* mutations are nearly universal in high-grade serous ovarian carcinoma (HGSOC) [68], with a significant percentage (41.7%) of patients developing p53-opposing antibodies [69]. High-throughput immunoassay based on xMAP (Multi-Analyte Profiling) beads significantly improved detection rates of *TP53* autoantibodies over CA-125 and risk value of ovarian cancer algorithm (ROCA) [70]. Combining p53 autoantibody with a variety of autoantibodies has a greater potential for improving ovarian cancer early detection accuracy. A panel of 11 autoantibodies shows promising specificity in distinguishing HGSOC patients from healthy individuals [71]. Even in CA-125-negative ovarian cancer patients, optimized combinations of autoantibodies are relatively sensitive, specific and accurate [72].

There are also other types of autoantibodies being investigated. Anti-PDLIM1 (PDZ and LIM Domain Protein 1 Antibody) autoantibody responses were positively correlated with high PDLIM1 expression in ovarian cancer tissues, suggesting PDLIM1 autoantibodies may serve as a supplementary indicator to CA-125. When combined with CA-125, the AUC increased to 0.846, with a 79.2% OC detection rate [73]. Pilyugin M.and colleagues evaluated the autoantibody reactivity to 20 BARD1 (BRCA1-associated RING domain protein 1) epitopes in serum samples from 480 OC patients and healthy controls, establishing a logistic regression model with 19 peptides. This model's ROC area under the curve (AUC) reached 0.921, with the combined CA-125 model's AUC at 0.979, achieving 0.9 sensitivity and 0.98 specificity of 0.98 [74]. Autoantibodies against LRDD (Leucine-Rich Repeats and Death Domain-containing Protein) and FOXA1 (Forkhead-box A1) in OC patients are also higher than in healthy individuals. The combined diagnostic sensitivity of anti-LRDD and anti-FOXA1 autoantibodies for OC was 58.1%, with 87.5% specificity and 72.8% accuracy.Combining this combination with CA-125 for testing OC patients increased the positive detection rate from 62.4% to 87.1% [75]. Additionally, a model constructed with CCL18 (C-C Motif Chemokine Ligand 18) and CXCL1 (C-X-C Motif Chemokine Ligand 1) antigens and C1D (C1D Nuclear Receptor Corepressor), FXR1 (Fragile X Mental Retardation Syndrome-Related Protein 1), ZNF573 (Zinc Finger Protein 573) and TM4SF1 (Transmembrane 4 L Six Family Member 1) IgG (Immunoglobulin G) autoantibodies was able to diagnose OC with an AUC of 0.958 [76].

3.6 Potential protein biomarkers

3.6.1 Osteopontin (OPN)

Recent studies have highlighted the significance of OPN as a potential biomarker, particularly in ovarian carcinoma. The presence of elevated levels of OPN in the blood of individuals with ovarian tumors has sparked interest in its diagnostic potential [77]. Compared to established biomarkers like CA-125 or HE4, OPN shows superior accuracy, especially in distinguishing early ovarian carcinoma from benign ovarian tumors [78]. PN's sensitivity and specificity in ovarian carcinoma were demonstrated by Lan *et al*. [79] at 0.766 and 0.897, respectively. Moreover, when combined with CA-125, OPN's sensitivity and specificity were further improved [79]. Interestingly, all ovarian carcinomas without CA-125 expression showed OPN expression, suggesting that it complements CA-125 and improves diagnostic sensitivity [80].

3.6.2 Other proteins also demonstrate potential diagnostic value

Thymidine kinase 1 (TK1) combined with HE4 and CA-125 forms the Ovarian Malignancy Risk Index (ROMI), which is superior in diagnosis to ROMA [81]. Tissue Factor Pathway Inhibitor 2 (TFPI2), as another potential biomarker, is comparable to ROMA in differentiating benign from malignant ovarian tumors [82]. Based on logistic regression models, CA-125, HE4, OPN, leptin and prolactin showed a promising diagnostic efficacy with an AUC of 0.96 in predicting ovarian malignancies [83].

4. Current multivariate index determinations for ovarian cancer

4.1 Risk of ovarian malignancy algorithm (ROMA)

Moore introduced the ROMA in 2009 to assess ovarian cancer risk based on menopausal status and HE4 and CA-125 levels. Patients are classified into low-risk and high-risk categories based on the predictive index (PI) computed from these variables. ROMA has demonstrated strong sensitivity (0.83), specificity (0.85) and AUC (0.90) when predicting EOC in meta-analyses [84]. Notably, ROMA exhibits superior diagnostic accuracy in postmenopausal ovarian cancer than premenopausal cases [85]. Furthermore, it is superior to CA-125 and HE4 in separating benign tumors from early-stage ovarian cancer [86]. ROMA demonstrates a positive predictive value (PPV) of 81.3% and a specificity of 85.0% for predicting peritoneal dissemination among premenopausal women. Further, ROMA exhibits a 93% detection rate for identifying micro-peritoneal dissemination with diameters less than 2 cm, outperforming CT scans [87]. ROMA demonstrates high diagnostic accuracy in distinguishing between endometriosis and ovarian cancer, with 90.91% sensitivity, 83.78% specificity and 85.42% accuracy, respectively [88].

Numerous studies have assessed ROMA's diagnostic value compared with other predictive models. ROMA is comparable to CPH-I (Copenhagen Psychosocial Questionnaire-Intermediate) [89]. Comparatively to OVA1, ROMA shows similar high sensitivity and negative predictive values, but with higher specificity. Consequently, ROMA as a follow-up strategy for high-risk patients identified by OVA1 yields a PPV of 69% [90].

There are also limitations to ROMA, despite its strengths. Following a transvaginal ultrasound examination with the ROMA score will not improve diagnostic accuracy and may even decrease test performance [91]. It was found that serum T3 levels and glomerular filtration rate (eGFR) may be factors that contribute to ROMA's false positive results [92]. In combination with lactate dehydrogenase (LD) markers, ROMA's predictive performance does not improve significantly, indicating ROMA alone is not more effective [93].

4.2 Risk of malignancy index (RMI)

RMI was first introduced by Jacobs *et al*. [94] to assess the likelihood of ovarian malignancy based on three factors: menopausal stage, CA-125 concentrations and ultrasound features. A preliminary model demonstrated 85.4% sensitivity and 96.9% specificity [94]. By adjusting the scoring or threshold, the RMI model has been refined over time, resulting in a variety of diagnostic efficiency options. RMI4 is superior in accuracy to RMI1-3 [95], but RMI2 may have the highest diagnostic efficiency overall [96].

In comparison with CA-125 alone, RMI demonstrated greater specificity (81% *vs.* 68%) in excluding benign ovarian lesions, albeit with slightly lower sensitivity [97]. For premenopausal women, RMI-I showed improved specificity than ROMA (89% *vs.* 78%) and similar sensitivity (73% *vs.* 80%) [98]. Among postmenopausal women, ROMA had comparable specificity to RMI but higher sensitivity [99, 100].

Integration of RMI with other biomarkers can improve its diagnostic accuracy. For instance, using different RMI thresholds ($\leq$200 and $>$200) in combination with various CA-125 levels can improve diagnostic accuracy for ovarian tumors [101]. Incorporating HE4 into the RMI framework could reduce unnecessary referrals by 32% while maintaining correct referrals [102]. Adjusting CA-125 threshold in RMI model based on menopausal status ($>$67 U/mL for premenopausal, $>$23 U/mL for postmenopausal) and conducting immediate cross-sectional imaging and multidisciplinary team (MDT) evaluations upon detecting abnormalities resulted in 90% accuracy in cancer detection and ensured prompt specialist evaluation for fewer than 20% of noncancerous cases [103].

Nevertheless, RMI often increases in noncancerous gynecological conditions, particularly endometriosis and pelvic inflammation [104].

4.3 OVA1

OVA1 is a multivariate index assay to assess the malignancy of pelvic masses by analyzing five biomarkers: ApoA-1, β2-microglobulin, CA-125, albumin and transferrin. Using these biomarkers, OVA1 categorizes individuals into low, medium and high-risk categories [105]. Low-risk patients can be treated with minimally invasive surgery and local treatment in a non-specialist medical setting, while high-risk patients need specialized surgery [106, 107]. It fully considers

a patient's medical needs, costs and satisfaction [105].

Premenopausal women and individuals with early-stage cancer are more sensitive to OVA1 than CA-125. For premenopausal women with normal CA-125 levels, it correctly diagnoses 63% of early-stage carcinomas and over 50% of ovarian malignancies. In similar conditions, OVA1 detects 83% of serous cancers, 58% of mucinous cancers and 50% of clear-cell ovarian cancers [108]. OVA1, however, has a high false-positive rate [109].

4.4 OVERA

Combining CA-125, transferrin, ApoA-1, follicle-stimulating hormone (FSH) and human epididymis protein 4 (HE4), Overa improves OVA1 specificity. Based on a support vector machine algorithm, Overa calculates a risk score ranging from 1.0 to 10.0 [109]. With FSH included, a single threshold can be used to distinguish between high and low cancer risks, irrespective of menopausal status. It possesses 91.7% sensitivity for early-stage ovarian cancer detection, which may be improved to 93.5% with combined ultrasound examinations [110]. In detecting specificity and PPV (Positive predictive value), Overa surpasses OVA1 while maintaining comparable sensitivity and NPV (Negative predictive value) [111]. Pairing Overa with IOTA-LR2 (International Ovarian Tumor Analysis Logistic Regression Model 2) can further reduce false positives and increase specificity to 85% [112].

4.5 CPH-I

CPH-I is another assessment that includes the patient's age, HE4 and CA-125. distinguishes benign ovarian tumors from ovarian cancer as effectively as ROMA and RMI [113, 114]. Women suspected of having ovarian cancer can use CPH-I more easily than RMI or ROMA, since it does not rely on ultrasound results or menopausal status. A comprehensive study combining multiple data sources revealed that CPH-I effectively detected malignant adnexal masses with a sensitivity of 0.81, specificity of 0.88 and an AUC of 0.91 [84]. CPH-I also outperformed CA-125 in distinguishing BOT (Borderline Ovarian Tumor) I + II and early EOC I + II [115].

4.6 The international ovarian tumor analysis (IOTA)

4.6.1 Simple rules

IOTA developed the "Simple Rules" for applying ultrasonography criteria to ovarian cancer detection. These rules consist of five features indicating benignity and five suggesting malignancy. With 90% specificity and 93% sensitivity, they aim to provide accurate diagnosis and treatment options for a significant portion of tumor patients [116]. When the rules do not apply, a two-step strategy supplemented by subjective ultrasound assessment can achieve similar diagnostic performance with 90% sensitivity and 93% specificity [117, 118]. In both pre-menopausal and postmenopausal women, the rules show good operability and consistency, irrespective of their experience level [118, 119].

4.6.2 ADNEX

IOTA developed the ADNEX model to evaluate different types of adnexal cancer. Three clinical factors (patient age, serum CA-125 levels, and type of medical center (oncology centers or other hospitals)) and six ultrasound factors. The model effectively differentiates between benign, borderline, stage I and stages II-IV ovarian tumors, with AUC values of 0.93, 0.73, 0.27 and 0.92, respectively [120]. However, it performs moderately in distinguishing between BOT, stage I OC and BOT *vs.* metastatic ovarian cancer, with AUC scores of 0.54 and 0.66, respectively [121].

ADNEX is available in two versions, with or without CA-125 values. The inclusion of CA-125 does not significantly improve the ability to distinguish benign from malignant tumors. However, stage II to IV ovarian cancer is significantly more differentiated by CA-125 than stage I ovarian cancer [121–123]. ADNEX is as reliable and effective as subjective assessment and outperforms RMI [118].

5. Conclusions

Ovarian cancer is a highly lethal disease with high recurrence and mortality rates. The primary treatments for ovarian cancer are surgery and platinum-based chemotherapy. A lack of noticeable symptoms causes late diagnosis, complicating treatment and increasing recurrence risks. The development of accurate and reliable diagnostic methods is therefore crucial to improving ovarian cancer survival rates.

A variety of potential biomarkers have been identified for early diagnosis and detection of ovarian carcinoma, including miRNA, lncRNA, DNA methylation, ctDNA, tumor-educated platelets, osteopontin and transthyretin (Table 1, Ref. [7, 10, 20, 36, 38, 55, 79, 84, 116]). However, these studies are in the early stages and need to be validated through a larger study.

AVAILABILITY OF DATA AND MATERIALS

This review is based on previously published literature, which is available through PubMed. No new data were generated or analyzed during this study.

AUTHOR CONTRIBUTIONS

MTX—wrote and edited the manuscript. RL—translated it into English. LLZ and ZZW—supervised it. AQZ—edited it. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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TABLE 1. Diagnostic performance of clinically used molecular biomarkers in the subset of studies cited in this article.

Molecular biomarkers	Se	Sp	AUC	Systematic Review or Meta-Analysis	Ref.
CA-125	74.0%	83.0%	0.85	Yes	[7]
HE4	79.4%	84.1%		Yes	[10]
MicroRNAs	78.0%	78.0%		Yes	[20]
lncRNA RP5-837J1.2	97.3%	94.6%	0.99	No	[36]
circRNA	85.0%	84.0%	0.89	Yes	[38]
a combination of gene methylation	81.0%	84.0%	0.91	No	[55]
ctDNA	84.0%	91.0%	0.94	Yes	[20]
OPN combined with CA-125	87.1%	88.1%		No	[79]
ROMA	83.0%	85.0%	0.90	Yes	[84]
CPH-I	81.0%	88.0%	0.91	Yes	[84]
Simple Rules	93.0%	90.0%		Yes	[116]

CA: Cancer antigen; HE4: Human epididymis protein 4; OPN: Osteopontin; ROMA: Risk of ovarian malignancy algorithm; AUC: area under the curve; Ref.: References; Se: Sensitivity; Sp: Specificity; CPH-I: Copenhagen Psychosocial Questionnaire-Intermediate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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