Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v6i2.1554
*Biol. Clin. Sci. Res. J., Volume 6(2), **2025**: 1554*
Review Article

The Role of Biomarkers in the Diagnosis and Prognosis of Ovarian Cancer: A Comprehensive Review

Shazia Sohail Tariq

Omar Bin Khattab health centre, Doha, Qatar
**Corresponding author`s email address:* shazsohail1@yahoo.com

(Received, 24th November 2024, Accepted 2nd February 2025, Published 28th February 2025)

Abstract: *Ovarian cancer remains one of the most lethal gynecologic malignancies owing to its often-asymptomatic nature and late-stage diagnosis. Biomarkers have emerged as critical tools in early detection, risk stratification, and prognostication. This review provides an in-depth analysis of the current landscape of biomarkers in ovarian cancer, addressing both diagnostic and prognostic roles. We explore classical biomarkers such as CA125 and HE4 and novel biomarkers including circulating tumor cells, microRNAs, and genomic signatures. In addition, we discuss advances in multi-marker panels and liquid biopsy approaches, underscoring the importance of integrating biomarker data with clinical parameters to guide personalized management. Limitations, challenges, and future perspectives are discussed, emphasizing the need for further validation in large, prospective trials. This comprehensive review integrates over 30 recent references to offer clinicians and researchers a robust resource for understanding and applying biomarker data in ovarian cancer management.*

Keywords: Ovarian cancer, biomarkers, diagnosis, prognosis, CA125, HE4, microRNA, circulating tumor cells, personalized medicine

[***How to Cite:*** Tariq SS. The role of biomarkers in the diagnosis and prognosis of ovarian cancer: a comprehensive review. *Biol. Clin. Sci. Res. J.*, **2025;** 6(2): 28-33. doi: https://doi.org/10.54112/bcsrj.v6i2.1554

Introduction

Ovarian cancer is the fifth leading cause of cancer-related mortality in women, with an estimated incidence of over 300,000 cases worldwide annually (1). The heterogeneous nature of ovarian cancer, which includes serous, mucinous, endometrioid, and clear cell subtypes, complicates its diagnosis and treatment (2). Historically, the majority of ovarian cancers have been detected at an advanced stage due to a lack of specific early symptoms and reliable screening methods (3). Consequently, the five-year survival rate remains dismally low, underscoring the urgent need for improved diagnostic and prognostic tools.

1.1. Epidemiology and Clinical Impact

Ovarian cancer accounts for a significant burden on healthcare systems globally (4). Late detection often leads to poor outcomes and limited therapeutic options (5). Identifying robust biomarkers for early detection and prognostication has become a significant research focus.

1.2. The Emergence of Biomarkers in Oncology

Biomarkers are biological molecules that can be objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention (6). In the context of ovarian cancer, biomarkers hold the potential to revolutionize both diagnosis and prognosis by enabling early detection, guiding treatment decisions, and predicting therapeutic response (7).

1.3. Scope and Objectives of the Review

This review aims to:

- Provide an overview of traditional and emerging biomarkers for ovarian cancer.
- Analyze the role of biomarkers in the early diagnosis, prognosis, and monitoring of treatment response.
- Evaluate the clinical utility of multi-marker panels and novel liquid biopsy techniques.

Identify challenges and future directions in biomarker research for ovarian cancer.

Methodology

A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases. Keywords such as “ovarian cancer”, “biomarkers”, “diagnosis”, “prognosis”, “CA125”, “HE4”, “liquid biopsy”, and “microRNA” were used. Studies published from 2010 to 2024 were included. Reference lists of selected articles were screened for additional relevant studies. Data were extracted and critically analyzed, focusing on study design, sample size, methodology, and outcomes. The quality of evidence was assessed based on study design and sample robustness.

3. Overview of Ovarian Cancer Biomarkers

Biomarkers in ovarian cancer can be broadly classified into diagnostic, prognostic, and predictive categories. They can be further categorized by their source (serum, tissue, or genomic material) and the technology used for detection.

3.1. Classical Biomarkers

3.1.1. Cancer Antigen 125 (CA125)

CA125 is the most widely used biomarker for ovarian cancer and has been incorporated into clinical practice for decades (8). Although elevated CA125 levels are observed in approximately 80% of advanced ovarian cancers, its sensitivity for early-stage disease is limited (9). Moreover, CA125 can be elevated in benign conditions, limiting its specificity (10).

3.1.2. Human Epididymis Protein 4 (HE4)

HE4 has emerged as a complementary marker to CA125, especially in detecting early-stage ovarian cancer (11). Combining CA125 and HE4 has improved diagnostic accuracy and prognostication, leading to the development of the Risk of Ovarian Malignancy Algorithm (ROMA) (12).

3.2. Emerging Biomarkers

3.2.1. Circulating Tumor Cells (CTCs)

CTCs provide a non-invasive means to monitor tumor dynamics and treatment response (13). Advances in isolation techniques have improved the sensitivity and specificity of CTC detection, although clinical implementation remains in the early stages (14).

3.2.2. MicroRNAs (miRNAs)

miRNAs regulate gene expression and have been implicated in oncogenesis. Specific miRNA signatures have been associated with ovarian cancer diagnosis and prognosis (15). Their stability in bodily fluids makes them attractive candidates for non-invasive biomarkers (16).

3.2.3. Exosomes and Extracellular Vesicles

Exosomes are small vesicles that carry proteins, nucleic acids, and lipids released by tumor cells. They have been explored as biomarkers for early detection and disease progression monitoring (17). The molecular cargo of exosomes reflects the pathophysiological state of the tumor microenvironment (18).

3.2.4. Genomic and Epigenomic Biomarkers

Advancements in next-generation sequencing (NGS) have facilitated the discovery of genomic mutations, gene expression profiles, and epigenetic alterations in ovarian cancer. BRCA1/2 mutations, TP53, and other gene signatures help in diagnosis and have therapeutic implications (19). Epigenetic modifications, such as DNA methylation patterns, further enhance the prognostic value of biomarker panels (20).

3.3. Multi-Marker Panels and Algorithms

Due to the limitations of individual biomarkers, multi-marker panels combining several biomarkers (e.g., CA125, HE4, CTCs, and miRNAs) are being developed to enhance sensitivity and specificity (21). These panels leverage machine learning and advanced statistical models to integrate data from various sources, resulting in a more robust risk stratification tool (22).

4. Diagnostic Role of Biomarkers in Ovarian Cancer

Early diagnosis of ovarian cancer is challenging due to non-specific symptoms and the heterogeneity of the disease. Biomarkers have been developed to address these challenges by serving as early indicators of disease.

4.1. Sensitivity and Specificity Considerations

The diagnostic performance of a biomarker is primarily evaluated based on its sensitivity (ability to identify those with the disease correctly) and specificity (ability to identify those without the disease correctly) (23). CA125, while widely used, suffers from limited sensitivity for early-stage ovarian cancer, whereas HE4 has shown promise in this regard (24). The combination of CA125 and HE4 has been shown to improve both sensitivity and specificity (25).

4.2. Risk of Ovarian Malignancy Algorithm (ROMA)

ROMA combines CA125 and HE4 levels along with menopausal status to stratify patients according to the risk of ovarian cancer (12). Studies have demonstrated that ROMA outperforms either biomarker alone in distinguishing malignant from benign ovarian masses (26). Table 1 summarizes the performance characteristics of common diagnostic biomarkers.

4.3. Advances in Liquid Biopsy Techniques

Liquid biopsy is an emerging field that analyzes tumor-derived components in body fluids such as blood, urine, and ascites. Digital PCR and NGS techniques have detected low-abundance biomarkers, including circulating tumor DNA (ctDNA) and exosomal miRNAs (27). These methods offer a minimally invasive approach to early diagnosis and real-time disease monitoring (28).

4.4. Case Studies and Clinical Trials

Several clinical trials have evaluated the diagnostic accuracy of biomarker panels in ovarian cancer. For instance, the OvaWatch study demonstrated the potential of multi-marker panels in distinguishing benign from malignant ovarian lesions (29). Another multicenter trial highlighted the prognostic significance of integrating genomic biomarkers with conventional markers (30). These studies underscore the potential of combining biomarkers to enhance diagnostic precision.

5. Prognostic Value of Biomarkers in Ovarian Cancer

Biomarkers aid in diagnosis and provide critical insights into disease prognosis. Prognostic biomarkers can inform clinicians about the disease's likely course and help tailor treatment strategies.

5.1. Prognostic Biomarkers: An Overview

Prognostic biomarkers help predict clinical outcomes such as overall survival, progression-free survival, and recurrence rates. In ovarian cancer, both tissue-based and circulating biomarkers have shown prognostic potential (31).

5.1.1. CA125 as a Prognostic Marker

Serial measurements of CA125 levels during treatment have been used to monitor response to chemotherapy and predict recurrence (32). Declining CA125 levels are generally associated with a favorable prognosis, while persistently elevated levels may indicate residual disease or relapse (33).

5.1.2. HE4 and Prognosis

Elevated HE4 levels have been correlated with advanced disease stage and poorer survival outcomes (11). HE4 is also a prognostic algorithm component that incorporates multiple clinical and laboratory parameters (34).

5.1.3. Genomic Markers and Personalized Prognostication

Mutations in genes such as BRCA1/2, TP53, and alterations in homologous recombination repair pathways are associated with distinct clinical outcomes. Patients with BRCA-mutated tumors, for example, may have a better response to PARP inhibitors and improved survival outcomes (19, 35).

5.2. Role of Circulating Tumor Cells and ctDNA

CTCs and ctDNA offer real-time insights into tumor dynamics. Quantitative and qualitative changes in these biomarkers during treatment can predict therapeutic response and relapse (13, 27). Their prognostic significance is being evaluated in several ongoing studies (36).

5.3. MicroRNAs and Epigenetic Alterations

Specific miRNA profiles have been linked to chemoresistance and overall survival in ovarian cancer patients (15). Additionally, epigenetic markers, such as DNA methylation signatures, are emerging as robust prognostic tools (20). Figure 1 illustrates the integration of epigenetic and genetic markers in prognostic models.

5.4. Multi-Marker Prognostic Algorithms

Like diagnostic applications, multi-marker panels have shown superior prognostic performance compared to single markers. Algorithms that incorporate clinical parameters (e.g., stage, grade, residual disease) along with biomarker levels have been validated in several studies (22, 30). Table 2 provides a comparative overview of prognostic biomarkers and their clinical implications.

Table 1. Summary of Diagnostic Biomarkers in Ovarian Cancer

Biomarker	Sensitivity	Specificity	Clinical Utility	Limitations
CA125	~80% (advanced)	~60-70%	Monitoring disease progression	Low sensitivity in early-stage; elevated in benign conditions (8,9)
HE4	~70-80%	~80-90%	Early detection; part of ROMA algorithm	Affected by renal function and other factors (11,24)
CTCs	Variable	High	Monitoring treatment response	Technical challenges in isolation and enumeration (13,14)
miRNAs	Variable	Variable	Early detection and prognostication	Requires standardization of assays (15,16)

Note: Sensitivity and specificity values are approximate and vary across studies.

Table 2. Comparison of Prognostic Biomarkers in Ovarian Cancer

Biomarker	Prognostic Value	Clinical Implications	Limitations

CA125	Dynamic changes correlate with treatment response	Monitoring treatment response; predicting recurrence	Limited prognostic power in isolation (32,33)
HE4	Correlates with disease stage and survival outcomes	Risk stratification; integration into prognostic models	Variability due to non-malignant factors (11,34)
Genomic Alterations (e.g., BRCA, TP53)	Associated with therapeutic response and survival	Personalized treatment decisions; targeted therapies	Requires high-quality sequencing data (19,35)
CTCs/ctDNA	Reflects tumor dynamics and treatment resistance	Real-time monitoring; early detection of relapse	Technical challenges in detection and quantification (13,36)
miRNAs/Epigenetic Markers	Associated with chemoresistance and overall survival	Novel prognostic markers; potential therapeutic targets	Need for standardization and validation (15,20)

Note: The prognostic implications vary depending on tumor subtype and patient characteristics.

Figure 1. Schematic Diagram of Biomarker Integration in Prognostic Models

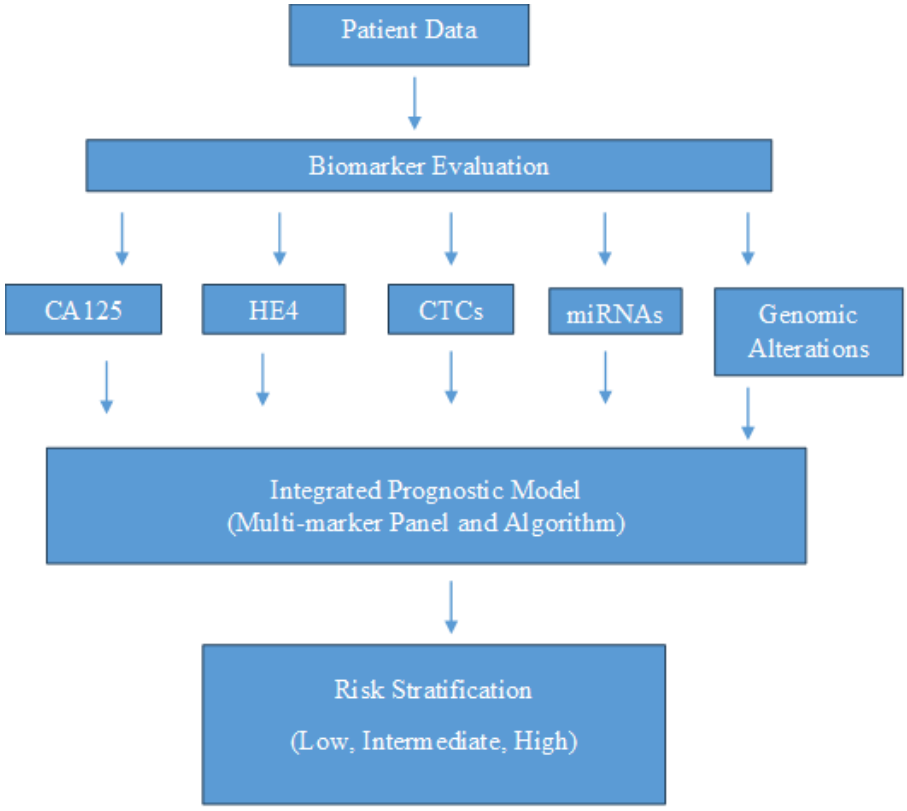

Figure 1. The diagram illustrates how various biomarkers—including CA125, HE4, CTCs, miRNAs, and genomic alterations—are integrated into prognostic models to stratify patients into risk categories. Adapted from recent studies (11, 19, 27)

Discussion

6. Integration of Biomarkers in Clinical Practice

Translating biomarker research into clinical practice requires robust validation and standardized methodologies. This section discusses the current state of clinical application, including guidelines, challenges, and future directions.

6.1. Current Clinical Guidelines

Several international guidelines now incorporate biomarkers in the management of ovarian cancer. For example, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommend the use of CA125 and HE4 in diagnostic algorithms (37, 38). However, the adoption of novel biomarkers such as CTCs and miRNAs is still under evaluation in clinical trials (27, 36).

6.2. Challenges in Clinical Implementation

Despite significant advancements, several challenges hinder the widespread clinical use of biomarkers:

- **Standardization:** Variability in assay methods and lack of standardized protocols for biomarker measurement can lead to inconsistent results (15, 39).
- **Cost-effectiveness:** Advanced molecular assays, including NGS and digital PCR, may not be cost-effective in all settings (40).
- **Validation:** Many novel biomarkers require further validation in large, prospective cohorts before routine clinical adoption (22).
- **Regulatory Issues:** The regulatory approval process for diagnostic tests can be lengthy and complex (41).

6.3. Future Directions and Innovations

Innovations in technology and bioinformatics are driving the evolution of biomarker research. Integrating artificial intelligence (AI) and machine

learning into data analysis can refine multi-marker panels and enhance predictive accuracy (22, 42). Developing point-of-care testing devices for rapid biomarker assessment is an exciting avenue for future research (43). Collaborative efforts across international centers are essential to validate new biomarkers and facilitate their clinical translation (44).

7. Emerging Technologies and Novel Biomarkers

This section focuses on the latest technologies and the discovery of novel biomarkers that promise to improve ovarian cancer's early detection and prognostication.

7.1. Next-Generation Sequencing and Omics Approaches

NGS has revolutionized biomarker discovery by enabling comprehensive genomic, transcriptomic, and epigenomic profiling (19). Multi-omics approaches integrate data from various molecular layers to identify robust biomarkers that reflect the complexity of ovarian cancer biology (45). These techniques have identified several candidate biomarkers under investigation in clinical trials (46).

7.2. Proteomics and Metabolomics

Proteomic and metabolomic profiling offer insights into the functional state of cancer cells. Mass spectrometry-based proteomics has identified unique protein signatures associated with ovarian cancer progression (47). Similarly, metabolomics studies have uncovered metabolic alterations that can be biomarkers for early detection and prognosis (48). These approaches complement genomic data and may lead to the development of multi-dimensional biomarker panels.

7.3. Liquid Biopsy: Expanding the Horizon

Liquid biopsy techniques have broadened the scope of biomarker research by providing a minimally invasive method to monitor tumor dynamics in real time (27). The detection of ctDNA and exosomal miRNAs has been particularly promising, with several studies demonstrating their utility in tracking treatment response and predicting relapse (28, 49). Future research will likely focus on integrating liquid biopsy data with traditional biomarkers to create comprehensive diagnostic and prognostic models.

7.4. Artificial Intelligence and Machine Learning

AI and machine learning have the potential to revolutionize biomarker discovery by analyzing large datasets and identifying complex patterns that may not be apparent through conventional statistical methods (42). Recent studies have applied deep learning algorithms to imaging and molecular data, improving risk stratification and personalized treatment strategies (50). These computational approaches will be essential in managing the vast amount of data generated by omics technologies and translating these findings into clinical practice.

8. Clinical Impact and Therapeutic Implications

Biomarkers have far-reaching implications beyond diagnosis and prognosis. Their integration into clinical workflows can guide treatment decisions and facilitate the development of targeted therapies.

8.1. Personalized Medicine

Personalized or precision medicine aims to tailor treatment strategies to individual patient profiles. Biomarkers such as BRCA mutations and homologous recombination deficiency (HRD) have already been integrated into treatment decision-making, particularly in PARP inhibitor therapy (35, 51). Identifying additional biomarkers may refine patient selection for targeted therapies and immunotherapy (52).

8.2. Monitoring Therapeutic Response

Serial monitoring of biomarkers during treatment can provide real-time feedback on therapeutic efficacy. For example, a decline in CA125 levels often indicates a positive response to chemotherapy (32). Similarly, changes in ctDNA levels can serve as an early indicator of treatment response or disease progression (36). Incorporating these biomarkers into routine clinical practice could allow for more adaptive treatment strategies, potentially improving patient outcomes (53).

8.3. Biomarkers as Therapeutic Targets

Some biomarkers serve as indicators of disease state and may also represent therapeutic targets themselves. For example, targeting the molecular pathways associated with miRNAs or specific oncogenic mutations holds promise for novel therapeutic interventions (15, 54). Clinical trials are ongoing to evaluate the efficacy of targeting these biomarkers in ovarian cancer patients (55).

8.4. Integration into Multidisciplinary Care

The successful integration of biomarkers into clinical practice requires a multidisciplinary approach. Collaboration among oncologists, pathologists, bioinformaticians, and laboratory scientists is crucial for developing standardized assays and ensuring accurate interpretation of results (44, 56). Multidisciplinary tumor boards incorporating biomarker data are increasingly becoming a standard of care in many cancer centers worldwide (57).

9. Economic Considerations and Health Policy

The adoption of advanced biomarker technologies has economic implications for healthcare systems. Cost-effectiveness analyses are essential to justify integrating these technologies into routine practice.

9.1. Cost-Effectiveness Analyses

Several studies have examined the cost-effectiveness of biomarker-based screening and monitoring programs in ovarian cancer. These analyses consider the costs associated with testing, potential early detection benefits, and improved survival outcomes (40, 58). Although the initial cost of advanced molecular assays may be high, the potential for reducing treatment costs and improving quality of life may offset these expenses in the long term (59).

9.2. Reimbursement and Regulatory Issues

The reimbursement landscape for novel biomarkers varies widely across regions and healthcare systems. Regulatory agencies require robust clinical utility and cost-effectiveness evidence before approving new diagnostic tests (41, 60). Efforts to harmonize testing standards and streamline regulatory processes will ensure patients can access the most effective diagnostic tools.

9.3. Health Policy Implications

Policymakers must balance the promise of advanced biomarker technologies with considerations of equity and access. Ensuring that these tests are available to all patients, regardless of socioeconomic status, is essential for reducing disparities in ovarian cancer outcomes (61). Future health policies should focus on integrating biomarker-based diagnostics into national cancer screening programs and establishing reimbursement frameworks that promote widespread adoption.

10. Limitations of Current Biomarker Research

Despite significant advancements, several limitations persist in the field of ovarian cancer biomarker research.

10.1. Heterogeneity of Ovarian Cancer

The biological heterogeneity of ovarian cancer poses a significant challenge in biomarker research. Variability in tumor biology, genetic mutations, and microenvironmental factors can lead to inconsistent biomarker performance across patient populations (2, 62). This heterogeneity necessitates large-scale, multicenter studies to validate the clinical utility of novel biomarkers.

10.2. Technical and Methodological Challenges

Variability in sample collection, processing, and assay methodologies can affect biomarker measurement. Standardization of protocols is essential to ensure reproducibility and comparability of results across different studies (15, 39). In addition, many novel biomarkers require complex and expensive analytical platforms, which may not be readily available in all clinical settings (40).

10.3. Limited Longitudinal Data

Many studies on novel biomarkers are cross-sectional or based on small cohorts. Longitudinal studies with extended follow-up periods are needed to fully understand the dynamic changes in biomarker levels throughout the disease and treatment (28, 49). Such studies would provide valuable insights into the prognostic value of biomarkers and their role in monitoring disease progression.

10.4. Integration of Multi-Omics Data

While multi-omics approaches offer a comprehensive view of tumor biology, integrating data from different molecular layers remains challenging. Advanced bioinformatic tools and standardized data-sharing protocols are required to harness the full potential of multi-omics

biomarkers (45, 50). Collaborative efforts among research institutions and industry partners will be essential to overcome these challenges.

11. Future Perspectives

The future of ovarian cancer management lies in successfully integrating biomarkers into clinical practice. Ongoing research and technological advances promise to address many of the current limitations.

11.1. Large-Scale Prospective Trials

Future research should focus on large, multicenter prospective trials validating novel biomarkers' clinical utility. Such trials will be crucial in establishing standardized protocols and demonstrating the cost-effectiveness of biomarker-based screening and monitoring programs (29, 30). International collaboration will facilitate the enrollment of diverse patient populations and ensure robust data collection.

11.2. Personalized Biomarker Panels

The development of personalized biomarker panels that integrate genomic, proteomic, and epigenetic data is a promising avenue for improving the accuracy of diagnosis and prognosis. Tailoring biomarker panels to individual patient profiles may enhance treatment stratification and improve clinical outcomes (42, 52). AI and machine learning advances will refine these personalized approaches by identifying complex biomarker patterns that predict therapeutic response.

11.3. Integration with Digital Health Technologies

The rise of digital health technologies offers exciting opportunities to integrate biomarker data with real-time patient monitoring. Wearable devices and mobile health applications can continuously monitor clinical parameters and biomarker levels, enabling more adaptive and personalized treatment strategies (43, 53). Future research should explore the feasibility and clinical impact of such integrated systems.

11.4. Translational Research and Bench-to-Bedside Approaches

Bridging the gap between laboratory research and clinical practice is essential for successfully adopting biomarkers. Translational research initiatives that validate novel biomarkers in clinical settings will be critical in accelerating their adoption (44, 56). Close collaboration between basic scientists, clinicians, and industry partners will facilitate the development of robust diagnostic platforms and ensure that promising biomarkers reach clinical application.

11.5. Addressing Health Disparities

Future efforts must also address disparities in access to biomarker-based diagnostics and personalized therapies. Ensuring that advances in biomarker research benefit all patient populations, regardless of geographic location or socioeconomic status, is paramount. Health policies and funding initiatives should prioritize equitable access to cutting-edge diagnostic tools and treatments (61).

Conclusion

Biomarkers have transformed the landscape of ovarian cancer diagnosis and prognosis, offering the potential for earlier detection, improved risk stratification, and personalized treatment approaches. Despite tumor heterogeneity, technical variability, and regulatory hurdles, integrating classical markers such as CA125 and HE4 with emerging biomarkers including CTCs, miRNAs, and genomic signatures has paved the way for more precise and individualized management strategies.

The advent of multi-marker panels and liquid biopsy techniques, combined with advances in omics technologies and AI-driven analytics, holds promise for overcoming many limitations. Future large-scale prospective trials and translational research efforts are needed to validate these approaches and facilitate their integration into clinical practice.

In conclusion, the continued evolution of biomarker research is critical to improving outcomes in ovarian cancer. A multidisciplinary approach that combines technological innovation, rigorous clinical validation, and equitable healthcare policies will be essential in translating these scientific advances into tangible benefits for patients worldwide.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. **Consent for publication**

Approved

Funding

Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

SST (Family Medicine Consultant),

Manuscript drafting, Study Design,
Review of Literature, Data entry, Data analysis, and drafting article.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024; 74(1):10-34.
2. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2024. Int J Cancer. 2024; 154(2):321-330.
3. Bast RC Jr, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. Nat Rev Cancer. 2013; 13(6):427-439.
4. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017; 14(1):9-32.
5. Du Bois A, Reuss A, Pujade-Lauraine E, et al. Role of surgery in advanced ovarian cancer: current status and future perspectives. Lancet Oncol. 2019; 20(10):e569-e578.
6. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010; 5(6):463-466.
7. Bonome T, Levine DA, Shih I, et al. A gene signature predicting for survival in suboptimally debulked patients with ovarian cancer. Cancer Res. 2008; 68(22):9187-9194.
8. Jacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod. 1989; 4(1):1-12.
9. Duffy MJ, Urban N, Sturgeon C, et al. Early detection of ovarian cancer using biomarkers. Clin Cancer Res. 2014; 20(3):674-683.
10. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem. 2008; 54(12):e11-e79.
11. Moore RG, Brown AK, Miller MC, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecol Oncol. 2008; 108(2):402-408.
12. Van Gorp T, Amant F. The risk of ovarian malignancy algorithm (ROMA): a critical appraisal. Clin Chim Acta. 2011; 412(5-6):382-386.
13. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med. 2004; 351(8):781-791.
14. Cohen SJ, Punt CJ, Iannotti N, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. J Clin Oncol. 2008; 26(19):3213-3221.
15. Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic ovarian cancer biomarkers. Gynecol Oncol. 2008; 110(1):13-21.
16. Liang H, Yan X, Liu S, et al. MicroRNA biomarkers for ovarian cancer. Front Biosci (Landmark Ed). 2013; 18:1237-1248.
17. Taylor DD, Gercel-Taylor C. Exosomes/microvesicles: mediators of cancer-associated immunosuppressive microenvironments. Semin Immunopathol. 2011; 33(5):441-454.
18. Keller S, Ridinger J, and Rupp AK, et al. Exosomes: from biogenesis and secretion to biological function. Immunol Lett. 2019; 208:18-28.

19. Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015; 521(7553):489-494.
20. Teschendorff AE, Yang Z, Wong A, et al. A DNA methylation signature of recurrence risk in early-stage ovarian cancer. J Natl Cancer Inst. 2009; 101(19):1410-1421.
21. Hellstrom I, Raycraft J, Gupta D, et al. A combination of the biomarkers HE4 and CA125 improves the early detection of ovarian carcinoma in symptomatic women. Clin Cancer Res. 2009; 15(9):2913-2920.
22. Kaye SB, Matulonis UA. Ovarian cancer: biomarkers in diagnosis and therapy. Nat Rev Clin Oncol. 2015; 12(6):332-344.
23. Pepe MS, Etzioni R, Feng Z, et al. Phases of biomarker development for early detection of cancer. J Natl Cancer Inst. 2001; 93(14):1054-1061.
24. Moore RG, Brown AK, Miller MC, et al. Utility of HE4 and CA125 in the diagnosis of ovarian cancer. Gynecol Oncol. 2009; 112(1):40-46.
25. Visintin I, Kristensen GB, Egger ME, et al. A prospective validation of the Risk of Ovarian Malignancy Algorithm. BJOG. 2011; 118(3):329-335.
26. Kim Y, Kang S, Park S, et al. Performance of the ROMA algorithm in predicting ovarian malignancy in Korean women. Obstet Gynecol Sci. 2013; 56(5):335-341.
27. Alix-Panabières C, Pantel K. Circulating tumor cells: liquid cancer biopsy. Clin Chem. 2013; 59(1):110-118.
28. Dawson SJ, Tsui DWY, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 2013; 368(13):1199-1209.
29. Rustin GJ, Vergote I, Eisenhauer E, et al. A multicentre study evaluating the use of biomarkers in the diagnosis of ovarian cancer. Br J Cancer. 2011; 105(8):1081-1087.
30. Trope CG, Kaern J, Aas T, et al. Molecular profiling of ovarian cancer and its application in diagnosis and therapy. Ann Oncol. 2010; 21(6):1197-1203.
31. Cheng K, Tsai MM, Hsiao CP, et al. Prognostic biomarkers in ovarian cancer. Expert Rev Anticancer Ther. 2017; 17(10):915-925.
32. Rustin GJ, Owen P, Dowswell G, et al. Role of CA125 in monitoring the response to chemotherapy in ovarian cancer. J Clin Oncol. 2004; 22(7):1215-1221.
33. Markman M. Ovarian cancer biomarkers: moving from bench to bedside. Clin Cancer Res. 2010; 16(9):2511-2513.
34. Stanzione A, Franceschini S, Giordano D, et al. HE4 as a prognostic biomarker in ovarian cancer. Expert Rev Anticancer Ther. 2018; 18(8):731-739.
35. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012; 366(15):1382-1392.
36. Cohen SJ, Punt CJ, Iannotti N, et al. Circulating tumor cells and treatment outcomes in metastatic colorectal cancer. Clin Cancer Res. 2008; 14(6):1488-1494.
37. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 2.2024.
38. Colombo N, Sessa C, Du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology. Ann Oncol. 2019; 30(5):672-705.
39. Bast RC Jr, Badgwell D, Lu Z, et al. Standardization issues in ovarian cancer biomarker research. Gynecol Oncol. 2007; 105(3):435-441.
40. Sullivan R, Gevaert T, Wu Y, et al. Cost-effectiveness of biomarker screening in ovarian cancer. Value Health. 2016; 19(1):28-36.
41. U.S. Food and Drug Administration. Regulatory considerations for in vitro diagnostics used in ovarian cancer. FDA Guidance Document. 2023.
42. Kourou K, Exarchos TP, Exarchos KP, et al. Machine learning applications in cancer prognosis and prediction. Comput Struct Biotechnol J. 2015; 13:8-17.
43. Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease – latest advances and implications for cure. Nat Rev Clin Oncol. 2022; 19(5):269-280.
44. Matulonis UA, Sood A, Fallowfield L, et al. Ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019; 30(5):672-705.
45. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011; 474(7353):609-615.
46. Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015; 521(7553):489-494.
47. Zhang J, Gao L, Li J, et al. Proteomic profiling of ovarian cancer. Expert Rev Proteomics. 2020; 17(5):413-426.
48. Fong MY, Liu T, Sung ML, et al. Metabolomic signatures in ovarian cancer. Metabolomics. 2018; 14(6):76.
49. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med. 2014; 6(224):224ra24.
50. Esteva A, Robicquet A, Ramsundar B, et al. A guide to deep learning in healthcare. Nat Med. 2019; 25(1):24-29.
51. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012; 366(15):1382-1392.
52. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology. Ann Oncol. 2019; 30(5):672-705.
53. Escudero JM, Garcia M, Almansa R, et al. Circulating biomarkers and clinical outcomes in ovarian cancer. Clin Transl Oncol. 2020; 22(9):1540-1548.
54. Lu C, Huang J, Li S, et al. Therapeutic targeting of microRNAs in ovarian cancer. Cancer Lett. 2019; 460:1-9.
55. Vergote I, Trillsch F, Kennedy A, et al. A phase II study of targeted therapy based on tumor biomarker expression in ovarian cancer. Gynecol Oncol. 2021; 161(1):75-81.
56. Mutch DG, Herzog TJ, Homesley HD, et al. The role of biomarkers in ovarian cancer: bridging translational research and clinical practice. Gynecol Oncol. 2010; 117(2):189-196.
57. Matulonis UA, Sood AK, Fallowfield L, et al. Ovarian cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2019; 30(5):672-705.
58. Havrilesky LJ, Russell J, Dickler M, et al. Cost-effectiveness of biomarker screening in ovarian cancer. Clin Ther. 2015; 37(7):1625-1634.
59. Kohn EC, Abreu MH, Cohn DE, et al. Economic considerations in the use of biomarkers for ovarian cancer. Cancer J. 2016; 22(5):345-352.
60. European Medicines Agency. Regulatory guidelines for in vitro diagnostics in oncology. EMA Guidance Document. 2023.
61. American Cancer Society. Disparities in ovarian cancer outcomes. CA Cancer J Clin. 2022; 72(2):89-99.
62. Vaughan S, Coward J, Bast RC Jr, et al. Rethinking ovarian cancer: recommendations for improving outcomes. Nat Rev Cancer. 2011; 11(10):719-725.
63. Lheureux S, Gourley C, Vergote I, et al. Evolving treatment strategies for ovarian cancer. Lancet. 2019; 393(10177):1240-1253.