Research Progress in Prognostic Factors and Biomarkers of Ovarian Cancer

Shuna Liu1,2, Ming Wu1,2, Fang Wang1,2 ★

1. Department of Laboratory Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, 210029.
2. National Key Clinical Department of Laboratory Medicine, Nanjing, China, 210029.

★ Corresponding author: Fang Wang, E-mail: wangfang@njmu.edu.cn, Tel./Fax: +86 2586862814.

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Abstract

Ovarian cancer is a serious threat to women’s health; its early diagnosis rate is low and prone to metastasis and recurrence. The current conventional treatment for ovarian cancer is a combination of platinum and paclitaxel chemotherapy based on surgery. The recurrence and progression of ovarian cancer with poor prognosis is a major challenge in treatment. With rapid advances in technology, understanding of the molecular pathways involved in ovarian cancer recurrence and progression has increased, biomarker-guided treatment options can greatly improve the prognosis of patients. This review systematically discusses and summarizes existing and new information on prognostic factors and biomarkers of ovarian cancer, which is expected to improve the clinical management of patients and lead to effective personalized treatment.

Key words: ovarian cancer; prognostic factor; biomarker

Introduction

Ovarian cancer is the most fatal gynecological tumor, its incidence is next to cervical cancer and endometrial cancer, but its mortality rate is the first among reproductive system malignancies. According to the data of cancer statistics in 2020, the number of new cases is about 21750 and the number of deaths is 13940 [1]. Ovarian is located in the posterolateral uterine bottom, the onset is insidious, the early symptoms lack specificity, and the screening effect is limited, so the early diagnosis of ovarian cancer is difficult. According to the American congress of obstetricians and gynecologists (ACOG), 70 to 75 percent of ovarian cancers are diagnosed late, and the 5-year survival rate for most women is 20 to 30 percent [2]. Compared with other gynecological tumors, ovarian cancer has complex pathological types, high recurrence rate and poor prognosis. Patients with distant metastasis due to delayed medical treatment and tolerance to chemotherapy have worse prognosis. Therefore, the identification of effective clinical prognostic factors and biomarkers is crucial to improve the prognosis of ovarian cancer patients. With the in-depth study of the molecular changes that drive the transformation of ovarian cancer and tumor progression, many new molecular analysis techniques have been widely used. Recent studies have shown that microRNAs (miRNAs) may play an important role in the pathogenesis of ovarian cancer and serve as potential biomarkers [3].

The main contents of this review are divided into two parts: classic prognostic factors and novel prognostic factors. Classic prognostic factors included clinicopathologic factors (FIGO stage, degree of differentiation, degree of tumor reduction surgery, course of chemotherapy) and serum CA125. New prognostic factors mainly include blood- or tissue-based biomarkers. The ovarian cancer field has lagged in incorporating targeted therapies into standard treatments, these novel biomarkers are expected to provide therapeutic targets for ovarian cancer, thus guiding clinical practice, improving patient prognosis and ultimately reducing the risk of death of ovarian cancer patients.

Search Methods

Based on the topics discussed in this review, we systematically searched the recent medical literatures on novel prognostic biomarkers of ovarian cancer in...
PubMed and PMC databases by using our search strategy. All the literatures included in the study were published between February 1, 2015 and February 1, 2021. After excluding the duplicated literatures in the two databases, a total of 1,923 literatures met the restriction conditions. Then the retrieved literatures were imported into the literature management software Endnote. Preliminary screening was performed by reading the titles and abstracts of the literatures to exclude irrelevant studies, and then the full text of the included literatures was evaluated. In order to ensure the reliability of the research results, we only selected studies with more than 50 ovarian cancer patients, and the biomarkers studied in the literature were consistent with the clinical results. The inclusion and exclusion criteria and search strategy are provided in the appendix. Finally, a manual search was conducted in major journals and the reference lists of the selected papers to find other relevant citations that were missing by the electronic search.

**Search Results**

A total of 297 different novel prognostic biomarkers were reported in 296 studies that met the inclusion criteria (Figure 1). These prognostic biomarkers were classified according to the purpose of the study; there were 45 studies on biomarkers in the blood of ovarian cancer patients (Table 1) and 251 studies on biomarkers in tumor tissues (Tables 2-4).

![Flowchart of article selection process](http://www.jcancer.org)

**Figure 1.** Flowchart of article selection process.
| Table I. Blood-based biomarkers in ovarian cancer |
|---------------------------------------------------|
| **Cell proliferation and invasion**                |
| Leptin | Increased | Poor prognosis | Kato, S., et al. (2015) | Leptin | EOC | 70 |
| miR-429 | Increased | Good prognosis | Meng, X., et al. (2015) | miR-429 | EOC | 180 |
| ADAM12 | Increased | Poor prognosis | Cheon, D. J., et al. (2015) | ADAM12 | HSOC | 84 |
| Septin-9, clusterin | Increased | Poor prognosis | Lyu, N., et al. (2018) | Septin-9, clusterin | EOC | 137 |
| MMP3, TIMP3 | Increased | Poor prognosis | Cymbaluk-Ploska, A., et al. (2018) | MMP3, TIMP3 | OC | 104 |
| MSLN | Increased | Poor prognosis | Karolina Okla et al. (2018) | MSLN | EOC | 97 |
| CYFRA21-1 | Increased | Poor prognosis | Jin, C., et al. (2019) | CYFRA21-1 | EOC | 203 |
| **Inflammation**                                  |
| NLR | Increased | Poor prognosis | Feng, Z., et al. (2016) | NLR | HSOC | 875 |
| NLR | Increased | Poor prognosis | Li, Z., et al. (2017) | NLR | EOC | 654 |
| CRP / Alb | Increased | Poor prognosis | Liu, Y., et al. (2017) | CRP / Alb | OC | 200 |
| NLR, LDH | Increased | Poor prognosis | Mauricio, P., et al. (2018) | NLR, LDH | HSOC | 128 |
| AFR | Decreased | Poor prognosis | Yu, W., et al. (2019) | AFR | EOC | 313 |
| NLR | Increased | Poor prognosis | Ceran, M. U., et al. (2019) | NLR | EOC | 244 |
| PLR | Increased | Poor prognosis | Ceran, M. U., et al. (2019) | PLR | EOC | 244 |
| NLR | Increased | Poor prognosis | Nomelini, R. S., et al. (2019) | NLR | OC | 72 |
| **Angiogenesis**                                  |
| Fibulin-4 | Increased | Good prognosis | Chen, J., et al. (2015) | Fibulin-4 | OC | 160 |
| VEGF | Increased | Poor prognosis | Dobrzycka, B., et al. (2015) | VEGF | SOC | 92 |
| VEGF-A | Increased | Poor prognosis | Komatsu, H., et al. (2017) | VEGF-A | EOC | 128 |
| LncRNA MALAT1 | Increased | Poor prognosis | Qiu, J. J., et al. (2018) | LncRNA MALAT1 | EOC | 60 |
| **Antioxidant**                                   |
| s-OHdG | Increased | Poor prognosis | Pylväs-Eerola, M., et al. (2015) | s-OHdG | EOC | 112 |
| **Immune response**                              |
| TNFα/IL-4 ratio | Increased | Poor prognosis | Hao, C. J., et al. (2016) | TNFα/IL-4 ratio | OC | 50 |
| sPD-L1 | Increased | Poor prognosis | Chatterjee, J., et al. (2017) | sPD-L1 | EOC | 71 |
| s-Cd95L | Increased | Poor prognosis | De La Motte Rouge, T., et al. (2019) | s-Cd95L | HSOC | 51 |
| absolute lymphocyte count | Decreased | Poor prognosis | Lee, Y. J., et al. (2019) | absolute lymphocyte count | OC | 537 |
| CD4/CD8 ratio | Decreased | Poor prognosis | Waki, K., et al. (2020) | CD4/CD8 ratio | OC | 52 |
| **Chemotherapeutic sensitivity**                 |
| CEBPA, C69.OC<T polymorphism (rs34529039) | Increased | Poor prognosis | Konopka, B., et al. (2016) | CEBPA, C69.OC<T polymorphism (rs34529039) | OC | 118 |
| hyperfibrinogenemia | Increased | Poor prognosis | Feng, Z., et al. (2016) | hyperfibrinogenemia | HSOC | 875 |
| ERCC1 | Increased | Poor prognosis | Chebouiti, E., et al. (2017) | ERCC1 | OC | 65 |
| miR-135a-3p | Increased | Poor prognosis | Fukagawa, S., et al. (2017) | miR-135a-3p | OC | 98 |
| Gal-8, Gal-9 | Increased | Poor prognosis | Labrie, M., et al. (2017) | Gal-8, Gal-9 | HSOC | 160 |
| **Mitotic process**                              |
| Aurora A codon 57 SNP | Increased | Good prognosis | Niu, H., et al. (2017) | Aurora A codon 57 SNP | OC | 122 |
| **EMT and metastasis**                           |
| miR 20a, miR 20b, miR 200c | Increased | Poor prognosis | Zuberi, M., et al. (2015) | miR 20a, miR 20b, miR 200c | EOC | 70 |
| miR-200b, miR-200c | Increased | Poor prognosis | Meng, X., et al. (2016) | miR-200b, miR-200c | EOC | 163 |
| **Deregulation of the cellular transport**       |
| KPN2A | Increased | Poor prognosis | Huang, L., et al. (2017) | KPN2A | EOC | 162 |
| **Apoptosis process**                            |
| survivin | Increased | Poor prognosis | Dobrzycka, B., et al. (2015) | survivin | SOC | 92 |
| Smac/DIABLO  | Decreased | Poor prognosis | Dobrzycka, B., et al. (2015) | Smac/DIABLO | SOC | 92 |
| **Others**                                       |
| miR-200c, miR-141 | Increased | Poor prognosis | Gao, Y.C., et al. (2015) | miR-200c, miR-141 | EOC | 93 |
| Platelet counts | Increased | Poor prognosis | Chen, Y., et al. (2015) | Platelet counts | OC | 816 |
| SFRA | Increased | Poor prognosis | Kuroasaki, A., et al. (2016) | SFRA | EOC | 128 |
| OPN | Increased | Poor prognosis | Zivny, J. H., et al. (2016) | OPN | SOC | 66 |
| microRNA-125b (miR-125b) | Increased | Poor prognosis | Zuberi, M., et al. (2016) | microRNA-125b (miR-125b) | EOC | 70 |
| miR-125b | Increased | Poor prognosis | Zhu, T., et al. (2017) | miR-125b | EOC | 135 |
| BGA | Expression | Poor prognosis | Montavon Sartorius, C., et al. (2018) | BGA | OC | 282 |
| RASSF1A rs1998939C > T SNP | Increased | Poor prognosis | He, W., et al. (2018) | RASSF1A rs1998939C > T SNP | OC | 1375 |
| MACCI and S100A4 | Increased | Poor prognosis | Link, T., et al. (2019) | MACCI and S100A4 | OC | 79 |
| sP (Hyp-Leu,Glu-Phe-Trp) | Decreased | Poor prognosis | Lu, X., et al. (2019) | sP (Hyp-Leu,Glu-Phe-Trp) | EOC | 98 |

**Abbreviations:** miR: MicroRNA; NLR: the ratio of neutrophil count to lymphocyte count; AFR: albumin-to-fibrinogen ratio; PLR: platelet lymphocyte ratio; SNP: single Nucleotide Polymorphism; MSLN: Mesothelin; AAK: Aurora A kinase; Gal: Galectin; VEGF: vascular endothelial growth factor; sP-D-L1: soluble PD - L1; OC: ovarian cancer; HSOC: High grade serous ovarian cancer; EOC: epithelial ovarian cancer.

http://www.jcancer.org
Table 2. Tissue-based immunohistochemistry biomarkers in ovarian cancer

| EMT and metastasis | Expression or ratio | Potential clinical use | Example study | Studied biomarkers | Subsite | Patients (n) |
|--------------------|---------------------|------------------------|---------------|-------------------|---------|-------------|
| CTHRC1             | Increased           | Poor prognosis         | Hou, M., et al. (2015) | CTHRC1          | EOC     | 88          |
| ZEB2               | Increased           | Poor prognosis         | Prisles, S., et al. (2015) | ZEB2            | EOC     | 143         |
| CD44v6             | Increased           | Poor prognosis         | Tjhay, F., et al. (2015) | CD44v6          | EOC     | 59          |
| mIR-30e            | Increased           | Good prognosis         | Sun, Y., et al. (2015) | mIR-30e         | EOC     | 204         |
| FILIP1L            | Increased           | Good prognosis         | Kwon, M., et al. (2016) | FILIP1L         | OC      | 369         |
| Par3               | Decreased           | Good prognosis         | Nakamura, H., et al. (2016) | Par3            | OC      | 50          |
| MMP-14, CD44       | Double expression   | Poor prognosis         | Vos, M. C., et al. (2016) | MMP-14, CD44    | OC      | 97          |

| Inflammation and immune response | CD8/Treg ratio | Increased | Good prognosis | Knutsen, K. L., et al. (2015) | CD8/Treg ratio | EOC | 405 |
|----------------------------------|----------------|-----------|----------------|--------------------------------|----------------|-----|-----|
| PD-1, PD-L1                     | Increased      | Good prognosis | Darb-Esfahani, S., et al. (2016) | PD-1, PD-L1 | HGSOC | 215 |
| Tumour-infiltrating B cell and plasma cell      | Increased      | Poor prognosis | Lundgren, S., et al. (2016) | Tumour-infiltrating B cell and plasma cell | EOC | 154 |
| TIL                              | Increased      | Good prognosis | James, F. R., et al. (2017) | TIL | EOC | 707 |
| T-bet+ TILs                     | Increased      | Good prognosis | Xu, Y., et al. (2017) | T-bet+ TILs | EOC | 81 |
| PD-L1                            | Increased      | Poor prognosis | Zhu, J., et al. (2017) | PD-L1 | OCCC | 138 |
| Transcription factors WT1 and p53   | Increased      | Poor prognosis | Carter, J. H., et al. (2018) | Transcription factors WT1 and p53 | OC | 96 |
| SOCS-1                           | Increased      | Poor prognosis | Nakagawa, S., et al. (2018) | SOCS-1 | OC | 83 |
| PD-L1                            | Increased      | Good prognosis | Kim, K. H., et al. (2019) | PD-L1 | EOC | 248 |
| TIL                              | Increased      | Good prognosis | Mauricio, P., et al. (2019) | TIL | HGSOC | 128 |
| RCAS1-Ir                        | Increased      | Poor prognosis | Szubert, S., et al. (2019) | RCAS1-Ir | EOC | 67 |
| VISTA                            | Expression     | Poor prognosis | Zong, L., et al. (2020) | VISTA | OC | 146 |
| Co-expression of CD8+ and granzyme B++ | Increased      | Good prognosis | Jäntti, T., et al. (2020) | Co-expression of CD8+ and granzyme B++ | HGSOC | 67 |

Antioxidant

| Nrf2                             | Expression     | Poor prognosis | Lieve, P. L., et al. (2015) | Nrf2 | OC | 108 |
| SOD2                             | Increased      | Poor prognosis | Amano, T., et al. (2019) | SOD2 | EAOCC | 61 |

Angiogenesis

| p53K                            | Expression     | Poor prognosis | Kinose, Y., et al. (2015) | p53K | OC | 94 |
| PDGFRβR                         | Increased      | Poor prognosis | Corvigo, S., et al. (2016) | PDGFRβR | SOC | 186 |
| VEGF-R1, VEGF-R2                | Expression     | Good prognosis | Skirnisdottir, I., et al. (2016) | VEGF-R1, VEGF-R2 | EOC | 131 |
| Nestin                          | Increased      | Poor prognosis | Onisim, A., et al. (2016) | Nestin | SOC | 85 |
| MIG-7                           | Increased      | Poor prognosis | Huang, B., et al. (2016) | MIG-7 | EOC | 121 |
| PTEN                            | Expression     | Good prognosis | Shen, W., et al. (2017) | PTEN | OC | 76 |
| HIF-1α and VEGF                 | Expression     | Poor prognosis | Shen, W., et al. (2017) | HIF-1α and VEGF | OC | 76 |
| AEG-1                           | Increased      | Poor prognosis | Yu, X., et al. (2018) | AEG-1 | EOC | 170 |
| VEGF, SEMA4D                    | Expression     | Poor prognosis | Chen, Y., et al. (2018) | VEGF, SEMA4D | OC | 124 |
| TBC1D16                         | Increased      | Good prognosis | Yang, Z., et al. (2018) | TBC1D16 | EOC | 156 |
| PGF                             | Increased      | Poor prognosis | Meng, Q., et al. (2018) | PGF | EOC | 89 |
| VEGF-A                          | Decreased      | Poor prognosis | Sopo, M., et al. (2019) | VEGF-A | OC | 86 |
| Vasoformin-1, MACC1             | Increased      | Poor prognosis | Yu, L., et al. (2019) | vasoformin-1, MACC1 | SOC | 124 |
| Tie-2                           | Increased      | Poor prognosis | Sopo, M., et al. (2020) | Tie-2 | HGSOC | 86 |

Cell proliferation

| FASN                             | Increased      | Poor prognosis | Cai, Y., et al. (2015) | FASN | OC | 60 |
| CD73                             | Increased      | Poor prognosis | Turcotte, M., et al. (2015) | CD73 | HGSOC | 208 |
| SPINK1                           | Increased      | Poor prognosis | Mehner, C., et al. (2015) | SPINK1 | EOC | 490 |
| KCNN4, S100A14                   | Increased      | Poor prognosis | Zhao, H., et al. (2016) | KCNN4, S100A14 | SOC | 127 |
| EGFR                             | Increased      | Poor prognosis | Xu, L., et al. (2016) | EGFR | EOC | 67 |
| Gab1                             | Increased      | Poor prognosis | Hu, L. and R. Liu (2016) | Gab1 | EOC | 124 |
| IL-36a                           | Decreased      | Poor prognosis | Chang, L., et al. (2017) | IL-36a | EOC | 750 |
| DOT1L                            | Increased      | Poor prognosis | Zhang, X., et al. (2017) | DOT1L | OC | 117 |
| KRT5, KRT6                      | Increased      | Poor prognosis | Ricciardelli, C., et al. (2017) | KRT5, KRT6 | SOC | 117 |
| hLSR                            | Increased      | Poor prognosis | Hiramatsu, K., et al. (2018) | hLSR | EOC | 104 |
| PAUF, TIR4                      | TLR4 and PAUF/TLR4 | Poor prognosis | Choi, C. H., et al. (2018) | PAUF, TIR4 | EOC | 205 |
| PCDH8                            | Decreased      | Poor prognosis | Cao, Y., et al. (2018) | PCDH8 | OC | 68 |
| RIF1                             | Increased      | Poor prognosis | Liu, Y. B., et al. (2018) | RIF1 | EOC | 72 |
| FGFRI                            | Increased      | Poor prognosis | Li, M., et al. (2018) | FGFRI | OC | 428 |
| Protein/Marker | Expression or ratio | Potential clinical use | Example study | Studied biomarkers | Subsite | Patients (n) |
|---------------|---------------------|------------------------|---------------|-------------------|--------|-------------|
| FOXO1/PAX3    | Increased           | Poor prognosis         | Han, G. H., et al. (2019)\(^{114}\) | FOXO1 / PAX3 | EOC   | 212         |
| pStat3        | Increased           | Poor prognosis         | Li, H., et al. (2020)\(^{135}\) | pStat3     | EOC   | 156         |
| ATAD2         | Increased           | Poor prognosis         | Liu, Q., et al. (2020)\(^{116}\) | ATAD2      | OC    | 60          |
| GRO-β         | Increased           | Poor prognosis         | Ye, Q., et al. (2015)\(^{127}\) | GRO-β      | OC    | 136         |
| B7-H6         | Increased           | Poor prognosis         | Zhou, Y., et al. (2015)\(^{118}\) | B7-H6      | OC    | 110         |
| OCT4, Notch1 and DLL4 | Increased | Poor prognosis         | Yu, L., et al. (2016)\(^{119}\) | OCT4, Notch1 and DLL4 | EOC | 207 |
| EphA8         | Increased           | Poor prognosis         | Liu, X., et al. (2016)\(^{120}\) | EphA8      | OC    | 233         |
| AGTR1         | Increased           | Poor prognosis         | Zhang, Q., et al. (2019)\(^{121}\) | AGTR1      | EOC   | 902         |
| CK2a          | Increased           | Poor prognosis         | Ma, Z., et al. (2017)\(^{122}\) | CK2a       | EOC   | 117         |
| CEP55         | Increased           | Poor prognosis         | Zhang, W., et al. (2017)\(^{123}\) | CEP55      | EOC   | 213         |
| ANXA1         | Increased           | Good prognosis         | Manai, M., et al. (2020)\(^{124}\) | ANXA1      | EOC   | 156         |
| MAP3K8        | Increased           | Poor prognosis         | Grussos, T., et al. (2015)\(^{125}\) | MAP3K8     | HGSOC | 139         |
| IL-33/ST2 axis | Increased           | Poor prognosis         | Tong, X., et al. (2016)\(^{126}\) | IL-33/ST2 axis | EOC | 152         |
| CDCP1, ADAM12  | Decreased           | Good prognosis         | Vlad, C., et al. (2016)\(^{127}\) | CDCP1, ADAM12 | SOC | 102         |
| FGFR1         | Increased           | Poor prognosis         | Tai, H., et al. (2018)\(^{128}\) | FGFR1      | OC    | 90          |
| HSDL2         | Increased           | Poor prognosis         | Sun, Q., et al. (2018)\(^{129}\) | HSDL2      | OC    | 74          |
| DUSP2         | Decreased           | Poor prognosis         | Liu, W., et al. (2019)\(^{130}\) | DUSP2      | HGSOC | 127         |
| Kallistatin (KAL) | Decreased       | Poor prognosis         | Wu, H., et al. (2019)\(^{131}\) | Kallistatin (KAL) | HGSOC | 312         |
| YTHDF1-EIF3C axis | Increased     | Poor prognosis         | Liu, T., et al. (2020)\(^{132}\) | YTHDF1-EIF3C axis | OC | 134         |
| IL-6R         | Increased           | Good prognosis         | Isobe, A., et al. (2015)\(^{133}\) | IL-6R      | OC    | 94          |
| Usp7, MARCH7   | Increased           | Poor prognosis         | Zhang, L., et al. (2016)\(^{134}\) | Usp7, MARCH7 | EOC | 121         |
| PPA1          | Increased           | Poor prognosis         | Li, H., et al. (2017)\(^{135}\) | PPA1       | SOC   | 139         |
| PATZ1         | Increased           | Good prognosis         | Zhao, C., et al. (2018)\(^{136}\) | PATZ1      | SOC   | 208         |
| ARMCh         | Increased           | Poor prognosis         | Jiang, G., et al. (2015)\(^{137}\) | ARMCh      | OC    | 247         |
| galectin-1    | Increased           | Poor prognosis         | Chen, L., et al. (2015)\(^{138}\) | galectin-1 | EOC | 110         |
| MAGE-A9       | Increased           | Poor prognosis         | Xu, Y., et al. (2015)\(^{139}\) | MAGE-A9    | EOC   | 128         |
| TROP2         | Increased           | Poor prognosis         | Xu, N., et al. (2016)\(^{140}\) | TROP2      | EOC   | 128         |
| Galectin-6    | Increased           | Poor prognosis         | Lin, T., C., et al. (2017)\(^{141}\) | Galectin-6 | OC | 78          |
| Galectin-1    | Increased           | Poor prognosis         | Schulz, H., et al. (2017)\(^{142}\) | Galectin-1 | OC | 156         |
| Galectin-3    | Increased           | Poor prognosis         | Schulz, H., et al. (2017)\(^{143}\) | Galectin-3 | OC | 156         |
| Galectin-7    | Increased           | Poor prognosis         | Schulz, H., et al. (2017)\(^{144}\) | Galectin-7 | OC | 156         |
| REDD1         | Increased           | Poor prognosis         | Chang, B., et al. (2018)\(^{145}\) | REDD1      | OC    | 229         |
| RacGAP1       | Decreased           | Good prognosis         | Wang, C., et al. (2018)\(^{146}\) | RacGAP1    | EOC   | 117         |
| PAI-1, PAI-RBP1 | Increased           | Poor prognosis         | Koersgen, D., et al. (2018)\(^{147}\) | PAI-1, PAI-RBP1 | OC | 156         |
| PRDX1         | Decreased           | Poor prognosis         | Sienko, J., et al. (2019)\(^{148}\) | PRDX1      | OC    | 55          |
| KAI1          | Decreased           | Poor prognosis         | Yu, L., et al. (2019)\(^{149}\) | KAI1       | SOC   | 124         |
| CAV1, ATG4C   | Increased           | Poor prognosis         | Zeng, Y., et al. (2020)\(^{150}\) | CAV1, ATG4C | EOC | 95          |
| CH13L1, FKB4P4 | Increased           | Poor prognosis         | Lavrenson, K., et al. (2015)\(^{151}\) | CH13L1, FKB4P4 | EOC | 200         |
| REG4          | Increased           | Poor prognosis         | Chen, S., et al. (2015)\(^{152}\) | REG4       | EOC   | 337         |
| Spry2         | Decreased           | Poor prognosis         | Masoumi-Moghadam, S., et al. (2015)\(^{153}\) | Spry2      | OC | 99          |
| P38a, AT2F2   | Increased           | Poor prognosis         | Song, W., et al. (2017)\(^{154}\) | P38a, AT2F2 | OSC | 120         |
| nERK5         | Increased           | Poor prognosis         | Chan, K. K., et al. (2017)\(^{155}\) | nERK5      | OC    | 106         |
| SENP3/SMT3P1  | Increased           | Poor prognosis         | Cheng, J., et al. (2017)\(^{156}\) | SENP3/SMT3P1 | EOC | 124         |
| BCL6, Lewis y  | Increased           | Poor prognosis         | Zhu, L., et al. (2017)\(^{157}\) | BCL6, Lewis y | OC | 103         |
| CXCL11, HMG2A | Increased           | Poor prognosis         | Jin, C., et al. (2018)\(^{158}\) | CXCL11, HMG2A | HGSOC | 110         |
| HSPG2         | Decreased           | Poor prognosis         | Huang, R.L., et al. (2018)\(^{159}\) | HSPG2      | EOC   | 115         |
| KIF2A         | Decreased           | Poor prognosis         | Sheng, N., et al. (2018)\(^{160}\) | KIF2A      | OC    | 108         |
| TRIM59        | Increased           | Good prognosis         | Wang, Y., et al. (2018)\(^{161}\) | TRIM59     | OC    | 192         |
| S100A10       | Increased           | Poor prognosis         | Wang, L., et al. (2019)\(^{162}\) | S100A10    | OC    | 138         |
| PYGB          | Increased           | Poor prognosis         | Zhou, Y., et al. (2019)\(^{163}\) | PYGB       | OC    | 94          |
| GalNAs T6, T14 | Increased           | Poor prognosis         | Sheta, R., et al. (2017)\(^{164}\) | GalNAs T6, T14 | HGSOC | 131         |

**Glycosylation disorder of protein**

- GalNAs T6, T14
- **Mitotic process**
- TOPK
- HER2, AURKA
- KIF14

**Apoptosis process**

- PDCD5

- **Example study**

- **Studied biomarkers**

- **Subsite**

- **Patients (n)**
| Expression or ratio | Potential clinical use | Example study | Subscribed markers | Patients (n) |
|---------------------|------------------------|---------------|-------------------|-------------|
| MDM2 | Increased | Poor prognosis | Mak, C., et al. (2016) | MDM2 | OCCC 75 |
| DNA-PKcs, Akt3, p53 | Increased | Poor prognosis | Shin, K., et al. (2016) | DNA-PKcs, Akt3, p53 | SOC 132 |
| Gal-1, Gal-8, Gal-9p | Increased | Poor prognosis | Labrie, M., et al. (2017) | Gal-1, Gal-8, Gal-9p | HGSOC 209 |

**Cell survival (telomerase activity)**

| Phosphorylated Akt, hTERT | Increased | Poor prognosis | Lee, Y. K., et al. (2015) | phosphorylated Akt, hTERT | EOC 92 |

**Chemotherapeutic sensitivity**

| JARI1D1B | Increased | Poor prognosis | Wang, L., et al. (2015) | JARI1D1B | EOC 120 |
| ALDH1 | Increased | Good prognosis | Aubry, T. H., et al. (2015) | ALDH1 | EOC 55 |
| PRP4K | Increased | Good prognosis | Corkery, D. P., et al. (2015) | PRP4K | OC 199 |
| HtrA2 | Decreased | Poor prognosis | Miyamoto, M., et al. (2015) | HtrA2 | HGSOC 142 |
| PTEN | Increased | Good prognosis | Wang, L., et al. (2015) | PTEN | EOC 161 |
| NF-kBp65 | Increased | Good prognosis | Wang, L., et al. (2015) | NF-kBp65 | EOC 161 |
| elf3A | Increased | Good prognosis | Zhang, Y., et al. (2015) | elf3A | OC 126 |
| GTF2H5 | Decreased | Good prognosis | Gayarre, J., et al. (2016) | GTF2H5 | HGSOC 117 |
| POSTN | Increased | Poor prognosis | Sun, P. L., et al. (2016) | POSTN | EOC 308 |
| SOX10 | Increased | Poor prognosis | Know, A. Y., et al. (2016) | SOX10 | EOC 203 |
| GOLPH3L | Increased | Poor prognosis | Ho, S., et al. (2017) | GOLPH3L | OC 177 |
| LCOA | Increased | Poor prognosis | Miyamoto, M., et al. (2017) | LCOA | HGSOC 117 |
| Stonin 2 (STON2) | Increased | Poor prognosis | Sun, X., et al. (2017) | Stonin 2 (STON2) | EOC 89 |
| GATA3 | Increased | Poor prognosis | Chen, H. J., et al. (2018) | GATA3 | OC 196 |
| EpCAM | Increased | Poor prognosis | Zhang, X., et al. (2018) | EpCAM | EOC 109 |
| UBC13 | Decreased | Poor prognosis | Zhang, X., et al. (2018) | UBC13 | OC 71 |
| 14-3-3σ | Increased | Poor prognosis | Kim, H. J., et al. (2018) | 14-3-3σ | OC 88 |
| KCNN3 | Increased | Poor prognosis | Liu, X., et al. (2018) | KCNN3 | OC 57 |
| HELQ | Increased | Poor prognosis | Long, J., et al. (2018) | HELQ | EOC 87 |
| P1S10 (KIAA0101) | Increased | Poor prognosis | Jin, C., et al. (2018) | P1S10 (KIAA0101) | HGSOC 118 |
| UTP23 | Decreased | Poor prognosis | Fu, Z., et al. (2019) | UTP23 | OC 133 |
| ABCB9 | Decreased | Poor prognosis | Hou, L., et al. (2019) | ABCB9 | OC 308 |
| PBK | Increased | Poor prognosis | Ma, H., et al. (2019) | PBK | HGSOC 234 |
| Sorcin | Decreased | Poor prognosis | Zhang, S., et al. (2019) | Sorcin | OC 60 |
| PRC1 | Increased | Poor prognosis | Bu, H., et al. (2020) | PRC1 | HGSOC 210 |
| NCAALD | Decreased | Poor prognosis | Feng, L. Y. and L. Li (2020) | NCAALD | EOC 239 |

**Cell cycle regulation**

| CAPE | Increased | Poor prognosis | Hua, M., et al. (2015) | CAPE | EOC 119 |
| CCNE1 | Increased | Poor prognosis | Ayhan, A., et al. (2017) | CCNE1 | HGSOC 120 |
| NUCKS | Increased | Poor prognosis | Shi, C., et al. (2017) | NUCKS | OC 121 |
| TK1 | Increased | Poor prognosis | Wang, J., et al. (2017) | TK1 | SOC 109 |

**Differentiation of cancer-associated fibroblasts (CAFs)**

| MARCKS | Increased | Poor prognosis | Doghri, R., et al. (2017) | MARCKS | EOC 118 |

**Immunosuppression**

| VEGF | Increased | Poor prognosis | Horiwaka, N., et al. (2017) | VEGF | HGSOC 56 |

**Metabolic reprogramming**

| TBC1D8 | Increased | Poor prognosis | Chen, M., et al. (2019) | TBC1D8 | OC 141 |

**Fatty acid metabolism**

| PAX2 | Increased | Poor prognosis | Feng, Y., et al. (2020) | PAX2 | EOC 152 |

**Defective DNA repair**

| WRAP53β | Decreased | Poor prognosis | Hedström, E., et al. (2015) | WRAP53β | EOC 151 |
| pH2AX | Increased | Poor prognosis | Mei, L., et al. (2015) | pH2AX | EOC 87 |

**Others**

| SLP-2 | Increased | Poor prognosis | Sun, F., et al. (2015) | SLP-2 | EOC 140 |
| CD44v8-10 | Expression | Good prognosis | Sosulski, A., et al. (2016) | CD44v8-10 | SOC 210 |
| P53 | Increased | Poor prognosis | Zuo, J., et al. (2016) | P53 | SOC 183 |
| Highly sulfated CS | Increased | Poor prognosis | Van der steen, S.C., et al. (2016) | Highly sulfated CS | EOC 255 |
| adiponectin receptor-1 (AdipoR1) | Increased | Good prognosis | Li, X., et al. (2017) | adiponectin receptor-1 (AdipoR1) | EOC 73 |
| TP53 | Increased | Poor prognosis | Rzepecka, I. K., et al. (2017) | TP53 | HGSOC 159 |
| SMAD3 | Increased | Poor prognosis | Sark, S., et al. (2017) | SMAD3 | GCT 88 |
| ALDH5A1 | Increased | Good prognosis | Tian, X., et al. (2017) | ALDH5A1 | OC 192 |
| GR | Increased | Poor prognosis | Veneris, J. T., et al. (2017) | GR | EOC 341 |
| LAMP3 | Increased | Poor prognosis | Wang, D., et al. (2017) | LAMP3 | EOC 135 |
| HBXIP | Increased | Poor prognosis | Wang, Y., et al. (2017) | HBXIP | OC 120 |
| HSF1 p.ser326 | Expression | Poor prognosis | Yasuda, K., et al. (2017) | HSF1 p.ser326 | EOC 122 |
| COX-1, COX-2 | Increased | Poor prognosis | Beeghly-Fadiel, A., et al. (2018) | COX-1, COX-2 | EOC 190 |
| GPRI | Expression | Poor prognosis | Zhu, C. X., et al. (2018) | GPRI | EOC 110 |
| JHURP | Increased | Poor prognosis | Li, L., et al. (2018) | JHURP | HGSOC 98 |
| Galactins-8 | Increased | Poor prognosis | Schulz, H., et al. (2018) | Galactins-8 | OC 156 |
| HER3 | Expression | Poor prognosis | Chang, Y. W., et al. (2019) | HER3 | EOC 105 |
## Table 3. Tissue-based DNA biomarkers in ovarian cancer

| Methylation | Expression or ratio | Potential clinical use | Example study | Studied biomarkers | Method | Subsite | Patients (n) |
|-------------|--------------------|------------------------|---------------|-------------------|--------|---------|-------------|
| MYLK3 Methylation | Increased | Good prognosis | Phelps, D.L., et al. (2017) | MYLK3 Methylation | Pyrosequencing | SOC | 803 |
| HNF1B | Expression | Poor prognosis | Bubancova, I., et al. (2017) | HNF1B | NGS, HRM, MS-PCR | OC | 64 |
| GATA4 | Expression | Good prognosis | Bubancova, I., et al. (2017) | GATA4 | NGS, HRM, MS-PCR | OC | 64 |
| HS3ST2 | Increased | Poor prognosis | Huang, R.L., et al. (2018) | HS3ST2 | Pyrosequencing | EOC | 115 |
| ZNF671 | Increased | Early relapse | Mase, S., et al. (2019) | ZNF671 | EOC | HGSOCC | 78 |
| Structural changes of nuclear chromatin | | | | | | | |
| Chromatin entropy nuclei | Increased | Poor prognosis | Nielsen, B. et al. (2018) | Chromatin entropy nuclei | Nuclear Texture analysis | OC | 246 |
| Mutation status | | | | | | | |
| BRCA1/2 wild type | Expression | Poor prognosis | Eoh, K. J., et al. (2017) | BRCA1/2 wild type | Direct sequencing | EOC | 116 |
| BRCA1/2 | Property | Good prognosis | Kim, S. I., et al. (2019) | BRCA1/2 | Sanger sequencing | HGSOCC | 128 |
| Cell proliferation and apoptosis | | | | | | | |
| ecDNA | Increased | Poor prognosis | Kalavská, K., et al. (2018) | ecDNA | RT-PCR | OC | 67 |
| Gene polymorphism | | | | | | | |
| The AT genotype of rs189897 | Expression | Poor prognosis | Liu, J., et al. (2019) | The AT genotype of rs189897 | Mass ARRAY | EOC | 200 |
| rs12921862 C/C | Expression | Good prognosis | Zhang, Y., et al. (2019) | rs12921862 C/C | PCR-RFLP | EOC | 165 |

**Abbreviations:** TIL: tumor infiltrates lymphocytes; Gal: Galectin; OC: ovarian cancer; HGSOCC: High grade serous ovarian cancer; EOC: epithelial ovarian cancer.

## Table 4. Tissue-based RNA biomarkers in ovarian cancer

| Cell proliferation | Expression or ratio | Potential clinical use | Example study | Studied biomarkers | Method | Subsite | Patients (n) |
|-------------------|--------------------|------------------------|---------------|-------------------|--------|---------|-------------|
| microRNA(miR)-498 | Decreased | Poor prognosis | Cong, J., et al. (2015) | microRNA(miR)-498 | qRT-PCR | OC | 175 |
| mir-193b | Decreased | Poor prognosis | Li, H., et al. (2015) | mir-193b | qRT-PCR | OC | 116 |
| mir-752 | Decreased | Good prognosis | Zhang, X., et al. (2015) | mir-752 | qRT-PCR | OC | 108 |
| C7 | Decreased | Poor prognosis | Ying, L., et al. (2016) | C7 | qRT-PCR | OC | 156 |
| HER2, STAT3 | Decreased | Poor prognosis | Shang, A. Q., et al. (2017) | HER2, STAT3 | qRT-PCR | OC | 136 |
| SOCS3 | Decreased | Poor prognosis | Shang, A. Q., et al. (2017) | SOCS3 | qRT-PCR | OC | 136 |
| IncRNA RAD51-A51 | Increased | Poor prognosis | Zhang, X., et al. (2017) | IncRNA RAD51-A51 | qRT-PCR | EOC | 163 |
| IncRNA LINC 00152 | Increased | Poor prognosis | Chen, P., et al. (2018) | IncRNA LINC 00152 | qRT-PCR | OC | 82 |
| mir-1294 | Increased | Good prognosis | Guo, T. Y., et al. (2018) | mir-1294 | qRT-PCR | EOC | 76 |
| IncRNA TUG1 | Increased | Poor prognosis | Li, T. H., et al. (2018) | IncRNA TUG1 | qRT-PCR | EOC | 96 |
| microRNA-424-5p (miR-424-5p) | Increased | Good prognosis | Liu, J., et al. (2018) | microRNA-424-5p (miR-424-5p) | qRT-PCR | EOC | 83 |
| Cell migration | | | | | | | |
| IncRNA LINC00092 | Increased | Poor prognosis | Zhao, L., et al. (2017) | IncRNA LINC00092 | qRT-PCR | SOC | 58 |
| IncRNA PTPRG-A51 | Increased | Poor prognosis | Ren, X. Y., et al. (2020) | IncRNA PTPRG-A51 | qRT-PCR | EOC | 184 |
| Cell invasion | | | | | | | |
| IncRNA NEAT1 | Increased | Poor prognosis | Chen, Z. J., et al. (2016) | IncRNA NEAT1 | qRT-PCR | OC | 149 |
| ASAP1-IT1 | Increased | Good prognosis | Fu, Y., et al. (2016) | ASAP1-IT1 | qRT-PCR | EOC | 266 |
| Cell proliferation and migration | | | | | | | |
| miR-145 | Decreased | Poor prognosis | Kim, T.H., et al. (2015) | miR-145 | qRT-PCR | HGSOCC | 74 |
| microRNA-196a | Decreased | Poor prognosis | Fan, Y., et al. (2015) | microRNA-196a | qRT-PCR | EOC | 156 |
| mir-522 | Increased | Poor prognosis | Zhao, W., et al. (2015) | mir-522 | qRT-PCR | OC | 110 |
| Cell proliferation and invasion | | | | | | | |
| IncRNA AB073614 | Increased | Poor prognosis | Cheng, Z., et al. (2015) | IncRNA AB073614 | qRT-PCR | OC | 75 |
| Expression or ratio | Potential clinical use | Example study | Studied biomarkers | Method | Subsite | Patients (n) |
|---------------------|------------------------|---------------|-------------------|--------|---------|--------------|
| TBL1X1R1           | Increased              | Poor prognosis | Ma, M. and N. Yu (2017) [50] | TBL1X1R1 | qRT-PCR | SOC 116      |
| IncRNA MXN1-AS1    | Increased              | Poor prognosis | Li, A. H. and H. H. Zhang (2017) [51] | IncRNA MXN1-AS1 | qRT-PCR | EOC 177      |
| IncRNA NEAT1       | Increased              | Poor prognosis | Yong, W., et al. (2018) [52] | IncRNA NEAT1 | qRT-PCR | HGSC 75      |
| miR-532-5p         | Decreased              | Poor prognosis | Wei, H., et al. (2018) [53] | miR-532-5p | qRT-PCR | EOC 145      |
| **Cell migration and invasion** |
| ANRIL              | Increased              | Poor prognosis | Qiu, J., et al. (2015) [54] | ANRIL | qRT-PCR | SOC 68        |
| IncRNA CAT1        | Increased              | Poor prognosis | Cao, Y., et al. (2015) [55] | IncRNA CAT1 | qRT-PCR | EOC 72        |
| miR-28a-5p         | Increased              | Good prognosis | Mei, J., et al. (2019) [56] | miR-28a-5p | qRT-PCR | OC 61         |
| STAT2              | Increased              | Poor prognosis | Chen, S., et al. (2020) [57] | STAT2 | RT-PCR | OC 62         |
| IncRNA miR5030HG   | Decreased              | Poor prognosis | Zhu, D., et al. (2020) [58] | IncRNA miR5030HG | qRT-PCR | OC 61         |
| **Cell proliferation, migration and invasion** |
| IncRNA CCAT2       | Increased              | Poor prognosis | Huang, S., et al. (2016) [59] | IncRNA CCAT2 | qRT-PCR | OC 109        |
| GOLPH3             | Increased              | Poor prognosis | Sun, J., et al. (2017) [60] | GOLPH3 | qRT-PCR | EOC 73        |
| IncRNA HOXA11as    | Increased              | Poor prognosis | Yim, G. W., et al. (2017) [61] | IncRNA HOXA11as | qRT-PCR | SOC 129       |
| miR-520b           | Increased              | Poor prognosis | Zhang, J., et al. (2018) [62] | miR-520b | qRT-PCR | EOC 116       |
| IncRNA SNHG16      | Increased              | Poor prognosis | Yang, X. S., et al. (2018) [63] | IncRNA SNHG16 | qRT-PCR | OC 103        |
| IncRNA EBIC        | Increased              | Poor prognosis | Xu, Q. F., et al. (2018) [64] | IncRNA EBIC | qRT-PCR | OC 126        |
| IncRNA MALAT1      | Increased              | Poor prognosis | Guo, C., et al. (2018) [65] | IncRNA MALAT1 | qRT-PCR | OC 60         |
| IncRNA RP11-552M11.4 | Increased          | Poor prognosis | Huang, K., et al. (2018) [66] | IncRNA RP11-552M11.4 | qRT-PCR | EOC 67        |
| IncRNA OUTF1-isoform2 | Increased            | Poor prognosis | Wang, S., et al. (2018) [67] | IncRNA OUTF1-isoform2 | qRT-PCR | OC 114        |
| HYOU1              | Increased              | Poor prognosis | Li, X., et al. (2019) [68] | HYOU1 | qRT-PCR | EOC 127       |
| miR-203a-3p        | Increased              | Good prognosis | Liu, H. Y., et al. (2019) [69] | miR-203a-3p | qRT-PCR | OC 152        |
| LINCO0339          | Increased              | Poor prognosis | Pan, L., et al. (2019) [70] | LINCO0339 | qRT-PCR | OC 75         |
| IncRNA SNHG20      | Increased              | Poor prognosis | Wang, D., et al. (2019) [71] | IncRNA SNHG20 | RT-PCR | EOC 60        |
| miR-149            | Increased              | Good prognosis | Zhao, L. W., et al. (2020) [72] | miR-149 | qRT-PCR | OC 72         |
| **Chemotherapeutic sensitivity** |
| microRNA-506 (miR-506) | Increased            | Good prognosis | Liu, G., et al. (2015) [73] | microRNA-506 (miR-506) | qRT-PCR | EOC 598       |
| CHI3L1             | Increased              | Poor prognosis | Chiang, Y. C., et al. (2015) [74] | CHI3L1 | qRT-PCR | EOC 180       |
| IMP3               | Increased              | Poor prognosis | Hsu, K. F., et al. (2015) [75] | IMP3 | qRT-PCR | EOC 140       |
| Lin28B             | Increased              | Poor prognosis | Hsu, K. F., et al. (2015) [76] | Lin28B | qRT-PCR | EOC 140       |
| Triptolides 2 (TRIB2) | Decreased              | Poor prognosis | Kritsch, D., et al. (2017) [77] | Triptolides 2 (TRIB2) | qRT-PCR | EOC 149       |
| let-7e             | Decreased              | Poor prognosis | Xiao, M., et al. (2017) [78] | let-7e | qRT-PCR | EOC 84         |
| MAL                | Increased              | Poor prognosis | Zanotti, L., et al. (2017) [79] | MAL | qRT-PCR | HGSC 74        |
| miR-98-5p          | Increased              | Good prognosis | Wang, Y., et al. (2018) [80] | miR-98-5p | qRT-PCR | OC 97         |
| miR-1180           | Increased              | Poor prognosis | Gu, Z. W., et al. (2019) [81] | miR-1180 | qRT-PCR | OC 59         |
| IncRNA GA55        | Increased              | Good prognosis | Long, X., et al. (2019) [82] | IncRNA GA55 | qRT-PCR | OC 53         |
| **Immune response** |
| APOBEC3G          | Increased              | Good prognosis | Leonard, B., et al. (2016) [83] | APOBEC3G | qRT-PCR | HGSC 354       |
| IncRNA MIR155HG    | Increased              | Good prognosis | Colvin, E. K., et al. (2020) [84] | IncRNA MIR155HG | qRT-PCR | HGSC 67        |
| **Chromosome structure and function** |
| SMYD3 genetic polymorphisms | Expression | Poor prognosis | Liu, T. T., et al. (2016) [85] | SMYD3 genetic polymorphisms | qRT-PCR | OC 154         |
| **Apoptosis process** |
| CPSI-1TI          | Increased              | Good prognosis | Wang, Y. S., et al. (2017) [86] | CPSI-1TI | qRT-PCR | EOC 91         |
| **Others**        |
| CRNDE             | Increased              | Poor prognosis | Szafron, L. M., et al. (2015) [87] | CRNDE | qRT-PCR | OC 135        |
| GADD45A (1506T>C)  | Increased              | Poor prognosis | Yuan, C., et al. (2015) [88] | GADD45A (1506T>C) | qRT-PCR | OC 258        |
| miR-510, miR-129-3P | Decreased              | Good prognosis | Zhang, X., et al. (2015) [89] | miR-510, miR-129-3P | RT-qPCR,ISH | EOC 78         |
| FAM215A           | Decreased              | Good prognosis | Fu, Y., et al. (2016) [90] | FAM215A | qRT-PCR | EOC 266        |
| LIN-28B/let-7a/IGF-II axis | Decreased | Good prognosis | Lu, L., et al. (2016) [91] | LIN-28B/let-7a/IGF-II axis | qRT-PCR | EOC 211        |
| miR-200b, miR-1274A (8RNA LyS) and miR-141 | Decreased | Good prognosis | Halvorsen, A. R., et al. (2017) [92] | miR-200b, miR-1274A (8RNA LyS) and miR-141 | qRT-PCR | OC 207         |
| miR-595            | Decreased              | Poor prognosis | Zhou, Q. H., et al. (2017) [93] | miR-595 | qRT-PCR | EOC 166        |
| KLK11, KLK15       | Decreased              | Good prognosis | Geng, X., et al. (2017) [94] | KLK11, KLK15 | RT-PCR | HGSC 139       |
| IncRNA LINC01088   | Decreased              | Poor prognosis | Ai, H., et al. (2018) [95] | IncRNA LINC01088 | qRT-PCR | EOC 184        |
| IncRNA HMMR-AS1    | Decreased              | Poor prognosis | Chu, Z. P., et al. (2018) [96] | IncRNA HMMR-AS1 | qRT-PCR | EOC 152        |
| circ LARP4         | Decreased              | Poor prognosis | Zou, T., et al. (2018) [97] | circ LARP4 | qRT-PCR | OC 87         |
| circ HIPK3         | Decreased              | Poor prognosis | Liu, N., et al. (2018) [98] | circ HIPK3 | qRT-PCR | OC 69          |
| IncRNA DGCR5       | Decreased              | Poor prognosis | Chen, H., et al. (2019) [99] | IncRNA DGCR5 | qRT-PCR | OC 66          |
Classic prognostic factors

Clinicopathologic factors and serum CA125 level are independent factors affecting the prognosis of ovarian cancer patients, which have been widely used to guide accurate and reasonable clinical treatment, so as to improve the survival rate of patients.

Clinicopathological factors

The clinicopathological factors that affect the prognosis of ovarian cancer mainly include: FIGO stage, degree of differentiation, degree of tumor reduction surgery, course of chemotherapy. Previous literature has reported the importance of ovarian cancer staging for prognosis and treatment options, ovarian cancer can be classified as stage I-IV according to FIGO staging criteria, and most patients have stage III disease. Studies have shown that patients with stage I ovarian cancer have a 5-year survival rate of more than 90%; when ovarian cancer is confined to the pelvis (stage II), the estimated 5-year survival rate is about 70%; when ovarian cancer has spread to the entire abdominal cavity (stage III) or to distant parts (stage IV), the 5-year survival rate is less than 30% [4]. The survival prognosis of patients in the early stage was significantly better than that in the late stage. Differentiation degree of ovarian cancer includes high differentiation, moderate differentiation and low differentiation (poor differentiation), there has been evidence that poor differentiation of ovarian cancer is associated with worse survival. A large sample study established a predictive model for overall survival in 1189 patients with primary ovarian epithelial carcinoma, cox regression analysis showed that the worse the differentiation, the greater the risk of death [5].

Surgery is the most effective treatment for ovarian cancer, once suspected for ovarian cancer, should be performed as early as possible. Staging surgery is performed for early stage cancer, including resection of the tumor and definite staging. Tumor cell reduction was performed for advanced cancer, and the primary tumor and all metastases were removed as far as possible to minimize the number of tumor cells. Studies have confirmed that the degree of tumor cell reduction and the number of residual lesions after the first operation are important prognostic factors for advanced ovarian cancer [6]. The research of Jing shui et al. shows that the size of residual tumor foci was negatively correlated with the survival rate of patients and those with residual tumor foci ≤ 2 cm had better prognosis [7]. It is helpful to improve the prognosis and long-term survival rate of patients by minimizing or removing residual tumor foci.

Chemotherapy is an important adjuvant treatment for ovarian cancer, and most ovarian cancer is sensitive to chemotherapy. Platinum-based drugs (cisplatin and carboplatin) and taxanes (paclitaxel and docetaxel) are chemotherapy drugs commonly used in the treatment of ovarian cancer [8]. Postoperative adjuvant chemotherapy should follow the principles of standard, early and adequate course of treatment. Currently, it is generally considered that the standard course of chemotherapy for ovarian cancer is 6 courses. Three trials of primary advanced ovarian cancer compared the efficacy of chemotherapy with cisplatin in 5-6 cycles and 8-12 cycles, and the results showed that there was no benefit after 6 cycles of chemotherapy [9]. Another study on prognostic factor analysis of 129 cases of epithelial ovarian cancer showed that the median OS of patients with postoperative chemotherapy course ≥ 6 courses was significantly higher than that of patients with less than 6 courses of chemotherapy, and the difference was statistically significant (P<0.0001). There was no statistically significant difference in median OS in patients with 6 courses of chemotherapy, 7 courses of chemotherapy, 8 courses of chemotherapy or more than 8 courses of chemotherapy (P=0.816) [10]. In summary, postoperative chemotherapy course is an important prognostic factor for ovarian cancer, and standard chemotherapy course is associated with higher overall survival.

CA125

CA125, encoded by the MUC16 gene, is a classic marker for the diagnosis of ovarian cancer and was first described in the study of Bast RC et al [11]. Serum CA125 lacks sensitivity and specificity and cannot be used as a single marker for early detection of ovarian cancer [12,13], but the CA125 value after surgery and chemotherapy plays an important role in monitoring recurrence and evaluating prognosis. Redman et al. detected the CA125 value before the third chemotherapy in 78 patients with stage II-IV ovarian cancer after the completion of two courses of
chemotherapy, and the analysis showed that those with CA125 ≤ 35U/mL had a 1-year survival rate of 96%, while those with CA125>35U/mL had a 1-year survival rate of 15% [14]. The half-life of CA125 is another widely reported indicator. In some studies, CA125 was regularly detected after surgery and chemotherapy in 225 patients with advanced ovarian cancer, and the complete remission rate of patients with serum CA125 half-life <25 d was found to be 3.6 times higher than that of patients with >25 d through analysis combined with the results of secondary exploration [15]. Therefore, continuous monitoring of CA125 is of great value for efficacy evaluation and prognosis analysis of ovarian cancer patients.

**Novel prognostic factors**

In order to develop a powerful predictive tool with both sensitivity and specificity to monitor ovarian cancer response to treatment, the research on prognostic biomarkers for ovarian cancer is continuously advancing.

**Blood-based prognostic biomarkers**

Blood test is minimally invasive, simple and easy to obtain specimens, and blood test results are widely used in clinic to assist the guidance of treatment. A variety of novel prognostic biomarkers derived from blood can provide a new tool for the clinical management of ovarian cancer. A total of 43 blood based biomarker studies met our selection criteria (Table 1), of which 13 were evaluated using ELISA methods for protein biomarkers [16,18-22,30-32,34,36,37,44]. PCR technology was used for detection of DNA or RNA source biomarkers [17,33,40-42,46,47,49,53,54,57]. The 41 novel prognostic biomarkers provided by 43 studies can be classified by biological function, including cell proliferation and invasion [16-22], inflammatory response [23-29], angiogenesis [30-33], antioxidant [34], immune response [35-39], chemotherapeutic sensitivity [40-44], mitosis process [45], EMT (epithelial-to-mesenchymal transformation) and metastasis [46,47], deregulation of the cellular transport [48] and apoptosis process [31]. The following are representative novel prognostic factors reported in the literature.

A large number of studies have shown that chronic inflammation is closely related to the occurrence and development of cancer, and a variety of inflammatory cells and inflammatory factors participate in and promote the proliferation, invasion and metastasis of tumor cells, and affect the prognosis of patients [310]. Neutrophils and lymphocytes are both important cells involved in the inflammatory response process. The changes in the number of them can directly reflect the degree of inflammatory response in the body. NLR (neutrophil to lymphocyte ratio) is an important biological indicator of systemic inflammatory response, which can be obtained by calculating the ratio after the complete blood count [311]. Previous studies have shown that elevated NLR is an independent prognostic risk factor for several malignant tumors, including ovarian cancer [312-314]. The study of Stanislaus Argeny et al. found that the non-specific inflammatory response in cancerous tissues would lead to changes in the level of peripheral blood cells, mainly manifested as an increase in NLR. Studies have shown that neutrophils can alter the tumor microenvironment by producing cytokines and chemokines, they also promote the transformation of normal cells into tumor cells by secreting substances like reactive oxygen species and proteases. Moreover, the migration and diffusion ability of tumor cells can be enhanced by secreting platelet activating factor, matrix metalloproteinase and other factors related to tumor cell metastasis. In addition, lymphocytes are important components of the immune system and play an important role in immune surveillance. The decreased number of lymphocytes indicates the weakened immunity of the body and the reduced monitoring and killing effect on tumor cells, which cannot effectively prevent the proliferation and migration of tumor cells. Therefore, an elevated preoperative NLR usually indicates a poor prognosis in ovarian cancer patients [315]. The study of Zhang H et al. suggested that NLR could be used to differentiate CA125-negative ovarian cancer and was superior to CA125 in predicting patients' overall survival (OS) and progression free survival (PFS) [316]. In addition, a multivariate analysis of clinical data in 165 initial treatment ovarian cancer patients also suggested that NLR is an independent prognostic factor for PFS and OS in ovarian cancer patients [28].

Alterations in energy metabolism are a decisive biochemical feature of tumor cells, in other words, abnormal activation of glycolytic pathway still exists in tumor cells even under the condition of sufficient oxygen supply, consume large amounts of glucose and eventually produce lactic acid in order to satisfy energy supply of malignant tumor cell proliferation, this phenomenon is called aerobic glycolysis of tumors, also known as the Warburg effect [317]. In the process of glycolysis of malignant tumors, there is an important catalytic enzyme, namely lactate dehydrogenase (LDH), which mainly catalyzes the exchange of pyruvate and lactic acid, and is highly expressed in hypoxic cells, especially in tumor cells. Compared with normal tissues, the levels of glycolysis in malignant tissues were higher, and the serum LDH level of patients increased with the
progression of the disease, especially in the advanced stage of the tumor [318]. A study shows that the LDH levels at different stages and grades differed significantly in ovarian cancer, survival curves revealed that higher LDH expression was correlated with shorter survival (P<0.05). In addition, SATB1 may reprogram energy metabolism in ovarian cancer by regulating LDH and MCT1 levels to promote metastasis [319]. As another marker of tissue damage and inflammation, elevated serum LDH level can promote the proliferation, metastasis and development of cancer cells, which is commonly seen in a variety of malignant tumors [320,321]. A study showed that preoperative higher LDH levels were significantly associated with poor survival in patients with high grade serous ovarian cancer through survival analysis, serum high LDH levels are a promising prognostic biomarker [26].

Mesothelial protein (MSLN) is a cell surface glycoprotein, which was found by Chang et al. [322] and is usually only expressed in mesothelial tissue of body cavity. In recent years, MSLN as a differentiation antigen has been proved to be overexpressed in malignant pleural mesothelioma, pancreatic cancer, ovarian cancer and other malignant tumors, and may through increased synthesis of cyclinD1 and suppress the degradation and forming MSLN/MUC16 complex pathways involved in tumor cell proliferation, adhesion and transfer process, it is related to transcoelomic spread of ovarian cancer cells [323]. In addition, MSLN inhibits paclitaxel-induced apoptosis through serine and threonine kinase pathways, leading to chemotherapy resistance and seriously affecting the prognosis of patients [324]. The study of Karolina Okla et al. confirmed that plasma MSLN concentration in EOC patients was significantly higher than that in benign ovarian tumor patients and healthy women. Kaplan-Meier analysis results showed that, compared with low MSLN level, only high MSLN concentration of EOC patients before treatment was significantly correlated with a shorter 5-year OS (P=0.03), which predicted poor prognosis [21]. Another study showed that MSLN can enhance the invasion of ovarian cancer by inducing MMP-7 through MAPK/ERK and JNK pathways, blocking the MSLN-related pathway may be a potential strategy to improve the prognosis of ovarian cancer patients [325].

Aurora A kinase (AAK) is encoded by the Aurka gene and is a member of the serine/threonine kinase family. And as an important mitotic regulator, it can participate in many processes of cell mitosis and maintain chromosome division and spindle stability together with centrosomes [326]. Overexpression of Aurora A has been observed in a variety of malignant tumor types and plays an important regulatory role in the key control points of the tumorigenic transformation response through p53/TP53 phosphorylation [327]. Aurora A overexpression can also lead to abnormal amplification of centrosomes, leading to multilevel allocation and instability of chromosomes during division, and then to activation of oncogenes or inactivation of tumor suppressor genes [328]. Through gene chip screening and RT-PCR, the study of Hellemann et al. confirmed that Aurora A was overexpressed in ovarian cancer tissues that did not respond to platinum therapy, compared with ovarian cancer patients who responded to platinum therapy, and patients with overexpression of Aurora A had a poor prognosis [329]. A single nucleotide polymorphism in G169A at codon 57 of Aurora A locus leads to the substitution of valine by isoleucine, leading to the production of variant II. Kimura et al. [45] showed that AAK activity was reduced by the II variant, and the inhibited AAK could lead to cell death by affecting the mitosis process. Therefore, the change of single nucleotide polymorphisms in AAK may be a protective factor for cancer risk.

Galectin is an important member of the lectin superfamily, it is widely expressed in a variety of cell types and plays an important role in apoptosis, angiogenesis, cell migration, and tumor immune escape. Dysfunction or altered expression of galectin is associated with a variety of cancer types [330]. Galectin-8 and galectin-9 both have two carbohydrate recognition domains and are tandem repeat galactosins that regulate a variety of biological functions, including cell aggregation, cell adhesion, and tumor cell apoptosis [331]. Recent studies have shown that galectin-9 promotes CD8 + T cell failure and induces proliferation of myeloid inhibitory cells by binding to T cell immunoglobulin mucin 3 (Tim-3), thereby participating in immune escape of tumor cells [332]. In addition, the expression of galectin-8 in solid tumors has also been proved to be closely related to tumor cell adhesion or metastasis [333]. Labrie M et al. showed that plasma Gal-8 and Gal-9 levels were significantly increased in HGSOC patients compared to healthy controls, and higher plasma galectin-8 and galectin-9 levels were associated with a shorter 5-year disease-free survival (DFS) and 5-year OS (P=0.005), multivariate analysis further demonstrated that both plasma galectin-8 and galectin-9 could be promising biomarkers for poor prognosis in high grade serous ovarian cancer patients [171].

Angiogenesis plays an important role in tumor growth and metastasis. Neovascularization provides oxygen and nutrients to tumor cells, which can enhance cell proliferation and invasion ability [334].
Tumor tissue can secrete a variety of proangiogenic substances to induce and regulate angiogenesis, among which vascular endothelial growth factor (VEGF) is the primary stimulator of tumor angiogenesis. VEGF family members include VEGF-A, VEGF-B, VEGF-C, VEGF-D, etc. Among them, the biologic activity of VEGF-A is the most important, which can promote neovascularization and increase vascular permeability through VEGF/VEGFR (Vascular Endothelial Growth Factor Receptor) signaling pathway [335]. Previous studies have shown that VEGF-A is closely related to the occurrence and development of cancer and some inflammatory diseases [336]. Studies have investigated the efficacy of serum VEGF-A levels as prognostic markers in Epithelial ovarian cancer (EOC) patients, the experiment confirmed that the OS of patients with high VEGF-A level was significantly lower than that of patients with low VEGF-A level, and the difference was statistically significant (P=0.015). Moreover, the VEGF-A level of patients was correlated with FIGO stage. Multivariate analysis showed that serum VEGF-A could be an independent prognostic factor for OS of patients [32]. The study of Dobrzycka B et al. showed that serum VEGF level was significantly increased in patients with serous ovarian cancer (SOC) compared with healthy control group, and higher serum VEGF level was significantly correlated with poor prognosis, and multivariate analysis confirmed that serum VEGF level was an independent risk factor for prognosis [31].

MicroRNAs (miRNAs) are a class of single-stranded small RNAs encoded by endogenous genes, which regulate the expression of target genes by acting on target mRNA to promote its degradation or inhibit its translation [337]. MiRNAs are involved in the regulation of a variety of human life activities, and studies have found that miRNAs are closely related to the occurrence and development of a variety of malignant tumors [338,339]. At present, more than 50% miRNA genes have been located in tumor-related chromosomal rearrangement regions, which have important research and application values in the diagnosis, treatment and prognosis prediction of malignant tumors. EMT is closely related to tumor invasion and metastasis, many miRNAs have been proved to directly regulate the expression of epithelial markers and indirectly regulate EMT-related growth factor signaling pathways and transcription factors to affect the EMT process [340,341]. At present, miR-200 family is the most studied miRNA related to EMT process. Gregory et al. found that TGF-Beta/ZEB/miR-200 signaling pathway can regulate the transformation of cell epithelial-mesenchymal phenotype [342]. MiR-200c and miR-141 belong to the miRNA-200 family, Gao,Y.C. et al. evaluated the value of these two miRNAs as novel prognostic biomarkers for ovarian cancer. Studies have shown that the expression levels of serum miR-200c and miR-141 in ovarian cancer patients are significantly increased compared with the normal control group, and the expression levels of the two miRNAs are correlated with different stages and pathological subtypes of ovarian cancer. Survival analysis showed that compared with the group with high serum miR-200c expression, the overall survival rate of the group with low serum miR-200c expression was significantly reduced. This is similar to the analysis results of different miR-141 expression groups, so both miR-200c and miR-141 are likely to be promising prognostic biomarkers for ovarian cancer [49]. Another study compared the expression levels of miR-200a, miR-200b and miR-200c in blood samples from 70 EOC patients and healthy controls, the results showed that these three miRNAs were significantly higher expressed in serum samples from EOC patients compared to normal controls, statistical analysis confirmed that the high expression of miR-200a, miR200b and miR-200c was significantly correlated with tumor histological subtypes, stages and lymph node metastasis, and all of them could be used as reliable indicators for predicting the prognosis of patients with EOC [46].

Tissue-based prognostic biomarkers

The overwhelming majority of selected biomarker studies investigated different tissue-based biomarkers using a variety of technical research methods. The selected tissue prognostic biomarkers can be divided into immunohistochemical biomarkers (68.77%) [59-232], DNA biomarkers (3.95%) [159,233-241] and RNA biomarkers (27.28%) [242-309]. The prognostic value of 172 protein biomarkers was evaluated by immunohistochemistry in 174 studies (Table 2). These markers are classified according to their biological functions, mainly including such functional pathways as EMT and metastasis [59-71], inflammation and immunity [72-84], antioxidant [85,86], angiogenesis [87-99], cell proliferation, migration and invasion [100-116], chemotherapeutic sensitivity [117-197] and cell cycle regulation [198-201]. The remaining 79 studies of prognostic biomarkers were based on genomic DNA or RNA (Tables 3-4), involving different functional pathways in the progression of ovarian cancer, such as gene locus methylation [159,233-235], mutation status [237,238], gene polymorphism [240,241] and the expression of non-coding RNA during cancer cell proliferation, migration and invasion [242-282].

As a new type of anti-tumor effector
lymphocytes with potential therapeutic value, the correlation between TIL and patient prognosis and survival has been widely concerned. Through systematic literature retrieval, we determined that TIL is a promising prognostic biomarker, and its level can be detected by immunohistochemistry. TIL can be classified by function and location in the tumor tissue, which is generally associated with better prognosis and survival, in which the presence of CD8+ T cells is positively correlated with survival [343,344]. The presence of TIL in a variety of tumor types, including metastatic melanoma, breast cancer, colorectal cancer, and ovarian cancer, has been found to be significantly correlated with patient clinical outcomes and is an important positive prognostic factor [345-349]. There is evidence that ovarian cancer patients are usually accompanied by systemic immunosuppression. In contrast, patients with a stronger immune response have improved survival and respond better to chemotherapy [350]. Mauricio P et al. [81] evaluated TIL as a prognostic survival indicator for a group of HGSOC patients, and examined the expression of matrix and intraepithelial TIL (CD4+ and CD8+) in tissue samples. Multivariate analysis showed that intraepithelial CD4+ TIL infiltration was associated with better PFS and OS, intraepithelial CD8+ TIL infiltration was only associated with better PFS. This confirms previous studies that ovarian cancer patients with high infiltration of CD4+ and CD8+ TIL have better prognosis. As a new method for the treatment of ovarian cancer, the potential value of targeted immunotherapy is an important research direction, which can be used to guide clinical practice, reduce recurrence and improve the long-term survival rate of patients.

Mitochondrial superoxide dismutase (MnSOD or SOD2) is the most important antioxidant enzyme in mitochondria, which protects cells from oxidative damage induced by reactive oxygen species (ROS) and lipid peroxidation by converting endogenous superoxide to hydrogen peroxide [351]. Studies have demonstrated that SOD2 overexpression can enhance the invasion and metastasis of tumor cells by increasing the expression of matrix metalloproteinases (MMP) family members or activating Redox sensitive signaling pathways [352]. New evidence suggests that inhibition of SOD2 activity in tumor cells leads to increased apoptosis, inhibition of proliferation and increased sensitivity to chemotherapeutics [353]. There is growing evidence that SOD2 overexpression is associated with poor prognosis in a variety of cancer types, including renal clear cell carcinoma and ovarian cancer [354-356]. A study based on SOD2 immunohistochemical staining confirmed the correlation between SOD2 expression and patient prognosis in the endometriosis-associated ovarian cancer (EAOC) case group. Kaplan-Meier analysis showed that high SOD2 expression was associated with shorter PFS (P=0.0669) and poorer OS (P=0.0405), and increased SOD2 expression was a predictive biomarker for poor prognosis in EAOC [86].

Genome-wide analysis has confirmed that epigenetic changes are common events in many cancers, cellular genomic epigenetic disorders are important causes of many diseases, including cancer and autoimmune diseases. Epigenetic changes in human malignancies mainly include DNA methylation, nucleosomal remodeling histone modification and non-coding RNA dysregulation [357]. Numerous studies have confirmed that abnormal methylation of multiple genes involved in DNA repair, Akt /mTOR, Redox response, apoptosis, cell adhesion and cancer stem cell signaling pathways are associated with poor prognosis in ovarian cancer patients [358]. Mase et al. [235] confirmed that the DNA methylation status of ZNF671 was closely related to the recurrence and prognosis of patients with serous ovarian cancer. Multiple analysis methods combined showed that the methylation status of ZNF671 was an independent factor to predict the early recurrence of patients and patients with DNA methylation of ZNF671 had poor prognosis (P<0.05). A subsequent study validated the prognostic significance of HS3ST2 methylation in patients with advanced EOC in three separate dataset of TSGH, AOCS, and TCGA, studies have confirmed that HS3ST2 inhibits the malignant phenotype of ovarian cancer by interfering with various carcinogenic ligand signals, such as IL-6, FGF2 and EGF, and patients with low HS3ST2 expression accompanied by high expression of carcinogenic cytokines or growth factors have the worst prognosis [159]. In conclusion, abnormal DNA methylation in tumor cells can be used as an effective prognostic marker for ovarian cancer. Non-coding RNA is an important part of epigenetic changes, among which long non-coding RNA (lncRNA) is an emerging regulatory RNA that is involved in the regulation of a variety of physiological and pathological processes and is abnormally expressed in a variety of types of cancers. It has been reported that the differential expression of IncRNA in ovarian cancer, lung cancer, gastric cancer and liver cancer is related to the prognosis of patients [359]. Cao Y et al. [265] confirmed that the expression of IncRNA CCAT1 was up-regulated in EOC tissues, and the high expression of IncRNA CCAT1 could promote the process of EMT of EOC cells, and enhance the migration and invasion ability of cells. Furthermore, high IncRNA CCAT1 expression was associated with
FIGO stage, histological grade, lymph node metastasis and poor survival. Multivariate cox regression analysis showed that CCAT1 expression was an independent prognostic factor. In addition, it has been demonstrated that silencing of IncRNA CCAT2 in cancer cells significantly inhibits cell proliferation, migration and invasion through the Wnt/β-catenin signaling pathway, and the results of subsequent survival analysis showed that high CCAT2 expression was associated with shorter OS or DFS, cox proportional risk regression model analysis showed that CCAT2 expression level was an independent prognostic indicator for overall survival, and these data results confirmed that IncRNA CCAT2 was a reliable prognostic marker for ovarian cancer [269].

Conclusion
Ovarian cancer is the most fatal gynecological malignancy with high incidence and low survival rate. By exploring the prognostic biomarkers associated with ovarian cancer recurrence and progression, independent risk factors affecting patient prognosis were identified, which laid a solid foundation for the development of novel treatment strategies and the improvement of patient treatment outcomes. This review searched the literature and database for the relevant reports on prognostic biomarkers of ovarian cancer, reviewed the classic clinical prognostic biomarkers, and focused on the recently discovered various prognostic markers. Advances in genomics, proteomics and metabolomics have provided favorable conditions for the discovery of novel prognostic biomarkers that have identified a variety of promising prognostic biomarkers, including miRNA, IncRNA and TIL, these biomarkers can affect the prognosis of patients through a variety of biological functional pathways. TCGA data sets and public databases can provide data information for large patient cohort genome studies, the application of bioinformatics modeling and high-throughput molecular analysis techniques has greatly enriched the knowledge related to biological processes such as cancer progression. The prognostic value of a variety of novel biomarkers was evaluated by integrating genomic, proteomic and metabolomic data and clinical information with a multivariate analysis model. The effectiveness of these novel prognostic biomarkers still needs to be further validated in large clinical trials. By studying the functional pathways of regulation of these molecular markers, the potential molecular mechanisms are revealed, so as to identify new therapeutic targets. This is a high-precision medical method, which may promote personalized treatment of ovarian cancer patients and improve their prognosis.

Supplementary Material
Supplementary materials.
http://www.jcancer.org/v12p3976s1.pdf

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Contributions
Shuna Liu and Ming Wu did the literature search and analysed and interpreted data. Shuna Liu wrote the manuscript. Ming Wu prepared the Tables and Figures. Fang Wang designed and supervised the manuscript before submission. We both reviewed and approved the final manuscript before submission.

Competing Interests
The authors have declared that no competing interest exists.

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