REVIEW
Anatomy and Histology Journal of Indonesia (ANHJALI), 2025, Volume 1, Number 1: 18-25

Histological marker of ovarian cancer prognostig characterization

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Received: 2024-12-07
Accepted: 2025-01-15
Published: 2025-02-16

ABSTRACT

This review investigates the role of histological markers in the prognostic characterization of ovarian cancer, focusing on their potential to improve diagnosis, prognosis, and personalized treatment strategies. This paper was created using a literature review methodology with Boolean logic operators "AND" and "OR" with keywords such as "CA-125," "HE4," "P53," "BRCA1/2" "Ki-67," "WT1," "PD-L1," "VEGF," "FOLR1," "ovarian cancer," "histology pattern," "prognostic marker," and "comparative analysis". We use several databases including PubMed, Springer Nature, Google Scholar and ScienceDirect. The results emphasize the significance of molecular pathways, genetic mutations, and immune cell infiltration in the tumor microenvironment, highlighting the prognostic value of biomarkers like CA-125, HE4, p53, BRCA1/2, WT1, PD-L1, FOLR1, and VEGF . The study also emphasizes the need of several biomarkers to improve prognosis accuracy and direct personalized treatments. This review also found M2 macrophages and CD8+ T lymphocytes are immune to cancer activity and treatment results. The review implies that combining conventional and new biomarkers with cutting-edge technologies and single-cell transcriptomics could enhance early identification and focused treatments. Improving patient outcomes and survival rates in ovarian cancer.

Keywords: Ki67, MCM2, Ovarian Cancer, CA-125, HE4, P53, BRCA1/2.
Cite This Article: Suputra, I.M.E.A., Putra, I.P.E.W., Arijana, I.G.K.N., Adiputra, P.A.T., Supadmanaba, I.G.P. 2025. Histological marker of ovarian cancer prognostig characterization. *Anatomy and Histology Journal of Indonesia* 1(1): 18-25.

INTRODUCTION

With increasing incidence and terrible prognostic consequences, ovarian cancer still poses a major public health issue worldwide. The seventh most prevalent disease among women and the eighth largest cause of cancer-related mortality. Sung et al. estimates that roughly 313,959 new cases of ovarian cancer were diagnosed worldwide in 2020 along with about 207,252 deaths attributable to this illness.[1] Ovarian cancer is rather common in many countries, including Indonesia, and accounts for over 7.84% of all female cancer cases, therefore affecting the total cancer load among women. Beyond just the figures, ovarian cancer's reputation as a "silent killer" emphasises the need of giving it top priority. This results from its sneaky start, usually accompanied by non-specific symptoms that could lead to late-stage diagnosis. According to reports, between 70 and 80 percent of patients receive advanced stage (III or IV) diagnosis; at five years following diagnosis, the survival rate falls to around 20 to 30 percent.[2] Therefore, better detection techniques and prognostic markers are becoming more and more important, thus investigating histology markers for ovarian cancer is not only relevant but also necessary for efficiently customising treatment plans and early diagnosis enhancement.[3]

A key part of figuring out how likely someone is to get ovarian cancer is using histological markers. This combines old and new methods to get better patient results. Although they have long been used widely for the diagnosis of epithelial ovarian cancer, historically biomarkers including carbohydrate antigen 125 (CA-125) developed in the 1980s have often shown limited specificity and sensitivity, especially in the early stages of the cancer.[4] Although CA-125 is still a common surveillance tool, more recent biomarkers such as DNA methylation profiles and circulating microRNAs show promise as alternatives with the possibility of improved early diagnosis and prognostic grouping.[5,6] Recent research underlines the importance of tumour-infiltrating lymphocytes along with systemic inflammatory markers, which offer insights into the tumour immune microenvironment and hence help to further improve prognostic assessments.[7,8] Furthermore, advances in single-cell transcriptomics have enabled a better knowledge of tumour heterogeneity and the function of the tumour microenvironment, underlining the need to combine several indicators for a complete prognostic model.[9] It is important to note that modern research remains to validate novel markers, including the RNA translation levels of CHEK1 and FOXM1, which are correlated with results in high-grade serous ovarian cancer.10 Clinicians want to create strong predictive tools that enable individualised treatment methods and eventually raise ovarian cancer patients' survival rates by

using a multifarious strategy integrating known biomarkers with novel discoveries. The clinical significance and consequences of continuing ovarian cancer research are profound and diverse, especially as we delve further into disease progression, prognosis, and therapy methods. Targeting medications helps to optimize patient outcomes. New advancements in histology marker studies have made a more customised and effective approach of treating ovarian cancer possible.[11] Combining new protein biomarkers with current ones, such as CA-125, will help to widen the diagnostic horizon and enhance therapeutic response evaluations, enabling clinicians to customize treatments for every patient.[12] Cell invasion indicators help to depict the immune milieu inside tumours, therefore clarifying tumour microenvironment and disease progression.[13] Thus, it is imperative to investigate the expression and interactions of these indicators in respect to clinical outcomes actively. Strong management techniques developed from this will enable successful battle against ovarian cancer and raise survival rates.[14] Patients will ultimately get the finest treatment available since a better knowledge of these elements will guide treatment approaches and lead professional decisions.

METHOD

The writing of this paper was conducted using a literature review methodology. The authors utilized keywords such as "CA-125," "HE4," "P53," "BRCA1/2," "Ki-67," "WT1," "PD-L1," "VEGF," "FOLR1," "ovarian cancer," "histology pattern," "prognostic marker," and "comparative analysis" with Boolean logic operators "OR" and "AND." The keyword combinations included: ("CA-125" OR "HE4"), ("P53" OR "BRCA1"), ("ovarian cancer" AND "histology pattern"), ("prognostic marker" AND "comparative analysis") and the synonym. Journal searches were performed on reputable databases, including PubMed, ScienceDirect, Springer Nature, and Google Scholar, to ensure the inclusion of high-quality and relevant sources.

The authors structured the topic according to the research focus and applied specific inclusion and exclusion criteria based on the gathered information. The inclusion criteria consisted of reference sources in English and adherence to the PICO framework (Population, Intervention, Comparison, Outcome), where: (1) Population: Ovarian cancer patients, (2) Intervention: Analysis of histological marker , (3) Comparison: Comparison of histology patterns and prognostic values between the markers, (4) Outcome: Evaluation of prognostic value and accuracy in ovarian cancer prognosis assessment. Studies published in peer-reviewed and indexed journals; and (4) publications within the last 10 years (2015–2025).

On the other hand, the exclusion criteria included reference sources published more than 10 years ago, studies not subjected to peer review (e.g., gray literature, commentaries, or case reports without in-depth analysis), and articles lacking comprehensive data on histological marker expression or failing to discuss prognostic aspects of ovarian cancer.

Applying these inclusion and exclusion criteria aimed to ensure the quality and relevance of the selected references while minimizing selection bias in the literature analysis. This methodological approach provides a solid foundation for comparing histological markers as prognostic markers in ovarian cancer. It contributes to a better understanding of their histology patterns and prognostic significance.

RESULT AND DISCUSSION

Pathogenesis and Prognosis of Ovarian Cancer

The complex molecular mechanisms involving the activation of significant signalling pathways, genetic alterations, and environmental elements define the course of ovarian cancer. Among the signalling pathways most clearly involved in the onset of ovarian cancer are Wnt/β-catenin pathway and PI3K/Akt paths. Cell survival, proliferation, and metabolism are all crucially regulated by the PI3K/Akt pathway. As well as resistance to chemotherapeutic medicines, this pathway is also frequently engaged in aberrant activation and results in increased cancer.[15] Research indicates that microRNAs, including miR-378a-3p, control downstream effectors, modify these signalling pathways, and influence tumour development. On the other hand, where its dysregulation can encourage cancer cell migration and invasion, the Wnt/β-catenin signalling pathway is also rather strongly associated with the development of ovarian cancer. Particularly Wnt/β-catenin activation has been connected to a higher potential for metastases, which in turn supports a significant part in tumour development.[16] Drawing on the International Federation of Gynaecology and Obstetrics (FIGO) classification, ovarian cancer has four stages.

The risk of developing ovarian cancer is substantially influenced by genetic and environmental factors, with hereditary predispositions playing a critical role in defining risk profiles. Abnormalities in the BRCA1 and BRCA2 genes are acknowledged as primary risk factors, among the most prominent genetic influences. Women who possess mutations in these genes are at a significantly increased lifetime risk of developing ovarian cancer. Statistics suggest that the risk is as high as 39-44% for those with BRCA1 mutations and 11-17% for those with BRCA2 mutations.[17] Nevertheless, the interaction between these genetic elements and a variety of environmental factors, including dietary habits, exposure to carcinogens, and lifestyle choices.[18] Moreover, the imperative need for the identification and validation of specific biomarkers is evident, as they have the potential to serve a dual purpose by facilitating the early detection of ovarian cancer and guiding personalized treatment strategies. We can make strides toward more effective prevention, timely diagnosis, and enhanced therapeutic options for those at risk of this challenging malignancy by refining biomarker discovery and enhancing our understanding of both genetic and environmental contributions.[19]

Histological disease helps to classify the several subtypes of ovarian cancer, such as endometrioid carcinoma, clear cell carcinoma, and high-grade serous carcinoma (HGSC). HGSC is identified as a common and subtype of ovarian cancer.20 This emphasises how urgently more customised treatment plans

considering the particular biological behaviours of every subtype are needed. The identification of certain biomarkers and molecular profiles increases the clinical relevance of these histological categories as they are so important in defining patient outcomes and direction of therapy.[21] For example, that there is efficient utilisation of PARP inhibiting drugs in treating harbouring BRCA1/2 mutations highlights the value of molecular characterisation. These medicines have shown amazing success in this genetically predisposed population.[22] Additionally, recent research has highlighted the potential of combining PARP inhibitors with other targeted therapies to improve the results of treatment in ovarian cancer patients.[23] Clinicians can considerably enhance therapy outcomes through the utilisation of a thorough knowledge of molecular signalling pathways, genetic susceptibilities, and category classifications, therefore improving the quality of life and prognosis for patients affected by this demanding disease.[24]

Protein Biomarkers in Ovarian Cancer

Currently, various protein biomarkers have been identified and studied in the context of ovarian cancer, serving as diagnostic, prognostic, and therapeutic tools. These biomarkers not only aid in detecting the presence of cancer but also provide crucial information about tumor characteristics, response to therapy, and the likelihood of recurrence. With a better understanding of these biomarkers, researchers and clinicians can develop more personalized approaches to ovarian cancer management, improving treatment outcomes and patient quality of life.

CA-125

Most usually found and watched for, ovarian cancer is tracked with CA-125—also known as MUC16. Often used in advanced-stage ovarian cancer diagnosis, this biomarker is a glycoprotein created on ovarian epithelial cell surface. One may evaluate therapy response and find recurrence by means of high levels of CA-125 in blood. [25] This connects tumors to this. Though highly sensitive, CA-125 has a limited specificity since non-cancerous diseases including endometriosis and pelvic inflammatory illness can also raise CA-125 levels.[26] Usually coupled with other biomarkers, CA-125 increases diagnosis accuracy.

HE4

In the diagnosis of ovarian cancer, HE4 (Human Epididymis Protein 4) is used in conjunction with CA-125. HE4 superior specificity in comparison to CA-125 enables it to aid in the differentiation of benign from cancerous ovarian tumors. Research indicates that HE4 can predict the risk of ovarian cancer in women with ovarian lesions, elevated HE4 levels have generally been associated with a poor prognosis.[27] Additionally, HE4 is a biomarker that is beneficial in the treatment of ovarian cancer, as it is able to detect recurrence and indicate the effectiveness of the treatment.

p53

Over 90% of serous ovarian cancer cases show TP53 gene mutations, which are common in ovarian cancer.[28] Studies indicate that altered p53 not only loses its ability to stop tumours but also fuels therapeutic resistance and cancer cell proliferation.[29] Moreover, p53 expression is a predictive biomarker, for instance, poor outcomes in ovarian cancer patients are usually associated with high p53 expression.[30] The immunohistochemical detection of p53 has demonstrated the accuracy of predicting the TP53 mutation status in ovarian cancer samples

BRCA1 dan BRCA2

Alterations in the BRCA1 and BRCA2 genes are significant hereditary risk factors for ovarian cancer. Women possessing these mutations face a considerable lifetime chance of developing ovarian cancer, estimated at 39-44% for BRCA1 and 11-17% for BRCA2.[31] These mutations significantly influence therapy alternatives, particularly the efficacy of PARP inhibitors, which are effective for individuals with BRCA mutations.[32] Research indicates that BRCA-targeted therapy enhances treatment efficacy and prolongs survival in individuals with ovarian cancer.[33] Thus, genetic testing for BRCA1 and BRCA2 is crucial in the management of ovarian cancer, especially for personalized prevention and treatment strategies.

Ki-67

Indicator of cell proliferation, Ki-67 is a nuclear antigen. In ovarian tumour tissues, high Ki-67 expression usually means more cell growth, which is linked to a worse prognosis.[34] Higher Ki-67 levels are linked to a higher chance of recurrence.[35] This means that Ki-67 levels can help predict how ovarian cancer patients will do in the future. Ki-67 is thus regarded as a necessary prognostic biomarker in ovarian cancer management since it helps doctors choose the most suitable course of action.

WT1

Linked in kidney development and linked in ovarian cancer, Wilms' Tumour 1 (WT1) is a protein Often linked with poor prognosis in ovarian cancer patients, positive WT1 expression is a major prognostic biomarker.[36] Research indicates that WT1 can be used in immunotherapy; methods include WT1 vaccines that have promise for boosting immune reactions against tumours. Furthermore, under investigation as a means of tracking therapy responses and identifying ovarian cancer recurrence is WT1 detection in serum.[37]

PD-L1

Target for cancer immunotherapy, PD-L1 Programmed Death-Ligand 1 (PD-L1) is a biomarker linked in immune response control. Often associated with tumour immune evasion, high PD-L1 expression in ovarian cancer cells is found in research indicates that treatments aiming at PD-L1 can boost immune responses against ovarian cancer and that combining these treatments with chemotherapy shows encouraging effects in terms of patient survival.[38] Thus, in the evolution of ovarian cancer immunotherapy, PD-L1 is seen as an indispensable biomarketer.

FOLR1

Many cancer types, including ovarian cancer, have FOLR1, a biomarketer overxpressed in them. FOLR1 helps folate get into cells; its high expression is usually correlated with higher cancer cell proliferation.[39] Studies show that FOLR1 can be specifically targeted for therapy—monoclonal antibody-based therapeutics delivering chemotherapy straight to

cancer cells.[40] FOLR1 thus has promise as a biomarketer for ovarian cancer detection and treatment.

VEGF

Factor that promotes angiogenesis Increased expression of Vascular Endothelial Growth Factor (VEFG) is a common finding in ovarian cancer. An increased risk of metastases and a worse prognosis are linked to raised VEFG levels in the blood of ovarian cancer patients.[41] Researchers have discovered that reducing VEGF may inhibit tumor growth and enhance the efficacy of cancer treatments, rendering it a significant target for combination therapy.[42] Thus, VEGF is considered a crucial prognostic marker in the treatment of ovarian cancer.

Mesothelin

Expressed on the surface of ovarian cancer cells, mesothelin is a protein whose target for immunotherapy has been found. Studies imply that mesothelin influences cancer cell growth and invasion as well as in interactions between tumour cells.[43] Strong anti-tumor effects in ovarian cancer models have been shown by treatments aiming at mesothelin, like CAR-T cells directed against mesothelin. Mesothelin is thus seen as a potential biomarketer for ovarian cancer immunotherapies development.

Histological Findings Marker in Ovarian Cancer

Unlike high-grade serous carcinoma (HGSC), endometrioid carcinoma is frequently linked to endometriosis and exhibits a glandular architecture combining solid and cystic sections and displays a reduced prevalence of p53 mutations.[44] Less often occurring subtype of ovarian cancer, clear cell carcinoma is distinguished by clear cytoplasm and hobnail cell form. When compared to other subtypes, this kind of ovarian cancer sometimes responds differently to specific chemotherapy drugs. Though some research indicates that clear cell carcinoma may respond differently to chemotherapy regimens, information on its sensitivity is insufficient to support such assertions.[45] Mucinous carcinoma is a type of ovarian cancer that looks like benign mucinous tumors but has mucus-filled cysts. It is hard to tell the difference between them. Kang et al.'s studies show that the similarities in appearance between benign lesions and mucinous carcinoma could cause a wrong diagnosis and need in-depth clinical investigation. This study underscores the need for using a larger biomarker panel to increase the accuracy of ovarian cancer detection over a mix of conventional biomarkers, including CA-125 and HE4.[46] Histopathological examination of ovarian cancer identifies various subtypes, with high-grade serous carcinoma (HGSC) being the most common. HGSC is characterized by dense sheets of atypical cells and high mitotic activity, reflecting aggressive growth and great invasiveness, and is often associated with mutations in the p53 gene. p53 mutations play an important role in the pathogenesis of HGSC and correlate with poor clinical outcomes, including lower therapeutic response and poor survival rates. Although there are other subtypes such as endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma that exhibit different characteristics, the focus of research remains on HGSC due to its high prevalence and aggressiveness, as well as the importance of histological characteristics for more effective management.[47] The tumor microenvironment in high-grade serous carcinoma (HGSC) is characterized by significant desmoplasia and a high degree of immune cell infiltration, which can affect tumor behavior and patient prognosis. Desmoplasia creates connective tissue that supports tumor growth, while infiltration of immune cells such as T cells and macrophages can contribute to the complexity of tumor behavior.[48]

Cell infiltration marker in ovarian cancer

Infiltration of immune cells into the tumor microenvironment (TME) in ovarian cancer is a critical factor that directly affects the host immune response and tumor progression. Several types of immune cells interact in a sophisticated way under this paradigm. Different immune cells—macrophages, dendritic cells, tumor infiltrating lymphocytes (TILs)—have different needs for an immunological response against the tumor. Furthermore, well-known to be very crucial in malignant tumors including ovarian cancer are CD8+ T cells. Usually, the presence of CD8+ T cells in TME matches with a better prognosis since they can clearly recognize and destroy cancer cells straightforwardly.[49] When it comes to ovarian cancer, infiltration of M2 is crucial for tumor formation and metastasis. Since M2 macrophage cells have immunosuppressive effects, they are frequently connected with cancer cell survival and growth. The study by Gao et al. addressed M1 macrophages and their effect on the TME preserving the immunological response. A good awareness of the balance of immune cell subpopulations, especially the M1 and M2 is a ratio, greatly affects the efficacy of treatment in ovarian cancer patients.[50]

In the field of ovarian cancer research, one of the most important considerations has been the relationship between immune cell infiltration and therapeutic response. Higher responses to chemotherapy and greater overall survival rates in ovarian cancer patients correspond, according to studies, with a higher density of CD8+ TILs.[51] Moreover, the existence of particular immune cell types, that is so Th1 cells, has been associated with positive clinical results, implying that a strong anti-tumor immune response can improve the efficacy of therapy. Conversely, a higher quantity of immunosuppressive cells, including regulatory T cells and M2 macrophages, has been linked to a worse prognosis and resistance to therapy.[52] With higher TMB corresponding with enhanced TIL invasion and improved responses to immune checkpoint inhibitors, recent data suggest that the tumor mutational burden (TMB) may also be a predictive biomarker for immunological response.[53] Consequently, the immunological terrain inside the TME not only affects the course of ovarian cancer but also is a major factor determining therapy effectiveness and patient survival.[54]

CONCLUSION

The elevated incidence of ovarian cancer, coupled with late-stage diagnosis and unfavorable prognosis, remains a significant global public health issue. In countries such as Indonesia, where it constitutes 7.84% of all female cancer

cases, this seventh most common disease among women and eighth leading cause of cancer-related mortality worldwide represents a significant portion of the cancer burden. The condition is said to be a "silent killer" because of the uncertainty around its first signs. In 70–80% of cases, this suggests that the disease has progressed to an advanced stage (Stage III or IV), hence just 20–30% of people surviving five years post-diagnosis. This highlights the pressing necessity for enhanced early detection methods, prognostic indicators, and customized treatment strategies. Despite frequent utilization, conventional biomarkers like CA-125 exhibit limitations in sensitivity and specificity, particularly in the early stages of disease. Advancements in biomarker research, including investigations of DNA methylation profiles, circulating microRNAs, and tumor-infiltrating lymphocytes, demonstrate potential for enhancing diagnostic accuracy and prognostic predictions. The integration of these novel biomarkers with established biomarkers such as HE4 and CA-125 is expected to facilitate the evaluation of early therapy response and the diagnosis. Immunotherapy and targeted treatments have been facilitated by essential proteins such as p53, BRCA1/BRCA2, Ki-67, PD-L1, and VEGF. These studies have yielded substantial new information regarding immune system evasion, tumor proliferation, and treatment resistance. Histological differences help tell the difference between different types of ovarian cancer, such as high-grade serous carcinoma (HGSC), endometrioid carcinoma, and clear cell carcinoma. This study emphasizes the necessity of genetic profiling in tailoring treatment to specific needs. The treatment of ovarian cancer with tumors possessing a BRCA mutation has demonstrated remarkable efficacy with PARP inhibitors. New immunotherapy options are now available as a result of immune checkpoint drugs that target PD-L1. The tumor microenvironment (TME), characterized by immune cell infiltration and desmoplasia, significantly affects tumor growth and therapeutic efficacy. Achieving optimal therapeutic outcomes necessitates the precise equilibrium between immune cells that promote inflammation, such as M2 macrophages, and those that inhibit it, including CD8+ T cells. In addition to advancements in genetic and histological profiling, the integration of new and traditional indicators holds significant promise for improving the diagnosis, prognosis, and treatment of ovarian cancer. The advancement of more potent pharmaceuticals to combat this dreadful disease relies on ongoing research into the tumor microenvironment, immune cell interactions, and novel biomarkers. Integrating these findings with tailored treatment protocols will empower physicians to ensure optimal care for each ovarian cancer patient, enhance survival rates, and improve patient outcomes.

SUGGESTION

Further research into combinations of more specific and sensitive histology biomarkers, such as CA-125, HE4, PD-L1, and FOLR1, is urgently needed to improve the effectiveness of early detection and prognosis of ovarian cancer, as well as facilitate more personalized and accurate therapeutic approaches; moreover, the development of immunotherapy-based strategies, including the utilization of checkpoint inhibitors targeting PD-L1 and combination with chemotherapy or PARP inhibitors, is expected to improve patients' immune response and prolong survival; Furthermore, the implementation of advanced technologies such as single-cell transcriptomics and microRNA analysis in the diagnosis and monitoring of ovarian cancer needs to be improved to better understand tumor heterogeneity, while artificial intelligence (AI) has the potential to be a revolutionary tool in biomarker analysis, medical imaging, and designing therapies based on patients' genetic profiles, so investment in AI research and development in oncology should be a priority to improve the overall effectiveness of ovarian cancer detection and treatment.

CONFLICT OF INTEREST

All authors declare no conflict of interest regarding this article's publication.

AUTHOR CONTRIBUTIONS

All authors contributed equally contribute to the study.

FUNDING

The study did not receive any specific government or private sector grant.

ETHICAL CONSIDERATION

None declared.

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APPENDIX
PROTEIN BIOMARKERS IN OVARIAN CANCER

Biomarker	Main Function	Advantages	Limitations	Source
CA-125	Diagnosis, therapy monitoring, recurrence detection	High sensitivity in advanced ovarian cancer	Low specificity, can be elevated in benign conditions	25, 26
HE4	Diagnosis, prognosis, recurrence detection	Higher specificity than CA-125, differentiates benign and malignant tumors	Less sensitive for certain ovarian cancer subtypes	27
p53	Prognosis, therapy resistance	Predicts TP53 mutation, associated with therapy resistance	High expression linked to poor prognosis	28, 29, 30
BRCA1 & BRCA2	Genetic risk factors, therapy response	Helps determine PARP inhibitor effectiveness, essential for targeted therapy	Mutations not present in all ovarian cancer patients	31, 32, 33
Ki-67	Prognosis, recurrence prediction	Indicates cell proliferation rate, aids in treatment strategy selection	High expression linked to poor prognosis	34, 35
WT1	Prognosis, immunotherapy target	Used in vaccine-based immunotherapy, helps monitor therapy response	Positive expression often associated with poor prognosis	36, 37
PD-L1	Immunotherapy target	Involved in tumor immune evasion, PD-L1-based therapy enhances immune response	Not all patients respond to PD-L1-based therapy	38
FOLR1	Therapeutic target	Can be used for monoclonal antibody-based therapy	Not all ovarian cancer types highly express FOLR1	39, 40
VEGF	Prognosis, anti-angiogenesis therapy target	VEGF reduction can inhibit tumor growth	High expression linked to increased metastasis	41, 42
Mesothelin	Immunotherapy target	Involved in cancer cell growth and invasion, potential for CAR-T therapy	Specific role in pathogenesis still under study	43