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Editorial

Current status and future directions of ovarian cancer prognostic models

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Although the progression free survival of ovarian cancer has changed significantly with the introduction of PARP inhibitors [1,2], the prognosis is still poor, especially in advanced or recurrent cases [3]. The identification of prognostic factors and the development of prognostic models have a lengthy history, but to date, only clinicopathological findings, such as stage, histology, grade, and residual tumor, are generally considered to be reliable prognostic factors [4]. Although many prognostic models have been reported so far, none have been generalizable. This is because most previous studies have only analyzed single gene or protein expression as prognostic factors in cases at a single institution and examined their association with prognosis. This is problematic due to confounding by institutional bias and lack of reproducibility. It is interesting to note that an ovarian cancer risk score based on the expression of 10 ovarian cancer-related genes reported by Lu et al. [5] not only predicts chemo-response and clinical outcome, but also has been validated in The Cancer Genome Atlas (TCGA) database. In this study, an ovarian cancer risk score was established utilizing a univariate Cox proportional-hazards model based on the median expression levels of 10 target genes (*GPC1*, *CYPB*, *MSLN*, *LIMK2*, *DOCK4*, *STK31*, *IGF1*, *CHI3L1*, *Survivin*, and *CBAP*) on chemoresistance. Validation, using the TCGA database, demonstrated that patients with a high ovarian cancer risk score had significantly shorter median overall survival than those with a low ovarian cancer risk score. In the future, construction of prognostic models will require not only examination of cases from multiple institutions, but also validation using such databases. Additionally, factors used in prognostic models should include not only conventional cancer-related genes, but also factors from related metabolic processes. Cancer cells, including ovarian cancer cells, use glycolysis as a source of energy, which is characterized by high glucose uptake and active glycolysis, which converts glucose into lactic acid to produce ATP [6]. Prognostic models focusing on the Warburg effect, which is characteristic of these cancer cells, are also being investigated. Glycometabolism-related genes that are closely related to patient prognosis were screened by bioinformatics analysis with data from the Gene Expression Omnibus database. A risk score model based on five glycometabolism-related genes, including *B3GAT3*, *COL5A1*, *FAM162A*, *IDUA*, and *PPP2R1A*, to predict the prognosis of ovarian cancer patients was constructed [7]. From a metabolic perspective, 11 lipid metabolism genes (*PI3*, *RGS*, *ADORA3*, *CH25H*, *CCDC80*, *PTGER3*, *MATK*, *KLRB1*, *CCL19*, *CXCL9* and *CXCL10*) were used to construct a prognosis prediction model with good prognostic ability for serous ovarian cancer [8]. Furthermore, mass spectrometry-based glycoproteomic characterization demonstrated that intact glycopeptide signatures of mesenchymal subtypes are associated with a poor clinical outcome in high-grade serous

ovarian cancer [9]. In the future, a prognostic model focusing on the glycolytic activity of ovarian cancer may become a mainstream-model.

In recent years, with the introduction of immunotherapy into clinical practice [10], a new immune-related signature can stratify ovarian cancer patients by risk-score and guide clinical decisions [11]. Tumor-infiltrating lymphocytes, including CD3+, CD4+, CD8+, and CD103+, are associated with the outcomes of patients with high-grade serous ovarian cancer [12]. In tumor mutation burden-related genes -based models, a high tumor mutation burden may combine with an immunogenic microenvironment to predict favorable outcomes [13]. These models may help to identify ovarian cancer patients most likely to benefit from immunotherapy.

As a more practical tool, a mathematical nomogram has been used to calculate the expected prognostic risk by integrating multiple clinicopathological factors. An established and validated nomogram could predict the 3-year recurrence risk for patients who achieved complete clinical remission following cytoreductive surgery and chemotherapy [14] and the possibility of chemotherapy response score 3 following neoadjuvant chemotherapy [15]. However, these nomograms only use conventional clinicopathological factors, and it is expected that additional factors will be incorporated in the future. However, at that point, the vast number of parameters will require the use of artificial intelligence (AI) to accurately produce a valid nomogram. The construction of prognostic models using AI has been attempted, and an artificial neuronal network analysis was found to be useful for weighing the relative importance of clinical variables to predict complete cytoreduction and survival [16]. Gradient boosting-guided classification accurately identified the prognostic subgroups of patients [17]. Machine learning systems can provide critical diagnostic and prognostic prediction for patients prior to their initial intervention based on blood biomarkers [18]. Deep learning methods are able to extract effective CT-based prognostic biomarkers for high-grade serous ovarian cancer [19].

Future prognostic models will be able to take into account the genomic, transcriptional, translational, and posttranslational molecular features of ovarian cancer. These models will move toward the construction of an integrated analysis using AI that incorporates not only conventional clinicopathological findings and cancer-related gene expression, but also changes in metabolic pathways and immune-related signatures. This trend will lead to these models' use in general clinical practice that is not currently possible.

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