Editorial Commentary

The prognostic nomogram in platinum-resistant ovarian cancer: how to develop and validate?

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Dr. Lee *et al.* reported "*Development and validation of a prognostic nomogram for overall survival in patients with platinum-resistant ovarian cancer treated with chemotherapy*", on Eur J Cancer (1). Via the data from chemotherapy-only arm in AURELIA and randomized cases in CARTAXHY trial as training cohort, Dr. Lee created a nomogram to predict the prognosis in ovarian cancer. This prognostic nomogram was developed and generated by the pretreatment characteristics such as patients' performance, tumor size, or CA-125, etc., under multivariable proportional hazards models. Further, Dr. Lee applied their nomogram in other two large-scale data, bevacizumab-chemotherapy arm of AURELIA and PENELOPE trial as validation cohort, to calibrate the performance. They selected six significant predicting markers including patients' performance, intra-abdominal ascites, size of largest tumor, serum CA-125, platinum-free interval, and platinum-resistance status. Surprisingly, we can notice rather powerful stratification of overall survival (OS) in the patients with platinum-resistant ovarian cancer. Not only training cohort but also validation cohort, Dr. Lee's nomogram can discriminately analyze OS in different prognosis groups. In training cohort (chemotherapy-only arm in AURELIA and randomized cases in CARTAXHY), the median OS of good, intermediate, and poor prognosis groups were 25.3, 15.2, and 7.4 months, respectively. As to validation cohort, PENELOPE (C-statistic 0.59) and bevacizumab-chemotherapy arm of AURELI (C-statistic 0.67), the median OS were 18.5, 10.3, 5.8 months and

26.7, 13.8, 10.0 months in the good, intermediate and poor prognosis groups. Their conclusion revealed that their nomogram may effectively predict or counsel the prognosis and survival status for the patients of platinum-resistant ovarian cancer. The current study is interesting and worthy of further discussion.

Firstly, these authors mainly developed several nomograms for different subtypes of ovarian cancer and other cancer, such as progression-free survival and overall survival in platinum-sensitive recurrent ovarian cancer (2), advanced breast cancer (3), metastatic gastrointestinal stromal tumor treated with imatinib (4). Therefore, they had good experiences to create a prediction tool. Nomogram, or called nomograph, is a graphical and mathematical calculating method to create a diagram reaching estimated graphical computation. A set of n scales, and one for each variable in an equation, were included in the nomogram. Knowing the values of n-1 variables, the value of the unknown variable can be found; alternatively, the relationship between the unfixed ones can be studied by fixing the values of some variables. It is widely used in chemistry, aeronautics, astronomical calculations, and oncology, etc. In the field of oncology, it is frequently used to predict cancer survival mainly because of reducing statistical predictive models into a single numerical estimate of the probability of an event, like patients' alive status (overall survival) and tumor recurrence (progression-free survival). The generation of these estimates by user-friendly graphical

interfaces facilitates the use of nomograms in clinical decision making. In practice, the clinicians can construct a new nomogram to aid in the prognosis of individual cases by using the clinical information and data from published datasets. After comparison with original cohort, interesting predicting parameters may be identified and further validated in current existed nomogram. By this model, other specialists had also designed and constructed a nomogram, six-mRNA risk score system, to predict the clinical prognosis and platinum response in ovarian cancer (5). Dr. Wang *et al.* downloaded copy number variation (CNV) information from The Cancer Genome Atlas (TCGA) and further validated with GSE63885 datasets. The panel combined with six mRNA genes (*TBXT*, *SYNM*, *TEKT5*, *GDF3*, *SLC22A3*, and *CACNA1C*) was found to be an independent factor in prognosis.

Furthermore, Dr. Lee and colleagues applied six significant OS predictors, including patients' performance, intra-abdominal ascites, size of largest tumor, serum CA-125, platinum-free interval, and platinum-resistance status, in their paper. These six parameters all were proven to be the important prognostic factor in human ovarian cancer according to many published studies. Performance status is an evaluation to score daily well-being and life activity of cancer patients. Eastern Cooperative Oncology Group (ECOG) (6) or Karnofsky system (7) are mostly used to rank performance status. Not only before treatment but also 3 months after chemotherapy, it can both be a significant predictor in overall survival (8). Ascites may be found in more half ovarian cancer patients; malignant ascites were associated to peritoneal seeding or poor prognosis (9). Malignant cells in ascites or peritoneal washing can be defined as IC3 in FIGO staging system. Ascites derived tumor cells were even highlighted as the cancer source carrying stem-like capability. As to the size of largest tumor, the average size in late stage was significantly smaller than that in early stage (4.8 *vs.* 10.7 cm, respectively) (10). The median survival months in the cases with ovarian tumor less than or equal to 6 cm was 17 months, while the median survival of the cases with tumor greater than 6 cm was 36 months (P=0.003) (11). The authors using prognostic nomogram CA-125 was also investigated in Dr. Matte and colleagues' paper (12). They found that serum CA125/ascites leptin being a potential novel biomarker to predict baseline clinical drug resistance to first-line chemotherapy and a predictor for poor outcome in ovarian cancer patients. Serum CA125/ascites leptin ratio was showed to be significantly elevated in platinum resistant, compared to drug-sensitive diseases. "Platinum resistant", was historically defined as ovarian cancer recurrence or tumor progression within 6 months after or during first-line adjuvant platinum-based chemotherapy. The platinum sensitivity and platinum-free interval were both the most important factors to predict the response of first line chemotherapy and overall survival (13). From many preclinical and clinical studies, the extension of platinum-free interval by using non-platinum-based regimen, such as Lipo-Dox or Topotecan, may restore platinum sensitive status, thus allowing improving survival (14). Except the nomogram factors selected in this paper, other parameters including serum HE4 (15), NLR/PLR (16), or molecular profiles, proven as novel indicators, may also be selected to generate new nomogram for chemo-resistance and prognosis in EOC (epithelial ovarian cancer).

On the third, nomogram is usually as a prognostic device to predict prognosis (17). However, how to simplify the complex mathematical formula is the key to improve nomogram friendly. A "Cancer-Specific Survival Following Surgery" provided by Memorial Sloan Kettering Cancer Center (www.mskcc.org/nomograms/ovarian) (18) is to predict the 5-year survival of ovarian cancer after surgery. After finishing the worksheet including age, stage, albumin level, and maximal diameter of tumor, ASA score, and family history of hereditary breast/ovary cancer, the cancer specific survival can be calculated. Therefore, the strength of the article is that the establishment of this kind of nomogram can be easily converted into an online tool for other physicians. The online tool can provide a convenient and effective evaluation method for other physicians. Other clinician can apply a published nomogram that was generated using data on cohorts that might be different than one's own population of interest. The training or validated groups for this nomogram have their own unique personal or disease characteristics. It generates that nomogram may not be able to be effectively represented in another group of patients. Under the circumstances, Iasonos *et al.* (19) provided several reviewing points for clinicians to perform their assessment to apply an existing nomogram for their patients, including such as data population, clinical outcome, all variables under considerations, reporting system and the validation of this nomogram. They also identify a set of basic questions for clinicians to consider before applying a nomogram in the clinical setting and let clinicians to evaluate accessibility of this nomogram based on their own patients characteristics, clinical characteristics (tumor type), previous treatment, race/ethnicity, previous

therapy, or clinical size and others factors. By their methodological approach, the researchers may be able to reduce statistical operation in using or even generating a nomogram.

Finally, although the nomogram is a powerful tool in prediction of survival, we must also remind some important issues in EOC. There are several different histological subtypes, such as high/low grade serous, clear cell, endometrioid, accompanied with their salient features. In HGSOC (high grade serous ovarian cancer), the key target genes are *TP53*, *BRCA1/2*, homologous recombination repair (*HRR*) genes; different genes like *BRAF*, *KRAS*, or *PI3KCA*, are more mutated in LGSOC (low grade serous ovarian cancer) (20). If we generate one predictive nomogram in HGSOC, it is unknown whether this can also be fitted in LGSOC. In the future, as the authors mentioned, the nomogram can be developed with big data from precision medicine, such as genotypes, epigenetic study and even omics studies, in order to get a more stable and wildly used prediction nomogram system.

Footnote

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