Clinical significance of PI3 and HLA-DOB as potential prognostic predicators for ovarian cancer

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Background: The outcomes of ovarian cancer patients are very poor, therefore it is necessary to find prognostic biomarkers and explore the potential underlying molecular mechanisms of ovarian cancer.

Methods: In this study, a gene expression microarray data set covering 562 ovarian serous cystadenocarcinomas and 12,042 genes was downloaded from The Cancer Genome Atlas (TCGA) database. For each candidate gene, samples were allocated into a “high group” or a “low group” according to the expression level. The overall survival (OS) rates were compared between the two groups. Then, a univariate analysis and a multivariate Cox proportional hazards test were carried out to examine the associations between genes and multiple clinicopathological parameters.

Results: Among all candidate genes, PI3 (peptidase inhibitor 3, often called elafin) and HLA-DOB (major histocompatibility complex, class II, DO beta) were identified as hub genes. PI3 (P=7.99e-7) and HLA-DOB (P=7.52e-6) showed significant associations with OS, especially in patients with stage III or IV disease. Both PI3 (HR =1.84, P=3.77e-7) and HLA-DOB (HR =0.68, P=0.001134) were identified as independent predictors of ovarian cancer patients OS. In addition, IRF1 (interferon regulatory factor 1) (P=1.16e-15) and SPI1 (Spi-1 proto-oncogene) (P=2.03e-6) were identified as the most significant transcription factors.

Conclusions: Our data indicate that PI3 and HLA-DOB are potential biomarkers that could be used to predict the prognosis of ovarian cancer patients, and may play important roles in ovarian cancer progression. Further experimental and clinical studies with larger sample sizes are needed to confirm these findings.

Keywords: Ovarian cancer; outcome; peptidase inhibitor 3 (PI3); HLA-DOB

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**Introduction**

Ovarian cancer is one of the most common malignant tumors in the female reproductive system and has the highest mortality among all gynecological tumors (1,2). Due to the absence of specific symptoms and detective tools, most ovarian cancer patients are diagnosed at advanced stages, and the 5-year survival rate remains at approximately 45% (3,4). Despite improvements in surgery and chemotherapy approaches, unfortunately, the majority of advanced patients eventually relapse and die of this disease. Moreover, the prognosis of patients remains poor, which emphasizes the importance of identifying novel biomarkers predicting patients’ outcomes.
Clinicopathological characteristics, such as age at diagnosis, tumor subtype, clinical stage, histological grade, treatment modalities, and residual disease, affect the prognosis of ovarian cancer (2,5,6). Genetic alterations, such as chromosomal rearrangement (7,8), copy number amplification (9,10), DNA methylation (11) and gene mutation (12,13), also contribute to ovarian tumorigenesis and progression. The expression levels of some genes have been discovered to have a significant relationship with clinical outcomes, and are proposed as prognostic markers (14-16).

However, there is currently a lack of systematic genome-wide screens for ovarian cancer prognostic factors. By using a self-developed pipeline, this study aims to find prognosis-related genes in The Cancer Genome Atlas (TCGA) ovarian serous cystadenocarcinoma gene expression data and to explore the potential underlying molecular mechanisms of ovarian cancer through bioinformatics methods.

**Methods**

**Data source**

Both ovarian serous cystadenocarcinoma gene expression data and clinicopathological data were downloaded from TCGA database (https://tcga.xenahubs.net/download/TCGA.OV.sampleMap). Subsequently, these data were matched by sample ID. Gene expression was measured experimentally by the Broad Institute of MIT and the Harvard University Cancer Genomic Characterization Center using Affymetrix HT Human Genome U133a microarray platform. Only primary tumor samples were kept. Finally, 12,042 genes from 562 samples were included in the data set.

**Data preprocessing**

Genes with the most obvious variance (upper 25%) were selected as candidate genes (n=3,011) and kept for further analysis. The expression of each gene was labeled as “low” or “high” when compared with the median expression level of that gene.

**Statistical analysis**

Candidate genes were subjected to Kaplan-Meier survival analysis, and OS was calculated as the number of days between the date of diagnosis and the date of death or the last follow-up, whichever came first. Statistical significance was calculated using the log-rank test. Fisher’s exact test was used to compare patients’ distribution and unknowns were excluded before the analysis. Tumor characteristics and multivariate Cox proportional hazards models were performed. Statistical tests were two-tailed and the threshold for the P value was set at <0.05. For comparisons of multiple candidate genes, the threshold for the P values was set at 1.66e-5 according to Bonferroni correction (0.05/3011).

**Bioinformative analysis**

In total, 542 genes that significantly correlated with PI3 or HLA-DOB (227 genes with PI3, 404 genes with HLA-DOB and 89 overlapping genes) were used for enrichment analysis, where the P value was corrected with the Benjamini and Hochberg method (BH correction).

**Software and packages**

R (3.3.1) (17) was used for data preprocessing and statistical analysis, and the “survival” package was used for the survival analysis. FunRich (version 3) software (18) was used for the bioinformatics analysis.

**Results**

**Kaplan-Meier survival analysis**

All 3,011 candidate genes were subjected one by one to a self-developed R program, in which Kaplan-Meier analysis carried out between different gene expression groups (“low” or “high”). Two genes showed significant associations under the Bonferroni threshold (P=1.66e-5): PI3 (P=7.99e-7) and HLA-DOB (P=7.52e-6). Patients with high PI3 levels experienced prolonged OS, while high HLA-DOB transcription showed a negative influence on OS. When samples were subdivided according to clinical stages, the effects of these two genes were observed in stage III/IV but not in stage I/II (Figure 1).

**Univariate analysis between genes and clinical parameters**

Then, clinicopathological characteristics were compared between the low and high expression groups, but there was no significant difference in most of them (such as age at diagnosis, clinical stage, histological grade and invasion).
For PI3, the anatomic subdivision of cancer was unevenly distributed between the low and high expression groups. Low PI3 levels were significantly associated with unilateral tumors, but patients with high PI3 levels were more likely to suffer bilateral lesions. Low HLA-DOB expression was significantly related to progressive diseases, but high HLA-DOB expression was more likely as a sign of stable disease (Table 1).

Multivariate Cox proportional hazards analysis

Gene expression level and clinicopathological characteristics were incorporated into a multivariate Cox proportional hazards model for survival analysis. Both PI3 and HLA-DOB were revealed as independent predictors of prognosis among these factors. Compared with a lower mRNA expression level of PI3, a higher PI3 mRNA expression level had a hazard ratio (HR) of 1.84 (P=3.77e-7), while a higher mRNA expression level of HLA-DOB had a HR of 0.68 (P=0.001134). In the model, age at diagnosis (more than 70 years), tumor residual disease, new neoplasm events (such as metastasis and recurrence) and primary therapy outcomes (such as partial remission and progressive disease) were significantly associated with OS (Table 2).
Table 1 Univariate analysis of PI3 and HLA-DOB in ovarian cancer (n=562)

| Factors                  | PI3 |  | HLA-DOB |  |
|--------------------------|-----|---|---------|---|
|                          | Low (n=281) | High (n=281) | P  | Low (n=281) | High (n=281) | P  |
| Age of diagnosis (year)  |     |   |         |   |
| <50                      | 59  | 55 | 0.9267  | 51 | 63 | 0.4439 |
| 50–59                    | 92  | 88 |          | 87 | 93 |
| 60–69                    | 65  | 69 |          | 71 | 63 |
| ≥70                      | 65  | 69 |          | 72 | 62 |
| Anatomic neoplasm subdivision |     |   |         |   |
| Bilateral                | 181 | 210| 0.00816  | 188| 203|
| Left                     | 50  | 27 |          | 37 | 40 |
| Right                    | 35  | 29 |          | 40 | 24 |
| Unknown                  | 15  | 15 |          | 16 | 14 |
| Clinical stage           |     |   |         |   |
| Stage I                  | 10  | 5 | 0.541    | 7 | 8 |
| Stage II                 | 13  | 14|          | 8 | 19 |
| Stage III                | 213 | 219|          | 215| 217|
| Stage IV                 | 45  | 39|          | 48 | 36 |
| Unknown                  | 0   | 4 |          | 3 | 1 |
| Histologic grade         |     |   |         |   |
| Grade 1/2                | 36  | 39| 0.7102   | 33 | 42 |
| Grade 3/4                | 240 | 234|          | 240| 234|
| Unknown                  | 5   | 8 |          | 8 | 5 |
| Venous invasion          |     |   |         |   |
| No                       | 32  | 38| 0.6312   | 31 | 39 |
| Yes                      | 43  | 43|          | 34 | 52 |
| Unknown                  | 206 | 200|          | 216| 190|
| Lymphatic invasion       |     |   |         |   |
| No                       | 36  | 43| 0.5701   | 39 | 40 |
| Yes                      | 67  | 66|          | 59 | 74 |
| Unknown                  | 178 | 172|          | 183| 167|
| Tumor residual disease   |     |   |         |   |
| No macroscopic disease   | 61  | 54| 0.5594   | 49 | 66 |
| 1–10 mm                  | 130 | 118|          | 139| 109|
| 11–20 mm                 | 19  | 17|          | 19 | 17 |
| >20 mm                   | 47  | 58|          | 46 | 59 |
| Unknown                  | 24  | 34|          | 28 | 30 |

Table 1 (continued)
Table 1 (continued)

| Factors                  | PI3          |            |          |          | HLADOB     |            |          |          |
|--------------------------|--------------|------------|----------|----------|------------|------------|----------|----------|
|                          | Low (n=281)  | High (n=281)| P        |          | Low (n=281)| High (n=281)| P        |          |
| New neoplasm event       |              |            | 0.3139   |          | 0.7704     |            |          |          |
| Locoregional disease     | 2            | 4          |          |          | 3          | 3          |          |          |
| Metastatic               | 1            | 0          |          |          | 1          | 0          |          |          |
| Progression of disease   | 19           | 11         |          |          | 13         | 17         |          |          |
| Recurrence               | 133          | 127        |          |          | 133        | 127        |          |          |
| Unknown                  | 126          | 139        |          |          | 131        | 134        |          |          |
| Primary therapy outcome  |              |            | 0.3571   |          |            | 0.04032    |          |          |
| Complete remission/response | 133       | 123        |          |          | 124        | 132        |          |          |
| Partial remission/response | 24        | 31          |          |          | 27         | 28          |          |          |
| Progressive disease      | 20           | 22         |          |          | 27         | 15         |          |          |
| Stable disease           | 19           | 11         |          |          | 9          | 21         |          |          |
| Unknown                  | 85           | 94         |          |          | 94         | 85         |          |          |

The association between clinicopathological characteristics and gene expression levels (low or high) was analyzed by Fisher’s exact test. Unknowns were excluded before calculation.

Table 2 Multivariate Cox proportional hazards analysis for gene expression and clinicopathologic factors (n=562)

| Factors                  | PI3          |            |          |          | HLADOB     |            |          |          |
|--------------------------|--------------|------------|----------|----------|------------|------------|----------|----------|
|                          | P            | Se         | HR (95% CI) |          | P          | Se    | HR (95% CI) |          |
| PI3/HLADOB               |              |            |          |          |            |          |          |          |
| Low                      |              |            |          |          | Reference  |          |          |          |
| High                     | 3.77e−07     | 0.12       | 1.84 (1.45–2.32) |          |            | 0.001134 | 0.12     | 0.68 (0.54–0.86) |
| Age of diagnosis (year)  |              |            |          |          | Reference  |          |          |          |
| <50                      |              |            |          |          | Reference  |          |          |          |
| 50–59                    | 0.52317      | 0.18       | 1.12 (0.79–1.58) |          |          | 0.249306 | 0.18     | 1.23 (0.87–1.73) |
| 60–69                    | 0.14116      | 0.19       | 1.32 (0.91–1.9)  |          |          | 0.089531 | 0.19     | 1.38 (0.95–1.99) |
| ≥70                      | 8.37e−06     | 0.19       | 2.31 (1.6–3.35)  |          |          | 1.62e−06 | 0.19     | 2.48 (1.71–3.6)  |
| Anatomic subdivision     |              |            |          |          | Reference  |          |          |          |
| Bilateral                |              |            |          |          | Reference  |          |          |          |
| Left                     | 0.24365      | 0.19       | 0.8 (0.55–1.17)  |          |          | 0.089538 | 0.19     | 0.72 (0.5–1.05)  |
| Right                    | 0.43376      | 0.19       | 1.16 (0.8–1.71)  |          |          | 0.884027 | 0.19     | 0.97 (0.67–1.41) |
| Unknown                  | 0.83131      | 0.26       | 0.95 (0.57–1.57) |          |          | 0.565114 | 0.26     | 0.86 (0.52–1.42) |
| Clinical stage           |              |            |          |          | Reference  |          |          |          |
| Stage I                  |              |            |          |          | Reference  |          |          |          |
| Stage II                 | 0.44687      | 0.71       | 0.58 (0.14–2.35) |          |          | 0.804682 | 0.71     | 0.84 (0.21–3.4)  |

Table 2 (continued)
Table 2 (continued)

| Factors                          | PI3       | HLA-DOB               | P          | PI3       | HLA-DOB               | P          |
|----------------------------------|-----------|-----------------------|------------|-----------|-----------------------|------------|
|                                  | Low (n=281) | High (n=281)      | P          | Low (n=281) | High (n=281)      | P          |
| Stage III                        | 0.73549   | 0.63                  | 0.81 (0.23–2.78) | 0.887218   | 0.63                  | 1.09 (0.32–3.74) |
| Stage IV                         | 0.75831   | 0.64                  | 1.22 (0.35–4.26) | 0.513961   | 0.64                  | 1.52 (0.43–5.28) |
| Unknown                          | 0.55735   | 1.03                  | 1.83 (0.24–13.63) | 0.320538   | 1.02                  | 2.76 (0.37–20.46) |
| Histologic grade                 |           |                       |            |           |                       |            |
| Grade 1/2                        | Reference |                       |            | Reference |                       |            |
| Grade 3/4                        | 0.19132   | 0.17                  | 1.25 (0.89–1.76) | 0.233345   | 0.17                  | 1.23 (0.88–1.72) |
| Unknown                          | 0.53482   | 0.42                  | 0.77 (0.34–1.75) | 0.62694    | 0.41                  | 1.22 (0.55–2.69) |
| Venous invasion                  |           |                       |            |           |                       |            |
| No                               | Reference |                       |            | Reference |                       |            |
| Yes                              | 0.23044   | 0.35                  | 0.66 (0.33–1.3) | 0.329182   | 0.35                  | 0.71 (0.36–1.41) |
| Unknown                          | 0.72904   | 0.28                  | 1.1 (0.64–1.9)  | 0.953708   | 0.28                  | 0.98 (0.57–1.69) |
| Lymphatic invasion               |           |                       |            |           |                       |            |
| No                               | Reference |                       |            | Reference |                       |            |
| Yes                              | 0.0568    | 0.3                   | 1.78 (0.98–3.22) | 0.105397   | 0.3                   | 1.62 (0.9–2.91)  |
| Unknown                          | 0.80288   | 0.27                  | 0.94 (0.56–1.58) | 0.54888    | 0.26                  | 0.86 (0.51–1.43) |
| Tumor residual disease           |           |                       |            |           |                       |            |
| ≥20 mm                           |           |                       |            |           |                       |            |
| No macroscopic disease           | 0.00122   | 0.22                  | 0.49 (0.32–0.76) | 0.000158   | 0.22                  | 0.44 (0.29–0.67) |
| 1–10 mm                          | 0.51364   | 0.15                  | 0.9 (0.67–1.22) | 0.066415   | 0.15                  | 0.75 (0.56–1.02) |
| 11–20 mm                         | 0.29633   | 0.25                  | 0.77 (0.47–1.26) | 0.175791   | 0.26                  | 0.71 (0.43–1.17) |
| Unknown                          | 0.0049    | 0.23                  | 0.52 (0.33–0.82) | 0.003007   | 0.24                  | 0.5 (0.31–0.79)  |
| New neoplasm event               |           |                       |            |           |                       |            |
| Locoregional disease             |           |                       |            |           |                       |            |
| Metastatic                       | 0.01282   | 1.17                  | 18.52 (1.86–184.46) | 0.04181    | 1.17                  | 10.75 (1.09–105.78) |
| Progression of disease           | 0.04482   | 0.57                  | 3.12 (1.03–9.51) | 0.042067   | 0.57                  | 3.17 (1.04–9.66)  |
| Recurrence                       | 0.00982   | 0.55                  | 4.13 (1.41–12.1) | 0.008815   | 0.55                  | 4.26 (1.44–12.59) |
| Unknown                          | 0.1781    | 0.56                  | 2.12 (0.71–6.3)  | 0.115512   | 0.56                  | 2.41 (0.81–7.22)  |
| Primary therapy outcome          |           |                       |            |           |                       |            |
| Complete remission               |           |                       |            |           |                       |            |
| Partial remission                | 1.14e-09  | 0.19                  | 3.17 (2.19–4.6)  | 3.94e-11   | 0.19                  | 3.53 (2.43–5.13)  |
| Progressive disease              | 1.84e-08  | 0.23                  | 3.73 (2.36–5.89) | 6.20e-09   | 0.23                  | 3.87 (2.45–6.12)  |
| Stable disease                   | 5.91e-06  | 0.27                  | 3.32 (1.98–5.59) | 7.19e-05   | 0.26                  | 2.85 (1.7–4.79)   |
| Unknown                          | 0.00546   | 0.19                  | 1.7 (1.17–2.47)  | 0.002214   | 0.19                  | 1.79 (1.23–2.59)  |

Influence of highlighted gene (PI3 or HLA-DOB) and clinicopathologic factors on overall survival were calculated with multivariate Cox proportional hazards analysis. HR, hazard ratio; CI, confidence interval; Se, standard error.
A coexpression analysis was performed to explore the potential mechanisms of \textit{PI3} and \textit{HLA-DOB} in ovarian cancer prognosis. The 20 genes that most significantly correlated with ovarian cancer prognosis are listed in Table 3, where \textit{SOD2} (superoxide dismutase 2) (with \textit{PI3}) and \textit{TAPI} (transporter 1, ATP binding cassette subfamily B member) (with \textit{HLA-DOB}) ranked first. Pathway and transcription factor analyses were carried out on genes that were coexpressed with these two genes. The most remarkable pathways are listed in Table 4, where “immune system” ranked first. Meanwhile, IRF1 (P=1.16e-15) and SPI1 (P=2.03e-6) were the most significant molecules in the transcription factor analysis, as shown in Table 5.

### Table 3 Genes most significantly related with \textit{PI3} or \textit{HLA-DOB}

| Order | \textit{PI3} | \textit{Gene} | P         | r  |
|-------|-------------|---------------|-----------|----|
| 1     | SOD2        | 2.03e-34      | 0.484     |    |
| 2     | SLPI        | 2.34e-33      | 0.478     |    |
| 3     | CXCL8       | 3.01e-30      | 0.456     |    |
| 4     | CXCL1       | 3.35e-30      | 0.456     |    |
| 5     | S100A8      | 6.72e-27      | 0.432     |    |
| 6     | CCL20       | 4.76e-26      | 0.425     |    |
| 7     | S100A9      | 8.97e-26      | 0.423     |    |
| 8     | LCN2        | 2.21e-23      | 0.403     |    |
| 9     | C1S         | 6.51e-22      | 0.390     |    |
| 10    | ICAM1       | 1.24e-20      | 0.379     |    |
| 11    | PTX3        | 4.06e-20      | 0.374     |    |
| 12    | RARRES1     | 3.77e-19      | 0.365     |    |
| 13    | NFKBIA      | 4.42e-19      | 0.364     |    |
| 14    | PDZK1IP1    | 5.30e-19      | 0.364     |    |
| 15    | PLAUR       | 4.53e-18      | 0.354     |    |
| 16    | CXCL5       | 2.19e-17      | 0.347     |    |
| 17    | HP          | 1.04e-16      | 0.340     |    |
| 18    | CFB         | 1.36e-16      | 0.339     |    |
| 19    | BCL2A1      | 1.85e-16      | 0.338     |    |
| 20    | TNFAIP6     | 1.06e-15      | 0.329     |    |

| Order | \textit{HLA-DOB} | \textit{Gene} | P         | r  |
|-------|------------------|---------------|-----------|----|
| 1     | TAPI             | 1.66e-54      | 0.592     |    |
| 2     | PSMB9            | 4.07e-51      | 0.577     |    |
| 3     | PSMB8            | 1.88e-49      | 0.569     |    |
| 4     | BTN3A3           | 9.86e-46      | 0.550     |    |
| 5     | CYCSP5           | 3.39e-45      | 0.547     |    |
| 6     | HLA-DMA          | 1.33e-44      | 0.544     |    |
| 7     | CXCL11           | 5.26e-41      | 0.524     |    |
| 8     | HLA-F            | 3.93e-40      | 0.519     |    |
| 9     | APOL3            | 1.71e-39      | 0.516     |    |
| 10    | HLA-E            | 2.82e-38      | 0.508     |    |
| 11    | HLA-DMB          | 6.13e-38      | 0.506     |    |
| 12    | UBD              | 1.12e-37      | 0.505     |    |
| 13    | HLA-DRB1         | 4.59e-37      | 0.501     |    |
| 14    | IRF1             | 1.46e-36      | 0.498     |    |
| 15    | CD38             | 7.09e-35      | 0.487     |    |
| 16    | HLA-DPB1         | 7.95e-35      | 0.487     |    |
| 17    | HLA-DRA          | 8.00e-35      | 0.487     |    |
| 18    | CD74             | 1.25e-34      | 0.486     |    |
| 19    | TMEM140          | 6.62e-34      | 0.481     |    |
| 20    | HLA-DPA1         | 8.97e-34      | 0.480     |    |

Correlations between highlighted gene (\textit{PI3} or \textit{HLA-DOB}) and other genes were calculated and the most significant genes with them were listed, respectively.

### Discussion

The prognosis of cancer patients can be influenced by many regulatory molecules, so it is challenging to search for significant genes associated with outcomes. The range for candidate genes should be extended, and many clinical features (including age, stage, histopathology, etc.) should be incorporated into the model. Thus, it cannot only improve the performance of screening but also help to explain the possible mechanisms involved. In our study, genome-wide screening was performed on 12,042 genes, and our selections were tested in a model containing extensive factors, which improved the reliability and interpretability of the results.

\textit{PI3}, which encodes an elastase-specific inhibitor,
functions as an antimicrobial peptide against bacteria, fungi and other inflammatory pathologies (19-21). Adam Clauss et al. reported that the PI3 protein was overexpressed in serous ovarian carcinomas and showed a significant association with poor OS in 2010 (22). Further analysis confirmed the relationship between PI3 overexpression and the short survival time of ovarian tumor patients (23,24). In addition, a high level of PI3 was also related to the poor outcomes of breast cancer patients (23,25), cutaneous graft-versus-host disease (26) and hematopoietic cell transplantation (27). Moreover, the level of PI3 was related to breast cancer (25) and esophageal squamous cell carcinomas (28). In ovarian cancer, the PI3 protein can promote cell proliferation (24) and decrease epithelial ovarian carcinoma (EOC) cell sensitivity to genotoxic agents (29). However, little is known about the function of PI3 in tumor progression, and its importance has not been completely assessed from a genomic perspective.

**HLA-DOB** is one of the two components (the beta chain) belonging to HLA-DO, a human leucocyte antigen (HLA) class II heterodimer. HLA-DO controls HLA-DM-mediated peptide loading onto MHC class II molecules and functions as a modulator of antigen presentation (30). Polymorphisms in **HLA-DOB** have been identified to have significant associations with several pathology processes, such as HCV infection and viral clearance (31,32), immune control of HIV-1 infection (33) and the poor prognosis of advanced-stage non-small cell lung cancer (NSCLC) (34). To date, the relationship between **HLA-DOB** and ovarian cancer has rarely been reported.

Our study indicated that the level of PI3 was an independent predictor for the prognosis of ovarian cancer.
patients, but there are still some inconsistencies with former reports, which the association between PI3 and OS was observed in stage I/II but not in stage III/IV (23). A possible explanation for this discrepancy is that the previous study used immunohistochemistry (IHC) to assess the PI3 protein, but we focused on the level of mRNA. Moreover, as most ovarian cancers are diagnosed at an advanced stage, the sample sizes in stage I/II were relatively small, which may have reduced the reliability of the results. Larger sample sizes are needed for further study in the future.

According to Adam Clauss and colleagues, no significant differences were found in the distribution of clinicopathological characteristics (age, debulking, stage, and platinum sensitivity or resistance) between the two PI3-expression level groups (22). However, Caruso reported that patients in the PI3-positive group had a higher proportion of advanced FIGO stages (III/IV) (23). In our study, almost all clinicopathological characteristics, including clinical stage, were evenly distributed in the PI3-low and high groups except for anatomic subdivision, but our PI3-grouping was based mainly on mRNA expression instead of IHC staining (Table 1). An uneven distribution of HLA-DOB was found in the primary therapy outcome. The majority of samples with “stable disease” showed high levels, while more samples with “progressive disease” were sorted into the low group, implying that HLA-DOB may affect the tumor’s response to treatment.

In the Cox proportional hazards test (Table 2), more variables were taken into account than those described in other studies (22-24). Both PI3 and HLA-BOD showed a significant influence on OS together with venous/lymphatic invasion, tumor residual disease, new neoplasm events and primary therapy outcomes, demonstrating that these two genes have good predictive value for ovarian cancer prognosis. An age at diagnosis of over 70 years was identified as a risk factor, while “no macroscopic disease” was identified as a protective factor (relative to their respective references). Among all factors, new neoplasm events (metastatic/progression of disease/recurrence) and primary therapy outcomes (partial remission/progressive disease/stable disease) had a decisive impact on OS. All of these results agreed with the consensus and confirmed the validity of our model.

Among the top 20 genes correlated with PI3, S100A8 (S100 calcium binding protein A8), S100A9 (S100 calcium binding protein A9) and NFKBIA (NFkB inhibitor alpha) participate in endogenous TLR (Toll-like receptor) signaling, while SOD2, CXCL8 (C-X-C motif chemokine ligand 8), ICAM1 (intercellular adhesion molecule 1), NFKBLA (NFKB inhibitor alpha), PLAUR (plasminogen activator, urokinase receptor) and BCL2A1 (BCL2 related protein A1) are involved in multiple biological pathways, such as PI3K-mTOR (phosphatidylinositol 3 kinase-mammalian target of rapamycin) and EGF (epidermal growth factor) receptor signaling. Among the top 20 genes correlated with HLA-DOB, many are related to immune system regulation such as antigen processing/presentation, the interferon pathway and cytokine signaling. The close relationship between the correlated genes and immunomodulation is also shown in Table 4. IRF1, which is a transcriptional regulator involved in both innate and acquired immune responses was revealed in the transcription factor analysis. IRF1 expression can be induced by cisplatin and attenuates drug sensitivity in ovarian cancer cells (35). It has also been identified as an independent predictor of prognosis in high-grade serous ovarian carcinoma (HGSOC) (36). SPI1 is an ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development (37), but the role of SPI1 in ovarian cancer is not clear.

Our results were obtained from statistical and bioinformation analyses and further experimental and clinical studies are warranted to verify these findings.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.11.30). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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