Original Article

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*).

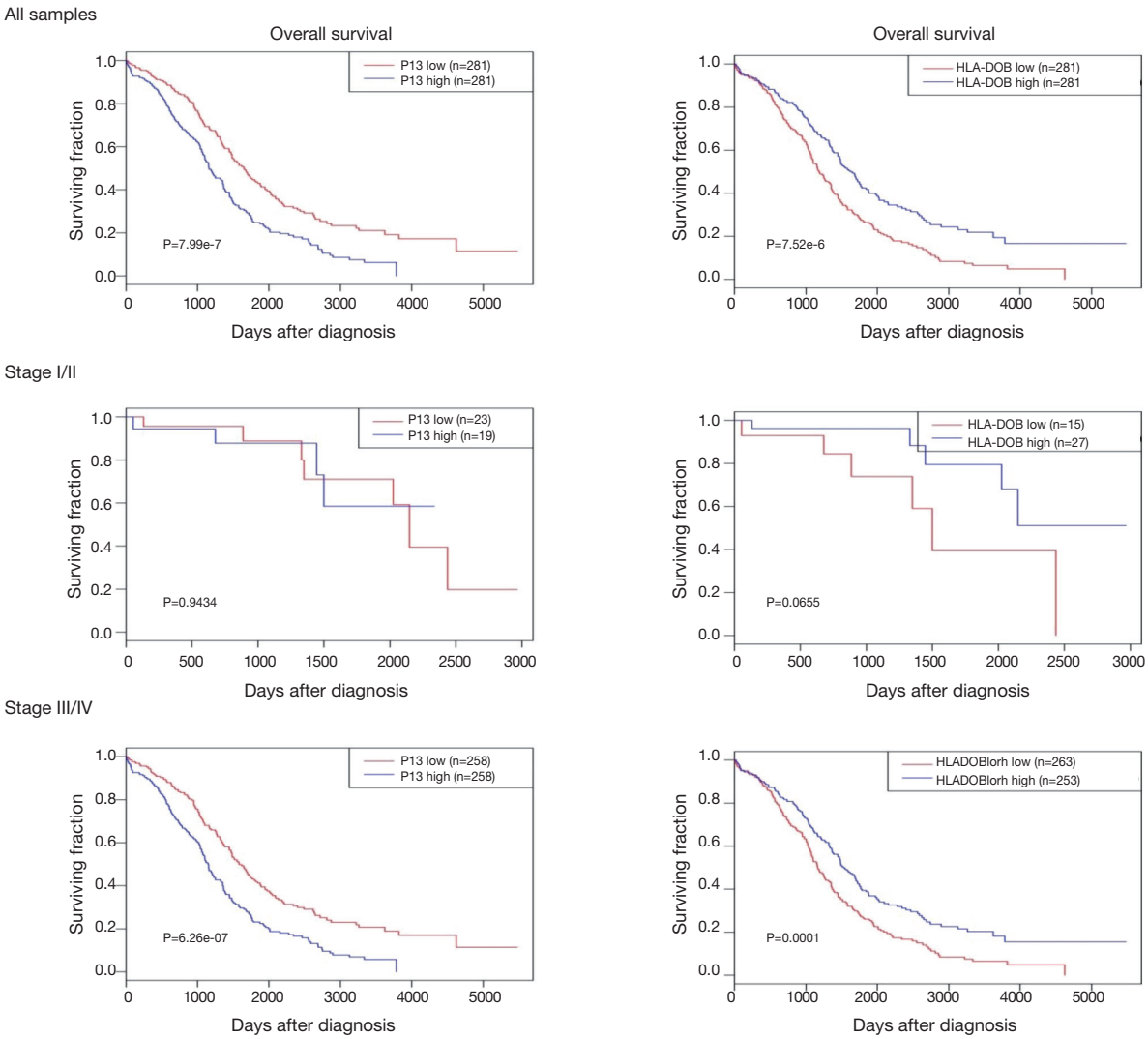

Figure 1 Kaplan-Meier analysis of overall survival between low and high cases (n=562). The top row represents all the patients, then patients were grouped according to the clinical stages and curves were drawn in middle and bottom rows, respectively.

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)			0.9267			0.4439
<50	59	55		51	63	
50–59	92	88		87	93	
60–69	65	69		71	63	
≥70	65	69		72	62	
Anatomic neoplasm subdivision			0.00816			0.09388
Bilateral	181	210		188	203	
Left	50	27		37	40	
Right	35	29		40	24	
Unknown	15	15		16	14	
Clinical stage			0.541			0.09709
Stage I	10	5		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			0.7102			0.3208
Grade 1/2	36	39		33	42	
Grade 3/4	240	234		240	234	
Unknown	5	8		8	5	
Venous invasion			0.6312			0.6249
No	32	38		31	39	
Yes	43	43		34	52	
Unknown	206	200		216	190	
Lymphatic invasion			0.5701			0.5689
No	36	43		39	40	
Yes	67	66		59	74	
Unknown	178	172		183	167	
Tumor residual disease			0.5594			0.04907
No macroscopic disease	61	54		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*			*HLA-DOB*		
	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*			*HLA-DOB*		
	P	Se	HR (95% CI)	P	Se	HR (95% CI)
PI3/HLA-DOB						
Low		Reference			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)						
<50		Reference			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						
Bilateral		Reference			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						
Stage I		Reference			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*		
	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						
Grade1/2		Reference			Reference	
Grade3/4	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		Reference			Reference	
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		Reference			Reference	
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		Reference			Reference	
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.

Table 3 Genes most significantly related with *PI3* or *HLA-DOB*

Order	*PI3*			*HLA-DOB*		
	Gene	P	r	Gene	P	r
1	*SOD2*	2.03e-34	0.484	*TAP1*	1.66e-54	0.592
2	*SLPI*	2.34e-33	0.478	*PSMB9*	4.07e-51	0.577
3	*CXCL8*	3.01e-30	0.456	*PSMB8*	1.88e-49	0.569
4	*CXCL1*	3.35e-30	0.456	*BTN3A3*	9.86e-46	0.550
5	*S100A8*	6.72e-27	0.432	*CYCSP5*	3.39e-45	0.547
6	*CCL20*	4.76e-26	0.425	*HLA-DMA*	1.33e-44	0.544
7	*S100A9*	8.97e-26	0.423	*CXCL11*	5.26e-41	0.524
8	*LCN2*	2.21e-23	0.403	*HLA-F*	3.93e-40	0.519
9	*C1S*	6.51e-22	0.390	*APOL3*	1.71e-39	0.516
10	*ICAM1*	1.24e-20	0.379	*HLA-E*	2.82e-38	0.508
11	*PTX3*	4.06e-20	0.374	*HLA-DMB*	6.13e-38	0.506
12	*RARRES1*	3.77e-19	0.365	*UBD*	1.12e-37	0.505
13	*NFKBIA*	4.42e-19	0.364	*HLA-DRB1*	4.59e-37	0.501
14	*PDZK1IP1*	5.30e-19	0.364	*IRF1*	1.46e-36	0.498
15	*PLAUR*	4.53e-18	0.354	*CD38*	7.09e-35	0.487
16	*CXCL5*	2.19e-17	0.347	*HLA-DPB1*	7.95e-35	0.487
17	*HP*	1.04e-16	0.340	*HLA-DRA*	8.00e-35	0.487
18	*CFB*	1.36e-16	0.339	*CD74*	1.25e-34	0.486
19	*BCL2A1*	1.85e-16	0.338	*TMEM140*	6.62e-34	0.481
20	*TNFAIP6*	1.08e-15	0.329	*HLA-DPA1*	8.97e-34	0.480

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

Coexpression and enrichment analyses

A coexpression analysis was performed to explore the potential mechanisms of *PI3* and *HLA-DOB* in ovarian cancer prognosis. The 20 genes that most significantly correlated with ovarian cancer prognosis are listed in *Table 3*, where *SOD2* (superoxide dismutase 2) (with *PI3*) and *TAP1* (transporter 1, ATP binding cassette subfamily B member) (with *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*.

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.

PI3, which encodes an elastase-specific inhibitor,

Table 4 Biological pathway analysis of genes co-expressing with *PI3* or *HLA-DOB*

Biological pathway	No. of genes	Fold enrichment	P value (BH corrected)
Immune system	79	5.460688	1.15e-32
Cytokine Signaling in Immune system	44	8.226512	6.66e-25
Interferon signaling	33	12.1512	2.11e-24
Interferon alpha/beta signaling	27	12.65382	2.37e-20
Interferon gamma signaling	18	13.8219	5.08e-14
Epithelial-to-mesenchymal transition	28	5.46213	6.95e-11
Integrin family cell surface interactions	86	2.25677	1.67e-10
Innate Immune system	26	5.127547	1.66e-09
TRAIL signaling pathway	81	2.205787	2.17e-09

Table 5 Transcription factor analysis of genes co-expressing with *PI3* or *HLA-DOB*

Transcription factor	No. of genes	Fold enrichment	P value (BH corrected)
IRF1	71	3.158911	1.16e-15
SPI1	52	2.305161	2.03e-06
NFIC	83	1.468055	0.010919
ELF1	31	1.912417	0.010919
FOS	72	1.48117	0.010919
FOSB	72	1.48117	0.010919
JUN	72	1.48117	0.010919
JUNB	72	1.48117	0.010919
JUND	72	1.48117	0.010919

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 esophagus 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* (AFKB 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), *NFKBIA* (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.

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