Original Article

# A novel lactylation-related gene signature for effectively distinguishing and predicting the prognosis of ovarian cancer

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**Background:** Lactylation has been found to regulate several types of biological processes in cancer. However, there is limited research on lactylation-related genes in predicting the prognosis of ovarian cancer (OC). This study aimed to explore the functional roles of lactylation-related genes in OC.

**Methods:** Based on TCGA database, we obtained RNA sequencing data and clinical characteristics of patients with OC. Fourteen lactylation-related genes were screened for bioinformatic analysis in OC. Tumor classification of OC was constructed via a consistency cluster analysis. We examined the prognosis, immune-cell infiltration, and immunotherapy in relation to a lactylation-related model for OC.

**Results:** A total of 707 prognostic genes and 14 key lactylation-related genes (*SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *AHNAK*, *MAGOHB*, *CALM1*, *EP300*, *HDAC1*, *HDAC2*, *HDAC3*, *SIRT1*, *SIRT2*, and *SIRT3*) were identified in TCGA-OC patients. Based on 14 genes involved in lactylation, TCGA-OC patients were split into low-risk (G1) and high-risk (G2) groups. Downregulated differentially expressed genes (DEGs) in the low-risk G1 group were associated with thermogenesis, oxidative phosphorylation, neutrophil extracellular trap formation, and interleukin 17 (IL-17) signaling pathway, whereas upregulated DEGs were associated with proteoglycans in cancer, focal adhesion, Wnt signaling pathway, extracellular matrix (ECM)-receptor interaction, and the adherens junction. The immune activity of the low-risk G1 group was lower than that of the high-risk G2 group. Gemcitabine, bleomycin, and doxorubicin had lower half-maximal inhibitory concentration ($IC_{50}$) values in the high-risk G2 patients with OC, while cisplatin and paclitaxel had higher $IC_{50}$ values compared to the low-risk G1 patients. The prognosis of patients with OC was also predicted with the help of an eight-lactylation-related gene prognostic model, comprising *SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *HDAC1*, *CALM1*, *HDAC2*, and *SIRT2*.

**Conclusions:** The lactylation-related genes are closely related to tumor classification and immunity in patients with OC. There was good prognostic predictive performance for OC based on a lactylation-related signature. Our findings may offer new insights into the diagnosis and treatment of OC.

**Keywords:** Ovarian cancer (OC); lactylation; prognostic model; lactylation-related gene signature; biomarkers

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## Introduction

Ovarian cancer (OC) is one of the most common malignant tumors of the female reproductive system, with its incidence being only second to that of cervical and uterine body cancer (1). Since effective screening tools are lacking and early diagnosis is difficult, 80% of patients with OC are already at an advanced stage when they are diagnosed (2,3). It is estimated that 50–70% of patients with OC will relapse within 2 years of treatment, and only 30% will survive 5 years after treatment (1-3). At present, the treatment of OC mainly includes surgical treatment and platinum-based chemotherapy. Although treatment has improved recently, the 5-year survival rates have only slightly increased (3). It is essential to identify new therapeutic targets for OC given the limitations of existing treatments, and thus there is an urgent need to develop reliable new prognostic models to make targeted therapy more feasible.

Lactic acid, which is a metabolic waste product of glycolysis, has been long overlooked as a purportedly poor prognostic marker in relation to tumor occurrence and development (4-7). There is growing evidence however that lactic acid plays a crucial role in tumor growth, immune escape, invasion, and metastasis, as well as metabolic regulation (5-7). Lactic acid, for example, is secreted by cancer cells and promotes cancer growth (5). Lactate efflux through proton-coupled pathways can influence tumor growth by regulating the tumor microenvironment (8). The presence of extracellular acidosis impairs T-cell-mediated immunity, while the neutralization of tumor acidity may improve immunotherapy's antitumor effects (9). Lactate metabolism-related genes (LRGs) in OC, however, remain unexplored bioinformatically.

### Highlight box

**Key findings**

- Subtypes of ovarian cancer (OC) were associated with 14 key lactylation-related genes, and an 8-lactylation-related gene prognostic model predicted the prognosis of patients with OC.

**What is known and what is new?**

- Key lactylation-related genes are critical in the emergence of OC.
- We identified the lactylation-related subtypes of OC and the lactylation-related biomarkers.

**What is the implication, and what should change now?**

- Lactylation-related biomarkers are strongly associated with the prognosis of patients with OC.

It is generally accepted that lactic acid plays a critical role in tumor development and antitumor processes. Despite this, little is known about its specific function in OC. As a result, we conducted a systematic study to determine LRG expression levels in OC, investigated the correlation between lactate and the tumor immune microenvironment, and determined its prognostic value. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-319/rc).

## Methods

### *Data acquisition from The Cancer Genome Atlas (TCGA)-OC cohort*

We downloaded 376 messenger RNA (mRNA) transcriptome profiles and the corresponding clinical data of TCGA-OC patients from TCGA database (https://portal.gdc.cancer.gov/repository). The filters used to select the samples as followed: a, primary site; b, Grade 3; c, stage of II–IV. TCGA data is downloaded from TCGA counts data, converted to TPM format based on the counts data, and then normalized to $\log_2$(TPM+1). There are a total of 332 LRGs listed in this study, as based on a published study (10). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Identification of prognostic LRGs in OC*

We performed a univariate Cox analysis to identify the prognostic genes with a P value of less than 0.05 in patients with OC. A Venn diagram was generated using the R package "venn" (v. 1.11; The R Foundation for Statistical Computing). The expression heatmap was then constructed with the R package "pheatmap" (v. 1.0.12). We conducted Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses with "clusterProfiler" package in R to identify signaling pathways of prognostic genes in OC. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) website and the "clusterProfiler" package were then used to construct a protein-protein interaction (PPI) network based on the PRGs in OC. The PPI network was visualized using Cytoscape. The R packages "corrplot" (v. 0.92) and "circlize" (v. 0.4.15) were used to analyze the correlation networks. The absolute value of the correlation coefficient represents different correlation strengths within different ranges: below 0.3, indicates no

correlation; 0.3 to 0.5, indicates low correlation; >0.5 to 0.9, indicates significant correlation; >0.9 to 1.0, indicates extremely high correlation.

### *Identification of lactylation-related tumor subtypes in OC*

The relationship between LRGs and OC subtypes was investigated. Consistent cluster analysis was conducted using the "ConsensusClusterPlus" package (version 1.54.0) on TCGA-OC cohort. Clustering variable (k) was set between 2 and 6. The "Pheatmap" (version 1.0.12) package was used to generate the heatmap. Based on Kaplan-Meier analysis, we compared the survival times among the different subgroups.

### *Identification of lactylation-related differentially expressed genes (DEGs) in OC*

The "DEseq2" package in R was used to identify the DEGs between OC clusters. The cutoff criteria included a P value <0.05 and $|\log_2$ fold change$|$ >0.75. In addition, the DEGs were visualized using the "ggplot2" R package. Based on the R package "pheatmap" (version 1.0.12), the DEG heatmap was created. The "clusterProfiler" package was then used to conduct Gene Ontology (GO) and KEGG analyses.

### *The immune activity of two lactylation-related clusters in OC*

"Immunoeconomics" was used to examine the immune activity of LRGs. The immune activity of two clusters related to lactylation was compared using eight immune checkpoint genes: *CD274*, *PDCD1*, *PDCD1LG2*, *CTLA4*, *LAG3*, *HAVCR2*, *TIGIT*, and *SIGLEC15*. We used the R packages "pheatmap" and "ggplot2" to generate the heatmap and box plot, respectively. We compared the degree of immune-cell infiltration and activated immune pathways between the two groups via the Wilcoxon test. Statistical significance was set as a P<0.05. The data is sourced from TIMER's website (https://cistrome.shinyapps.io/timer/), which uses deconvolution algorithms to infer the abundance of tumor infiltrating immune cells (TIICs) from gene expression profiles.

### *Two lactylation-related clusters of drug susceptibility*

The pRRophetic algorithm was used to assess the drug sensitivity between two lactylation-related clusters in OC. Pharmacogenomics databases (https://www.cancerrxgene.org/) were used to evaluate each patient's chemotherapy response. Predictions were made using the R package "pRRophetic". An estimation of the $IC_{50}$ was completed using the ridge regression method. Statistical significance was set at a P value of ≤0.05.

### *The development of a prognostic model based on LRGs*

With the "glmnet" R package, Cox regression analysis was also applied to assess the prognostic value of the LRGs in the TCGA-OC cohort. Based on the minimum criteria, the λ condition was determined for variables with nonzero coefficients. The risk score was calculated using the following formula: risk score = sum (expression level of each gene × corresponding coefficient). On the basis of median risk scores, TCGA-OC patients were divided into low- and high-risk subgroups. Using the R package "survival", we compared OS times among the different subgroups. Cox proportional hazard was conducted to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

### *Statistical analysis*

Perform statistical analysis using R language (version 3.6.3). Survival analysis was used to determine independent prognostic factors for HCC, with a significance level of P<0.05. Bilateral P values <0.05 are considered statistically significant.

## Results

### *Identification of key LRGs in OC*

Univariate Cox analysis was conducted to identify the prognostic genes in TCGA-OCC patients and to clarify their roles. This analysis yielded 707 prognostic genes for OC (*Figure 1A* and Table S1). The prognostic LRGs were screened out using a Venn diagram (*Figure 1A* and Table S1). We eventually identified eight lactylation-related prognostic genes: *SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *AHNAK*, *MAGOHB*, *HDAC1*, and *CALM1* (*Figure 1A* and Table S1).

A study indicated lactase and delactylases to be the most important regulatory genes (10), one lactase and six delactylases were included as key LRGs: *EP300*, *HDAC1*, *HDAC2*, *HDAC3*, *SIRT1*, *SIRT2*, and *SIRT3*. Finally, we identified 14 key LRGs *SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *AHNAK*, *MAGOHB*, *CALM1*, *EP300*, *HDAC1*,

 

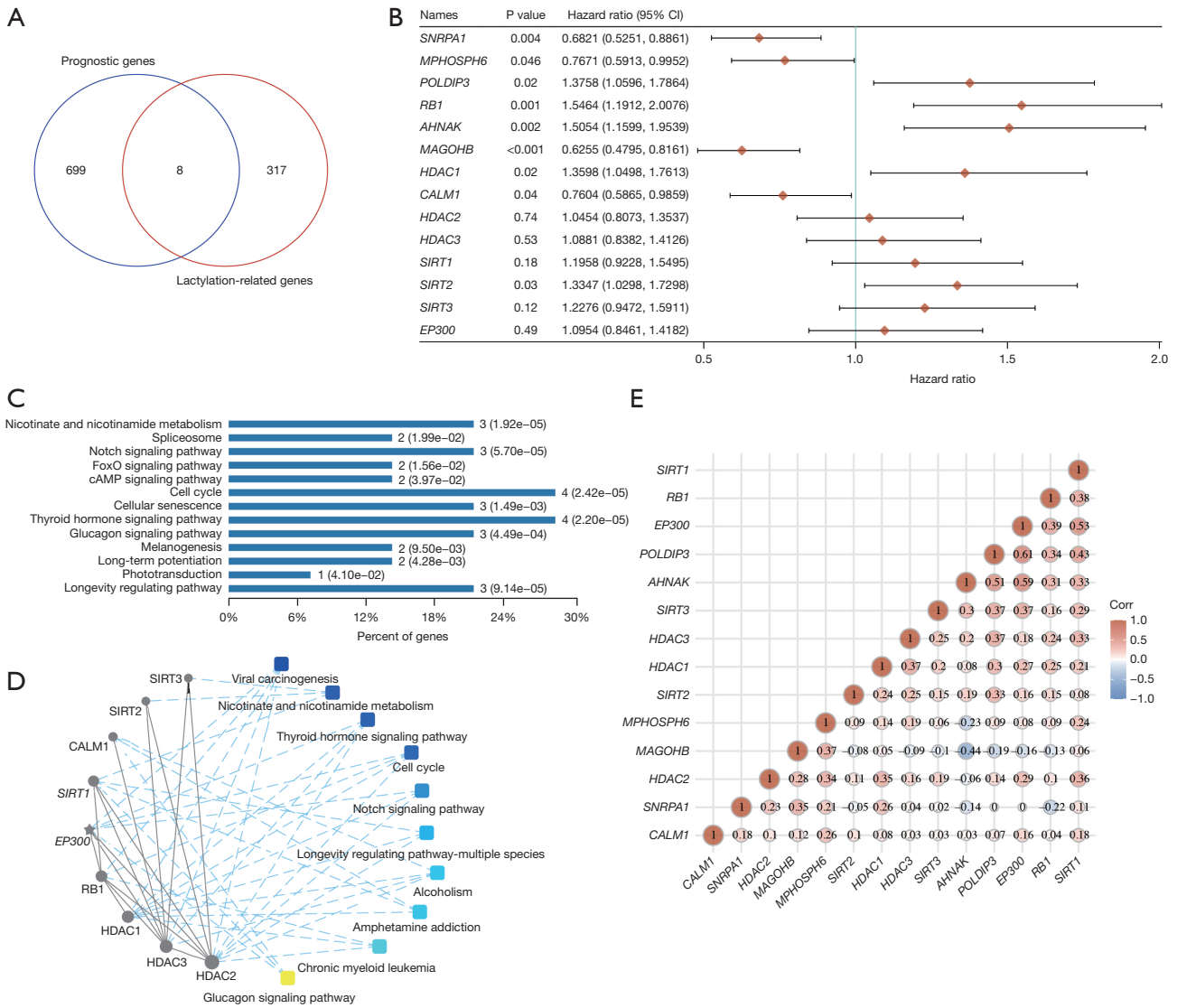


**Figure 1** Identification of key lactylation-related genes in OC. (A) The prognostic lactylation-related genes were screened out using a Venn diagram. Univariate Cox analysis identified 707 prognostic genes, and 325 lactylation-related genes are listed in this study; (B) fourteen key lactylation-related genes were identified; (C) KEGG enrichment analysis of 14 key lactylation-related genes in OC; (D) PPI networks of 14 key lactylation-related genes in OC; (E) the gene correlation analysis of key lactylation-related genes. CI, confidence interval; corr, correlation; OC, ovarian cancer; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction.

*HDAC2*, *HDAC3*, *SIRT1*, *SIRT2*, and *SIRT3* (*Figure 1B*). KEGG enrichment indicated that these pathways may play a crucial role in OC via nicotinate and nicotinamide metabolism, spliceosome, thyroid hormone signaling pathway, cell cycle, and glucagon signaling pathway (*Figure 1C*). Additionally, these pathways were confirmed to be associated with these genes through PPI network analysis (*Figure 1D*).

The results of the gene correlation analysis are summarized in *Figure 1E*. At the transcriptome level, the follow genes exhibited strong positive correlations: *EP300*, *POLDIP3*, *SIRT1*, and *AHNAK*; *POLDIP3* and *AHNAK*; and *HDAC1* and *HDAC3* (*Figure 1E* and Table S1).

### *OC subtypes based on the LRGs*

Despite lactylation's close association with tumor development (4-6), the role of LRGs in OC remains to be investigated in detail. Via consensus clustering analysis,

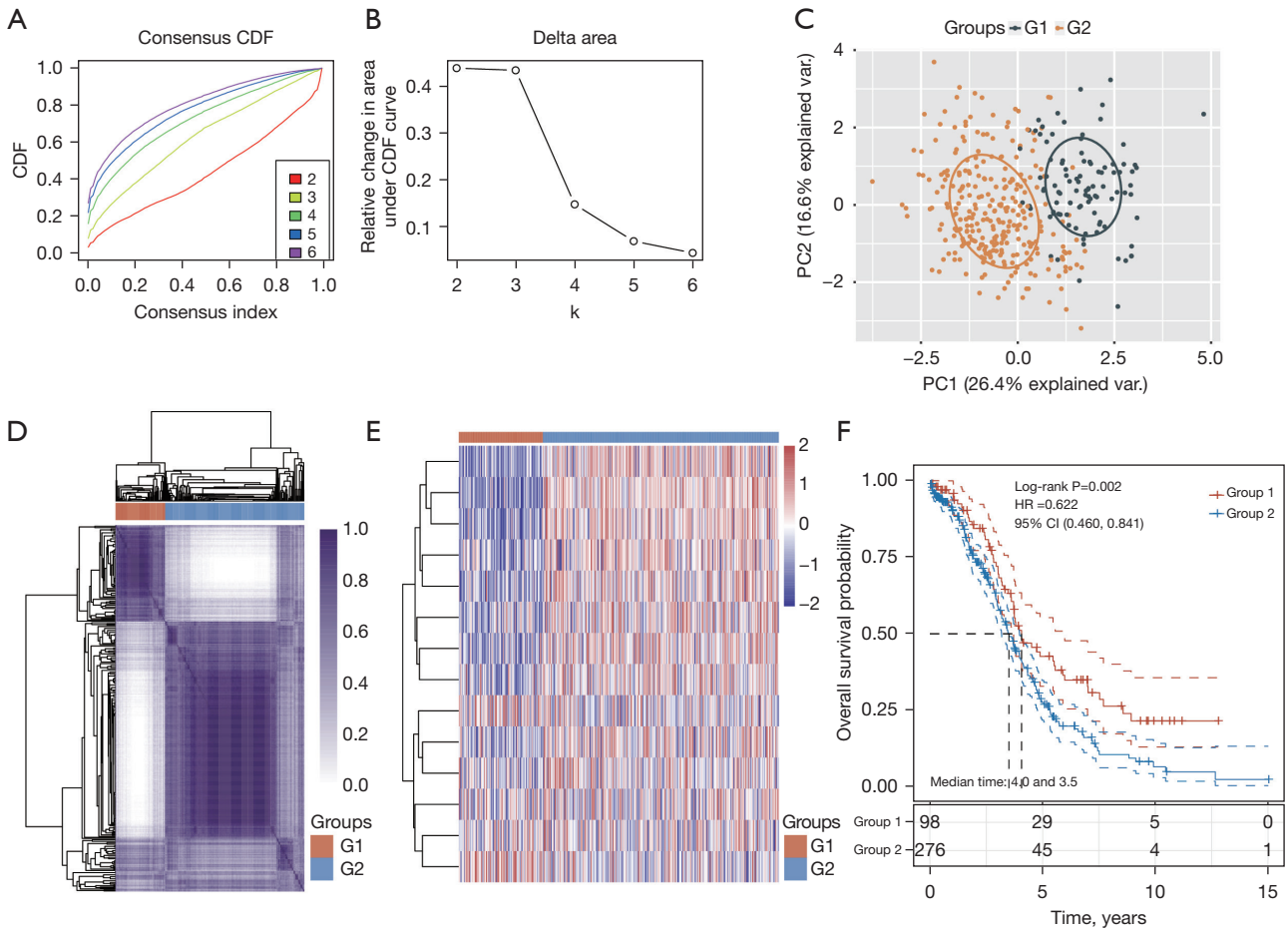


**Figure 2** OC Subtypes based on the lactylation-related genes. (A) CDF plot for k=2 to 6; (B) AUC changes; (C) principal component analysis of the two groups; (D) consensus clustering matrix of the two groups in OC; a value close to 1 indicates that the two samples are consistently assigned to the same cluster in most or all clustering processes, indicating that the clustering result is highly consistent and reliable. A value close to 0 indicates that the two samples are rarely or never assigned to the same cluster, indicating that they belong to different groups. (E) Heatmap of the two groups in OC. In different subgroups, the heat maps of gene expression are shown. Red represents high expression, and blue represents low expression; (F) Kaplan-Meier OS curves for the two groups. CDF, cumulative distribution function; PC, principal component; G1, Group 1 (low-risk); G2, Group 2 (high-risk); HR, hazard ratio; CI, confidence interval; OC, ovarian cancer; AUC, area under the curve; OS, overall survival.

we stratified TCGA-OC patients into different subtypes based on the 14 LRGs (*Figure 2A-2C* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-1.xlsx). A consistency cluster and principal component analysis (PCA) showed that TCGA-OC patients were well stratified into two clusters when clustering variable (k) was 2 (*Figure 2A-2D* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-1.xlsx). Similar results have also been obtained in other study (7). A heatmap of LRGs in TCGA-OC patients showed good separation between the two groups (*Figure 2E*). We hope to monitor patients for a longer survival time. Overall survival was statistically significantly longer in the low-risk group 1 than in high-risk group 2 (HR: 0.622, 95% CI: 0.460–0.841; P=0.002; *Figure 2F* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-1.xlsx).

### *Identification of underlying mechanisms between the two OC groups*

A volcano plot was used to identify 3918 DEGs between the G1 and G2 groups to (P value <0.05; $|\log_2$ fold change$|$ >0.5850; *Figure 3A* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-2.xlsx). The DEGs

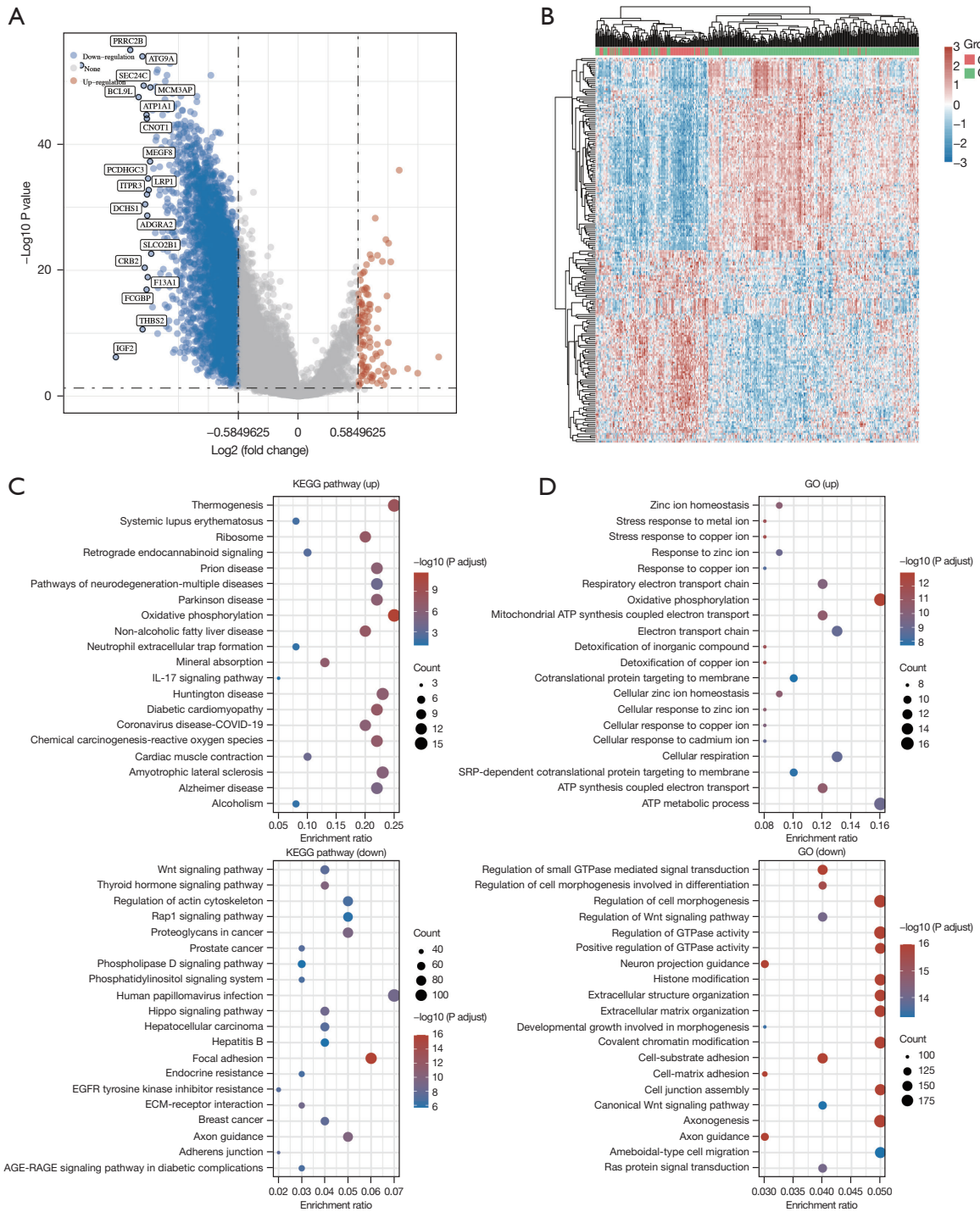


**Figure 3** Identification of underlying mechanisms between the two OC groups. (A) Volcano plots of DEGs in the G1 OC samples compared to G2 samples. Red indicates an upregulated gene, while blue indicates a downregulated gene; (B) Heatmap of DEGs in the two groups in OC; in different subgroups, the heat maps of gene expression are shown. Red represents high expression, and blue represents low expression. (C) KEGG pathways enriched for upregulated and downregulated DEGs; (D) the enriched biological processes for upregulated and downregulated DEGs. G1, Group 1 (low-risk); G2, Group 2 (high-risk); KEGG, Kyoto Encyclopedia of Genes and Genomes; IL-17, interleukin 17; EGFR, epidermal growth factor receptor; ECM, extracellular matrix; AGE-RAGE, advanced glycation end product-the receptor of advanced glycation end products; GO, Gene Ontology; ATP, adenosine triphosphate; SRP, signal-recognition particle; OC, ovarian cancer; DEGs, differentially expressed genes.

included 104 upregulated and 3,814 downregulated genes in G1 compared with G2. There was a difference in the expression of the top 50 DEGs between the two groups visualized in the heatmap (*Figure 3B* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-2.xlsx).

KEGG and GO enrichment analyses were conducted to clarify the biological roles of the 3,918 DEGs. In the KEGG analysis, 104 upregulated genes were found to be primarily involved in thermogenesis, oxidative phosphorylation, neutrophil extracellular trap formation, and IL-17 signaling pathway, while 3,814 downregulated genes were primarily involved in proteoglycans in cancer, focal adhesion, Wnt signaling pathway, ECM-receptor interaction, and the adherens junction (*Figure 3C* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-2.xlsx). According to the GO analysis of the biological process results, most of the upregulated genes were involved in oxidative phosphorylation, respiratory electron transport chain, adenosine triphosphate metabolic process, and response to zinc ion, while the downregulated genes were involved in ECM organization, regulation of GTPase activity, cell-substrate adhesion, and axonogenesis (*Figure 3D* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-2.xlsx). Studies have shown that proteoglycans in cancer, focal adhesion, ECM-receptor interaction, and adherens junction are tumor markers (10-12). According to the results above, G2 OC subtypes might be more capable of migrating and dividing than might be the G1 OC subtypes.

### *The immune activity of two lactylation-related groups in OC*

Research suggests there to be a close relationship between lactylation and immune activity in many cancers (13,14). We compared the immunity between two lactylation-related clusters of patients with OC. The resulting box plots revealed a clear difference in immune cells, with the abundance of $CD4^+$ T cells and endothelial cells being lower in the G1 than in the G2 OC samples (*Figure 4A* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-3.xlsx). Moreover, the box plots indicated that the expressions six of the eight immune checkpoint inhibitor (ICI) related genes (i.e., *CD274*, *HAVCR2*, *PDCD1LG2*, and *SIGLEC15*) were lower in the G1 OC samples compared to the G2 samples (*Figure 4B* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-3.xlsx). The findings suggested that lactylation is closely related to immune activity.

### *A comparison of the drug susceptibilities of the two OC groups*

The two OC groups were then tested using the pRRophetic algorithms for drug sensitivity. The drug sensitivity analysis in one cluster of OC was conducted using gemcitabine, bleomycin, doxorubicin, cisplatin, and paclitaxel.

Gemcitabine, bleomycin, and doxorubicin had lower $IC_{50}$ values in the high-risk G2 patients compared to the low-risk G1 patients (*Figure 5A-5C* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-4.xlsx). Compared to the G1 patients with OC, the G2 patients had higher $IC_{50}$ values for cisplatin and paclitaxel (*Figure 5D*,*5E* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-4.xlsx). Based on these results, the chemotherapy drugs gemcitabine, bleomycin, and doxorubicin might be more effective for low-risk G1 patients, while cisplatin and paclitaxel might be more effective for high-risk G2 patients. The results further suggested that lactylation-related classification might be a useful predictor of chemotherapy response.

### *The development of a prognostic model based on LRGs*

The 14 LRGs in OC were further selected via least absolute shrinkage and selection operator (LASSO) and Cox regression analyses (*Figure 6A* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-5.xlsx). We developed an eight-gene signature using the optimal λ value (*Figure 6B* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-5.xlsx). The risk score was calculated as follows: Risk score = *SNRPA1* expression × (–0.1835) + MPHOSPH6 expression × (–0.1804) + *POLDIP3* expression × 0.0807 + *RB1* expression × 0.1033 + *HDAC1* expression ×0.1565 + *CALM1* expression × (–0.1174) + *HDAC2* expression×0.0651 + *SIRT2* expression × 0.1234.

A low-risk and a high-risk group were established for TCGA-OC patients based on this gene signature (*Figure 6C*). Patients with a low-risk score had a higher overall survival rate than did those with a high-risk score (HR: 1.934, 95% CI: 1.486–2.518; P=9.33e–07; *Figure 6D* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-5.xlsx). Prognostic models were tested using the area under the receiver operating characteristic (ROC) curve (AUC). The AUCs for 1, 3, and 5 years were 0.744, 0.649, and 0.649, respectively (*Figure 6E* and table available at

 

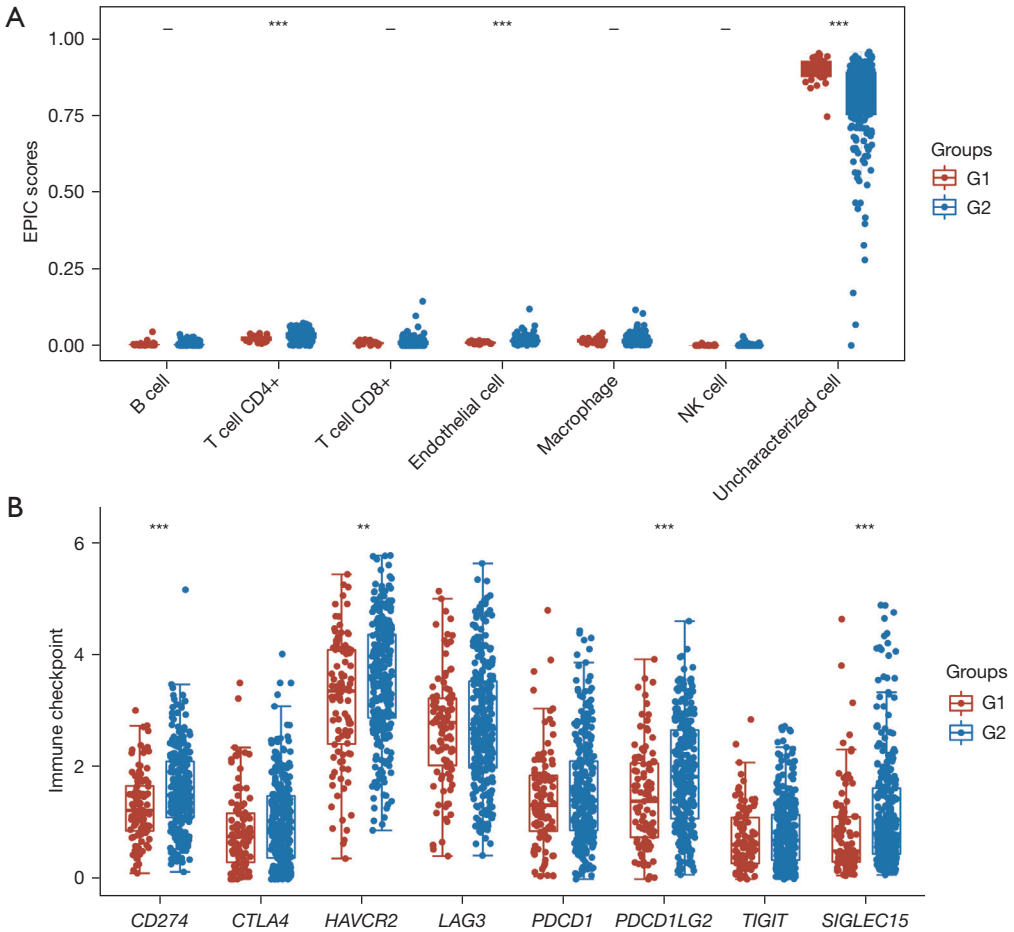


**Figure 4** The immune activity of the two lactylation-related groups in OC. (A) Comparison of the enrichment scores of seven types of immune cells between the two lactylation-related groups in OC; (B) comparison of the enrichment scores of the ICIs between the two lactylation-related groups in OC. -, P>0.01; **, P<0.01; ***, P<0.001. EPIC, estimating the proportions of immune and cancer cells; NK, natural killer; G1, Group 1 (low-risk); G2, Group 2 (high-risk); OC, ovarian cancer; ICIs, immune checkpoint inhibitors.

https://cdn.amegroups.cn/static/public/tcr-24-319-5.xlsx), indicating that this model was a good prognosticator.

### *A comparison of the tumor stemness of the two OC groups*

There is a low survival rate after immune checkpoint blockade (ICB) treatment when the tumor immune dysfunction and exclusion (TIDE) score is high. TIDE scores of G2 TCGA-OCC patients were higher than those of G1 patients, suggesting an inadequate response to ICB therapy and a poor prognosis (*Figure 7A* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-6.xlsx).

Cancer stem cells (CSCs) play an important role in tumor development, relapse, metastasis, and chemotherapy resistance. A significant difference was observed between G2 and G1 TCGA-OC patients in terms of CSC scores (*Figure 7B* and table available at https://cdn.amegroups.cn/static/public/tcr-24-319-6.xlsx). According to these results, lactylation-related classification might be a good indicator of ICB therapy response.

## Discussion

A total of 707 prognostic genes and 14 key LRGs (*SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *AHNAK*, *MAGOHB*, *CALM1*, *EP300*, *HDAC1*, *HDAC2*, *HDAC3*, *SIRT1*, *SIRT2*, and *SIRT3*) were identified in TCGA-OC patients. Based on the 14 genes involved in lactylation, TCGA-OC patients were divided into low-risk and high-risk groups. Downregulated DEGs in the low-risk G1 group were

 

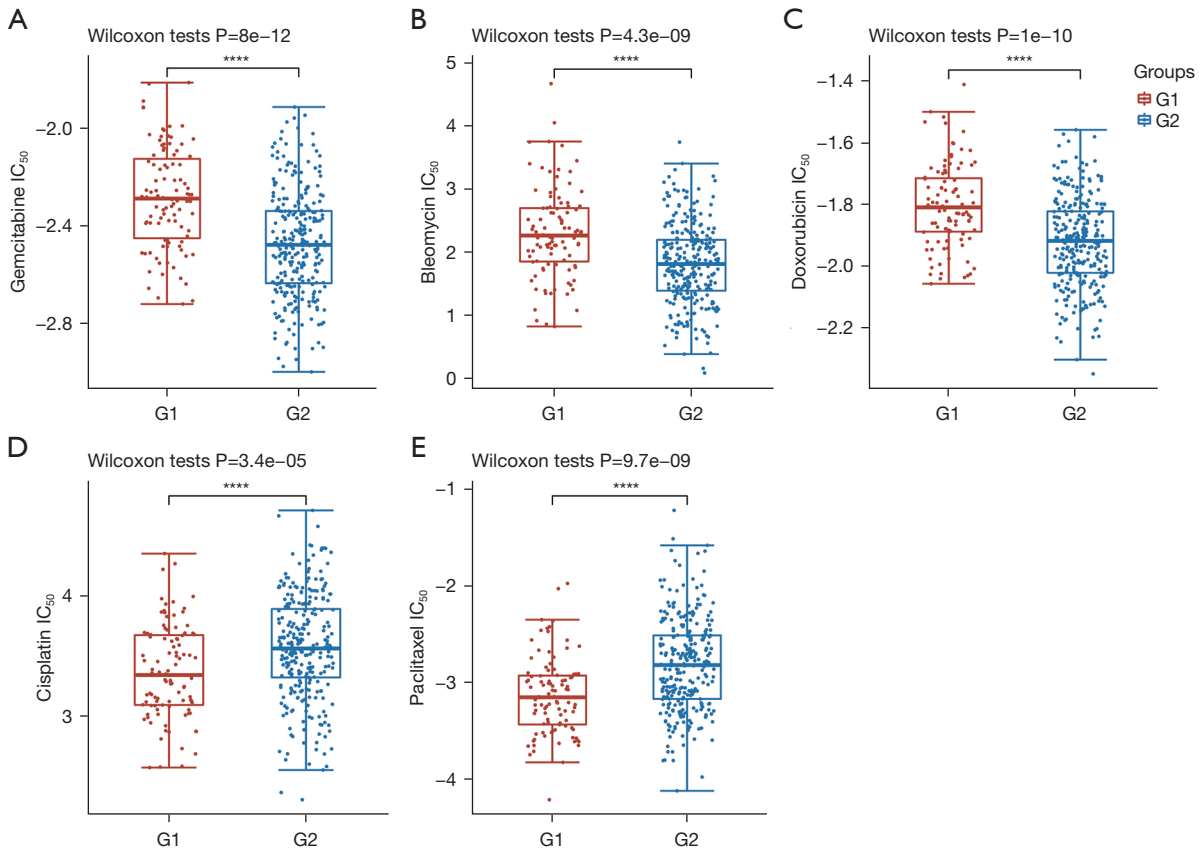


**Figure 5** A comparison of the drug susceptibilities of the two OC groups. $IC_{50}$ values of gemcitabine (A), bleomycin (B), doxorubicin (C), cisplatin (D), and paclitaxel (E) in the two OC groups. ****, P<0.0001. $IC_{50}$, 50% inhibitory concentration; G1, Group 1 (low-risk); G2, Group 2 (high-risk); OC, ovarian cancer.

associated with thermogenesis, oxidative phosphorylation, neutrophil extracellular trap formation, and IL-17 signaling pathway, whereas upregulated DEGs were associated with proteoglycans in cancer, focal adhesion, Wnt signaling pathway, ECM-receptor interaction, and adherens junction. The immune activity of the low-risk G1 group was lower than that of high-risk G2 group; and gemcitabine, bleomycin, and doxorubicin had lower $IC_{50}$ values in the high-risk G2 OC patients, while cisplatin and paclitaxel had higher $IC_{50}$ values in the low-risk G1 patients. The prognosis of patients with OC was also predicted with the help of an eight-gene prognostic model that included *SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *HDAC1*, *CALM1*, *HDAC2*, and *SIRT2*.

According to a series of studies, lactylate plays a significant role in inflammation, fibrosis, and oncogenic processes (5,6). For example, lactylate accumulates in the periphery of tumor tissues, causing vascular endothelial growth factor (VEGF) to be released, promoting angiogenesis and boosting cancer cell motility (5). Extracellular acidosis impairs T-cell-mediated immunity, and neutralizing tumor acidity may increase immunotherapy's antitumor effectiveness (9). However, the relationship between lactylation and OC, remains largely unexplored.

LRGs were used to group divide TCGA-OC patients into two groups (high risk and low risk). The low-risk G2 subgroup had higher levels of immune activity than did the high-risk G1 subgroup. Compared to G1 OC patients, G2 OC patients had higher $IC_{50}$ values for vinorelbine, paclitaxel, and cisplatin. These results suggest that OC tumors can be classified into two subgroups based on LRGs.

The expression of LRGs had a positive correlation with prognosis in patients with OC, and a prognostic model consisting of eight LRGs (*SNRPA1*, *MPHOSPH6*, *POLDIP3*, *RB1*, *HDAC1*, *CALM1*, *HDAC2*, and *SIRT2*) was developed for patients with OC.

 

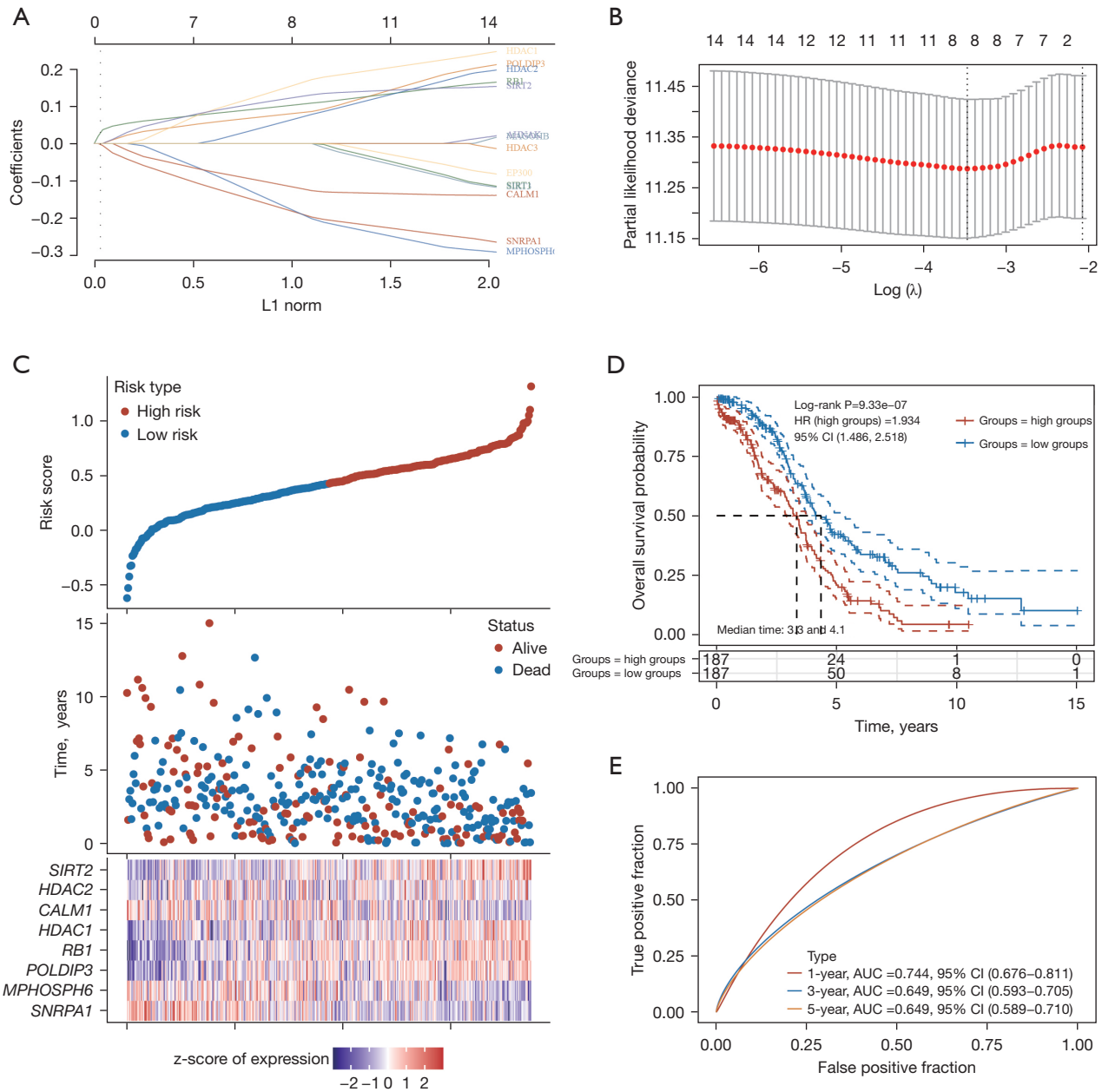


**Figure 6** The development of a prognostic model based on lactylation-related genes. (A) LASSO regression of lactylation-related genes in OC; (B) cross-validation of the LASSO regression; (C) a low-risk group and a high-risk group were established for TCGA-OC patients. The levels of lactylation-related genes in the high- and low-risk group are shown in red and blue, respectively; (D) survival analysis of the high-risk and low-risk groups in TCGA-OC patients; (E) AUC curves of the high-risk and low-risk groups in TCGA-OC patients. L1 norm, Manhattan-norm; HR, hazard ratio; CI, confidence interval; AUC, area under the curve; OC, ovarian cancer; LASSO, least absolute shrinkage and selection operator; TCGA, the Cancer Genome Atlas.

U1 small nuclear ribonucleoprotein A (*SNRPA1*) has been shown to abrogate RMRP regulation of p53 and tumor cell growth (15). M-phase phosphoprotein 6 (*MPHOSPH6*) has been reported to be associated with a risk of hepatocellular carcinoma (16). POLDIP3 protein (*POLDIP3*) has been found to promote the progression of hepatocellular

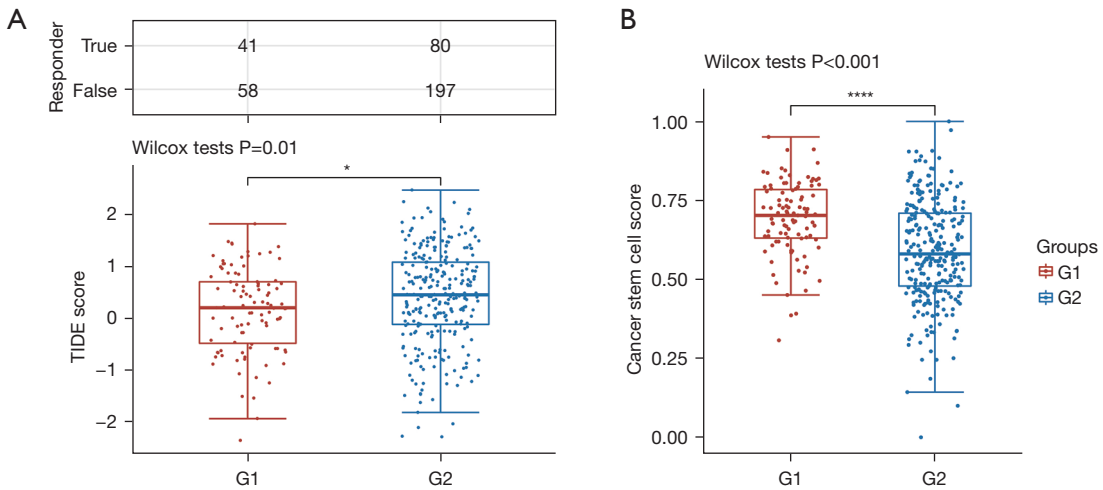


**Figure 7** Comparison of the tumor stemness between the OC groups. (A) TIDE scores and (B) cancer stem cell score of both OC groups. *, P<0.05; ****, P<0.0001. TIDE, tumor immune dysfunction and exclusion; G1, Group 1 (low-risk); G2, Group 2 (high-risk); OC, ovarian cancer.

carcinoma (17). Retinoblastoma-associated protein (*RB1*) was demonstrated to regulate cell cycle progression and the downstream cyclin-dependent kinase in cancers (18). In one study, silencing histone deacetylase 1 (*HDAC1*) enhanced the chemotherapy response for OC (19). Calmodulin-1 (*CALM1*) was shown to promote the progression and impaired chemosensitivity to epidermal growth factor receptor (EGFR) inhibitor in esophageal squamous cell carcinoma (20). Histone deacetylase 1 (*HDAC2*) is considered to be a target for anticancer drugs (21). Finally, NAD-dependent protein deacetylase sirtuin-2 (*SIRT2*) has been associated with high risk across numerous cancers (22).

Some limitations to this study should be mentioned. It is still necessary to confirm these findings *in vivo* and *in vitro* by examining these eight LRGs. Furthermore, future research should also consider the related molecular mechanisms.

## Conclusions

In conclusion, LRGs are closely related to tumor classification and immunity in patients with OC. The lactylation-related signature demonstrated good prognostic predictive performance for OC. These findings may offer new insights into the diagnosis and treatment of OC.

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## Footnote

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