The Pyroptosis-Related Signature Predicts Prognosis in Uterine Corpus Endometrial Carcinoma

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Research Article

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Abstract

Background: Uterine Corpus Endometrial Carcinoma (UCEC) is difficult to evaluate the prognosis. The prognostic evaluation model based on pyroptosis-related genes (PRGs) has shown good predictive power for prognosis in tumors, but there is no relevant research in UCEC.

Methods: Based on the gene expression data and clinical prognosis information of UCEC patients from TCGA database, PRGs related to the prognosis were screened out. Based on PRGs, a prognostic evaluation model related was established.

Comprehensive analysis of clinical characteristics and prognosis was performed. The potential molecular mechanisms of the prognostic evaluation model was explored by GSEA. The relationship between the prognostic evaluation model and the tumor immune microenvironment (TIME) was delved.

Results: 4 key PRGs related to the prognosis (NLRP2, GSDME, NOD2, GPX4) were identified. A prognostic evaluation model based on these 4 key PRGs was established: $\text{Riskscore} = (0.4323) * \text{GPX4} + (0.2385) * \text{GSDME} + (0.0525) * \text{NLRP2} + (-0.3299) * \text{NOD2}$. A higher risk score was an independent risk factor for the prognosis and closely related to clinical characteristics. The gene expression of the high-risk group was mainly enriched in immune response. The higher risk score was closely related to the degree of immune cell infiltration and the gene expression level of immune checkpoints. **Conclusion:** The prognostic evaluation model based on 4 key PRGs (NLRP2, GSDME, NOD2 and GPX4) has certain value for the prognosis evaluation and treatment selection of UCEC patients and may affect the prognosis by regulating the TIME.

Background

Uterine Corpus Endometrial Carcinoma (UCEC) is the second most common malignant tumor of the female reproductive system in China and is ranked first in developed countries^{1, 2}. In recent years, its incidence and mortality rates are continuously increasing and tend to be younger³. According to the National Cancer Center, in 2019, the incidence of UCEC in China was 10.28 per 100,000 with a mortality rate of 1.9 per 100,000. It is usually associated with genital bleeding, which leads to early diagnosis. However, about 30% of the patients are diagnosed at an advanced stage. Unfortunately, the patients with advanced, recurrent, or distant metastasis have a poor prognosis with a 5-year survival rate of less than 20%⁴. It is well-known that the personalized prognostic evaluation and reasonable adjuvant treatment options can be carried out based on the various clinical characteristics and genetic sequencing of the pathological samples from patients after malignant tumor resection, which is of great significance for the reduction of recurrence rate and improvement of prognosis. For UCEC, the construction of a risk model based on the clinical, pathological, and molecular characteristics of a patient, and then the formulation of an individualized prognostic evaluation and treatment plan for the patient based on the constructed risk model is a major project for the gynecological oncology clinicians.

As a form of programmed cell death, pyroptosis is inevitable in the cell cycle^{5, 6}. Its key components include inflammatory vesicles, gasdermin protein, and inflammatory cytokines. It was initially thought to be related to immune diseases⁷. However, in recent years, many studies have shown that pyroptosis is closely related to the occurrence and development of many diseases, especially cancer, which has increased researchers' interest in studying pyroptosis⁸⁻¹¹. Pyroptosis is a double-edged sword for cancer. It can not only inhibit the occurrence and progression of tumors but also provides nutrients and accelerates their growth¹². It has been well-demonstrated that pyroptosis can affect the proliferation, invasion, and metastasis of a variety of cancer cells, including kidney, colorectal, lung, and ovarian cancer cells, thereby leading to poor prognosis¹³⁻¹⁶. However, few studies have investigated pyroptosis and UCEC. The in-depth study of multiple omics and molecular mechanisms related to the pyroptosis in UCEC might provide a powerful weapon to overcome the diagnosis and treatment dilemma of UCEC and provide novel perspectives for its prognostic evaluation. It might also provide directions to develop targeted gene therapy and immunotherapy for the refractory, relapsed, and advanced UCEC patients.

Although studies on the causes and mechanisms of UCEC have made great advancements, the evaluation of its recurrence and prognosis is still elusive. The further understanding of the genome and functions of the pathogenic genes of UCEC has made it possible to combine the traditional pathological parameters with genome discovery and explore new risk models for the prediction of prognosis to make better treatment decisions. At the same time, the role of pyroptosis in UCEC remains to be explored. Based on the above reasons, a multi-level scientific analysis related to pyroptosis was conducted on a large sample of data from the UCEC patients, which was obtained from the TCGA database, and a prognosis evaluation model was established based on the clinicopathological characteristics and expression levels of specific gene related to pyroptosis, which might bring a qualitative leap for the prognostic evaluation and treatment options of UCEC patients.

Results

1. The expression and potential pathways of pyroptosis-related genes (PRGs).

First explored the expression levels of 33 PRGs in UCEC tissues and normal control tissues based on the TCGA database. As shown in Figure 2A, a total of 15 PRGs were up-regulated (AIM2, CASP3, CASP5, CASP8, GPX4, GSDMB, GSDMC, GSDMD, IL18, NLRP2, NLRP7, NOD2, PYCARD, TNF) and 12 PRGs were down-regulated (CASP9, ELANE, GSDME, IL6, NLRP1, NLRP3, NOD1, PJKV, PLCG1, PRKACA, SCAF11, TIRAP). Then, based on these 15 up-regulated PRGs and 12 down-regulated PRGs, GO analysis and KEGG analysis were performed to further explore the possible functions of these meaningful PRGs in UCEC. As shown in Figure 2B, the biological processes were mainly enriched in immune regulation and inflammation regulation, such as 'activation of innate immune response' and 'positive regulation of activated T cell'. At the same time, Figure 2C showed that cell signaling pathways were mainly enriched in

NOD-like, TNF, Toll-like and MAPK. The results of GO analysis and KEGG analysis will help future detailed research on these PRGs.

2. NLRP2, GSDME, NOD2 and GPX4 were key PRGs related to the prognosis of UCEC patients and were related to genetic mutations.

After exploring the differential expression levels and functions of 33 PRGs genes, an attempt was made to screen out key PRGs related to the prognosis of UCEC patients. The univariate COX analysis in Figure 3A showed that NLRP2, GSDME, NOD2, and GPX4 were the prognostic factors of UCEC patients. The Kaplan-Meier survival analysis in Figure 3B-E also showed that these 4 key PRGs have an impact on the survival of UCEC. The combination of univariate COX analysis and Kaplan-Meier survival analysis showed that the high expression of NLRP2 and GSDME were risk factors for the survival and prognosis of UCEC, while the high expression of NOD2 and GPX4 were the protective factors for the survival and prognosis of UCEC. Afterwards, the genetic mutations of these 4 key PRGs were explored. Figure 4A-B showed that NOD2 ($P=0.04$) and GPX4 ($P=6.18e-05$) were significantly correlated with MSI, while GPX4 ($P=1.42e-16$) and GADME ($P=0.01$) were significantly correlated with TMB. Interestingly, it can be seen that GPX4 had a significant positive correlation with MSI and TMB. Then Figure 4C showed the genetic mutation spectrum of these 4 key PRGs in UCEC. Figure 4D indicated that the prognosis of altered group of the 4 key PRGs was worse for UCEC patients ($P=0.0319$). In general, these four key PRGs were closely related to genetic mutations and may affect the survival prognosis of UCEC patients through this reason.

After that, the 4 key PRGs and multiple key clinical characteristics were combined to conduct univariate and multivariate COX analysis. The results were shown in Figure 4F-G. Only NOD2 was meaningful in univariate and multivariate COX analysis, while most of the other factors were only meaningful in univariate COX analysis. This also suggested that when the variables involved were too many and too complex, univariate and multivariate COX analysis were too simple to be used for prognostic evaluation of UCEC, therefore a more complex and effective prognostic evaluation model was inevitably needed.

3. The prognostic evaluation model based on 4 key PRGs has important evaluation value for the prognosis of UCEC patients.

The gene expression levels of 4 key PRGs and the survival prognosis of UCEC patients were included in the Lasso Cox regression analysis, and the risk score calculation formula was obtained: $\text{Riskscore} = (0.4323) * \text{GPX4} + (0.2385) * \text{GSDME} + (0.0525) * \text{NLRP2} + (-0.3299) * \text{NOD2}$, as shown in Figure 5A. At the same time, the upper part of Figure 5B showed the distribution of the risk scores of 542 UCEC patients in the TCGA database. The median value of the risk score is -4. According to this median value, UCEC

patients are divided into high-risk group/low-risk group. The middle part of Figure 5B showed the survival status of UCEC patients. The lower part of Figure 5B showed the expression of 4 key PRGs in UCEC patients, and it can be seen that there are obvious differences in their expression between the two groups. And Figure 5C-D was the verification of Lasso Cox regression analysis results.

Figure 6A showed the distribution and differences of gene expression and clinical characteristics of the high-risk group/low-risk group. It can be seen that the FIGO stage was different in the two groups. Figure 6B-I also showed that there were significant differences in the risk scores of the two clinical characteristics of Molecular infiltration ($P=0.01$) and Hypertension ($P=0.02$). For FIGO stage, both stage III ($P=1.9e-05$) and stage IV ($P=7.0e-03$) have higher risk scores than stage II.

Figure 7A showed that the survival of the high-risk group was significantly worse than that of the low-risk group ($P=6.45e-05$). Figure 7B showed that the prognostic assessment model has a certain diagnostic value for predicting the 5-year survival probability of UCEC patients ($AUC=0.711$). Figure 7C-D showed that the high-risk group, age and FIGO stage were all independent risk factors for the prognosis of UCEC patients ($p < 0.05$, $HR > 1$). Figure 7E showed that when the prognostic assessment model, age, FIGO stage, pathological grade, Fertility, and Molecular infiltration were included in the AUC curve, the prognostic assessment model still has a certain diagnostic value for predicting the 5-year survival probability of UCEC patients ($AUC=0.69$). The DCA curve in Figure 7E showed that the prognostic evaluation model has a certain predictive evaluation value for the prognosis of UCEC patients. Finally, the nomogram in Figure 8A showed how the prognostic assessment model combined with clinical characteristics can be used to predict the survival of UCEC patients after surgery. This also improves the clinical translation value of this research. In general, the prognostic evaluation model based on 4 key PRGs has important evaluation value for the prognosis of UCEC patients.

4. Enriched signaling pathways in the high-risk group of the prognostic evaluation model.

Figure 9 indicated that the gene expression of the high-risk group was mainly enriched in endometrial cancer, JAK STAT, natural killer cell-mediated cytotoxicity, T cell receptors, cancer pathways, MAPK, B cell receptors and chemokine signaling pathway. This showed that the prognostic evaluation model was closely related to the molecular pathological mechanism of UCEC and was inseparable from the regulation of the immune microenvironment of UCEC.

The determination of the signal pathways related to the prognostic evaluation model on the one hand supported the scientific nature of the model, and on the other hand, it also provided a direction for the discussion of the detailed molecular mechanism of the model.

5. The relationship between the prognostic assessment model and the immune microenvironment.

Figure 2B-C indicated that PRGs were closely related to immune regulation, and Figure 9 also indicated that the prognostic evaluation model based on 4 key PRGs was closely related to the tumor immune microenvironment, so we try to explore the relationship between the prognostic evaluation model and the immune microenvironment. For the aspect of immune infiltration, Figure 10B indicated that based on the EPIC algorithm, the degree of immune cell infiltration (CD8+ T cells, CD4+ T cells, macrophages, and NK cells) in the high-risk group was lower than that in the low-risk group, and the correlation analysis also suggested that there were significant negative correlations between the risk score and the degree of immune cell infiltration. Similar results can be obtained in Figure S1 and Figure S2. As for immune checkpoints, Figure S3 indicated that the expression of LAG3, SIGLEC15, and CD274 in the high-risk group was significantly increased compared with the low-risk group. On the other hand, the expressions of CTLA4, PDCD1LG2, and PDCD1 in the high-risk group were significantly reduced.

In short, the prognostic evaluation model was closely related to the immune microenvironment, and it may be used to predict the degree of immune infiltration and the expression of immune checkpoints in UCEC patients, and to better develop individualized immunotherapy programs for patients to improve the prognosis.

Discussion

The evaluation of UCEC prognosis is still elusive¹⁷. Pyroptosis has been demonstrated to play a key role in tumorigenesis and prognosis in a variety of human malignant cancers, including lung cancer, liver cancer, colorectal cancer, cervical cancer, and leukemia¹⁸⁻²¹. Pyroptosis can be combined with immunotherapy to improve the prognosis²². Therefore, a prognostic evaluation model was established in this study based on the specific genes related to pyroptosis and clinicopathological characteristics in order to improve the accuracy of the prognostic evaluation model and treatment selection of UCEC patients.

Figure 1 presents the general flow of this study to facilitate readers. Figure 2 shows a total of 15 up-regulated and 12 down-regulated pyroptosis-related genes in the UCEC patients. The main functions of these 27 PRGs were enriched in immune regulation and inflammation regulation. In addition, the main enriched signaling pathways included NOD-like, toll-like, MAPK, and TNF signaling pathways. Many studies have shown that all these enriched signaling pathways play a key role in the development of UCEC and regulation of the tumor immune microenvironment²³⁻²⁶. This indicated that these PRGs in UCEC might participate in the occurrence of tumors by regulating their immune microenvironment. In Figure 3A-3E, a total of 4 key PRGs, including *NLRP2*, *GSDME*, *NOD2*, and *GPX4*, were screened, which had an impact on the prognosis of UCEC. *NLRP2* gene is useful in predicting the survival rate among patients with head and neck squamous cell carcinoma²⁷. As an important gene for the execution of cell death, the

expression of the *GSDME* gene is closely related to the prognosis after chemotherapy²⁸. *NOD2* enhances sensitivity to chemotherapy in hepatocellular carcinoma by targeting the AMPK pathway and inhibiting tumors²⁹. *GPX4* might induce apoptosis in drug-resistant cells by regulating the mitochondrial mediator apoptosis of breast cancer cells through *EGR1*, thereby affecting their drug resistance^{30, 31}. On the other hand, UCEC is rich in mutations, which has a strong correlation with TMB and MSI³². Studies have shown that the genetics of 20% of the UCEC have alterations in the MSI³³. In addition, studies have also shown that the TMB is related to the overall survival rate and degree of immune infiltration among UCEC patients³⁴. Therefore, the correlation of the 4 key PRGs with TMB, MSI, and mutation status was further studied. Figure 4 suggested that the *GPX4* was significantly positively correlated with the TMB and MSI. The prognosis of an altered group of the 4 key PRGs was worse for the UCEC patients. In short, these previous studies all corroborate the prognostic evaluation of the 4 key PRGs, which are explored in this study. However, Figures 3F and 3G show that when the included parameters were too many and complicated, a more complicated and scientific prognostic evaluation model was needed for the prediction of prognosis.

The accuracy of the prognostic evaluation model for the patients with malignant tumors based on routine clinical characteristics, such as age and pathological grade, is needed to be improved. The establishment of a prognostic evaluation model, involving gene expression levels and clinical characteristics, is a promising and valuable research direction³⁵⁻³⁸. For UCEC, studies have shown that the prognostic evaluation models based on metabolism-related, immune-related, and variable splicing-related genes can be used to predict the prognosis of UCEC³⁹⁻⁴². The prognostic evaluation models based on PRGs have been used to predict the prognosis of postoperative patients with head and neck squamous cell carcinoma, lung adenocarcinoma, gastric cancer, and melanoma, thereby demonstrating their clinical value⁴³⁻⁴⁶. On the other hand, the prognostic evaluation model based on the PRGs in UCEC has not been studied yet. Therefore, the first prognostic evaluation model was established for UCEC based on the PRGs in this study. As shown in Figure 5, the aim of this model based on the four key PRGs was to calculate the risk score, which is provided in Eq. (1). The median reference value of the risk score was -4, based on which, the UCEC patients were divided into the high-risk and low-risk groups. Figure 6 shows that the risk score was closely related to the important clinical characteristics, such as FIGO stage, molecular infiltration, and hypertension; the importance of these clinical characteristics to the prognosis of UCEC was self-evident^{17, 47, 48}. Figure 7 shows that the value of this prognostic evaluation model for the prognosis of UCEC was accurate. The nomogram was a more intuitive and easier method to understand and operate for the prognostic evaluation of cancer patients and has been reported in various cancers, especially UCEC^{17, 47, 48}. Figure 8 shows an attempt based on this. The nomogram, involving the PRGs-based prognostic evaluation model, was established in this study and the common clinical characteristics were used to evaluate and predict the prognosis of UCEC patients in clinical work, which greatly improved the clinical translational value of this study.

After confirming the clinical significance of the prognostic evaluation model based on PRGs, the molecular mechanism of this model, involving gene regulation, was explored. The GSEA analysis in

Figure 9 shows that this prognostic evaluation model might be closely related to the regulation of the tumor immune microenvironment. The disorder of the tumor immune microenvironment plays an irreplaceable role in the occurrence and development of tumors⁴⁹⁻⁵¹. This not only corroborates the scientific nature of this study but also provides directions for deeper studies. Therefore, the correlation between the prognostic evaluation model based on PRGs and the tumor immune microenvironment was explored. Figure 10 suggests that the risk score of this model was significantly negatively correlated with the degree of the infiltration of immune cells (CD8+ T cells, CD4+ T cells, macrophages, and NK cells). Studies have the association of a high degree of CD8+ T cell infiltration with a good prognosis in a variety of human tumors⁵². Moreover, a meta-analysis of the UCEC suggested that the infiltration of immune cells, such as CD8+ T cells, could lead to a better prognosis of UCEC⁵³. Studies have also reported that the CD4+ T cells were an independent protective factor for the prognosis of UCEC⁵⁴. There is another study that is worthy of reference. A meta-analysis, involving 53 related studies and covering a period of 1989-2020, showed that the NK cells could improve the prognosis of a variety of solid tumors⁵⁵. These studies suggested that the risk score, as the core of the prognostic evaluation model proposed in this study, was closely related to the degree of immune cells infiltration, where a high-risk score was likely to indicate a bad prognosis for the UCEC patients. The immune checkpoints, as another important factor in the immune microenvironment, were then studied. They have been extensively studied in recent years and the therapies based on the immune checkpoint inhibitors have shown good prospects⁵⁶⁻⁵⁸. Figure S3 indicates that the risk score has a complex but close relationship with a variety of immune checkpoints. This complex relationship is worthy to be investigated further and perhaps can be combined with immunotherapy for the development of more precise treatment plans to improve the prognosis of UCEC.

This study comprehensively studied the influence of PRGs on the prognosis of UCEC for the first time and proposed a prognostic evaluation model. The calculation of the risk score evaluated the prognosis of UCEC patients more intuitive and accurate. However, this study still has certain shortcomings, which are needed to be improved. For example, this study only included the data of 542 UCEC patients taken from the TCGA database. If the data from multiple centers and larger sample sizes are included, the study results will become more universal and valuable. Although this study also proposed a deeper study direction that might be the tumor immune microenvironment, the specifics still need to be verified via experiments. In short, the advantages and disadvantages of this study coexist, but it has still certain scientific value.

Conclusions

In general, the prognostic evaluation model based on the 4 key PRGs proposed in this study has a good predictive potential for the prognosis of UCEC. This model is closely related to the tumor immune microenvironment, which might help in the choice of immunotherapy and the establishment of future study direction.

Methods

1. Clinical information and gene expression profiles of the patients.

The data of 542 UCEC samples and 35 normal control samples, including various clinical characteristics, survival data, and gene expression profiles, were obtained from the TCGA database (<https://portal.gdc.ancer.gov/>). Then, the clinical baseline data of UCEC patients were summarized and listed in Table S1. These basic data were used for the subsequent screening of key pyroptosis-related genes (PRGs), comprehensive prognostic analysis of key PRGs, mutation-related analysis, construction and verification of prognostic evaluation models, Gene Set Enrichment Analysis(GSEA), etc.

2. Screening and prognostic evaluation of 4 key PRGs.

First, a total of 33 PRGs were obtained from the published pyroptosis-related review articles. Then, the expression levels of these 33 PRGs in UCEC and normal tissues adjacent to cancer were analyzed. The Gene Ontology(GO) and Kyoto Encyclopedia of Genes and Genomes(KEGG) analyses of the 33 PRGs were also performed with statistical differences to explore the cell signaling pathways related to pyroptosis in UCEC and establish future research directions, The results are presented in Figure 2. Then, the impact of these PRGs on the prognosis of UCEC patients was analyzed, which resulted in 4 key PRGs. Then, survival and single multivariate analyses were performed on the key PRGs, respectively, and presented in Figure 3. Spearman's method was used to analyze the correlation among 4 key PRGs, and microsatellite instability (MSI), and tumor mutation burden (TMB) in UCEC. The genetic alterations in the 4 key PRGs and their influence on the prognosis were discussed. The results are shown in Figure 4.

3. Establishment of the prognostic evaluation model based on 4 key PRGs and verification of its clinical significance.

After screening the 4 key PRGs and identifying their significance for prognostic evaluation, a prognostic evaluation model was established based on the expression levels of the 4 key PRGs using Lasso Cox regression analysis. The prognostic evaluation model aimed to establish a correlation for the calculation of risk score, which is given in Eq; Risk score = $(0.4323) * GPX4 + (0.2385) * GSDME + (0.0525) * NLRP2 + (-0.3299) * NOD2(1)$

Then, the distribution of risk score, survival status, and expression levels of the 4 key PRGs was recorded for UCEC patients, which are presented in Figure 5. The correlation between the key clinicopathological characteristics and risk score was explored and shown in Figure 6. The patients were divided into high-risk and low-risk groups based on the median value of the risk scores of 542 UCEC patients. Survival analysis, ROC curve, DCA curve, and univariate and multivariate Cox regression analysis were performed on these groups. The results are shown in Figure 7. Finally, in order to use this prognostic evaluation model for clinical transformation, it was combined with clinicopathological characteristics in the form of

a nomogram and used in clinical work to evaluate the prognosis of postoperative UCEC patients. The results are shown in Figure 8.

4. Gene function enrichment analysis of the prognostic evaluation model.

After evaluating the clinical significance of this prognostic evaluation model, the molecular pathways and mechanisms, in which it might participate, were explored. GSEA, developed by a group of researchers from the Massachusetts Institute of Technology and the Broad Institute of Harvard University, is an ideal tool for analyzing the enrichment of cell signaling pathways. The gene expression data of the two groups (high-risk/low-risk groups) of UCEC patients were analyzed by GSEA. GSEA software (V4.0.3) was used for the enrichment analysis. The number of permutations was set to 1000 and the genome database was set to KEGG. The gene sets with $|NES| > 1$, NOM P -value < 0.05 and FDR q -value < 0.25 were considered significantly enriched. The relevant results are shown in Figure 9.

5. Relationship between the prognostic evaluation model and immune microenvironment.

The previous GSEA analysis showed that the major enriched cell signaling pathways of gene expression in the high-risk group of the prognostic evaluation model included T cell receptor, B cell receptor, and natural killer (NK) cell-mediated cytotoxicity. These cells signaling pathways suggested that the prognostic evaluation model might be related to the immune microenvironment. Therefore, the relationship between risk score and the degree of immune cell infiltration was analyzed using four different immune algorithms: EPIC, TIMER, quanTIseq, and MCPcounter, which are now mainstream. The results are shown in Figure 10 and Supplementary Figures S1 and S2. In addition, the immune checkpoints were the other important parts of the immune microenvironment of malignant tumors. Therefore, the correlations between the risk score and gene expression levels of several mainstream immune checkpoints were also analyzed. The results are shown in Figure S3.

6. Statistical analysis

All the statistical analyses were carried out using R software (v4.0.2). Mann-Whitney test was used to analyze the differences in gene expression levels between the UCEC and normal tissues. The survival analysis using the Kaplan-Meier method, ROC curve, and univariate and multivariate Cox regression models were used to analyze the impact on prognosis. Spearman's correlation method was used for all the correlation analyses. Lasso Cox regression analysis was used to construct the prognostic evaluation model. Mann-Whitney test was used to analyze the differences in risk scores among the different clinical

characteristics of UCEC patients. This test was also used to analyze the differences in the degree of cells infiltration between the high-risk or low-risk group and gene expression level of immune checkpoints.

Abbreviations

pyroptosis-related genes (PRGs)

tumor immune microenvironment (TIME)

Uterine Corpus Endometrial Carcinoma (UCEC)

Gene Set Enrichment Analysis (GSEA)

Kyoto Encyclopedia of Genes and Genomes (KEGG)

Gene Ontology (GO)

Gene Expression Omnibus (GEO)

The Cancer Genome Atlas (TCGA)

Tumor immune estimation resource (TIMER)

Tumor mutational load (TMB)

Microsatellite instability (MSI)

Declarations

Ethics approval and Consent to participate

The study protocol was approved by The Ethics Committee of the Harbin Medical University Cancer Hospital (Harbin, China). The use of patient samples conformed to the declaration of Helsinki. All patients provided informed written consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. The data can be obtained through the email under reasonable request: 1427@hrbmu.edu.cn.

Conflicts of interest

There are no conflicts to declare.

Author Contributions

Haodi Yue designed this study and supervised the research. Mengjun Zhang performed analyzed data, wrote the manuscript. Siyu Hou performed the analysis. Jialin Wang assisted the statistical and bioinformatics analysis. Haodi Yue and Mengjun Zhang revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Schematic diagram of the study.

Figure 2

Expression and functional enrichment analysis of 33 PRGs in UCEC and control group. (A) Expression heat map and box scatter plot of 33 PRGs in UCEC patients (N = 552) and control adjacent normal group (N = 35) from the TCGA database. *P < 0.001, **P < 0.01, *P < 0.05. (B) Enrichment status of 33 PRGs analyzed by GO analysis. BP, biological process; CC, cell composition; MF; molecular function. (C) Enrichment pathway of Kyoto Encyclopedia of Gene and Genome analysis. The size of the inverted triangle represents the number of abundant genes. The parameters were set to P adjust < 0.05 and FDR q-value < 0.25. FDR: false discovery rate.

Figure 3

Comprehensive prognostic analysis of the total 33 PRGs and 4 key PRGs in UCEC. (A) Univariate cox regression analysis of OS for each PRG. The 4 key PRGs, including NLRP2, GSDME, NOD2, and GPX4, were statistically significant with $P < 0.05$. (B-E) Kaplan-Meier survival analysis plot, showing the influence of the expression levels of NLRP2, GSDME, NOD2, and GPX4 on the survival prognosis. (F-G) Forest plot for the univariate and multivariate Cox regression analysis results of the expression levels of NLRP2, GSDME, NOD2, GPX4, and multiple key clinical features. Clinical characteristics included age, race, TNM stage, histological grade, and recurrence. $P < 0.05$ was considered statistically significant.

Figure 4

Correlation between the expression levels of 4 key PRGs and gene mutations in the UCEC patients. (A) Correlation between the 4 key PRGs in UCEC and MSI. (B) Correlation between the 4 key PRGs in UCEC and TMB. (A-B) Horizontal and vertical axes in the figure represent the distributions of gene expression and TMB/MSI scores, respectively; the right and upper density curves represent the trends of TMB/MSI score distribution and gene expression distribution, respectively; and the top value represents the relevant

P-value, correlation coefficient, and correlation calculation method. (C) Gene mutation profile of the 4 key PRGs based on cBioPortal database. (D) Kaplan-Meier survival analysis chart based on the cBioPortal database, showing the difference in survival prognosis between the mutant and non-mutated groups.

Figure 5

Prognostic evaluation model for the UCEC patients based on the expression levels of 4 key PRGs calculated by Lasso regression analysis. (A) Equation for the calculation of risk score. The risk score was calculated based on the expression levels and correlation coefficients of the 4 key PRGs. (B) Distribution of the risk scores, survival status, and 4 key PRGs expression levels of UCEC patients. (C) Lasso coefficient distribution of 4 key PRGs. (D) Plots for the ten-fold cross-validation error rates of the prognostic evaluation model.

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Figure 6

Correlation analysis between the 4 key PRGs-based prognosis model and clinical characteristics of UCEC patients. (A) Heat map of the clinical characteristics and expression levels of 4 key PRGs in the high-risk and the low-risk groups. ***($P < 0.001$), **($P < 0.01$), and *($P < 0.05$). (B-I) Violin plots, showing the difference in risk scores among the different groups of various clinical characteristics. (B) Age, (C) Pathological type, (D) Muscular infiltration, (E) Hypertension, (F) Fertility, (G) FIGO staging, (H) Histological grade, and (I) Menopausal status. $P < 0.05$ indicates that the difference was statistically significant.

Figure 7

Prognostic evaluation of UCEC patients based on the 4 key PRGs. (A) Overall survival curve of UCEC patients in the high-risk and low-risk groups. (B) ROC curves of the 1-year, 3-year, and 5-year survival rates of UCEC patients in the two groups. (C-D) Univariate and multivariate Cox regression analysis of the prognostic risk model and 5 clinical characteristics. (E) ROC curve of the prognostic risk model and 5

clinical characteristics. (F) DCA curve of the prognostic risk model and 5 clinical characteristics, showing the prognostic value of the 4 key PRGs-based prognosis model.

Figure 8

Construction of a nomogram for the prognostic prediction of UCEC patients. (A) First locate the 8 parameters of Age, Grade, Stage, Risk score, Risk, Fertility, Pathological type, and Muscular infiltration of UCEC patients on each horizontal axis, and then make a vertical line to intersect the 'Points' axis at each anchor point, convert to the corresponding Point, and then add up to get Total Points and converts to the corresponding Linear Predictor, which is finally used to predict the 1, 3, and 5-year survival probabilities of UCEC patients. (B) Dashed diagonal line represents the ideal nomogram.

A

Cell signaling pathway	NES	NOM p-val	FDR q-val
KEGG JAK STAT SIGNALING PATHWAY	1.7923073	0	0.018015567
KEGG NATURAL KILLER CELL MEDIATED CYTOTOXICI	1.7707984	0	0.018304495
KEGG T CELL RECEPTOR SIGNALING PATHWAY	1.667965	0	0.02909405
KEGG PATHWAYS IN CANCER	1.645926	0	0.02909947
KEGG MAPK SIGNALING PATHWAY	1.470396	0.003992016	0.06011599
KEGG B CELL RECEPTOR SIGNALING PATHWAY	1.5512539	0.006437768	0.043893833
KEGG ENDOMETRIAL CANCER	1.600988	0.01026694	0.035133008
KEGG CHEMOKINE SIGNALING PATHWAY	1.4202079	0.016494846	0.078059316

B

Figure 9

GSEA analysis based on the PRG prognostic model. (A) After UCEC patients in TCGA are divided into high-risk/low-risk groups according to the 4 key PRGs prognosis model, GSEA analysis is performed to obtain the pathways of gene expression profile enrichment of patients in the high-risk group. The corresponding result parameters are recorded. (B) Detailed map of the GSEA signaling pathway enrichment of the eight cell signaling pathways. NES, normalized enrichment score; NOM, nominal; FDR, false discovery rate. Gene sets with $|NES| > 1$, NOM P-value < 0.05 and FDR q-value < 0.25 were considered significantly enriched.

Image not available with this version

Figure 10

Correlation between the PRGs-based prognostic model and immune cell infiltration in the UCEC patients based on the EPIC database. (A) Heat map of the degree of immune cell infiltration in the high-risk and low-risk groups. (B) Scattered box plot of the degree of immune cell infiltration in the high-risk and low-risk groups. NS: no significant difference; *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

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