Identification of Model Based on Oxidative Stress-related Genes for Predicting Prognosis and Therapeutic Features in Bladder Cancer

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Abstract

Background: Bladder cancer is one of the most common malignant tumors, presenting as a heterogenous entity that requires a severe stratified strategy to enhance clinical decision-making and patient counseling. Multiple studies have investigated the relationship between oxidative stress and tumor progression, highlighting its potential role in cancer pathogenesis. Herein, our study aimed to establish a prognostic model based on the oxidative stress-related gene for risk stratification in bladder cancer.

Methods: Differentially expressed oxidative stress genes (oxidative stress DEGs) were identified using microarray and clinical data from the GEO database. Functional enrichment and survival analyses were performed in screened oxidative stress DEGs. A risk score model was constructed, and its diagnostic value and relationship with the prognosis as well as its sensitivity to chemotherapy and immunotherapy were verified through Cox regression, receiver operating characteristic curve and drug sensitivity analysis. The TCGA-BLCA cohort was set as the training cohort, GSE13507 and GSE32894 were used for external validation. A nomogram was constructed to facilitate the clinical application.

Results: The risk score model demonstrated a significant difference in overall survival between the high- and low-risk groups. The area under the curve and hazard ratio revealed the independent prognostic value of the model. There are differences in the sensitivity of chemotherapy and immunotherapy between the high- and low-risk groups.

Conclusions: Our findings provide a new prognostic model that can serve as a reliable reference for the prognosis and personalized therapy of patients with bladder cancer.

Introduction

Bladder cancer is the tenth most common and most frequent urinary tract malignancy worldwide. Overall, bladder cancer accounts for 3% of newly diagnosed cancer cases, with men being more affected than women. Specifically, bladder cancer accounts for 4.4% of newly diagnosed cancer cases and 2.9% of cancer deaths in men(1, 2). Depending on the level of tumor infiltration into the bladder wall, bladder cancer can be classified into non-muscle-invasive disease (Ta, T1, and Tis) and muscle-invasive disease (≥ T2 disease) subtypes(3). The treatment strategies for bladder cancer vary according to the subtype and the patient’s risk level. Based on NCCN guidelines, the non-muscular-invasive disease is usually managed through intravesical treatment or cystectomy for high-risk patients(4). In contrast, muscle-invasive bladder cancer typically requires neoadjuvant chemotherapy, radical cystectomy (RC), postoperative systemic chemotherapy, or second-line immunotherapy(5). Intravesical BCG therapy is commonly used to reduce the risk of recurrence and progression after transurethral resection of bladder tumor (TURBT) for intermediate and high-risk non-muscle-invasive disease(3, 6). However, approximately one-third of patients will progress to muscle-invasive stages, significantly decreasing cancer special survival (CSS)(7, 8). Ultimately, these patients require RC to remove the bladder, and approximately half of them relapse with distant metastases that negatively impact long-term survival(3, 9). Recurrence-free
survival (RFS) is dependent on the progression. In a surgery-only study, the 5-yr RFS decreases with the increase of the T stage \((10)\). Some studies have suggested that a delay of 3 months is associated with worse survival outcomes \((11)\). Therefore, the high-risk non-muscle-invasive disease patients’ outcomes will be significantly improved by undergoing RC early. However, it is difficult for physicians to provide personalized treatment and management strategies for patients based on current classification systems. For example, some patients who showed highly invasive biological characteristics and early metastasis were pathologically classified as low-risk classification \((6)\).

Oxidative stress refers to the state of imbalance between oxidants and antioxidants in which levels of reactive oxygen species (ROS) exceed the antioxidant defense mechanisms of the cell \((12)\). Previous studies have revealed increased ROS levels in malignancies and identified chronic oxidative stress as a driver of DNA damage, metabolic malformations, hypoxia, and proteotoxic stress \((13)\). ROS generation can be attributed to NADPH oxidase (NOX) activity. In bladder cancer, NOX-4 has been shown to be overexpressed in high-grade and invasive carcinomas but not found in low-grade and non-invasive ones \((14)\) in previous studies. Consistent with previous studies on different hallmarks of cancer, oxidative stress is broadly engaged in cancer biology, and it has been suggested that the progression of bladder cancer may be associated with lipid peroxidation (LPO) products resulting from oxidative stress \((15)\). LPO can increase arachidonic acid metabolism, producing malondialdehyde (MDA) due to elevated levels of cyclooxygenase-2 (COX-2) \((16)\). MDA levels can serve as a marker of oxidative stress, and Pande et al. demonstrated that MDA levels correlated with the clinical stage of breast cancer \((17)\). Higher T stages and high-grade patients were associated with significantly elevated levels of MDA \((18)\). Thus, oxidative stress-related genes may contribute to the progression of bladder cancer.

Advanced bladder cancer is a malignant disease with a poor prognosis and high mortality. Early identification of high-risk cases that may progress to muscle-invasive bladder cancer is crucial to the prognosis and management of these patients. Therefore, a stratified risk model based on oxidative stress-related genes can be a valuable tool for predicting patient survival and guiding therapeutic decision-making. In this study, we developed a predictive model using bioinformatics to identify the prognostic significance of oxidative stress-related genes in bladder cancer. Firstly, the list of oxidative stress-related genes (OSRGs) was downloaded from GeneCards (www.genecards.org). Then, differentially expressed genes (DEGs) related to oxidative stress were identified to construct the oxidative stress-related risk score model and nomogram. Finally, we evaluated the potential roles of the oxidative stress-related risk score model in the progression, prognosis, and personalized treatment of bladder cancer patients.

**Materials And Methods**

**Data Acquisition**

We retrieved the gene expression profiles and clinical data from a total of 408 bladder cancer patient samples as the derivation cohort from the TCGA public database (https://cancergenome.nih.gov/). The two independent testing cohorts, the GSE13507 and GSE32894, datasets were downloaded from GEO.
The Series Matrix File data of GSE13507 involves 165 cases of BLCA samples, and the Series Matrix File data of GSE32894 includes 224 bladder cancer patient samples. To identify oxidative stress-related genes, we obtained 2642 genes with a Relevance Score > 3 from GeneCards (https://www.genecards.org).

Identification of Differentially Expressed Oxidative Stress Gene (Oxidative Stress DEGs) and Functional Analysis

Data from 165 bladder cancer patients were downloaded from the official website of GEO (https://www.ncbi.nlm.nih.gov/geo/) database. Within these patients, 104 had Ta and T1 samples, while 61 had >T1 samples. We set the fold change > 1.5 and P-value < 0.05 as the inclusion criteria to determine oxidative stress DEGs. Next, we used the ClusterProfiler R package to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses based on the oxidative stress DEGs. GO and KEGG enrichment pathways with P and Q values less than 0.05 were considered significant categories.

Model Construction and Prognosis

The TCGA-BLCA cohort was set as the training cohort to analyze the oxidative stress DEGs using univariate COX regression analysis. A total of 72 prognostic candidates (p < 0.05) were identified from the analysis. Further filtering using the least absolute shrinkage and selection operator (LASSO) COX regression analysis identified 21 genes. To enhance the effectiveness and accuracy of prognostic prediction, we subjected the prognosis-related DEGs to further analysis by multivariate COX regression. This approach yielded a final set of 11 oxidative stress DEGs, and the oxidative stress risk score was calculated based on these optimal candidate DEGs.

\[
\text{Risk score} = \sum (\beta_i \times \text{Exp}_i)
\]

(i refers to the number of screened prognostic oxidative stress-related genes, \(\beta\) refers to the regression coefficient of the gene).

We calculated the risk score of each sample using the formula and determined the optimal cutpoint of risk score by the survminer R package. Based on the optimal cutpoints, patients were classified into high-risk and low-risk subgroups, and we conducted Kaplan–Meier analyses to compare survival differences between patients in the two subgroups. To evaluate the prognostic value of the risk model, we utilized the time-dependent receiver operating characteristic (ROC) curves and corresponding areas under the curve (AUC) values in both the training and testing cohorts. In addition, univariate and multivariate COX regression analyses were conducted to further validate the prognostic capability of the risk model. The nomogram and calibration plots were constructed based on the important clinicopathological characteristics and the risk scores to help visualize the clinical significance of the risk model.

Gene Set Enrichment Analysis
The Gene Set Enrichment Analysis software (version 4.3.2) was utilized to perform the functional enrichment analysis between the high-risk and low-risk subgroups. The dataset was set as ftp.broadinstitute.org://pub/gsea/msigdb/human/gene_sets/c5.go.bp.v2022.1.Hs.symbols.gmt and ftp.broadinstitute.org://pub/gsea/msigdb/human/gene_sets/c2.cp.kegg.v2022.1.Hs.symbols.gmt, and we used 1000 permutations for the analysis. The normalized enrichment score (NES) represented the degrees of over-expression of gene sets in the low-risk subgroups. The FDR q < 0.25 and nominal P-value < 0.05 were considered statistical differences.

Drug Sensitivity Analysis

We predicted the chemotherapy sensitivity of each sample using the pRRophetic R package and compared the IC50 value of each specific chemotherapeutic agent commonly used for bladder cancer between the high-risk and low-risk subgroups.

Risk Subgroup Predicted the Therapeutic Response of Immune Checkpoint Blockades (ICBs)

ICBs response scores of each sample were calculated using Tumor Immune Dysfunction and Exclusion (TIDE) (http://tide.dfci.harvard.edu/). Based on TCGA datasets, the limma, reshape2, ggplot2, and ggpubr R packages were used to analyze the correlation of the risk score with immune checkpoint expression and visualize the results.

Statistical Analysis

Several R packages, including limma, survival, survminer, glmnet, and timeROC, were employed to perform our data analysis. The empirical Bayesian approach of the limma R package was utilized to identify oxidative stress-related DEGs. Survival curves were generated by the Kaplan-Meier method and compared using the log-rank test. The R language (version 4.2.1) was used for all statistical studies. All statistical tests were bilateral, and we considered a p-value less than 0.05 as a statistically significant difference.

Results

Identification of Oxidative Stress Related DEGs between Muscle-Invasive Bladder Cancer and Non–Muscle-Invasive Bladder Cancer

The Series Matrix File data of GSE13507 involves 165 BLCA samples, including 104 non–muscle-invasive bladder cancer tissue samples and 61 muscle-invasive bladder cancer tissue samples. Using criteria of |fold change| ≥ 1.5 and P-value < 0.05, we compared the non–muscle-invasive bladder cancer tissue samples (Ta, T1) and muscle-invasive bladder cancer tissue samples (> T1) of the GSE13507 and found that 146 oxidative stress-related genes were upregulated and 38 genes were downregulated. The
expression of differentially oxidative stress-related genes was visualized via the heatmap and the volcano plots (Fig. 1, a, and b).

**Functional Enrichment Analysis Based on 184 DEGs**

In order to investigate the potential functions of DEGs, a total of 184 DEGs were subjected to the functional enrichment analysis. The top 30 most enriched GO and KEGG pathways are shown in bar charts (Fig. 1, c, and d). GO analysis results reveal that DEGs were mainly related to wound healing, response to oxidative stress, regulation of inflammatory response, response to oxygen levels, and response to reactive oxygen species. In addition, KEGG analysis results show that DEGs were mainly associated with the IL-17 and TNF signaling pathways.

**Prognostic Model Construction Based on the TCGA Training Set**

A total of 72 survival-related oxidative stress-related DEGs in bladder cancer patients were identified by univariate COX regression analysis based on 403 bladder cancer samples in the TCGA database, and results are shown in the forest plot. Of these, 55 genes with HRs > 1, indicating risk genes, while the remaining 17 genes had HRs < 1, suggesting protection genes (p < 0.05, as shown in Fig. 2a). Using the least absolute shrinkage and selection operator (LASSO) COX regression analyses with \( \lambda = 0.02774709 \), 21 genes were further identified (as seen in Fig. 2, b, and c). Ultimately, a prognostic risk model was constructed from the 11 selected oxidative stress-related DEGs using multivariate COX regression analysis. Additionally, *AKR1B1, CDK6, CYP1B1, EGR1, HSPB6, LDLR, MT1A, and PHGDH* were identified as risk genes. In contrast, *ALDH1A2, CARD11, and CTLA4* were identified as protection genes. The risk score formula was as follows:

\[
\text{Risk score} = (0.1653) \times \text{AKR1B1} + (-0.2276) \times \text{ALDH1A2} + (-0.1243) \\
- \times \text{CARD11} + (0.2525) \times \text{CDK6} + (-0.6258) \times \text{CTLA4} + (0.1737) \\
- \times \text{CYP1B1} + (0.1097) \times \text{EGR1} + (0.0666) \times \text{HSPB6} + (0.1844) \\
- \times \text{LDLR} + (0.1056) \times \text{MT1A} + (0.2065) \times \text{PHGDH}
\]

The patients in both the training and the testing cohorts were stratified into high-risk and low-risk subgroups by the optimal cutpoint of risk score. According to the risk plot distribution and survival status of included patients, patients in the high-risk subgroup had significantly higher mortality rates than those in the low-risk subgroup (Fig. 3, a-c). The heatmap of the included genes indicated that the expressions of *AKR1B1, CDK6, CYP1B1, EGR1, HSPB6, LDLR, MT1A, and PHGDH* were higher in the high-risk subgroup, while the expressions of *ALDH1A2, CARD11, and CTLA4* were lower in the high-risk subgroup (Fig. 3a).

Kaplan–Meier survival analyses showed that the patients in the high-risk subgroup had shorter survival time than those in the low-risk subgroup in both the training and testing cohorts (p < 0.001; Fig. 4, a-c).
The 1-, 2-, and 3-year AUC values of ROC curves for the prognostic risk model in the training cohort were 0.740, 0.735, and 0.758, respectively (as shown in Fig. 4d). For the testing cohort (GSE13507), the AUC values at 1, 2, and 3 years were 0.740, 0.603, and 0.591, respectively (Fig. 4e). Furthermore, the 1-, 2-, and 3-year AUC values of ROC curves for the prognostic risk model in the testing cohort (GSE32894) were 0.859, 0.881, and 0.853, respectively (Fig. 4f).

**Prognostic Model Associated with Overall Survival and Clinicopathology Characteristics**

The results of univariate and multivariate COX regression analysis revealed that the age, stage, and risk score were independent prognostic factors (p < 0.001, Fig. 5, a, and b). The heatmap was generated to evaluate the gene expression and clinical characteristics of patients in the low-risk and high-risk groups. The analysis results indicated that the difference in clinical characteristics between the low-risk and high-risk groups was statistically significant, with grade (p < 0.001) and stage (p < 0.01) being the most significant factors (Fig. 5e). However, according to the statistical principle, the small number of samples in stage I of the TCGA-BLCA cohort prevented a comparison with other stages. As a result, comparisons were limited to stages II, III, and IV, and the risk score was found to be significantly higher in patients with the higher stage and grade (Fig. 5, c, and d). A comprehensive nomogram was developed based on the age, stage, and risk score of the bladder cancer patients (Fig. 6a). The calibration curves indicated a significant consistency between nomogram predictions and actual observations (Fig. 6b). In addition, the 1-, 2-, and 3-year AUC values of ROC curves for the nomogram in the TCGA cohort were 0.794, 0.772, and 0.791, respectively (Fig. 6c).

In order to evaluate the predictive ability of the prognostic risk model for prognosis in multiple bladder cancer subtypes, stratification survival analysis was conducted based on age (< 60 years and ≥ 60 years), gender (Male and Female), and stage (Stage I ~ II and Stage III ~ IV). The Kaplan–Meier survival analyses showed that the high-risk patients had significantly shorter overall survival than the low-risk patients in all subtypes (p < 0.01; Supplementary Fig. 1, a-f). These findings suggest that the prognostic risk model has a reliable and independent predictive value for the prognosis of bladder cancer.

**Gene Enrichment Analysis Based on High- and Low-Risk Groups**

The GSEA analysis was used to compare gene expression between high- and low-risk groups. Our results indicated that the KEGG pathway enrichment revealed significant enrichment of cell cycle, WNT-signaling, oocyte meiosis, and focal adhesion in the high-risk group (Fig. 7, a-d). The GO BP pathway enrichment results indicated that cell growth, negative regulation of apoptotic signaling pathway, regulation of cellular response to growth factor stimulus, and negative regulation of oxidative stress-induced cell death were significantly upregulated in the high-risk group (Fig. 7, e-h).
Drug Sensitivity Analysis between High- and Low-Risk Groups

To further understand the chemotherapy sensitivity between high- and low-risk groups, we analyzed IC50, the most commonly used to assess chemotherapy sensitivity. Our finding showed a significant decrease in IC50 values in the high-risk groups when receiving Cisplatin treatment (p < 0.001, Fig. 8a). However, the IC50 of the high-risk group was higher than the low-risk group for Gefitinib and Methotrexate (p < 0.01, Fig. 8b and c).

The High-risk Group May Have a Weaker Response to Immunotherapy

According to the ICB response score (TIDE score), we examined the direct difference in the efficacy of immunotherapy in high- and low-risk groups. The results indicated that the high-risk subgroup had lower ICB response scores than the low-risk subgroup (p < 0.01, Fig. 9a). To further investigate the relationships between immune checkpoints and the risk score, we calculated the expression levels of 19 immune checkpoint genes, including CD274, CD200, CD27, CD276, CD40, CD40LG, CD44, CTLA4, LGALS9, NRP1, PDCD1, PDCD1LG2, TMIGD2, TNFRSF14, TNFRSF25, TNFSF15, TNFSF4, TNFSF9, and VTCN1. We observed that the expression levels of the CD200, CD274, CD276, CD44, NRP1, PDCD1LG2, TNFSF4, TNFSF9, and VTCN1 were higher in the high-risk group than in the low-risk group, while the expressions of CD27, CD40, CD40LG, CTLA4, LGALS9, PDCD1, TMIGD2, TNFRSF14, TNFRSF25, and TNFSF15 were lower in the high-risk group (All p < 0.05, Fig. 9b).

Discussion

In this study, we aimed to establish a prognostic model based on oxidative stress-related signatures, revealing the potential relationship between bladder cancer progression and oxidative stress reaction. Current classification systems make it difficult to provide patients with personalized treatment and management strategies. Therefore, a prognostic model that can predict the clinical outcomes and assist in the individualized treatment of bladder cancer patients is essential. The signature was built on the basis of 184 oxidative stress-related DEGs between non–muscle-invasive bladder cancer tissue samples (Ta, T1) and muscle-invasive bladder cancer tissue samples (> T1). However, the large number of genes included in the oxidative stress-related signature decreased the efficacy of the model's prediction. Therefore, we refined the signature using cross-validation methods (LASSO regression). The proposed prognostic model can classify patients into high- and low-risk subgroups, while significant differences are shown in survival time, chemotherapy sensitivity, and immunotherapy responsiveness.

Our prognostic model identified eleven genes, including AKR1B1, CDK6, CYP1B1, EGR1, HSPB6, LDLR, MT1A, and PHGDH, which acted as risk factors. In contrast, ALDH1A2, CARD11, and CTLA4 acted as protective factors. AKR1B1 is necessary for tumor growth(19) and was found to interact with signal
transducer and activator of transcription 3 (STAT3) (20), participating in anti-cell death processes and leading to drug resistance. Acting at the interface of p53 and RB, CDK6 contributes to tumor formation by driving cell-cycle progression and antagonizing stress responses (21). CYP1B1 upregulates in the advanced stages of bladder cancer and participates in the activation of procarcinogen (22, 23). EGR1 has been shown to regulate genes influencing proliferation, apoptosis, immune cell activation, and matrix degradation, among others (24). Metallothioneins (MTs) are small cysteine-rich proteins that play significant roles in tumor formation, progression, and drug resistance, with MT1A being one of the functional isoforms (25). PHGDH is amplified in the malignant tumor and is essential for nucleotide production and cell proliferation in highly aggressive brain metastatic cells (26). In addition, CTLA4 is implicated in cancer immunity and can be a useful prognostic biomarker in some cancer types (27).

The enrichment analysis results reveal that the high-risk group is associated with some biological processes and pathways that promote tumor progression. One representative pathway is the Wnt-signaling pathway, which is significantly enriched in the high-risk group. This pathway is frequently activated in solid tumors and aids in epithelial-mesenchymal transformation, tumor progression, and metastasis (28–30). Moreover, the high-risk group is also enriched in cell growth, negative regulation of apoptotic signaling pathway, regulation of cellular response to growth factor stimulus, and negative regulation of oxidative stress-induced cell death, explaining the high mortality rate of this group and providing a new direction for the mechanism of bladder cancer progression and treatment.

Research has shown that neoadjuvant and adjuvant chemotherapy treatments can help prolong the survival of bladder cancer patients (4, 31–33). EGFR plays a crucial role in the progression of bladder cancer, and Gefitinib can influence EGFR downstream signal transduction by inhibiting the phosphorylation of EGFR (34). Methotrexate can prevent the progression of tumor cells by blocking dihydrofolate reductase. For patients with locally very-advanced bladder tumors that are not amenable to surgical treatment, the application of cisplatin has been shown to improve their outcomes (5, 35). Additionally, the drug sensitivity analyses revealed that Gefitinib and Methotrexate could be more effective for the low-risk group, while the high-risk group was more sensitive to Cisplatin.

We also investigated the correlations between immune checkpoints and the risk score in our study. Immunotherapy has become a crucial treatment option for bladder cancer patients in recent years (36, 37). The differential expression of immune checkpoint genes across different subtypes can facilitate the development of personalized immunotherapy strategies. In order to forecast the response to the immune checkpoint-blocking therapy (ICB), we compared the TIDE score between the high-risk and the low-risk groups. A high TIDE score suggests the poor efficacy of the ICB. The comparison results indicate that the patients in the high-risk group are more suitable for immunotherapy.

Despite the significant finding in our study, there are still some limitations that should be acknowledged. Firstly, the sample size of bladder cancer patients included in our study was relatively small, and larger datasets are required in future research to enhance the reliability and generalizability of our prognostic model. Secondly, although we have validated the risk model’s clinical value of our model in multiple
public cohorts, further prospective clinical trials and molecular mechanism experiments are still necessary to confirm its clinical significance and elucidate the underlying mechanisms.

**Conclusion**

In conclusion, our study successfully developed a predictive risk model based on 11 oxidative stress-related genes. The risk score was proved to be a reliable independent risk factor for overall survival prediction and closely associated with the progression of the disease in bladder cancer patients. Moreover, by examining the correlation between immunotherapy, chemotherapy, and risk score, our findings provided valuable insights for personalized immunotherapy and drug treatment for bladder cancer patients.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Data Availability**


**Conflicts of Interests**

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authors’ contributions

Jianxu Huang and Weihan Luo conceived the idea, performed the bioinformatic analysis and wrote the paper. Yuqing Li and Yingrui Li reviewed the draft of the manuscript and gave amendments. All authors contributed to the article and approved the submitted version.

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References


Figures
Figure 1

Enrichments of differentially expressed oxidative stress-related genes. (a) Differentially expressed oxidative stress-related genes of GSE13507 between non–muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) were shown in the volcano plot. The blue and red dots represented DEGs filtered based on the cutoff criteria of $|\text{fold change}| \geq 1.5$ and $P$-value < 0.05. The grey dots represented genes that do not satisfy the cutoff criteria. (b) The heatmap showed the oxidative
stress-related DEGs. (c-d) The oxidative stress-related DEGs were analyzed by Kyoto Encyclopedia of Genes and Genomes (KEGG) and gene ontology (GO). Significantly enriched pathways (c) and terms (d) were shown.

**Figure 2**

Identification of genes in model construction. (a) Forest plot of 72 oxidative stress-related DEGs that related to overall survival via univariate Cox regression analyses. (b) The parameter was screened by LASSO regression. (c) LASSO regression of 72 oxidative stress-related DEGs.
Figure 3

Differences in prognosis between the high-risk subgroup and low-risk subgroup. (a) Risk plot distribution, survival status of patients, and heat map of expression of included genes in the training cohort. (b, c) Risk plot distribution and survival status of patients in the testing cohort.
Figure 4

Evaluating the capacity of the prognostic model in survival prediction. (a-c) Kaplan–Meier survival curves for the prognostic risk model. (d-f) The time-dependent ROC curves of the prognostic risk model.
Figure 5

The clinical prognostic value of the prognostic risk model. (a) Univariate analysis. (b) Multivariate analysis. (c, d) Associations between the risk score and tumor stage and grade. (e) Heat map of clinicopathological features. *p < 0.05, **p < 0.01, ***p < 0.001.
Figure 6

Construction and validation of the nomogram. (a) The nomogram based on age, stage and risk score to predict the 1-year, 3-year, and 5-year overall survival. (b) Calibration plots for the overall survival nomogram model. (c) Receiver operating characteristic (ROC) curves for the nomogram based on the TCGA-BLCA cohort.
Figure 7

Gene enrichment analysis of risk model. (a) KEGG_Cell_Cycle; (b) KEGG_WNT_SIGNALING_PATHWAY; (c) KEGG_OOCYTE_MEIOSIS; (d) KEGG_FOCAL_ADHESION; (e) GOBP_CELL_GROWTH; (f) GOBP_NEGATIVE_REGULATION_OF_APOPTOTIC_SIGNALING_PATHWAY; (g) GOBP_REGULATION_OF_CELLULAR_RESPONSE_TO_GROWTH_FACTOR_STIMULUS; (h) GOBP_NEGATIVE_REGULATION_OF_OXIDATIVE_STRESS_INDUCED_CELL_DEATH.
Figure 8

The prognostic model distinguishes bladder cancer sensitivity to (a) Cisplatin, (b) Gefitinib and (c) Methotrexate.

Figure 9

The prognostic model provides a potential guideline for the individualized immunotherapy of bladder cancer. (a) Comparison of ICB response scores. (b) Comparison of immune checkpoint genes between high- and low-risk groups. *p < 0.05, **p < 0.01, ***p < 0.001.

Supplementary Files

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- SupplementaryFigure.docx