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Personalized Therapies in Hepatocellular Carcinoma: Insights from a Disulfidptosis-Related Signature

Yi Wan[1], Dan Xu[2], Zhiyong Zhou[1], Yi Ouyang[3], Zugui Zhang[6], Li Zhang[7], Tao Chen[2] and Zheng Gong[4,5*]

[1]Department of Clinical Laboratory, Jiangxi Medical College, Nanchang University, Nanchang, China
[2]Department of Blood Transfusion, The First Hospital of Jiaxing, Jiaxing, China
[3]Departmento of Pathology, The First Affiliated Hospital of Nanchang University, Nanchang, China
[4]Department of Pharmaceutics, Qingdao University, Qingdao, China
[5]Department of Basic Medicine, Xiangnan University, Chenzhou, China
[6]Department of Health Care, Christiana Care Health System, New York, USA
[7]Department of Immunology, School of Basic Medicine, Qingdao University, Qingdao, China

Abstract

Hepatocellular Carcinoma (HCC) is the predominant pathological type of liver cancer with an unfavorable prognosis. Disulfidptosis is the newest cell death form and plays a vital role in tumorigenesis. However, the role of Disulfidptosis-Related Genes (DRGs) in HCC remains unknown. The RNA-seq and clinical data of HCC patients were obtained from The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) databases. Based on DRGs in TCGA cohort, the predictive model was established *via* regression analysis of the Least Absolute Shrinkage and Selection Operator (LASSO) and subsequently validated using ICGC cohort. Moreover, we investigated the relationship between predictive model and clinical features, somatic mutations, molecular mechanism, immune microenvironment and drug response. This study created an eight-gene signature. Here, we noticed a higher level of those eight genes in HCC patients in both RNA and protein levels. The patients in the high risk group had a poor prognosis. It was found the predictive model was an independent prognostic factor by Multivariate Cox analyses. Pathways involved in cancer, cell membrane and metabolism was significantly enriched. In addition, Tumor Mutation Burden (TMB) and immune checkpoint genes expression were higher in the high-risk group. Furthermore, the high-risk group was more sensitive to immunotherapy and some targeted therapy. We comprehensively and systematically identified a new disulfidptosis-related signature, which could serve as a valuable tool for predicting prognosis, immune cell infiltration and therapy response of HCC patients. Thus, these discoveries could have potentially clinical value in directing personalized therapies in the future.

Keywords: Hepatocellular carcinoma; Disulfidptosis; Prognostic signature; Tumor immune microenvironment

Introduction

Hepatocellular Carcinoma (HCC) is increasingly prevalent worldwide [1,2]. This lethal form of cancer is associated with mortality and is influenced by various factors including environmental circumstances, vaccinations and changes in lifestyle [3]. Current evidence demonstrates that it's five years survival rate was approximately 18%, only second to pancreatic cancer [4]. Despite the remarkable advancements in the treatment of liver cancer, including surgical resection, liver transplant, systemic treatment, targeted therapy and immune therapy, but only some patients benefit from these treatments and certain patients still suffer cancer recurrence, metastasis and drug resistance, rendering the prognosis poor [5,6]. The complex etiopathogenesis of HCC and its high level of heterogeneity pose a significant challenge in predicting its prognosis [7]. Moreover, the scarcity of therapeutic strategies available for HCC highlights the need for developing novel prognostic models. Therefore, identifying a new signature for risk stratification is of utmost importance.

In recent years, malignant cell death has gradually become a promising approach for cancer therapy and scientists have been working to develop a range of therapeutic approaches that target cancer cell death [8]. Cellular suicide pathways, such as autophagy, ferroptosis, necroptosis, pyroptosis and apoptosis, have been discovered and investigated in the context of antitumor treatments, involving different cell death mechanisms [9,10]. A recent inquiry found that the excessive accumulation of intracellular disulfides in cells, when SLC7A11 is highly expressed during glucose deprivation, results in cell death that has not been previously documented. This type of cell death differs from both apoptosis and ferroptosis [11]. They term this phenomenon as disulfidptosis. The results of their study on renal clear cell carcinoma indicated that the actin cytoskeleton was vulnerable to disulfide stress-induced disulfidptosis, highlighting a potential therapeutic approach for targeting disulfidptosis in cancer treatment. We obtained 46 genes from this study and defined these genes as Disulfidptosis-Related Genes (DRGs). The investigation of these genes' expression and their prognostic significance for patients with HCC is still pending.

***Corresponding author:** Zheng Gong, Department of Pharmaceutics, Qingdao University, Qingdao, China; E-mail: xblong2000@gmail.com

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The study developed a predictive risk model for Hepatocellular Carcinoma (HCC) patients using diagnostic related DRGs. Those DRGs were selected by bioinformatics analysis for the risk model. Moreover, the predictive patients sourced from ICGC database. Moreover, a nomograph was developed to evaluate the outlook of individuals diagnosed with HCC. The performance of this novel risk model in predicting patients' survival and drug sensitivity of chemotherapies was evaluated. In addition, hallmark gene sets analysis was conducted to determine the correlation with cancer related pathways. A potential correlation between immune checkpoint genes and the risk model was further performed by immune infiltration analysis. To summarize, our findings provide HCC patients a fresh perspective on the molecular mechanisms and individualized therapeutic choices.

Literature Review

Data source and collection

The 46 DRGs were analyzed in this study from a previous article [11]. The clinical information and transcriptome RNA sequencing were obtained from the online databases of TCGA (tumor cases: 374 and normal cases: 50) and ICGC (tumor cases: 240 and normal cases: 197). HTseq-TPM and HTseq-FPKM were the respective workflow types utilized for TCGA and ICGC. The clinicopathological characteristics of HCC individuals were summarized.

In addition, we obtained single-cell sequencing data from GSE156625, which included 57 samples of HCC. The Seurat R package was utilized for the Quality Control (QC) procedure. To identify the primary cell clusters, the subsequent action involved the utilization of Seurat's FindClusters function and visualizing them using 2D tSNE [12]. Based on the CellMarker database and SingeR package, the major cell types were identified and annotated [13].

Construct the co-expression network base on the DRGs

The present study utilized the "limma" and "pheatmap" R packages to perform differential gene expression analysis (FDR=0.05). We constructed a network of protein interactions by utilizing the "STRINGDB" R package and Cytoscape software. Then we used univariate Cox regression analysis to determine 30 prognostic genes and visualized them through forest plots. The intersection of prognostic genes and DEGs was obtained using a Venn diagram and the "igraph" R package was employed to establish a co-expression network of the intersection genes.

Development and verification of a predictive model for DRGs

In order to minimize the possible danger of overfitting, we utilized the LASSO regression method with the 'glmnet' package in R. To find the best value of λ, we employed ten-fold cross-validation (10FCV). The risk score based on 8-gene was computed:

$$\text{Risk score} = \sum_{n=1}^{8} A_n * B_n$$

The equation consisted of A as the coefficient and B as the value of the DRGs expression. The PCA was performed in R using the packages 'ggplot2' and 'Rtsne' to investigate potential differences between two risk groups.

Creating and assessing the nomogram

We conducted Cox regression analyses, both univariate and multivariate using the R package 'survival'. The nomogram based on DRGs was created using the 'regplot' R package. The calibration curves were acquired using the 'rms' R package, whereas the AUCs were obtained using the 'survivalROC' R package.

Genomic mutation analysis in HCC

The TCGA mutational data was extracted using the R package called 'TCGAbiolinks', and the mutational waterfall plots were generated by the "maftools" R package.

Functional enrichment analyses

The GSEA function was using the 'clusterProfiler' R package. The statistical significance was determined by considering a nominal q-value and FDR, both of which were less than 0.05.

Tumor-infiltrating immune cells and immune checkpoint genes analysis

CIBERSORT [14] algorithm was employed to compute the proportion of immune cells that have infiltrated the tumor. Moreover, we gathered data of immune checkpoint genes expression from TCGA-HCC dataset. In both risk groups, the immune cells and expression profiling of immune checkpoint genes were analyzed using the Wilcox test.

Predictive methods for immunotherapy and chemotherapy

The TIDE score is a computational framework that evaluates the possibility of tumor immune evasion in the gene expression analysis of tumor samples, by assessing the dysfunction and exclusion of the tumor immune system [15]. We used the 'pRRophetic' R package to determine the half-maximal Inhibitory Concentration (IC_{50}) of standard chemotherapy drugs frequently employed in HCC treatment for two subgroups to evaluate the correlation between model grouping and response rate to chemotherapy.

Immunohistochemistry

Our study utilized 20 clinical samples acquired from the First Hospital of Jiaxing. The Ethics Committee of the First Hospital of Jiaxing granted approval for our study. Proteintech provided the following polyclonal antibodies: INF2 (Cat 20466-1-AP), BOP1 (Cat 28366-1-AP), IPO7 (Cat 28289-1-AP), SLC7A11/xCT (Cat 26864-1-AP), RPN1 (Cat 12894-1-AP), LRPPRC (Cat 21175-1-AP), BRK1 (Cat 22157-1-AP) and SLC2A1 (Cat 21829-1-AP). The paraffin sections of liver were dewaxed with xylene and ethanol with concentration gradient. Then the endogenous peroxidase was blocked by 3% H2O2 and antigens were repaired by microwave. Next, we used 5% Bovine Serum Albumin (BSA) to block the antigens. Following that, we introduced the aforementioned polyclonal antibodies and allowed it to incubate overnight at a temperature of 4°C. On the following day, we introduced the anti-rabbit IgG (SV00002 from BOSTER) and allowed it to incubate at a temperature of 37°C for a duration of 30 minutes. After that, 3,3′-diaminobenzidine (DAB) solution was added to develop the color of the slices and then the slices were re-stained with hematoxylin. The slices were washed with water and then blued with saturated

Na_2HPO_4. Finally, we dehydrated the slices with ethanol and xylene with concentration gradient and sealed them with resin glue. We chose the two fields in each section and took photos and analyzed.

Statistical analysis

R (version 4.2.3) was utilized for all statistical analyses performed in our study. To identify differences in gene expression between two groups, the Wilcoxon rank sum test was employed. Correlation coefficients were established through the use of Pearson correlation analysis. The disparity in survival rates among different groups was evaluated through the utilization of Kaplan-Meier survival analysis and the log-rank test. $p<0.05$ was statistically significant.

Identification of differentially expressed and prognosis-related DRGs in HCC

In this research, we obtained 46 DRGs from Liu's study [11]. 41 genes had significant differential expression between the normal and tumor groups. The co-expression analysis indicated a correlation network among the 41 genes. Out of the 41 DRGs, 30 exhibited greater significance in predicting the prognosis of HCC and all of them were associated with a poorer prognosis. Additionally, the correlation network diagram of these 30 DRGs was shown and these genes were found to have strong co-expression positive relationships.

Development of a DRGs signature prognosis model for HCC patients

To create a prognostic signature related to disulfidptosis, the 30 genes underwent additional analysis through LASSO regression analysis. This was done to reduce the risk of over-fitting and collinearity, ultimately aiding in the identification of the most suitable characteristics. And the regression coefficient was calculated. Following that, an 8-DRGs signature (INF2, BOP1, IPO7, SLC7A11, RPN1, LRPPRC, SLC2A1, BRK1) was constructed and could have optimum performance for predicting the HCC patient's prognosis. The individuals diagnosed with HCC who were classified as high-risk exhibited an increased likelihood of mortality and a reduced overall survival. When compared to individuals classified as low-risk. Furthermore, the predictability and accuracy of the prognostic model were assessed using time-dependent ROC curve analysis. The AUC values achieved for survival at 1, 2 and 3 years were 0.773, 0.699 and 0.685, correspondingly. The findings indicated that the predictive model linked to disulfidptosis was able to successfully differentiate between these two categories. Hence, these findings demonstrated the outstanding forecasting capability of this risk prognostic model based on DRGs.

Then, we utilized the ICGC dataset comprising of 231 samples of HCC cancer as the validation group. The low-risk group demonstrated longer survival periods and lower mortality rates in comparison to their high-risk counterparts. Furthermore, our model demonstrated strong predictive accuracy, as evidenced by time-dependent ROC analysis (AUC of 0.797 for 1 year, 0.775 for 2 years and 0.781 for 3 years). Moreover, the outcomes of our PCA examination demonstrated a distinct distinction between the two risk categories. In combination, these discoveries underscore the capability of our risk model based on DRGs to precisely forecast the outlook of patients with HCC and stress its significance in clinical environments.

Additional validation of the expressions of the 8 DRGs for constructing the prognosis risk model

Then, we conducted additional validation of 8 DRGs at the single cell and protein levels. This dataset consisted of 43 different cell populations, encompassing 12 major cell types, which included endothelial, epithelial, fibroblast, myeloid and lymphocytes. The distribution and quantities of the different cell types. Malignant hepatocytes predominantly expressed BOP1 and SLC7A11, whereas the majority of cells expressed other genes demonstrated that the levels of INF2, BOP1, IPO7, SLC7A11, RPN1, LRPPRC, SLC2A1 and BRK1 proteins were elevated in HCC tissues compared to para-tumor tissues obtained from twenty patients.

Validated the independent prognostic value of DRGs risk score for HCC patients

The risk score and clinical stage were significantly poor prognostic factors for overall survival. In addition, risk score as a separate prognostic factor that is strongly correlated with unfavorable survival in patients with HCC ($p<0.001$). Additionally, the findings further confirmed the predictive significance of the risk score as a standalone marker in the ICGC cohort ($p=0.002$). The remaining findings indicated that the risk score attained the highest AUC value in both the TCGA (AUC=0.765) and ICGC cohort (AUC=0.797). Therefore, it demonstrated a higher ability to predict survival for the individual patient compared to other clinicopathological factors.

Developed and validated a novel nomogram to predict the prognosis for HCC patients

Then we developed a groundbreaking nomogram using the TCGA-HCC dataset. The performance of our nomogram was assessed by utilizing calibration curves for one, three and five years, which exhibited remarkable agreement between the projected and observed rates of overall survival. In most instances, the nomogram exhibited higher AUC values on the time-dependent ROC curves, thereby further confirming its strong discriminatory capability. Furthermore, the DCA plot demonstrated that the nomogram's ability to predict clinical prognosis for HCC was superior to other factors in the overall, training and test groups. The findings indicated that the nomogram exhibited a positive level of precision in forecasting the overall survival of HCC patients.

Explored the correlation between clinicopathological characteristics and the prognostic model of DRGs for HCC patients

To examine the model's predictability for overall survival, the TCGA cohort's HCC patients were categorized into various groups according to their clinicopathological characteristics in this research study. Additionally, the heat map exhibited the association, along with the clinical factors like survival status, age, gender, grade and TNM stage. The risk scores were compared among the subgroups, revealing notable differences in pathological grade, clinical stage and T stage ($p<0.05$). Based on the Kaplan-Meier analysis, individuals with low-risk scores exhibited superior survival rates compared to those with high-risk scores in terms of pathological grade (G 1-2, $p=0.003$; G 3-4, $p=0.007$), clinical stage (Stage I-II, $p=0.029$; Stage III-IV, $p=0.010$) and T stage (I-II, $p=0.024$; III-IV, $p=0.007$). These results demonstrated the DRGs-based risk prognostic model was robust with

broad applicability to clinical research studies in the different populations and settings.

Genetic mutation feature and TMB analysis in the signature

This research also analysis the mutation patterns of HCC patients belonging to both two risk groups. Among the high-risk group, the three genes with the greatest occurrence of mutations were TP53 (38%), CTNNB1 (30%) and TTN (21%). Conversely, the genes TTN (26%), CTNNB1 (22%) and TP53 (20%) exhibited the highest mutation frequency in the low risk group. Furthermore, we analyzed the Tumor Mutational Burden (TMB) in both groups and noticed a noteworthy rise in TMB among the high-risk category ($p<0.05$) showed that individuals with elevated TMB experience poorer survival outcomes compared to those with lower TMB levels. The individuals classified as low risk with a low TMB had the most positive prognosis.

Exploring the correlation between risk groups and cancer pathways

The heat map revealed that most of the pathways linked to cancer exhibited a notable correlation with the genes of the risk model. These pathways include DNA repair, TGF-β signaling, mTORC1 signaling and the P53 pathway. We observed an increase in specific pathways linked to the cellular membrane in the high risk group. The pathways contained molecules that were associated with cell adhesion, the communication between cytokines and cytokines receptors and the interaction with receptors in the extracellular matrix. However, the group with minimal risk primarily exhibited an abundance of pathways related to metabolic processes, such as the breakdown of fatty acids, the metabolism of glycine serine and threonine and the conversion of pyruvate. Furthermore, the group at high risk exhibited a notable enrichment in certain GO terms, such as homophilic cell adhesion through transporter complex, adhesion on the plasma membrane and structural constituent of the extracellular matrix. The low-risk group exhibited a plethora of pathways associated with metabolic enzyme function, such as the function of cyclooxygenase in arachidonic acid.

The relationship between the prognosis model and TME through immune infiltration and checkpoint analysis

TME was a complex ecosystem comprising supporting non-tumor cells, such as stromal and immune cells, drastically influencing tumor progression, invasion and metastasis [16]. The proportions of immune cell subpopulations in the TME were analysis using seven algorithms (TIMER, CIBERSORT, CIBERSORT-ABS, QUANTISEQ, MCPCOUNTER, XCELL and EPIC). In the high-risk category, there was a greater percentage of memory B cells, dormant dendritic cells and stimulated mast cells were found to be increased. Nevertheless, it was noted that the elevated levels of inactive NK cells, M2 macrophages and inactive mast cells were present in the low risk group.

Inhibiting the PD-1/PD-L1 immune checkpoint shows great potential as an immunotherapeutic strategy for treating cancer. In order to further examine its potential usefulness, this research examined the manifestation of typical immune checkpoint genes in patients with HCC. Our findings suggested that immune checkpoint genes exhibited a notably elevated expression in high-risk group. Additionally, the risk score demonstrated a positive correlation with the majority of immune checkpoint gene expression. Hence, the approach of utilizing checkpoint blockade therapy might be better suited for the high-risk population.

Prediction of drug sensitivity based on risk score

Finally, we additionally investigated the correlation between the sensitivity of drugs in immune, chemo and targeted therapy and the prognostic signature. Our initial approach involved assessing the TIDE score to appraise the possible immune system impairment in both tumors and nearby lymph nodes. It indicated that individuals in the LR category had an increased likelihood of responding positively to immunotherapy. Furthermore, we assessed the immune therapy response using the TIDE score. Significant variations were observed in the risk scores among various response groups, indicating a greater percentage of CR/PR in the high risk category.

Our investigation aimed to determine if the risk model had the ability to anticipate the reaction of patients towards targeted therapy and chemotherapy. Selected were drugs commonly used for patients with HCC in clinical settings. It was discovered that the high-risk category displayed greater responsiveness to specific targeted medications like lapatinib, Nilotinib, Gefitinib and Axitinib. In contrast, the low-risk category exhibited heightened sensitivity to chemotherapeutic agents like Mitomycin C, Gemcitabine, Doxorubicin and Cisplatin. In addition, the risk assessment model could also provide guidance for tailoring clinical treatment for patients with HCC.

Discussion

HCC, being a prevalent cancerous growth on a global scale, exhibits a significant fatality rate and a highly aggressive nature [17]. Nevertheless, additional investigation is necessary to elucidate the fundamental process involved in the growth and advancement of HCC. The proposed theory of disulfidptosis provides a novel theoretical rationale for developing induced disulfidptotic therapeutics against HCC [11]. Although disulfidptosis has been observed in different types of tumors such as bladder cancer [18,19], renal cell carcinoma [20], thyroid carcinoma, there is still a considerable lack of understanding in relation to HCC. Our study demonstrated that the DRGs were markedly increased in HCC, indicating a strong correlation with an unfavorable prognosis, thus providing clarification on the role of the disulfidptosis process in HCC.

During the functional assessment, the pathways in high-risk groups related to the structure of the cell membrane, particularly the cellular architecture pathways, were enriched. The disulfidptosis caused abnormal disulfide linkages in proteins of the actin cytoskeleton, leading to the disruption of the structure of the cell membrane [11]. In addition, the low-risk group exhibited a decrease in metabolic activity. The involvement of pyruvate metabolism through the TCA cycle connected to amino acid metabolism may have a crucial biological function in liver functionality. The glycine combines with bile acids to generate glycocholic acid, which is then eliminated through the bile duct, thereby enhancing optimal liver functionality.

HCC could create an immunosuppressive tumor microenvironment conducive to tumor growth and metastasis. A comprehensive examination was conducted to assess the infiltration of immune cells in patients with HCC. There was no notable disparity in the infiltration of immune cells between the two risk categories. Notably, the high-

risk group showed a significant reduction in the percentage of M2 macrophages. The M2 macrophages are often considered the main contributors to tumor growth, as they are thought to stimulate the multiplication and spread of HCC cells. Nevertheless, the M2 macrophages are also involved in tissue repair, such as secreting repair-promoting cytokines, promoting proliferation and differentiation and even directing extracellular matrix deposition, allowing it to bind to and regulate growth factors. Consequently, it had an adverse effect on the initiation and progression of disulfidptosis. This outcome was consistent with our GSEA enrichment results. The findings indicate that the elevated ratio of M2 macrophages in the low-risk cohort may enhance cellular membrane restoration and inhibit cell death associated with disulfidptosis. Additionally, it was noted that the higher-risk group displayed a rise in the expression of inhibitory immune checkpoint molecules such as CTLA-4 and PD-1/L1. These molecules hindered the signaling of T cell receptors and led to the deactivation of T cells, ultimately causing evasion of the immune system. Furthermore, a multitude of treatment studies have shown the favorable real-life efficacy of CTLA-4 or PD-1/L1 antibody therapy for HCC.

Moreover, the prediction of drug sensitivity revealed a notable disparity in the response to different chemotherapy medications among the two risk cohorts. The TMB has the ability to accurately indicate the mutation status of tumor samples, making it a promising and novel predictive biomarker for immunotherapy. Based on our risk assessment, the results showed that TMB was significantly higher in the high-risk category. Additionally, when examining patient survival, it was observed that individuals with elevated TMB in the high-risk group had the worst prognosis. The results indicated that utilizing TMB in conjunction with DRGs in our risk model may enhance the precision of prognosis prediction.

In the course of our study, two groups have reported that signature based on DRGs could predict the prognosis and immune profile of HCC patients, but genes of signature are not direct from DRGs. Here, we collected 46 DRGs reported in the Xiaoguang Liu, et al., and constructed a risk model consists of 8 DRGs using LASSO regression analysis, which can well predict the prognosis and the response to chemotherapy, targeted therapy and immunotherapy of HCC patients. Totally 8 DRGs (INF2, BOP1, IPO7, SLC7A11, RPN1, LRPPRC, SLC2A1 and BRK1) in HCC were confirmed via multiple bioinformatics and IHC analysis. Reportedly, these genes are crucial in the initiation and advancement of tumors. INF2, also known as Inverted formin 2, is a unique formin protein that controls the movement of actin filaments. The INF2 serves as the main facilitator of mitochondrial malfunction and assumes various functions in various types of cancers. BOP1 (Block of Proliferation 1) was up-regulation in HCC and promoted epithelial-to-mesenchymal transition. A recent report states that the BOP1 protein is stabilized by long non-coding RNA SNHG6, leading to glycolytic reprogramming in HCC. The IPO7 (Importin-7) belongs to the importin-β family and mediates the nuclear import of cargo. In cervical cancer, the IPO7 promoted tumor growth and inversely associated with the infiltration of $CD8^+$ T cells. The SLC7A11 gene regulates the absorption of external cystine in return for glutamate at a 1:1 ratio to produce Glutathione (GSH), which has crucial functions in preserving cellular redox balance. The SLC7A11 is upregulated in different tumor types and has the ability to anticipate the progression and spread of cancers, including those affecting the liver, breast and lungs. Overexpression of the LRPPRC, which acts as a reader of m6A modification, has been linked to adverse prognostic outcomes in HCC. Regarding the molecular mechanisms, LRPPRC promotes the advancement of tumors and evasion of the immune system by increasing the m6A modification of PD-L1 mRNA in hepatocellular carcinoma. The SLC2A1 codes for a glucose transporter protein primarily situated on cellular membranes and exteriors. Furthermore, the SLC2A1 serves as a prognostic biomarkers in hepatocellular carcinoma associated with immune infiltration. Pan-cancer analysis suggests that the BRK1 gene is abundantly expressed in various types of tumors, making it a promising candidate for tumor immunotherapy.

Nevertheless, the study also had several limitations. Firstly, to enhance the accuracy of the risk model, further independent external cohort and a larger sample size are required for validation, despite some independent cohort being utilized in this HCC study. Secondly, we did not investigate the roles of the eight-DRGs in HCC. Our future efforts will focus on improving basic research to verify those genes' function and mechanism.

Conclusion

To sum up, our DRGs-based risk model had a significant clinical application value for improving prognostication, diagnostics and therapy. Moreover, combined with other clinical indicators, it could have better clinical utility in HCC. Furthermore, this research expanded our knowledge of HCC progression and provided important clues for further investigating the underlying mechanisms of disulfidptosis in HCC.

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Author Contribution

YW and ZG conceived the concept of the study; YW and DX wrote the manuscript; TC and YW was involved in data analysis; LZ, YZ and YO prepared the figure; ZZ, TC and ZG contributed to the supervision.

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Data Availability

The datasets analyzed in this study were available from TCGA database (https://portal.gdc.cancer.gov/) ICGC (https://dcc.icgc.org/repositories) and GSE156625 dataset (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE156625).

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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