Hindawi
Journal of Nanomaterials
Volume 2022, Article ID 4642477, 10 pages
https://doi.org/10.1155/2022/4642477

Research Article

A Prognostic Model for Patients with Hepatocellular Carcinoma Based on Hypoxia-Related Long Noncoding RNAs

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Received 23 February 2022; Accepted 22 March 2022; Published 1 April 2022

Academic Editor: Weiguo Li

Objective. The prognosis of patients with hepatocellular carcinoma (HCC) varies greatly due to the hypoxic environment and multiple factors driving metastasis progress. In this study, we aimed to correlate the expression of hypoxia-related long noncoding RNAs (lncRNAs) with the survival of patients with HCC to develop a prognostic model for HCC. *Methods*. The Pearson correlation analysis was used to screen hypoxia-related lncRNAs between differentially expressed lncRNAs by analyzing lncRNA expression profiles in The Cancer Genome Atlas (TCGA) database and 200 hypoxia genes downloaded from the Molecular Signatures Database (M5891). The univariate and multivariate Cox regression analyses were used to identify significantly predictive hypoxia-related lncRNAs, and a prognostic model based on these factors was constructed to predict the survival of HCC. The Kaplan-Meier (K-M) survival analysis and receiver operating characteristic curve (ROC) were performed to evaluate the performance of the model. *Results*. A total of 490 hypoxia-related lncRNAs were screened out. A prognostic model comprising 10 significantly predictive hypoxia-related lncRNAs was constructed by the multivariate Cox regression analysis. The hypoxia-related risk scores were calculated and were divided into high-risk and low-risk groups. The K-M survival analysis showed a lower overall survival rate of patients in the high-risk group ($P < 0.05$). ROC analysis showed that the AUC value of hypoxia-related risk score was 0.799, demonstrating that the hypoxia-related risk score was an independent prognosis factor of HCC. *Conclusion*. Our study indicates that identified 10 key hypoxia-related lncRNAs have potential prognostic values for HCC patients and may provide new targets for the treatment of HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the main type of liver cancer, accounting for 85%-90% of the primary liver cancers, and the global disease burden caused by HCC is also increasing [1]. Although some new advances have been made in the treatment of HCC in recent years, the rate of 5-year overall survival in patients with HCC is still no more than 20% [2]. Nowadays, molecular mechanism research based on bioinformatics analysis has become one of the important tools in cancer research [3, 4]. Therefore, using bioinformatics technique to explore new molecular markers for predicting the survival of HCC is of great significance for individualized and precision therapy of HCC.

Hypoxia, which manifested as a decrease in the level of available oxygen in the tissues, often occurs in patients with acute and chronic vascular diseases, lung diseases, and cancer [5]. Due to the imbalance between tumor cell proliferation speed and vascular nutrient supply, hypoxia is a common phenomenon in solid tumors [6]. Many studies had recognized the important role of hypoxia in tumor angiogenesis, cell proliferation, cell differentiation, and apoptosis [7, 8]. The liver is one of the three most vulnerable organs to hypoxia, and HCC is a hypermetabolic tumor that consumes more oxygen than its surrounding normal tissues. Previous studies have found that hypoxia was related to HCC metastasis, poor prognosis, and treatment resistance [9, 10]. A recent study found that an increased expression of hypoxia-inducible factor-1α (HIF-1α) in HCC tissues may contribute to the invasion and metastasis of HCC and poor prognosis [11]. Besides, HIF-1α is also the main reason for the resistance of HCC to sorafenib [12].

Long noncoding RNAs (lncRNAs) are noncoding RNAs with a length of more than 200 nucleotides [13]. Recently, lncRNAs are gaining increasing attention from researchers because they are involved in several key molecular and biological processes of the body, such as they affect the occurrence and development of tumors [14]. Besides, studies have shown that various lncRNAs responding to hypoxia environment played an important role in the occurrence and development of tumors [15]. Based on this, we speculate that hypoxia-related lncRNAs may be served as prognostic markers for HCC patients. Therefore, this study was aimed at exploring prognostic markers of HCC based on hypoxia-related lncRNAs by a bioinformatics approach and constructing a prognostic model for predicting the survival outcomes in HCC.

2. Materials and Methods

2.1. Data Acquisition and Processing. The gene expression profiles and clinical data of HCC patients were downloaded from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/repository) on August 10, 2021. We excluded those with an overall survival period of ≤30 days (because these patients may die from unpredictable factors such as infection or bleeding) and those with unknown survival time and survival status. A total of 350 HCC patients (cancerous liver tissues and adjacent noncancerous liver tissues) were included in this study.

2.2. Screening Hypoxia-Related lncRNAs. The transcriptome data of 350 HCC patients were annotated into mRNAs and lncRNAs. Differentially expressed lncRNAs between cancerous liver tissues and adjacent noncancerous liver tissues were screened by analyzing raw data of gene expression profiles using the Limma package from the R/Bioconductor software in accordance with $|\log 2(\text{fold change [FC]})| > 0$ and adjusted $P \leq 0.05$. A total of 200 iconic hypoxia genes on the hypoxia-related pathway (HALLMARK-HYPOXIA) were downloaded from the Molecular Signatures Database V7.4 (http://www.gseahttp://msigdb.org/gsea/msigdb/index.jsp). Then Pearson correlation analysis was used to analyze the correlation between the hypoxia score and the expression of lncRNAs, and the hypoxia-related lncRNAs were screened out according to the criteria of correlation coefficient $(|r|) > 0.4$ and $P < 0.001$.

2.3. Identifying Key Hypoxia-Related lncRNAs Associated with the Prognosis of HCC. The univariable Cox regression was used to identify the key hypoxia-related lncRNAs associated with the prognosis of HCC. Hypoxia-related lncRNAs with significant prognostic value ($P < 0.001$) were defined as key hypoxia-related lncRNAs and were screened out for subsequent research.

2.4. Constructing the Hypoxia-Related Prognostic Model. The multivariate Cox regression analysis was used to construct the hypoxia-related prognostic model, and the risk score of each sample was calculated by the following algorithm: $\text{Risk score} = \text{Expression}_{\text{lncRNA1}} \times \text{Coefficient}_{\text{lncRNA1}} + \text{Expression}_{\text{lncRNA2}} \times \text{Coefficient}_{\text{lncRNA2}} + \cdots + \text{Expression}_{\text{lncRNAn}} \times \text{Coefficient}_{\text{lncRNAn}}$ (Expression $_{\text{lncRNA}}$ refers to the expression level of hypoxia-related lncRNA; Coefficient $_{\text{lncRNA}}$ is the regression coefficient of lncRNA obtained by multivariate Cox regression analysis). Then, patients were divided into low-risk group and high-risk group according to their median value of the risk score.

2.5. Bioinformatics Analysis. Receiver operating characteristic (ROC) curve was used to evaluate the performance of the prognostic model. Principal component analysis (PCA) and gene set enrichment analysis (GSEA) (http://www.gsea-msigdb.org/gsea/msigdb/index.jsp) were performed to determine whether the hypoxia-related lncRNA set is statistically significantly enriched in some distribution pattern and some functional pathways between high-risk group and low-risk group.

2.6. Statistical Analysis. The Pearson correlation analysis was used to identify the hypoxia-related lncRNAs. The Kaplan-Meier (K-M) analysis was used to draw survival curve, and log-rank test was used to compare the survival rate of patients in high-risk and low-risk groups. The univariate and multivariate Cox regression analyses were used to determine the prognostic hypoxia-related lncRNAs of HCC. All statistical analysis was performed by R software (Version 4.0.2; https://mirror.lzu.edu.cn/CRAN/). $P < 0.05$ indicated that the difference is statistically significant.

3. Results

3.1. Identification of Hypoxia-Related lncRNAs. After downloading the transcriptome data and clinical data of HCC samples from the TACG database, converting the ID of the data into the gene name, we annotated the transcriptome data into lncRNAs and mRNAs. The iconic hypoxia genes including 200 genes were downloaded from the Molecular Signatures Database. By constructing a hypoxia lncRNA-mRNA coexpression network, a total of 490 hypoxia-related lncRNAs were screened out following the selection criteria of $|r| > 0.4$ and $P < 0.001$.

3.2. Construction of the Hypoxia-Related Prognostic Model. Among the 490 hypoxia-related lncRNAs screened out above, a total of 37 hypoxia-related lncRNAs were associated with the prognosis of HCC by the univariate Cox regression analysis (Figure 1). The multivariate Cox regression identified 10 key hypoxia-related lncRNAs to construct the prognostic model, including AL365203.2, AC015908.3, MSC-AS1, AC145207.5, AL117336.3, TMEM220-AS1, AL031985.3, AC009005.1, THUMPD3-AS1, and PRRT3-AS1 (Table 1). Based on the expression levels of 10 hypoxia-related lncRNAs and their coefficients from the multivariable Cox regression, we then calculated the risk score of each patient by using the following algorithm: $\text{Risk score} = (0.254 \times \text{the expression level of AL365203.2}) + (-1.420 \times \text{the expression level of AC015908.3}) + (0.334 \times \text{the expression level of MSC} - \text{AS1}) + (0.445 \times \text{the expression level of AC145207.5}) + (0.482 \times \text{the expression level of AL117336.3}) + (1.117 \times \text{the expression level of TMEM220} - \text{AS1}) + (0.433 \times \text{the expression level of AL031985.3}) + (0.363 \times$

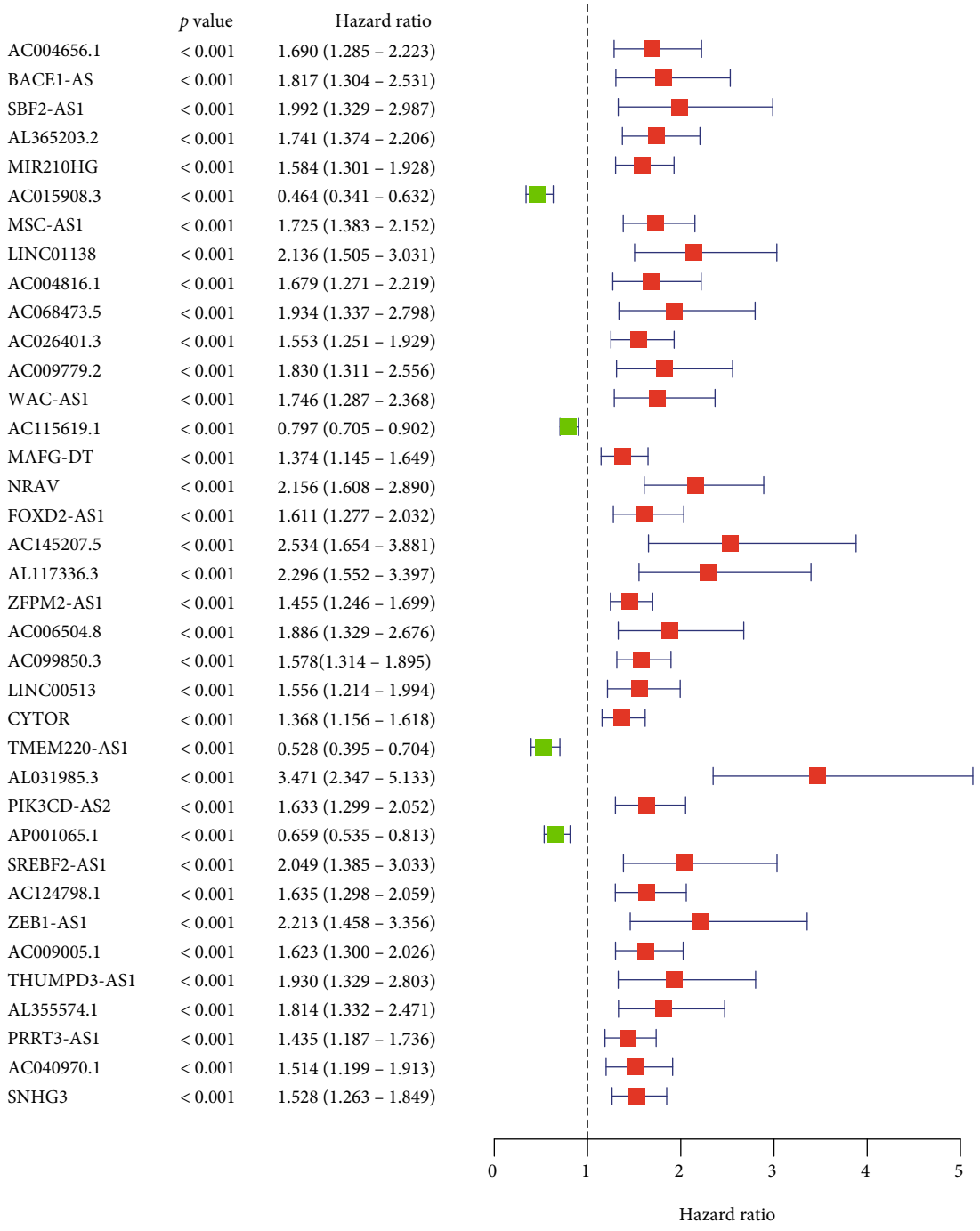


Figure 1: A forest map showed that 37 hypoxia-related lncRNAs identified by the univariate Cox regression analysis were associated with the prognosis of HCC.

the expression level of AC009005.1) + (−0.596 × the expression level of THUMPD3 − AS1) + (0.267 × the expression level of PRRT3 − AS1). The details of the 10 hypoxia-related lncRNAs are shown in Table 1.

3.3. Clinical Characteristics of HCC Patients in High-Risk and Low-Risk Groups. Based on the above risk score calculation formula, 350 HCC patients were divided into high-risk and low-risk groups according to the median value of risk score. The survival status, risk score distribution, and key gene expression are shown in Figure 2, from which we can see that the low-risk group had significantly lower hypoxia-related risk score (Figure 2(a)) and higher survival rate (Figure 2(b)). Furthermore, as the hypoxia-related risk score increased, the expression levels of AL365203.2, MSC-AS1, AC145207.5, AL117336.3, AL031985.3, AC009005.1, THUMPD3-AS1, and PRRT3-AS1 were increased, while the expression levels of AC015908.3 and TMEM220-AS1

Table 1: 10 key hypoxia-related lncRNAs selected as prognosis-associated factors in HCC.

lncRNA	Coef	HR	HR.95L	HR.95H	*P* value
AL365203.2	0.254	1.289	0.971	1.712	0.048
AC015908.3	-1.420	0.242	0.088	0.663	0.006
MSC-AS1	0.334	1.396	1.063	1.834	0.016
AC145207.5	0.445	1.560	0.925	2.632	0.010
AL117336.3	0.482	1.620	0.999	2.625	0.009
TMEM220-AS1	1.117	3.056	1.174	7.953	0.002
AL031985.3	0.433	1.541	0.914	2.598	0.014
AC009005.1	0.363	1.437	1.098	1.880	0.008
THUMPD3-AS1	-0.596	0.551	0.314	0.965	0.037
PRRT3-AS1	0.267	1.306	1.041	1.639	0.021

were decreased (Figure 2(c)). In addition, the K-M survival analysis showed that the overall survival rate of the high-risk group was significantly lower than that of the low-risk group ($P < 0.05$) (Figure 2(d)).

3.4. Correlation between Hypoxia-Related Risk Scores and Clinical Characteristics. We analyzed the correlation between the hypoxia-related risk scores and clinical and demographic characteristics such as age, gender, grade, T stage, N stage, and M stage. The results showed that C009005.1, AC015908.3, AC145207.5, AL031985.3, THUMPD3-AS1, and TMEM220-AS1 were correlated with T stage (all $P < 0.05$). AC145207.5, AL031985.3, AC009005.1, and THUMPD3-AS1 have low expression in stage T1 and high expression in stages T2-T4, while TMEM220-AS1 and AC015908.3 have low expression in stages T2 and T3 but high expression in stages T1 and T4 (Figure 3). In addition, both univariate and multivariate Cox regression analysis results showed that only hypoxia-related risk scores were significantly related to the prognosis of HCC patients (all $P < 0.001$) (Table 2). ROC analysis showed that the AUC values of hypoxia-related risk score, age, gender, classification, staging, T stage, N stage, and M stage were 0.799, 0.454, 0.506, 0.475, 0.743, 0.752, 0.508, and 0.508, respectively (Figure 4), demonstrating that the hypoxia-related risk score was an independent prognosis factor of HCC.

3.5. Analysis of Hypoxia Characteristics of Patients in High-Risk and Low-Risk Groups. Based on the key hypoxia-related lncRNAs for constructing the prognostic model and all hypoxia-related lncRNAs, we used PCA to explore the different distribution patterns between the high-risk and low-risk groups. The results showed that the distribution of hypoxia-related lncRNAs in the high-risk and low-risk groups was significantly different, showing two separate parts (Figures 5(a) and 5(b)). The GSEA analysis further indicated that hypoxia-related phenotypes were significantly enriched in the high-risk group (Figure 6).

4. Discussion

HCC is a highly invasive malignant tumor of the digestive system [16, 17]. Despite some progress has been made in the diagnosis and treatment of HCC in recent years, the prognosis of HCC is still poor [18]. Therefore, identifying new prognostic markers to optimize treatment is a great challenge in the field of tumor research. Studies have shown that the occurrence and development of HCC is a complex process affected by many factors [19, 20].

Hypoxia is an important feature of the microenvironment of most malignant tumors, especially HCC, and it is closely related to the poor prognosis of patients [21]. Several studies have shown that hypoxia is associated with the aggressive development of HCC [5, 8]. Recently, lncRNA-related signatures have received more and more attention due to their higher prediction accuracy compared with standard benchmarks [22–24]. Previous studies have also demonstrated that lncRNAs are involved in the occurrence, development, and metastasis of HCC [25, 26]. Hypoxia can affect the expression of some lncRNAs [27]. In view of the role of lncRNAs in the biological process of cancer and their correlation with hypoxia, it is of great clinical significance to explore the predictive value of hypoxia-related lncRNAs in the prognosis of HCC. However, prognostic markers based on the hypoxia-related lncRNA expression profile have not been studied in HCC.

In this study, we focused on hypoxia-related lncRNA signatures with the prognosis value of HCC. We analyzed the transcriptome information and clinical data of HCC patients in TCGA database, and found a group of hypoxia-related lncRNAs by coexpression analysis. A total of 37 hypoxia-related lncRNAs were found to be associated with the prognosis of HCC by the univariate Cox regression analysis, indicating that these hypoxia-related lncRNAs were involved in the development of HCC. In further analysis of the data by the multivariate Cox regression, we identified 10 key hypoxia-related lncRNAs (AL365203.2, AC015908.3, MSC-AS1, AC145207.5, AL117336.3, TMEM220-AS1, AL031985.3, AC009005.1, THUMPD3-AS1, and PRRT3-AS1) which were associated with the prognosis of HCC. A prognostic model of HCC was constructed based on these10 key hypoxia-related lncRNAs. The prognosis of patients in the high-risk group was worse than those in the low-risk group. Besides, we also found that the hypoxia-related risk score was significantly correlated with T stage. Therefore, these results further

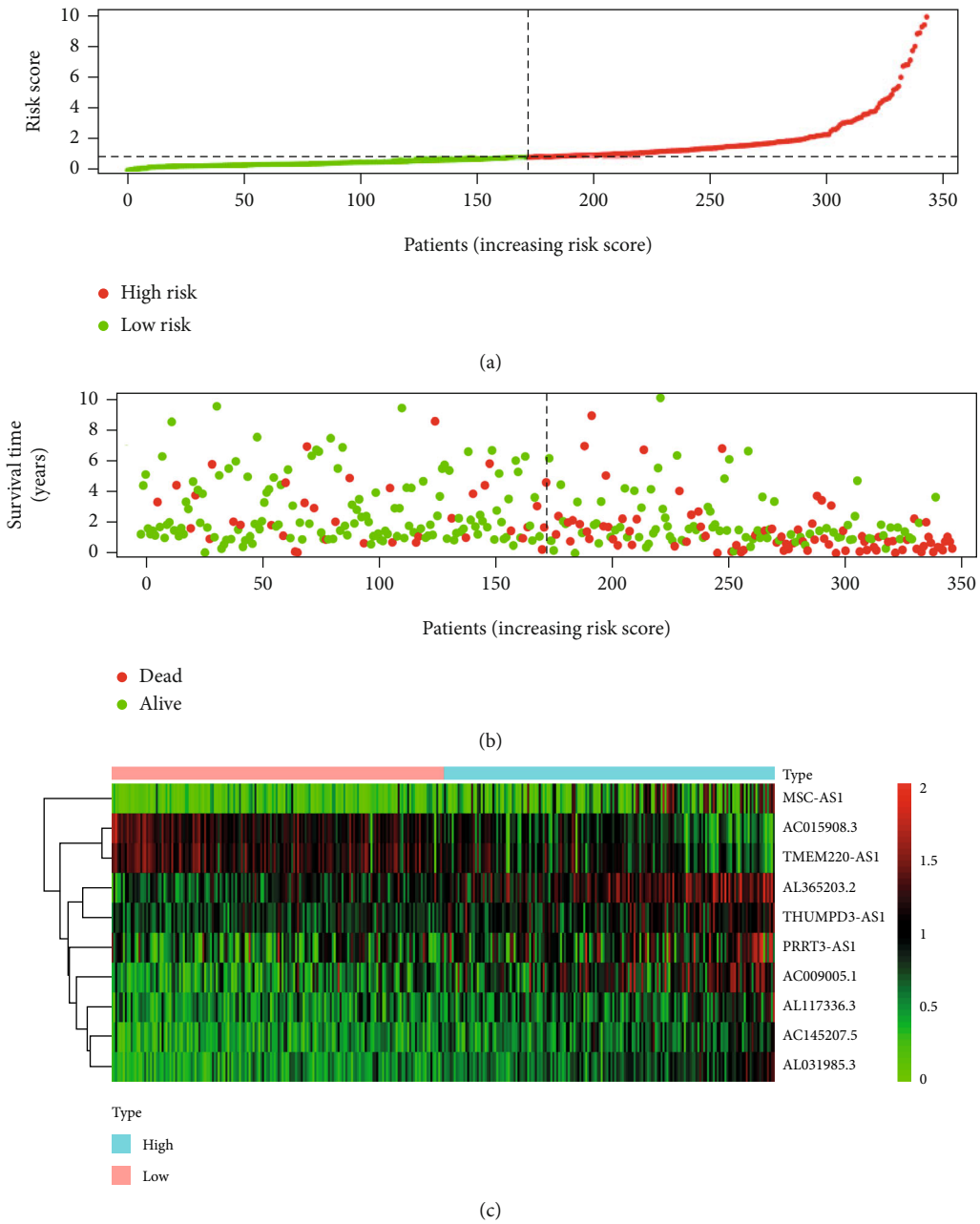
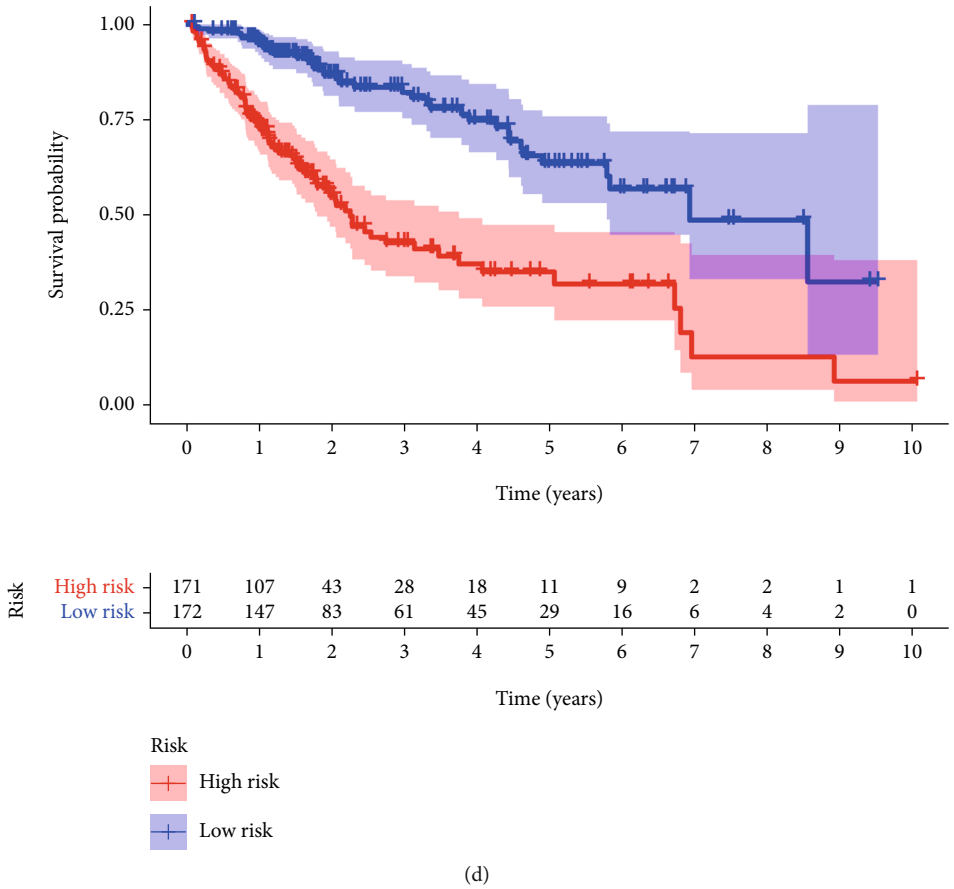


Figure 2: Continued.



(d)

Figure 2: The prognostic model constructed based on 10 key hypoxia-related lncRNAs. (a) Distribution of high-risk and low-risk groups of patients. (b) Survival status of high-risk and low-risk groups of patients. (c) Heat map of the expression of the 10 key hypoxia-related lncRNAs in HCC. (d) Kaplan-Meier curves for the OS of patients in the high-risk and low-risk groups.

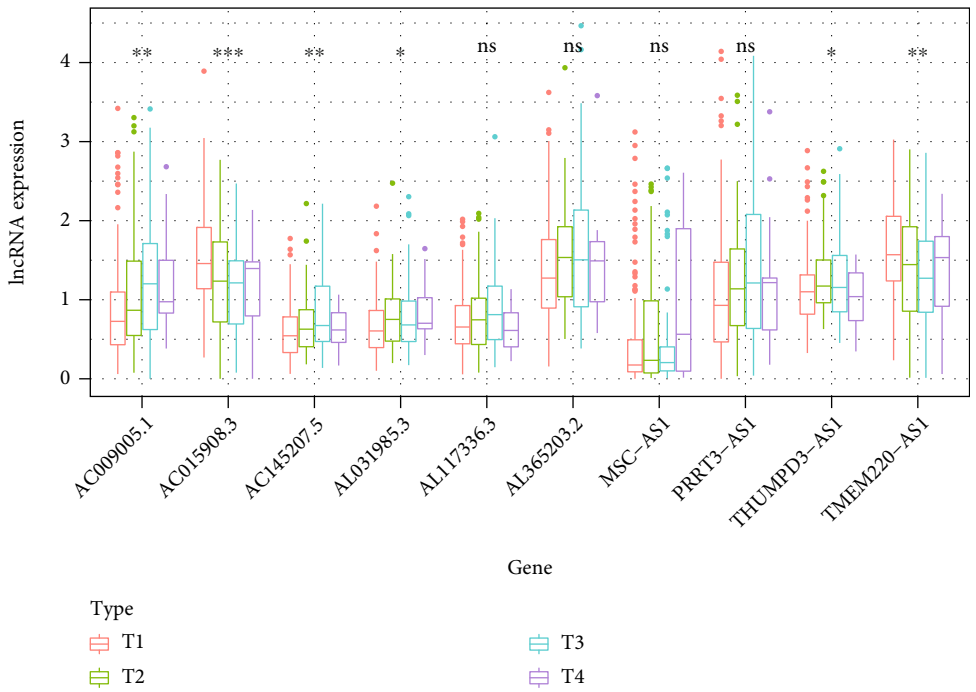


Figure 3: Correlation analysis of the10 key hypoxia-related lncRNAs and clinical T staging of HCC (∗ represents $P < 0.05$, ∗∗ represents $P < 0.01$, ∗∗∗ represents $P < 0.001$, and ns represents $P > 0.05$).

Table 2: Univariate and multivariate independent prognostic analysis of HCC.

Variables	Univariate analysis				Multivariate analysis			
	HR	HR 95% low	HR 95% high	*P* value	HR	HR 95% low	HR 95% high	*P* value
Age	0.996	0.978	1.015	0.678	1.001	0.982	1.019	0.940
Gender	0.770	0.471	1.257	0.296	0.830	0.476	1.449	0.513
Grade	1.023	0.739	1.415	0.892	1.069	0.744	1.537	0.719
Stage	2.077	1.599	2.696	0.000	0.970	0.349	2.699	0.954
T	1.990	1.564	2.532	0.000	1.847	0.735	4.638	0.192
M	4.294	1.342	13.742	0.014	1.263	0.331	4.821	0.732
N	2.246	0.547	9.219	0.261	2.339	0.393	13.906	0.350
Risk score	1.372	1.267	1.486	6.38E-15	1.332	1.219	1.455	2.16E-10

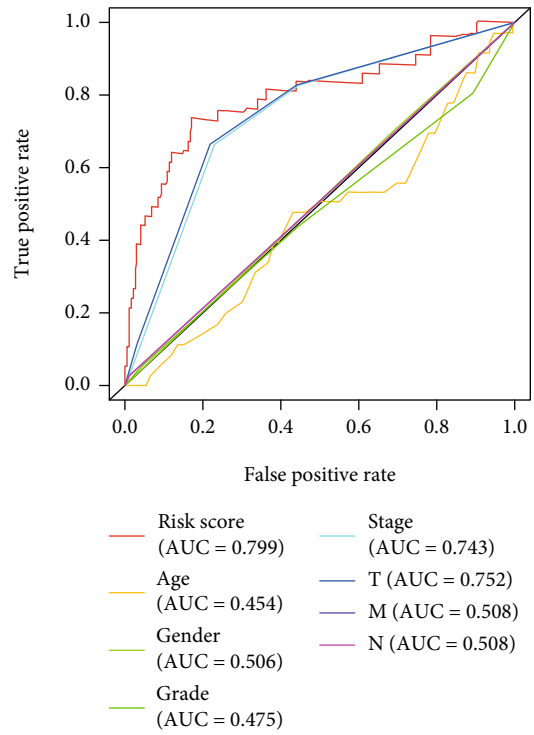


Figure 4: ROC curves evaluated the prognostic performance of the HCC prognostic model.

confirmed that these key hypoxia-related lncRNAs were associated with the progress of HCC. ROC analysis indicated that the 10 key hypoxia-related lncRNA signatures can be a good indicator for the prognosis of HCC.

Among the 10 key hypoxia-related lncRNAs found in HCC, AL365203.2 has been reported in previous studies as autophagy-related lncRNA, epithelial-mesenchymal transition-related lncRNA, and immune-related lncRNA to participate in the progress of HCC [28–30]. It was reported that AC015908.3 was also involved in the regulation of HCC cells' stemness, which was closely related to drug resistance and poor prognosis of HCC [28–30]. MSC-AS1 can promote HCC oncogenesis via inducing the expression of phosphoglycerate kinase1 [31]. AC145207.5, AL031985.3, and PRRT3-AS1 participated in the infiltration of immune cells, which was associated with immunotherapy response in patients with HCC [30, 32]. AL117336.3 and AC009005.1 can also regulate the process of autophagy and participate in the occurrence and development of HCC [28, 32]. TMEM220-AS1 has been demonstrated to suppress HCC by regulating the miR-484/MAGI1 axis as a competing endogenous RNA [28, 33]. THUMPD3-AS1 has been reported to be associated with the prognosis of non-small-cell lung cancer and HBV-related HCC [34, 35].

In addition, we also used PCA to study the different distribution patterns between the high-risk and low-risk groups based on the expression sets of key hypoxia-related lncRNAs for constructing the risk scoring model and all hypoxia-related lncRNAs. According to the gene sets of the two hypoxia-related lncRNAs, patients in the high-risk and low-risk groups were clearly divided into two parts, and the hypoxia risk score of the low-risk group

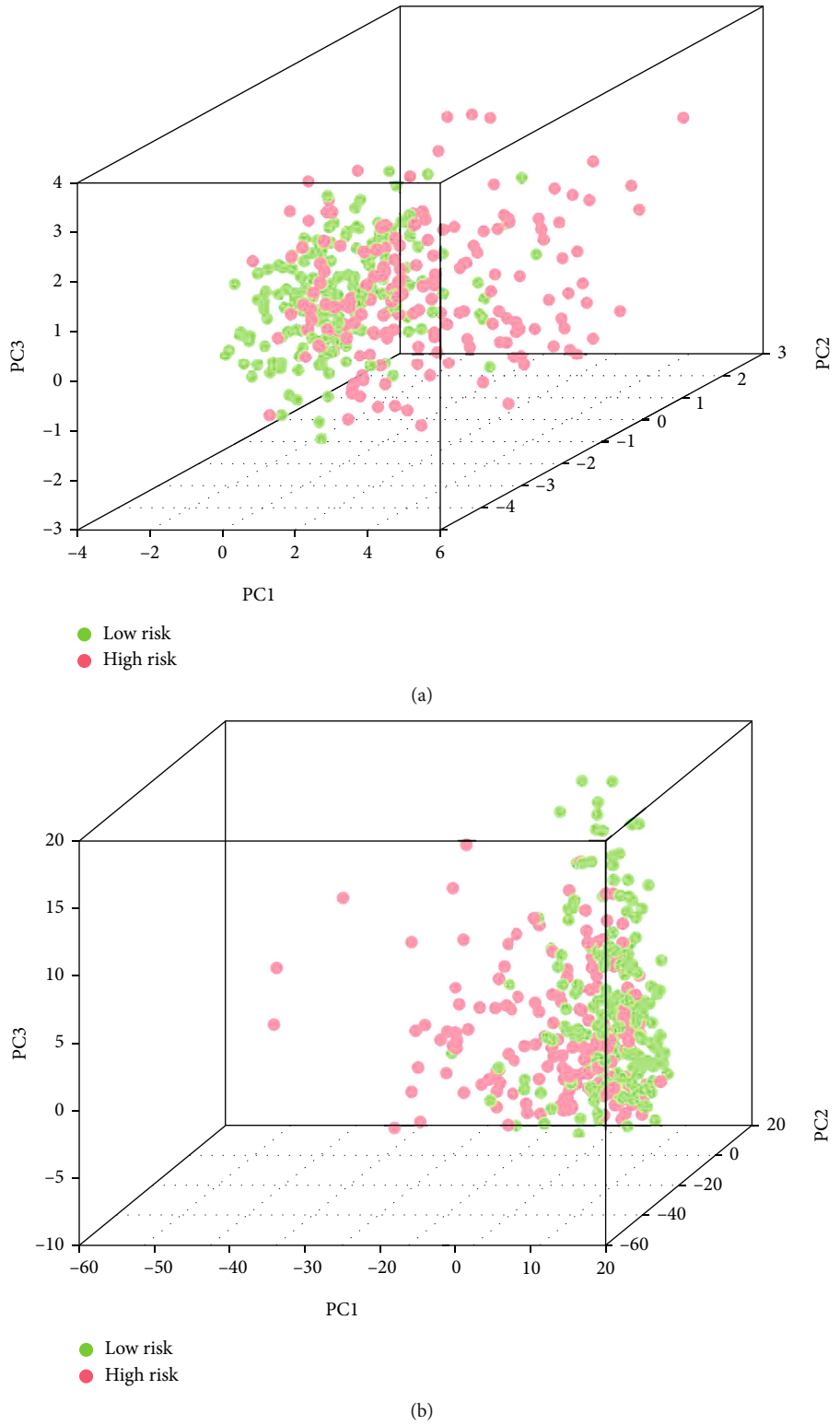


Figure 5: Principal component analysis (PCA). (a) The PCA of high-risk and low-risk groups based on the 10 key hypoxia-related lncRNAs constructed the prognostic model. (b) The PCA of high-risk and low-risk groups based on all hypoxia-related lncRNAs.

was lower than that of the high-risk group. GSEA showed that hypoxia-related phenotypes were abundant in high-risk patients. These results suggest that the prognostic model based on the 10 key hypoxia-related lncRNAs can help identify high-risk patients from patients with the same clinical or molecular characteristics, make accurate judgments on the prognosis of patients, and thus achieve individualized treatment.

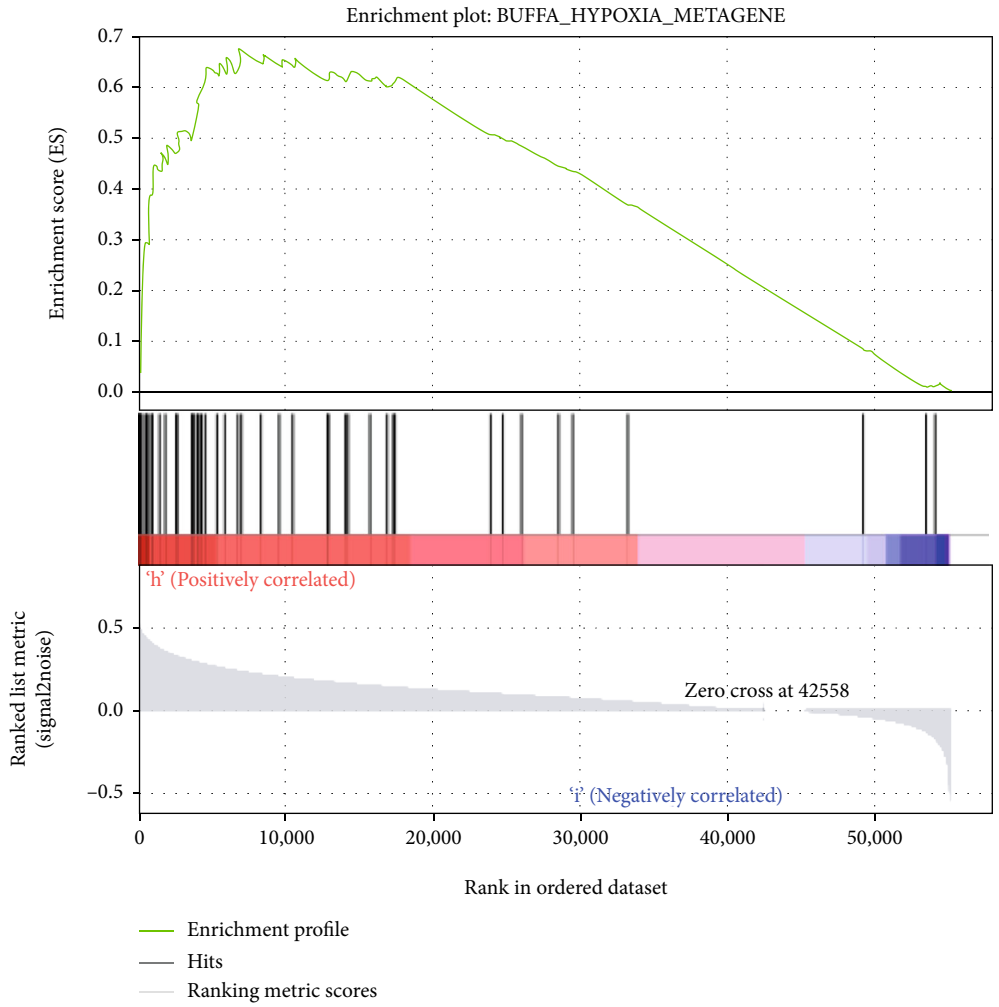


Figure 6: Gene set enrichment analysis (GSEA) of the hypoxia-related lncRNAs.

However, the current study has the following limitations that need to be acknowledged. Firstly, we failed to find an available independent lncRNA dataset to verify the usefulness of the prognostic model. Secondly, the samples in this study mainly come from international databases, lacking our own samples to verify the model. Thirdly, we just screened out 10 hypoxia-related lncRNAs that were associated with the prognosis of HCC by a series of bioinformatics method; further in vivo and in vitro experiments are needed to explore their potential mechanisms affecting the prognosis of HCC.

In conclusion, this study identified 10 key hypoxia-related lncRNAs that were associated with the prognosis of HCC by a series of bioinformatics methods based on the TCGA database, indicating that hypoxia-related lncRNAs have potential prognostic value for HCC patients and it may provide a new target for the treatment of HCC.

Data Availability

The data used to support the findings of this study are included in the article.

Conflicts of Interest

No potential conflicts of interest need to be declared.

Authors' Contributions

Lan Jiang and Huacheng Li equally contributed to the work.

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