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Construction and Validation of a Prognostic Model for Hepatocellular Carcinoma Based on Hypoxia-Related lncRNAs

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Abstract: *Objective*: To explore the correlation between hypoxia-related long non-coding RNA (lncRNA) and the prognosis of hepatocellular carcinoma (HCC) patients, and to construct and validate a prognostic risk model based on hypoxia-related lncRNA. *Method*: Obtain RNA transcriptome sequencing data and clinical follow-up data of HCC patients from the Cancer Genome Atlas (TCGA) database. Based on the HALLMARK-HYPOXIA gene set in the Molecular Signature Database (MSigDB), Spearman correlation analysis was used to screen hypoxia-related lncRNAs. Further, single-factor Cox proportional hazards regression, Least Absolute Shrinkage and Selection Operator (LASSO) - Cox regression, and multiple-factor Cox regression were used to screen for key lncRNAs associated with HCC prognosis, and a risk scoring model was constructed based on these results. According to the median risk score, patients were divided into high-risk and low-risk groups. Kaplan Meier survival analysis was used to compare the overall survival differences between the two groups, and the discriminant ability and clinical application value of the model were evaluated through a time-dependent receiver operating characteristic (ROC) curve and consistency index (C-index). Further combining clinical pathological characteristics for univariate and multivariate Cox regression analysis, screening for independent prognostic factors, and constructing a column chart prediction model. *Result*: A total of 367 HCC patients were included. Finally, 14 hypoxia related lncRNAs closely related to the prognosis of HCC were screened, namely MAPKAPK5-AS1, KDM4A-AS1, LINC00674, HCG15, NEAT1, EIF3J-AS1, BSG-AS1, FRMD6-AS1, HMMR-AS1, MRVI1-AS1, SZT2-AS1, SLC1A5-AS, CPS1-IT1 And AC115619, and based on this, construct a prognostic risk scoring model. The Kaplan Meier survival analysis results showed that the overall survival rate of high-risk group patients was lower than that of the low-risk group, and the difference was statistically significant ($P < 0.01$). ROC curve analysis showed that the area under the curve (AUC) of the model for predicting the survival of HCC patients at 1, 3, and 5 years was 0.59, 0.61, and 0.65, respectively, indicating that the model has good survival prediction performance. Multivariate Cox regression analysis showed that age, T stage, and risk score were independent risk factors affecting the prognosis of HCC patients ($P<0.05$). The Nomogram model was constructed on this basis. The calibration curve results confirm that the model has good predictive value for the 1, 3, and 5-year survival probabilities of HCC patients. *Conclusion*: 14 hypoxia-related lncRNAs are closely related to the prognosis of HCC patients. The risk scoring model constructed based on them has good prognostic stratification and survival prediction ability, and can

provide a reference for individualized risk assessment and clinical decision-making of HCC patients.

Keywords: Hypoxia; lncRNAs; Hepatocellular carcinoma; Prognostic model

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1. Introduction

Primary liver cancer still poses a heavy burden of morbidity and mortality worldwide. GLOBOCAN 2020 data show that liver cancer ranks third in global cancer deaths, accounting for approximately 8.3% of all cancer deaths. In 2020, there were approximately 905700 new cases of liver cancer and 830200 deaths worldwide. Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer, accounting for approximately 75% to 90%. Due to its insidious onset, significant tumor heterogeneity, and unsatisfactory overall survival outcomes, its clinical management still faces significant challenges [1–3]. In recent years, further research has shown that HCC exhibits significant individual differences in molecular subtyping, tumor immune microenvironment, and treatment response, suggesting that relying solely on traditional clinical indicators such as TNM staging often makes it difficult to fully achieve refined prognostic risk stratification [4,5]. Hypoxia is one of the important characteristics of the solid tumor microenvironment. Abnormal angiogenesis and high metabolic status in tumors can lead to insufficient local oxygen supply, which in turn activates hypoxia-inducible factor (HIF) related pathways and promotes malignant biological processes such as angiogenesis, glycolysis reprogramming, invasion and metastasis, and treatment resistance. There is a close relationship between hypoxia and acquired resistance to sorafenib in HCC [6-7]. At the same time, increasing evidence suggests that long non-coding RNAs (lncRNAs) are widely involved in key processes such as cell proliferation, apoptosis, invasion and metastasis, and immune escape during the development of HCC. Some lncRNAs also have the potential to serve as diagnostic and prognostic biomarkers [8,9]. Based on this, this study aims to screen hypoxia-related lncRNAs using a publicly available database system, construct and validate a prognostic risk model for HCC, in order to provide a reference for risk stratification and personalized treatment decision-making in patients.

2. Materials and methods

2.1. Data download and filtering

2.1.1. TCGA-LIHC data source and download

The transcriptome and clinical follow-up data from the TCGA database can be obtained through (https:// portal. gdc. cancer. gov/). Traceable download and preprocessing through R/Bioconductor's TCGAbiolinks package. This study included a total of 367 patients with hepatocellular carcinoma. The baseline characteristics showed that there were 194 cases of age>60 years old and 173 cases of age ≤ 60 years old; There were 248 males and 119 females. The T stage was mainly the T1 stage (181 cases), followed by the T2 stage (92 cases) and the T3 stage (78 cases), with 13 cases in the T4 stage and 3 cases missing. In the N stage, there were 249 cases in the N0 stage, 4 cases in the N1 stage, and 114 cases were missing. In the M stage, there were 264 cases in the M0 stage, 3 cases in the M1 stage, and 100 cases were missing.

2.2. Screening of hypoxia-related lncRNAs

Use the HALLMARK-HYPOXIA gene set from the MSigDB Hallmark set. Calculate the Spearman correlation coefficient between lncRNA and hypoxia genes using | Rho | > 0.3 and $P < 0.001$. Screening for hypoxia-related lncRNAs.

2.3. Preliminary screening of prognostic hypoxia-related lncRNAs

Using overall survival (OS) as the primary endpoint, a univariate Cox proportional hazards regression model was employed to analyze the relationship between hypoxia-related lncRNAs and OS in HCC patients. Hazard ratio (HR), 95% confidence interval (CI), and P-value were calculated. Using $P < 0.05$ as the screening criterion, hypoxia lncRNAs significantly correlated with patient prognosis were included in the subsequent Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression analysis.

2.4. Construction of risk scoring model

Based on the results of single-factor Cox regression screening, the LASSO Cox regression model was used to further reduce the dimensionality of candidate hypoxia-related lncRNAs. By introducing a penalty function to compress regression coefficients, we can reduce collinearity between variables and avoid overfitting of the model. Using the cross-validation method to determine the optimal penalty parameter λ value, and selecting key lncRNAs based on the non-zero regression coefficient corresponding to the optimal λ value. Subsequently, the lncRNAs selected by LASSO were included in a multivariate Cox proportional hazards regression model to determine the final lncRNAs and their regression coefficients to be included in the prognostic model. Based on this, a risk score formula was constructed: Risk score = $\sum (\beta_i \times Exp_i)$, where β_i is the regression coefficient of each variable and Exp_i is the expression level of the corresponding variable. Quantify the prognostic risk of patients based on risk scoring.

2.5. Risk stratification and survival analysis

According to the risk score of each patient, divide them into high-risk and low-risk groups based on the median. The Kaplan Meier method was used to plot the survival curves of two groups of patients, and the Log-rank test was applied to compare the differences in OS between the two groups, in order to evaluate the stratification ability of the constructed model for the prognosis of HCC patients.

2.6. Evaluation of the discriminative power and calibration ability of prognostic models

The time-dependent receiver operating characteristic curve (ROC) was used to evaluate the predictive ability of the risk scoring model for patients' 1, 3, and 5-year survival outcomes, and the area under the curve (AUC) was calculated. Further, use the consistency index (C-index) to evaluate the overall prediction accuracy of the model.

2.7. Independent prognostic factor analysis and column chart construction

To further evaluate the independent prognostic value of risk score, age, gender, tumor stage, tumor grade, and other clinical pathological variables were included in univariate and multivariate Cox proportional hazards regression analysis along with risk score. After screening for statistically significant independent prognostic factors, a column chart prediction model was constructed by integrating risk scores with independent clinical variables for personalized prediction of 1, 3, and 5-year survival probabilities in HCC patients. By calculating

the C-index of the column chart model, drawing the calibration curve and DCA curve, a comprehensive evaluation is conducted on its discrimination, calibration degree, and clinical application value.

2.8. Statistical analysis

All data organization and statistical analysis were completed using R 4.0.2 software. Quantitative data is described and compared using corresponding statistical methods based on the distribution characteristics of the data; Count data is presented in terms of examples and percentages, and comparison between groups is conducted using the χ^2 test or Fisher's exact probability method. Survival analysis was performed using the Kaplan–Meier method to plot survival curves, and the log-rank test was used to compare differences between groups. Using the Cox proportional hazards regression model to analyze the influencing factors of prognosis in patients with hepatocellular carcinoma. The discrimination and predictive performance of the time-dependent subject work characteristic curve, consistency index, and area under the curve evaluation model are evaluated. The difference is statistically significant when $P<0.05$ is used for bilateral testing.

3. Results

3.1. Screening and risk scoring of hypoxia-related lncRNAs

Using | Rho | > 0.3 and $P < 0.001$ as screening criteria, a total of 213 hypoxia-related lncRNAs were screened. On this basis, further single-factor Cox proportional hazards regression analysis was used to preliminarily screen candidate lncRNAs. The results showed that a total of 36 hypoxia-related lncRNAs were significantly correlated with the prognosis of hepatocellular carcinoma patients ($P < 0.05$). Using the Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis for dimensionality-reduction screening, we identified 16 hypoxia-related lncRNAs that may be associated with the prognosis of hepatocellular carcinoma, as shown in **Figure 1**. Further analysis was conducted by incorporating the aforementioned candidate lncRNAs into a multivariate Cox proportional hazards regression model, resulting in the selection of 14 hypoxia-related lncRNAs that are independently associated with the prognosis of hepatocellular carcinoma, as shown in **Table 1**. Among them, CPS1-IT1 and AC115619 are protective factors, while MAPKAPK5-AS1, KDM4A-AS1, LINC00674, HCG15, NEAT1, EIF3J-AS1, BSG-AS1, FRMD6-AS1, HMMR-AS1, MRVI1-AS1, SZT2-AS1, SLC1A5-AS For risk factors. Constructing a risk scoring model based on regression coefficients of various lncRNAs: Risk rating = 0.316 × Exp(MAPKAPK5-AS1) + 0.376 × Exp(KDM4A-AS1) + 0.450 × Exp(LINC00674) + 0.464 × Exp(HCG15) + 0.748 × Exp(NEAT1) + 1.015 × Exp(EIF3J-AS1) + 0.231 × Exp(BSG-AS1) + 0.568 × Exp(FRMD6-AS1) + 0.515 × Exp(HMMR-AS1) + 0.619 × Exp(MRVI1-AS1) + 0.652 × Exp(SZT2-AS1) + 0.494 × Exp(SLC1A5-AS) - 0.551 × Exp(CPS1-IT1) - 0.411 × Exp(AC115619).

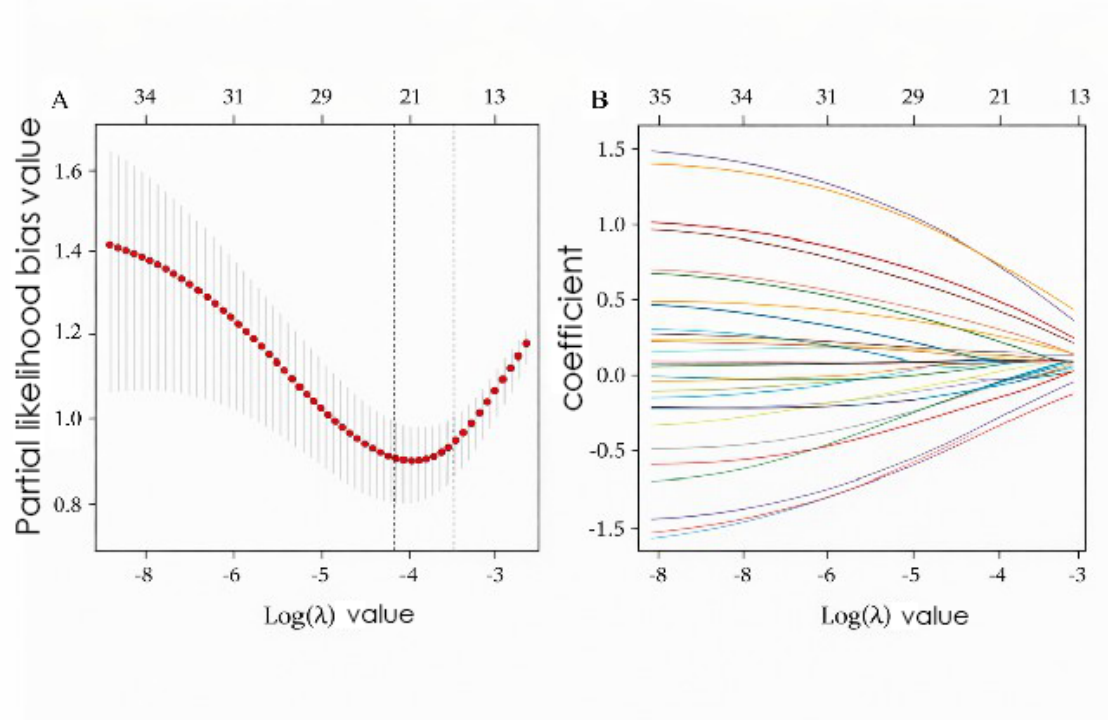


Figure 1. LASSO regression analysis results. A is the partial likelihood bias plot of hypoxia-related lncRNAs, and B is the profile plot of LASSO coefficients.

Table 1. Results of multivariate Cox regression analysis

lncRNA	β value	SE value	Wald χ^2 value	HR value(95% CI)	*P* value
MAPKAPK5-AS1	0.316	0.088	12.742	1.371 (1.153, 1.631)	< 0.001
KDM4A-AS1	0.376	0.079	22.707	1.456 (1.248, 1.699)	< 0.001
LINC00674	0.45	0.13	11.937	1.568 (1.215, 2.025)	< 0.001
HCG15	0.464	0.118	15.42	1.590 (1.262, 2.004)	< 0.001
NEAT1	0.748	0.137	29.738	2.112 (1.614, 2.763)	< 0.001
EIF3J-AS1	1.015	0.188	29.276	2.759 (1.910, 3.984)	< 0.001
BSG-AS1	0.231	0.095	5.867	1.259 (1.045, 1.518)	0.015
FRMD6-AS1	0.568	0.198	8.205	1.765 (1.197, 2.605)	0.004
HMMR-AS1	0.515	0.17	9.153	1.674 (1.199, 2.337)	0.002
MRVI1-AS1	0.619	0.192	10.395	1.857 (1.275, 2.704)	0.001
SZT2-AS1	0.652	0.155	17.638	1.919 (1.416, 2.602)	< 0.001
SLC1A5-AS	0.494	0.147	11.295	1.639 (1.229, 2.186)	< 0.001
CPS1-IT1	-0.551	0.111	24.514	0.576 (0.463, 0.717)	< 0.001
AC115619	-0.411	0.132	9.703	0.663 (0.512, 0.859)	0.002

3.2. Verification of risk assessment

Using a median risk score of 18.28 as the threshold, hepatocellular carcinoma patients were divided into a low-risk group (< 18.28, n = 183) and a high-risk group (≥ 18.28, n = 184) as shown in **Figure 2**. Kaplan Meier survival analysis showed that the survival rate of high-risk group patients was lower than that of the low-risk group, and the difference was statistically significant (HR = 2.31, $P < 0.001$), as shown in **Figure**

3. The C-index of the risk-scoring model is 0.836, indicating good prognostic performance. Time dependent ROC curve analysis showed that the AUC predicted by this risk score for the 1-year, 3-year, and 5-year survival of hepatocellular carcinoma patients were 0.59 (95% CI: 0.551-0.672, $P < 0.05$), 0.61 (95% CI: 0.564-0.685, $P < 0.05$), and 0.65 (95% CI: 0.601-0.708, $P < 0.05$), respectively. **Figure 4** indicates that the model has good survival prediction performance.

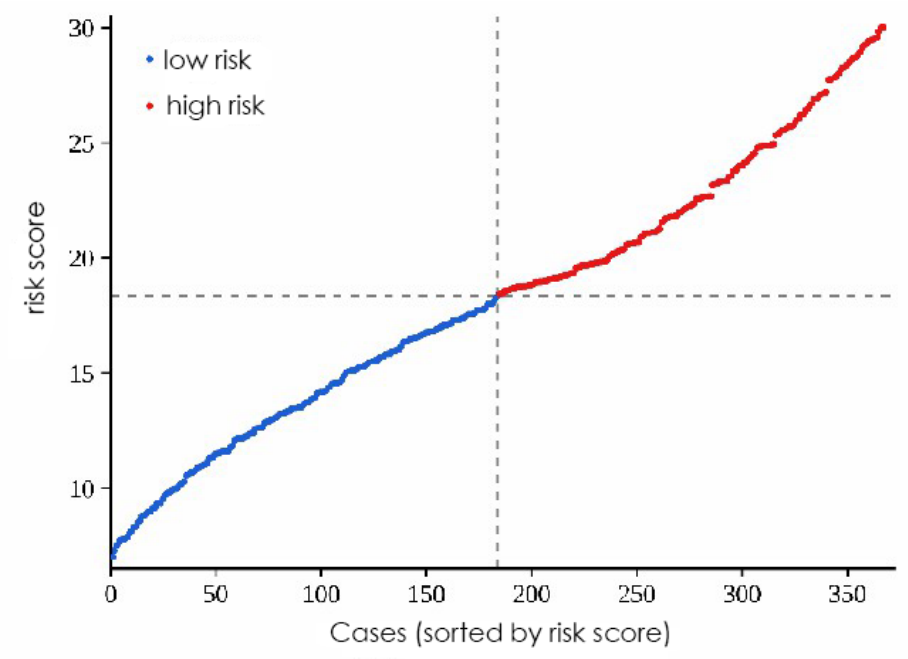


Figure 2. Distribution of patient risk scores.

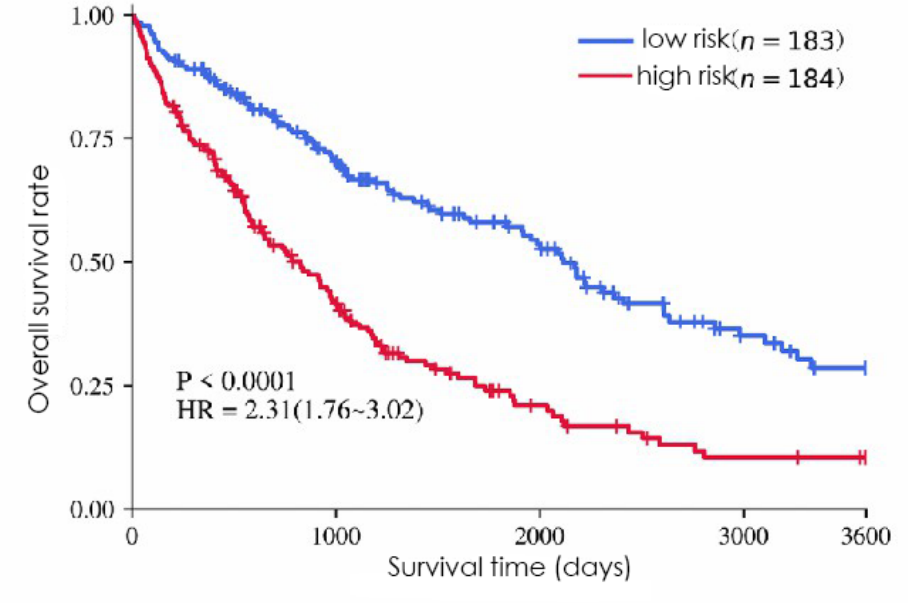
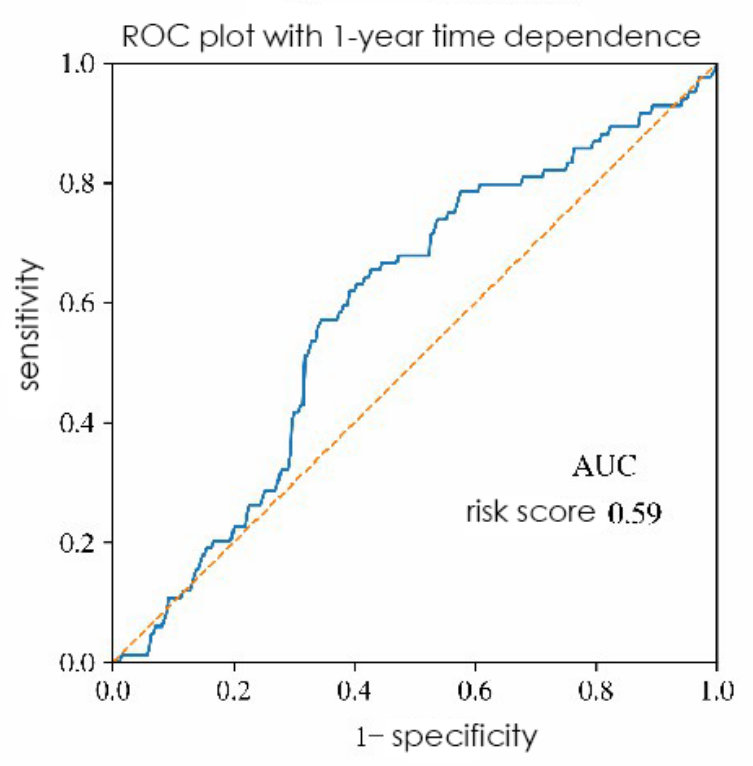
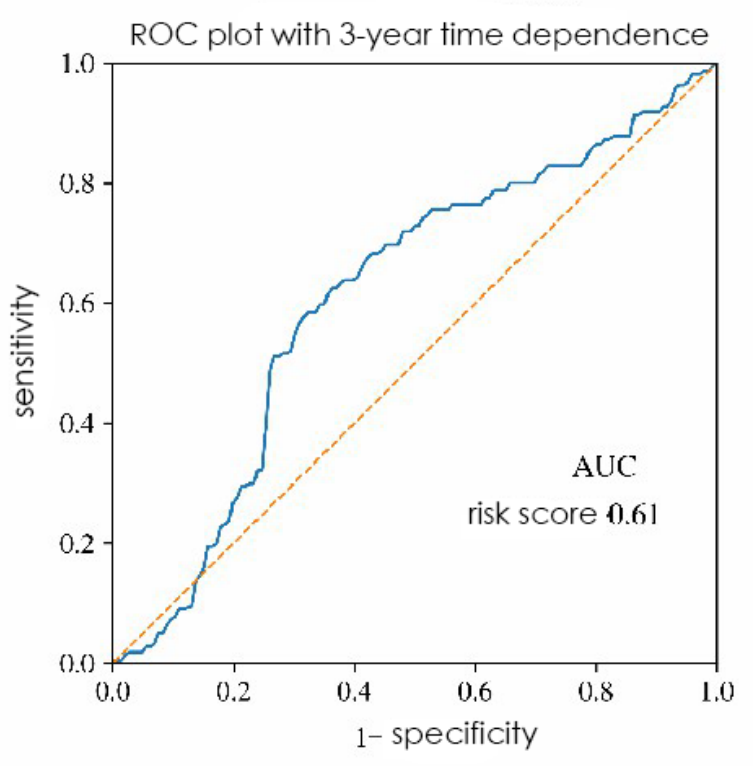


Figure 3. Kaplan Meier survival curve.


ROC plot with 1-year time dependence
sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1– specificity
AUC
risk score 0.59


ROC plot with 3-year time dependence
sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1– specificity
AUC
risk score 0.61

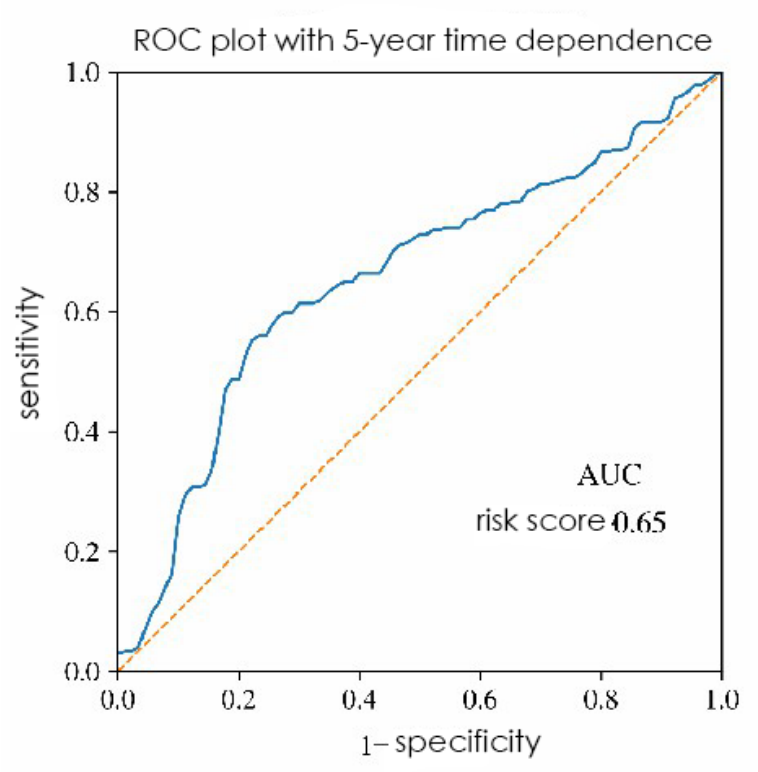


Figure 4. Evaluation of risk scores for 1, 3, and 5-year survival prediction ability.

3.3. Construction and validation of a prognostic column chart model for hepatocellular carcinoma based on hypoxia-related lncRNA

Using patient age, gender, T stage, M stage, N stage, and risk score as independent variables, with age assigned as < 60 years = 0 and ≥ 60 years = 1; Gender is female = 0, male = 1; T staging is as follows: Stage I = 1, Stage II = 2, Stage III = 3, Stage IV = 4; The value of M staging is M0 = 0 and M1 = 1; The value of N stages is set to N0 stage = 0 and N1 stage = 1; The risk score is assigned as < 18.28 points = 0, ≥ 18.28 points = 1. Using the patient's survival time and status as dependent variables, a univariate Cox proportional hazards regression model was employed to analyze the factors influencing the prognosis of hepatocellular carcinoma patients. The results showed that age, gender, T stage, M stage, N stage, and risk score were all correlated with the survival of hepatocellular carcinoma patients, and the differences were statistically significant (all $P < 0.05$), as shown in **Table 2**. Further incorporating the above six variables into a multivariate Cox proportional hazards regression model for analysis, the results showed that age, T stage, and risk score were still independently correlated with the survival of hepatocellular carcinoma patients, and the differences were statistically significant (all $P < 0.05$), as shown in **Table 3**. On this basis, age, T stage, and risk score were included in the column chart model to construct an individualized risk prediction model for predicting the 1, 3, and 5-year survival probabilities of hepatocellular carcinoma patients, as shown in **Figure 5**. The calibration curve results show that the model exhibits good calibration in predicting 1, 3, and 5-year survival rates. The predicted values are basically consistent with the actual observed values, and the curves at each time point are close to the reference line, as shown in **Figure 6**.

Table 2. Single factor Cox regression analysis of the impact on the survival of hepatocellular carcinoma patients

Variable	β value	SE value	Wald χ^2 value	HR value (95% CI)	*P* value
Age	0.039	0.006	40.449	1.040 (1.028, 1.053)	< 0.001
Gender	0.548	0.172	10.104	1.729 (1.234, 2.424)	0.001
T stage	0.466	0.074	39.180	1.593 (1.377, 1.843)	< 0.001
M stage	1.056	0.222	22.549	2.875 (1.859, 4.446)	< 0.001
N stage	0.428	0.093	21.354	1.534 (1.279, 1.839)	< 0.001
Risk score	0.220	0.071	9.450	1.246 (1.083, 1.433)	0.002

Table 3. Multivariate Cox regression analysis of factors affecting the survival of patients with hepatocellular carcinoma

Variable	β value	SE value	Wald χ^2 value	HR value (95% CI)	*P* value
Age	0.035	0.013	6.902	1.036 (1.009, 1.063)	0.009
Gender	0.201	0.128	2.447	1.221 (0.951, 1.569)	0.118
T stage	0.428	0.099	18.864	1.534 (1.265, 1.861)	< 0.001
M stage	0.152	0.122	1.507	1.162 (0.914, 1.476)	0.220
N stage	0.245	0.214	1.309	1.278 (0.840, 1.945)	0.253
Risk score	1.075	0.441	5.933	2.930 (1.234, 6.961)	< 0.001

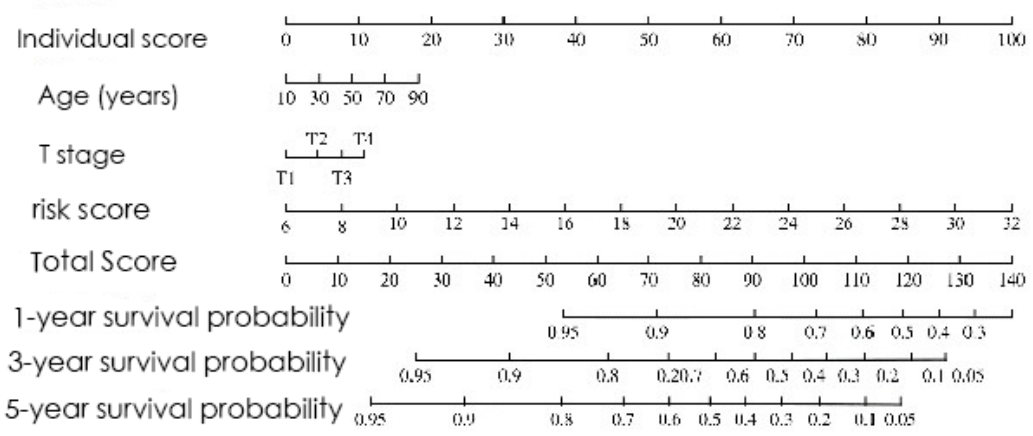


Figure 5. Column chart constructed based on prognostic features of hypoxia related lncRNAs.

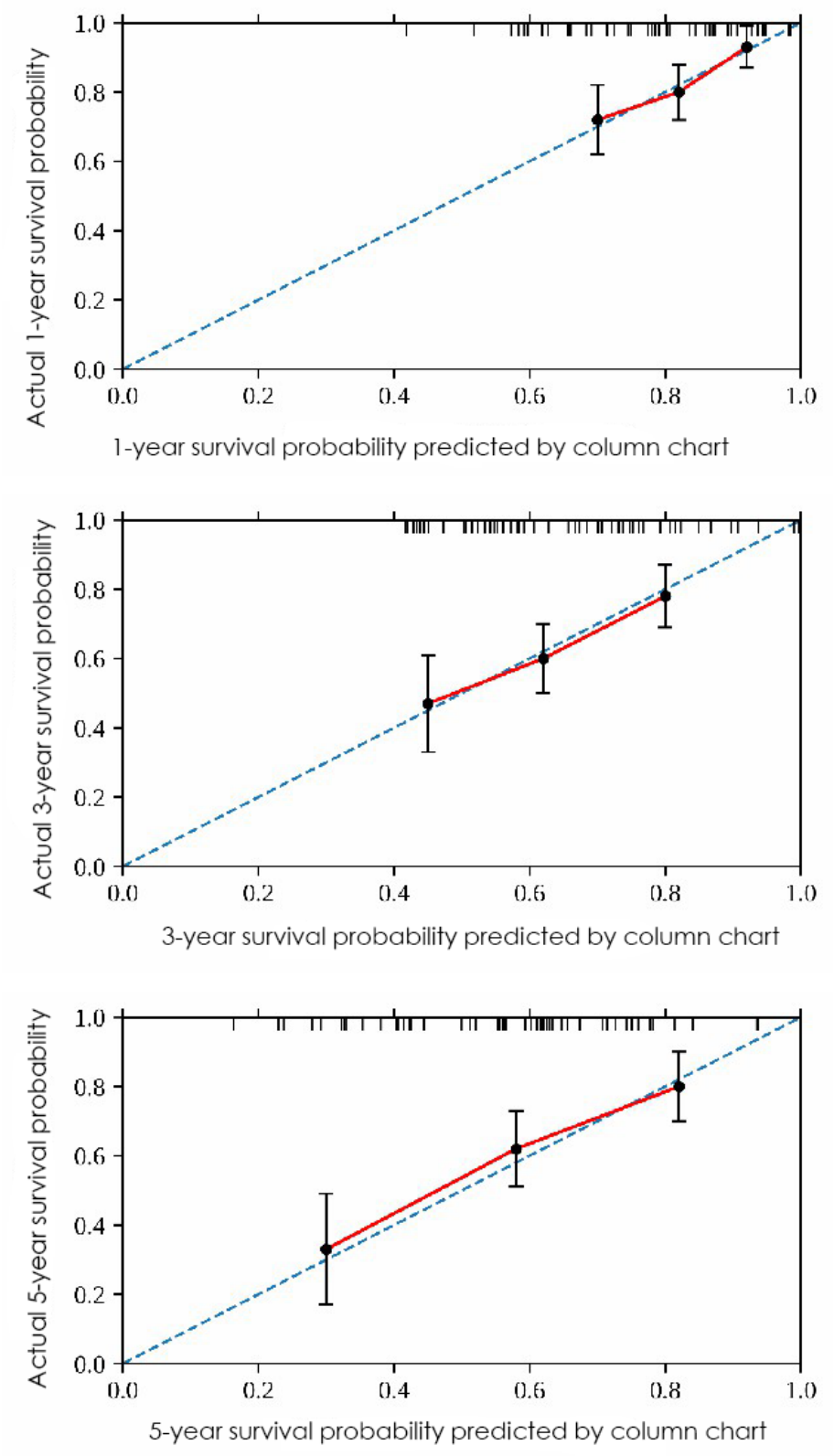


Figure 6. Validation of prognostic column chart based on hypoxia-related lncRNA.

4. Discussions

The results of this study show that the risk score constructed based on hypoxia-related lncRNAs can effectively distinguish different prognostic populations. The overall survival outcome of the high-risk group is poor, and the risk score still maintains independent predictive value in multivariate analysis. This suggests that hypoxia-related lncRNAs are not just accompanying molecular changes, but are more likely to be important molecular phenotypes reflecting the malignant biological behavior of HCC. Previous studies have constructed hypoxia-related lncRNA prognostic models based on the TCGA cohort, all of which have shown that they can effectively distinguish between high-risk and low-risk patients, and exhibit certain stability in time-dependent ROC, column chart, and clinical stratification analysis [10–12]. This study supports the feasibility of using the hypoxia lncRNA axis as a starting point for HCC prognosis assessment. Compared with traditional clinical pathological indicators, lncRNA features can capture deep molecular information, such as tumor microenvironment remodeling, metabolic adaptation, and epigenetic regulation to a certain extent, which is expected to improve the refinement level of risk stratification.

From a mechanistic perspective, hypoxia-related lncRNAs may promote HCC progression through multiple pathways. Firstly, under hypoxic conditions, HIF-1α can directly regulate the transcription of various lncRNAs, which in turn can enhance the HIF signal in reverse, forming a positive feedback loop and continuously amplifying the tumor's adaptability to hypoxic environments [13,14]. KDM4A-AS1 has been reported as a hypoxia-responsive lncRNA activated by HIF-1 α, which can promote proliferation, migration, and invasion through miRNA/AKT signaling, and form a positive feedback loop of KDM4A-AS1/KPNA2/HIF-1 α [15]. LINC00674 can be induced by hypoxia in HCC and serves as a HIF-1 target gene, activating signals such as NOX1/mTOR to promote HCC progression; It is suggested that it can serve as both a marker of hypoxia status and a functional driving factor [16]. HCG15 has been reported as a hypoxia-responsive lncRNA, and its expression can be upregulated by hypoxia and HIF-1α, which is associated with poor prognosis in TCGA data; Mechanistically, it can enhance the transcription factor axis to promote tumor cell invasion and proliferation [17]. NEAT1, as an important representative of HIF-related non-coding transcriptional response, can be activated by HIF transcription and promotes tumor cell survival under hypoxia; Studies have also shown that knocking down HIF-1α inhibits NEAT1 and reduces tumor progression in HCC, consistent with its role in hypoxia adaptation and poor prognosis [18,19]. BSG-AS1 has been reported to promote HCC proliferation and migration in hypoxic environments and is associated with poor prognosis; HMMR-AS1 can mediate immune cell polarization (such as macrophage M2) through exosomes in hypoxic environments, thereby affecting HCC progression [20,21]. CPS1-IT1 has been reported to have anti-cancer effects in HCC, low expression is associated with poor survival, and can inhibit metastasis by suppressing HIF-1α activity and EMT [22]. The above research suggests that hypoxia-related lncRNAs are not only effector molecules of hypoxia-related proteins, but may also be important nodes in regulating metabolic reprogramming and invasion and metastasis.

Evidences suggest that hypoxia-related lncRNAs are closely related to tumor immune microenvironment remodeling. Hypoxia can promote upregulation of immune checkpoint molecule expression, induce immune cell dysfunction, and enhance tumor immune escape ability [23,24]. Recent studies have shown that MIR155HG can enhance the stability of HIF-1 α mRNA under hypoxic conditions, thereby upregulating PD-L1 expression and promoting HCC immune escape [25]. Previous studies on hypoxia-related lncRNA risk models have also found that high-risk groups are often accompanied by activation of immune-related pathways,

differential expression of immune checkpoint molecules, and changes in immune cell infiltration profiles [26-28].The value of hypoxia-related lncRNA models may not be limited to "predicting survival", but may also extend to "suggesting biological behavior" and "assisting treatment decisions".

Of course, this study still has certain limitations. Firstly, if the model is mainly established based on public databases, such as TCGA, there may be selection bias in sample sources, etiology composition, treatment strategies, and follow-up completeness, which affects the extrapolation of the model. Secondly, the key lncRNAs obtained through bioinformatics co-expression or regression screening cannot completely replace the verification of their functions and regulatory mechanisms in cell and animal experiments. Again, HCC has significant etiology and spatiotemporal heterogeneity, and hypoxia status, immune infiltration, and lncRNA expression profiles may not be consistent under different etiological backgrounds. Therefore, the applicability of the model in HBV-related, HCV-related, or metabolism-related HCC still needs further comparison. Prospective validation should be conducted in multi-center, independent external cohorts in the future, and combined with single-cell sequencing, spatial transcriptomics, and in vitro and in vivo functional experiments, to further elucidate the role of key hypoxia-related lncRNAs in HCC progression and their clinical translation prospects.

5. Conclusion

In summary, the hypoxia-related lncRNA prognostic model constructed in this study can effectively evaluate the survival risk of HCC patients. This model provides new research ideas for individualized risk stratification and potential targeted interventions for HCC. However, its clinical promotion still depends on further validation at larger sample sizes, multi-center, and mechanistic levels.

Disclosure statement

The author declares no conflict of interest.

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