A four-long noncoding RNA signature predicts survival of hepatocellular carcinoma patients

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Abstract

Background: Hepatocellular carcinoma (HCC) is a common neoplasm located in the liver. Accumulating evidence has highlighted that long noncoding RNAs (lncRNAs) are correlated with the survival of HCC patients. This study focuses on finding a lncRNA signature to predict the prognostic risk of HCC patients.

Methods: Statistical and machine learning analyses were conducted to analyze the lncRNA expression data and corresponding clinical data of 180 HCC patients collected from the public online Tanric and The Cancer Genome Atlas (TCGA) databases.

Results: From the training dataset, we obtained the four-lncRNA model comprising RP11-495K9.6, RP11-96O20.2, RP11-359K18.3, and LINC00556 which can divide HCC patients into two different groups with significantly different prognosis (n = 90, median 1.81, 95% confidence interval [CI]: 1.50-4.91 vs 8.56 years, 95% CI: 6.96-9.97, log-rank test \( P < .001 \)). The test dataset confirmed the prognostic ability of the signature (n = 90, median 1.95, 95% CI: 1.14-4.08 vs 5.80 years, 95% CI: 3.11-6.82, log-rank test \( P = .007 \)). Receiver operating characteristic curve displayed the better prediction efficiency of the four-lncRNA signature than the tumor/node/metastasis stage. Cox analysis showed the four-lncRNA signature was an independent predictor of HCC prognosis.

Conclusion: The four-lncRNA signature can be used as an independent biomarker for HCC patients to predict the prognostic risk.

KEYWORDS
biomarker, hepatocellular carcinoma, lncRNA, prognostic, signature

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; lncRNA, long noncoding RNA; TCGA, The Cancer Genome Atlas.
1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is a refractory tumor that kills 746,000 people every year,\(^1,2\) ranked as the third cause of cancer-induced death. The main reasons for the high mortality of HCC are the following two points. First, the disease is insidious and difficult to be detected early; thus, most of the HCC patients are diagnosed at advanced stages when they are in poor physical condition and miss the opportunity of surgery; second, there are few effective treatments for patients with advanced HCC who are not only insensitive to radiotherapy but also poorly responsive to conventional chemotherapy drugs.\(^3\) In recent years, it has been recognized that molecular characteristics are closely related to the prognosis and therapeutic effectiveness of HCC patients.\(^4\) Therefore, identifying molecular indicators will result in more accurate prognostic judgments and improved treatments, which are urgently needed for HCC patients.

Long noncoding RNAs (lncRNAs) are a group of noncoding RNAs with the length more than 200 bp.\(^5,6\) Recent studies have found that lncRNAs play important roles in the regulation of important biological processes in various types of cancer, especially the oncogenic or onco-suppressive role,\(^7,8\) implying the potential of lncRNAs as biomarkers and therapeutic targets for cancer.\(^9,10\) In addition, the prognostic role of lncRNA in HCC has been reported in many studies. For instance, lncRNA PTTG3P was found to be associated with short survival in HCC patients and could be used as an unfavorable prognostic predictor.\(^11\) LncRNA ASB16-AS1 was demonstrated to promote the malignant behavior of HCC through regulating miR-1827/FZD4/Wnt/β-catenin pathway and has the prognostic value.\(^12\) CTC-297N7.9 was observed to be highly expressed in HCC patients with good prognosis, indicating its protective role.\(^13\) Subsequently, due to better prediction performance than a single lncRNA molecule, lncRNA signatures for HCC prognosis prediction are being discovered.\(^14-16\)

### TABLE 1 Clinicopathological parameters of hepatocellular carcinoma patients in each cohort

| Characteristic                          | Training set | Testing set |
|----------------------------------------|--------------|-------------|
| Age (y)                                |              |             |
| >63                                    | 48           | 44          |
| ≤63                                    | 42           | 46          |
| Sex                                    |              |             |
| Female                                 | 28           | 39          |
| Male                                   | 62           | 51          |
| Vital status                           |              |             |
| Living                                 | 59           | 47          |
| Dead                                   | 31           | 43          |
| Tumor/node/metastasis stage            |              |             |
| I                                      | 37           | 34          |
| II                                     | 22           | 22          |
| III                                    | 26           | 21          |
| IV                                     | 1            | 2           |
| Unknown                                | 4            | 11          |

![FIGURE 1](image_url) Constructing the prognostic long noncoding RNA (lncRNA) signature in the training dataset. A, The process of selecting the survival-related lncRNAs. B, Based on the associated expression score, random survival forests-variable hunting analysis was performed to filter lncRNAs. C, Receiver operating characteristic analysis of the selected signature.
In the present study, we aimed to identify IncRNAs that could predict outcomes of HCC patients and construct a prognostic IncRNA signature based on IncRNA expression profile data of HCC from the The Cancer Genome Atlas (TCGA) and Tanric databases.

2 | MATERIALS AND METHODS

2.1 | Construction process of the IncRNA risk score model

LncRNA transcriptome expression data of 180 HCC patients were downloaded from the Tanric database (https://www.tanric.org/). Corresponding clinical information of 180 HCC patients was downloaded from TCGA database (https://xenabrowser.net/datapages/). We omitted IncRNAs expressing value with coefficient of variance >0.1 and selected survival-related lncRNAs from training samples by performing Cox analysis (P < .05). Then, we used the random survival forests-variable hunting algorithm to further filter nodes until nine lncRNAs were screened out. We developed risk score models to estimate prognosis risk as follows:

\[
\text{Risk score} = \sum_{i=1}^{N} (\text{IncRNAexp} \times \text{coefficientCOXi}),
\]

where \( N \) represents the lncRNAs number in the model, IncRNAexp is the lncRNAs expression value, and coefficientCOXi is the coefficient of lncRNAs in the Cox analysis. We selected signatures which predicted the HCC OS with AUC > 0.7 and log-rank \( P < .05 \) from all \( 2^9 = 511 \) signatures.

**TABLE 2** The feature of the long noncoding RNAs (IncRNAs) in the prognostic expression signature

| IncRNA name | Ensembl ID  | Coefficient | \( P \) value | Gene expression level association with poor prognosis |
|-------------|-------------|-------------|--------------|------------------------------------------------------|
| RP11-495K9.6 | ENSG00000249926 | 1.13 | .01 | High |
| RP11-96O20.2 | ENSG00000259681 | 1.35 | .01 | High |
| RP11-359K18.3 | ENSG00000259788 | 1.42 | <.001 | High |
| LINCO0556 | ENSG00000260131 | 2.17 | <.001 | High |

*Derived from the univariable Cox analysis in the training set.

**FIGURE 2** The performance of the four-long noncoding RNAs (IncRNA) signature in Hepatocellular carcinoma prognosis prediction. A-C, Kaplan-Meier analysis of the SIGNATURE in the training, test, and entire The Cancer Genome Atlas datasets. D-F, Comparing the survival prediction power between the IncRNA signature and tumor/node/metastasis stage by receiver operating characteristic in the training, test, and entire datasets.
2.2 | Statistical analysis

We used R program, including pROC, TimeROC, Survival, and RandomForestSRC (from Bioconductor: http://www.bioconductor.org/) to perform statistics and machine learning analysis. Using the receiver operating characteristic (ROC) and the Time ROC analysis, we compared the prognostic performance of tumor/node/metastasis (TNM) stage and the lncRNA signature. Cox analysis was performed on the data processing to identify the prognostic factors with significance defined as $P < .05$. Pearson’s test with $P < .05$ and the Pearson coefficient $>|-.2|$ were used to select co-expressed protein-coding genes with lncRNAs which were visualized by Cytoscape (3.2.3). We performed Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analysis by the R package clusterProfiler.

### RESULTS

#### 3.1 | Constructing the lncRNA signature for predicting HCC prognosis in the training group

Table 1 displayed the detailed clinical information of the 180 HCC patients. The median age of the enrolled patients was 63 years (20-90 years) including 67 female and 113 male patients. A total of 165 HCC patients were categorized as TNM stage I to IV. These 180 HCC patients were randomly divided into two groups, one as the training ($n = 90$) group and one as the test group ($n = 90$). We constructed prognostic lncRNA signature from the training group and then verified its predictive power in the test group.

First, we selected 9683 lncRNAs with coefficient of variance $<0.1$ based on their expression value from 12727 lncRNAs. Then, we used univariate Cox regression analysis and got a 642-lncRNA set associated with HCC patient OS (Figure 1A, $P < .05$). Finally, through random survival forests analysis, we obtained 9 prognostic lncRNAs according to importance score (Figure 1A, B).

Kaplan-Meier and ROC analyses were performed on $2^{29} - 1 = 511$ signatures. The lncRNA combination including RP11-495K9.6, RP11-96O20.2, RP11-359K18.3, and LINC00556 was considered as the final lncRNA signature since its AUC value was the largest (AUC > 0.70) and log-rank $P < .001$ (Figure 1C). The lncRNA signature risk score (Table 2) = $(1.13 \times \text{RP11-495K9.6 expression value}) + (1.35 \times \text{RP11-96O20.2 expression value}) + (1.42 \times \text{RP11-359K18.3 expression value}) + (2.17 \times \text{LINC00556 expression value})$.

### TABLE 3  Association of the long noncoding RNA signature with clinicopathological characteristics in the hepatocellular carcinoma patients

| Variables                      | Train group |          | Test group |          | Entire group |          |
|--------------------------------|-------------|----------|------------|----------|--------------|----------|
|                                | Low risk $^a$ | High risk $^a$ | P          | Low risk $^a$ | High risk $^a$ | P          | Low risk $^a$ | High risk $^a$ | P          |
| Age (y)                        |             |          |            |          |              |          |              |              |            |
| >63                            | 17          | 25       | .14        | 21        | 23           | .83       | 38           | 48           | .18        |
| ≤63                            | 28          | 20       |            | 24        | 22           |           | 52           | 42           |
| Sex                            |             |          |            |          |              |          |              |              |            |
| Female                         | 10          | 18       | .11        | 23        | 16           | .20       | 33           | 34           | .35        |
| Male                           | 35          | 27       |            | 22        | 29           |           | 57           | 56           |
| M stage                        |             |          |            |          |              |          |              |              |            |
| M0                             | 39          | 32       | .16        | 31        | 29           | .27       | 70           | 61           | .21        |
| M1                             | 0           | 1        |            | 2         | 0            |           | 2            | 1            |
| N stage                        |             |          |            |          |              |          |              |              |            |
| N0                             | 28          | 31       | .37        | 29        | 23           | .31       | 57           | 54           | .62        |
| N1                             | 2           | 0        |            | 0         | 1            |           | 2            | 1            |
| N2                             | 14          | 14       |            | 16        | 21           |           | 30           | 35           |
| T stage                        |             |          |            |          |              |          |              |              |            |
| T1                             | 22          | 17       | .09        | 14        | 22           | .22       | 36           | 39           | .17        |
| T2                             | 14          | 9        |            | 17        | 9            |           | 31           | 18           |
| T3                             | 8           | 17       |            | 9         | 10           |           | 17           | 27           |
| T4                             | 0           | 2        |            | 5         | 3            |           | 5            | 5            |
| Tumor/node/metastasis stage    |             |          |            |          |              |          |              |              |            |
| I                              | 20          | 17       | .22        | 14        | 20           | .20       | 34           | 37           | .29        |
| II                             | 13          | 9        |            | 14        | 8            |           | 27           | 17           |
| III                            | 9           | 17       |            | 11        | 10           |           | 20           | 27           |
| IV                             | 0           | 1        |            | 2         | 0            |           | 2            | 1            |

$^a$Low risk ≤ median of risk score; high risk > median of risk score; the chi-squared test; $P$ value < .05 was considered significant.
3.2 | The predictive performance of the four-lncRNA signature

Based on the four-lncRNA signature, HCC patients obtained their risk scores. We used the median risk score as a cutoff point for Kaplan-Meier analysis, and HCC patients in the training group (n = 90) were subgrouped into two risk groups with significantly different survival. The median survival of the high-risk group was shorter than that of the low-risk group (median survival time: 1.81 years, 95% confidence interval [CI]: 1.50-4.91 vs 8.56, 95% CI: 6.96-9.97, log-rank test P < .001; Figure 2A). Then, we test the survival predictive performance of the signature in the test set. Kaplan-Meier result revealed the outcome of high-risk patients were significantly different from low-risk patients (median survival time: 1.95, 95% CI: 1.14-4.96 vs 5.80 years, 95% CI: 3.11-6.82, P = .007; Figure 2B). At last, we tested the risk identification ability of the signature in the entire TCGA dataset (n = 180) and the Kaplan-Meier result showed that the HCC patients of the low-risk group (n = 90) outlived the high-risk group (n = 90) in Figure 2C (log-rank P < .001).

3.3 | Prognostic independence test of the four-lncRNA signature

Chi-square test found there was no correlation between the signature and other clinical features (Table 3). We further performed univariable and multivariable Cox analysis to evaluate the prognostic independence of the four-lncRNA signature. As shown in Table 4, the four-lncRNA signature was proved to be an independent indicator in the training group (high-risk vs low-risk, HR = 3.95, 95% CI 3.65-8.90, P < .001, n = 90). The test group and the entire TCGA set verified the accuracy of the independence test (HR = 2.38, 95% CI 1.14-4.96, P = .02, n = 90; HR = 3.82, 95% CI 2.17-6.71, P < .001, n = 180).

3.4 | Comparison of the lncRNA signature with TNM stage system

Receiver operating characteristic analyses found that the AUC value of the lncRNA signature was greater than that of the

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**TABLE 4** Univariable and multivariable Cox regression analysis of the lncRNA signature with survival of hepatocellular carcinoma patients in the training group, test group, and entire group

| Variables                       | The training set (n = 90) | The Test set (n = 90) | The TCGA dataset (n = 180) |
|--------------------------------|--------------------------|-----------------------|-------------------------------|
|                                | HR Lower Upper P         | HR Lower Upper P      | HR Lower Upper P             |
| Univariable analysis           |                          |                      |                              |
| Age >63 vs ≤63                 | 0.76 0.37 1.55 .44       | 1.51 0.79 2.88 .22   | 1.09 0.68 1.74 .73          |
| Sex Male vs female             | 1.60 0.73 3.50 .24       | 1.15 0.62 2.13 .65   | 1.26 0.78 2.03 .34          |
| TNM stage IV vs I + II         | 1.36 0.90 2.06 .15       | 1.24 0.85 1.81 .27   | 1.30 0.98 1.71 .07          |
| lncRNA signature High risk vs  | 3.34 3.23 7.03 <.001     | 2.03 1.08 3.84 .03   | 3.56 2.11 6.00 <.001        |
| Multivariable analysis         |                          |                      |                              |
| Age >63 vs ≤63                 | 0.93 0.43 2.01 .85       | 1.45 0.71 2.97 .31   | 1.18 0.71 1.98 .52          |
| Sex Male vs female             | 2.59 1.09 6.15 .03       | 1.13 0.55 2.32 .73   | 1.34 0.80 2.22 .27          |
| TNM stage IV vs I + II         | 1.10 0.71 1.70 .68       | 1.40 0.94 2.08 .10   | 1.35 1.02 1.78 .04          |
| lncRNA signature High risk vs  | 3.95 3.65 8.90 <.001     | 2.38 1.14 4.96 .02   | 3.82 2.17 6.71 <.001        |

Abbreviation: TNM, tumor/node/metastasis.
TNM stage system in the training, test, and entire datasets (n = 90/90/180), (lncRNA model-AUC = 0.73/0.62/0.67 vs TNM-AUC = 0.60/0.60/0.60, Figure 2D-F), demonstrating the lncRNA signature had better survival predictive performance. Combining the lncRNA signature and the TNM stage had the largest AUC value, indicating the signature could be used as an auxiliary prognostic marker (Both-AUC = 0.76/0.65/0.71, Figure 2D-F).

On the other hand, the result of TimeROC demonstrated that the predictive ability of lncRNA signature outperformed that of the TNM stage. The AUCs of the four-lncRNA signature in the training group were 0.75/0.75/0.72/0.78 at 2/3/4/5 years, greater than the corresponding AUC values of TNM stage (Figure 3A,B). Similar results were also visible in the entire TCGA dataset (signature-AUC training = 0.67/0.65/0.62/0.69 at 2/3/4/5 years vs TNM-AUC training = 0.50/0.57/0.58/0.61 at 2/3/4/5 years, Figure 3C,D).
3.5 | Stratified analysis for TNM stage

Combined the TNM stage with lncRNA signature risk scores, we stratified the HCC patients into different subgroups. HCC patients with TNM I + II stage were stratified into high-risk and low-risk subgroups. Kaplan-Meier analysis showed there was a significant difference in survival time between the two subgroups (log-rank test $P < .001$, Figure 4A). HCC patients with TNM III + IV stage were also divided into two risk subgroups with different survival (log-rank test $P = .0043$, Figure 4B).

3.6 | Function prediction of the four lncRNAs in the signature

First, we used Pearson's test to compute the co-expressed mRNAs with the four lncRNAs in the entire TCGA dataset ($n = 180$). A total of 749 mRNAs were selected which were co-expressed with at least one of the four lncRNAs (coefficient >0.2/<=0.2, $P < .05$, Table S1, Figure 5A). Then, we used those co-expressed genes to predict the biological function of the four lncRNAs. We found the four lncRNAs were enriched in 27 GO terms and KEGG pathways and the top 20
pathways were visualized in Figure 5B, such as DNA replication and cell cycle checkpoint \( (P < .05 \text{ Figure 5B}) \).

4 | DISCUSSION

A vast amount of research suggests that lncRNAs might serve as biomarkers in the diagnosis and prognosis of various tumors, including HCC. In addition, IncRNA has the advantage of being a marker because it is easy to detect in body fluids.\(^{24}\) Thus, there have been many articles on the prognostic IncRNA markers of HCC. Based on high throughput sequencing data, IncRNAs associated with the HCC prognosis have been identified, such as ASB16-AS1, LINC01138, and CTC-297N7.9.\(^{12,13,25}\) These IncRNAs were found play important roles in HCC carcinogenesis through regulating tumor proliferation and migration. Because of its better predictive efficacy, IncRNA signatures have been developed for prognostic prediction in many cancers such as esophageal squamous cell carcinoma, glioblastoma, lung adenocarcinoma, and pancreatic ductal adenocarcinoma, among others.\(^{19,26-28}\)

In this study, we collected and downloaded the expression data and clinical information of HCC cohort from Tanric and TCGA. Using statistical and machine learning analysis, we found 642 IncRNAs significantly correlated with overall survival and constructed a four-IncRNA signature which was proved to be a reliable indicator of HCC survival in 180 samples. The independence test detected the survival prediction ability of the four-IncRNA signature in HCC was not affected by age, gender, and TNM stage. In addition, stratification analysis discovered the four-IncRNA signature or the four-IncRNA-based risk score model can further subdivide HCC patients at same TNM stage into different risk groups with significantly different outcomes, suggesting that the four-IncRNA signature can be used as an advanced prognostic model for TNM stage in HCC. Moreover, we found high expression of RP11-495K9.6, RP11-96020.2, RP11-359K18.3, and LINC00556 was correlated with poor prognosis of HCC patients \( (HR > 1, P < .05) \). Since the function of these four IncRNAs has not been reported yet, we performed Go and KEGG analysis and found that the coding genes co-expressed with the four IncRNAs were enriched in terms related to DNA replication and repair, indicating that the four IncRNAs in the signature may participate in the HCC progression through DNA replication and repair related pathways. The specific mechanism of these IncRNAs regulates the prognosis of HCC remains to be elucidated.

In summary, using statistical and machine learning analyses, we constructed a four-IncRNA signature including RP11-495K9.6, RP11-96020.2, RP11-359K18.3, and LINC00556 which could be used effectively to predict clinical outcome of HCC patients. The four-IncRNA signature exerts great applicable value in prognosis prediction, therapy selection, and disease recognition.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS
Haitao Jiang contributed to data analysis, interpretation, and drafting. Lianhe Zhao contributed to data collection. Yunjie Chen and Liang Sun involved in study design, study supervision, and final approval of the article. All authors read and approved the final article.

DATA AVAILABILITY STATEMENT
LncRNA transcriptome expression data of patients were downloaded from the Tanric database (https://www.tanric.org/home).

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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