



Identification of a Somatic Mutation-Derived Long Non-Coding RNA Signatures of Genomic Instability in Renal Cell Carcinoma

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Specialty section:

This article was submitted to
Genitourinary Oncology,
a section of the journal
Frontiers in Oncology

Received: 21 June 2021

Accepted: 09 September 2021

Published: 05 October 2021

Citation:

Fang X, Liu X, Lu L and Liu G (2021)
Identification of a Somatic Mutation-
Derived Long Non-Coding RNA
Signatures of Genomic Instability in
Renal Cell Carcinoma.
Front. Oncol. 11:728181.
doi: 10.3389/fonc.2021.728181

Background: Renal cell carcinoma (RCC) is a malignant tumor with high morbidity and mortality. It is characterized by a large number of somatic mutations and genomic instability. Long non-coding RNAs (lncRNAs) are widely involved in the expression of genomic instability in renal cell carcinoma. But no studies have identified the genome instability-related lncRNAs (GlnLncRNAs) and their clinical significances in RCC.

Methods: Clinical data, gene expression data and mutation data of 943 RCC patients were downloaded from The Cancer Genome Atlas (TCGA) database. Based on the mutation data and lncRNA expression data, GlnLncRNAs were screened out. Co-expression analysis, Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were conducted to explore their potential functions and related signaling pathways. A prognosis model was further constructed based on genome instability-related lncRNAs signature (GlnLncSig). And the efficiency of the model was verified by receiver operating characteristic (ROC) curve. The relationships between the model and clinical information, prognosis, mutation number and gene expression were analyzed using correlation prognostic analysis. Finally, the prognostic model was verified in clinical stratification according to TCGA dataset.

Results: A total of 45 GlnLncRNAs were screened out. Functional analysis showed that the functional genes of these GlnLncRNAs were mainly enriched in chromosome and nucleoplasmic components, DNA binding in molecular function, transcription and complex anabolism in biological processes. Univariate and Multivariate Cox analyses further screened out 11 GlnLncSig to construct a prognostic model (AL031123.1, AC114803.1, AC103563.7, AL031710.1, LINC00460, AC156455.1, AC015977.2, 'PRDM16-dt', AL139351.1, AL035661.1 and LINC01606), and the coefficient of each GlnLncSig in the model was calculated. The area under the curve (AUC) value of the ROC curve was 0.770. Independent analysis of the model showed that the GlnLncSig model was significantly correlated with the RCC patients' overall survival. Furthermore, the GlnLncSig model still had prognostic value in different subgroups of RCC patients.

Conclusion: Our study preliminarily explored the relationship between genomic instability, lncRNA and clinical characteristics of RCC patients, and constructed a GlnLncSig model consisted of 11 GlnLncSig to predict the prognosis of patients with RCC. At the same time, our study provided theoretical support for the exploration of the formation and development of RCC.

Keywords: renal cell carcinoma, lncRNA, genomic instability, genome instability-related lncRNAs (GlnLncRNAs), prognostic risk model

INTRODUCTION

As the most common urinary malignancy in the United States, there are about 73,820 new cases of RCC each year, and 14,770 deaths from the disease (1). At present, surgical resection is the main treatment for patients with RCC (2, 3). However, about 1/3 of patients have metastases at the time of diagnosis, and 1/5 patients have metastases or recurrences after radical treatment (4). RCC has a poor sensitivity to radiotherapy and chemotherapy. Targeted therapy and immunotherapy are the other treatment options (5–7). Currently, there is no biomarker in clinical practice that can well predict the prognosis of RCC patients.

In recent years, scientists have found that an important part of the non-coding genome is transcribed to produce non-coding RNAs, among which a subset longer than 200 nt at length, capped polyglanular transcripts transcribed by RNA polymerase II, which are known as long non-coding RNAs (lncRNA). It has been confirmed that lncRNA plays an important role in genomic function and gene expression, as well as in the etiology and treatment of malignant tumors (8). Some researchers have found that several lncRNAs are related to the prognosis of RCC patients. lncRNA B7H4 was expressed in the endothelium of tumor cells or tumor blood vessels but not in normal tissues. Therefore, low expression of B7H4 can be used as a predictor of survival in patients with RCC (9–11). TRAF3IP2-AS1 functioned as a tumor suppressor in RCC progression. Overexpression of TRAF3IP2-AS1 inhibited the proliferation, migration and invasion of UOK109 cells (12). Generally, single biomarkers have their limitations in terms of sensitivity and specificity. Therefore, some researchers have tried to construct prognostic models to predict the prognosis of RCC patients in a broader sense by screening a panel of biomarkers (13, 14).

Genomic instability plays a key role in the development of cancer. For example, structural changes in proto-oncogenes and tumor suppressor genes may lead to abnormalities in cell functions, including cell growth, cell cycle, cell senescence and apoptosis, cell invasion and metastasis (15–18). The genomic

instabilities of cancer mainly include gene mutation, chromosome rearrangement and aneuploidy (19). Genomic instability has been identified as a key prognostic factor, and it is of great importance to explore its clinical significance.

MATERIALS AND METHODS

Clinical Data Download and Data Consolidation

Gene transcriptome profiling, gene mutation data and clinical information of RCC patients were downloaded from the TCGA database as of March 2021. Perl software was used to extract all the mRNAs and lncRNAs and then annotated them with the HUGO Gene Nomenclature Committee (HGNC) database. This study complied with the publication guidelines of TCGA. And no additional ethical consent was required.

Screening and Identification of lncRNAs Related to Genomic Instability

We extracted the lncRNA expression profile and the cumulative mutation frequency of each sample from the entire annotated transcriptome data. Wilcoxon rank sum test was used to screen GlnLncRNAs differentially expressed between the top 25% of samples and the bottom 25% of samples with cumulative mutation frequency by using “limma” package in R software. Heat maps of differentially expressed GlnLncRNAs in the two groups were constructed using the “pheatmap” package in the R software. Subsequently, the expression level of each sample was calculated according to the above GlnLncRNAs and were divided into two groups. Median mutation frequency values of the two groups were calculated respectively. The two groups with higher and lower median values were set as Genomic Unstable type (GU-like) and Genomic Stable type (GS-like), respectively. Heatmaps of the two groups of differentially expressed lncRNAs were constructed using the “pheatmap” package in the R software. Next, the mutation frequency of all samples in the GU-like group and the GS-like group as well as the expression level of the genomic instability driver gene “UBQLN4” (20) were compared. Then the “ggpubr” package was used to construct a boxplot of the difference in mutation frequency and expression of “UBQLN4” gene between the two groups in R software.

Gene Co-Expression Network

The expression levels of lncRNA and mRNA were retrieved using the “limma” package in R software. Pearson correlation

Abbreviations: RCC, Renal cell carcinoma; lncRNAs, Long non-coding RNAs; GlnLncRNAs, genome instability-related lncRNAs; TCGA, The Cancer Genome Atlas; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GlnLncSig, genome instability-related lncRNA signature; ROC, receiver operating characteristic; AUC, area under the curve; HGNC, HUGO Gene Nomenclature Committee; GU-like, Genomic Unstable type; GS-like, Genomic Stable type; CC, chromosome and nucleoplasmic components; MF, molecular function; BP, biological processes; KICH, Kidney chromophobe; UCEC, Uterine Corpus Endometrial Carcinoma; NGS, next-generation sequencing.

analysis was performed to determine the target mRNA of GlnLncRNA. The top ten genes with the highest correlation were selected as the target genes of this GlnLncRNA according to Pearson correlation coefficient, and the co-expression network was visualized by Cytoscape software.

Functional Enrichment Analysis

In order to predict the potential function and pathway of the GlnLncRNAs, we performed functional enrichment analysis on related mRNAs co-expressed with GlnLncRNAs to determine significantly enriched GO terms and KEGG pathways. The packages of “clusterProfiler”, “org.Hs.eg.db”, “enrichplot” and “ggplot2” in R software were used with P value and adjust P value < 0.05.

Construction of a Prognostic Risk Model

After matching the expression of lncRNA transcriptional profile, somatic mutation data and clinicopathological features of the RCC patients, we randomly divided 857 samples into two groups in a ratio of 1:1 and named Train set and Test set, using the “caret” package in R software. The 429 samples of the Train set were designed to identify GlnLncSig and to construct prognostic model. Besides, the 428 samples of the Test set were used to investigate the performance of the prognostic model. Univariate Cox analysis was conducted to find out the GlnLncSig in the Train set with the “Survival” package in R software. Subsequently these GlnLncSig were used to construct a prognostic model.

Assessment of the Performance of the Prognostic Risk Model

Each patient’s risk value in the Train set was calculated by the coef of GlnLncSig in the prognostic model. According to the median risk value of the Train set, patients in the Test set and entire TCGA cohort were divided into high-risk group and low-risk group. The packages “survival” and “survminer” were used to perform log-rank test ($P < 0.05$) for patients in the high-risk and low-risk groups in R software. Furthermore, the Kaplan-Meier method was used to draw the survival curves of the Test set and entire TCGA cohort. The Receiver Operating Characteristic (ROC) curve with Areas Under Curve (AUC) values of the prognostic model was assessed by the “survival ROC” package in R software.

Independent Analysis of the Model Constructed by GlnLncSig in Clinical Stratification

In order to test whether the prognostic model constructed by GlnLncSig can be used as an independent prognostic factor, we extracted the clinical information of RCC patients in TCGA database and deleted the cases with clinical information gaps. Univariate Cox regression analysis was performed to explore the prognostic values of age, gender, tumor grade, tumor clinical stage and prognostic model using the “survival” package of R software. And Multivariate prognostic analysis was performed for factors with $P < 0.05$ in the extraction results. Next, we divided the RCC patients of the TCGA database into different

subgroups according to clinical parameters, including age (≤ 65 years and > 65), gender (female and male), tumor grade (G1-2 and G3-4), and tumor stage (I-II and III-IV). Patients in each clinical subgroup were further divided into high-risk and low-risk groups based on the median risk value. The Kaplan-Meier analysis and log-rank test were used to compare the differences in survival between high-risk and low-risk groups in each clinical subgroup.

Statistical Analysis

Gene expression, mutation data and clinical information from the TCGA dataset were retrieved in R software (R3.6.2) or Perl software (Strawberry Perl(64-bit)). All the statistical analyses were evaluated by R software. AP-value < 0.05 was statistically significant.

RESULTS

Screening of Genomic Instability-Related lncRNAs of RCC Patients in TCGA Database

The somatic mutation information of 336 patients with RCC, lncRNA and mRNA transcriptional profiles of 895 patients with RCC, and clinicopathological features of 943 patients with RCC were downloaded from the TCGA database. Each sample was ranked according to the number of mutations. There were 45 GlnLncRNAs differentially expressed between the GU-like group and GS-like group. All the differentially expressed GlnLncRNAs were demonstrated by heat maps (**Supplementary Figure 1**). Subsequently, boxplot showed that there were significant differences in the somatic mutation count (**Figure 1A**) and the expression of genomic instability driver gene “UBQLN4” (**Figure 1B**) between the two groups.

Analysis of Potential Functions and Pathways of the GlnLncRNAs

In order to determine whether the functions and pathways of these 45 differential GlnLncRNAs were related to genomic instability, we explored the potential functions of GlnLncRNAs by co-expression analysis, GO function enrichment analysis and KEGG pathway analysis. **Figure 2A** showed the co-expression network of lncRNA-mRNA which reflecting the relationship between them. The names of the top 10 mRNAs co-expressed with each GlnLncRNA were labeled according to Pearson correlation coefficient analysis. GO function enrichment analysis of GlnLncRNA-related genes showed that their functions were mainly enriched in chromosome and nucleoplasmic components (CC), DNA binding in molecular function (MF), and transcription and complex anabolism in biological processes (BP) ($P < 0.05$) (**Figure 2B**). By analyzing the KEGG pathways of lncRNA-associated protein-related genes, 18 pathways were found to be significantly enriched. And most of the enriched pathways were related to genomic instability, including HIF-1 signaling pathway, AMPK signaling pathway and Oxidative phosphorylation (**Figure 2C**).

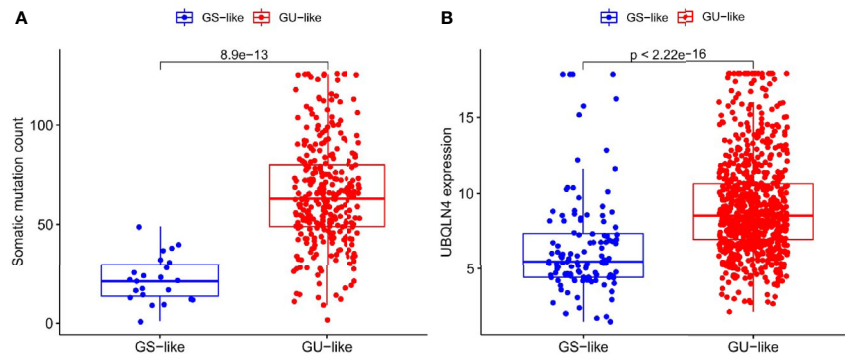


FIGURE 1 | Differences in somatic mutation counts and UBQLN4 between GU-like group and GS-like group. **(A)** Differences in somatic mutation counts between GU-like group and GS-like group. The mutation counts of the GS-like group were significantly lower than that of the GU-like group ($P < 0.001$, Mann-Whitney U test). **(B)** Differences in expression of UBQLN4 between GU-like group and GS-like group. The expression of UBQLN4 in GU-like group were significantly higher than that of the GS-like group ($P < 0.001$, Mann-Whitney U test).

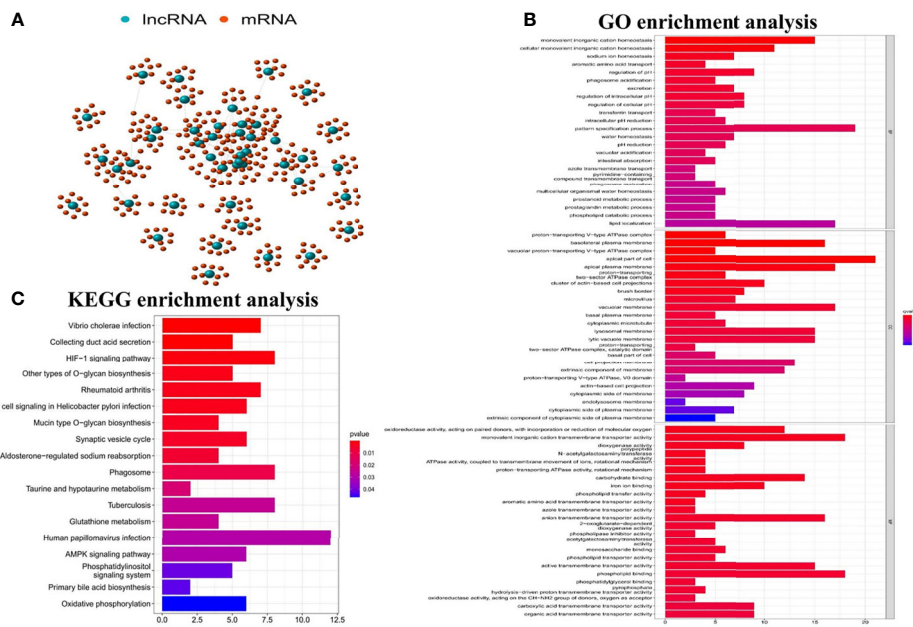


FIGURE 2 | Functional analyses of the GlnLncRNAs. **(A)** The relationship networks between GlnLncRNAs and their top 10 co-expressed protein-coding genes were constructed according to Pearson correlation coefficient. The GlnLncRNAs and protein-coding mRNAs were represented by blue and orange circles, respectively. **(B)** Barplot of GO enrichment analysis of protein genes co-expressed with the GlnLncRNAs ($P < 0.05$). **(C)** Barplot of KEGG enrichment analysis of protein genes co-expressed with the GlnLncRNAs ($P < 0.05$).

Construction of a Prognostic Model

A total of 857 RCC patients in the TCGA database had complete lncRNA expression profiles, somatic mutation data and clinicopathological characteristics. **Table 1** showed that there were no significant differences in clinicopathological characteristics between Train set (429 cases) and Test set (428 cases) (including age, gender, tumor grade, clinical stage, T stage, N stage, and M stage).

Univariate Cox proportional hazard regression analysis was used for screening. And 25 out of 45 GlnLncRNAs in the Train

set were significantly associated with overall survival ($P < 0.05$, **Figure 3** and **Supplementary Table 1**). Subsequently, a survival prediction model with 11 GlnLncRNAs was constructed by Multivariate Cox proportional hazard regression analysis (**Supplementary Table 2**). Among them, the coefficient of four GlnLncRNAs (AL031123.1, AC114803.1, AC103563.7 and AL031710.1) were negative, indicating that they might act as protective factors. Up-regulated expression of them were associated with better survival. Otherwise, the coefficient of

seven GlnLncRNAs (LINC00460, AC156455.1, AC015977.2, 'PRDM16-dt', AL139351.1, AL035661.1, LINC01606) were positive, indicating that they were risk factors and up-regulated expression of them were associated with poor prognosis.

Assessment of the Prognostic Model

In order to evaluate the predictive effectiveness of the prognostic model, patients in the Test set and entire TCGA cohort were divided into high-risk group and low-risk group according to the median risk value of patients in the Train set. It was obvious that the overall survival of patients in the low-risk group was significantly better than the high-risk group ($P < 0.001$, log-rank test; **Figures 4A, B**). The AUC of the ROC curves in the Test set and entire TCGA cohort were 0.743 and 0.770, respectively, which suggesting that the risk model had a good predictive effectiveness (**Figures 4C, D**).

Independent Analysis of the Prognostic Model in Clinical Stratification

To explore whether the prognostic model constructed by GlnLncSig can be used as an independent prognostic factor, Univariate and Multivariate Cox regression analyses were performed to analyze the prognostic values of age, gender, tumor grade, tumor clinical stage and the prognostic model. As shown in **Table 2**, clinical information, including age, gender, tumor grade, tumor clinical stage as well as the prognostic model were significantly correlated with the patients' overall survival in univariate Cox analysis. And Multivariate Cox analysis showed that age, tumor grade, tumor clinical stage and the prognostic model still retained prognostic significance.

In order to verify whether the prognostic model still had prognostic value in different subgroups of RCC patients, we divided the RCC patients into different subgroups according to various clinical parameters, including age (≤ 65 years and > 65 years), gender (female and male), tumor grade

(G1-2 and G3-4), and tumor stage (I-II and III-IV). Kaplan-Meier analysis showed that patients with a low-risk value had significantly better survival outcomes than those with a high-risk value in all the subgroups except for the G1-2 subgroup (**Figure 5**). These results suggested that the model constructed by GlnLncSig can be used as an independent prognostic factor for different subgroups of RCC patients.

DISCUSSION

Genomic instability was a characteristic feature of most human cancers (21). Generally, genomic instability included single-base, double-base, or cluster-base substitutions, copy number changes, small insertions and deletions, and genome rearrangements. The accumulation of genetic changes could turn normal cells into malignant cells (22–24). In addition, persistent genomic instability allowed tumor cells to adapt to their microenvironment under selective pressure and thus become resistant to antitumor therapies (25, 26). Processes of genomic instability drove tumors genetics. Studies had found that proto-oncogenes and tumor suppressor genes in nearly 20 common malignant tumors, in which Kidney chromophobe (KICH) was the fewest with 2 genes and Uterine Corpus Endometrial Carcinoma (UCEC) were the most with 55 genes (22). Furthermore, genomic instability was widely involved in the diagnosis and prognosis of various malignant tumors, especially esophageal, bladder, breast, and lung cancers (15, 17, 27, 28). Long non-coding RNAs (lncRNAs) were major components of the mammalian transcriptome and played central roles in a variety of cellular mechanisms. At present, there was evidence indicating that lncRNA was closely related to genomic instability (29). It could promote the occurrence, development and metastasis of RCC (30–32). However, there were still few studies concerning the

TABLE 1 | Clinicopathological information of the patients with RCC in TCGA cohort.

Covariates	Type	Total (n = 857)	Test (n = 428)	Train (n = 429)	Pvalue
Age	<=65	560 (65.34%)	283 (66.12%)	277 (64.57%)	0.5818
Age	>65	292 (34.07%)	141 (32.94%)	151 (35.2%)	
Age	unknown	5 (0.58%)	4 (0.93%)	1 (0.23%)	
Gender	FEMALE	274 (31.97%)	139 (32.48%)	135 (31.47%)	0.8079
Gender	MALE	583 (68.03%)	289 (67.52%)	294 (68.53%)	
Grade	G1-2	231 (26.95%)	109 (25.47%)	122 (28.44%)	
Grade	G3-4	274 (31.97%)	140 (32.71%)	134 (31.24%)	
Grade	unknown	352 (41.07%)	179 (41.82%)	173 (40.33%)	
Stage	Stage I-II	543 (63.36%)	271 (63.32%)	272 (63.4%)	1
Stage	Stage III-IV	281 (32.79%)	140 (32.71%)	141 (32.87%)	
Stage	unknown	33 (3.85%)	17 (3.97%)	16 (3.73%)	
T	T1-2	592 (69.08%)	294 (68.69%)	298 (69.46%)	0.7837
T	T3-4	261 (30.46%)	133 (31.07%)	128 (29.84%)	
T	unknown	4 (0.47%)	1 (0.23%)	3 (0.7%)	
M	M0	532 (62.08%)	267 (62.38%)	265 (61.77%)	0.7314
M	M1	89 (10.39%)	47 (10.98%)	42 (9.79%)	
M	unknown	236 (27.54%)	114 (26.64%)	122 (28.44%)	
N	N0	312 (36.41%)	153 (35.75%)	159 (37.06%)	0.2965
N	N1-2	48 (5.6%)	28 (6.54%)	20 (4.66%)	
N	unknown	497 (57.99%)	247 (57.71%)	250 (58.28%)	

Chi-squared test, $P < 0.05$ means significantly different.

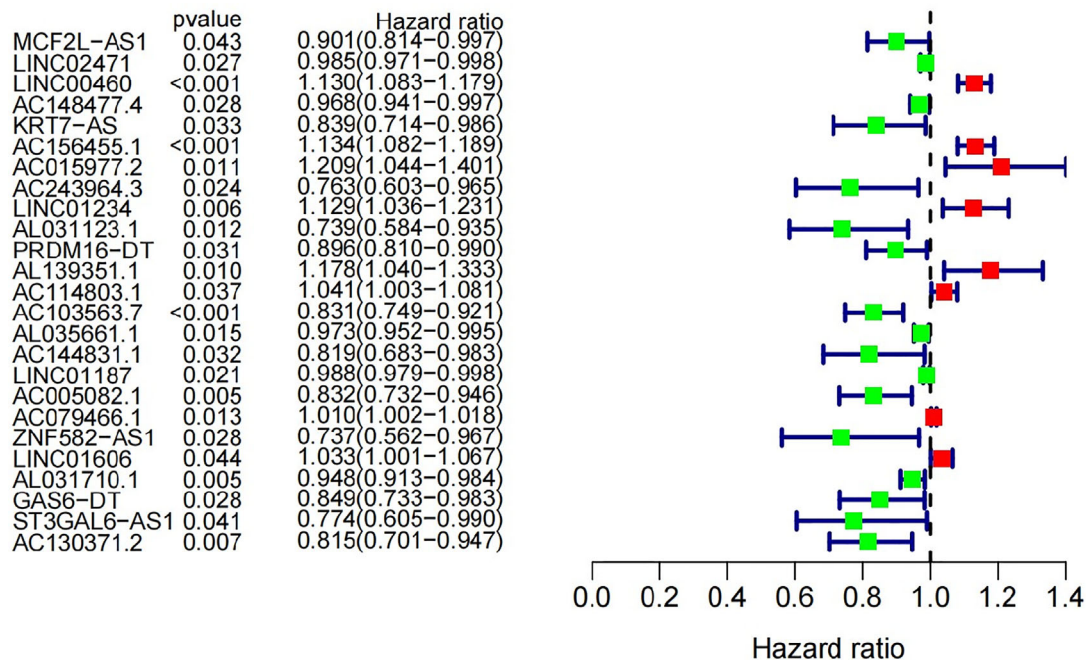


FIGURE 3 | Univariate Cox regression analysis was used in the Train set to construct forest plot of 25 GlnLncRNAs associated with patients' overall survival. Eight GlnLncRNAs were protecting factors for patients' survival (LINC00460, AC156455.1, AC015977.2, LINC01234, AL139351.1, AC114803.1, AC079466.1 and LINC01606), while the other seventeen GlnLncRNAs were the risk factors for patients' survival.

relationship between lncRNA associated with genomic instability in RCC, which was the main purpose of this research.

In our study, 45 lncRNAs were identified by comparing the expression levels of lncRNAs between genetic-unstable and genetic-stable RCC tumors from the selected patients based on TCGA database. Co-expression analysis, GO enrichment analysis and KEGG pathway analysis showed that the genes co-expressed with these 45 lncRNAs mainly enriched in pathways including HIF-1 signaling pathway, AMPK signaling pathway and Oxidative phosphorylation signaling pathway, which had also been proven to be related to genomic instability of tumors (33–35). These results suggested that the differentially expressed GlnLncRNAs may have direct or indirect causal relationships with genomic instability through the above mentioned pathways. Next, Univariate Cox regression analysis was used to screen 25 GlnLncRNAs that were significantly related to the survival of RCC patients from the 45 differentially expressed GlnLncRNAs in the Train set. Moreover, Multivariate Cox regression analysis was used to screen 11 GlnLncRNAs from the 25 prognostic GlnLncRNAs to build a prognostic model. The correlation coefficient calculation formula of the prognostic model for each GlnLncSig was obtained, and the risk value of each patient in the Test set was calculated according to the prognostic model. The results showed that patients with high risk value tended to have poor overall survival. The AUC of the model was > 0.7 in both the Train set and the Test set, which indicating that the model had good prediction performance. According to Multivariate Cox regression analysis, we found that

the prognostic model had independent prognostic value as well as age, tumor grade and tumor clinical stage. Furthermore, the prognostic model had prognostic value in patients with different ages (≤ 65 years and > 65 years), gender (female and male), tumor grade (G3-4) and clinical stage (I-II and III-IV). These results enabled the GlnLncSig model to have a wider range of application, and which could well predict the prognosis of RCC patients in different stratification.

Scholars had explored some prognostic models in RCC. May et al. predicted the disease-free and tumor-related survival rate of patients with RCC undergoing reoperation by using three pathological factors of tumor microvascular invasion, size and grade (36). Later studies gradually moved to the detection of molecules in the blood, including tumor markers (37), protein expression (38), and RNA-binding proteins (39). Some research also explored corresponding prognostic models according to metastatic (40–42) and non-metastatic (43, 44) RCC. With the development of next-generation sequencing (NGS) technologies, the detection of DNA, microRNA and lncRNA in the blood or tissues of patients had become more and more convenient and accessible. There were also studies that systematically evaluated the expression of DNA methylation markers (45), microRNA (46), and lncRNA (47, 48) to predict the prognosis of patients with RCC. However, these models were not relate to genomic instability, and some models could only predict the prognosis of specific patients, such as metastatic or non-metastatic RCC. In contrast, our prognostic model constructed by using genomic instability could not only effectively predict the prognosis of all

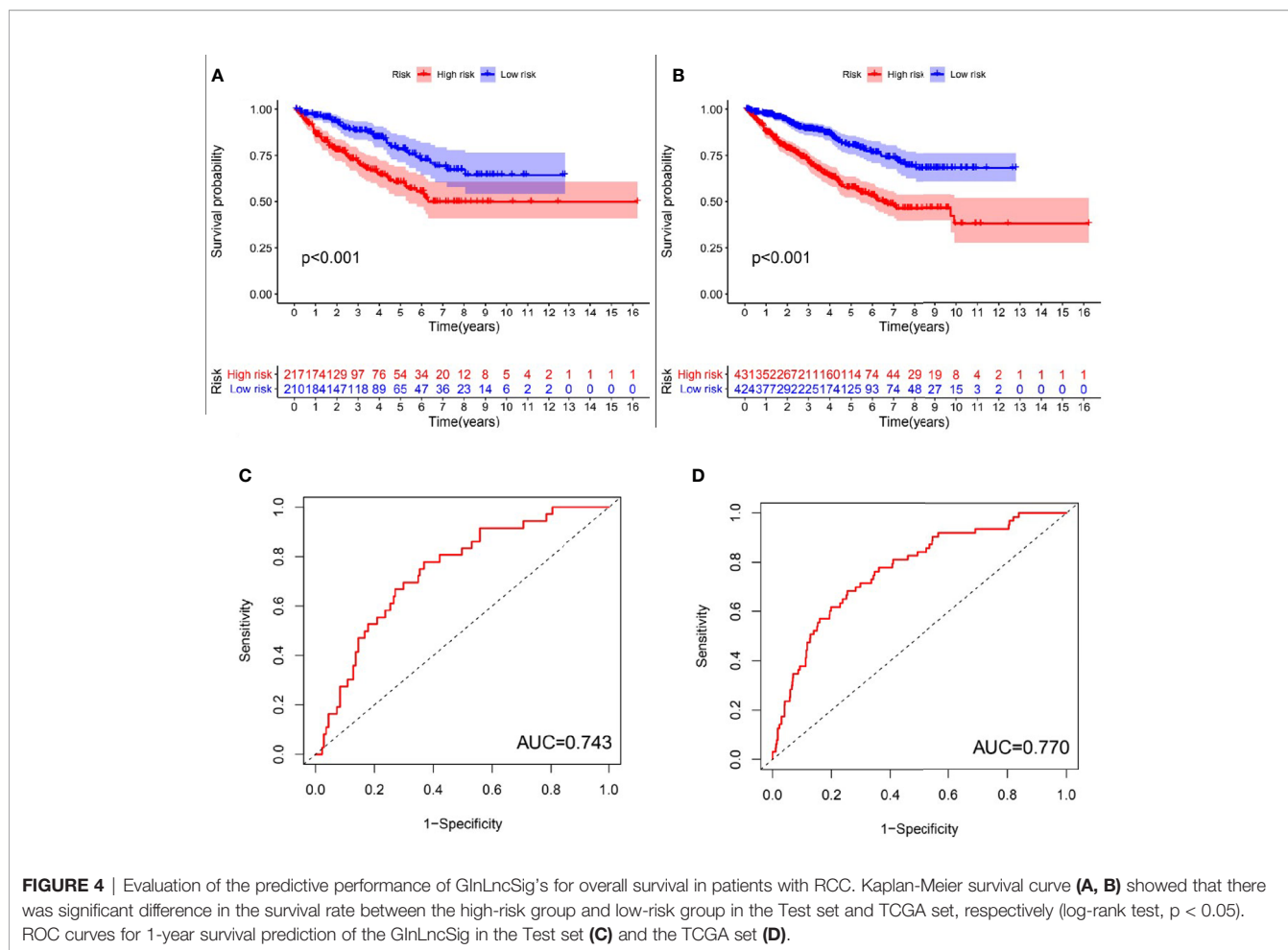


TABLE 2 | Univariate and Multivariate Cox regression analysis of the prognostic model and overall survival in TCGA set.

Variables	Univariable model				Multivariable model			
	HR	HR.95L	HR.95H	pvalue	HR	HR.95L	HR.95H	pvalue
Age	1.029	1.015	1.042	<0.001	1.031	1.016	1.046	<0.001
Gender	0.964	0.703	1.323	0.821				
Grade	2.268	1.845	2.787	<0.001	1.466	1.163	1.848	0.001
Stage	1.896	1.658	2.168	<0.001	1.669	1.433	1.945	<0.001
GlnLncSig model	1.026	1.016	1.036	<0.001	1.012	1.001	1.022	0.037

patients with RCC, but also had predictive value for patients with different stratification.

Some of the GlnLncSig in our model had also been verified to be abnormally expressed in a variety of malignant tumors and had prognostic values. LINC00460 was located on chromosome 13q33.2 and was transcribed as a 935nt transcript (49). Currently, abnormal expression of LINC00460 had been found in many cancers, including nasopharyngeal carcinoma (50), esophageal squamous cell carcinoma (51), colorectal carcinoma (52–54), lung adenocarcinoma (49), non-small cell lung cancer (55–57), etc. Upregulated expression of LINC00460 predicted poorer differentiation, advanced stage, and worse overall survival (58). In

addition, mechanism studies had shown that overexpression of LINC00460 may promote invasion and metastasis of NSCLC cells through epithelial-mesenchymal transformation pathway (57). Data had shown that LINC01606 was significantly overexpressed in gastric cancer cells compared with normal cells, and it promoted the migration and invasion of gastric cancer cells by acting as a ceRNA of miR-423-5p in Wnt/ β -catenin-dependent pathway (59). This suggested that LINC01606 may act as an oncogene in gastric cancer. Zimta et al. found that the expression of PRDM16-DT was down-regulated in acute myeloid leukemia, and patients with lower expression of PRDM16-DT had better prognosis than those with higher expression (60).

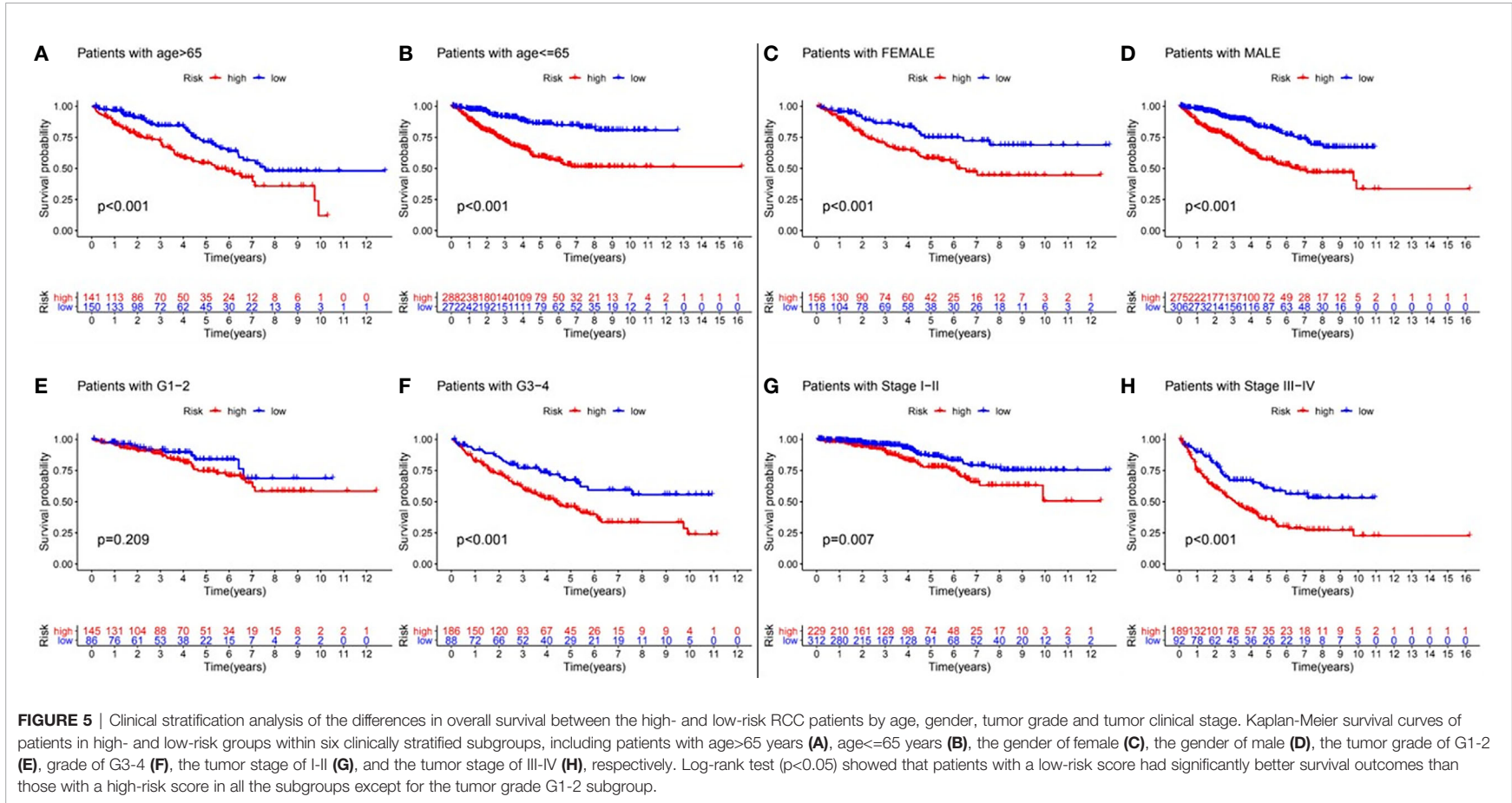


FIGURE 5 | Clinical stratification analysis of the differences in overall survival between the high- and low-risk RCC patients by age, gender, tumor grade and tumor clinical stage. Kaplan-Meier survival curves of patients in high- and low-risk groups within six clinically stratified subgroups, including patients with age>65 years (A), age<=65 years (B), the gender of female (C), the gender of male (D), the tumor grade of G1-2 (E), grade of G3-4 (F), the tumor stage of I-II (G), and the tumor stage of III-IV (H), respectively. Log-rank test (p<0.05) showed that patients with a low-risk score had significantly better survival outcomes than those with a high-risk score in all the subgroups except for the tumor grade G1-2 subgroup.

This is a preliminary study that explores the relationship between genomic instability, lncRNA and clinical characteristics of RCC patients. We constructed a GlnLncSig model, which could provide prognostic information in different clinical stratification. However, there were still several limitations of our study. First of all, the data sources of this study were only limited to TCGA database, and had not been further verified in multiple databases or clinical data of our hospital. Secondly, it was necessary to further explore the respective functions of each lncRNA in the prognostic model. Finally, given the NGS is becoming more available, consequently changes in gene expression are expected to be monitored during the treatment in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

GL and LL designed the study. XF performed the data analysis, graphing, and writing. XL was responsible for the critical reading

of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded by the Guangdong Medical Science and Research Foundation (No. B2021023), Guangzhou Planned Project of Science and Technology (No. 202102080609, No. 201904010427), the Natural Science Foundation of Guangdong Province, China (No. 2021A1515011113).

ACKNOWLEDGMENTS

We sincerely acknowledge the contributions from the TCGA project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2021.728181/full#supplementary-material>

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