Observational Study

Medicine

OPEN

Prognostic significance of MALAT1 in clear cell renal cell carcinoma based on TCGA and GEO

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Abstract

Long noncoding RNAs metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) can regulate tumorigenesis and progression of various cancers. However, there is little known about the tumor biology and regulatory mechanism of MALAT1 in clear cell renal cell carcinoma (ccRCC). The objective of this study was to evaluate the prognostic value and potential functions of MALAT1 in ccRCC based on the cancer genome atlas. Through bioinformatics research, we analyzed the expression of MALAT1 in ccRCC, and the relationship with clinicopathological features, overall survival and infiltration of immune cells, and established the prognostic models. The results showed that MALAT1 was highly expressed in ccRCC tissues and predicted poor ccRCC patient outcome. The expression level of MALAT1 was significantly correlated with histologic grade, pathologic grade, T stage, M stage. ROC curve showed that MALAT1 had a good diagnostic accuracy, area under the curve of 0.752. The univariate and multivariate cox regression analysis showed that high MALAT1 expression was an independent prognostic factor for overall survival in the cancer genome atlas (hazard ratio = 2.271, 95% confidence interval: 1.435–3.593, $P < .001$). Gene set enrichment analysis revealed that MALAT1 expression was associated with the DNA methylation, epigenetic regulation of gene expression signaling pathway. In addition, the prognostic models were established to predict 1-, 3- and 5-year survival. This study showed that high expression of MALAT1 might be a potential diagnostic and prognostic biomarker.

Abbreviations: ccRCC = clear cell renal cell carcinoma, DEGs = differentially expressed genes, GEO = gene expression omnibus, GO = gene ontology, GSEA = gene set enrichment analysis, KEGG = Kyoto encyclopedia of genes and genomes, MALAT1 = metastasis-associated lung adenocarcinoma transcript 1, OS = overall survival, ssGSEA = single sample gene set enrichment analysis, TCGA = the cancer genome atlas.

Keywords: biomarker, clear cell renal cell carcinoma, MALAT1, prognosis

1. Introduction

Clear cell renal cell carcinoma (ccRCC) arises from renal tubular epithelial cells and is the most common histological subtype of renal cancer, accounting for nearly 75% of all renal malignancies.[1] Each year, there are estimated to be 400,000 new cases of ccRCC worldwide,[2] and it is rising in incidence.[3] ccRCC is not only the most aggressive subtype of kidney cancer, but also one of the most resistant of solid tumors to conventional chemotherapy.[4] ccRCC is insensitive to radiotherapy and chemotherapy,[5] and surgical resection remains the mainstay of treatment for ccRCC patients.[6] Despite significant progress in using targeted therapies, the treatment of advanced or recurrent ccRCC remains largely ineffective.[7] Moreover, early ccRCC is usually asymptomatic and 30% patients are diagnosed in the advanced metastatic stage, with the 5-year survival rate <15%.[8] Therefore, it is essential to explore novel and reliable prognostic markers and therapeutic targets.

Long noncoding RNAs (lncRNAs) are a class of RNAs with over 200 nucleotides in length and nonprotein coding ability.[9] As a major lncRNA, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) plays an important role in tumorigenesis and the development of various tumors.[10] Upregulation of MALAT1 is identified as a hallmark of tumor progression and metastasis.[11,12] It has been found that high expression of MALAT1 in lung cancer[13,14] and colorectal cancer[15] is associated with increased tumor proliferation and metastasis. Zhang et al[16] showed that upregulation of MALAT1 promotes renal cancer cell proliferation, migration, and invasion, associated with tumor progression and poor prognosis. Despite these advances, the exact mechanisms of MALAT1 in tumor progression and prognosis remain unclear.

DNA methylation is the predominant forms of epigenetic regulations, involved in cell differentiation, proliferation, development. In non-small cell lung cancer, the effect of MALAT1 on tumor invasion relies on DNA methylation.[17]

This work was supported by Henan Medical Science and Technology Research Program Joint Construction Project (No. LHGJ20200769).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Liu K, Gao Y, Zhang Q. Prognostic significance of MALAT1 in clear cell renal cell carcinoma based on TCGA and GEO. Medicine 2023;102:37(e35249).

Received: 14 June 2023 / Received in final form: 29 July 2023 / Accepted: 24 August 2023

http://dx.doi.org/10.1097/MD.0000000000035249

Nevertheless, it remains unclear whether the progression and poor prognosis of ccRCC is related to the regulation of DNA methylation. Therefore, it is necessary to identify the MALAT1 biomarker for the therapy and prognosis of ccRCC patients.

In this study, we evaluated the prognostic value of MALAT1 expression in patients with ccRCC using data from the cancer genome atlas (TCGA). We further validated MALAT1 expression using data obtained from Gene Expression Omnibus (GEO). In addition, we identified differentially expressed genes (DEGs) between ccRCC and normal control. To gain further insight into the biologic functions and molecular mechanisms of MALAT1 in ccRCC, we conducted single-gene gene set enrichment analysis (GSEA) on DEGs. Finally, GSEA and immune infiltrating analyses were performed to explore the role of MALAT1 in the tumor microenvironment.

2. Methods

2.1. Data acquisition

Data for RNA expression and clinical information of ccRCC were obtained from TCGA project (https://portal.gdc.cancer.gov/projects/TCGA-KIRC) and GEO database (http://www.ncbi.nlm.nih.gov/geo/). The expression profile of MALAT1 was extracted from TCGA RNA-seq data of 602 samples (530 ccRCC tissues and 72 normal tissues). TCGA and GEO belong to public databases. The patients involved in the database have obtained ethical approval. Users can download relevant data for free for research and publish relevant articles. This study is based on open source databases, so there are no ethical issues or other conflicts of interest. The level 3 high-throughput sequencing fragments per kilobase per million data were transformed to transcripts per kilobase million format for the following analyses. In this study, clinical data and prognostic information of all available samples were extracted. Patients with ccRCC were classified into low- and high-expression groups according to their median expression value of MALAT1. R statistical software was used to download the MALAT1 expression data from GSE66270 (14 ccRCC tissues and 14 normal tissues) and GSE66272 (27 ccRCC tissues and 27 normal tissues) as an external validation.

2.2. The expression of MALAT1 in the TCGA databases

TIMER2 website (http://timer.cistrome.org/) was used to query the expression of MALAT1 in different tumor tissues and adjacent normal tissues in TCGA database.

2.3. Analysis of DEGs

Expression profiles were compared between the high and low MALAT1 expression groups to identify the DEGs using the limma package of R software.[18] A $P < .05$ and $|\log2$ fold change (FC)$| > 1$ were considered the threshold for the DEGs. The volcano plot and heatmap were drawn using the ggplot2 package.[19]

2.4. Establishment and validation of a prognostic nomogram

Multivariate cox regression analysis was used to determine the optimal prognostic model. A nomogram was constructed to predict the prognosis by R packages rms.[20] The nomogram-based prediction model was evaluated by calibration plots and concordance index. The patients were stratified into high- and low-risk groups based on the median value of their risk scores. The difference in survival outcomes between the high- and low-risk group were performed by the survival curve. The Kaplan–Meier curves analysis were performed by log-rank test in R packages

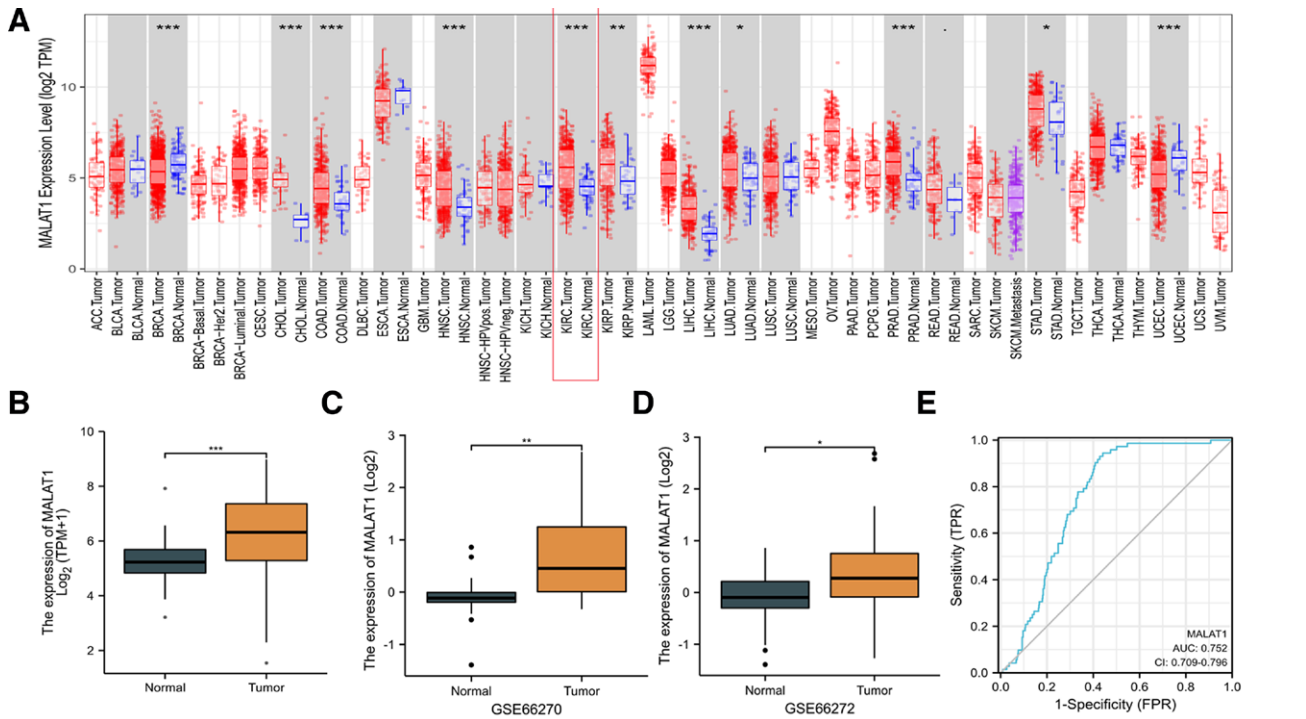

Figure 1. MALAT1 expression in ccRCC. MALAT1 expression in the pan-cancer cohort (A). In the TCGA cohort (B), MALAT1 expression levels were significantly higher in ccRCC tissues than in normal tissues. In the GSE66270 (C) and GSE66272 (D), MALAT1 expression levels were significantly higher in ccRCC tissues than in normal tissues. ROC curve (E) suggests the reliability of the prognostic model. *$P < .05$, **$P < .01$, ***$P < .001$. ccRCC = clear cell renal cell carcinoma, MALAT1 = metastasis-associated lung adenocarcinoma transcript 1, ROC = receiver operating characteristic.

(survminer and survival).[21] As sensitivity analysis, the ROC curves and its area under the curve values were plotted by R packages (pROC and ggplot2).[22]

2.5. Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis

In this study, GO enrichment analysis was used to analyze the enrichment of MALAT1 related DEGs for enriched GO terms. GO and KEGG enrichment analysis were performed by R package clusterProfiler.[22]

Table 1

Clear cell renal cell carcinoma patient characteristics.

Clinical characteristics	Levels	Overall n (%)
Age	≤60	264 (49.8%)
	>60	266 (50.2%)
Gender	Female	186 (35.1%)
	Male	344 (64.9%)
T stage	T1	271 (51.1%)
	T2	69 (13%)
	T3	179 (33.8%)
	T4	11 (2.1%)
N stage	N0	239 (93.7%)
	N1	16 (6.3%)
M stage	M0	420 (84.3%)
	M1	78 (15.7%)
Pathologic stage	Stage I	265 (50.3%)
	Stage II	57 (10.8%)
	Stage III	123 (23.3%)
	Stage IV	82 (15.6%)
Histologic grade	G1	14 (2.7%)
	G2	227 (43.5%)
	G3	206 (39.5%)
	G4	75 (14.4%)

2.6. GSEA

GSEA is a computational method that determines whether a priori defined set of genes shows statistically significant, concordant differences between 2 biological states.[23] In our study, GSEA was performed using the R package clusterProfiler (3.14.3).[24] The significant function and pathways differences between the low- and high-MALAT1 groups were elucidated via GSEA. Gene set permutations were performed 1000 times for each analysis. The expression level of MALAT1 was used as phenotype label. The reference gene collection used in this study was curated (c2.cp.v7.2.symbols.gmt) from MSigDB collections. An adjusted $P < .05$ and false discovery rate < 0.25 were considered as statistically significantly.

2.7. Immune infiltration analysis

The marker of 24 immune cells was extracted from the research of Bindea and colleagues.[25] The single sample gene set enrichment analysis (ssGSEA) method from the GSVA package in R was used to analyze the infiltration of 24 types of immune cells in the tumor, and Spearman correlation was used to analyze the correlation between the MALAT1 and these 24 types of immune cells.[22]

2.8. Statistical analysis

The R software (version.3.6.3; http://www.Rproject.org) was used for all statistical analyses. Wilcoxon rank sum test was used to analyze MALAT1 expression of the data from TCGA, GSE66270, and GSE66272. Logistic regression analysis was used to analyze the relationship between clinicopathological features and MALAT1. The uni- and multivariable regressions were performed with dichotomized MALAT1 expression scores. Survival analysis was performed using the survminer and survival R packages. The log-rank test was used to analyze the differences between survival curves. The gene expression correlation was accessed by Spearman R package GSVA. An adjusted $P < .05$ was considered to be statistically significant.

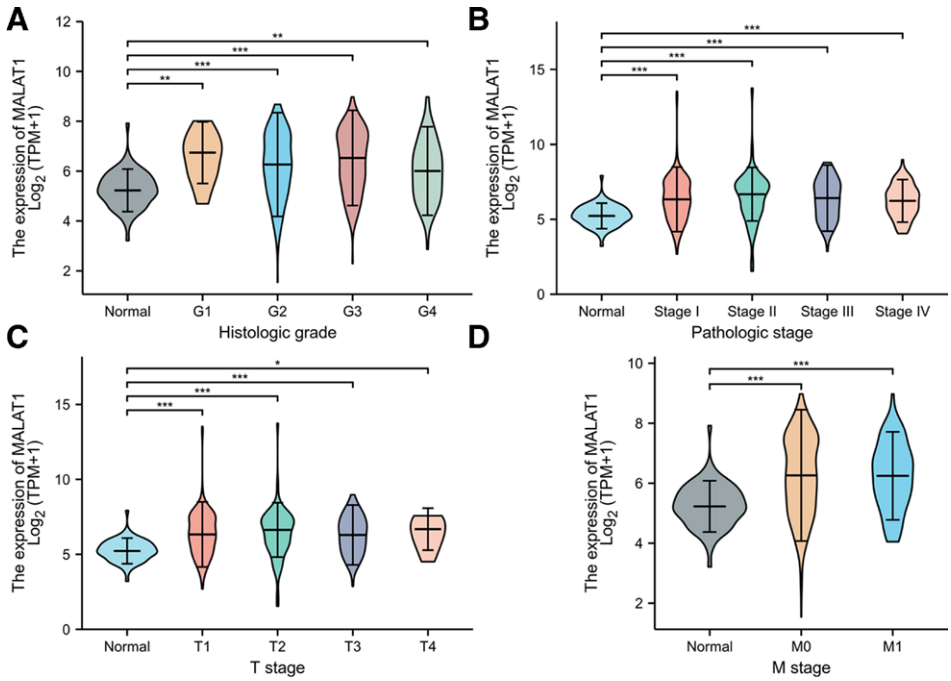

Figure 2. The association of MALAT1 expression with clinicopathological characteristics in patients with ccRCC in TCGA cohort. This relationship between MALAT1 expression and histologic grade (A). This relationship between MALAT1 expression and pathologic grade (B). This relationship between MALAT1 expression and T stage (C). This relationship between MALAT1 expression and M stage (D). *$P < .05$, **$P < .01$, ***$P < .001$. ccRCC = clear cell renal cell carcinoma, MALAT1 = metastasis-associated lung adenocarcinoma transcript 1.

3. Results

3.1. Expression of MALAT1 in ccRCC and normal tissues

In the TCGA databases, we applied the TIMER2 to analyze the expression status of MALAT1 across various types of cancer. Results showed that the expression level of MALAT1 was upregulated in most tumors, including kidney renal clear cell carcinoma (Fig. 1A, $P < .001$). Clinical information and expression data of 530 cases of ccRCC were downloaded from TCGA data (Table 1). In this study cohort, MALAT1 expression levels were significantly higher in ccRCC tissues than in normal samples (Fig. 1B, $P < .001$). Furthermore, we performed external validation by downloading the full microarray dataset (GSE66270 and GSE66272; Fig. 1C and D). ROC curves showed that the area under the curve value for prognostic risk-related signature was 0.752 (Fig. 1E). This may indicate a good predictive effect for the prognostic risk model.

3.2. The association of MALAT1 expression with clinicopathological characteristics in ccRCC patients

To better understand the relevance of MALAT1 in ccRCC, we examined the relationship between MALAT1 expression and clinicopathological characteristics of 530 ccRCC samples (Fig. 2). We observed that high MALAT1 expression was positively correlated with indicators of tumor aggressiveness:

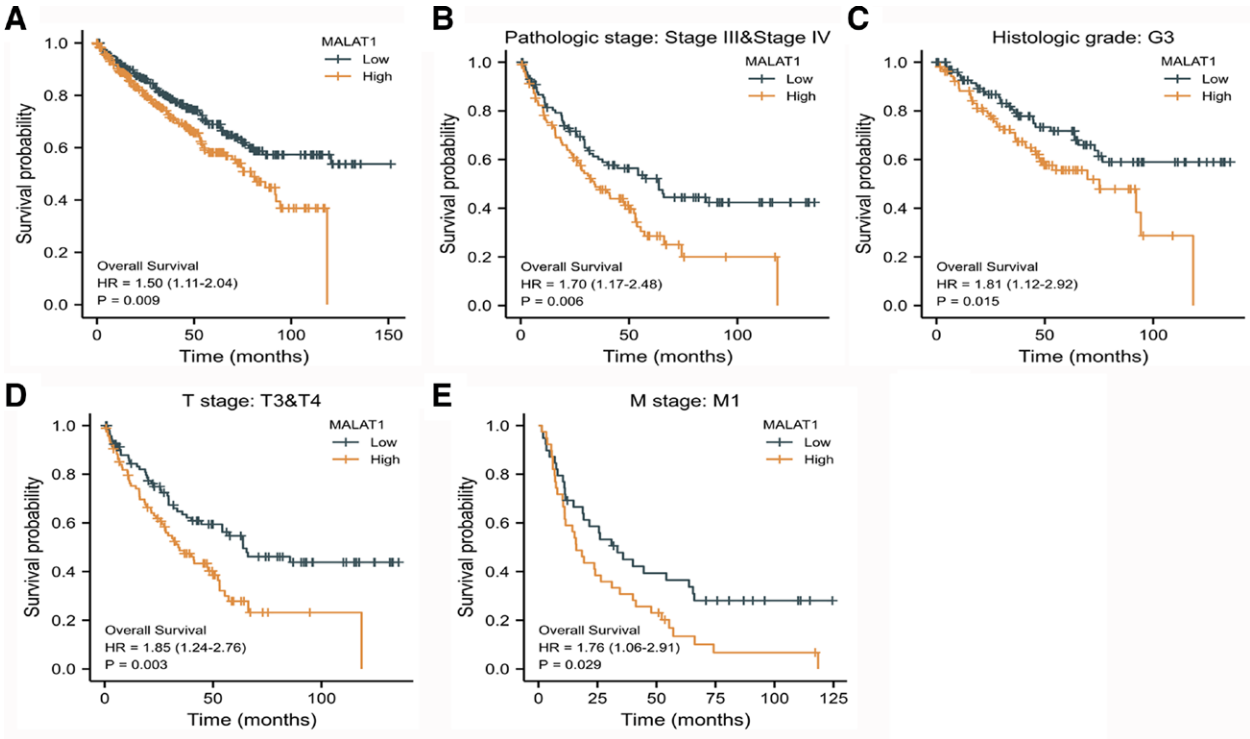

Figure 3. The effect of the high- and low-risk subgroups on overall survival (OS) in ccRCC patients clinicopathological features. The high expression of MALAT1 can predict the lower survival rate (A) in ccRCC patients. The high-risk subgroups showed worse survival in patients with pathologic grade (B), histologic grade (C), T stage (D), M stage (E). ccRCC = clear cell renal cell carcinoma, MALAT1 = metastasis-associated lung adenocarcinoma transcript 1.

Table 2

Association with overall survival and clinicopathologic characteristics in patients with clear cell renal cell carcinoma.

			Univariate analysis		Multivariate analysis	
Characteristics		**Total**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Age	≤60	264	1		1	
	>60	266	1.753 (1.290–2.383)	<.001	1.829 (1.190–2.813)	.006
Gender	Female	186	1			
	Male	344	0.951 (0.697–1.296)	.750		
T stage	T1 + T2	340	1		1	
	T3 + T4	190	3.160 (2.332–4.283)	<.001	1.374 (0.602–3.134)	.450
N stage	N0	239	1		1	
	N1	16	3.426 (1.818–6.456)	<.001	1.408 (0.689–2.878)	.348
M stage	M0	420	1		1	
	M1	78	4.333 (3.170–5.922)	<.001	2.713 (1.587–4.639)	<.001
Pathologic stage	I + II	322	1		1	
	III + IV	205	3.860 (2.809–5.305)	<.001	1.640 (0.639–4.207)	.304
Histologic grade	G1 + G2	241	1		1	
	G3 + G4	281	2.660 (1.888–3.748)	<.001	1.688 (1.026–2.777)	.039
MALAT1	Low	265	1		1	
	High	265	1.593 (1.173–2.163)	.003	2.271 (1.435–3.593)	<.001

95% CI = 95% confidence interval, HR = hazard ratio.

histologic grade ($P = .002$), pathologic grade ($P < .001$), T stage ($P < .001$) and M stage ($P < .001$).

3.3. The relationship between MALAT1 expression and clinicopathological features correlated with prognosis

To assess the predictive ability of MALAT1 prognostic signature, we conducted a stratified analysis to predict overall survival (OS) in high-and low-risk subgroups based on clinicopathological features (Fig. 3), including pathologic grade (stage III + IV), histologic grade (G3), T stage (T3 + T4) and M stage (M1). For OS, high MALAT1 expression predicted a much worse prognosis (Fig. 3A). Survival analysis showed that the high-risk subgroups had a poorer prognosis than those with low-risk subgroups in different clinical characteristics (all $P < .05$; Fig. 3B–E).

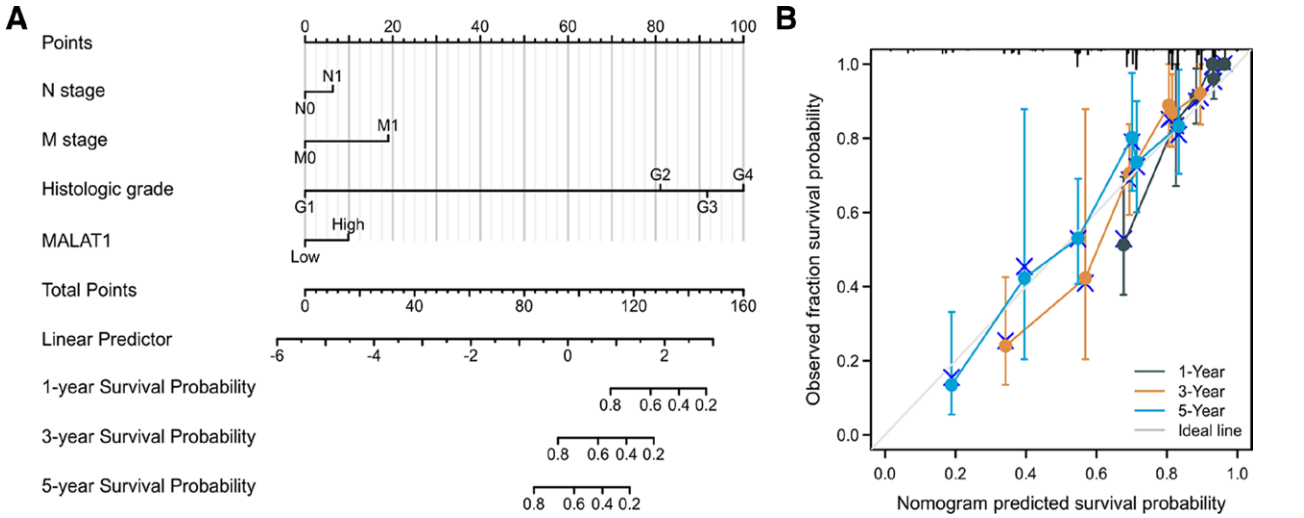

Figure 4. Establishment and validation of prognostic model. Establishment of a prognostic model (A) was used to evaluate the survival probability. Performance of the nomogram was assessed by calibration curve (B).

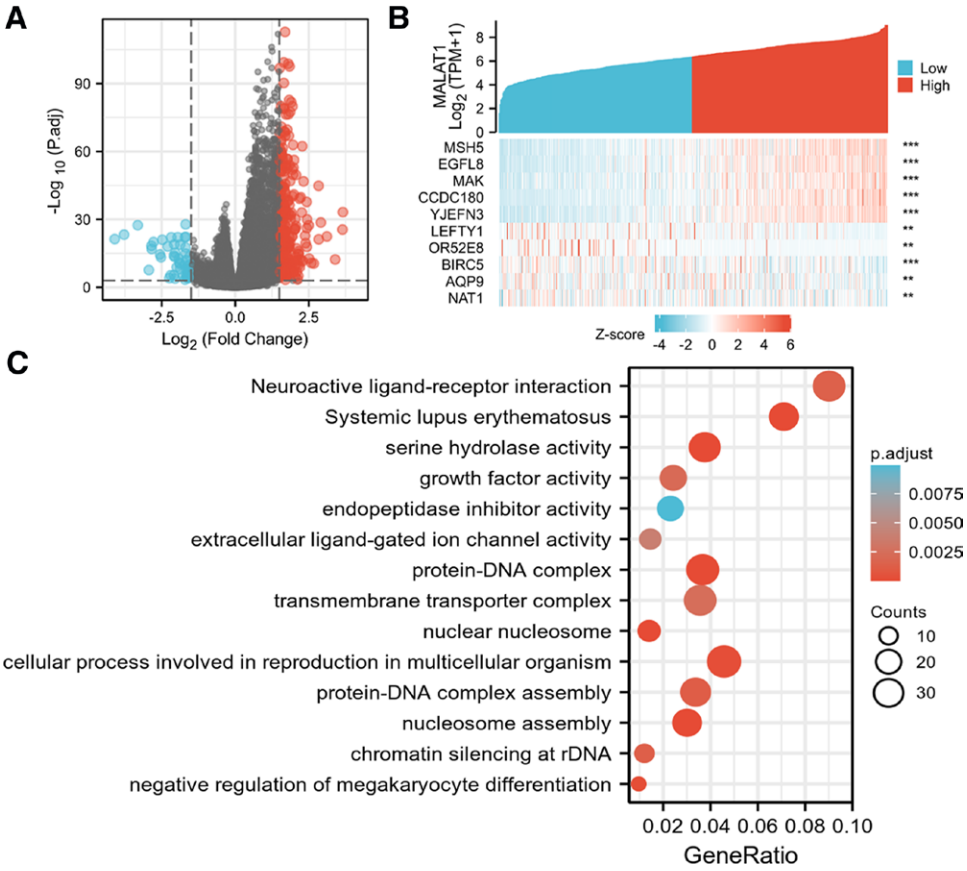

Figure 5. Differentially expressed genes (DEGs) of MALAT1 in ccRCC. (A) Volcano plot of DEGs. (B) Heatmap of DEGs. (C) GO and KEGG enrichment analysis of DEGs. $^{**}P < .01$, $^{***}P < .001$. GO = gene ontology, KEGG = kyoto encyclopedia of genes and genomes.

3.4. Cox regression analysis of MALAT1 expression and OS for patients with ccRCC in the TCGA cohort

We found that the poor OS in ccRCC was associated with other clinicopathological features, including T stage, N stage, M stage, age, pathologic stage, histologic grade (Table 2). Univariate (hazard ratio 1.593, 95% confidence interval 1.17–2.16, $P = .003$) and multivariate Cox regression analysis (hazard ratio 2.271, 95% confidence interval 1.44–3.59, $P < .001$) showed that high MALAT1 expression was an important and independent predictor of worse overall survival in patients with ccRCC.

3.5. Establishment of the prognostic models for ccRCC

The above results indicated that MALAT1 might be an independent prognostic factor in ccRCC. In order to confirm this, we established a predictive model for OS by fitting MALAT1 expression and other clinicopathological features from the TCGA data.

We established a nomogram for OS via integrating MALAT1 expression and other prognostic factors, including N stage, M stage, histologic grade (Fig. 4A). The prognostic score was based on the total number of points obtained from the nomogram and the higher the prognostic score, the lower the survival probability. To validate the prediction model, the performance of the nomogram was assessed using the calibration plot of the model for the 1-, 3- and 5-year survival. Calibration curve of the nomogram indicated that the predictive accuracy of the nomogram was well-calibrated and the C-index of was 0.749 (Fig. 4B).

3.6. Functional enrichment analysis of low- and high-MALAT1 expression samples

To further study how MALAT1 promotes tumor progression, we analyzed DEGs in ccRCC samples of the low- and high-MALAT1 expression. Differential gene expression analysis identified 258 and 51 genes up- and down-regulated, respectively (Fig. 5A). Genes significantly associated with MALAT1 co-expression were identified and shown in the heatmap (Fig. 5B). To investigate the molecular functions and possible mechanism of co-expressed genes in ccRCC, we performed GO term and KEGG pathway enrichment analysis (Fig. 5C). In GO biological analysis, enriched genes were associated with cell growth and proliferation. In KEGG pathway analysis, the most significantly enriched pathways were related to systemic lupus erythematosus and neuroactive ligand-receptor interaction. We also utilized GSEA to identify the key regulatory pathways related to MALAT1. GSEA analysis found 61 gene sets were enriched at false discovery rate < 0.25 and $P < .05$. Pathway enrichment analysis showed that enriched genes were mainly involved in DNA methylation (Fig. 6A), positive epigenetic regulation of rRNA expression (Fig. 6B), epigenetic regulation of gene expression (Fig. 6C), systemic lupus erythematosus (Fig. 6D).

3.7. The correlation between MALAT1 expression and infiltration of immune cells

Using GO enrichment, we found that MALAT1 might be involved in the immune responses. To further confirm this, we evaluated the relationship between MALAT1 expression and immune infiltrates using ssGSEA (Fig. 7A). The results showed that MALAT1 expression was negatively correlated with Th2

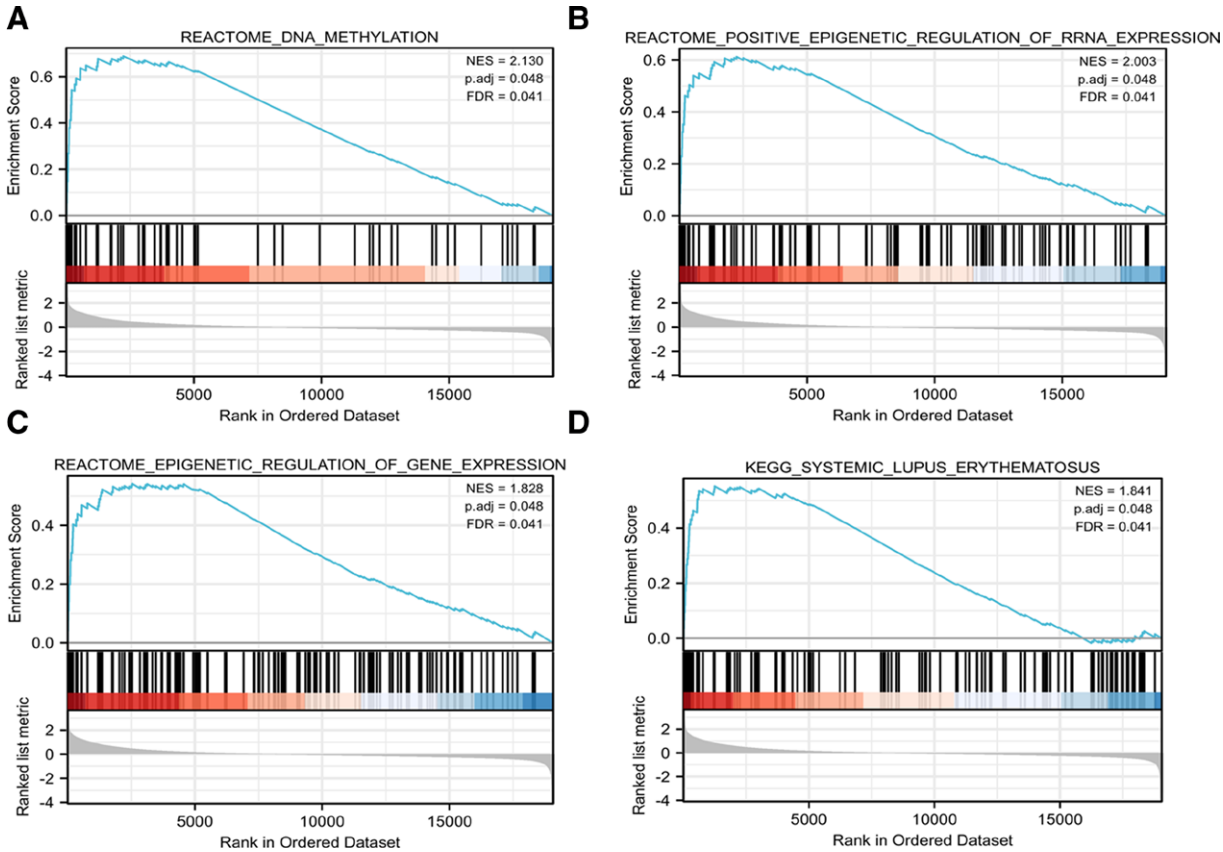

Figure 6. Gene set enrichment analysis (GSEA) of MALAT1 in ccRCC. (A) Enrichment of genes in the DNA methylation by GSEA. (B) Enrichment of genes in the positive epigenetic regulation of rRNA expression signaling pathway by GSEA. (C) Enrichment of genes in the epigenetic regulation of gene expression signaling pathway by GSEA. (D) Enrichment of genes in the systemic lupus erythematosus signaling pathway by GSEA. ccRCC = clear cell renal cell carcinoma.

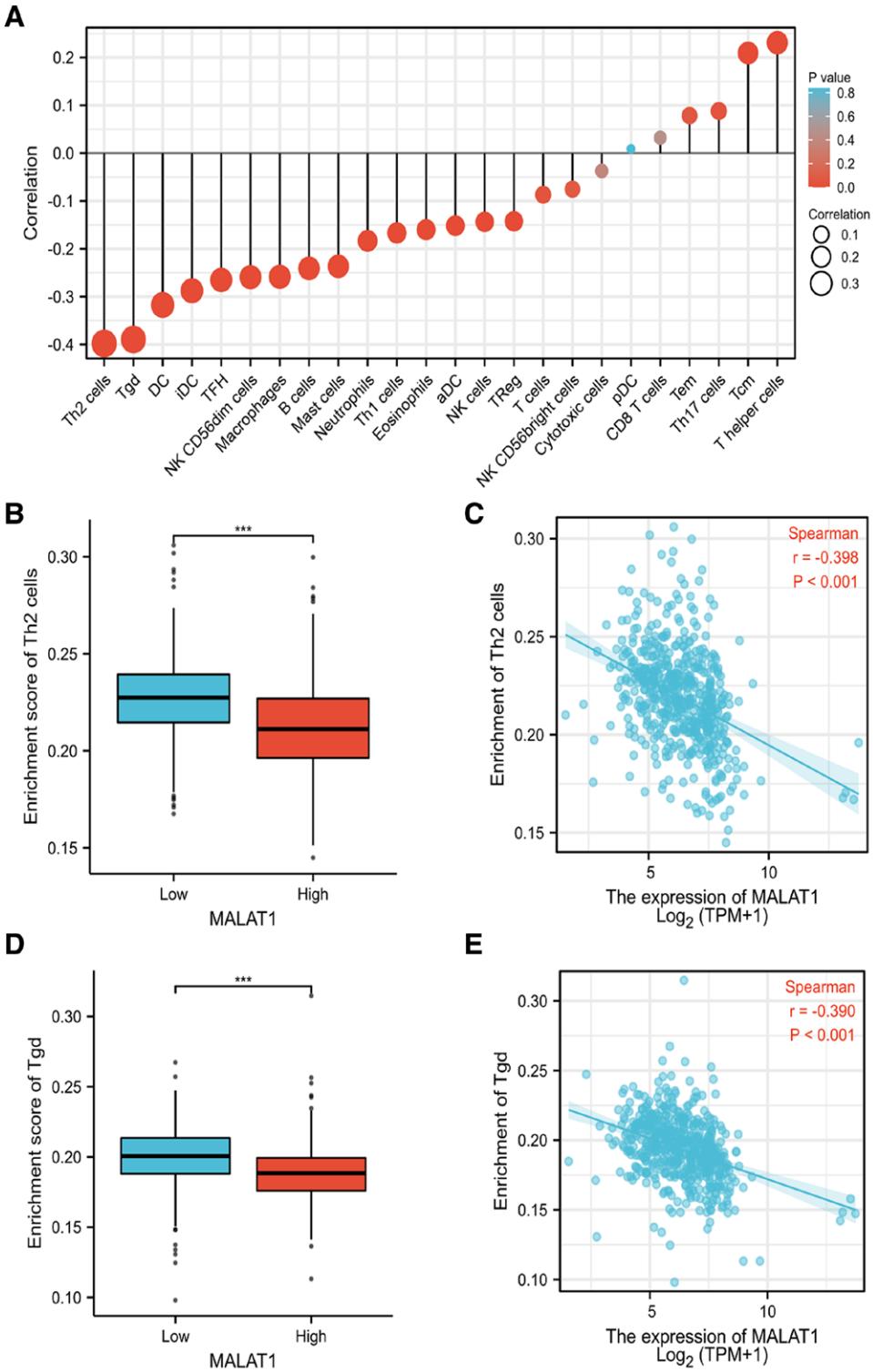

Figure 7. The correlation between MALAT1 expression and infiltration of immune cells in ccRCC. (A) The correlation between MALAT1 expression and infiltration of immune cells. (B) In the high expression group of MALAT1, the enrichment score of Th2 cells was lower. (C) MALAT1 expression was negatively correlated with Th2 cells. (D) In the high expression group of MALAT1, the enrichment score of Tgd cells was lower. (E) MALAT1 expression was negatively correlated with Tgd cells. ***P < .001. ccRCC = clear cell renal cell carcinoma, MALAT1 = metastasis-associated lung adenocarcinoma transcript 1.

cells (R = –0.398, P < .001, Fig. 7B and C), Tgd (R = –0.390, P < .001, Fig. 7D and E).

4. Discussion

Because of the limitations of traditional therapy and the development of molecular level, it is urgent to find the new therapeutic targets and the effective biomarkers for assessing ccRCC prognosis. LncRNAs are associated with tumorigenesis and progression of cancer. Li et al[26] showed that DNA methylation was an important epigenetic regulator of lncRNA expression in colon adenocarcinoma. Several studies have described that MALAT1 was associated with the biological behavior and poor prognosis and of ccRCC.[27,28] While the mechanisms by which MALAT1

played important roles in tumorigenesis and prognosis of ccRCC are less well known. To better understand the role of MALAT1 in ccRCC, we performed the functional enrichment analysis of ccRCC samples in TCGA database.

This study found that MALAT1 was highly expressed in ccRCC tissues, and its overexpression is associated with adverse OS in ccRCC. We also validated the results of TCGA dataset using a GEO database, and this finding was consistent with previous results. We also found that MALAT1 was highly expressed in a variety of cancers, such as cholangiocarcinoma, colon adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, prostate adenocarcinoma, stomach adenocarcinoma. The multivariate Cox regression analysis demonstrated that high MALAT1 expression, M stage, age, histologic grade, were independently prognostic for OS. These results demonstrate that MALAT1 has the potential as a diagnostic marker in ccRCC, which is consistent with previous studies.[16] Moreover, our findings demonstrate that MALAT1 is associated with histologic grade, pathologic grade, T stage, M stage of ccRCC, and high MALAT1 expression is a marker of poor prognosis for patients with ccRCC, which further suggestes that the expression of MALAT1 may be associated with the malignancy of ccRCC.

Considering the poorer prognosis of high MALAT1 expression, we constructed a nomogram to estimate the survival of ccRCC patients. The nomogram as prognostic tool shows better prognostic performance and may better estimate an individual risk using specific clinical variables.[29] The identification of high-risk patients is conducive to the implementation of more effective interventions. Furthermore, we explored the mechanism of MALAT1 in ccRCC, and our results found that MALAT1 may be associated with DNA methylation. DNA methylation is an important and stable epigenetic regulator of gene transcription.[30] DNA methylation mainly occurs in cytosine-guanine dinucleotides (CpG), involving DNA methylation and DNA demethylation. In malignant tumors, CpG island hypermethylation is often observed.[31] As a tumor suppressor gene, hypermethylation of the VHL promoter silences the VHL gene, which is an important driving factor for the occurrence of ccRCC.[32] The ras association domain family 1 isoform A (RASSF1A) is a tumor suppressor gene involved in the development of various malignancies. Studies have shown that RASSF1A methylation is significantly associated with RCC risk and tumor grade.[33,34] DNA methylation of tissue inhibitor of metalloproteinase-2 (TIMP2) can promote bone metastasis of RCC.[35] The available evidence has shown that epigenetic changes in DNA methylation can interfere with lncRNA expression pattern and contributes to carcinogenesis.[36] A recent study reported that lncRNAs can recruit DNA methyltransferases directly or indirectly to regulate DNA methylation of target gene, thereby regulating the biological behavior of cancer cells.[37] A study provided solid evidence that MALAT1 as an epigenetic messenger was involved in metabolic reprogramming in HCC cells.[38] Furthermore, ssGSEA also showed that the expression level of MALAT1 is negatively correlated with the infiltration of Th2 cell and Tgd. No positive correlation was found between immune infiltrate and high MALAT1 expression in ccRCC in this study. The relationship between MALAT1 and immune infiltrates in ccRCC might further explain the clinical heterogeneity.

In the present study, we showed that MALAT1 was significantly associated with poor prognosis in ccRCC, and clarified the biological function of MALAT1 and further investigated the molecular mechanism by which MALAT1 contributed to the progression of ccRCC. Despite the extensiveness of our investigation, there is still room for development. First, this study lacks in vivo and in vitro experiment verification. Second, key molecular pathways and mechanisms associated with MALAT1 may be missed due to design limitations. The relevant work will require future validations in future.

5. Conclusions

Altogether, MALAT1 expression was upregulated in ccRCC tissues, and high expression of MALAT1 was correlated with poor prognosis for OS of ccRCC. In addition, high expression of MALAT1 may affect gene expression in ccRCC through epigenetic mechanisms such as DNA methylation. MALAT1 might be a diagnostic and prognostic marker in ccRCC and likely plays a crucial part, but need further research.

Acknowledgements

This work was supported by Henan Medical Science and Technology Research Program Joint Construction Project (No. LHGJ20200769).

Author contributions

Funding acquisition: Kai Liu.
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Supervision: Quanwu Zhang.
Writing – original draft: Kai Liu.
Writing – review & editing: Quanwu Zhang.

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