



# Upregulation of matrix metalloproteinase 14 (MMP14) is associated with poor prognosis in renal clear cell carcinoma – a bioinformatics analysis

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**Background:** Matrix metalloproteinase 14 (MMP14) has been reported to be upregulated in some types of cancer and to promote cancer cell invasion and metastasis. However, the expression profile and functional role of MMP14 in kidney renal clear cell carcinoma (KIRC) remains unknown. This study investigated the association between MMP14 expression level and prognosis in KIRC.

**Methods:** The messenger RNA (mRNA) expression profile and clinical data (including T stage, N stage, M stage, pathologic stage, gender, race, age, histologic grade, serum calcium, hemoglobin) were obtained from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) database. Protein expression was evaluated by immunohistochemistry in the Human Protein Atlas (HPA) database. Correlation analyses between MMP14 and all mRNAs in KIRC were batch calculated, and gene set enrichment analyses (GSEA) were then conducted of Disease Ontology (DO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways using R packages. Multivariate logistic regression analysis was used to explore the prognostic factors of KIRC patients.

**Results:** The gene expression of MMP14 was significantly upregulated in KIRC tissues when compared with the normal tissue ( $P < 0.001$ ). The predictive ability of MMP14 as a variable for predicting tumor and normal outcomes had certain accuracy based on the receiver operating characteristic (ROC) model [area under the curve (AUC) = 0.881, confidence interval (CI): 0.844–0.917]. When compared with the normal kidney tissue, the protein expression of MMP14 in KIRC got an increased trend, but due to the limited sample size, the difference is not statistically significant ( $P > 0.05$ ). Survival analysis revealed that MMP14 was significantly associated with overall survival in KIRC ( $P = 0.013$ ). GSEA of DO terms indicated high expression of MMP14 was related to KIRC, and GSEA of KEGG pathways showed that MMP14 and its coexpressed genes were significantly positively correlated with pathways in cancer. Signaling pathway GSEA indicated the upregulation of MMP14 in KIRC may activate cancer pathways.

**Conclusions:** MMP14 may be associated with poor prognosis in KIRC and may be a potential prognostic marker for KIRC.

**Keywords:** Kidney cancer; clear cell carcinoma; matrix metalloproteinase 14 (MMP14); The Cancer Genome Atlas (TCGA); prognosis

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## Introduction

Renal cell cancer (RCC) represents about 3% of all cancers, with the highest incidence occurring in Western countries (1). It was estimated that there were 76,080 new cases and 13,780 deaths in the United States in 2021 (2). The most common type of RCC is kidney renal clear cell carcinoma (KIRC) (~80–90%), followed by papillary RCC (10–15%) and chromophobe RCC (4–5%) (3). Improved early detection and treatment of KIRC has improved patient survival status. However, KIRC still results in numerous deaths. Therefore, a novel biomarker and potential therapeutic target must be identified to improve clinical treatment for KIRC patients. However, KIRC is characterized by its heterogeneous clinical outcomes. Due to its uncertain behavior and the lack of conventional biomarkers, it is difficult to identify high-risk patients with recurrence after therapeutic nephrectomy. At present, the commonly used imaging examination, as the main means to determine whether the tumor remains after surgery, has limitations, such as poor sensitivity and serious hysteresis.

Matrix metalloproteinase 14 (MMP14) is a member of the matrix metalloproteinase (MMP) family, which interact with tissue metalloproteinase inhibitors (TIMPs) and are involved in both normal physiological functions and tumor-related processes, including cell migration, invasion, metastasis, angiogenesis, and proliferation (4,5). MMP14 has been reported to be upregulated in some types of cancer (6–8) and to promote cancer cell invasion and metastasis (3,7,9). However, the expression profile and functional role of MMP14 in KIRC remains unknown. Therefore, this is the first data mining study to explore the possible role of MMP14 in KIRC based on publicly available databases.

In the present study, we first investigated the messenger RNA (mRNA) and protein expression of MMP14 in KIRC from The Cancer Genome Atlas (TCGA) and Human Protein Atlas (HPA) database and the association between MMP14 expression and survival prognosis in KIRC. We then identified the functional and signaling pathways. We present the following article in accordance with the REMARK reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-619/rc>).

## Methods

### Data acquisition

This is a bioinformatics analysis. All data were acquired from TCGA (<https://cancergenome.nih.gov>) (10), GTEx (Genotype-

Tissue Expression; <https://www.gtexportal.org>) (11), and HPA (<https://www.proteinatlas.org>) databases (12). Data from TCGA and GTEx databases were downloaded using Xena (<https://xenabrowser.net>) (13). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### The expression profile of MMP14 in pan-cancer analysis and KIRC

The mRNA expression level of MMP14 in tumors and corresponding normal tissues were examined in TCGA combined with GTEx data. The quantitative expression units of genes were unified as transcripts per million (TPM) reads format and then  $\log_2$  (TPM+1) conversion. The protein expression of MMP14 in KIRC and normal kidney tissue was validated in immunohistochemistry images retrieved from the HPA database.

### Prognostic survival analysis

To comprehensively investigate the association between MMP14 expression and prognosis in KIRC, univariate Cox regression survival analysis of MMP14 based on pan-cancer analysis was first evaluated, and then Kaplan-Meier survival analysis of MMP14 in KIRC was further performed. Finally, time-dependent receiver operating characteristic (ROC) curve models at 1, 3, and 5 years were constructed to predict the accuracy of the model for survival analysis results. All normal patients and patients without gene expression and prognostic information in TCGA datasets were filtered out. The clinical data also included T stage, N stage, M stage, pathologic stage, gender, race, age, histologic grade, serum calcium, hemoglobin.

### Gene set enrichment analyses (GSEA)

To further explore the relevant roles and mechanism of MMP14 and its coexpressed genes in KIRC, the correlation coefficients between MMP14 and all genes in the TCGA-KIRC dataset were first batch calculated and ranked using the `cor.test` function in R, and the Spearman method was used for correlation analysis. Next, GSEA of Disease Ontology (DO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways were performed using the R packages 'DOSE' (14) and 'clusterProfiler' (15) online, respectively. The DO (<https://disease-ontology.org/>) (16) and DisGeNET (<https://www.disgenet.org>) (17)

database data were selected for DO category GSEA. Pathway visualization was realized through R package 'pathview' (18). |Neuroendocrine syndrome (NES)| >1 combined adjusted P value <0.05 were considered significant differences.

### ***Protein-protein interaction analysis (PPI)***

To further explore the interaction networks between MMP14 and the coexpressed genes in KIRC, genes with a correlation coefficient for MMP14 in the TCGA-KIRC dataset greater than 0.5 were selected, and PPI analysis was then performed using the String database (<https://string-db.org/>) (19). Spearman's correlation coefficient value was used for ranking.

### ***Statistical analysis***

All statistical analyses were carried out with R software. The ROC model was constructed using R packages 'pROC' and 'timeROC', and Cox and Kaplan-Meier analyses were conducted using R package 'survival' to analysis the influencing factors of survival in KIRC patients. Categorical variables were compared using  $\chi^2$  analysis, and continuous data were compared using *t*-tests. *P*<0.05 was considered a significant difference (two tail).

## **Results**

### ***The gene expression level of MMP14 was significantly upregulated in KIRC***

TCGA and GTEx data were combined to evaluate the quantitative difference in gene expression levels of MMP14 using pan-cancer analysis and corresponding healthy tissues. The results showed that except for the significant downregulation in a few cancer types (acute myeloid leukemia, ovarian serous cystadenocarcinoma, prostate adenocarcinoma, thyroid carcinoma, and uterine corpus endometrial carcinoma), MMP14 was significantly upregulated in most cancer types (*Figure 1A*), including KIRC tissues (*P*<0.001) (*Figure 1B*). The predictive ability of MMP14 as a variable for predicting tumor and normal outcomes had certain accuracy based on the ROC model [area under the curve (AUC) =0.881, confidence interval (CI): 0.844–0.917] (*Figure 1C*). Finally, paired samples in the TCGA-KIRC dataset showed MMP14 in tumor tissue was also significantly higher than the average level in normal

kidney tissue (*P*<0.001) (*Figure 1D*).

### ***The protein expression level of MMP14 was significantly upregulated in KIRC***

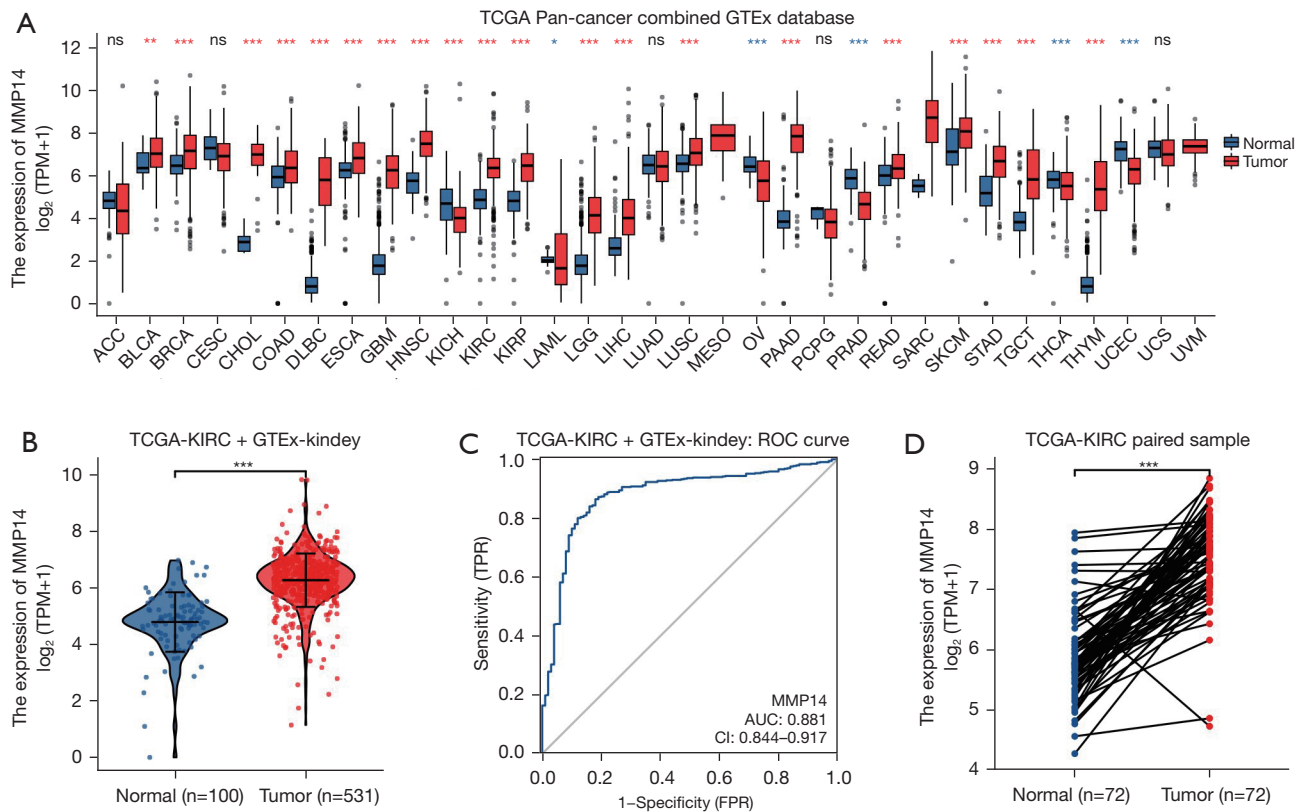
To validate the protein expression level of MMP14 in KIRC tissues, we retrieved immunohistochemical results from the HPA database. In the case of HPA051432 antibody staining, no positive staining was found in the glomerular cells and tubules cells of all 3 normal kidney tissues. However, in 11 cases of KIRC tissue, 3 cases of patients showed positive staining, of which 1 case was medium positive staining, and 2 cases were low positive staining. In addition, 6 cases showed positive intensity. These results support the trend of upregulation of MMP14 in KIRC compared to normal kidney tissue, but more basic experiments are needed to validate this trend.

### ***Upregulation of MMP14 was related to the higher pathological tumor (T)-stage and grade of KIRC***

To better assess the clinicopathological association of MMP14 in KIRC, we divided patients into high- and low-expression groups according to the median quantitative gene expression of MMP14 and then statistically analyzed the differences between the 2 groups. The results showed a significant correlation between MMP14 and T-stage, age, and histological grade of KIRC (*Table 1*). Specifically, the high expression group had higher pathological T-stage and higher histological grade, and the patients in the high expression group were younger, suggesting that MMP14 may have a worse clinical prognosis in KIRC patients. To better assess whether MMP14 expression was an independent variable in KIRC, multiple risk factors for KIRC were analyzed by univariate and multivariate Cox hazard models. The results of univariate analysis showed that the survival prognosis of KIRC was associated with MMP14 expression, age, grade, pathological stage, and T-stage. However, the results of multifactorial Cox regression analysis found the expression parameters of MMP14, although suggestive of a risk factor, were not highly significant (*Table 2*).

### ***Upregulation of MMP14 was significantly positively correlated with poor survival prognosis in KIRC***

To comprehensively assess the prognostic value of MMP14 in KIRC patients, a univariate Cox regression prognostic



**Figure 1** Gene expression levels of MMP14 in TCGA combined GTEx database. (A) Quantitative difference of MMP14 expression based on pan-cancer analysis. (B) Quantitative difference of MMP14 expression in the TCGA-KIRC dataset combined with the GTEx-kidney dataset. (C) The ROC curve of MMP14 expression between tumor and normal tissue in TCGA-KIRC combined GTEx-kidney dataset. (D) Quantitative difference of MMP14 expression in TCGA-KIRC paired samples. ns,  $P \geq 0.05$ ; \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . Red represents upregulation, and blue represents downregulation. MMP14, matrix metalloproteinase 14; TPM, transcripts per million; TCGA, The Cancer Genome Atlas; GTEx, Genotype-Tissue Expression; ns, not statistically; KIRC, kidney renal clear cell carcinoma; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; TPR, true positive rate; FPR, false positive rate.

analysis was first performed based on pan-cancer analysis of TCGA data. The results showed that MMP14 was a significant poor prognostic factor for overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI) prognosis [hazard ratio (HR)  $> 1$ ,  $P < 0.05$ ] (Figure 2A-2C). The clinical prognostic information of KIRC patients was then extracted for Kaplan-Meier survival analysis. We divided the patients into high- and low-expression groups according to the median of MMP14 gene expression, and the log-rank test results indicated that the 2 groups had statistically significant differences in OS, DSS, and PFI prognosis (Figure 2D-2F), specifically that the prognosis of the high-expression group was poorer. Finally, we constructed time-dependent ROC curve models at 1, 3, and 5 years to predict the accuracy of the model for

the survival analysis results. The ROC analysis results also showed that MMP14 had good accuracy in predicting the different survival times of KIRC patients (Figure 2G-2I).

#### DO GSEA indicated a significant positive correlation between MMP14 and KIRC

To verify the disease association between MMP14 and KIRC, we first calculated the Spearman correlation coefficients between MMP14 and all genes in the KIRC dataset and then ranked them by coefficients. GSEA of DO was performed by R language online crawler DO and the DisGeNET database. The results indicated that in both sets of datasets, MMP14 and its coexpressed genes had a significant positive correlation with kidney cancer-related

**Table 1** Relationship between MMP14 expression level and clinicopathological variables in KIRC patients

Characteristic	Low expression of MMP14 (n=265)	High expression of MMP14 (n=265)	P
T stage, n (%)			0.003
T1	127 (24.0)	144 (27.2)	
T2	44 (8.3)	25 (4.7)	
T3	93 (17.5)	86 (16.2)	
T4	1 (0.2)	10 (1.9)	
N stage, n (%)			0.734
N0	123 (48.2)	116 (45.5)	
N1	7 (2.7)	9 (3.5)	
M stage, n (%)			0.464
M0	216 (43.4)	204 (41.0)	
M1	36 (7.2)	42 (8.4)	
Pathologic stage, n (%)			0.124
Stage I	123 (23.3)	142 (26.9)	
Stage II	34 (6.5)	23 (4.4)	
Stage III	69 (13.1)	54 (10.2)	
Stage IV	38 (7.2)	44 (8.3)	
Gender, n (%)			0.172
Female	85 (16.0)	101 (19.1)	
Male	180 (34.0)	164 (30.9)	
Race, n (%)			0.188
Asian	2 (0.4)	6 (1.1)	
African American	24 (4.6)	32 (6.1)	
White	234 (44.7)	225 (43.0)	
Age, median (IQR)	62 (52, 72)	60 (51, 68)	0.012
Histologic grade, n (%)			0.007
G1	3 (0.6)	11 (2.1)	
G2	118 (22.6)	109 (20.9)	
G3	111 (21.3)	95 (18.2)	
G4	27 (5.2)	48 (9.2)	
Serum calcium, n (%)			0.078
Elevated	3 (0.8)	7 (1.9)	
Low	112 (30.9)	91 (25.1)	
Normal	68 (18.7)	82 (22.6)	
Hemoglobin, n (%)			0.492
Elevated	4 (0.9)	1 (0.2)	
Low	130 (28.9)	131 (29.1)	
Normal	94 (20.9)	90 (20.0)	

MMP14, matrix metalloproteinase 14; KIRC, kidney renal clear cell carcinoma; IQR, interquartile range.

**Table 2** Univariate and stepwise multivariate Cox hazard analysis of MMP14 in KIRC

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
MMP14	1.35	1.1–1.67	0.005	1.2	0.97–1.47	0.096
Age	1.03	1.01–1.04	<0.001	1.03	1.02–1.05	<0.001
Gender	0.96	0.7–1.31	0.798	–	–	–
Grade	2.27	1.85–2.78	<0.001	1.49	1.19–1.87	0.001
Pathological stage	1.87	1.64–2.14	<0.001	2.09	1.65–2.65	<0.001
T-stage	1.89	1.61–2.23	<0.001	0.71	0.52–0.96	0.026

MMP14, matrix metalloproteinase 14; KIRC, kidney renal clear cell carcinoma; HR, hazard ratio; CI, confidence interval.

diseases and also for clear cell carcinoma (Figure 3A,3B).

#### **Signaling pathway GSEA indicated the upregulation of MMP14 in KIRC may activate cancer pathways**

Based on the RNA-seq data of the TCGA-KIRC dataset, the Spearman correlation coefficients of MMP14 and its coexpressed genes were calculated to evaluate the potential mechanism of the upregulation of MMP14 in KIRC patients. The KEGG signaling pathway GSEA results indicated that MMP14 and its coexpressed genes may play a role in promoting cancer progression in KIRC patients by activating the typical cancer activation pathways, including ‘MicroRNAs in cancer’, ‘Estrogen signaling pathway’, ‘Pathways in cancer’, ‘PI3K-Akt signaling pathway’, and ‘Proteoglycans in cancer’ (Figure 4). We then visualized the ‘Pathways in cancer’ and found that the key molecules of cancer-related pathways were upregulated (Figure 5).

#### **PPI analysis of genes significantly and positively associated with MMP14 in KIRC**

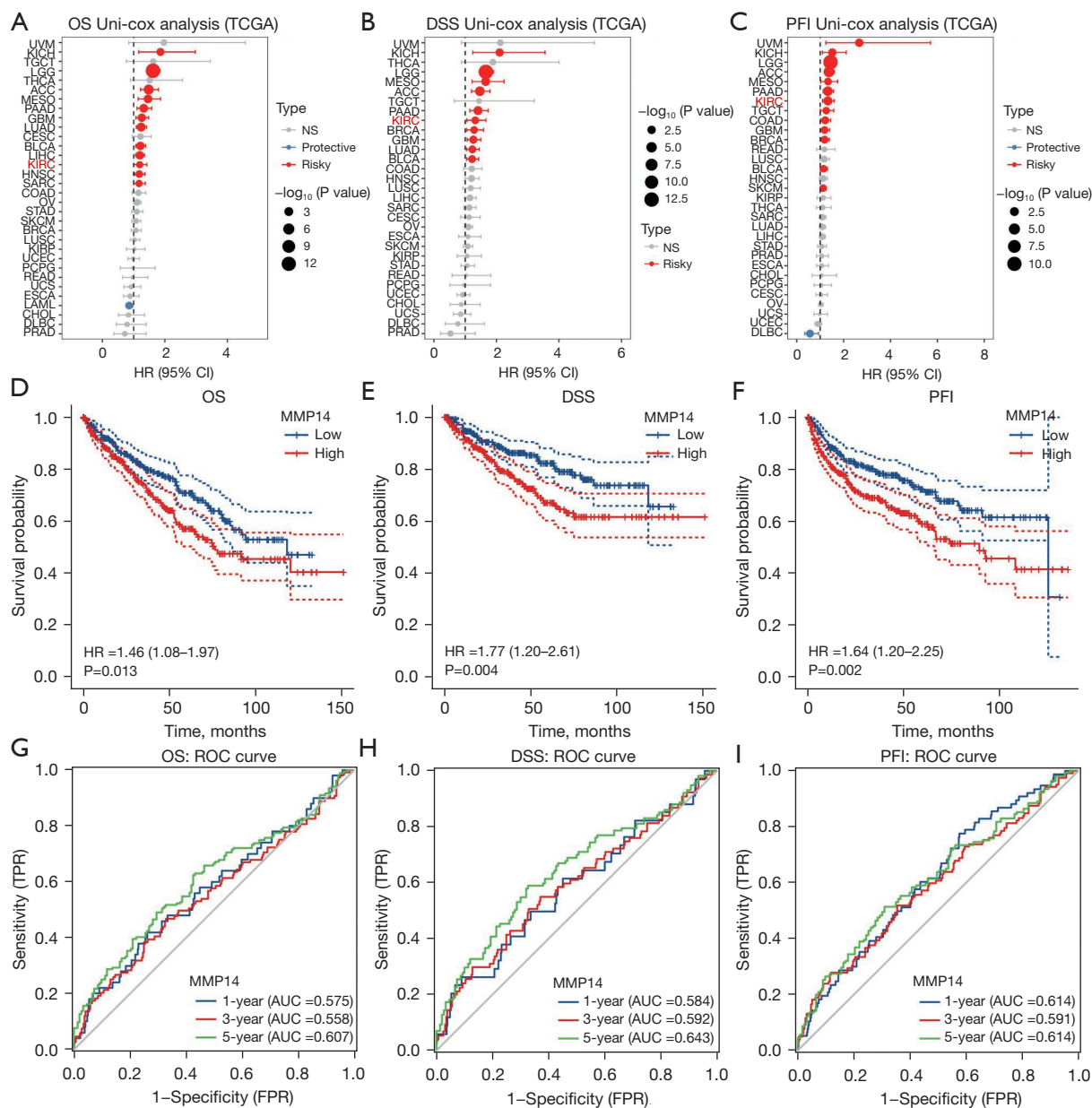
To construct PPIs between MMP14 and its significantly positively correlated genes in KIRC, we extracted the gene list with Spearman correlation coefficients >0.5 and performed PPI analysis using the ‘Proteins with Values/Ranks function’ of String database. The results showed a total of 24 genes (*MMP14*, *GLT25D1*, *SERPINH1*, *CD276*, *SH3PXD2B*, *ACTN1*, *LEPRE1*, *LOXL2*, *CNTNAP1*, *ARHGAP1*, *COL5A1*, *IGDCC4*, *TRAM2*, *COL1A1*, *ITGA5*, *LAMB1*, *PODNL1*, *COL6A2*, *AP2A1*, *COL6A1*, *PXDN*, *SRPX2*, *CPXM1*, and *MEX3B*), and these coexpressed genes had relatively strong interaction network confidence (Figure 6).

## **Discussion**

In multicellular organisms, the complex network composed of a variety of macromolecules around cells is called extracellular matrix (ECM). ECM contains a large number of signaling molecules and actively participates in regulating cell growth, polarity, shape, migration, and metabolic activities (20,21). The degradation of ECM depends on a set of enzymes secreted by inflammatory cells, keratinocytes, and fibroblasts, and MMPs are some of the most important (22). MMPs can degrade almost all protein components in ECM and disrupt the histological barrier to tumor cell invasion, which is closely related to tumor growth and development, involving tumor infiltration, metastasis, microenvironment, and angiogenesis (23–25). MMPs play a key role in tumor invasion and metastasis.

MMP14 was one of the earliest reported membrane-type matrix metalloproteinases (9). Previous studies on MMP14 focused mainly on tumor angiogenesis and invasion (7–9,26). Recent studies have shown that higher expression of MMP14 is associated with poor prognosis in most cancer types, including gastric cancer (27), squamous cell carcinoma (8,28), muscle-invasive bladder cancer (29), liver cancer (30), and colorectal cancer (26,31). However, its role in KIRC has not been fully investigated. Therefore, we explored the clinicopathological significance of MMP14 in KIRC. As the expression profile and functional role of MMP14 in KIRC remain unknown, we used bioinformatic methods to systematically explore the clinicopathological features and potential biological effects of MMP14 on KIRC.

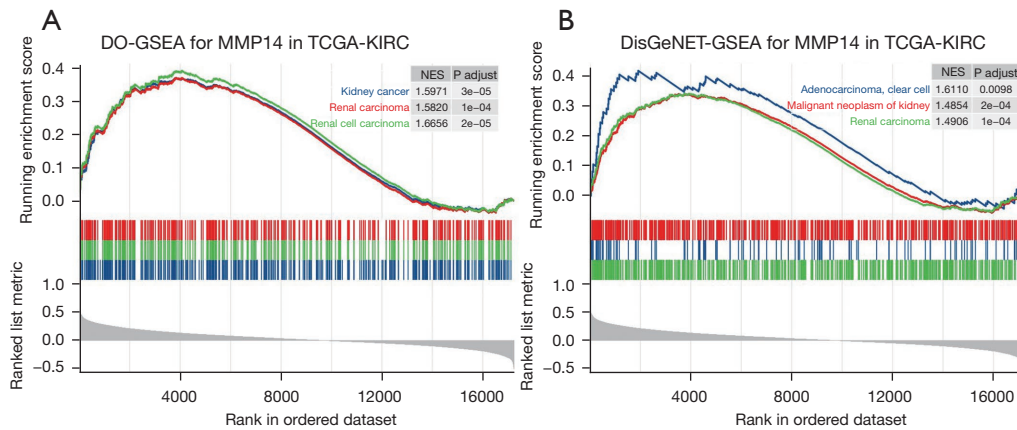
To our knowledge, the expression pattern and clinical prognostic implications of MMP14 have not been explored in KIRC. In this study, we first assessed differences in the quantitative levels of MMP14 gene expression based on



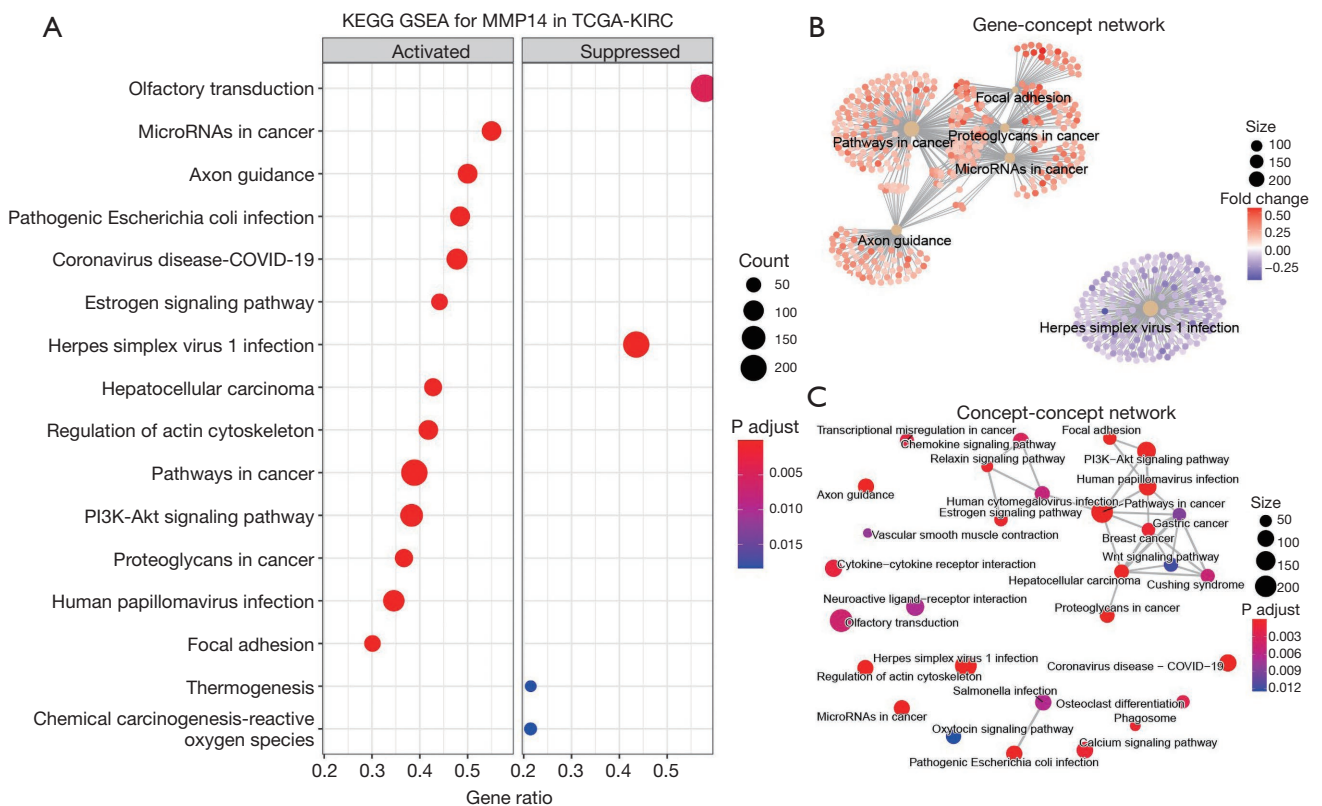
**Figure 2** Prognostic analysis of MMP14 in TCGA database. (A-C) Univariate Cox regression prognostic analysis based on TCGA pan-cancer analysis. The X-axis represents HR and 95% CI, Y-axis represents cancer type, the circle size represents  $-\log_{10}$  P value, and the color of the circle represents risk type. (D-F) Kaplan-Meier survival analysis of MMP14 in the TCGA-KIRC dataset. (G-I) Time-dependent ROC analysis of MMP14 in the TCGA-KIRC dataset. OS, overall survival; TCGA, The Cancer Genome Atlas; KIRC, kidney renal clear cell carcinoma; NS, not statistically; DSS, disease-specific survival; PFI, progression-free interval; HR, hazard ratio; CI, confidence interval; MMP14, matrix metalloproteinase 14; ROC, receiver operating characteristic; AUC, area under the curve; FPR, false positive rate.

pan-cancer analysis and corresponding normal tissues and found that MMP14 showed a significant upregulation trend in most cancer types and was significantly upregulated in KIRC patients. We then constructed a ROC model

for accuracy validation. Finally, analysis of tumor-normal paired samples in the TCGA-KIRC dataset also showed that MMP14 gene expression was significantly higher in KIRC tissues than in normal kidney tissues adjacent



**Figure 3** Disease ontology GSEA. (A) Kidney cancer-related diseases from the DO database. (B) Kidney cancer-related diseases from the DisGeNET database. DO, Disease Ontology; GSEA, gene set enrichment analyses; MMP14, matrix metalloproteinase 14; TCGA, The Cancer Genome Atlas; KIRC, kidney renal clear cell carcinoma; NES, neuroendocrine syndrome.



**Figure 4** KEGG signaling pathway GSEA. (A) The dotplot of top 12 KEGG gene set analyses results. (B) The gene-concept network for top 5 KEGG gene set analyses results. (C) The concept-concept network for top 30 KEGG gene set analyses results. KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, gene set enrichment analyses; MMP14, matrix metalloproteinase 14; TCGA, The Cancer Genome Atlas; KIRC, kidney renal clear cell carcinoma; COVID-19, coronavirus disease 2019.



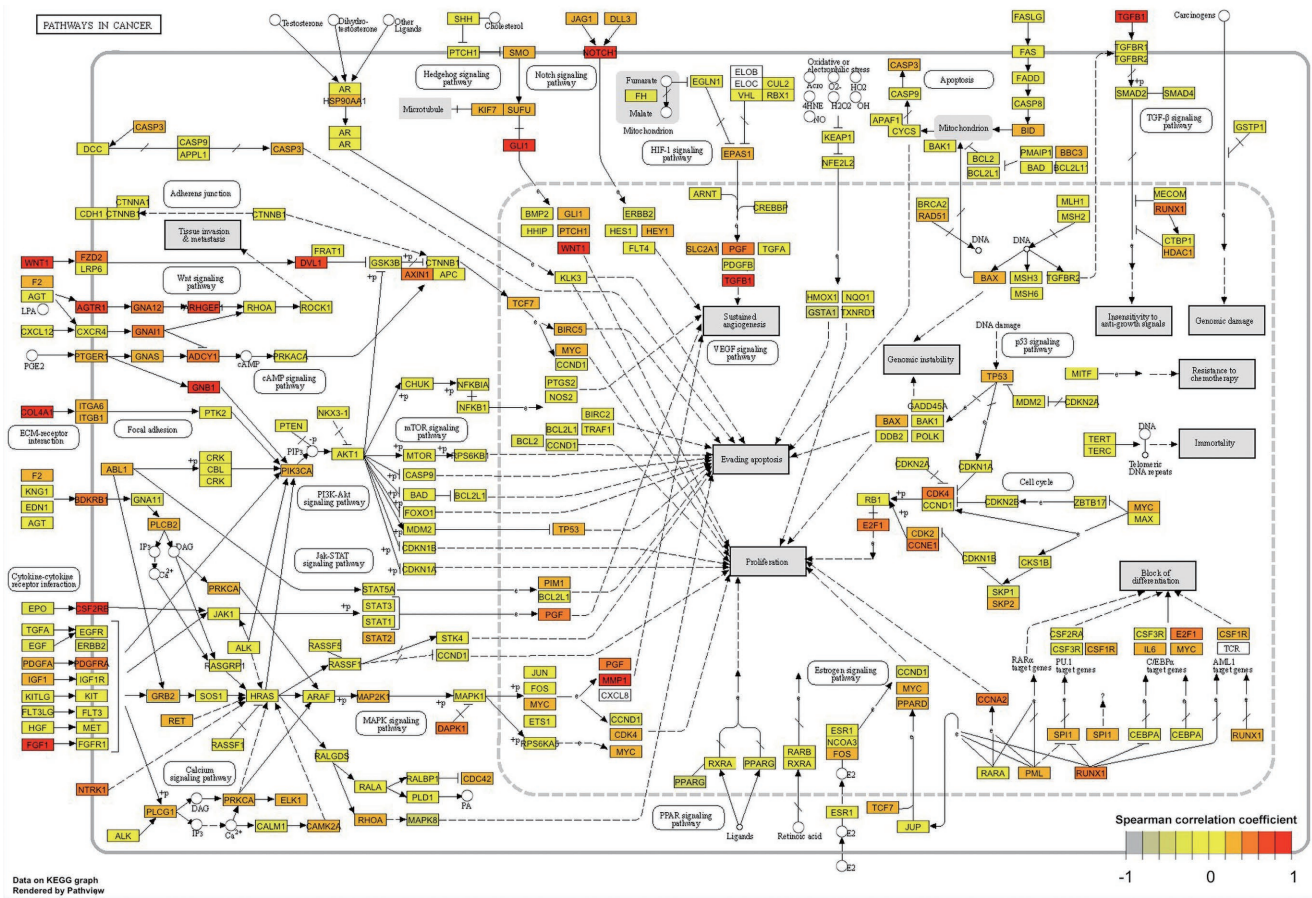


Figure 5 KEGG view of 'Pathways in cancer'. KEGG, Kyoto Encyclopedia of Genes and Genomes.

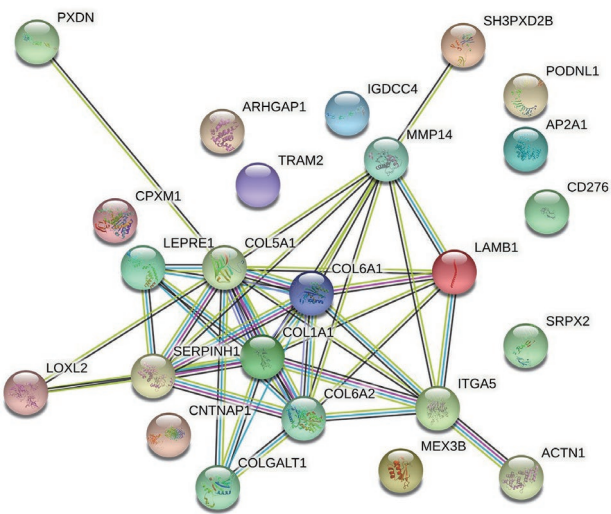


Figure 6 Protein-protein interaction network of genes significantly and positively associated with MMP14 in KIRC. MMP14, matrix metalloproteinase 14; KIRC, kidney renal clear cell carcinoma.

to the carcinoma. To better assess the trend of MMP14 protein expression level in KIRC patients, we validated immunohistochemical images from the HPA database by selecting immunohistochemical staining images of HPA051432 antibody and found no positive staining for MMP14 protein in normal kidney tissues, while medium and low positive staining cases were found in KIRC tissues, although the present results need further validation in a large sample. Overall, the combination of results at the gene level and protein level indicated that MMP14 was significantly upregulated in KIRC tissues. In recent years, scholars have done a lot of researches on the role of different biological indicators in different diseases, with a view to providing new targets for the diagnosis and treatment of different diseases (32-36). MMP14 may also become a new therapeutic target for KIRC.

Next, we divided patients into high- and low-expression groups according to the median quantitative gene expression

of MMP14 in KIRC. By assessing the clinicopathological characteristics of KIRC in both groups, we showed that patients in the MMP14 high-expression group had higher pathological T-stage, higher histological grade, and younger age, indicating that upregulation of MMP14 may have contributed to poor prognosis in KIRC. To further systematically assess the clinical prognostic outcome of MMP14 in KIRC, we first constructed a univariate Cox regression model for the survival data of MMP14 in patients based on pan-cancer analysis, and the results suggested that MMP14 was a significant poor prognostic factor for KIRC in terms of OS, DSS, and PFI. We then performed Kaplan-Meier survival analysis in KIRC patients, and the results also showed that patients in the MMP14 high-expression group had worse prognosis for OS, DSS, and PFI. Thus, we could conclude that MMP14 upregulation led to a poor clinical prognosis in KIRC patients.

The results of expression and prognostic analysis of MMP14 in KIRC patients indicated that the upregulation of MMP14 may have promoted cancer progression in KIRC patients; however, the underlying mechanism is not yet known. Tumorigenesis and progression are complex biological processes involving multiple genes and multiple signaling pathway interactions. A synergistic network of the multiple genes associated with the gene expression prominence and the interaction of multiple signaling pathways can be used to explore the potential function of a specific gene in a specific cancer. In this study, we performed correlation analysis of MMP14 with all coexpressed genes in the TCGA-KIRC dataset in order to uncover signaling pathways significantly associated with KIRC disease progression. The results of DO gene set enrichment analysis showed that upregulation of MMP14 was significantly and positively associated with KIRC-associated disease, while the KEGG pathway could be enriched for a variety of tumor-related signaling pathways ('MicroRNAs in cancer', 'Estrogen signaling pathway', 'Pathway in cancer', 'PI3K-Akt signaling pathway', and 'Proteoglycans in cancer') to be activated, which suggested that MMP14 may play a potential cancer-promoting role in KIRC through the interaction of these cancer-related signaling pathways with related coexpressed genes. However, more basic experiments are needed to validate the mechanism of MMP14 and its coexpressed genes in the malignant biological behavior of KIRC.

## Conclusions

MMP14 expression was significantly upregulated in KIRC

and associated with poor prognosis in KIRC patients. It was hypothesized that upregulation of MMP14 may promote carcinogenesis and tumor progression in KIRC.

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## Footnote

*Reporting Checklist:* The authors have completed the REMARK reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-619/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-619/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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