

# Overexpression of MMP14 predicts the poor prognosis in gastric cancer

## Meta-analysis and database validation

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### Abstract

**Background:** Plenty of studies have showed matrix metalloproteinase 14 (MMP14) expression might be associated with the prognosis of gastric cancer (GC). However, no definite conclusion has been obtained for the contradictory results.

**Methods:** We searched PubMed, Web of science, Embase, and Cochrane library for eligible studies. The association between MMP14 expression and prognostic outcomes of GC was evaluated. Hazard ratio (HR) and 95% confidence interval (CI) were integrated to show the effect of MMP14 expression on the overall survival (OS) or recurrence-free survival (RFS). Data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) was used to validate the association of MMP14 expression with OS or RFS in GC. A brief bioinformatics analysis was also performed to determine the prognostic role of MMP14 expression in GC.

**Results:** High MMP14 expression was associated with shorter OS compared to low MMP14 expression in GC (HR = 1.95,  $P < .01$ ). Patients with high MMP14 expression tended to have worse differentiation ( $P = .03$ ), deeper tumor invasion ( $P < .01$ ), earlier lymph node metastasis ( $P < .01$ ), earlier distant metastasis ( $P < .01$ ) and more advanced clinical stage ( $P < .01$ ) compared to those with low MMP14 expression. The data from TCGA and GEO showed MMP14 was overexpressed in tumor tissues compared to normal tissues ( $P < .05$ ), and high MMP14 expression was significantly related to shorter OS (HR = 1.70, 95% CI = 1.32–2.20,  $P < .01$ ) and RFS (HR = 1.45, 95% CI = 1.15–1.83,  $P < .01$ ) compared to low MMP14 expression in GC. Expression of MMP14 was linked to functional networks involving the biological process, metabolic process, response to stimulus, cell communication and so on. Functional network analysis suggested that MMP14 regulated the protein digestion and absorption, extracellular matrix receptor interaction, focal adhesion, ribosome, spliceosome, and so on.

**Conclusion:** High MMP14 expression was associated with worse prognosis of GC compared to low MMP14 expression. MMP14 expression could serve as a prognostic factor and potential therapeutic target of GC.

**Abbreviations:** CI = confidence interval, GC = gastric cancer, GEO = gene expression omnibus, HR = hazard ratio, KEGG = Kyoto Encyclopedia of Genes and Genomes pathways, MMP14 = matrix metalloproteinase 14, NOS = Newcastle-Ottawa Scale, OS = overall survival, RFS = recurrence-free survival, TCGA = the Cancer Genome Atlas.

**Keywords:** bioinformatics analysis, gastric cancer, matrix metalloproteinase 14, meta-analysis, prognosis

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## 1. Introduction

Gastric cancer (GC) has become the leading common malignant disease and one of the most common cause of cancer mortality worldwide, especially in eastern Asia.<sup>[1]</sup> With the increasing popularity of immunotherapy,<sup>[2,3]</sup> to improve the clinical decision-making and prognosis of GC patients, researchers begin to seek biomarkers to predict the prognosis and serve as the potential therapeutic target in GC.<sup>[4,5]</sup>

Matrix metalloproteinase 14 (MMP14) is the first membrane type matrix metalloproteinase discovered.<sup>[6]</sup> MMP14 has been prove to involve in several biological processes, including the angiogenesis, proliferation, invasion and basement membrane remodeling, therefore, MMP14 might play an important role in the tumorigenesis, invasion and metastasis.<sup>[7]</sup> Recently, accumulating evidence showed that MMP14 was overexpressed in cancer tissues and might be involved in the tumor progression of GC.<sup>[8–17]</sup> Dong et al. conducted a meta-analysis containing 594 GC patients, and found that high MMP14 expression was a poor prognostic factor in Chinese patients with GC.<sup>[8]</sup> He et al study analyzed 205 GC patients who received surgical treatment, and their results showed MMP14 expression was an independent negative prognostic factor of patients with GC.<sup>[11]</sup> Kasurinen et al retrospectively analyzed 240 GC patients treated with surgical

treatment, and found that high serum MMP14 level was associated with worse prognosis.<sup>[18]</sup> Duan et al performed a meta-analysis and databases validation to explore the prognostic value of MMP14 expression in digestive system carcinoma, and found that high MMP14 expression might predict poor prognosis in digestive system carcinoma, including GC.<sup>[19]</sup> Dong et al. study showed that MMP14 expression was overexpressed in GC tissues compared to normal tissues, and high MMP14 expression was associated with unfavorable clinicopathological parameters, such as earlier lymph node metastasis and advanced clinical stage.<sup>[9]</sup> Similarly, Tian et al also found that high MMP14 expression was associated with earlier lymph node or distant metastasis, advanced clinical stage and shorter overall survival (OS) when compared to low MMP14 expression in GC.<sup>[9]</sup> However, differently, Kasurinen et al failed to observe the significant association between MMP14 expression and OS of GC in the multivariate analysis.<sup>[12]</sup> Therefore, there is a dispute about the prognostic role of MMP14 expression in GC account of the contradictory results of existing evidence.<sup>[8–17]</sup> Here, we performed this meta-analysis and validated the results using public databases to determine the prognostic significance of MMP14 expression in GC.

## 2. Materials and methods

This study has been approved by the ethics committee of our hospital and was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses.<sup>[20]</sup>

### 2.1. Inclusion and exclusion criteria

Inclusion criteria for the eligible studies included: (a) Participants: GC patients; (b) Intervention: Patients with high MMP14 expression; (c) Control: Patients with low MMP14 expression; (d) Outcomes: clinicopathological parameters, OS and recurrence-free survival (RFS); (e) Study design: prospective or retrospective studies. Exclusion criteria for the articles included: (a) studies without presenting data with relevant values, (b) duplicated publications, (c) letters, reviews, case reports and expert opinions.

### 2.2. Literature search

Comprehensive literature search was performed on February 26, 2020 in the following databases: PubMed, Web of Science, Embase, and Cochrane Database. The following key words were used: (“gastric cancer” OR “stomach cancer” OR “gastric carcinoma”) AND (“matrix metalloproteinase-14” OR “MMP-14” OR “membrane-type 1 matrix metalloproteinase” OR “MT1-MMP”) AND (“survival” OR “prognosis”). The literature strategy was shown in Supplementary Table S1, <http://links.lww.com/MD/G357>.

### 2.3. Data extraction and risk of bias

The following items were extracted: name of first author, published year, country, sample size, number of patients in high or low MMP14 expression, clinical stage, outcomes, source of experimental sample, method for detecting MMP14 expression, treatment, analysis model of OS, adjusted factors in the multivariate analysis of OS. For studies only reporting the survival curve of OS or RFS, the survival data was extracted from

the survival curve.<sup>[21]</sup> The risk of bias of included studies were assessed by Newcastle-Ottawa Scale (NOS), which ranged from 0 to 9. One study with an NOS score more than 5 was regarded as high quality.<sup>[22]</sup> The data extraction was independently evaluated by 2 investigators, and a consensus was reached by group discussion when the disagreement occurred.

### 2.4. Database validation and bioinformatics analysis

The Gene Expression Profiling Interactive Analysis (<http://gepia.cancer-pku.cn/index.html>), based on the data from the Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), was used to compare the expression level of MMP14 in gastric cancer tissue and normal tissue.<sup>[23]</sup> GEO is a common database for bioinformatics research. GEO is an international public repository that archives and freely distributes microarray, next-generation sequencing, and other forms of high-throughput functional genomics data submitted by the research community.<sup>[24]</sup>

The Kaplan–Meier-plotter (<http://kmplot.com/analysis/index.php?p=service>), based on the data from TCGA, was used to explore the effect of MMP14 expression on the OS and RFS of GC patients.<sup>[25]</sup> TCGA, a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types (<https://www.cancer.gov/tcga>).

The LinkedOmics database (<http://www.linkedomics.org/login.php>), based on TCGA data, is a web-based platform for analyzing cancer-associated multi-dimensional datasets.<sup>[26]</sup> We used the LinkFinder module of LinkedOmics to study genes differentially expressed in correlation with MMP14 expression in GC using Pearson’s correlation coefficient. Results were presented using the volcano plot and heat map. The LinkFinder was also used to generate the scatter plot for the top 3 positively or negatively correlated genes. The Link Interpreter module performs pathway and network analyses of differentially expressed genes. Data from the LinkFinder results were signed and ranked, and gene-set enrichment analysis (GSEA) was used to perform analyses of gene ontology (cellular component, biological process and molecular function) and Kyoto Encyclopedia of Genes and Genomes (KEGG). KEGG is used to understand high-level functions and utilities of the biological system, such as the cell, the organism and the ecosystem, from molecular-level information, especially large-scale molecular datasets generated by genome sequencing and other high-throughput experimental technologies (<https://www.genome.jp/kegg/>).

### 2.5. Statistical analysis

We used the Stata 12.0 (StataCorp, College Station, TX, USA) and Review Manager 5.3 (Cochrane Collaboration, London, UK) to analyze the data in the current study. The heterogeneity among included studies was determined by the Chi Squared-based Q test and  $I^2$  statistics. Random-effect model was used when  $P$  for heterogeneity  $< .05$  and  $I^2 > 50\%$ , otherwise, the fixed effects model was applied. Forest plot was generated to determine the association of MMP14 expression with OS and clinicopathological parameters. Hazard ratio (HR) and 95% confidence interval (CI) were integrated to show the effect of MMP14 expression on the OS/RFS. Odd ratio and 95% CI were used to show association of MMP14 expression with clinicopathological parameters. Subgroup analysis was performed to comprehen-

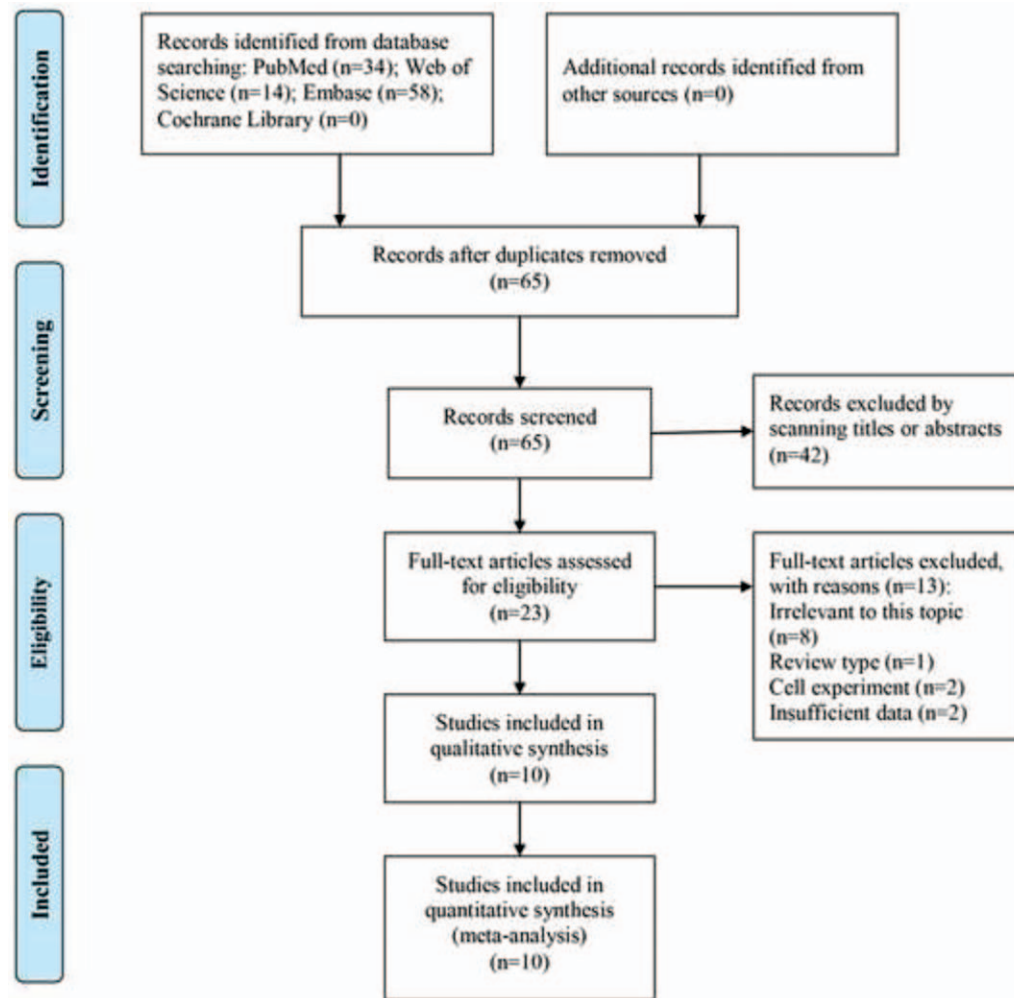


Figure 1. Flow chart of literature search and selection.

sively explore the association between MMP14 expression and OS. Sensitivity analysis was also carried out to assess the stability of the results by removing 1 included study at a time. Potential publication bias among included studies was assessed with Begg test and Egger test. Pearson test was used to check the relationship between MMP14 expression and other genes. The  $P$  value less than .05 was considered to be statistically significant.

### 3. Results

#### 3.1. Literature search and selection

As showed in Figure 1, a total of 106 records were retrieved in the initial search from 4 common databases, and 10 studies were finally included into this meta-analysis.<sup>[8–17]</sup>

#### 3.2. Characteristics of included studies

A total of 10 studies containing 2015 GC patients (833 patients with high MMP14 expression and 1182 patients with low MMP14 expression) were included into this meta-analysis<sup>[8–17]</sup> (Table 1). Six retrospective studies were conducted in China<sup>[8,9,11,15–17]</sup> and 4 retrospective studies were conducted in other countries.<sup>[10,12–14]</sup> The expression level of MMP14 was

detected using immunohistochemistry in 8 studies<sup>[8–12,14–16]</sup> and using quantitative real time polymerase chain reaction in 2 studies.<sup>[13,17]</sup> The sample was tumor tissue in 9 studies<sup>[8–12,14–17]</sup> and peripheral blood in 1 study.<sup>[13]</sup> The sample size varied from 44 to 810 patients among included studies. All patients received the surgical treatment with or without postoperative chemotherapy. Ten studies reported clinicopathological parameters,<sup>[8–17]</sup> 6 studies reported OS<sup>[9,11,12,14,15,17]</sup> and 1 study reported RFS.<sup>[13]</sup> The prognostic role of MMP14 expression was analyzed using the multivariate analysis model in 6 studies,<sup>[9,11,12,14,15,17]</sup> and the adjusted factors were listed in Supplementary Table S2, <http://links.lww.com/MD/G358>. All included studies had a relatively high quality with NOS score more than 5.<sup>[8–17]</sup>

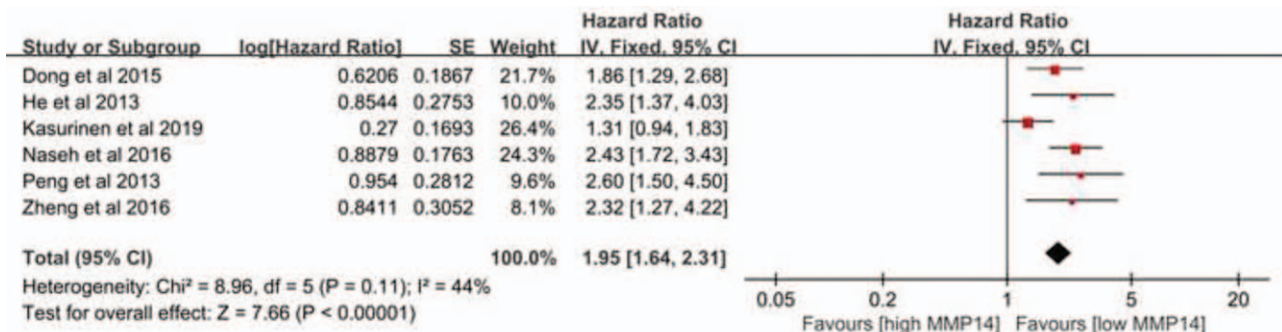
#### 3.3. Meta-analysis of the association between MMP14 expression and overall survival

As showed in Figure 2, a fixed-effect model was used for tiny heterogeneity among included studies ( $I^2=44\%$ ,  $P=.11$ ), and high MMP14 expression was significantly associated with shorter OS compared to low MMP14 expression in GC (HR=1.95, 95% CI=1.64–2.31,  $P<.01$ ). The subgroup analysis stratified by the country, sample size and detection method was

**Table 1****Basic information of included studies.**

Study	Country	Study design	Detection method	Source	MMP14 expression (total/high/low) (n)	Clinical stage (I+II/III+IV)(n)	Treatment	Outcome	Analysis model	NOS
Dong et al 2013 <sup>[9]</sup>	China	R	IHC	Tissue	86/51/35	30/56	Surgery	CP	NA	6
Dong et al 2015 <sup>[8]</sup>	China	R	IHC	Tissue	193/103/90	70/135	Surgery	CP,OS	M	8
Gurgel et al 2014 <sup>[10]</sup>	Brazil	R	IHC	Tissue	69/51/18	NA	Surgery	CP	NA	6
He et al 2013 <sup>[11]</sup>	China	R	IHC	Tissue	205/109/96	96/109	Surgery	CP,OS	M	8
Kasurinen et al 2019 <sup>[12]</sup>	Finland	R	IHC	Tissue	278/80/198	117/161	Surgery	CP,OS	M	8
Mimori et al 2008 <sup>[13]</sup>	Japan	R	qRT-PCR	Blood	810/185/625	592/218	Surgery	CP,RFS	NA	7
Naseh et al 2016 <sup>[14]</sup>	Iran	R	IHC	Tissue	96/58/38	38/58	Surgery	CP,OS	M	8
Peng et al 2013 <sup>[15]</sup>	China	R	IHC	Tissue	184/138/46	58/126	Surgery	CP,OS	M	8
Shen et al 2011 <sup>[16]</sup>	China	R	IHC	Tissue	44/23/21	NA	Surgery	CP	NA	6
Zheng et al 2016 <sup>[17]</sup>	China	R	qRT-PCR	Tissue	50/35/15	17/33	Surgery	CP,OS	M	7

CP = clinicopathological parameters, IHC = immunohistochemistry, M = multivariate, MMP14 = matrix metalloproteinase 14, NA = not available, NOS = Newcastle-Ottawa Scale, OS = overall survival, qRT-PCR = quantitative real-time reverse transcriptase-polymerase chain reaction, R = retrospective, RFS = recurrence-free survival.

**Figure 2.** Meta-analysis of the association between MMP14 expression and overall survival.

performed, and the association between MMP14 expression and OS remained statistically significant in most analyzes ( $P < .05$ ) except for the countries outside of China ( $P = .06$ ) (Table 2).

### 3.4. Meta-analysis of the association between MMP14 expression and clinicopathological parameters

As listed in Table 3, GC patients with high MMP14 expression tended to have worse differentiation (HR = 1.31, 95% CI = 1.02–1.68,  $P = .03$ ), deeper tumor invasion (HR = 1.97, 95% CI = 1.19–3.26,  $P < .01$ ), earlier lymph node metastasis (HR = 2.35,

95% CI = 1.34–4.11,  $P < .01$ ), earlier distant metastasis (HR = 2.41, 95% CI = 1.05–5.56,  $P < .01$ ) and more advanced clinical stage (HR = 2.88, 95% CI = 1.65–5.01,  $P < .01$ ) compared to those with low MMP14 expression. Nevertheless, there was no significant association of MMP14 expression with age ( $P = .55$ ), gender ( $P = .86$ ) or Lauren classification ( $P = .95$ ).

### 3.5. Sensitivity analysis

The sensitivity analysis of the association between MMP14 expression and OS showed the pooled result was not altered after the removal of any included study (Fig. 3).

**Table 2****Subgroup analysis of the association between MMP14 expression and OS.**

Factors	Studies (n)	HR 95% CI	P	I <sup>2</sup> (%)	P heterogeneity	Model
Country						
China	4	2.16 (1.69, 2.75)	<.01 <sup>†</sup>	0	0.75	Fixed
Others	2	1.78 (0.97, 3.26)	.06	84	0.01	Random
Sample size (n)						
≤100	2	2.40 (1.78, 3.24)	<.01 <sup>†</sup>	0	0.89	Fixed
>100	4	1.86 (1.36, 2.53)	<.01 <sup>†</sup>	51	0.10	Random
Detection method						
IHC	5	1.98 (1.51, 2.59)	<.01 <sup>†</sup>	54	0.07	Random
qRT-PCR	1	2.32 (1.27, 4.22)	<.01 <sup>†</sup>	0	1.00	Fixed

CI = confidence interval, HR = hazard ratio, IHC = immunohistochemistry, MMP14 = matrix metalloproteinase 14, OS = overall survival, qRT-PCR = quantitative real-time reverse transcriptase-polymerase chain reaction.

<sup>†</sup>  $P < .05$  indicating the statistical association between MMP14 expression and OS.

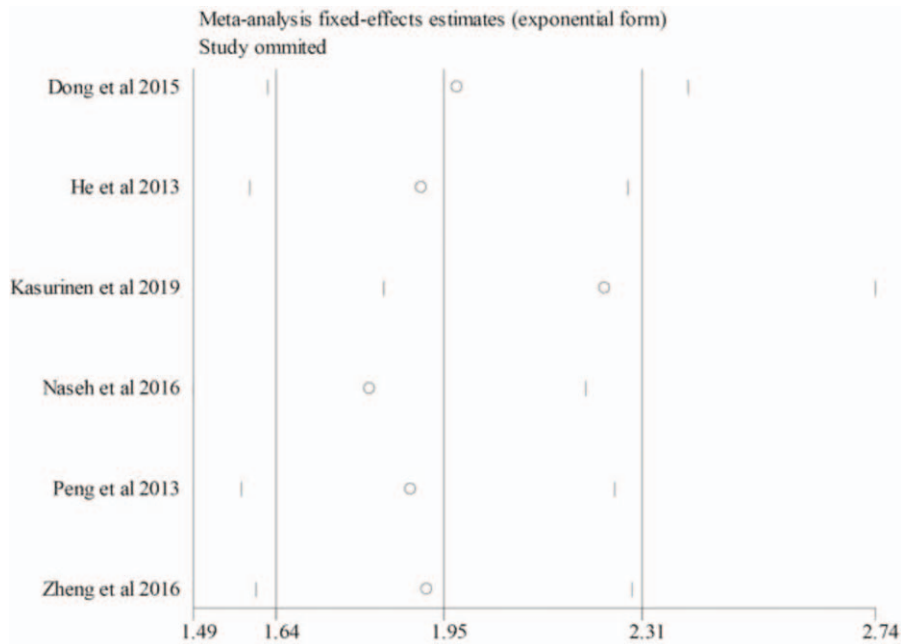
**Table 3**

**Meta-analysis of the association between MMP14 expression and clinicopathological parameters.**

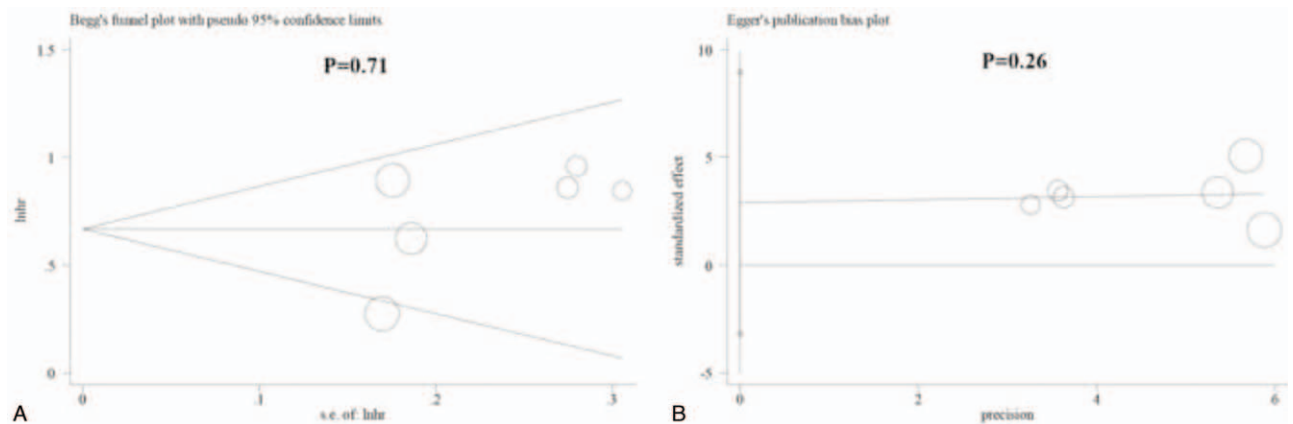
Factors	Studies (n)	Patients (n)	OR 95% CI	P	Heterogeneity (%)	P for heterogeneity	Model	Begg test	Egger test
Age (old/young)	7	1094	1.08 (0.84, 1.40)	.55	0	0.59	Fixed	0.76	0.46
Gender (male/female)	9	1948	1.02 (0.83, 1.25)	.86	0	0.79	Fixed	0.75	0.53
Tumor differentiation (poor/moderate + well)	6	1524	1.31 (1.02, 1.68)	.03 <sup>†</sup>	39	0.15	Fixed	0.13	0.12
Laurén classification (intestinal/diffuse)	3	533	1.01 (0.70, 1.46)	.95	0	0.81	Fixed	1.00	0.82
Tumor invasion (T3+T4/T1+T2)	8	1852	1.97 (1.19, 3.26)	<.01 <sup>†</sup>	75	<0.01	Random	0.27	0.09
Lymph node metastasis (yes/no)	9	1812	2.35 (1.34, 4.11)	<.01 <sup>†</sup>	79	<0.01	Random	0.35	0.40
Distant metastasis (yes/no)	6	1634	2.41 (1.05, 5.56)	.04 <sup>†</sup>	65	0.01	Random	0.06	0.09
Clinical stage (III+IV/I+II)	8	1904	2.88 (1.65, 5.01)	<.01 <sup>†</sup>	82	<0.01	Random	0.17	0.28

CI = confidence interval, MMP14 = matrix metalloproteinase 14, OR = odd ratio.

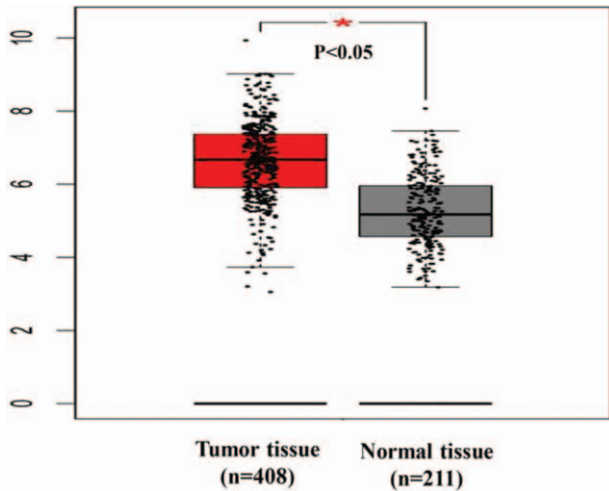
<sup>†</sup>indicating the statistical association between MMP14 expression and CP.



**Figure 3.** Sensitivity analysis of the association between MMP14 expression and overall survival.



**Figure 4.** Publication bias of the association between MMP14 expression and overall survival.



**Figure 5.** Expression of MMP14 in tumor tissues of gastric cancer and normal tissues.

### 3.6. Publication bias

Publication bias among included studies was evaluated by the Begg test and Egger test. There was no obvious publication bias for the meta-analysis of the association between MMP14 expression and OS (Begg test,  $P = .71$ ; Egger test,  $P = .26$ ) (Fig. 4).

### 3.7. Database validation and bioinformatics analysis

The database validation was conducted by the GEPAI and Kaplan–Meier-plotter using the data from TCGA and GEO. Results from the gene expression profiling interactive analysis showed that the level of MMP14 expression was obviously increased in tumor tissue compared to normal tissue ( $P < .05$ ) (Fig. 5).

Kaplan–Meier-plotter indicated, compared to low MMP14 expression, high MMP14 expression was significantly related to worse RFS (median, 10.1 versus 24.3 months) ( $HR = 1.70$ , 95% CI = 1.32–2.20,  $P < .01$ ) (Fig. 6A).

CI = 1.32–2.20,  $P < .01$ ) (Fig. 6A) and OS (median, 20.3 vs 30.4 months) ( $HR = 1.45$ , 95% CI = 1.15–1.83,  $P < .01$ ) (Fig. 6B).

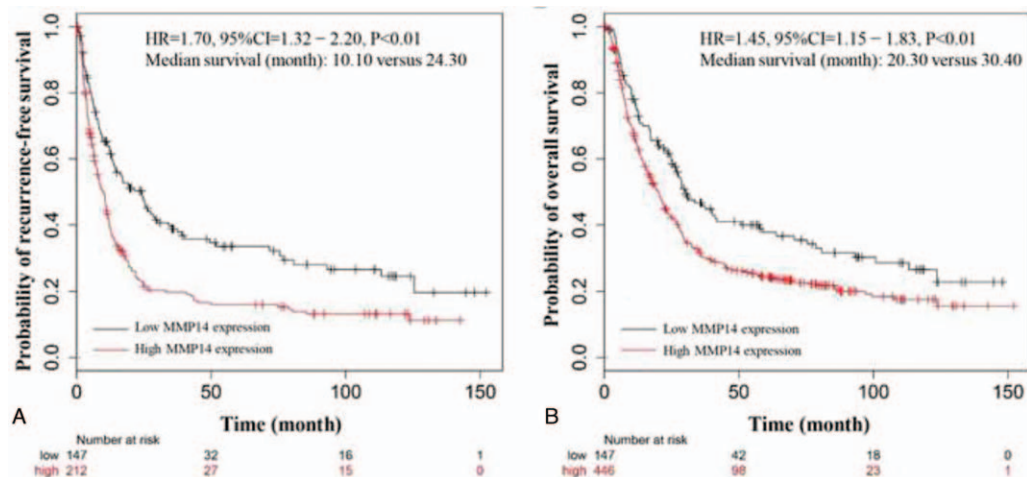
The Function module of LinkedOmics was used to analyze mRNA sequencing data from GC patients in the TCGA. As shown in the volcano plot (Fig. 7A), 3908 genes (red dots) showed significant positive correlations with MMP14, whereas 3495 genes (green dots) showed significant negative correlations ( $FDR < 0.01$ ). The 50 significant gene sets positively and negatively correlated with MMP14 expression as shown in the heat map (Fig. 7B, 7C). This result suggests a widespread impact of MMP14 expression on the transcriptome.

As shown in Figure 8, MMP14 expression showed a strong positive association with expression of Collagen Type V Alpha 1 Chain ( $r = 0.77$ ,  $P = 1.17e-81$ ) (Fig. 8A), Mannose Receptor C Type 2 ( $r = 0.77$ ,  $P = 3.017e-81$ ) (Fig. 8B) and ADAM Metalloproteinase with Thrombospondin Type 1 Motif 2 ( $r = 0.77$ ,  $P = 4.074e-81$ ) (Fig. 8C). Besides, MMP14 expression had a significant negative association with the expression of Coiled-Coil Domain-Containing Protein 76 ( $r = 0.47$ ,  $P = 2.437e-24$ ) (Fig. 8D), Chromosome 6 Open Reading Frame 26 ( $r = 0.44$ ,  $P = 2.437e-24$ ) (Fig. 8E) and T-Complex-Associated-Testis-Expressed 3 ( $r = 0.44$ ,  $P = 1.376e-20$ ) (Fig. 8F).

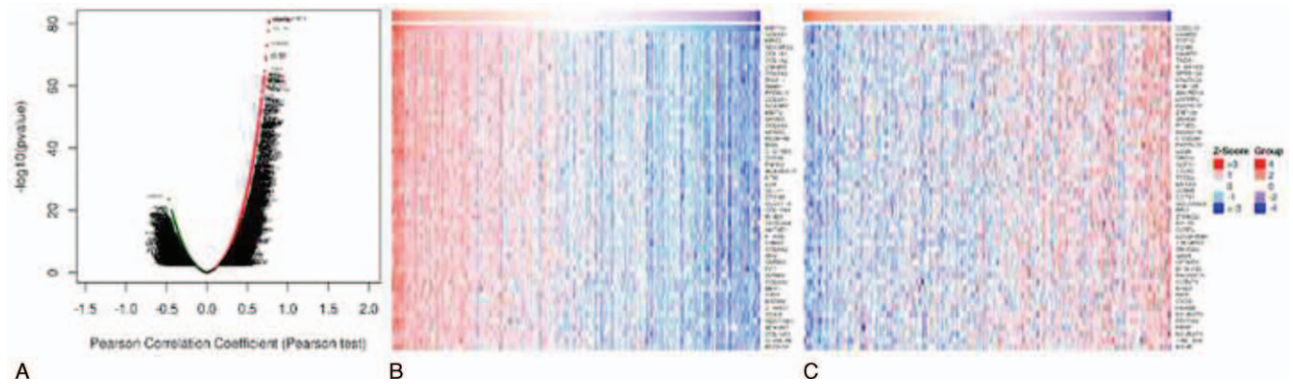
Significant gene ontology term analysis by GSEA showed that genes differentially expressed in correlation with MMP14 were located mainly in the membrane, nucleus, membrane-enclosed lumen, protein-containing complex and cytosol, where they participated primarily in biological process, metabolic process, response to stimulus, cell communication and so on (Fig. 9). The KEGG pathway analysis showed enrichment in the pathways of protein digestion and absorption, extracellular matrix receptor interaction, focal adhesion, ribosome, spliceosome, and so on (Fig. 10).

## 4. Discussion

Although plenty of studies have showed that the overexpression of MMP14 might facilitate the tumor progression of GC, definite conclusion has not been obtained for the contradictory results.<sup>[8–17]</sup> To determine the prognostic role of MMP14 expression in GC, we pooled the data from existing 10 relevant studies,<sup>[8–17]</sup> and



**Figure 6.** Database validation to explore the relationship between MMP14 expression and recurrence-free survival; (A), the association between MMP14 expression and overall survival in gastric cancer based on TCGA and GEO (A), the association between MMP14 expression and overall survival; (B), the association between MMP14 expression and overall survival).

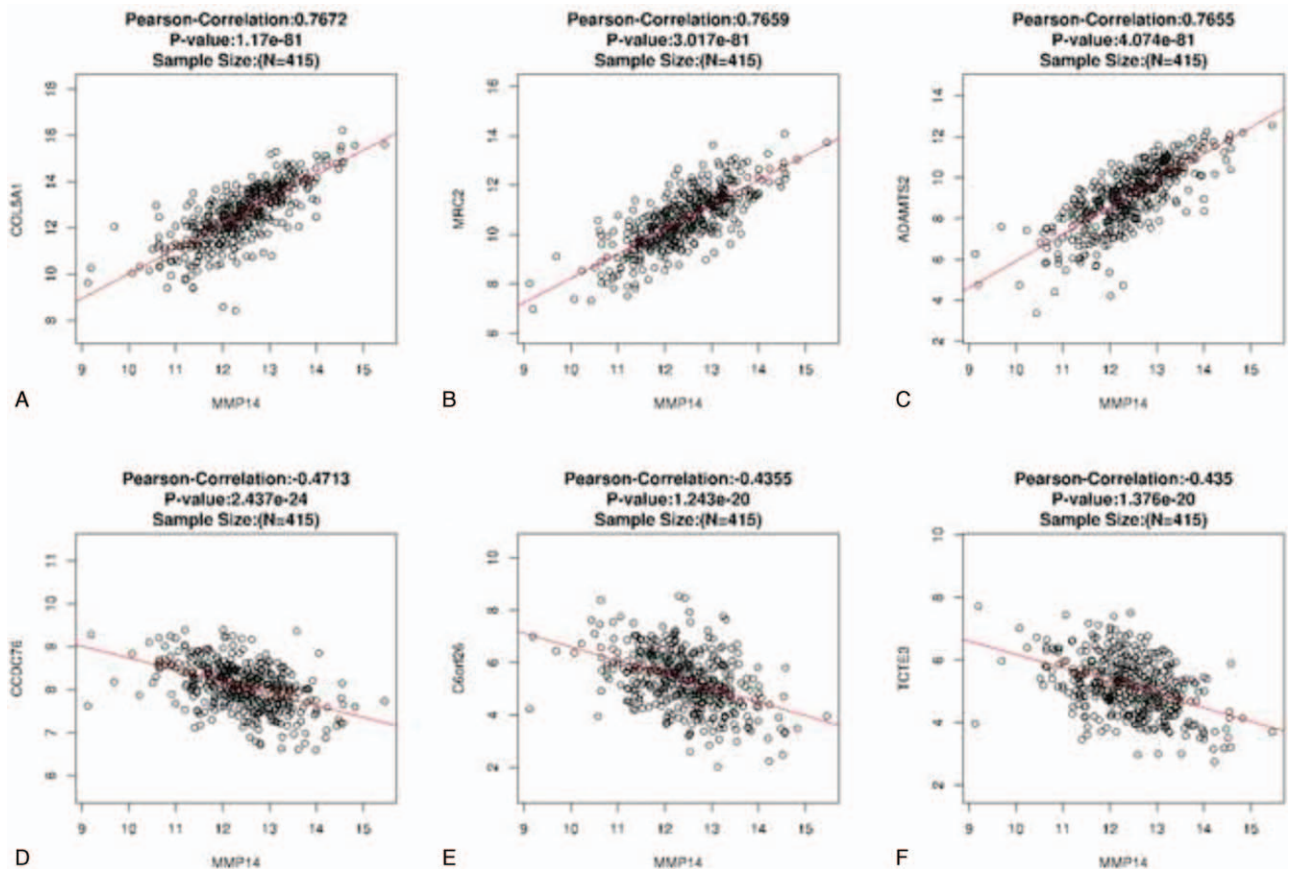


**Figure 7.** Co-expression genes correlated with MMP14 expression in gastric cancer based on public database (A), volcano plot showing all genes with false discovery rate [FDR] < 0.01; (B), heat map showing top 50 genes positively correlated with MMP14 expression; (C), heat map showing top 50 genes negatively correlated with MMP14 expression).

our results showed GC patient with high MMP14 expression tended to have shorter OS, worse differentiation, deeper tumor invasion, earlier lymph node metastasis, earlier distant metastasis and more advanced clinical stage compared to those with low expression. And our findings were validated by data from TCGA and GEO, which indicated that high MMP14 expression was significantly related to shorter OS and RFS compared to low MMP14 expression in GC. Therefore, our study suggested that high MMP14 expression was an unfavorable prognostic factor of

GC patients. To the best of our knowledge, our study was the first to determine the prognostic role of MMP14 expression in GC by integrating the existing evidence and then validated using public databases.

Although the prognostic role of MMP14 expression in GC has been explored in many studies, the underlying mechanism remains unclear.<sup>[8-17]</sup> Li et al study showed that MMP14 expression was elevated in GC cells, and the silencing of MMP14 inhibited the proliferation and invasion of tumor cells via the



**Figure 8.** Scatter plots for the top 3 genes positively or negatively correlated with MMP14 expression in gastric cancer using public database.

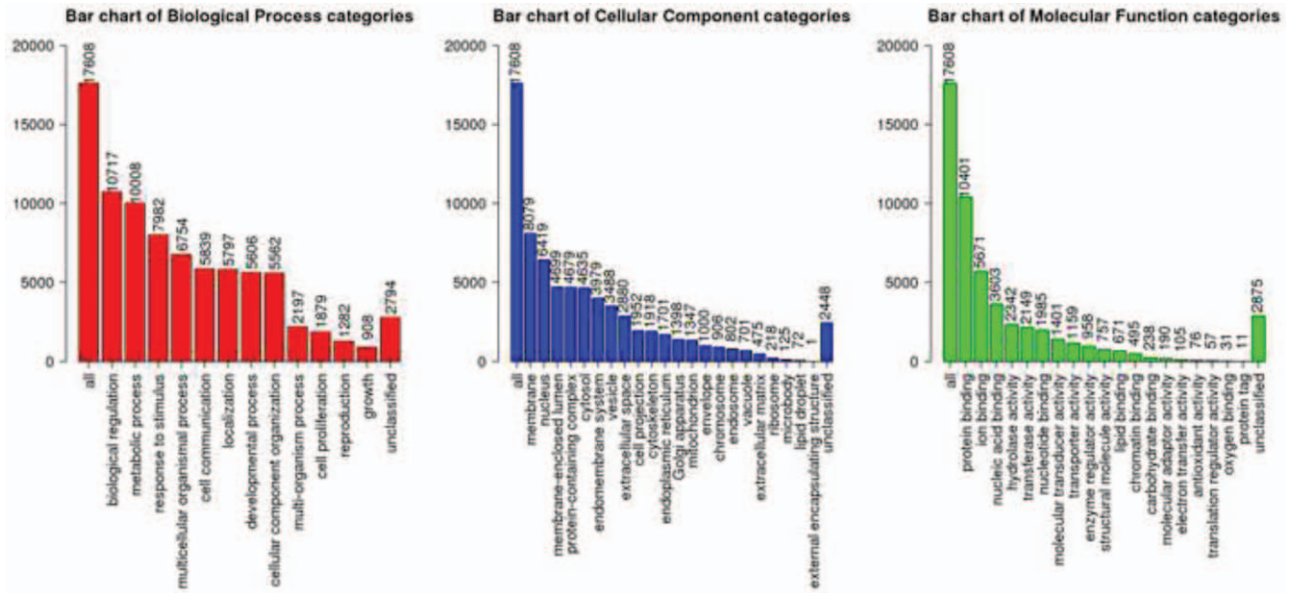


Figure 9. GO analysis of MMP14 expression in gastric cancer (A), cellular components; (B), biological processes; (C), molecular functions).

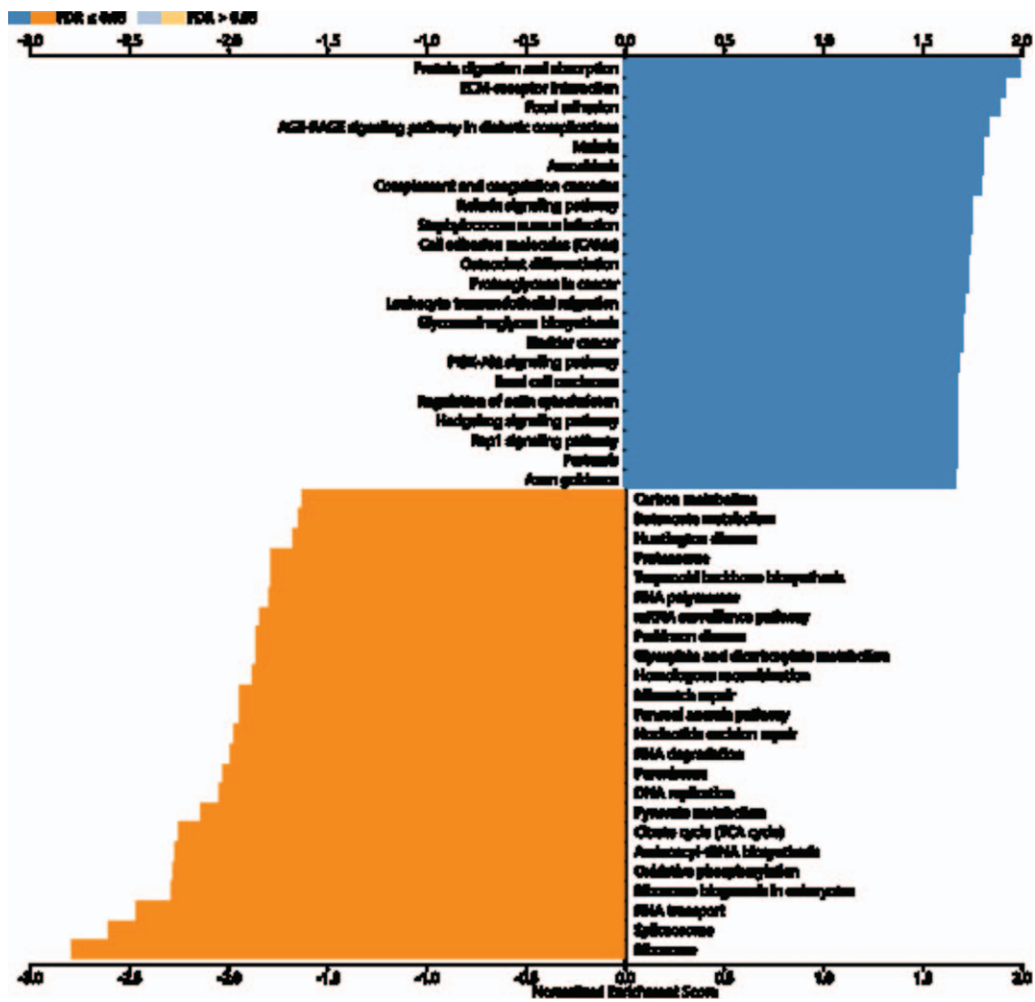


Figure 10. KEGG pathway analysis of MMP14 expression in gastric cancer.



regulation of vimentin and E-cadherin.<sup>[27]</sup> Zheng et al found miRNA-337-3p could inhibit the progression of GC through repressing myeloid zinc finger 1-facilitated expression of MMP14.<sup>[17]</sup> Zuo et al study showed miRNA-22 downregulation could promote the invasion and metastasis of GC by upregulating MMP14 and Snail, and then inducing extracellular matrix remodeling and epithelial-to-mesenchymal transition.<sup>[28]</sup> Our study showed that MMP14 were located mainly in the membrane, nucleus, membrane-enclosed lumen, protein-containing complex and cytosol, and they participated primarily in biological process, metabolic process, response to stimulus, cell communication and so on. And KEGG pathway analysis showed enrichment in the pathways of protein digestion and absorption, extracellular matrix receptor interaction, focal adhesion, ribosome, spliceosome, and so on. Therefore, no definite underlying mechanism has been determined up to now, and more basic experiments should be conducted to evaluate the underlying mechanism.

Our meta-analysis integrated the existing evidence with contradictory results to determine the prognostic value of MMP14 expression in GC, and our findings showed high MMP14 expression was associated with worse OS compared to low MMP14 expression in GC. It was worth mentioning that the database validation based TCGA and GEO supported our findings about the unfavorable role MMP14 expression in the prognosis of GC patients. We also performed a simple bioinformatics analysis to further determine the prognostic role of MMP14 expression in GC. Therefore, our study provided the value evidence about the prognostic role of MMP14 expression in GC, which benefitted the clinical decision-making and promoting the relevant research. However, some limitations should be considered when interpreting our findings. First, all included studies had a retrospective design, therefore, selection bias of patients might exist. Second, heterogeneity was obvious in some analysis (e.g., lymph node metastasis and clinical stage), as a result, random-effect model had to be used, which might reduce the accuracy of results. Third, the detection method and cut-off value of MMP14 expression differed a lot among studies, which might limit the application of our conclusion. Forth, although our results showed MMP14 expression was associated with the prognosis of GC patients, however, confounding factors (e.g., surgery type and chemotherapy regimens) was not considered because individual's information was unavailable for us. Sixth, the publication with positive results was easier to be published, which also induced a bias and might affect our results. To eliminate these limitations, prospective studies with well study design and enough follow-up period should be performed in future work.

## 5. Conclusions

High MMP14 expression was associated with shorter OS, shorter RFS and worse clinicopathological parameters in GC. Therefore, MMP14 expression could serve as a prognostic factor and potential therapeutic target of GC.

## Author contributions

**Conceptualization:** Yanlu Gao.

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