The clinicopathological and prognostic values of TAZ and YAP expression in gastric cancer

SHUAI SHI
Cangzhou People's Hospital
YING XIN HAN
Cangzhou People's Hospital
RUI YU ZHANG
Cangzhou People's Hospital
GANG ZHI ZHANG (zhzhg001518@126.com)

Research

Keywords: TAZ, YAP, gastric cancer, bioinformatics analysis, clinicopathological features

Posted Date: March 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17406/v1

Abstract

Background: The transcriptional co-activator with PDZ-binding motif(TAZ) and Yes-associated protein(YAP) are well-known members of the Hippo signaling pathway, which may correlated with organ development regulation and interaction between organ and tumor. At the same time, it is closely related to the occurrence and development of tumors.

Methods: The purpose of this study is to explore a potential marker that is specific for gastric cancer. In our study, we designed a bioinformatics analysis of the clinicopathological features of TAZ and YAP mRNA expression in gastric cancer using Kaplan-Meier plotter, Oncomine and TCGA databases.

Results: According to Kaplan-Meier plotter, the mRNA expression of TAZ and YAP are negatively related with the overall post-progression and first progression survival rates of gastric cancer patients(p 0.05), even stratified by clinicopathological features(p 0.05). As shown in Oncomine, TAZ and YAP mRNA expression is higher in gastric cancers than gastric tissue and gastric mucosa(p 0.05). In TCGA data, univariate analysis showed that age, TNM staging, lymph node metastasis, distant metastasis was correlated with prognosis in patients with gastric cancer(p 0.05). COX multivariate analysis showed that age and distant metastasis are risk factors affecting the survival of patients with gastric cancer(p 0.05).

Conclusion: TAZ/YAP may be employed as a good molecular market for patients and might help researchers discover a targeted inhibitor for treating gastric cancer.

Background

Gastric cancer is a highly malignant gastrointestinal tumor in China. It may not have been discovered and treated systematically until the advanced stage due to lack of specific clinical symptoms in the early stages of tumor. With the advancement of surgical treatment, radiation therapy and chemotherapy, the survival rate of gastric cancer patients has increased significantly. But recurrence and metastasis are still the main causes of poor prognosis and death in patients with gastric cancer[1–2]. TAZ(known as WWTR1) and YAP were are key effector molecules downstream of the Hippo signaling pathway. They play an important role in organ growth, tissue regeneration, apoptosis and proliferation[3]. When the Hippo signal pathway is activated, MST1/2 kinase binds to the Sav protein, and then LATS1/2 kinase is activated. The activated LATS1/2 kinase phosphorylates YAP and TAZ, thereby initializing the regulation of TAZ/YAP[4]. The TAZ gene is situated on chromosomes 3q23-q24 and has a molecular weight of 43KD, including a TEAD binding domain, a WW domain, and a C-terminal PDZ binding motif. The YAP gene is situated on the 11q13 region of the chromosome and encodes a YAP protein with a molecular weight of about 65KD, which is one more WW domain, SH3 binding motif, and N-terminal proline domain hindering J than TAZ[5]. TAZ and YAP are paralogs and are very similar in topology. Their functions are similar and highly dependent on TEAD family transcription factors in transcriptional activity[6–7]. Although TAZ and YAP are similar in structure, they have some differences in function. It was found in the

knockout mouse model that YAP/TAZ also has some independent costimulators. After knocking out the YAP gene, it will cause the stagnation of embryonic development, and when knocking out the TAZ gene, mice will develop defects in the kidneys and lungs[8]. These results suggest that they may regulate different physiological processes.

TAZ and YAP proteins are overexpressed in various tumors, such as breast cancer, lung cancer, oral squamous cell carcinoma, and bladder cancer[9–12]. Chen et al. found that TAZ and YAP proteins are highly expressed in non-small cell lung cancer and are significantly related to the clinical stage[13]. TAZ and YAP proteins are highly expressed in oral squamous cell carcinoma and are closely related to clinical and pathological features such as tumor differentiation and tumor volume[11]. Hao et al. Found the expression of TAZ and YAP were significantly increased in gliomas[14]. In ovarian and colorectal cancer, TAZ mRNA expression levels are significantly elevated, indicating a poor prognosis for patients[15–16]. The experimental results of Ge et al.[17] showed that TAZ is highly expressed in gastric cancer cells, and knocking out TAZ can reverse cisplatin-resistant gastric cancer cells that have undergone epithelial-mesenchymal transition. The mRNA expression of YAP was upregulated in gastric cancer tissues, and it was positively associated with TNM staging, differentiation, age, depth of invasion and lymph node metastasis[18]. In our study, we performed a bioinformatics analysis to clarify the clinical-pathological and prognostic significances of TAZ and YAP mRNA expression in gastric cancer.

Materials And Methods

Kaplan-Meier plotter analysis (https://kmplot.com/analysis/)

The Kaplan-Meier plotter database is a gene expression database, which integrates gene expression and clinical data simultaneously. The Kaplan-Meier plots were used to analyze the prognostic significance of specific gene, The patients cohorts was divided into high and low expression group by survival analysis plot, and the hazard ratio with 95% confidence intervals and logrank P value are calculated. The database contains more than 50000 genes, which includes four largest datasets(mRNA gene chip), respectively breast (n = 6,234), ovarian (n = 2,190), lung (n = 3,452), and gastric (n = 1,440) cancer. The system also includes mRNA RNA-seq, which contains liver cancer and pan-cancer(21 tumor types). The sources of the databases was downloaded from GEO, EGA, and TCGA. The prognostic roles of TAZ and YAP mRNA were analyzed in gastric cancer. KM plotter analyze the clinical impact of independent genes in different cancers, including Overall survival (OS) and Post-progression survival(PPS), First progression(FP). A collection of clinicopathological features, including Gender, TNM staging, Perforation, Treament, Differentiation, Lauren’s classification, HER2 positivity.

Oncomine database analysis(www.oncomine.org)

TAZ and YAP mRNA expression were analyzed using Oncomine, which was a large tumor gene chip database, covering 65 gene chip data sets, 4,700 gene chips and 480 million gene expression data. The Oncomine database can be used to compare the differential expression analysis of major cancer tumor types and their respective normal tissues. It can also be used to explore various tumor subtypes and

clinical and pathological-based analysis. The database can query one or more genes to visualize the results. There are two main analysis methods, including Fold change and P value. In our study, we compared the differents in TAZ and YAP mRNA between cancer and normal tissues.

TCGA database analysis(www.cancer.gov)

The Cancer Genome Atlas (TCGA), which was a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. We downloaded gastric cancer(n = 407) sample data set from TCGA using TCGA-assembler in Rsoftware. At the same time, the median method was used to standardize the data. We organized the data, analyzed the mRNA expression of TAZ and YAP in gastric cancer, and compared it with prognostic and clinicopathological database of the gastric cancer patients. Cox's proportional hazards model was employed for univariate analysis and multivariate. Two-sided $p < 0.05$ was considered as statistically significant difference. SPSS 13.0 software was employed to analyze all data.

Result

The prognostic values of TAZ mRNA expression in gastric cancer

According to Kaplan-Meier plotter, up-regulated TAZ mRNA expression was negative associated with Overall, Post-progression and First progression survival rates of gastric cancer patients(Fig. 1A, $p < 0.05$). As shown in Table I, high mRNA expression of TAZ was relationship with worse OS of gastric cancer patients, even stratified by tumor(topography) status, metastasisin status, treatment, and her2 positivity. It has the same result in male patients of stage II, stage III, stage IV, N1-3, N1, N2, N3, perforation none, poor-differentiated, diffuse type($p < 0.05$). The Post-progression survival rate of the gastric cancer patients were associated with worse prognosis in patients, even stratified by gender, lymph node status, metastasisin status, lauren's classification, her2 positivity. It had the same result in patients with stage II, stage III, stage IV, T2, T3, surgery alone, other adjuvant. The First progression survival rate of the gastric cancer patients were associated with worse prognosis, even stratified into gender, treatment. It also had the same result in patients of stage II, stage III, T2, T3, M0, none-perforation, intestinal or diffuse-type, and her2 negative. According to DErrico's datasets, we found that the expression of TAZ mRNA was higher in gastric adenocarcinoma(including mixed and diffuse-type) than gastric mucosa(Fig. 1B, $p < 0.05$). Cho's datasets shown that TAZ mRNA expression was higher in gastric cancers than gastric tissue, even stratified into intestinal and mixed-type adenocarcinoma(Fig. 1B, $p < 0.05$). Wang's, Chen's and Cui's datasets also shown the same results(Fig. 1B, $p < 0.05$). Univariate analysis showed that age, TNM staging, lymph node metastasis, distant metastasis was correlated with prognosis in patients with gastric cancer(Table III, p□0.05). COX multivariate analysis showed that age and distant metastasis are risk factors affecting the survival of patients with gastric cancer(Table IV, p□0.05).

The prognostic values of YAP mRNA expression in gastric cancer

In Kaplan-Meier plotter, higher YAP mRNA expression was negative associated with Overall, Post-progression and First progression survival rates of gastric cancer patients(Fig. 2A, $p < 0.05$). As shown in the study, high mRNA expression of YAP was negatively related with male patients with OS, T2, T3, N1-3, N2, M0, surgery alone, diffuse-type, or Her2 negative(Table II, $p < 0.05$). We found that a higher YAP mRNA expression was negatively associated with Post-progression survival rates of gastric cancer patients, even stratified by gender and Her2 positivity. It was also the same result for the gastric cancer patients with stage II-IV, T2, T3, M0, surgery alone, or intestinal-type. The First progression survival rate of the gastric cancer patients were associated with worse prognosis in male, stage III-IV, T2, N1-3, N3, M0, urgery alone, intestinal-type, or Her2 negative(Table II, $p < 0.05$). According to Cho's, we found that the expression of YAP mRNA was higher in gastric adenocarcinoma than gastric tissue, even stratified into intestinal, diffuse and mixed-type adenocarcinoma(Fig. 2B, $p < 0.05$). Chen's datasets also shown that YAP mRNA expression was higher in gastric adenocarcinoma than gastric mucosa, even stratified into intestinal, diffuse and mixed-type adenocarcinoma(Fig. 2B, $p < 0.05$). Wang's and Cui's datasets shown that YAP mRNA expression was higher in gastric cancer than gastric mucosa and gastric tissue(Fig. B, $p < 0.05$). Derrico's datasets also shown that YAP mRNA expression was higher in gastric ntestinal type adenocarcinoma than gastric mucosa(Fig. 2B, $p < 0.05$). univariate analysis showed that age, TNM staging, lymph node metastasis, distant metastasis was correlated with prognosis in patients with gastric cancer(Table III, p□0.05). COX multivariate analysis showed that age, sex and distant metastasis are risk factors affecting the survival of patients with gastric cancer(Table IV, p□0.05).

Discussion

As a transcriptional co-activator, TAZ is highly expressed in a variety of tumors and has various carcinogenic effects. TAZ plays an important role in tumor differentiation, metastasis, growth, and maintenance of stem cell characteristics through signaling pathways such as Hippo, Wnt, and GPCR in tumors[19]. TAZ also plays an important role in regulating angiogenesis. The high expression of TAZ in gastric cancer cells may enhance the angiogenesis ability of gastric cancer by promoting the expression of β-catenin and VEGF[20, 21]. TAZ is highly expressed in breast cancer, and upregulation of TAZ promotes epithelial-mesenchymal transition (EMT), invasion, migration, and proliferation of breast cancer cells[22]. High expression of TAZ was found in non-small cell lung cancer, which is closely related to poor differentiation, poor prognosis, and short survival of the patients[23, 24]. The expression of TAZ was also correlated with tumor grade, TNM stage, distant metastasis and recurrence in gastric cancer tissue[21]. According to our study, the expression of TAZ was overall negatively associated with post-progression and first progression survival. Furthermore, we also found up-regulated TAZ mRNA expression is closely related to clinical and pathological characteristics such as TNM staging, differentiation, lauren's classification.

As an oncogene, YAP interacts with TEAD to activate YAP target genes, and can promote the proliferation and migration of multiple tumor cells by activating target genes[25]. In tumor cells, the expression of YAP is increased and its activity is enhanced. Studies have found that YAP regulates cell proliferation and apoptosis, controls organ growth and tumor formation in Drosophila[26]. Similarly in Drosophila, the

homologous protein Yki of YAP induces the expression of some cell growth-related genes such as cyclin E and Diap1 by binding to the homologous protein of TEAD, thereby promoting cell proliferation and inhibition cell apoptosis[27]. Overexpression of YAP in human breast epithelial cell line MCF10 can induce epithelial-mesenchymal transition (EMT), inhibit apoptosis and promote cell proliferation. These results suggest that YAP promotes malignant transformation of tumor[28]. In liver cancer tissues, the expression level of YAP is upregulated, and it is closely related to the expression of AFP in serum and tumor differentiation. YAP is an independent prognostic indicator of overall and disease-free survival in patients with liver cancer[29]. Our study shown that higher YAP mRNA expression is negatively associated with overall, post-progression and first progression survival rates of gastric cancer patients. These results indicate that YAP may be considered as a gene therapy target for gastric cancer patients.

Hippo signaling pathway plays a key important in tumorigenesis, and it can not only regulate the growth of cancer cells, but also is closely related to the resistance of cancer cells to chemotherapy drugs[30, 31]. Although TAZ/YAP is the main factor of the Hippo signaling pathway, it may also be closely related to other tumor-related signaling pathways such as Notch, Wnt/β, JAK/STAT signaling pathway[32]. TAZ/ YAP is the junction of multiple signal pathways, which means it may provide some potential treatment options. According to KM-plotter, result showed that a higher TAZ /YAP mRNA expression was negatively correlated with the patients receiving treatment including surgery alone, 5-FU-based-adjuvant, and other adjuvant. TAZ/ YAP is closely associated with the occurrence of multiple malignancies. Silencing the expression of TAZ/YAP will provide new treatments for human malignant tumors. We can select some potential therapeutic targets based on the relationship between TAZ/ YAP and several signaling pathways.

Conclusion

we analyzed the expression of TAZ/YAP mRNA in gastric cancer patients by KM-plotter and oncomine databases. Our results shown that higher TAZ/ YAP mRNA expression was associated with worse prognosis. Our study provides a novel insights into the prognostic of gastric cancer patients. TAZ/YAP may be employed as a good molecular market for patients and might help researchers discover a targeted inhibitor for treating gastric cancer.

Declarations

Acknowledgements

No applicable.

Authors contributions

SS and ZGZ designed the study. SS wroted the main manuscript. XXH and YRZ participated in the research of the study and performed the statistical analysis. All authors read and approved the final manuscript.

Funding

No funding was received.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Oncomine database (www. oncomine. org), Kaplan-Meier plotter (kmplot.com) and TCGA database(www.cancer.gov).

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

Department of Pathology, Cangzhou People's Hospital, 7 Qingchi Avenue, Cangzhou City, Cangzhou 061000, China.

References

1. Okuyama A, Saika K. The estimates of 5-year stomach cancer prevalence in adult population in 2012. Japanese Journal of Clinical Oncology. 2017; 47:777-778.
2. Vogelaar IP, Post RSVD, Krieken JHJV. Unraveling genetic predisposition to familial or early onset gastric cancer using germline whole-exome sequencing. European Journal of Human Genetics. 2017; 25.
3. Sinicrope FA, Sargent DJ: Molecular Pathways. Microsatellite Instability in Colorectal Cancer: Prognostic, Predictive, and Therapeutic Implications. Clinical Cancer Research. 2012; 18:1506-1512.
4. Hansen CG, Ng YLD, Lam WLM. The Hippo pathway effectors YAP and TAZ promote cell growth by modulating amino acid signaling to mTORC1. Cell Research. 2015; 25:1299.
5. Hong W, Guan KL. The YAP and TAZ transcription co-activators: Key downstream effectors of the mammalian Hippo pathway. Seminars in Cell & Developmental Biology. 2012; 23:785-793.
6. Zhang K, Qi HX, Hu ZM. YAP and TAZ take center stage in cancer. Biochemistry. 2015; 151014083847001.
7. Piccolo S, Dupont S, Cordenonsi M. The Biology of YAP/TAZ: Hippo Signaling and Beyond. Physiological Reviews. 2014; 94:1287-1312.

8. Piccolo S, Cordenonsi M, Dupont S. Molecular Pathways: YAP and TAZ Take Center Stage in Organ Growth and Tumorigenesis. Clinical Cancer Research An Official Journal of the American Association for Cancer Research. 2013; 19:4925-4930.
9. Rashidian J, Scolan EL, Ji X. Ski regulates Hippo and TAZ signaling to suppress breast cancer progression. Science Signaling. 2015; 8:ra1.
10. Xiao H, Jiang N, Zhou B. TAZ regulates cell proliferation and epithelial-mesenchymal transition of human hepatocellular carcinoma. Cancer Science. 2015; 106:151-159.
11. Li Z Wang Y, Zhu Y. The Hippo transducer TAZ promotes epithelial to mesenchymal transition and cancer stem cell maintenance in oral cancer. Molecular Oncology. 2015; 9:1091-1105.
12. Liang D, Fan L, Wanjun W. Transcriptional cofactor Mask2 is required for YAP-induced cell growth and migration in bladder cancer cell. Journal of Cancer. 2016; 7:2132-2138.
13. Chen P, Zhao JL, Lu RZ. Changes and significance of TAZ and YAP protein expression in non-small cell lung cancer tissues. Shandong Medical Journal. 2018; 58: 61-63.
14. Zhang H, Geng D, Gao J. Expression and significance of Hippo/YAP signaling in glioma progression. Tumor Biology. 2016; 37:1-12.
15. Liu CY, Yu T, Huang Y. ETS (E26 transformation-specific) up-regulation of the transcriptional co-activator TAZ promotes cell migration and metastasis in prostate cancer. Journal of Biological Chemistry. 2017; 292:9420.
16. Yue HF, Mccrudden CM, Han YH. TAZ Expression as a Prognostic Indicator in Colorectal Cancer. PLoS ONE. 2013; 8:e54211-.
17. Liang G, Dong-Song L, Fei C. TAZ overexpression is associated with epithelial-mesenchymal transition in cisplatin-resistant gastric cancer cells. International Journal of Oncology. 2017; 51:307-315.
18. Han X, Liu H, Cai C. Expression of VGLL4 and YAP protein in gastric carcinoma tissues and its relationship with prognosis of gastric carcinoma. Minerva Medica. 2018; 109(6):429-435.
19. Hwang JH, Kim AR, Kim KM. TAZ couples Hippo/Wnt signalling and insulin sensitivity through Irs1 expression. Nat Commun. 2019; 10:421.
20. Wang X, Freire Valls A, Schermann, Géza. YAP/TAZ Orchestrate VEGF Signaling during Developmental Angiogenesis. Developmental Cell. 2017; S1534580717306305.
21. Bai JR, Zhao XL, Sun R, *et al*. TAZ promoting angiogenesis and its mechanism in gastric cancer. Chinese Journal of Clinical Oncology. 2019; 46:272-277.
22. Chan SW, Lim CJ, Guo K. A Role for TAZ in Migration, Invasion, and Tumorigenesis of Breast Cancer Cells. Cancer Research. 2008; 68:2592-2598.
23. Wang Y, Han Y, Guo Z. Nuclear TAZ activity distinctly associates with subtypes of non-small cell lung cancer. Biochem Biophys Res Commun. 2019; 509:828-832.
24. Xie M, Zhang L, He CS, *et al*. Prognostic Significance of TAZ Expression in Resected Non-Small Cell Lung Cancer. Journal of thoracic oncology. 2012; 7:799-807.

25. Deng X, Fang L. VGLL4 is a transcriptional cofactor acting as a novel tumor suppressor via interacting with TEADs. American Journal of Cancer Research. 2018;8:932-943.
26. Udan RS, Kango-Singh M, Nolo R. Hippo promotes proliferation arrest and apoptosis in the Salvador/Warts pathway. Nature Cell Biology. 2003; 5:914-920.
27. Wu S, Liu Y, Zheng Y. The TEAD/TEF Family Protein Scalloped Mediates?Transcriptional Output of the Hippo Growth-Regulatory Pathway. Developmental Cell. 2008; 14:388-398.
28. Overholtzer M, Zhang J, Smolen GA: Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proceedings of the National Academy of Sciences 103:12405-12410, 2006.
29. Xu MZ, Yao TJ, Lee NPY. Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. Cancer. 2009; 115:4576-4585.
30. Mao B, Hu F and Cheng J. SIRT1 regulates YAP2-mediated cell proliferation and chemoresistance in hepatocellular carcinoma. Oncogene. 2014; 33:1468-1474.
31. Wang DY, Wu YN, Huang JQ. Hippo/YAP signaling pathway is involved in osteosarcoma chemoresistance. Chinese Journal of Cancer. 2016; 35:47.
32. Kim W, Khan SK, Gvozdenovic-Jeremic J. Hippo signaling interactions with Wnt/β-catenin and Notch signaling repress liver tumorigenesis. The Journal of clinical investigation. 2016; 127:137-152.

Tables

Table I. The prognostic significance of TAZ mRNA in gastric cancer

Clinicopathological features	Overall survival		Post-Progression survival		First-Progression survival	
	Hazard ratio	p	Hazard ratio	p	Hazard ratio	p
Sex						
Female	1.41(0.99-2.00)	0.055	2.16(1.26-3.68)	0.0039	1.76(1.21-2.56)	0.0029
Male	1.26(1.02-1.57)	0.033	1.41(1.09-1.83)	0.0089	1.35(1.06-1.71)	0.013
TNM staging						
1	0.48(0.17-1.33)	0.15	0.49(0.112.19)	0.34	0.52(0.17-1.60)	0.24
2	2.21(1.13-4.30)	0.017	2.78(1.30-5.97)	0.0061	2.21(1.14-4.32)	0.017
3	1.51(1.14-2.02)	0.0044	2.38(1.51-3.76)	0.00012	2.41(1.61-3.62)	1.1e-05
4	1.93(1.28-2.90)	0.0014	2.65(1.43-4.94)	0.0015	1.41(0.94-2.12)	0.096
T						
2	1.78(1.16-2.73)	0.0071	1.80(1.15-2.83)	0.0091	2.01(1.33-3.05)	8.0e-04
3	1.79(1.25-2.56)	0.0013	1.90(1.29-2.79)	0.00094	1.72(1.19-2.48)	0.0037
4	2.57(1.08-6.11)	0.028	2.14(0.75-6.08)	0.14	2.06(0.94-4.49)	0.065
N						
0	2.56(0.87-7.54)	0.077	4.33(1.17-16.00)	0.017	2.30(0.93-5.65)	0.063
1-3	2.23(1.70-2.93)	2.9e-09	2.18(1.62-2.93)	1.4e-07	2.12(1.64-2.73)	3.4e-09
1	2.50(1.52-4.11)	0.00019	3.04(1.67-5.55)	0.00014	2.38(1.61-3.52)	7.7e-06
2	2.18(1.38-3.43)	0.00061	2.22(1.37-3.59)	0.00082	2.16(1.40-3.35)	4.0e-04
3	2.03(1.19-3.47)	0.0085	2.01(1.11-3.64)	0.019	1.72(0.98-3.01)	0.058
M						

0	1.95(1.46-2.59)	3.1e-06	2.10(1.55-2.85)	1.0e-06	1.96(1.50-2.55)	4.2e-07
1	2.16(1.19-3.92)	0.0095	3.38(1.48-7.73)	0.0023	1.44(0.79-2.63)	0.23
Perforation						
-	1.66(1.11-2.47)	0.013	1.53(0.89-2.61)	0.12	1.88(1.16-3.07)	0.0099
Treatment						
Surgery alone	1.76(1.30-2.40)	0.00024	1.79(1.31-2.45)	0.00021	1.70(1.27-2.28)	3.0e-04
5-FU-based adjuvant	0.51(0.34-0.77)	0.001	0.85(0.56-1.27)	0.42	0.53(0.35-0.78)	0.0013
Other adjuvant	3.86(1.59-9.33)	0.0013	3.54(1.42-8.33)	0.0039	4.44(2.01-9.81)	5.4e-05
Differentiation						
Well-differentiated	2.05(0.79-5.31)	0.31	-	-	-	-
Moderately-differentiated	1.45(0.76-2.79)	0.26	0.56(0.18-1.70)	0.30	1.56(0.83-2.93)	0.16
Poorly-differentiated	1.54(0.97-2.45)	0.064	1.46(0.76-2.81)	0.25	1.47(0.91-2.39)	0.12
Lauren's classification						
Intestinal-type	1.58(1.14-2.19)	0.0051	2.09(1.33-3.29)	0.0012	1.84(1.29-2.62)	0.00058
Diffuse-type	2.25(1.55-3.28)	1.3e-05	2.73(1.80-4.16)	1.0e-06	2.56(1.72-3.80)	1.5e-06
Mixed-type	2.61(0.93-7.36)	0.06	-	-	1.96(0.71-5.47)	0.19
Her2 positivity						
-	1.50(1.20-1.88)	0.00039	1.62(1.22-2.16)	0.00072	1.60(1.23-2.08)	0.00035
+	1.48(1.14-1.93)	0.0029	1.78(1.25-2.55)	0.0013	1.23(0.87-1.74)	0.25

Table II. The prognostic significance of YAP mRNA in gastric cancer

Clinicopathological features	Overall survival		Post-progression survival		First-progression survival	
	Hazard ratio	p	Hazard ratio	p	Hazard ratio	p
Sex						
Female	1.30 (0.89 − 1.89)	0.17	2.00 (1.24 − 3.22)	0.0037	1.31 (0.87 − 1.98)	0.20
Male	1.36 (1.09 − 1.69)	0.0056	1.45 (1.12 − 1.87)	0.0047	1.46 (1.15 − 1.86)	0.0018
TNM staging						
1	2.09 (0.48 − 9.23)	0.32	2.48 (0.55 − 11.12)	0.22	3.63 (0.47 − 27.91)	0.19
2	1.73 (0.95 − 3.13)	0.068	2.13 (1.09 − 4.18)	0.023	1.54 (0.83 − 2.87)	0.17
3	1.26 (0.93 − 1.71)	0.13	2.04 (1.19 − 3.52)	0.0086	1.54 (1.01 − 2.35)	0.044
4	0.66 (0.41 − 1.06)	0.084	1.77 (1.10 − 2.84)	0.017	0.61 (0.38 − 0.96)	0.032
T						
2	1.78 (1.13 − 2.80)	0.011	2.11 (1.34 − 3.32)	0.00094	1.75 (1.13 − 2.72)	0.011
3	1.69 (1.11 − 2.57)	0.013	1.67 (1.14 − 2.45)	0.0081	1.47 (0.98 − 2.19)	0.059
4	1.03 (0.92 − 1.15)	0.58	1.17 (0.75 − 1.82)	0.48	0.74 (0.34 − 1.59)	0.44
N						
0	2.37 (0.93 − 6.03)	0.063	2.97 (0.80 − 11.01)	0.088	2.44 (0.96 − 6.23)	0.053
1-3	1.56 (1.12 − 2.17)	0.0077	1.65 (1.16 − 2.35)	0.0049	1.36 (1.01 − 1.83)	0.039
1	1.34 (0.89 − 2.03)	0.16	1.61 (1.01 − 2.58)	0.045	1.29 (0.87 − 1.91)	0.20
2	1.92 (1.07 − 3.45)	0.026	1.92 (1.03 − 3.59)	0.037	1.51 (0.88 − 2.57)	0.13
3	1.73 (0.93 − 3.24)	0.081	1.46 (0.80 − 2.66)	0.21	1.81 (1.04 − 3.15)	0.032
M						

0	1.62 (1.14 − 2.29)	0.006	1.71 (1.25 − 2.33)	0.00064	1.41 (1.07 − 1.85)	0.015
1	0.60 (0.33 − 1.09)	0.088	0.61 (0.28 − 1.32)	0.20	0.49 (0.26 − 0.90)	0.02
Perforation						
-	1.39 (0.87 − 2.21)	0.17	1.47 (0.79 − 2.74)	0.23	1.34 (0.85 − 2.12)	0.21
Treatment						
Surgery alone	1.38 (1.02 − 1.86)	0.035	1.57 (1.14 − 2.17)	0.0058	1.36 (1.02 − 1.82)	0.037
5-FU-based adjuvant	1.33 (0.94 − 1.89)	0.11	0.71 (0.47 − 1.07)	0.10	1.37 (0.94 − 1.99)	0.10
Other adjuvant	3.77 (0.87 − 16.23)	0.056	3.78 (0.87 − 16.44)	0.057	2.28 (0.68 − 7.63)	0.17
Differentiation						
Well-differentiated	2.12 (0.71 − 6.31)	0.17				
Moderately-differentiated	0.74 (0.38 − 1.46)	0.39	0.54 (0.18 − 1.62)	0.27	1.20 (0.63 − 2.30)	0.57
Poorly-differentiated	0.67 (0.42 − 1.07)	0.088	0.61 (0.30 − 1.25)	0.17	1.45 (0.84 − 2.49)	0.17
Lauren's classification						
Intestinal-type	1.38 (1.00 − 1.92)	0.052	2.12 (1.40 − 3.21)	0.00028	1.77 (1.20 − 2.60)	0.0033
Diffuse-type	1.61 (1.05 − 2.45)	0.026	1.57 (0.98 − 2.49)	0.057	1.38 (0.92 − 2.08)	0.12
Mixed-type	0.47 (0.15 − 1.51)	0.20			0.59 (0.21 − 1.68)	0.32
Her2 positivity						
-	1.37 (1.08 − 1.73)	0.0079	1.56 (1.16 − 2.10)	0.0029	1.47 (1.12 − 1.93)	0.0049
+	1.13 (0.87 − 1.46)	0.37	1.55 (1.07 − 2.24)	0.019	1.29 (0.92 − 1.81)	0.14

Table III. Univariate analysis of prognostic risk factors in the patients with gastric cancer

Characteristics	TAZ expression			YAP expression		
	Patients(%)	Relative Risk(95% CI)	*p* Value	Patients(%)	Relative Risk(95% CI)	*p* Value
Sex						
Female	134(35.8)	0.774(0.532-1.126)	0.180	134	0.774(0.532-1.126)	0.180
Male	240(64.2)			240		
Age(years)						
<60	91(26.1)	1.691(1.124-2.544)	0.012	112	0.598(0.397-0.901)	0.014
≥60	258(73.9)			258		
TNM staging						
I-II	160(46.1)	1.701(1.196-2.421)	0.003	160(46.1)	1.636(1.156-2.315)	0.005
III-IV	187(53.9)			187(53.9)		
Depth of invasion						
-	23(6.2)	1.685(0.689-4.125)	0.253	23(6.2)	1.620(0.662-3.963)	0.291
+	347(93.8)			347(93.8)		
Lymph node metastasis						
-	108(30.7)	1.703(1.117-2.596)	0.013	108(30.7)	1.725(1.132-2.629)	0.011
+	244(69.3)			244(69.3)		
Distant metastasis						
-	327(92.9)	1.592(1.023-2.477)	0.039	327(92.9)	1.742(1.126-2.695)	0.013
+	25(7.1)			25(7.1)		
Differentiation						
Well-differentiated	10(2.8)	0.789(0.563-1.105)	0.168	10(2.8)	0.931(0.690-1.257)	0.642
Moderated-differentiated	131(36.4)			131(36.4)		
Poorly-differentiated	219(60.8)			219(60.8)		

CI, confidence interval; TNM, tumor-node-metastasis

Table IV. Multivariate analysis of clinicopathological variables for the survival of the patients with gastric cancer

Clinicopathological Parameters	TAZ expression		YAP expression	
	Relative Risk (95% CI)	***P***	**Relative Risk (95% CI)**	***P***
TAZ/YAP expression (+)	0.776(0.486-1.239)	0.288	1.138(0.776-1.669)	0.507
Age (≥60 years)	2.216(1.405-3.498)	0.001*	2.242(1.417-3.550)	0.001*
Sex (female)	0.669(0.442-1.013)	0.058	0.659(0.435-1.000)	0.050*
Depth of invasion (T2-4)	3.945(0.543-29.165)	0.119	3.761(0.510-27.760)	0.194
Lymph node metastasis (+)	0.952(0.517-1.753)	0.875	0.958(0.517-1.8775)	0.892
Distant metastasis (+)	2.428(1.250-4.714)	0.009*	2.382(1.228-4.622)	0.010*
TNM staging (III–IV)	1.506(0.870-2.609)	0.144	1.544(0.889-2.681)	0.123
Differentiation(poorly)	1.436(0.952-2.165)	0.084	1.500(0.999-2.254)	0.051

CI, confidence interval; TNM, tumor-node-metastasis

Figures

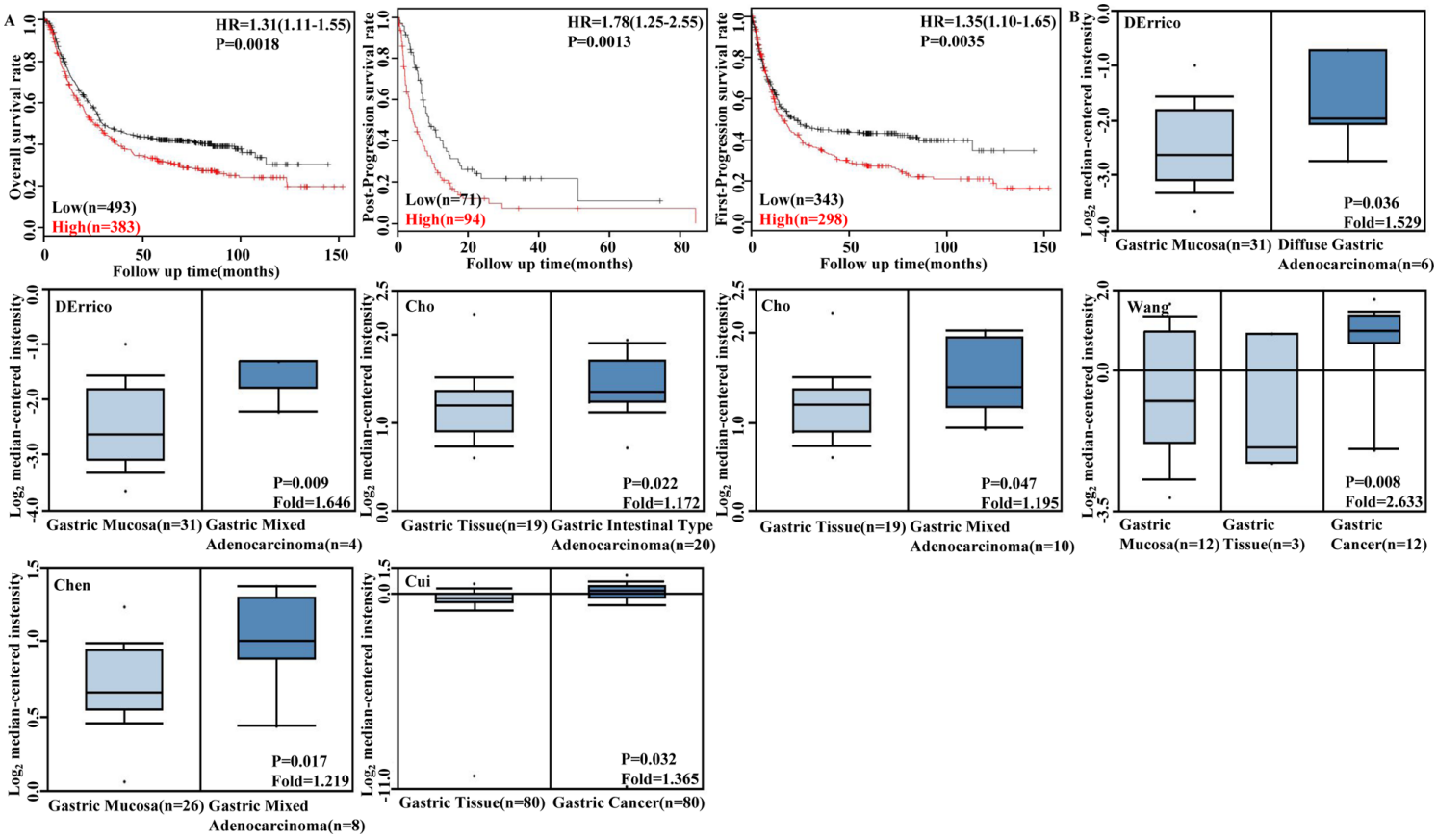

Figure 1

The clinicopathological and prognostic value of TAZ mRNA expression levels in gastric cancer. The relationship between TAZ mRNA expression and Overall, Post-progression or First progression survival rates was analyzed according to Kaplan Meier plotter(A, p□0.05). According to DErrico's datasets, TAZ mRNA expression was higher in gastric adenocarcinoma(including mixed and diffuse-type) than gastric mucosa(B, p□0.05). Cho's data, TAZ mRNA expression was higher in gastric cancer than gastric tissue, even stratified into intestinal and mixed-type adenocarcinoma(B, p□0.05). Wang's, Chen's and Cui's datasets also shown the same results(B, p□0.05). HR, hazard ratio.

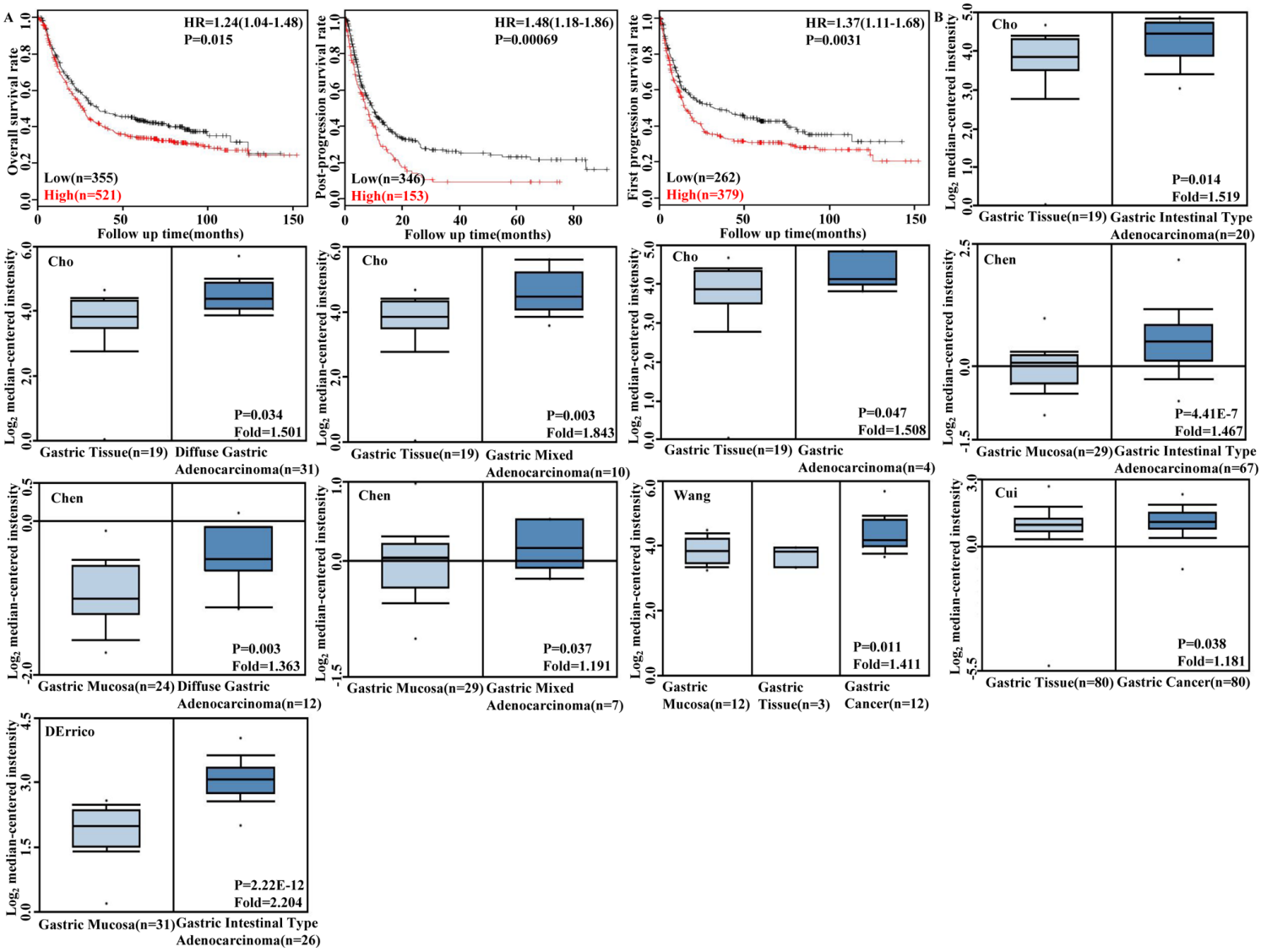

Figure 2

The clinicopathological and prognostic value of YAP mRNA expression levels in gastric cancer. The relationship between YAP mRNA expression and Overall, Post-progression or First progression survival rates was analyzed according to Kaplan Meier plotter(A, p□0.05). According to Cho's, YAP mRNA expression was higher in gastric adenocarcinoma than gastric tissue, even stratified into intestinal, diffuse and mixed-type adenocarcinoma(B, p□0.05). Chen's datasets also shown that YAP mRNA expression was higher in gastric adenocarcinoma than gastric mucosa, even stratified into intestinal, diffuse and mixed-type adenocarcinoma(B, p□0.05). Wang's and Cui's datasets shown that YAP mRNA expression was higher in gastric cancer than gastric mucosa and gastric tissue(B, p□0.05). Derrico's datasets also shown that YAP mRNA expression was higher in gastric ntestinal type adenocarcinoma than gastric mucosa(B, p□0.05). HR, hazard ratio.