The roles of CD82 expression in gastric cancer: a meta and bioinformatics analysis

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ABSTRACT

CD82 **encodes a transmembrane glycoprotein of tetraspanins family, and functions as a tumor metastasis suppressor. We performed a systematic meta and bioinformatics analysis through multiple online databases up to March 14, 2017. We¬ found down-regulated CD82 expression in gastric cancer, compared with normal mucosa (*p* < 0.05). CD82 expression was negatively with depth of invasion, lymph node and distant metastasis, TNM staging and dedifferentiation of gastric cancer (*p* < 0.05). A positive association between CD82 expression and favorable overall survival was found in patients with gastric cancer (*p* < 0.005). According to bioinformatics analysis, *CD82* mRNA expression was higher in gastric cancer than normal tissues (*p* < 0.05). According to Kaplan-Meier plotter and TCGA database, we found that a higher *CD82* expression was positively correlated with overall or progression- free survival rates of all cancer patients, even stratified by aggressive parameters or as an independent factor (*p* < 0.05). These findings indicated that CD82 expression might be employed as a potential marker to indicate gastric carcinogenesis and subsequent progression, even favorable prognosis.**

INTRODUCTION

KAI1 (CD82/C33/R2/IA4) is initially identified as a tumor metastasis suppressor gene on human chromosome 11p11.2, and encodes a transmembrane glycoprotein of tetraspanins family (TM4SF). CD82 protein interacts with integrin α4β1 and other TM4SF proteins (CD4, CD8, CD19, CD21 and MHC class I and II) on cell surface to establish "the tetraspanin web" [1]. It directly binds to N-terminal region of TIMP-1 through its large extracellular loop, and facilitates membrane-bound TIMP-1 endocytosis [2]. CD82 inhibits fibronectin adhesion- induced epithelial-to-mesenchymal transition in prostate cancer cells by repressing the associated integrin signaling [3], and CD44 alternative splicing-dependent melanoma metastasis by mediating U2AF2 ubiquitination and degradation [4]. Abe et al. [5] found that CD82 strengthened E-cadherin-mediated intercellular adhesion, stabilized E-cadherin/ β-catenin complex formation, and reduced tyrosine phosphorylation of β-catenin on HGF stimulation. CD82 specifically suppressed ubiquitylation of EGFR after stimulation with heparin-binding EGF or amphiregulin [6], and attenuated compartmentalisation and ligand- induced dimerization of EGFR [7].

Risinger et al. [8] found no obvious genotype-associated defects and histopathological abnormalities after 12 or 18 months of *CD82*-deficient (-/-) mice. Differentially expressed genes in mouse embryonic fibroblast of male *CD82* (-/-) and wild mice were surprisingly enriched for cell division related processes. Reportedly, CD82 overexpression significantly decreased the migratory and invasive abilities of gastric cancer cells with the hypoexpression of bFGF and uPA [9]. miR-362-3p expression induced the metastasis of gastric cancer cells by targeting CD82 with E-cadherin hypoexpression, N-cadherin, and vimentin hyperexpression [10]. In the present study, we performed a meta- and bioinformatics analysis to clarify the clinicopathological and prognostic significances of CD82 expression at both mRNA and protein levels.

RESULTS

Characteristics of eligible studies

Figure 1 is a flow diagram of paper selection for our meta-analysis. As shown in Table 1, a total of 26 articles on the relationship between CD82 expression and cancer risk, clinicopathological or prognostic parameters of gastric cancer were retrieved for our meta-analysis by immunohistochemistry in PubMed, Web of Science, BIOSIS, SciFinder and CNKI. Only 16 articles contained the samples of normal gastric mucosa [11–26]. There appeared the comparison between CD82 expression and clinicopathological characteristics of gastric cancer in 26 studies, including depth of invasion, lymph node metastasis, distant metastasis, TNM staging and Lauren's classification [9, 11–35]. Finally, the authors discussed the prognostic significance of CD82 expression in 7 articles [9, 16, 18, 20, 26, 27, 34].

Association between CD82 expression and cancer susceptibility of gastric mucosa

We analyzed the association between CD82 expression and cancer susceptibility of gastric normal mucosa in 16 studies with 1478 cancers and 918 controls. As a result, we found down-regulated CD82 expression in gastric cancer, compared with normal mucosa (Figure 2A, $p < 0.00001$).

Association between CD82 expression and clinicopathological parameters of gastric cancer

A higher CD82 expression was detected in T0-1 than T2-4 gastric cancers (Figure 2B, $p < 0.00001$), and in T0-2 than T3-4 ones (Figure 2C, $p < 0.000001$). CD82 expression was negatively related to lymph node metastasis (Figure 2D, $p < 0.00001$) and distant metastasis (Figure 2E, $p < 0.01$) of gastric cancer. Gastric cancers with stage 0-I or 0-II showed CD82 overexpression, compared with ones with stage II-IV or III-IV (Figure 2F and 2G, $p < 0.01$) respectively. CD82 protein was more expressed in intestinal-type than diffuse-type carcinomas (Figure 2H, $p < 0.00001$).

Association between CD82 expression and survival rate of gastric cancer

As indicated in Figure 2I, the pooled result from 8 datasets demonstrated a positive association between

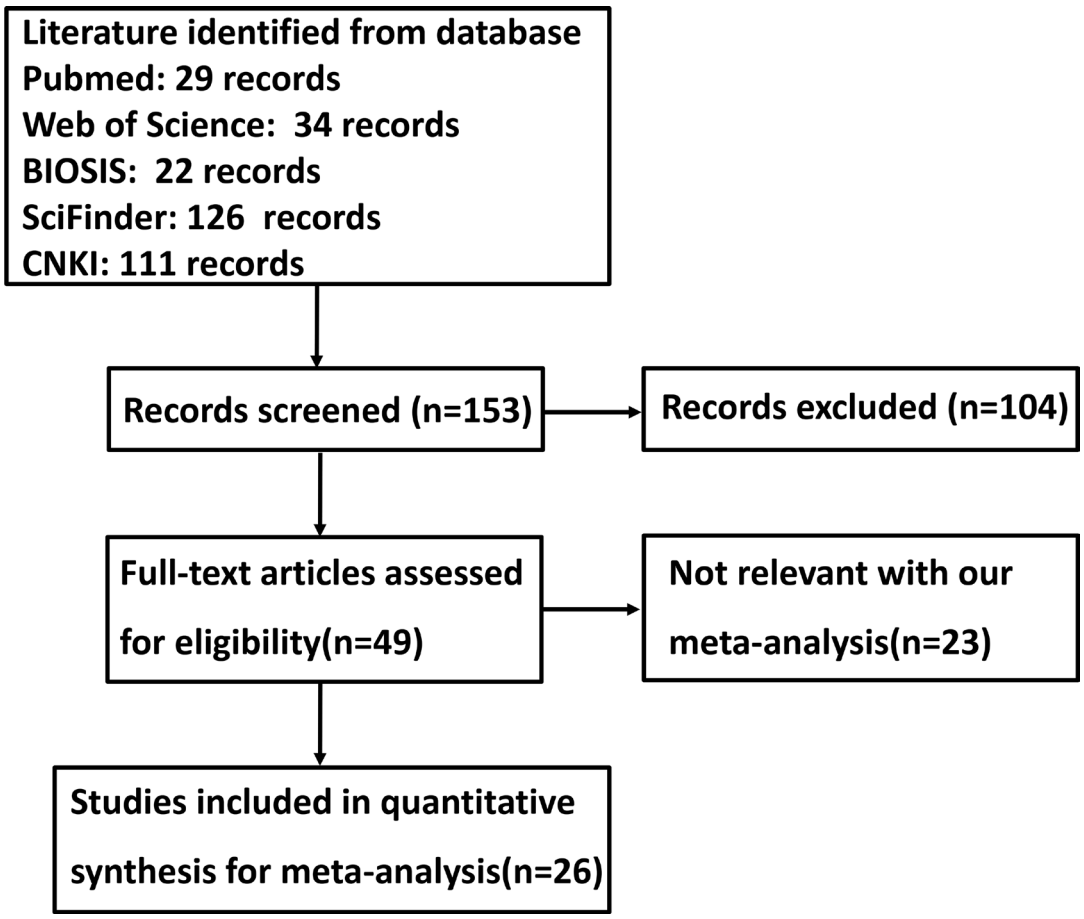


Figure 1: Flow diagram of the selection process in this meta-analysis.

Table 1: Main characteristics of eligible studies

First author	Year	Country	Ethnicity	AS	Cases	Control	Risk to cancer	Outcome	Quality
Hinoda Y	1998	Japan	Asian	Santa Cruz	73				8
Lee HS	2003	Korea	Asian	Santa Cruz	329			Positive	9
Zheng HC	2004	China	Asian	Santa Cruz	113	182	Down		9
Ilhan O	2009	Turkey	Turkish	Santa Cruz	257				8
Knoener M	2012	Germany	European	Santa Cruz	271			Positive	8
Guo J	2015	China	Asian	BD Biosci	128			Positive	8
Lu GY	2016	China	Asian	Abcam	325	325	Down	Positive	9
Wang XX	2005	China	Asian	Santa Cruz	68	20	Down	Positive	9
Cheng HM	2005	China	Asian	Santa Cruz	62			Positive	8
Tan L	2005	China	Asian	Zhongshan	51				8
Liu ML	2006	China	Asian	Pharmingen	74	22	Down		8
Mao SX	2007	China	Asian	Pharmingen	30	30	Down		8
Zhang HJ	2007	China	Asian	Neomarker	71	20	Down		8
Xia YB	2007	China	Asian	Santa Cruz	62	62	Down		8
Yin K	2008	China	Asian	Pharmingen	75	75	Down		8
Wei B	2008	China	Asian	Santa Cruz	54	15	Down		8
Shi YP	2008	China	Asian	Zymed	92	10	Down	Positive	8
Zhang ZL	2009	China	Asian	Pharmingen	50	7	Down		8
Zhang ZJ	2009	China	Asian	Santa Cruz	110	30	Down		8
Xu FY	2010	China	Asian	Santa Cruz	65				8
Ji RY	2012	China	Asian	Boster	63				8
Zhang XN	2013	China	Asian	Santa Cruz	223				8
Zhou L	2014	China	Asian	Maxim	145	50	Down	Positive	8
Qi Q	2014	China	Asian	Santa Cruz	96	20	Down		8
Wang W	2014	China	Asian	Santa Cruz	61	20	Down		8
Kang LX	2015	China	Asian	Changdao	52	30	Down		8

AS, antibody source; Down, down-regulated expression.

CD82expression and favorable overall survival in patients with gastric cancer (HR = 1.76, 95% CI: 1.37–2.25, $p < 0.00001$).

Publication bias

The heterogeneity test was performed as shown in Figure 3. Sensitivity analysis was used to evaluate individual study's influence on the pooled results by deleting one single study each time from pooled analysis. As a result, the correlation between CD82 expression and distant metastasis in Knoener's study had a significant effect on the pooled OR. When this study was excluded, the heterogeneity test was significantly reduced (data not shown).

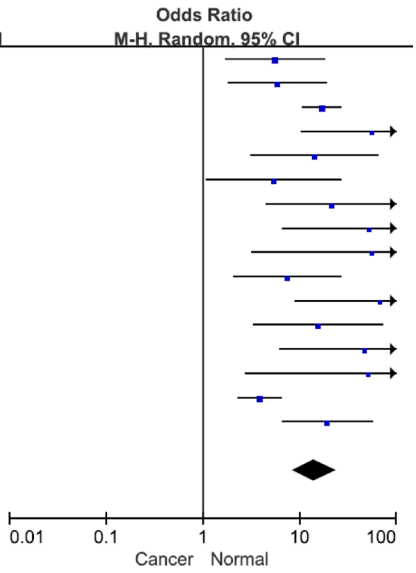
The clinicopathological and prognostic significances of *CD82* mRNA expression in gastric cancer

Then, we used Cho's, Cui's, DErrico's and Wang's datasets to perform bioinformatics analysis and found that *CD82* mRNA expression was lower in gastric cancer than normal tissues, even stratified into intestinal-, diffuse- and mixed-type carcinomas (Figure 4A, $p < 0.05$). According to Kaplan-Meier plotter, we found that a higher *CD82* mRNA expression was positively correlated with overall and progression-free survival rates of all cancer patients (Figure 4B, $p < 0.05$). As shown in Table 2, the overall and progression-free survival rates of the female or male patients, the patients receiving surgery alone, the patients with stage II or III, T2 or T3, N0, N1-3, N1, N3, M0, intestinal-type, diffuse-type, Her2-positive or Her2-negative cancers were higher in the group of high *CD82* mRNA expression than that of its low expression ($p < 0.05$). According to TCGA's database, univariate analysis showed a positive link between *CD82* mRNA expression and the overall better prognosis of the patients with gastric cancer (Figure 4C, $p < 0.05$). Multivariate analysis using Cox's hazard proportional model indicated that *CD82* mRNA expression was an independent prognostic factor for gastric cancer (Table 3, $p < 0.05$).

A

Study or Subgroup	Normal Events	Normal Total	Cancer Events	Cancer Total	Weight	Odds Ratio M-H, Random, 95% CI
Kang LX (2015)	26	30	28	52	7.6%	5.57 [1.70, 18.23]
Liu ML (2006)	18	22	32	74	7.6%	5.91 [1.82, 19.16]
Lu GY (2016)	300	325	134	325	11.5%	17.10 [10.76, 27.20]
Mao SX (2007)	28	30	6	30	5.4%	56.00 [10.33, 303.68]
Qi Q (2014)	18	20	37	96	6.0%	14.35 [3.15, 65.46]
Shi YP (2008)	8	10	39	92	5.7%	5.44 [1.09, 27.02]
Wang W (2014)	18	20	18	61	5.9%	21.50 [4.51, 102.42]
Wang XX (2005)	19	20	18	68	4.1%	52.78 [6.58, 423.22]
Wei B (2008)	15	15	19	54	2.6%	56.44 [3.20, 995.20]
Xia YB (2007)	59	62	45	62	7.1%	7.43 [2.05, 26.92]
Yin K (2008)	74	75	39	75	4.3%	68.31 [9.02, 517.24]
Zhang HJ (2007)	18	20	26	71	6.0%	15.58 [3.34, 72.56]
Zhang ZJ (2009)	29	30	42	110	4.3%	46.95 [6.17, 357.59]
Zhang ZL (2009)	7	7	11	50	2.5%	51.52 [2.73, 971.73]
Zheng HC (2004)	145	182	57	113	11.3%	3.85 [2.30, 6.45]
Zhou L (2014)	46	50	54	145	8.2%	19.38 [6.61, 56.82]
Total (95% CI)		**918**		**1478**	**100.0%**	**14.27 [8.53, 23.89]**
Total events	828		605			

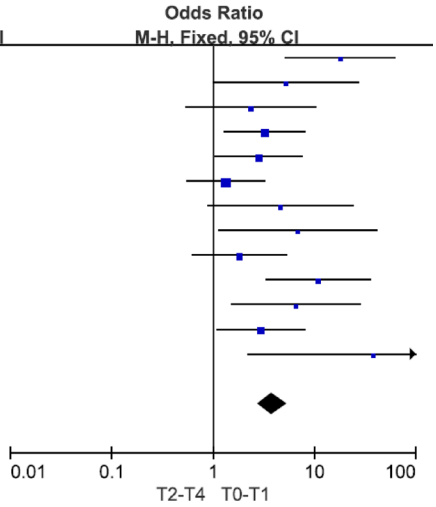
Heterogeneity: Tau² = 0.54; Chi² = 39.06, df = 15 (P = 0.0006); I² = 62%
Test for overall effect: Z = 10.12 (P < 0.00001)



B

Study or Subgroup	T0-T1 Events	T0-T1 Total	T2-T4 Events	T2-T4 Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Guo J (2015)	12	16	16	112	2.6%	18.00 [5.16, 62.78]
Ilhan O (2009)	5	7	81	250	3.2%	5.22 [0.99, 27.46]
Kang LX (2015)	7	10	21	42	6.2%	2.33 [0.53, 10.27]
Knoener M (2012)	28	34	140	237	15.8%	3.23 [1.29, 8.10]
Liu ML (2006)	15	25	17	49	11.7%	2.82 [1.05, 7.62]
Lu GY (2016)	12	21	182	364	21.7%	1.33 [0.55, 3.24]
Shi YP (2008)	6	8	33	84	3.7%	4.64 [0.88, 24.36]
Wang XX (2005)	4	6	14	62	2.1%	6.86 [1.13, 41.43]
Xu FY (2010)	9	20	14	45	12.1%	1.81 [0.61, 5.35]
Zhang ZJ (2009)	17	21	25	89	4.6%	10.88 [3.33, 35.52]
Zhang ZL (2009)	6	12	5	38	3.1%	6.60 [1.52, 28.75]
Zheng HC (2004)	20	26	46	87	12.5%	2.97 [1.09, 8.11]
Zhou L (2014)	9	9	45	136	0.8%	38.21 [2.18, 671.17]
Total (95% CI)		**215**		**1595**	**100.0%**	**3.81 [2.75, 5.30]**
Total events	150		639			

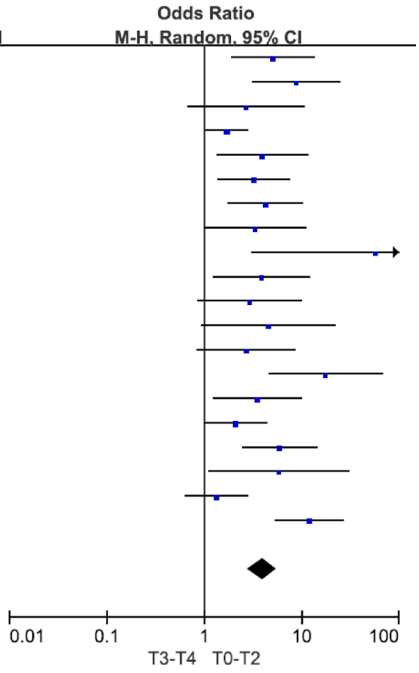
Heterogeneity: Chi² = 20.88, df = 12 (P = 0.05); I² = 43%
Test for overall effect: Z = 8.00 (P < 0.00001)

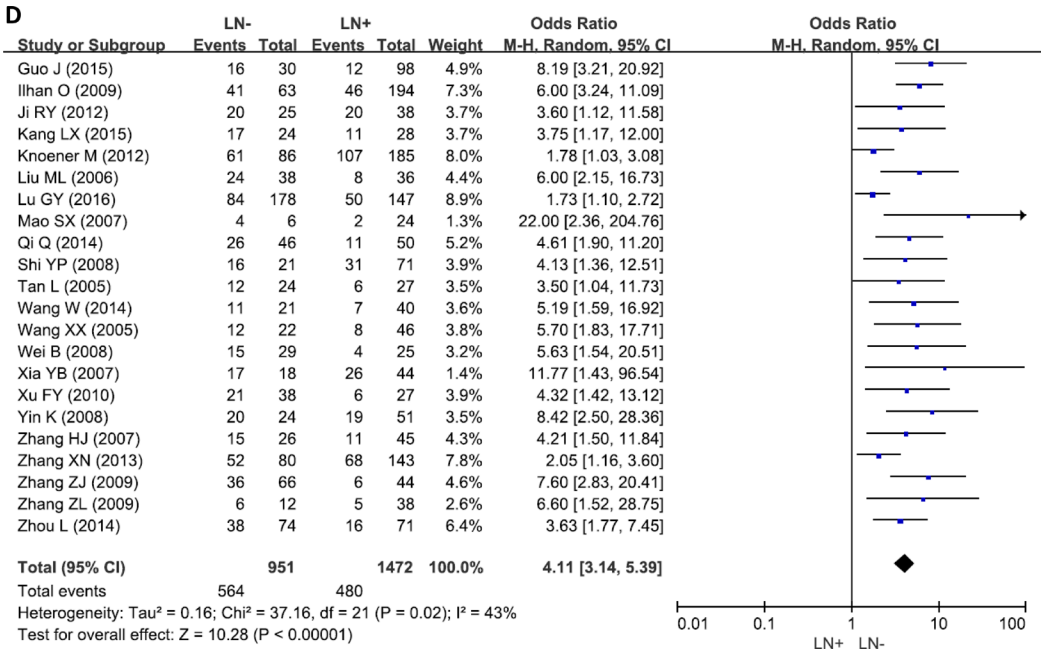


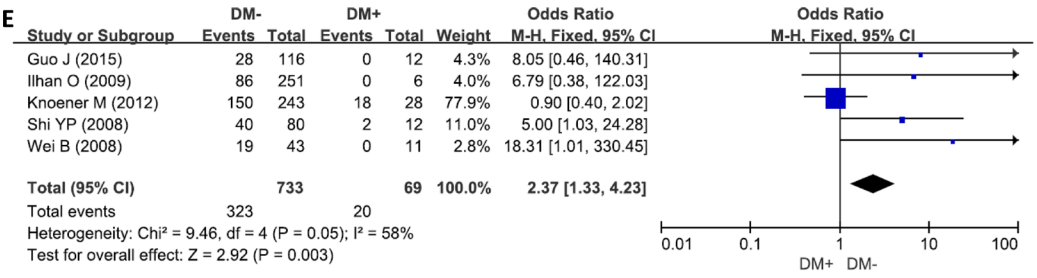
C

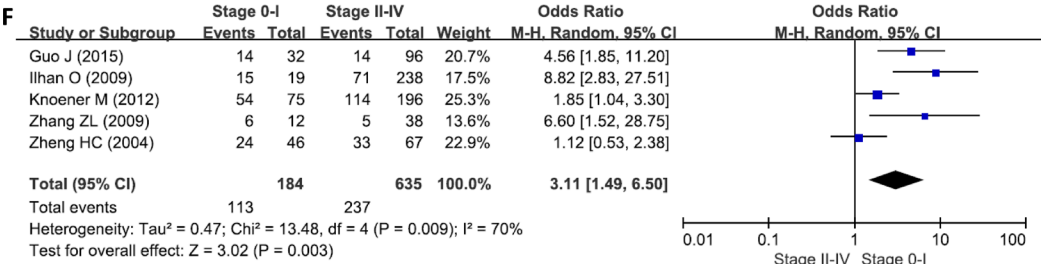
Study or Subgroup	T0-T2 Events	T0-T2 Total	T3-T4 Events	T3-T4 Total	Weight	Odds Ratio M-H, Random, 95% CI
Guo J (2015)	22	64	6	64	5.4%	5.06 [1.89, 13.58]
Ilhan O (2009)	18	23	68	234	5.2%	8.79 [3.14, 24.62]
Ji RY (2012)	6	10	19	53	3.7%	2.68 [0.67, 10.71]
Knoener M (2012)	108	161	60	110	8.4%	1.70 [1.03, 2.80]
Liu ML (2006)	26	48	6	26	5.0%	3.94 [1.35, 11.54]
Qi Q (2014)	23	43	14	53	6.1%	3.20 [1.36, 7.54]
Shi YP (2008)	26	43	13	49	6.0%	4.24 [1.76, 10.22]
Tan L (2005)	10	19	8	32	4.4%	3.33 [1.00, 11.12]
Wang W (2014)	8	8	10	45	1.2%	57.48 [3.06, 1080.81]
Wang XX (2005)	12	29	6	39	4.7%	3.88 [1.24, 12.16]
Wei B (2008)	8	15	11	39	4.3%	2.91 [0.85, 9.96]
Xia YB (2007)	17	19	28	43	3.1%	4.55 [0.93, 22.41]
Xu FY (2010)	18	42	5	23	4.6%	2.70 [0.84, 8.65]
Yin K (2008)	24	27	15	48	3.9%	17.60 [4.58, 67.65]
Zhang HJ (2007)	13	23	13	48	5.1%	3.50 [1.24, 9.92]
Zhang XN (2013)	26	38	94	185	6.8%	2.10 [1.00, 4.41]
Zhang ZJ (2009)	33	59	9	51	6.0%	5.92 [2.45, 14.35]
Zhang ZL (2009)	9	26	2	24	2.9%	5.82 [1.11, 30.56]
Zheng HC (2004)	37	60	29	53	6.8%	1.33 [0.63, 2.82]
Zhou L (2014)	38	53	16	92	6.4%	12.03 [5.38, 26.91]
Total (95% CI)		**810**		**1311**	**100.0%**	**3.95 [2.83, 5.51]**
Total events	482		432			

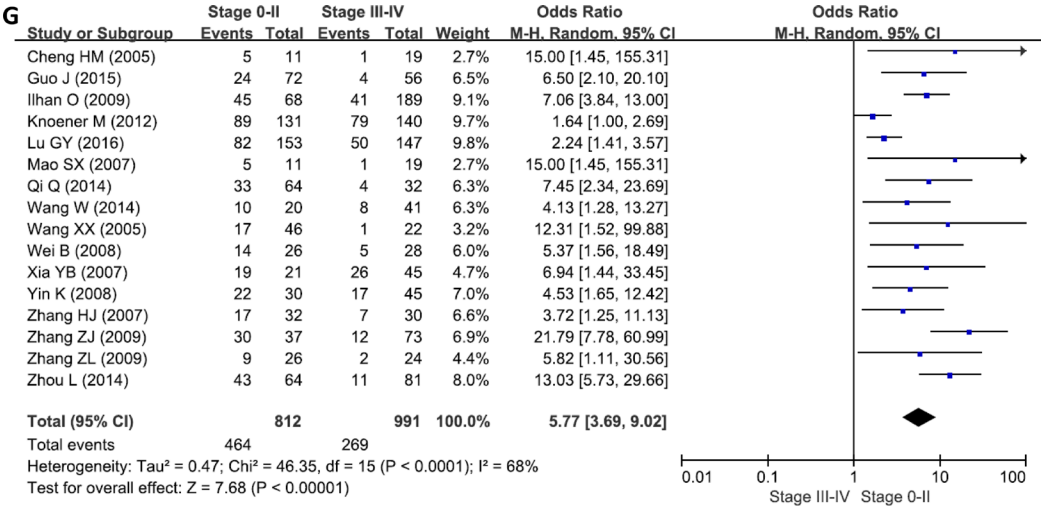
Heterogeneity: Tau² = 0.28; Chi² = 40.58, df = 19 (P = 0.003); I² = 53%
Test for overall effect: Z = 8.06 (P < 0.00001)




D
LN- LN+ Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Guo J (2015) 16 30 12 98 4.9% 8.19 [3.21, 20.92]
Ilhan O (2009) 41 63 46 194 7.3% 6.00 [3.24, 11.09]
Ji RY (2012) 20 25 20 38 3.7% 3.60 [1.12, 11.58]
Kang LX (2015) 17 24 11 28 3.7% 3.75 [1.17, 12.00]
Knoener M (2012) 61 86 107 185 8.0% 1.78 [1.03, 3.08]
Liu ML (2006) 24 38 8 36 4.4% 6.00 [2.15, 16.73]
Lu GY (2016) 84 178 50 147 8.9% 1.73 [1.10, 2.72]
Mao SX (2007) 4 6 2 24 1.3% 22.00 [2.36, 204.76]
Qi Q (2014) 26 46 11 50 5.2% 4.61 [1.90, 11.20]
Shi YP (2008) 16 21 31 71 3.9% 4.13 [1.36, 12.51]
Tan L (2005) 12 24 6 27 3.5% 3.50 [1.04, 11.73]
Wang W (2014) 11 21 7 40 3.6% 5.19 [1.59, 16.92]
Wang XX (2005) 12 22 8 46 3.8% 5.70 [1.83, 17.71]
Wei B (2008) 15 29 4 25 3.2% 5.63 [1.54, 20.51]
Xia YB (2007) 17 18 26 44 1.4% 11.77 [1.43, 96.54]
Xu FY (2010) 21 38 6 27 3.9% 4.32 [1.42, 13.12]
Yin K (2008) 20 24 19 51 3.5% 8.42 [2.50, 28.36]
Zhang HJ (2007) 15 26 11 45 4.3% 4.21 [1.50, 11.84]
Zhang XN (2013) 52 80 68 143 7.8% 2.05 [1.16, 3.60]
Zhang ZJ (2009) 36 66 6 44 4.6% 7.60 [2.83, 20.41]
Zhang ZL (2009) 6 12 5 38 2.6% 6.60 [1.52, 28.75]
Zhou L (2014) 38 74 16 71 6.4% 3.63 [1.77, 7.45]
Total (95% CI) 951 1472 100.0% 4.11 [3.14, 5.39]
Total events 564 480
Heterogeneity: Tau² = 0.16; Chi² = 37.16, df = 21 (P = 0.02); I² = 43%
Test for overall effect: Z = 10.28 (P < 0.00001)
0.01 0.1 1 10 100
LN+ LN-


E
DM- DM+ Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Guo J (2015) 28 116 0 12 4.3% 8.05 [0.46, 140.31]
Ilhan O (2009) 86 251 0 6 4.0% 6.79 [0.38, 122.03]
Knoener M (2012) 150 243 18 28 77.9% 0.90 [0.40, 2.02]
Shi YP (2008) 40 80 2 12 11.0% 5.00 [1.03, 24.28]
Wei B (2008) 19 43 0 11 2.8% 18.31 [1.01, 330.45]
Total (95% CI) 733 69 100.0% 2.37 [1.33, 4.23]
Total events 323 20
Heterogeneity: Chi² = 9.46, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 2.92 (P = 0.003)
0.01 0.1 1 10 100
DM+ DM-


F
Stage 0-I Stage II-IV Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Guo J (2015) 14 32 14 96 20.7% 4.56 [1.85, 11.20]
Ilhan O (2009) 15 19 71 238 17.5% 8.82 [2.83, 27.51]
Knoener M (2012) 54 75 114 196 25.3% 1.85 [1.04, 3.30]
Zhang ZL (2009) 6 12 5 38 13.6% 6.60 [1.52, 28.75]
Zheng HC (2004) 24 46 33 67 22.9% 1.12 [0.53, 2.38]
Total (95% CI) 184 635 100.0% 3.11 [1.49, 6.50]
Total events 113 237
Heterogeneity: Tau² = 0.47; Chi² = 13.48, df = 4 (P = 0.009); I² = 70%
Test for overall effect: Z = 3.02 (P = 0.003)
0.01 0.1 1 10 100
Stage II-IV Stage 0-I


G
Stage 0-II Stage III-IV Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Cheng HM (2005) 5 11 1 19 2.7% 15.00 [1.45, 155.31]
Guo J (2015) 24 72 4 56 6.5% 6.50 [2.10, 20.10]
Ilhan O (2009) 45 68 41 189 9.1% 7.06 [3.84, 13.00]
Knoener M (2012) 89 131 79 140 9.7% 1.64 [1.00, 2.69]
Lu GY (2016) 82 153 50 147 9.8% 2.24 [1.41, 3.57]
Mao SX (2007) 5 11 1 19 2.7% 15.00 [1.45, 155.31]
Qi Q (2014) 33 64 4 32 6.3% 7.45 [2.34, 23.69]
Wang W (2014) 10 20 8 41 6.3% 4.13 [1.28, 13.27]
Wang XX (2005) 17 46 1 22 3.2% 12.31 [1.52, 99.88]
Wei B (2008) 14 26 5 28 6.0% 5.37 [1.56, 18.49]
Xia YB (2007) 19 21 26 45 4.7% 6.94 [1.44, 33.45]
Yin K (2008) 22 30 17 45 7.0% 4.53 [1.65, 12.42]
Zhang HJ (2007) 17 32 7 30 6.6% 3.72 [1.25, 11.13]
Zhang ZJ (2009) 30 37 12 73 6.9% 21.79 [7.78, 60.99]
Zhang ZL (2009) 9 26 2 24 4.4% 5.82 [1.11, 30.56]
Zhou L (2014) 43 64 11 81 8.0% 13.03 [5.73, 29.66]
Total (95% CI) 812 991 100.0% 5.77 [3.69, 9.02]
Total events 464 269
Heterogeneity: Tau² = 0.47; Chi² = 46.35, df = 15 (P < 0.0001); I² = 68%
Test for overall effect: Z = 7.68 (P < 0.00001)
0.01 0.1 1 10 100
Stage III-IV Stage 0-II

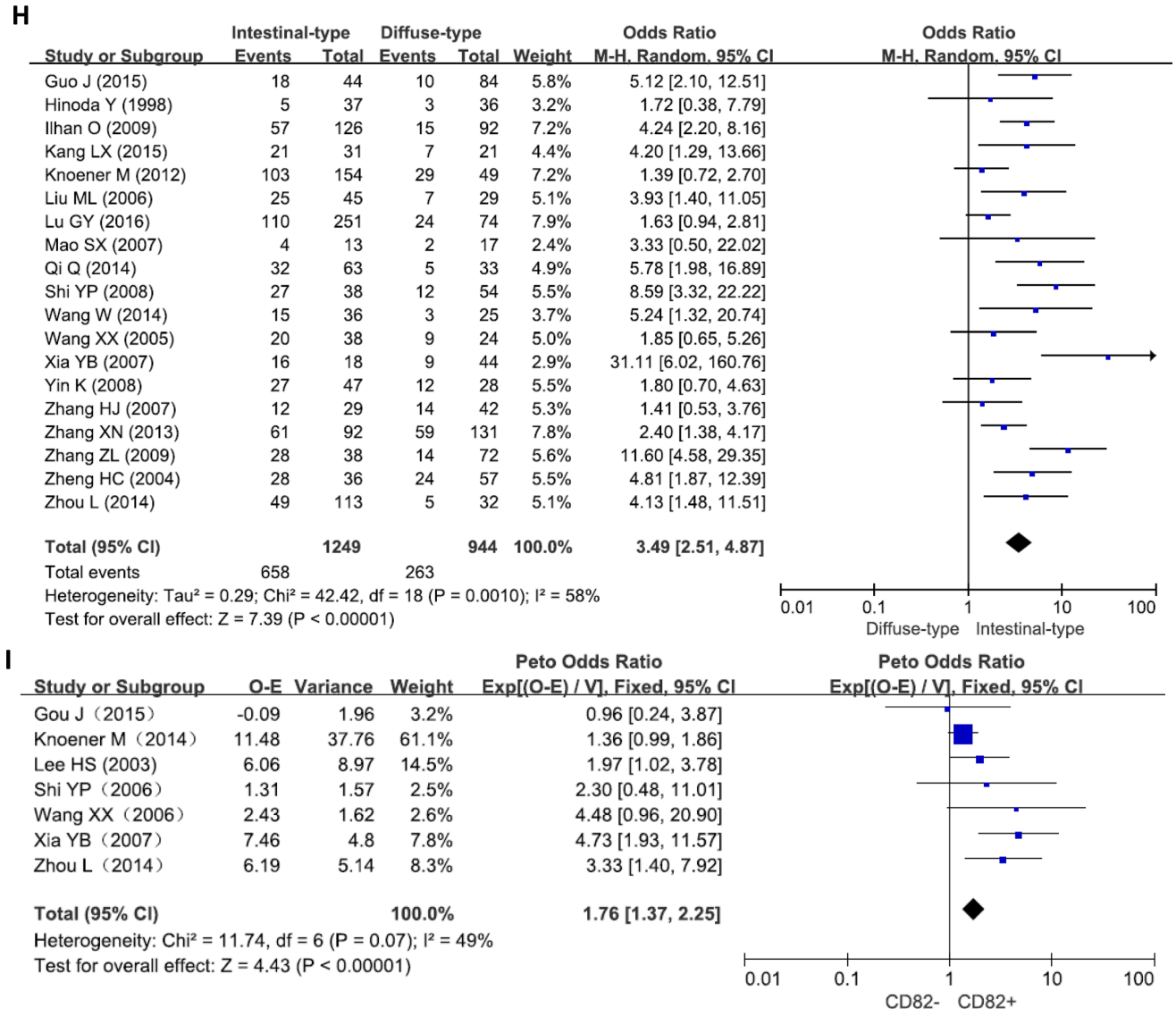


Figure 2: Forest plot for the relationship between CD82 expression and clinicopatholoiocal parameters of gastric cancer. (**A**) gastric carcinogenesis (cancer *vs* normal mucosa); (**B**) correlation between T staging and CD82 expression (T0-1 *vs* T2-4); (**C**) correlation between T staging and CD82 expression (T0-2 *vs* T3-4); (**D**) correlation between lymph node metastasis (LN) and CD82 expression (LN- *vs* LN+); (**E**) correlation between distant metastasis (DM) and CD82expression (DM- *vs* DM+); (**F**) correlation between TNM staging and CD82 expression (stage 0-I *vs* II-IV); (**G**) correlation between TNM staging and CD82 expression (stage 0-II *vs* III-IV); (**H**) correlation between differentiation and CD82 (intestinal-type *vs* diffuse-type). (**I**) correlation between prognosis and CD82 expression (CD82- *vs* CD82+).

DISCUSSION

A body of evidences indicates that CD82 inhibits migration and invasion by strengthening the cell adhesion, and weakening cellular protrusion and mobility [38–43]. Reportedly, CD82 overexpression down-regulated VEGF-C expression via Src/STAT3 pathway in pancreatic cancer cell [36] and sLea/x expression via the down-regulation of ST3GAL4 expression to thereby reduce the adhesion of cancer cells to blood vessels [37]. CD82 overexpression significantly inhibited migration and invasion of melanoma cells by reducing Rho-associated kinase-mediated formation of stress fiber or MMP2 activity [38]. It also inhibited polarized protrusion and retraction events by disrupting actin reorganization with deregulated Rac1, RhoA, and their effectors cofilin, and Rho kinase by perturbing the plasma membrane lipids [39]. CD82 suppressed HIF-1α and VEGF expression by blocking CDCP1- enhanced Src activation in prostate cancer [40], HGF-induced migration of hepatoma cells via upregulation of Sprouty2 [41] or the inactivation of small GTP-binding proteins of the Rho family via c-Met adapter proteins [42]. Chigita et al. [43] concluded that CD82 attenuated Wnt signaling by inhibition of β-catenin nuclear translocation

Table 2: The prognostic significance of *CD82* mRNA expression in gastric cancer

Clinicopathological features	Overall survival		Progression-free survival	
	Hazard ratio	*p*	Hazard ratio	*p*
Sex				
Female	0.55 (0.36 − 0.85)	0.0056	0.53 (0.35 − 0.81)	0.0029
Male	0.57 (0.42 − 0.78)	3e−04	0.6 (0.44 − 0.81)	0.00069
T				
2	0.53 (0.34 − 0.83)	0.0046	0.53 (0.35 − 0.82)	0.0032
3	0.67 (0.47 − 0.95)	0.026	0.68 (0.48 − 0.96)	0.029
4	0.57 (0.25 − 1.32)	0.18	0.74 (0.33 − 1.66)	0.46
N				
0	0.39 (0.16 − 0.94)	0.03	0.4 (0.17 − 0.95)	0.031
1–3	0.55 (0.41 − 0.72)	1.3e−05	0.59 (0.46 − 0.76)	3.5e−05
1	0.44 (0.29 − 0.67)	9.4e−05	0.43 (0.29 − 0.64)	2.1e−05
2	0.64 (0.41 − 1.02)	0.059	0.64 (0.4 − 1.03)	0.067
3	0.44 (0.24 − 0.8)	0.0059	0.42 (0.22 − 0.79)	0.0054
M				
0	0.57 (0.42 − 0.76)	0.00011	0.6 (0.46 − 0.78)	0.00011
1	0.63 (0.33 − 1.2)	0.15	0.64 (0.33 − 1.26)	0.2
TNM staging				
I	0.45 (0.15 − 1.36)	0.15	0.47 (0.16 − 1.41)	0.17
II	0.5 (0.26 − 0.98)	0.04	0.39 (0.21 − 0.72)	0.0019
III	0.58 (0.39 − 0.86)	0.006	0.63 (0.43 − 0.92)	0.017
IV	0.69 (0.46 − 1.05)	0.083	1.24 (0.81 − 1.91)	0.32
Differentiation				
Moderately-differentiated	1.61 (0.82 − 3.14)	0.16	1.74 (0.83 − 3.66)	0.14
Poorly-differentiated	1.15 (0.68 − 1.94)	0.6	0.84 (0.53 − 1.33)	0.45
Lauren's classification				
Intestinal-type	0.54 (0.35 − 0.85)	0.0071	0.6 (0.42 − 0.87)	0.0062
Diffuse-type	0.57 (0.41 − 0.81)	0.0013	0.56 (0.4 − 0.79)	0.00092
Mixed-type	0.4 (0.12 − 1.32)	0.12	2.24 (0.69 − 7.24)	0.17
Her2 positivity				
−	0.54 (0.41 − 0.72)	1.7e−05	0.55 (0.41 − 0.74)	8.3e−05
+	-	-	0.67 (0.43 − 1.04)	0.074
Treatment				
Surgery alone	0.68 (0.5 − 0.92)	0.013	0.71 (0.54 − 0.94)	0.015
5-FU-based adjuvant	0.5 (0.19 − 1.31)	0.15	0.34 (0.14 − 0.82)	0.012
Other adjuvant	2.06 (0.84 − 5.04)	0.11	0.5 (0.23 − 1.1)	0.078

by down-regulation of Fzd receptor proteins, accumulation of β-catenin at the cell membrane by down-regulation of GSK-3β and CK1α, and stabilization of the E-cadherin-β-catenin complex. To investigate the clinicopathological and prognostic significances of CD82 expression, we analyzed 26 studies, which met specific inclusion criteria and had moderate to high quality according to their NOS scores.

Chai et al. [44] found that CD82 overexpression suppressed *in vitro* cell growth, migration, invasion and xenograft growth in oral cancer. A progressive down-regulation of CD82 was during colorectal mucosa-adenoma-the primary adenocarcinoma to the liver metastasis [45]. Zhou et al. [46] found that CD82 expression was markedly lower in cervical cancer than in the normal cervix, chronic cervicitis, or cervical intraepithelial neoplasia. Reportedly, the promoter CpG-Site methylation and LOH of *CD82* contributed to its epigenetic repression [47, 48]. Consistent with the data

Table 3: Multivariate analysis of hazard factors of the prognosis of the patients with gastric cancer

Clinicopathological features	Hazard ratio (95% CI)	*p*
Stage T (T1-2/T3-4)	1.012 (0.510–2.009)	0.973
Lymph node status (−/+)	0.742 (0.331–1.665)	0.470
Distant metastasis	0.000 (0.000–4.373e–284)	0.969
TNM staging (I-II/III-IV)	0.950 (0.404–2.237)	0.907
Lauren's classification(IT/DT)	0.698 (0.375–1.299)	0.256
CD82 mRNA expression	0.536 (0.300–0.959)	0.036

IT, intestinal-type; DT, diffuse-type; CI, confidence interval.

about hepatocellular carcinoma, laryngeal squamous cell carcinoma (LSCC), lung cancer, breast cancer, endometrial cancer, prostate cancer, and bladder cancer [49–55], we found down-regulated CD82 expression was detectable in gastric cancer, compared with normal mucosa, and positively correlated with depth of invasion, lymph node and distant metastasis, TNM staging and dedifferentiation of gastric cancer. These fingings suggest that CD82 hypoexpression promotes gastric carcinogenesis and subsequent progression, in line with our previous work [25]. Although anti-CD82 antibodies come from 10 companies, the subjects of 5 countries are involved in our study, and different statistical methods are employed, CD82 expression and its correlation with clinicopathological parameters are comparatively consistent, indicating that these antibodies mainly recognize CD82 protein and its expression is independent of population or not determined by statistics. It was noted that *CD82* mRNA overexpression was observed in gastric cancer according to bioinformatics analysis, in agreement with the finding about thyroid papillary carcinoma [56] and colorectal cancer [57]. The discrepancy might be due

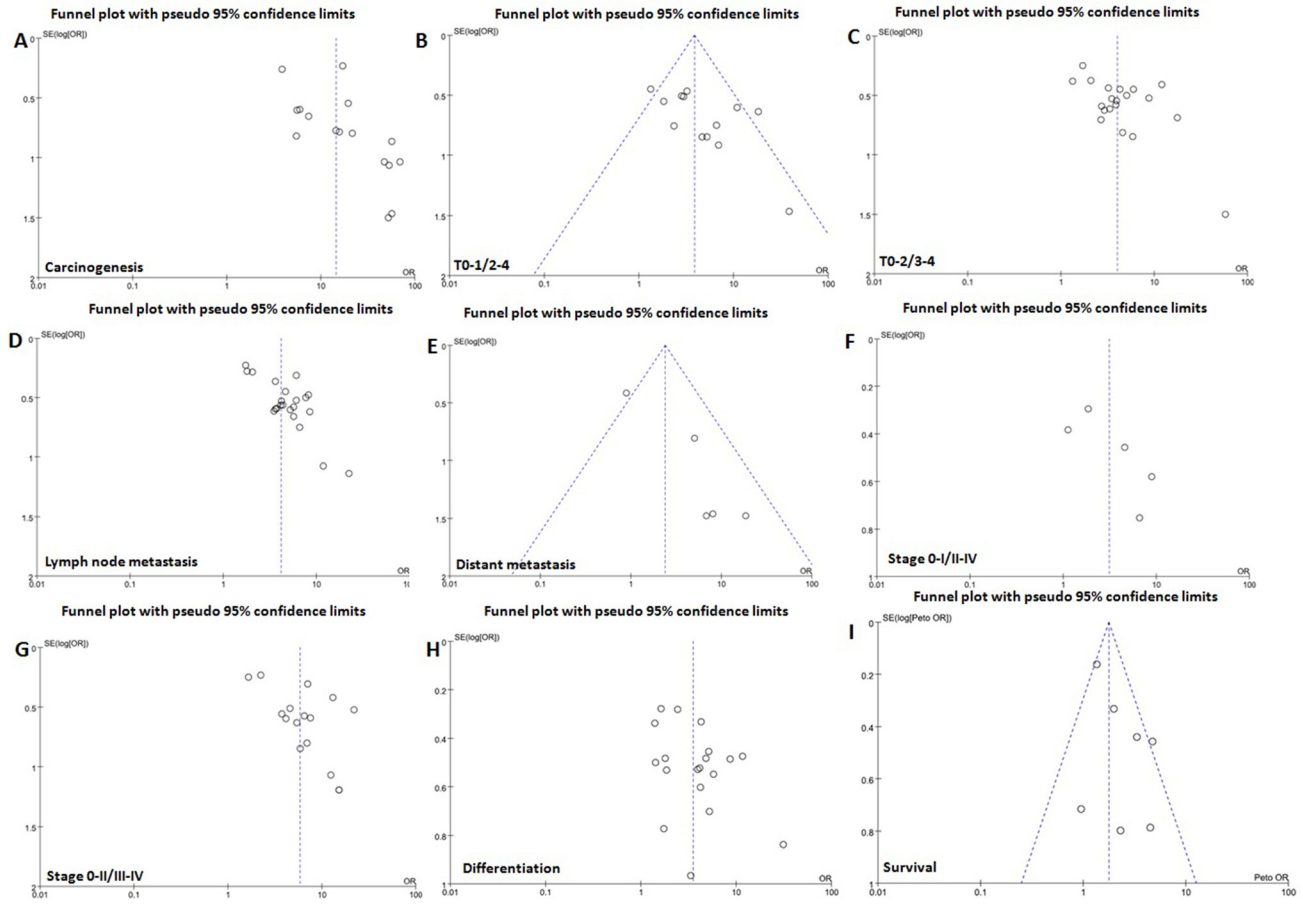


Figure 3: Funnel plot for publication bias test **between CD82 expression and gastric carcinogenesis or progression.** The bias was analyzed about risk degrees of CD82 expression in gastric mucosa (**A**) for gastric carcinogenesis. Additionally, it was tested between CD82 expression and clinicopathological features of gastric cancer, including depth of invasion (**B** and **C**), lymph node metastasis (**D**), distant metastasis (**E**), TNM staging (**F** and **G**), and differentiation (**H**) and prognosis (**I**).

to tissue specificity, long distance from mRNA to protein, and different methodologies (immunohistochemistry, transcriptomic sequencing and real-time PCR).

A body evidences showed that CD82 expression was negatively related to the poor prognosis of the patients with breast, lung, and oral cancers [58–60]. CD82 expression might be demonstrated to indicate the favorable prognosis of colorectal cancer, LSCC and melanoma as an independent factor [50, 61, 38]. Our meta-analysis showed that CD82 expression was positively linked to the better prognosis of the patients with gastric cancer. Additionally, our bioinformatics data indicated that *CD82* mRNA expression was positively associated with a higher survival rates of the patient with gastric cancer, even stratified by clinicopathological features or as an independent factor. The findings can be explained by inverse correlation between CD82 expression and aggressiveness of gastric cancer.

In conclusion, CD82 expression was down-regulated from gastric carcinogenesis, but versa for its mRNA. It was negatively correlated with depth of invasion, lymph node and distant metastasis, TNM staging and dedifferentiation of gastric cancer. CD82 expression might be employed as a good potential marker for favorable prognosis of gastric cancer patients at either mRNA or protein level. Several limitations included the potential publication bias stems from published results being predominantly positive, subjective bias of survival data extracted from survival curves, and country bias of gastric cancer cases.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a publication search using PubMed, Web of Science, BIOSIS and SciFinder updated on March 14, 2017. The following search terms were used: (CD82 OR Kai1) AND (gastric OR stomach) AND (cancer OR carcinoma OR adenocarcinoma). Searching was done without restriction on language or publication years.

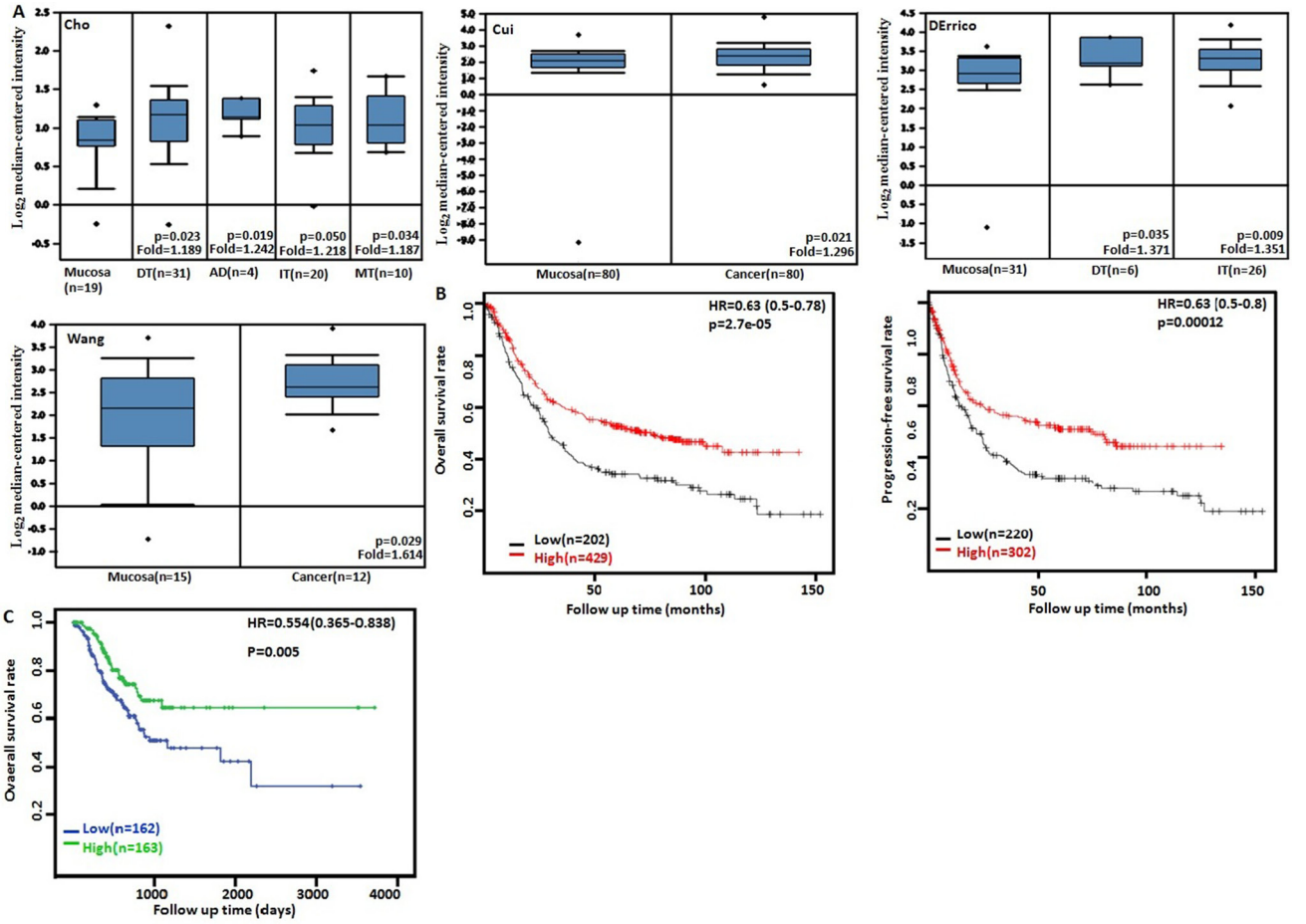


Figure 4: *CD82* mRNA expression in gastric carcinogenesis and subsequent progression. Cho', Cui's, DErrico's and Wang's datasets were employed for bioinformatics analysis to analyze *CD82* mRNA expression during gastric carcinogenesis. A higher *CD82* mRNA expression was detectable in gastric cancer than that in normal gastric mucosa, even stratified into intestinal-, diffuse-, and mixed-type carcinomas by Lauren's classification (**A**, $p < 0.05$). According to the data from KM plotter, *CD82* mRNA expression was positively related to both overall and progression-free survival rates of the patients with gastric cancer (**B**, $p < 0.05$). It was the same from TCGA database (**C**, $p < 0.05$). HR, hazard ratio.

Inclusion criteria for studies included: (1) articles to observe the alteration in CD82 expression in gastric cancer by immunohistochemistry; (2) papers to compare CD82 expression with pathobiological behaviors and prognosis of gastric cancer by immunohistochemistry. Exclusion criteria included: (1) abstract, comment, review and meeting; (2) duplication of the previous publications; (3) Western blot, RT-PCR, cDNA microarray, or transcriptomic sequencing for CD82 expression; (4) lack of sufficient information.

Data extraction

Based on the inclusion criteria, two reviewers (BC Gong and HC Zheng) independently extracted information from all eligible publications. The following information was included name of first author, year of publication, country, ethnicity, antibody source, numbers of cases and controls, expression alteration, and follow-up outcome. Regarding survival analysis, we used Engauge Digitizer software to extract data from Kaplan-Meier curves and calculated the Hazard ratios (HR) and their corresponding 95% confidence interval. Any disagreement was resolved through discussion until the two reviewers reached a consensus.

Quality score assessment

Two reviewers (BC Gong and HC Zheng) independently assessed the quality of the included studies according to Newcastle Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The scale consists of three components related to sample selection, comparability and ascertainment of outcome.

Bioinformatics analysis

The individual gene expression level of CD82 was analyzed using Oncomine (www. oncomine.org), a cancer microarray database and web-based data mining platform for a new discovery from genome-wide expression analyses. We compared the differences in *CD82* mRNA level between gastric normal tissue and cancer. All data were log-transformed, median centered per array, and standard deviation normalized to one per array. The expression (RNA-seqV2) and clinicopathological data of 392 gastric cancer patients were downloaded from the Cancer Genome Atlas (TCGA) database by TCGA-assembler in R software. We integrated the raw data, analyzed *CD82* mRNA expression in gastric cancer, and compared it with clinicopathological and prognostic data of the patients with gastric cancer. Additionally, the prognostic significance of *CD82* mRNA was also analyzed using Kaplan-Meier plotter (http://kmplot.com).

Statistics analysis

HWE was evaluated using Chi-square test in control groups of each study. Strength of association between CD82 expression and cancer risk was assessed by odds ratios with 95% confidence intervals. Statistical significance of the pooled OR was determined by *Z* test. If there was no significant heterogeneity, the fixed effect model (Mantel-Haenszel method) would be employed. Otherwise, the random effect model (DerSimonian and Laird method) would be used excluding prognostic analysis. Heterogeneity effect was then quantified by I^2 test, which was subdivided into low, moderate and high degrees of heterogeneity according to the cut-off values of 25%, 50% and 75% respectively. Publication bias was evaluated by funnel plot and quantified by Begg's test and Egger's test to assess funnel plot asymmetry. Meta-analyses were performed with Revman software 5.3 and data from TCGA database was dealt with SPSS 10.0 software using student *t* test. *Kaplan-Meier* survival plots were generated and comparisons between survival curves were made with the log-rank statistic. Cox's proportional hazards model was employed for multivariate analysis. Two-sided $p < 0.05$ was considered as statistically significant.

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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