

Glutathione S-transferases genes variants and chemotherapy efficacy in gastrointestinal cancer patients: a meta-analysis based on 50 pharmacogenetic studies

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Additional supporting information

Table S1 ORR, PFS, and TTP of chemotherapy in GIC patients with *GSTP1* Ile105Val variants

Tumor types	Author	Year	ORR (Good + Poor)			PFS/TTP (HR)			OS time (HR)		
			Ile/Ile	Ile/Val	Val/Val	Ile/Ile	Ile/Val	Val/Val	Ile/Ile	Ile/Val	Val/Val
GC	Meulendijks D	2016	146(80+66)		27(16+11)	reference		0.9(0.6–1.4)	reference		0.9(0.6–1.4)
GC	Liu R	2016	75(64+11)	31(24+7)	1(1+0)	reference	1.24(0.78–1.96)		reference	1.33(0.74–2.37)	
GC	Liang J	2010				2.19(1.13-3.66)*	reference		2.19(1.31-2.74)	reference	
GC	Li QF	2010	44(17+27)	41(29+12)		2.36 (1.36-4.09)*	reference		2.27 (1.28-4.02)	reference	
GC	Shim HJ	2010	133(46+87)	60(26+34)	7(5+2)	reference	1.02 (0.73–1.42)	0.84 (0.39–1.84)	reference	1.12 (0.79–1.58)	0.76 (0.33–1.77)
GC	Huang ZH	2009							reference	2.13 (1.14–3.97)	
GC	Ott K	2008	55(12+43)	59(14+45)	18(7+11)						
GC	Goekkurt E	2006	30(7+23)	12(2+10)	6(4+2)						
GC	Seo BG	2009	47(10+37)	38(18+20)							
GC	Goekkurt E	2009	64(26+38)	47(19+28)	22(7+15)						
GC	Ruzzo A	2006	87(20+67)	70(38+32)	18(12+6)						
GC	Keam B	2008	44(22+22)	29(10+19)		reference	1.24(0.75–2.06)*		reference	0.62(0.45–1.61)	
GC	Ji M	2013	23(3+20)	21(4+17)	15(11+4)						
GC	JI YU ZHI	2011	48(22+26)	25(9+16)	7(3+4)						
CRC	Kap EJ	2014							reference, 0.78 (0.38–1.57)	0.82 (0.39–1.73)	0.60 (0.14–2.62)
CRC	Lai CY	2013							reference, 1.10(0.85–1.43)	1.10(0.84–1.44)	1.12(0.57–2.20)
CRC	Li HY	2012							reference	0.85(0.58-1.28)	0.44(0.18-0.98)
CRC	Fariña Sarasqueta(1)	2011							reference	2.1(0.84-5.25)	1.57(0.31-7.9)

CRC	Fariña Sarasqueta(2)	2011							reference	0.9(0.35-2.28)	0.41(0.05-3.15)
CRC	Stoehlmacher J	2004				reference	1.22 (0.56-2.67)*	2.13 (0.95-4.76)*	reference	1.82 (0.71-4.66)	2.96 (1.15-7.61)
CRC	Stoehlmacher J	2002							reference	0.47 (0.27-0.81)	0.16 (0.04-0.63)
CRC	Jones BA	2009							reference,0.35(0.16-0.79)	0.50(0.20-1.23)	0.23(0.08-0.68)
CRC	Bohanes P	2015							reference	0.83(0.65-1.05)	1.46(1.01-2.11)
CRC	Boige V	2010				reference	1.09(0.84-1.39)	1.12(0.78-1.61)			
CRC	Huang MY	2011				2.77(0.34–22.48)	1.72(0.36–8.22)	reference			
CRC	Ruzzo	2007				reference	0.99(0.60-2.14)	1.15(0.70-2.01)			
CRC	Kumamoto K	2013	44(14+30)	16(11+5)	2(1+1)						
CRC	Nishina T	2013	49(27+22)	19(8+11)							
CRC	Paez D	2011	45(30+15)	47(25+22)	8(3+5)						
CRC	Zarate R	2010	20(10+10)	34(30+4)	6(5+1)	2.6(1.3 –5.4)	reference				
CRC	Le Morvan V(1)	2007	32(15+17)	15(7+8)							
CRC	Le Morvan V(2)	2007	26(12+14)	27(16+11)							
CRC	Chen Jian Guo	2016	41(16+25)	19(13+6)							
CRC	Dong Ning ning	2014	43(20+23)	31(20+11)							
CRC	Ying bei bei	2009	54(14+40)	48(30+18)		reference	3.41(2.14-5.43)*				
CRC	HAN lei	2015	51(31+20)	20(6+14)							
CRC	Shen Dong Ya	2015	80(25+55)	47(26+21)							
CRC	Liang Jun	2009	10(6+4)	112(29+83)							
CRC	Joerger M	2015	19(2+17)	25(8+17)	11(9+2)	reference	0.61(0.35–1.06)	0.24(0.12–0.49)	reference	0.70(0.40–1.22)	0.23(0.11–0.48)
CRC	Ye Chung Chen	2009	125(47+78)	41(23+18)					reference	2.45(1.30–4.62)	
CRC	Hong J	2011	37(16+21)	14 (8+6)		reference	0.47(0.21-1.04)				

CRC	Lamas MJ	2011	35(23+12)	37 (33+4)					2.38(0.22–3.79)	2.12(0.41–11.03)	reference
EAC	Rumiato E	2013	32(17+15)	24(8+16)	7(4+3)				reference	1.36 (0.70–2.64)	
EAC	Wang Y	2011	182(84+98)	59(19+40)							
EAC	Gui Yan	2016	97(37+60)	71(42+29)							
EAC	Joerger M	2015	30(12+18)	37(18+19)	9(7+2)				reference	0.79(0.49–1.28)	0.71(0.34–1.49)

HR: hazard ratio; OS, overall survival; TTP, time to progression; PFS, progression-free survival; ORR: objective response rate. EC, esophageal cancer; GC, gastric cancer; CRC, colorectal cancer. * The HR of TTP.

Table S2 ORR, PFS and OS of chemotherapy in GIC patients with *GSTM1/GSTT1* variants

Tumor types	<i>GSTT1</i>
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	Author	Year	ORR (Good + Poor)		PFS/HR		OS/HR	
			Present	Null	Present	Null	Present	Null
GC	Meulendijks D	2016	136(80+56)	37(16+21)	reference	1.1(0.7–1.6)	reference	1.1(0.7–1.6)
GC	Shim HJ	2010	94(37+57)	106(40+66)	reference	0.98(0.72–1.32)	reference	0.77(0.57–1.06)
GC	Ott K	2008	87(24+63)	23(5+18)				
GC	Goekkurt E	2006	12(5+7)	38(8+30)				
GC	Seo BG	2009	36(10+26)	39(8+31)				
GC	Goekkurt E	2009	52(47+5)	82(64+18)	reference	0.99(0.69-2.88)	reference	1.94(1.14 -3.32)
GC	Ruzzo A	2006	154(64+90)	21(6+15)				
CRC	Kap EJ	2014					reference	1.25 (0.89–1.75)
CRC	Kumamoto K	2013	3(13+17)	32(13+19)				
CRC	Lai CY	2013					1.15(0.90–1.46)	reference
CRC	Zarate R	2010	46(34+12)	14(11+3)				
CRC	Stoehlmacher J	2004			reference	0.98 (0.60, 1.60)*	reference	1.33 (0.78-2.28)
CRC	Stoehlmacher J	2002					reference	0.94 (0.61-1.87)
CRC	Ruzzo	2007			reference	1.23(0.50-3.40)		
CRC	Boige V	2010			reference	1.26(0.92-1.72)		
EC	Rumiato E	2013	48(25+23)	15(4+11)			reference	1.89 (0.83–4.34)
	<i>GSTMI</i>							
Tumor types	Author	Year	ORR (Good + Poor)		PFS/HR		OS/HR	
			Present	Null	Present	Null	Present	Null
GC	Meulendijks D	2016	84(43+41)	89(53+36)	reference	1.0(0.7–1.4)	reference	1.0(0.7–1.4)
GC	Shim HJ	2010	76(29+47)	124(48+76)	reference	0.98 (0.72–1.33)	reference	1.10 (0.80–1.51)

GC	Ott K	2008	60(13+47)	52(15+37)				
GC	Goekkurt E	2006	18(4+14)	32(9+23)				
GC	Huang ZH	2009			reference	1.291 (0.774–2.154)	reference	1.43(0.82–2.47)
GC	Seo BG	2009	26(6+20)	49(12+37)				
GC	Goekkurt E	2009	52(26+26)	82(36+46)				
GC	Ruzzo A	2006	97(34+63)	78(36+42)				
CRC	Kap EJ	2014					reference	0.79 (0.61–1.04)
CRC	Kumamoto K	2013	23(9+14)	39(17+22)				
CRC	Zarate R	2010	25(21+4)	35(24+11)				
CRC	Stoehlmacher J	2004			reference	1.13 (0.72-1.76)*	reference	1.14 (0.69-1.88)
CRC	Stoehlmacher J	2002					reference	1.25 (0.68-2.30)
CRC	Ruzzo	2007			reference	0.88(0.46-1.87)		
CRC	Boige V	2010			reference	0.88(0.70-1.11)		
EC	Rumiato E	2013	28(14+14)	35(15+20)			reference	1.05 (0.54–2.05)

HR: hazard ratio; PFS, progression-free survival; OS, overall survival; ORR: objective response rate. * The HR of TTP.

Table S3 The association between *GSTP1* Val carriers vs. Ile/Ile and ORR of chemotherapy in GIC patients base on subgroups

No. of studies	Study groups	Test of association			Models	Test of heterogeneity			Tau-squared
		OR/HR (95% CI)	Z	P-value		χ^2	P-value	I ² (%)	
	Genotyping method								
8	TaqMan assay	1.207(0.645-2.259)	0.59	0.556	R	34.14	<0.001	76.60%	0.6621
14	PCR-RFLP	1.960(1.265- 3.039)	3.01	0.003	R	35.48	0.001	60.50%	0.3908
3	Sequenom-MassARRAY	1.342(0.285- 6.322)	0.37	0.71	R	11.97	0.003	83.30%	1.5589
1	HRM-SNP	2.724(1.294-5.734)	2.64	0.008	R	-	-	-	-
5	DNA sequencing	1.359(0.590-3.130)	0.72	0.471	R	20.22	<0.001	80.20%	0.689
	Evaluation criterion								
24	RECIST	1.662(1.136-2.431)	2.62	0.009	R	78.54	<0.001	73.30%	0.5737
5	NR	1.482(0.691-3.181)	1.01	0.312	R	14.95	0.005	73.30%	0.5409
5	WHO	1.277(0.571-2.856)	0.6	0.551	R	6.37	0.095	52.90%	0.3559
	Chemotherapy regimens								
29	Platinum-based	1.587(1.145-2.201)	2.77	0.006	R	101.5	<0.001	72.40%	0.5538
2	Non-platinum	1.583(0.747-3.354)	1.2	0.231	R	0.89	0.346	0	0
	QS								
23	High QS	1.528(1.071-2.181)	2.34	0.019	R	78.72	<0.001	72.10%	0.5162
8	Low QS	1.758(0.894-3.458)	1.64	0.102	R	23.44	0.001	70.10%	0.6535
	Study types								
6	Prospective study	1.180(0.631-2.208)	0.52	0.065	R	11.09	0.05	54.9%	0.3244
25	Retrospective study	1.677(1.183-2.378)	2.9	0.004	R	87.28	<0.001	72.5%	0.5471

OR, odds ratio; CI, confidence interval; R, random effect model; QS, quality score; PCR-RFLP, PCR-restriction fragment length polymorphism; RECIST, Response Evaluation

Criteria in Solid Tumors; WHO, World Health Organization; NR: not reported.

Figure S1 The sensitivity analysis of pooling ORs of ORR in GIC patients. (a)

ORR of *GSTP1* Val carriers vs. Ile/Ile model; (b) ORR of *GSTP1* Val/Val vs. Ile/Ile

model;(c) ORR of *GSTP1* Val/Val vs. Ile carriers model; (d) ORR of *GSTT1* null vs.

present; (e) OS of *GSTP1* Ile/Val vs. Ile/Ile model.

Figure S1

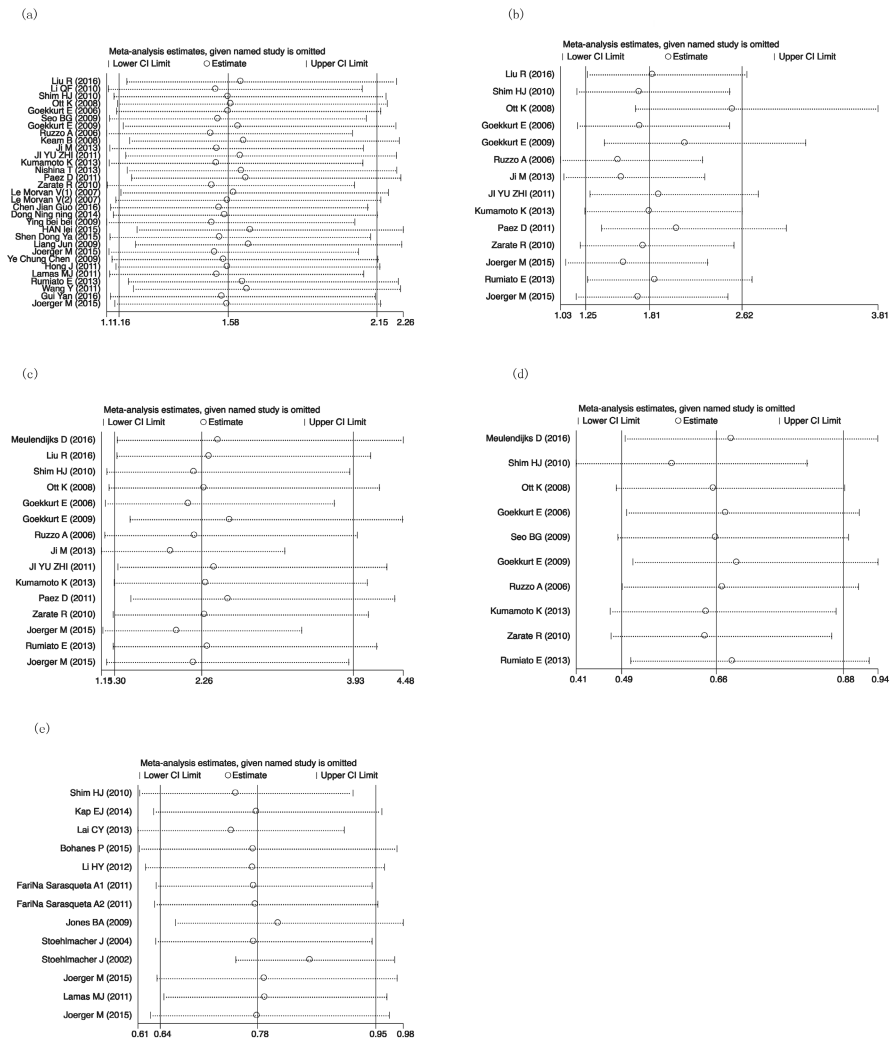


Figure S2 Forest plots of ORR in GIC patients harboring different *GSTP1* Ile105Val variants. OR: odds ratio; SE: standard error. (a) (Val/Val vs. Ile/Ile) stratified by ethnicity under random model; (b) (Val/Val vs. Ile carriers) stratified by ethnicity under random model.

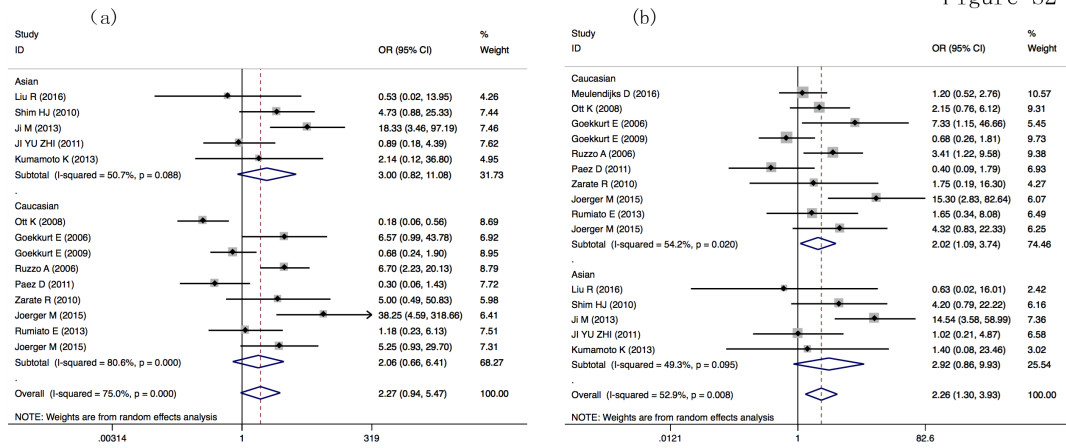


Figure S3 Begg's and Egger's bias plot for publication bias test on the association between the *GSTP1* Ile105Val variant (Val carriers vs. Ile/Ile) and ORR of GIC patients. OR: odds ratio; SE: standard error. (a) Begg's bias plot; (b) Egger's bias.

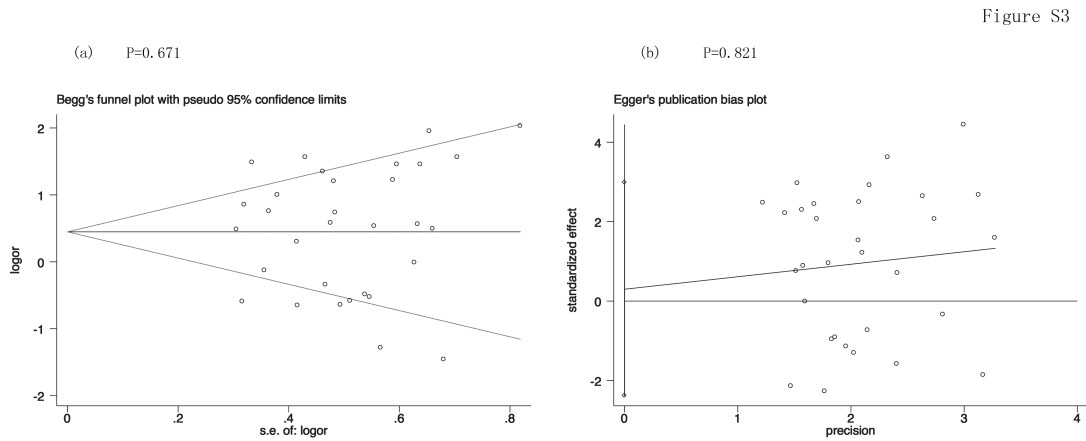


Figure S4 Begg's and Egger's bias plot for publication bias test on the association

between *GSTT1* Ile105Val variant (Val/Val vs. Ile/Ile; Val/Val vs. Ile carriers) and ORR of GIC patients. OR: odds ratio; SE: standard error. (a) Begg's bias plot under Val/Val vs. Ile/Ile model; (b) Egger's bias plot under Val/Val vs. Ile/Ile model; (c) Begg's bias plot under Val/Val vs. Ile carriers model; (d) Egger's bias plot under Val/Val vs. Ile carriers model.

Figure S4

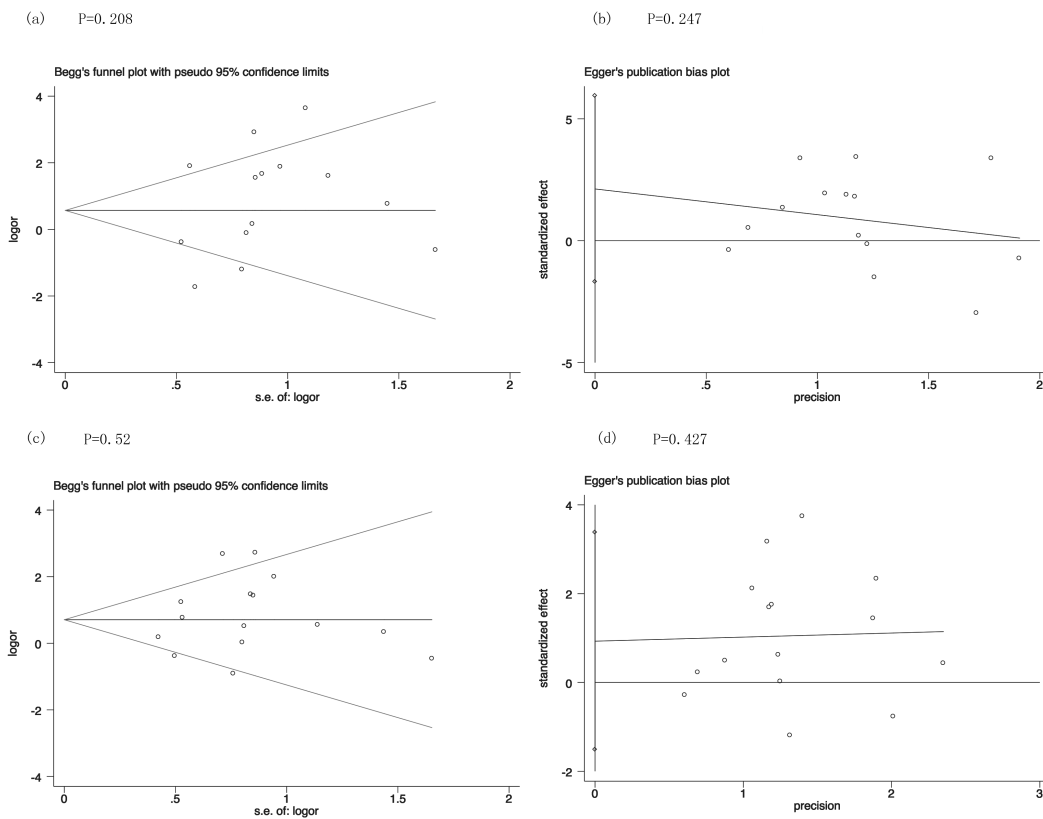


Figure S5 Begg's and Egger's bias plot for publication bias test on the association

between *GSTT1*/*GSTM1* null or present variant (null vs. present) and ORR of GIC patients. OR: odds ratio; SE: standard error. (a) *GSTT1* Begg's bias plot; (b) *GSTT1* Egger's bias plot; (c) *GSTM1* Begg's bias plot; (d) *GSTM1* Egger's bias plot.

Figure S5

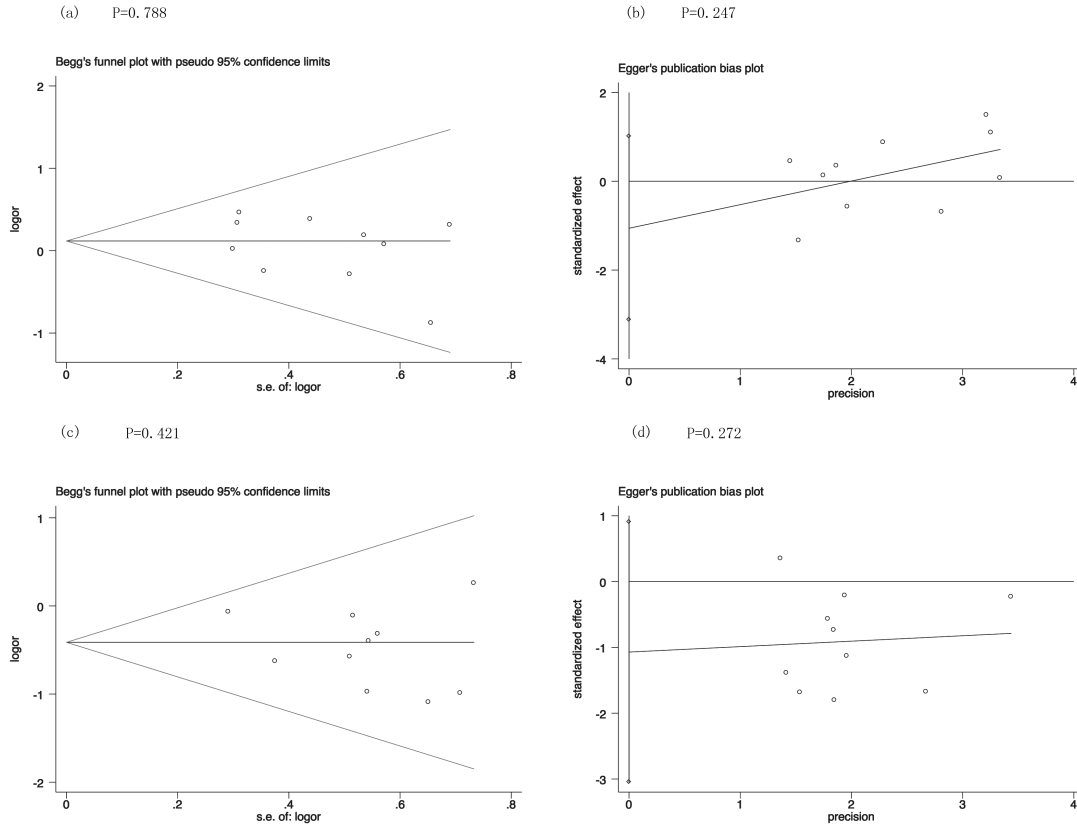


Figure S6 Begg's and Egger's bias plot for publication bias test on the association between *GSTP1* Ile105Val variant (Ile/Val vs. Ile/Ile) and the OS of GIC patients,

***GSTP1* Ile105Val variant (Val carriers vs. Ile/Ile) and PFS of GIC patients. OR:**
odds ratio; SE: standard error. (a) Begg's bias plot under Val/Val vs. Ile/Ile model; (b)
Egger's bias plot under Val/Val vs. Ile/Ile model; (c) Begg's bias plot under Val carriers
vs. Ile/Ile model; (d) Egger's bias plot under Val carriers vs. Ile/Ile model.

Figure S6

