Meta-Analysis

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

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Keywords: maspin, gastric cancer, meta analysis, bioinformatics analysis

Received: March 31, 2017 Accepted: August 02, 2017 Published: August 11, 2017

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ABSTRACT

Maspin is a mammary serine protease inhibitor that is encoded by human SERPINB5 gene, and inhibits invasion and metastasis of cancer cells as a tumor suppressor. We performed a systematic meta- and bioinformatics analysis through multiple online databases up to Feb 10, 2017. We found down-regulated maspin expression in gastric cancer, compared with normal mucosa and dysplasia (p < 0.05). Maspin expression was negatively correlated with depth of invasion, TNM staging and dedifferentiation of gastric cancer (p < 0.05). Nuclear maspin expression was higher in intestinal- than diffuse-type carcinoma (p < 0.05). An inverse association between maspin expression and unfavorable overall survival was found in patients with gastric cancer (p < 0.005). According to bioinformatics databases, SERPINB5 mRNA expression was higher in gastric cancer than normal tissues (p < 0.05), and negatively correlated with depth of invasion, TNM staging and dedifferentiation of gastric cancer (p < 0.05). According to KM plotter, we found that a higher SERPINB5 expression was positively correlated with overall and progression-free survival rates of all cancer patients, even stratified by aggressive parameters (p < 0.05). These findings indicated that maspin expression might be employed as a potential marker to indicate gastric carcinogenesis, subsequent progression, and even prognosis.

INTRODUCTION

Maspin is a mammary serine protease inhibitor that is encoded by human SERPINB5 gene, and inhibits invasion and metastasis of cancer cells [1, 2]. SERPINB5 has been identified as a type II tumor suppressor gene in normal mammary epithelial cells by subtractive hybridization, and is located on human chromosome 18q21.3-q23 along with other serpin genes, such as squamous cell carcinoma antigens 1 and 2, PAI-2 and headpin [3, 4]. Maspin is a cytosolic, cell surfaceassociated, and secretory protein with a reactive center loop that is incompatible with protease inhibition. Maspin has been found to inhibit angiogenesis by stopping the migration, mitogenesis and tube formation of endothelial cells, and to enhance apoptotic sensitivity of cancer cells to extracellular and intracellular stimuli through mitochondria pathway. Maspin retarded Ca²⁺ reductioninduced detachment via a novel interaction with the urokinase-type plasminogen activator/plasminogen [5], and acted as a molecular bridge between the plasminogen activator system and $\beta 1$ integrin that facilitated cell adhesion in mammary epithelial cells [6]. Odero-Marah et al. [7] found that maspin might inhibit cell motility by suppressing Rac1 and PAK1 activity, and promote cell adhesion via PI3K/ERK pathway. Khalkhali-Ellis et al. [8] reported that secretory maspin could deposit in the extracellular milieu and be incorporated into the matrix for tissue remodeling to suppress invasion. Tamazato et al. [9] demonstrated that EGFR signaling promoted maspin phosphorylation and nuclear localization, where it inhibited gene transcription directly or via histone deacetylase 1, including CSF-1, Bax, cytokeratin 18, and *p21* [10–12].

According to the review [13], maspin expression was down-regulated in melanoma, breast, prostate and

gastric cancers, but up-regulated in pancreatic, gallbladder, colorectal, and thyroid cancers, suggesting that maspin might play different roles in various kinds of cancers. SERPINB5 haploinsufficiency lead to hyperplastic lesions in prostate, and a high sceptibility to hepatocellular carcinoma [14, 15]. Homozygous loss of SERPINB5 was lethal at the periimplantation stage, due to visceral endoderm dysfunction by reducing cell proliferation and adhesion, thereby controlling early embryonic development [16]. In vial knockout mice, SERPINB5 deficiency was associated with a reduction in maximum body weight and a variety of context-dependent epithelial abnormalities, such as pulmonary adenocarcinoma, myoepithelial hyperplasia of the mammary gland, hyperplasia of luminal cells of dorsolateral and anterior prostate, and atrophy of luminal cells of ventral prostate and stratum spinosum of epidermis [17].

Since its discovery in 1994, the number of the articles about maspin was increased to 442 in Pubmed database until Feb 10th 2017. The investigators concluded that pattern and level of maspin expression had cell-specific characteristics in malignancies, and closely correlated with its complicated regulators [18–21]. The nuclear or cytoplasmic distribution of maspin has different clinicopathological and prognostic significances in cancers [22–24, 27], even gastric cancer [25–47]. Therefore, we performed a meta and bioinformatics analysis to clarify the roles of maspin expression in gastric cancers.

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 23 articles

about the relationship between maspin protein expression and cancer risk, clinicopathological and prognostic parameters of gastric cancer were retrieved for our metaanalysis from PubMed, Web of Science, BIOSIS, SciFinder and CNKI (Chinese). Only 15 articles contained the samples of normal gastric mucosa [27, 32–34, 37–47] and 6 did gastric precancerous lesion-dysplasia [25, 27, 38, 44, 46, 47]. There appeared the comparison between maspin expression and clinicopathological characteristics of gastric cancer in 19 studies, including sex, depth of invasion, lymph node metastasis, TNM staging and Lauren's classification. Finally, the authors discussed the prognostic significance of maspin expression in 3 articles [33, 35, 36]. There were three articles to compare nuclear or cytoplasmic maspin expression with clinicopathogical features of gastric cancer [27, 29, 36].

Association between maspin expression and cancer susceptibility of gastric mucosa or dysplasia

We analyzed the difference in maspin expression between gastric mucosa and cancer in 15 studies with 1447 cancers and 819 controls. As a result, we found downregulated maspin expression in gastric cancer, compared with normal mucosa (p = 0.02, Figure 2A). Additionally, the same trend was observed using 838 cancers and 292 dysplasia (p < 0.00001, Figure 2B).

Association between maspin expression and clinicopathological parameters of gastric cancer

As shown in Figure 2C, there was no difference in maspin expression between male and female patients with gastric cancer (p > 0.05). A higher maspin expression was detected in T_{is-2} than T₃₋₄ gastric cancer (p < 0.00001,



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

Figure 2D). Maspin expression was not related to lymph node metastasis of gastric cancer (p > 0.05, Figure 2E). The patients with stage 0–II cancer showed maspin overexpression, compared with those with stage III-IV cancer (p < 0.00001, Figure 2F). Maspin protein showed more expression in intestinal- than diffuse-type carcinomas (p < 0.00001, Figure 2G).

As indicated in Figure 3A and 3B, neither cytoplasmic nor nuclear maspin expression was correlated with the gender or lymph node metastasis of the patients with gastric cancer (p > 0.05). Nuclear maspin expression was higher in diffuse- than intestinal-type carcinomas (p < 0.05), but cytoplasmic maspin expression showed no difference between intestinal- and diffuse-type carcinomas (p > 0.05, Figure 3C).

Association between maspin expression and survival rate of gastric cancer

As indicated in Figure 2H, the pooled result from 3 datasets demonstrated a significantly negative association between maspin expression and favorable overall survival in patients with gastric cancer (HR = 1.66, 95% CI: 1.30-2.14, p < 0.0001).

Publication bias

The heterogeneity test was performed as shown in Figure 4. 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 prognostic result of maspin expression in Lee's study had 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 *SERPINB5* expression in gastric cancer

We used TCGA's, Cui's and Cho's datasets to perform bioinformatics analysis, and found that SERPINB5 mRNA expression was lower in gastric normal than cancer tissues, even stratified into intestinal-, diffuseand mixed-type carcinomas (Figure 5A–5D, p < 0.05). In TCGA data, *SERPINB5* expression was higher in gastric cancers with than without Barret's esophagus (p < 0.05, Figure 5E). It was negatively correlated with depth of invasion and TNM staging of gastric cancer (p < 0.05, Figure 5F and 5G). Forester's data showed a higher *SERPINB5* mRNA expression in intestinal-type than diffuse-type carcinomas (p < 0.05, Figure 5H).

According to Kaplan-Meier plotter, we found that a higher *SERPINB5* mRNA expression was positively correlated with overall and progression-free survival rates of all cancer patients, the patients with surgery alone or 5-FU-based adjuvant treatment, the patients with Her2- or Her2+, the patients with no distant metastasis, no lymph node metastasis, lymph node metastasis, N₁ or N₂ status, and female or male patients (p < 0.05, Figure 6A and 6B and Table 2). Stage I-IV cancer patients with high SERPINB5 mRNA expression showed a long overall survival time than those with its low expression (p < 0.05), while it was the same for progression-free survival in the patients with stage II and III cancer (p < 0.05). There appeared a positive relationship between SERPINB5 mRNA expression and the overall survival rate of the intestinal- and diffuse-type carcinoma patients (p < 0.05), whereas the same correlation between SERPINB5 mRNA expression and progression-free survival was observed in diffuse- and mixed-type carcinoma patients (p < 0.05). The overall survival rate of the patient with T_2 or T_2 cancer was positively linked to SERPINB5 mRNA expression (p < 0.05). Positive association between SERPINB5 mRNA expression and progression-free prognosis was observed in T₂ cancer patients (p < 0.05).

DISCUSSION

Metastasis is the most critical impediment for the survival of cancer patients. Maspin reintroduction was found to reverse epithelial-to-mesenchymal transition of prostate cancer cells by inhibiting HDAC1 activity and suppressing TGF-\u03b3/\u03b3-catenin /E-cadherin pathway [48, 49]. Lee et al. [50] demonstrated that maspin increased Ku70 acetylation by inhibiting HDAC1, and subsequently caused Bax-mediated cell death by dissociation of Bax from Ku70. Endsley et al. [51] found that maspin mediated the molecular bridge between the plasminogen activator system and $\beta 1$ integrin that facilitated cell adhesion in mammary epithelial cell. To investigate the clinicopathological and prognostic significances of maspin expression, we analyzed 23 studies, which met specific inclusion criteria and had moderate to high quality according to their NOS scores. Additionally, we also added our unpublished data about maspin expression.

According to the literature [52], precancerous lesions appear from gastric epithelium to adenocarcinoma, including adenomatous, regenerative, crysptal or globoid dysplasia. Consistent with the data about breast, colonic, bladder and gastric cancers [15, 27], we found downregulated maspin expression in gastric cancer, compared with gastric mucosa or dysplasia in the present study, suggesting that maspin hypoexpression contributed to gastric carcinogenesis as a late event. Previously, we performed maspin immunostaining using 2 individual samples of gastric cancer and found its upregulation. The discrepancies might be largely attributable to organ-specificity, criteria for positive staining, statistical analysis and subjects. Moreover, we confirmed the similar maspin expression in gastric cancer cells despite different antibodies from Novocastra and BD Pharmagin used [27].



Ε		LN-		LN+			Odds Ratio		Odds Ratio	
	Study or Subgroup	Events 1	Total Ev	ents To	otal W	/eight	M-H, Random, 95% CI		M-H, Random, 95% CI	
	Chen AJ (2009)	16	24	13	36	7.9%	3.54 [1.19, 10.50]			
	Cheng SH (2012)	16	42	14	21	7.8%	0.31 [0.10, 0.92]			
	Deng W (2006)	16	24	13	36	7.9%	3.54 [1.19, 10.50]			
	Gao P (2007)	10	26	7	54	7.7%	4.20 [1.37, 12.86]			
	He Y (2007)	34	118	35	54	9.2%	0.22 [0.11, 0.44]			
	Kim SM(2007)	13	18	26	44	7.5%	1.80 [0.55, 5.94]			
	Lee DY (2008)	61	71	47	80	8.8%	4.28 [1.92, 9.56]			
	Liang QL (2007)	28	42	25	60	8.7%	2.80 [1.23, 6.37]			
	Son HJ (2002)	5	5	23	25	2.8%	1.17 [0.05, 28.00]			-
	Terashima M (2005)	35	41	23	24	4.6%	0.25 [0.03, 2.25]	_		
	Zhang LM (2005)	29	54	27	83	9.1%	2.41 [1.19, 4.87]			
	Zhang LP (2012)	12	53	14	26	8.1%	0.25 [0.09, 0.68]			
	Zheng HC (unpublish)	129	247	67 1	173	9.9%	1.73 [1.17, 2.57]			
	Total (95% CI)		765	7	16 1	00.0%	1.36 [0.73, 2.53]		-	
	Total events	404		334						
	Heterogeneity: Tau ² = 0.9	9; Chi ² = 7	1.90, df	= 12 (P <	0.000	01); l ² = 8	33%	- 01		100
	Test for overall effect: Z =	0.95 (P =	0.34)					0.01	0.1 1 10	100
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F		Stage	0-2	Stage 3-	-4		Odds Ratio		Odds Ratio	
	Study or Subgroup	Events	Total	Events	otal	Weight	M-H, Random, 95% C	1	M-H, Random, 95% Cl	
	Bai YX (2007)	17	24	14	37	7.4%	3.99 [1.32, 12.02]			
	Cheng SH (2012)	17	24	13	39	7.4%	4.86 [1.61, 14.64]			
	Gao P (2007)	12	36	5	44	7.0%	3.90 [1.22, 12.45]			
	He Y (2007)	54	86	17	86	10.8%	6.85 [3.44, 13.62]			
	Ito R (2004)	34	60	3	40	6.2%	16.13 [4.47, 58.16]			
	Kim SM(2007)	20	28	18	34	7.7%	2.22 [0.77, 6.42]			
	Lee DY (2008)	68	80	41	12	10.0%	4.28 [1.98, 9.26]			
	Liang QL (2007)	30	54	23	48	9.9%	1.36 [0.62, 2.96]			
	Son HJ (2002)	14	15	13	15	2.3%	2.15 [0.17, 26.67]			
	Zhang LM (2005)	34	81	22	56	10.7%	1.12 [0.56, 2.24]			
	Zhang LP (2012)	13	31	13	48	8.5%	1.94 [0.75, 5.06]			
	Zheng HC(unpublished)	92	135	43	97	12.1%	2.69 [1.57, 4.61]			
	Total (95% CI)		654		616	100 0%	3 12 [2 06 4 74]		•	
	Total (95% CI)	405	054	225	010	100.0%	3.12 [2.00, 4.74]		•	
	Hotorogonoity: Tou ² = 0.2	405 0. Chi2 = 1	07 00 df	220 = 11 (D =	0.004	12 - 609	,	—		
	Helefogeneity. Tau- = 0.3	$50, C11^{-} - 2$	27.25, 01	- 11 (P -	0.004	$1^{-} = 00^{-7}$	0	0.01	A 4 40	400
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	Test for overall effect: Z =	= 5.35 (P <	0.00001)				0.01	0.1 1 10 Stage 3-4 Stage 0-2	100
	Test for overall effect: Z =	= 5.35 (P <	0.00001)				0.01	0.1 1 10 Stage 3-4 Stage 0-2	100
G	Test for overall effect: Z =	5.35 (P <	0.00001) Diffuse	type	Woigh	Odds Ratio	0.01	0.1 1 10 Stage 3-4 Stage 0-2 Odds Ratio	100
G	Study or Subgroup	5.35 (P < Intestina Events	0.00001 al type Total) Diffuse Events	type Tota	l Weigh	Odds Ratio t M-H. Fixed, 95% C	1	0.1 1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	100
G	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chap A L (2000)	5.35 (P < Intestina Events 11	0.00001 al type <u>Total</u> 14) Diffuse Events 20	type Tota 4	al Weigh 7 1.99	Odds Ratio t M-H, Fixed, 95% C 4.95 [1.22, 20.10]	1	0.1 1 1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Study or Subgroup Bai YX (2007) Chen AJ (2009) Chen SH (2012)	5.35 (P < Intestina Events 11 15	0.00001 al type Total 14 30) Diffuse Events 20 14	type Tota 4 3	al Weigh 7 1.99 0 6.69	Odds Ratio <u>M-H. Fixed, 95% C</u> 4.95 [1.22, 20.10] 1.14 [0.41, 3.15] 4.69 [4.50, 12, 94]	I	0.1 1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006)	5.35 (P < Intestina Events 11 15 18	0.00001 al type <u>Total</u> 14 30 26 30) Diffuse Events 20 14 12 14	type Tota 4 3 3	al Weigh 7 1.99 0 6.69 7 2.99	Odds Ratio t M-H. Fixed. 95% C 4.95 [1.22, 20.10] 1.14 [0.41, 3.15] 4.69 [1.59, 13.81] 4.14 [0.41, 3.15]	I	0.1 1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	100
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao B (2007)	= 5.35 (P < Intestina Events 11 15 18 15	0.00001 al type Total 14 30 26 30 36) Diffuse Events 20 14 12 14	type Tota 3 3 3	al Weigh 7 1.99 0 6.69 7 2.99 0 6.69	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 5.1.4 [0.41, 3.15] 4.69 [1.59, 13.81] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15]	I	O.1 1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007)	5.35 (P < Intestina Events 11 15 18 15 8 21	0.00001 al type Total 14 30 26 30 36 38) Diffuse Events 20 14 12 14 9 48	type Tota 4 3 3 3 4 4 13	al Weigh 7 1.99 0 6.69 7 2.99 0 6.69 4 6.09 4 9.09	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 1.14 [0.41, 3.15] 4.11 [0.38, 3.25] 4.211 [1.07, 4.59]	I	0.1 5tage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl	
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G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007)	5.35 (P < Intestina Events 11 15 18 15 8 21 26 22	al type Total 14 30 26 30 36 38 58 27) Diffuse Events 20 14 12 14 9 48 42 17	type Tota 4 3 3 3 3 4 13 3 3	al Weigh 7 1.99 0 6.69 7 2.99 0 6.69 4 6.09 4 9.09 3 5 2.69	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.69 [1.59, 13.81] 4.69 [1.59, 13.81] 5.1.14 [0.41, 3.15] 4.1.14 [0.41, 3.15] 5.2.21 [1.07, 4.59] Not estimable 4.66 [1.44, 15, 10]	I	0.1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl	
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G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005)	5.35 (P ≤ Intestina Events 111 15 18 15 8 21 26 22 59 6 21 12 24 41	0.00001 al type Total 14 300 266 300 366 388 588 277 74 122 355 14 366 102) Diffuse Events 20 14 12 14 9 48 42 17 50 14 22 15 24 15 24	type Tota 3 3 3 4 13 3 3 3 3 3 7 5 6 1 1 5 3	Weight 7 1.9° 0 6.6° 7 2.9° 0 6.6° 4 9.0° 3 3 5 2.6° 8 9.3° 7 4.1° 7 5.7° 6 1.9° 7 5.9° 5 12.6°	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.95 [1.59, 13.81] 4.69 [1.59, 13.81] 5.1.14 [0.41, 3.15] 5.2.114 [0.41, 3.15] 5.2.11 [0.38, 3.25] 5.2.21 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 5.2.20 [1.06, 4.58] 5.2.20 [1.06, 4.58] 5.2.21 [1.32, 7.16] 5.2.75 [1.15, 6.56] 5.0.90 [0.41, 1.95] 5.2.75 [1.15, 6.56] 5.2.75 [1.15, 6.55] 5.2.75 [1.15, 6.55] 5.2.75 [1.15, 6.55] 5.2.75		0.1 5tage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LP (2012)	5.35 (P ≤ Intestina Events 111 15 18 15 8 8 21 26 22 59 6 21 12 24 41 14	0.00001 al type Total 14 300 266 300 366 388 588 277 74 122 355 144 366 1022 288) Diffuse 200 14 12 14 9 48 42 17 50 14 22 15 24 15 12 15 15 15 15 15 15 15 15 15 15	type Tota 4 3 3 3 3 4 13 7 5 6 6 1 5 5 3 3 5	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 6.09 3 3 5 2.69 8 9.39 7 5.79 6 1.99 7 5.95 5 12.69 1 4.00	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.14 [0.41, 3.15] 5.21 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 5.220 [1.06, 4.58] 5.03 [0.24, 3.62] 6.3.07 [1.32, 7.16] 5.040 [0.03, 4.96] 6.2.75 [1.15, 6.56] 5.325 [1.22, 8.69] 6.325 [1.22, 8.69] 7.325 [1.225 [1.225 [1.255		0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LP (2012) Zheng HC (2008)	5.35 (P < Intestina Events 111 15 18 15 18 21 26 22 59 6 21 12 24 41 14 71	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150) Diffuse Events 200 14 12 14 12 14 9 48 42 17 50 14 22 15 24 15 12 38	type Tota 33 33 44 133 34 33 34 22 66 61 111 5 33 35 5 12	Weight 7 1.9° 0 6.6° 7 2.9° 0 6.6° 4 6.0° 4 9.0° 3 5 5 2.6° 8 9.3° 7 4.1° 7 5.7° 6 1.9° 7 5.9° 5 12.6° 1 4.0° 0 21.0°	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 6.1.14 [0.41, 3.15] 7.4.69 [1.59, 13.81] 7.5.111 [0.38, 3.25] 7.5.111 [0.38, 3.25] 7.5.111 [0.38, 3.25] 7.5.111 [0.7, 4.59] 8.2.21 [1.07, 4.59] 9.03 [0.24, 3.62] 7.5.12, 7.16] 7.5.12, 7.16] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.656] 7.5.5.5.656] 7.5.5.5.656] 7.5.5.5.656] 7.5.5.5.656] 7.5.5.5.656] 7.5.5.5.656] 7.5.5.5.5.5.656] 7.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5		O.1 Stage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl	
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G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LP (2012) Zheng HC (2008) Total (95% CI)	5.35 (P < Intestina Events 11 15 18 15 8 21 26 21 26 21 12 24 41 14 71	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710) Events 20 14 12 14 9 48 42 17 50 14 22 15 24 15 24 15 12 38	type <u>Tota</u> 4 3 3 3 4 4 13 3 3 3 4 4 13 5 7 7 2 2 6 6 11 5 3 3 5 12 81 12 81 12 12 12 12 12 12 12 12 12 1	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 9.09 3 5 5 2.69 8 9.33 7 4.19 7 5.79 6 1.99 7 5.26 1 4.09 0 21.09 1 100.09	Odds Ratio tt M-H. Fixed, 95% C 6 4.95 [1.22, 20.10] 6 1.14 [0.41, 3.15] 6 4.69 [1.59, 13.81] 6 1.14 [0.41, 3.15] 6 1.14 [0.41, 3.15] 6 1.11 [0.38, 3.25] 7 2.21 [1.07, 4.59] Not estimable 0.466 [1.44, 15.10] 6 4.66 [1.44, 15.10] 7 2.20 [1.06, 4.58] 8 0.93 [0.24, 3.62] 6 0.40 [0.03, 4.96] 7 0.40 [0.03, 4.96] 8 2.75 [1.15, 6.56] 8 0.90 [0.41, 1.95] 8 3.25 [1.22, 8.69] 6 1.94 [1.18, 3.20]	- -	O.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events	5.35 (P ≤ Intestina Events 111 15 18 15 8 21 26 22 59 6 21 12 24 41 12 24 41 14 71	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710) <u>Events</u> 200 14 12 14 9 48 42 17 50 14 22 15 24 15 12 38 366	type <u>Tota</u> 4 3 3 3 4 4 13 3 3 3 3 4 4 13 5 6 6 11 5 3 3 5 12 81 *	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 9.09 3 5 5 2.69 8 9.33 7 4.19 7 5.76 6 1.99 7 5.98 1 4.09 0 21.09 1 100.09	Odds Ratio tt M-H. Fixed, 95% C 6 4.95 [1.22, 20.10] 6 1.14 [0.41, 3.15] 6 4.69 [1.59, 13.81] 6 1.14 [0.41, 3.15] 6 1.14 [0.41, 3.15] 6 1.11 [0.38, 3.25] 7 2.21 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 6 2.03 [0.24, 3.62] 7 2.00 [1.06, 4.58] 6 0.93 [0.24, 3.62] 8 3.07 [1.32, 7.16] 6 0.40 [0.03, 4.96] 7 2.75 [1.15, 6.56] 6 0.90 [0.41, 1.95] 7 3.25 [1.22, 8.69] 8 1.94 [1.18, 3.20] 7 2.00 [1.59, 2.51]	- -	O.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events Heterogeneity: Chi ² = 1	5.35 (P ≤ Intestina Events 111 15 18 15 8 21 26 22 59 6 21 12 24 41 14 71 384 48.95, df =	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710 14 (P = 0) Diffuse 200 14 12 14 9 48 42 17 50 14 22 15 24 15 24 15 22 38 3666 0.17); I ² =	type Tota 3 3 3 4 4 1 3 3 3 7 7 2 2 6 6 1 1 1 1 1 1 5 3 3 5 1 2 1 8 1 2 8 1 2 2 6%	Weight 7 1.99 0 6.69 7 2.99 0 6.69 3 5 5 2.69 8 9.39 7 5.79 6 1.99 7 5.269 1 4.00 0 21.09 1 100.09	Odds Ratio M-H. Fixed, 95% C 4.95 [1.22, 20, 10] 1.14 [0.41, 3.15] 4.69 [1.59, 13.81] 1.14 [0.41, 3.15] 4.69 [1.59, 13.81] 1.11 [0.38, 3.25] 0.221 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 0.221 [1.07, 4.59] 0.03 [0.24, 3.62] 3.07 [1.32, 7.16] 0.93 [0.24, 3.62] 6 0.90 [0.41, 1.95] 6 3.25 [1.22, 8.69] 1.94 [1.18, 3.20] 2.00 [1.59, 2.51]	-	O.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl	100
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G	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2	5.35 (P Intestina <u>Events</u> 11 15 18 15 8 21 22 59 6 21 12 24 41 14 71 384 18.95, df = Z = 5.99 (F	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710 14 (P = (2 < 0.000 E Variat) Diffuse Events 200 14 12 14 9 48 42 17 50 14 22 15 24 15 24 15 24 38 366 0.17); I ² = 01) mce Wei	type <u>Tote</u> 4 3 3 3 4 4 13 3 3 3 3 3 3 5 12 81 226% ight	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 6.00 5 2.69 8 9.33 7 4.19 7 5.79 6 1.99 7 5.269 1 4.09 0 21.09 1 100.09 Petr Expl(O)	Odds Ratio tt M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.2.01 [1.06, 4.58] 5.2.01 [1.06, 4.58] 5.2.01 [1.06, 4.58] 5.2.01 [1.06, 4.58] 5.2.01 [1.32, 7.16] 5.2.01 [1.32, 7.16]	- 0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl 	100
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LM (2005) Zhang LM (2005) Zhang LM (2005) Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 <u>Study or Subgroup</u> zheng HC (unpublished)	E 5.35 (P < Intestina Events 111 15 18 15 8 21 26 22 59 6 21 12 24 41 14 71 384 48.95, df = Z = 5.99 (F 0- cd) 39.19	0.00001 al type Total 144 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710 14 (P = 0 < 0.000 E Varian 9 40) Diffuse <u>Events</u> 200 14 12 14 9 9 48 42 17 50 14 22 15 24 15 12 38 366 0.17); I ² = 01) mce Wei 21 80	type <u>Tota</u> 4 3 3 3 4 4 1 3 3 3 7 7 2 6 1 1 5 5 12 81 2 26% ight 1 1%	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 6.09 5 2.69 8 9.39 7 5.79 5 12.69 1 4.09 0 21.09 1 100.09 Petr Exp[(O-	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.221 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 5.220 [1.06, 4.58] 5.0307 [1.32, 7.16] 5.040 [0.03, 4.96] 5.275 [1.15, 6.56] 5.090 [0.41, 1.95] 5.25 [1.22, 8.69] 5.200 [1.59, 2.51] 5.00dds Ratio 5.200 [1.59, 2.51] 5.221 [1.68, 2.93]	- - 0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl 	
G	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LM (2005) Zhang LM (2005) Zhang LM (2005) Total (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 1 Study or Subgroup zheng HC(unpublished Lei KF(2012)	E 5.35 (P < Intestina Events 111 15 18 15 18 21 26 22 59 6 21 12 24 41 14 71 384 48.95, df = Z = 5.99 (F 0-1 2 ed) 39.19 2.66	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710 14 (P = (< 0.000) E Varial) Diffuse Events 200 14 12 14 9 48 42 17 50 14 22 15 24 15 12 38 3666 0.17); I ² = 01) mcc Wei 0.21 80 .64 5	type <u>Tota</u> 4 3 3 3 3 4 4 13 3 3 3 3 4 4 13 5 5 12 81 ¹ 26% 81 ¹ 26% 11/2 81 ² 26%	Weight 7 1.99 0 6.69 7 2.99 0 6.69 3 5 5 2.69 8 9.39 7 5.79 5 12.69 1 4.00 0 21.09 1 100.09 Pet Exp[(O-	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20, 10] 4.69 [1.59, 13, 81] 4.69 [1.59, 13, 81] 4.69 [1.59, 13, 81] 5.1.14 [0.41, 3, 15] 5.2.21 [1.07, 4.59] Not estimable 4.66 [1.44, 15, 10] 5.2.02 [1.06, 4.58] 5.0.93 [0.24, 3.62] 5.0.93 [0.25, 2.51] 5.0.94 [1.18, 3.20] 5.0.94 [1.18, 3.20] 5.	0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl 	
G	Test for overall effect: Z = <u>Study or Subgroup</u> Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 <u>Study or Subgroup</u> Zheng HC(unpublishe Lei KF(2012) Lee DY (2008)	$\begin{array}{c} \text{Intestina} \\ \hline \text{Events} \\ 11 \\ 15 \\ 18 \\ 15 \\ 8 \\ 21 \\ 26 \\ 22 \\ 59 \\ 6 \\ 21 \\ 26 \\ 22 \\ 24 \\ 41 \\ 14 \\ 71 \\ 22 \\ 24 \\ 41 \\ 14 \\ 71 \\ 384 \\ 18.95, df = \\ Z = 5.99 (f \\ \hline \begin{array}{c} 0 \\ -10.6 \\ 21 \\ 22 \\ 24 \\ 41 \\ 14 \\ 71 \\ 384 \\ 24 \\ 384 \\ 24 \\ 384 \\ 24 \\ 384 \\ 24 \\ 384 \\ 24 \\ 384 \\ 25 \\ 22 \\ 24 \\ 384 \\ 384 \\ 24 \\ 384 \\ 384 \\ 24 \\ 384 \\ 384 \\ 24 \\ 384 \\ 384 \\ 24 \\ 384 \\ 3$	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 12 35 14 36 102 28 150 710 14 (P = (C < 0.000 E Varian 9 45 9 3 1 8) Diffuse Events 20 14 12 14 9 48 42 17 50 14 22 15 15 24 15 12 38 366 0.17); l ² = 01) mce Wei 3.21 80 3.64 5 3.57 14	type <u>Tote</u> 4 3 3 3 4 4 13 3 3 7 7 2 2 6 6 11 5 3 3 5 12 81 2 26% ight .1% .9% .9% .9% .0%	Weight 7 1.99 0 6.66 7 2.99 0 6.66 4 9.09 3 5 5 2.66 8 9.33 7 4.19 7 5.73 6 1.99 5 12.69 1 4.09 5 12.69 1 100.09 1 100.09 Pett Exp[(O-	Odds Ratio t. M-H. Fixed, 95% C 4.95 [1.22, 20.10] 5.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.20 [1.06, 4.58] 5.20 [1.06, 4.58] 5.20 [1.02, 4.362] 5.20 [1.02, 4.362] 5.20 [1.22, 8.69] 5.20 [1.59, 2.51] 5.20 [1.59, 2.51] 5.20 [1.59, 2.51] 5.20 [1.59, 5.55] 5.29 [0.15, 0.57] 5.20 [0.15, 0	- - 0.01	0.1 1 10 Stage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl 	100
G	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2005) Zhang LP (2012) Zheng HC (2008) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 3 Study or Subgroup zheng HC(unpublished Lei KF(2012) Lee DY (2008)		0.00001 al type <u>Total</u> 14 30 26 30 36 38 58 27 74 12 35 14 12 35 14 12 28 150 710 710 14 (P = (C < 0.000) E Varia 9 45 9 31 8 E Varia 9 45 9 31 8 E Varia 9 45 9 31 8 8 8 8 8 8 8 8 8 8 8 8 8) Diffuse Events 20 14 12 14 9 48 42 17 50 14 22 15 24 4 15 12 38 366 0.17); I ² = 01) mce Wei 0.21 80 3.657 14	type Tota 4 3 3 3 4 4 13 3 3 3 3 4 4 13 3 3 3 3 3 3 4 4 13 3 3 3 3 4 4 13 3 3 3 3 4 4 13 3 3 3 3 3 3 3 3 3 3 3 3 3	Weigh 7 1.99 0 6.69 7 2.99 0 6.69 4 9.09 3 5 5 2.69 8 9.33 7 4.19 7 5.79 6 1.99 7 5.40 9 21.09 1 100.09 1 100.09	Odds Ratio tt. M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.15 [1.15, 0.56] 5.15 [1.15, 0.56] 5.15 [1.15, 0.56] 5.15 [1.22, 8.69] 5.15 [1.22, 8.69] 5.15 [1.22, 8.69] 5.15 [1.22, 8.69] 5.20 [1.59, 2.51] 5.20 [1.59, 2.51] 5.20 [1.59, 2.51] 5.20 [0.75, 5.85] 5.29 [0.75, 5.85] 5.29 [0.15, 0.57]	- - 0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl 	100
G	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2005) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 1 Study or Subgroup zheng HC(unpublishe Lei KF(2012) Lee DY (2008)		0.00001 al type Total 144 30 266 30 366 388 588 27 744 122 355 14 366 102 288 150 710 14 (P = (2 < 0.000) E Variar 9 32 1 8) Diffuse Events 200 14 12 14 9 48 42 17 50 14 22 15 24 15 24 15 24 15 24 55 12 38 366 0.17); I ² = 01) mce Wei 0.21 80 3.657 14 100	type Tote 4 3 3 3 3 3 3 3 3 3 3 3 3 3	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 6.00 5 2.69 8 9.33 7 4.19 7 5.79 6 1.99 7 5.269 1 4.09 0 21.09 1 100.09 Petr Exp[(O-	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.1.14 [0.41, 3.15] 5.2.12 [1.07, 4.59] Not estimable 5.2.0 [1.06, 4.58] 5.2.0 [1.06, 4.58] 5.2.0 [1.06, 4.58] 5.2.0 [1.06, 4.58] 5.2.0 [1.06, 4.58] 5.2.0 [0.033, 0.24, 3.62] 5.2.0 [0.159, 2.51] 5.2.0 [1.59, 2.51] 5.2.0 [0.75, 5.85] 5.2.9 [0.150, 0.57] 5.2.6 [1.30, 2.14]	- 0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl 	100
G	Test for overall effect: Z =		0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 36 102 28 150 710 14 (P = (0 < 0.000 E Varian 9 33 1 8) Diffuse Events 200 14 12 14 9 9 48 42 17 50 14 22 15 24 15 12 38 366 0.17); I ² = 01) mce Wei 3.57 14 100	type Tota 4 3 3 3 4 4 13 3 3 7 7 2 6 11 5 5 12 81 2 26% ight .1% .9% .0%	I Weigh 7 1.99 0 6.69 7 2.99 0 6.69 4 6.09 5 2.69 8 9.33 7 4.19 7 5.79 6 1.99 7 5.99 5 12.69 1 4.09 0 21.09 1 100.09 Petr Exp[(O	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20, 10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.221 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 5.220 [1.06, 4.58] 5.030 [1.32, 7.16] 6.0,93 [0.24, 3.62] 6.0,93 [0.24, 3.62] 6.0,93 [0.24, 3.62] 6.0,93 [0.24, 3.62] 6.0,90 [0.41, 1.95] 6.3,25 [1.22, 8.69] 6.0,90 [0.41, 1.95] 6.3,25 [1.22, 8.69] 6.1,94 [1.18, 3.20] 7.222 [1.68, 2.93] 2.09 [0.75, 5.85] 0.29 [0.15, 0.57] 1.66 [1.30, 2.14]	- - 0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl 0.1 1 10 Diffuse type Intestinal type Peto Odds Ratio Exp[(0-E) / V], Fixed, 95% Cl	
Б	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LM (2005) Zhang LM (2005) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events Heterogeneity: Chi ² = 1 Test for overall effect: 2 Study or Subgroup zheng HC(unpublishte Lei KF(2012) Lee DY (2008) Total (95% CI) Total (95% CI) Total events Hotoroconsite Ch ²		0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 25 14 36 102 28 150 710 14 (P = (2 < 0.000 E Variation 49 9 33 1 8 5 5 5 5 5 5 5 5 5 5 5 5 5) Diffuse Events 200 14 12 14 9 9 48 42 17 50 14 22 15 24 15 12 38 366 0.17); I ² = 01) mcc Wei 3.57 14 100	type Tota 4 3 3 3 3 4 4 13 3 3 3 3 4 4 13 5 6 6 11 5 5 12 81 2 26% 11 5 5 12 81 18	Weight 7 1.99 0 6.69 7 2.99 0 6.69 4 6.09 5 2.69 8 9.39 7 5.79 6 1.99 7 5.266 1 4.00 0 21.09 1 100.09 Pett Exp[(O-	Odds Ratio t M-H. Fixed, 95% C 4.95 [1.22, 20, 10] 4.69 [1.59, 13, 81] 4.69 [1.59, 13, 81] 5.14 [0.41, 3, 15] 5.21 [1.07, 4.59] Not estimable 4.66 [1.44, 15, 10] 5.221 [1.06, 4.58] 5.03 [1.32, 7.16] 6.0, 93 [0.24, 3.62] 7.30 [1.32, 7.16] 6.0, 03 [0.24, 3.62] 7.30 [1.32, 7.16] 7.30 [1.30, 2.14]	0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H, Fixed, 95% Cl 0.1 1 10 Diffuse type Intestinal type Peto Odds Ratio Exp[(0-E) / V], Fixed, 95% Cl	100
G	Test for overall effect: Z = Study or Subgroup Bai YX (2007) Chen AJ (2009) Cheng SH (2012) Deng W (2006) Gao P (2007) He Y (2007) Ito R (2004) Kim SM(2007) Lee DY (2008) Li JJ (2004) Liang QL (2007) Son HJ (2002) Wang MC (2004) Zhang LP (2012) Zheng HC (2008) Total (95% CI) Total events Heterogeneity: Chi² = 1 Test for overall effect: 2 Study or Subgroup zheng HC (unpublishte) Lei KF(2012) Lee DY (2008) Total (95% CI) Total events Heterogeneity: Chi² = 7 Total (95% CI) Total events Lei KF(2012) Lee DY (2008) Total (95% CI) Total events Heterogeneity: Chi² = 1 Total (95% CI) Total events Heterogeneity: Chi² = 1 Total (95% CI) <t< td=""><td>= 5.35 (P < Intestina Events 11 15 18 15 18 21 26 22 59 6 21 22 24 41 14 71 384 18.95, df = Z = 5.99 (F 0-1 2.63 -10.6 = 30.41, df + Z = 2.90</td><td>0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 12 35 14 36 102 28 150 710 14 (P = (C 2 < 0.000 E Varian 9 45 9 3 1 8 5 5 5 5 5 5 5 5 5 5 5 5 5</td><td>) Diffuse Events 20 14 12 14 9 48 42 17 50 14 22 15 15 24 15 12 38 366 0.17); l² = 01) mce Wei 3.57 14 100 100 100 100 100 100 100 1</td><td>type <u>Tote</u> 4 3 3 3 3 3 4 4 13 3 3 7 7 2 2 6 6 11 15 3 3 5 12 81 - 26% 11 26% 0.0% 0.0%); ² = §</td><td>Weight 7 1.99 0 6.66 7 2.99 0 6.66 4 9.09 3 5 5 2.66 8 9.39 7 4.19 7 5.79 6 1.99 5 12.69 1 4.09 0 21.09 1 100.09 Pett Exp[(O-</td><td>Odds Ratio t. M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 4.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.221 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 5.220 [1.06, 4.58] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.90 [0.41, 1.95] 6.3.25 [1.22, 8.69] 6.1.94 [1.18, 3.20] 7.20 [1.59, 2.51] 5.0 Odds Ratio E) / V], Fixed, 95% CI 2.22 [1.68, 2.93] 2.09 [0.75, 5.85] 0.29 [0.15, 0.57] 1.66 [1.30, 2.14]</td><td>0.01</td><td>0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl 0.1 1 10 Diffuse type Intestinal type Peto Odds Ratio Exp[(0-E) / V], Fixed, 95% Cl 0.1 1 10 Diffuse type Intestinal type Peto Odds Ratio</td><td>100</td></t<>	= 5.35 (P < Intestina Events 11 15 18 15 18 21 26 22 59 6 21 22 24 41 14 71 384 18.95, df = Z = 5.99 (F 0-1 2.63 -10.6 = 30.41, df + Z = 2.90	0.00001 al type Total 14 30 26 30 36 38 58 27 74 12 35 14 12 35 14 36 102 28 150 710 14 (P = (C 2 < 0.000 E Varian 9 45 9 3 1 8 5 5 5 5 5 5 5 5 5 5 5 5 5) Diffuse Events 20 14 12 14 9 48 42 17 50 14 22 15 15 24 15 12 38 366 0.17); l ² = 01) mce Wei 3.57 14 100 100 100 100 100 100 100 1	type <u>Tote</u> 4 3 3 3 3 3 4 4 13 3 3 7 7 2 2 6 6 11 15 3 3 5 12 81 - 26% 11 26% 0.0% 0.0%); ² = §	Weight 7 1.99 0 6.66 7 2.99 0 6.66 4 9.09 3 5 5 2.66 8 9.39 7 4.19 7 5.79 6 1.99 5 12.69 1 4.09 0 21.09 1 100.09 Pett Exp[(O-	Odds Ratio t. M-H. Fixed, 95% C 4.95 [1.22, 20.10] 4.14 [0.41, 3.15] 4.69 [1.59, 13.81] 4.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.14 [0.41, 3.15] 5.221 [1.07, 4.59] Not estimable 4.66 [1.44, 15.10] 5.220 [1.06, 4.58] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.93 [0.24, 3.62] 6.0.90 [0.41, 1.95] 6.3.25 [1.22, 8.69] 6.1.94 [1.18, 3.20] 7.20 [1.59, 2.51] 5.0 Odds Ratio E) / V], Fixed, 95% CI 2.22 [1.68, 2.93] 2.09 [0.75, 5.85] 0.29 [0.15, 0.57] 1.66 [1.30, 2.14]	0.01	0.1 Stage 3-4 Stage 0-2 Odds Ratio M-H. Fixed, 95% Cl 0.1 1 10 Diffuse type Intestinal type Peto Odds Ratio Exp[(0-E) / V], Fixed, 95% Cl 0.1 1 10 Diffuse type Intestinal type Peto Odds Ratio	100

Figure 2: Forest plot for the relationship between maspin expression and clinicopathological parameters of gastric cancer. (A) gastric carcinogenesis (cancer vs normal mucosa); (B) gastric carcinogenesis (cancer vs dysplasia); (C) correlation between sex and maspin expression (male vs female); (D) correlation between depth of invasion and maspin expression (T_{is-2} vs T_{3-4}); (E) correlation between lymph node metastasis (LN) and maspin expression (LN- vs LN+); (F) correlation between TNM staging and maspin expression (0–II vs III–IV); (G) correlation between differentiation and maspin (intestinal-type vs diffuse-type). (H) correlation between survival rate and maspin expression.

- J - F F F	Male	•	Fema	ale		Odds Ratio		Odds Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 9	5% CI	
Gurzu S (2016)	91	120	46	60	30.5%	0.96 [0.46, 1.98]				
Lei KF (2012)	54	82	33	45	30.0%	0.70 [0.31, 1.57]				
Yu (2007)	102	170	32	57	39.5%	1.17 [0.64, 2.15]				
of the Accelerated F						•				
Total (95% CI)		372		162	100.0%	0.96 [0.65, 1.44]		•		
Total events	247		111							
Heterogeneity: Chi ² =	= 1.00, df = 3	2 (P = 0	0.61); l ² =	= 0%					+	
Test for overall effect	t: Z = 0.18 (I	P = 0.8	6)				0.01	0.1 1	10	100
Nuclear masnin			,					Female Mai	e	
ivucicai maspin	Male		Fema	le		Odds Ratio		Odds Ratio)	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95	% CI	
Gurzu S (2016)	52	120	26	60	38.4%	1.00 [0.54, 1.87]				
Lei KF (2012)	38	82	21	45	28.4%	0.99 [0.48, 2.05]				
Yu (2007)	86	170	23	57	33.2%	1.51 [0.82, 2.78]		+		
Total (95% CI)		372		162	100.0%	1.17 [0.80, 1.69]		•		
Total events	176		70							
Heterogeneity: Chi ² =	1.14, df = 2	(P = 0)	.57); I ² =	0%			0.01		10	100
Test for overall effect:	Z = 0.81 (P	= 0.42	2)				0.01	U.1 1 Female Male	10	100
_								remaie wale		
3										
Cytoplasmic maspin						Odda Datia		Odda Dati	-	
Study on Subanova	LN-	Tetel	LN+	Tatal	Mainha I	Odds Ratio		Odds Ratio		
Study or Subgroup	Events		Events	Total	weight i	<u>и-н, капdom, 95% С</u>		M-H, Kandom, S	95% CI	
Gurzu S (2016)	29	35	108	145	30.3%	1.66 [0.64, 4.30]				
Lei KF (2012)	9	40	50	87	32.1%	0.21 [0.09, 0.51]				
Yu (2007)	69	138	65	99	31.1%	0.52 [0.31, 0.89]				
Total (95% CI)		213		331	100.0%	0 56 [0 21 1 49]				
Total (35% CI)	107	215	222	551	100.076	0.00 [0.21, 1.49]				
Hotorogonoity: Tau ² -	0 50: Chi2 -	0.75	223 df = 2 (D	- 0 009	1. 12 - 70%		—			
neterogeneity. rau -	0.59, 011 -	- 9.75, 0	ui – 2 (F	- 0.008	(1 - 19)		0.01	0.1 1	10	100
Test for overall effect:	7 = 1.17 / D	- 0.24	\ \				0.0.			
Test for overall effect:	Z = 1.17 (P	= 0.24))					LN+ LN-	-	
Test for overall effect: Nuclear maspin	Z = 1.17 (P	= 0.24))					LN+ LN-		
Test for overall effect: Nuclear maspin	Z = 1.17 (P LN-	= 0.24)) LN+			Odds Ratio		LN+ LN- Odds Ratio		
Test for overall effect: Nuclear maspin Study or Subgroup	Z = 1.17 (P LN- Events T	= 0.24)) LN+ Events 1	fotal V	Veight N	Odds Ratio I-H. Random. 95% CI		LN+ LN- Odds Ratio <u>M-H. Random. 9</u>	- 5% Cl	
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016)	Z = 1.17 (P LN- Events T 10	= 0.24) otal E 35) LN+ Events 1 68	<u>Fotal V</u> 145	<u>Veight N</u> 31.3%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01]		UN+ UN- Odds Ratio M-H. Random. 9	- 5% Cl	
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012)	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30	= 0.24) otal E 35 40) LN+ <u>Events</u> 68 57	<u>Fotal V</u> 145 87	<u>Veight N</u> 31.3% 30.3%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66]		UN+ UN Odds Ratio	- 5% Cl	
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007)	Z = 1.17 (P LN- Events T 10 30 57	= 0.24) <u>otal E</u> 35 40 138) <u>Events</u> 68 57 62	<u>Fotal V</u> 145 87 99	<u>Veight N</u> 31.3% 30.3% 38.3%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71]		LN+ LN Odds Ratio <u>M-H. Random. 9</u>	- 5% Cl	
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007)	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57	= 0.24) <u>otal E</u> 35 40 138) Events 1 68 57 62	<u>Fotal V</u> 145 87 99	<u>Veight N</u> 31.3% 30.3% 38.3%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71]		LN+ LN- Odds Ratio	- 5% Cl	
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI)	Z = 1.17 (P LN- <u>Events T</u> 10 30 57	= 0.24) <u>fotal E</u> 35 40 138 213) Events 1 68 57 62	T <u>otal V</u> 145 87 99 331 1	Veight N 31.3% 30.3% 38.3% 00.0%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41]		LN+ LN- Odds Ratio <u>M-H. Random. 9</u>	- 5% Cl	
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 2.05 012	= 0.24) <u>Total E</u> 35 40 138 213 7 00) Events 1 68 57 62 187	<u>Fotal V</u> 145 87 99 331 1	Veight N 31.3% 30.3% 38.3% 00.0%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41]		LN+ LN- Odds Ratio M-H. Random. 9	- 5% CI	
Test for overall effect: Nuclear maspin <u>Study or Subgroup</u> Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² =	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² =	= 0.24) <u>fotal E</u> 35 40 138 213 7.23, d) Events 1 68 57 62 187 if = 2 (P =	Fotal V 145 87 99 331 1 = 0.03);	<u>Veight N</u> 31.3% 30.3% 38.3% 00.0% I ² = 72%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41]	0.01	LN+ LN- Odds Ratio M-H. Random, 9	- <u>-</u> - 10	100
Test for overall effect: Nuclear maspin <u>Study or Subgroup</u> Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	Z = 1.17 (P) <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P)	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27)) Events 1 68 57 62 187 if = 2 (P =	<u>Fotal V</u> 145 87 99 331 1 = 0.03);	Veight N 31.3% 30.3% 38.3% 00.0% I ² = 72%	Odds Ratio <u>I-H. Random, 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41]	0.01	LN+ LN- Odds Ratio M-H. Random. 9	- - - - 10	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27)) <u>Events 1</u> 68 57 62 187 if = 2 (P =	Fotal V 145 87 99 331 1 = 0.03);	<u>Veight N</u> 31.3% 30.3% 38.3% 00.0% I ² = 72%	Odds Ratio <u>I-H. Random, 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41]	0.01	UN+ LN- Odds Ratio M-H. Random, 9	- - - - 10	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . C Cytoplasmic maspin	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P =	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27)) <u>Events</u> 68 57 62 187 If = 2 (P =	Total V 145 87 99 331 1 = 0.03);	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41]	0.01	UN+ LN- Odds Ratio M-H. Random, 9	- - - - 10	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype) Events 1 68 57 62 187 if = 2 (P =	<u>Fotal V</u> 145 87 99 331 1 = 0.03); type	Veight N 31.3% 30.3% 38.3% 00.0% I ² = 72%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] Odds Ratio	 0.01	UN+ LN- Odds Ratio M-H. Random, 9 Odds Ratio	- - - - 10	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t <u>Events</u>	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u>) <u>Events</u> 68 57 62 187 if = 2 (P = Diffuse 1 <u>Events</u>	Total V 145 87 99 331 1 = 0.03); type Total	Veight N 31.3% 30.3% 38.3% 00.0% I ² = 72% Weight	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] Odds Ratio M-H. Random. 95% C		LN+ LN- Odds Ratio M-H. Random. 9 Odds Ratio	- 5% CI - 10 5% CI	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014)	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t <u>Events</u> 81	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132) <u>Events</u> 68 57 62 187 if = 2 (P = Diffuse t <u>Events</u> 40	Total V 145 87 99 331 1 = 0.03); type Total 59	Veight N 31.3% 30.3% 38.3% 00.0% I ² = 72% Weight 27.1%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] Odds Ratio <u>M-H. Random. 95% C</u> 0.75 [0.39, 1.44]	0.01	LN+ LN- Odds Ratio M-H. Random. 9 0.1 1 LN+ LN- Odds Ratio M-H. Random. 9	- - - - 10 5% CI	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016)	Z = 1.17 (P <u>LN-</u> <u>Events T</u> 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t <u>Events</u> 81 68	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84) <u>Events</u> 68 57 62 187 if = 2 (P = Diffuse (<u>Events</u> 40 69	Total V 145 87 99 331 1 = 0.03); type Total 59 96	Veight N 31.3% 30.3% 38.3% 00.0% I ² = 72% Weight 27.1% 25.7%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] Odds Ratio <u>M-H. Random. 95% C</u> 0.75 [0.39, 1.44] 1.66 [0.82, 3.36]	0.01	UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 UN+ UN- Odds Ratio M-H. Random. 9	- - - - 10 5% CI	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14) Events 1 68 57 62 187 If = 2 (P = Diffuse 1 Events 40 69 81	Fotal V 145 87 99 331 1 = 0.03); 1 = 0.03); 1 type Total 59 96 113 1	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% <u>Weight</u> 27.1% 25.7% 16.7%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] Odds Ratio M-H. Random, 95% C 0.75 [0.39, 1.44] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92]	0.01	LN+ LN- Odds Ratio M-H. Random. 9 Odds Ratio 0.1 1 LN+ LN- Odds Ratio M-H. Random. 9	- - - - 10 - 5% Cl	100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P Intestinal t Events 81 68 6 77	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125) Events 1 68 57 62 187 if = 2 (P = Diffuse 1 Events 40 69 81 60	Total V 145 87 99 331 1 = 0.03); - type Total - 59 96 - 113 115 -	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% 27.1% 27.1% 25.7% 16.7% 30.5%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] Odds Ratio M-H. Random. 95% C 0.75 [0.39, 1.44] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46]	0.01	LN+ LN- Odds Ratio M-H. Random. 9 0.1 1 LN+ LN- Odds Ratio M-H. Random. 9		100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Testal (05% Ci)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 67	= 0.24) <u>fotal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 255) <u>Events</u> 68 57 62 187 187 if = 2 (P = Diffuse (<u>Events</u> 40 69 81 60	Total V 145 87 99 331 1 = 0.03); 1 = 0.03); 1 Sype 59 9 91 113 115	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] Odds Ratio M-H. Random, 95% CC 0.75 [0.39, 1.44] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46]	0.01	LN+ LN- Odds Ratio M-H. Random, 9 0.1 1 LN+ LN- Odds Ratio M-H. Random, 9		100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P Intestinal t Events 81 68 6 77	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 355) <u>Events</u> 68 57 62 187 if = 2 (P = Diffuse + <u>Events</u> 40 69 81 60	Cotal V 145 87 99 331 1 = 0.03); - = 0.03); - type - - 59 - - 913 - - 115 - -	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5% 100.0%	Odds Ratio <u>I-H. Random, 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.30, 1.44] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79]	0.01	UN+ UN- Odds Ratio M-H. Random, 9 0.1 1 UN+ UN- Odds Ratio M-H. Random, 9		100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: . C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P Intestinal t Events 81 68 6 77 232 205 (Chi ² = 200)	= 0.24) otal E 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 125 355) <u>Events</u> 68 57 62 187 if = 2 (P = 187 if = 2 (P = 250 250	Total V 145 87 99 331 1 = 0.03); 1 = 0.03); 1 = 0.03); 1 59 96 113 115 383 0.00,000	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5% 100.0%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79]	0.01	UN+ UN- Odds Ratio M-H. Random, 9 0.1 1 UN+ UN- Odds Ratio M-H. Random, 9		100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = C	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 6 2 = 0.10 (P = 6 2 = 0.	= 0.24) <u>fotal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 355 3.98, df) <u>Events</u> 68 57 62 187 if = 2 (P = 187 if = 2 (P = 200 81 60 250 = 3 (P = 10)	Cotal V 145 87 99 331 1 = 0.03); 1 = 0.03); 1 59 96 113 115 383 0.03); 12	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5% 100.0% = 67%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79]	0.01	UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 UN+ UN- Odds Ratio M-H. Random. 9		100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P =	= 0.24) <u>fotal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 355 3.98, df 0.92)) Events 1 68 57 62 187 if = 2 (P = 187 if = 2 (P = 200 81 60 250 = 3 (P = 1)	Fotal V 145 87 99 331 1 = 0.03); = 59 96 113 115 383 0.03); 12	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5% 100.0% = 67%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] Odds Ratio <u>M-H. Random. 95% C</u> 0.75 [0.39, 1.44] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79]	0.01	UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 UN+ UN- Odds Ratio M-H, Random, 9		
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Nuclear maspin	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P = 1) 242 25; Chi ² = 10 242 25; Chi ² = 10 242 242 242 242 242 242 242 24	= 0.24) otal E 35 40 138 213 7.23, d = 0.27) ype Total 132 84 14 125 355 3.98, df 0.92) tupa) Events 1 68 57 62 187 16 27 187 19 187 19 187 187 19 187 19 187 19 187 19 187 19 19 19 19 10 10 10 10 10 10 10 10 10 10	Fotal V 145 87 99 331 1 = 0.03); = type Total 59 96 113 115 383 0.03); 12	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5% 100.0% = 67%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] Odds Ratio <u>M-H. Random. 95% C</u> 0.75 [0.39, 1.44] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79]	0.01	UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 Diffuse type Intes		
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = C Test for overall effect: Z Nuclear maspin	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P = Intestinal Events	= 0.24) <u>otal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 355 3.98, df 0.92) type <u>Total</u>) LN+ Events 1 68 57 62 187 if = 2 (P = Diffuse 1 Events 40 69 81 60 250 = 3 (P = Diffuse 2 Events	Fotal V 145 87 99 331 1 = 0.03); = 59 96 113 115 383 0.03); 12 0.03); 12 12 383 0.03); 12	Veight N 31.3% 30.3% 38.3% 00.0% ² = 72% Veight 27.1% 25.7% 16.7% 30.5% 100.0% = 67%	Odds Ratio <u>I-H. Random. 95% CI</u> 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79] Odds Ratio M H. Fixed 25% C	0.01	UN+ UN- Odds Ratio M-H. Random, 9 0.1 1 UN+ UN- Odds Ratio M-H. Random, 9 0.1 1 Diffuse type Intes Odds Ratio		 100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = C Test for overall effect: Z Nuclear maspin	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P = 10) Intestinal Events 2 = 0.25; Chi ² = 2 2 = 0.25; Chi ² = 0.25; Chi ² = 2 2 = 0.25; Chi ²	= 0.24) otal E 35 40 138 213 7.23, d = 0.27) ype Total 132 84 14 125 355 3.98, df 0.92) type Total) Events 1 68 57 62 187 if = 2 (P = Diffuse 1 Events 40 69 81 60 250 = 3 (P = Diffuses 250 = 3 (P = Diffuses 250	Total V 145 87 99 331 1 = 0.03); = 0.03); type Total 115 383 115 383 0.03); 12 12 = type Total 15	Veight N 31.3% 30.3% 30.3% 38.3% 00.0% 12 12 72% 27.1% 25.7% 16.7% 30.5% 100.0% = 67% 1 Weight 2 -24.0%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79] Odds Ratio M-H. Fixed, 95% CC 0.24 [0.40, 0.00]	0.01	UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 Diffuse type Intes Odds Ratio		 100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = C Test for overall effect: Z Nuclear maspin Study or Subgroup Gurzu S (2014) Gurzu S (2014)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 67 77 232 0.25; Chi ² = 8 Z = 0.10 (P = Intestinal Events 36 32	= 0.24) <u>fotal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 355 3.98, df 0.92) type <u>Total</u> 132) Events 1 68 57 62 187 187 187 187 187 187 187 187	Total V 145 87 99 331 1 = 0.03); = 0.03); Total 99 96 113 115 383 0.03); 12 383 0.03); 12 5 * type Total 5	Veight N 31.3% 30.3% 30.3% 38.3% 00.0% 12 12 72% 27.1% 25.7% 16.7% 30.5% 100.0% = 67% 1 Weight 9 31.8% 20 21.8%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79] Odds Ratio M-H. Fixed. 95% C 0.34 [0.18, 0.64] 0.72 [0.14, 0.68]	0.01	UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 Diffuse type Intess Odds Ratio		100
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = C Test for overall effect: Z Nuclear masnin Study or Subgroup Gurzu S (2014) Gurzu S (2014) Gurzu S (2014) Gurzu S (2014) Gurzu S (2016) Lei KF (2012)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P = Intestinal Events 36 33 2	= 0.24) <u>fotal E</u> 35 40 138 213 7.23, d = 0.27) ype <u>Total</u> 132 84 14 125 355 3.98, df 0.92) type <u>Total</u> 132 84 4) Events 1 68 57 62 187 187 187 187 187 187 187 187	Total V 145 87 99 331 1 = 0.03); = 59 96 113 115 383 0.03); 12 • type	Veight N 31.3% 30.3% 38.3% 00.0% 2 = 72% 27.1% 25.7% 16.7% 30.5% 100.0% = 67% 31.8% 6 26.1% 2.18%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79] Odds Ratio M-H. Fixed, 95% C 0.34 [0.18, 0.64] 0.73 [0.41, 1.33] 0.96 0.71 [0.71, 1.32]	0.01	UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 Diffuse type Intess Odds Ratio M-H. Fixed. 95		
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Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: . C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = 0 Test for overall effect: .2 Nuclear maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P = Intestinal Events 36 33 3 62	= 0.24) fotal E 35 40 138 213 7.23, d = 0.27) ype Total 132 84 125 3.98, df 0.92) type Total 132 84 14 125) LN+ <u>Events</u> 187 62 187 62 187 16 2 (P = 0 0 0 187 187 187 187 187 187 187 187	Ids 145 87 99 331 1 = 0.03); Total 59 96 113 115 383 0.03); I ² • type 50 96 113 383 0.03); I ² • type 59 91 112 51 92 112	Veight N 31.3% 30.3% 38.3% 00.0% I² = 72% I² = 72% Weight 27.1% 25.7% 30.5% 100.0% = 67% I Weight 9 31.8% 6 26.1% 3 9.9% 5 32.2%	Odds Ratio I-H. Random, 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79] Odds Ratio M-H. Fixed, 95% C 0.34 [0.18, 0.64] 0.73 [0.41, 1.33] 0.28 [0.07, 1.05] 0.90 [0.54, 1.50]	0.01	UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 UN+ UN- Odds Ratio M-H, Random, 9 0.1 1 Diffuse type Intes Odds Ratio M-H, Fixed, 95		
Test for overall effect: Nuclear maspin Study or Subgroup Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: . C Cytoplasmic maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Nuclear maspin Study or Subgroup Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Gurzu S (2014) Gurzu S (2016) Lei KF (2012) Yu (2007) Total (95% Cl)	Z = 1.17 (P LN- Events T 10 30 57 97 0.35; Chi ² = Z = 1.10 (P = Intestinal t Events 81 68 6 77 232 0.25; Chi ² = 8 Z = 0.10 (P = Intestinal Events 36 33 3 62	= 0.24) fotal E 35 40 138 213 7.23, d = 0.27) ype Total 132 84 14 125 3.98 , df 0.92) type Total 132 84 14 125 3.98 , df 0.92) type Total 132 3.55 3.98 , df 0.92) type Total 132 3.55 3.98 , df 0.92) type Total 132 3.55 3.98 , df 0.92) 5.5 5.98 , df 0.92) 5.5 5.98 , df 0.92) 5.5 5.98 , df 0.92) 5.5 5.98 , df 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5) LN+ Events 1 68 57 62 187 187 167 207 187 187 187 187 187 187 187 18	Ids 145 87 99 331 = 0.03); = 0.03); Total 59 96 113 115 383 0.03); I ² = type 50 90 115 383 0.03); I ² = type 50 90 11: 91 11: 92	Veight N 31.3% 30.3% 30.3% 38.3% 00.0% 12 27.1% 25.7% 16.7% 30.5% 100.0% = 67% 16.7% 30.5% 100.0% = 67% I Weight 9 31.8% 6 26.1% 3 9.9% 5 32.2%	Odds Ratio I-H. Random. 95% CI 0.45 [0.20, 1.01] 1.58 [0.68, 3.66] 0.42 [0.25, 0.71] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 0.64 [0.29, 1.41] 1.66 [0.82, 3.36] 0.30 [0.10, 0.92] 1.47 [0.88, 2.46] 0.97 [0.53, 1.79] Odds Ratio M-H. Fixed, 95% C 0.34 [0.18, 0.64] 0.73 [0.41, 1.33] 0.28 [0.07, 1.05] 0.90 [0.54, 1.50] 0.92 [0.45, 0.55]	0.01	UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 UN+ UN- Odds Ratio M-H. Random. 9 0.1 1 Diffuse type Intes Odds Ratio		
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Figure 3: Forest plot for the relationship between cytoplasmic or nuclear maspin expression and clinicopathological parameters of gastric cancer. (A) correlation between sex and maspin expression (male vs female); (B) correlation between lymph node metastasis (LN) and maspin expression (LN– vs LN+); (C) correlation between differentiation and maspin (intestinal-type vs diffuse-type).





Figure 4: Funnel plot for publication bias test between maspin expression and gastric carcinogenesis or progression. The bias was analyzed about risk degrees of maspin expression in gastric mucosa (**A**) and dysplasia (**B**) for gastric carcinogenesis. Additionally, it was tested between maspin expression and clinicopathological features of gastric cancer, including sex (**C**), depth of invasion (**D**), lymph node metastasis (**E**), TNM staging (**F**), and differentiation (**G**) and prognosis (**H**). The bias was analyzed between cytoplasmic or nuclear maspin expression and clinicopathological features of gastric cancer, including age (**I**), lymph node metastasis (**J**), and differentiation (**K**).

Another explanation might be disadvantage of tissue microarray: too small sample not enough to represent the overall appearance. If the area of maspin negativity was frequently selected, the positive rate of maspin was decreased. Although Dabiri et al. [53] found that *SERPINB5* mRNA level was considerably lower in the cancer samples compared with normal breast samples, up-regulated expression of *SERPINB5* mRNA was observed from 2 databases in line with 8-fold increase of *SERPINB5*



Figure 5: *SERPINB5* mRNA expression in gastric carcinogenesis and subsequent progression. Cui's and Cho's datasets were employed for bioinformatics analysis to analyze *SERPINB5* mRNA expression during gastric carcinogenesis. A higher maspin expression was detectable in gastric cancer than that in normal gastric mucosa ((A), p < 0.05), even stratified into intestinal- (B), diffuse- (C), and mixed-type (D) carcinomas by Lauren's classification. TCGA database shows that *SERPINB5* was more expressed in gastric cancer with than without Barrett's esophagus ((E), p < 0.05). *SERPINB5* expression was negatively correlated with T staging (F) and TNM staging (G) of gastric cancers (p < 0.05). According to Forester's database, there appeared a higher *SERPINB5* expression in gastric intestinal- than diffuse- type carcinomas ((H), p < 0.05).

First author	Year	Country	Ethnicity	Antibody source	Cases	Ctronl	Risk to cancer	Outcome	Quality
Ito R	2004	Japan	Asian	Novo	100		Up		8
Terashima M	2005	Japan	Asian	Pharm	78				8
Yu M	2007	Japan	Asian	Novo	237	23	Up	Neg	9
Zheng HC	2008	Japan	Asian	Novo					8
Gurzu S	2014	Romania	Romanian	Novo	191				8
Gurzu S	2016	Romania	Romanian	Novo	180				8
Kim SM	2005	Korea	Asian	Pharm	62	62	Up		9
Kim YJ	2008	Korea	Asian	BD	109				8
Lee DY	2008	Korea	Asian	Cayman	152	152	Down	Pos	8
Son HJ	2002	Korea	Asian	Pharm	30	26	Up		7
Lei KF	2012	China	Asian	Novo	120			Neg	8
Lei KF	2012	China	Asian	Novo	127				8
Li JJ	2004	China	Asian	Novo	39	39	Up		8
Wang MC	2004	China	Asian	Novo	113	182	Down		8
Bai YX	2007	China	Asian	Maxin	61	10	Down		7
Chen AJ	2009	China	Asian	Neomarker	60	20	Down		7
Cheng SH	2012	China	Asian	Santa	63	20	Down		7
Deng W	2006	China	Asian	Neomarker	60	20	Down		7
Gao P	2007	China	Asian	Neomarker	80	20	Down		7
He Y	2007	China	Asian	Neomarker	172	24	Down		7
Liang QL	2007	China	Asian	Neomarker	102	102	Down		8
Zhang LM	2005	China	Asian	Neomarker	137	54	Down		8
Zhang LP	2012	China	Asian	Neomarker	79	65	Down		8

Table 1: Main characteristics of eligible studies

Note: up, up-regulated; down, down-regulated; Pos, positive correlation; Neg, negative correlation.

mRNA in gastric cancer [26]. Lu et al. [54] found that *SERPINB5* mRNA expression was up-regulated in pulmonary adenocarcinoma samples in comparison to the adjacent normal tissues. This is not surprising since mRNA levels do not usually predict the corresponding protein levels because it takes a long distance from mRNA to functional protein by translation and posttranslational modification.

Previously, we found that the high expression of cytoplasmic and nuclear maspin was positively correlated with aggressive parameters of gastric cancer, including invasion, metastasis and tumor size [27]. Pföhler el al. [55] found that maspin expression in the invasive margin of primary melanomas might reflect aggressive phenotypes, including Clark level, tumor thickness and disease stage. In contrast, our findings showed maspin expression was inversely linked to depth of invasion, TNM staging and dedifferentiation of gastric cancer regardless of its mRNA and protein, indicating that its hypoexpression was involved in invasion and progression of gastric cancer, in agreement with the reports about breast, prostatic, colonic, bladder, and cervical cancers [15, 27]. Here, nuclear maspin immunoreactivity also appeared positive association with differentiation of gastric cancer, which

might be attributed to the selection bias because only 3 studies were involved in our analysis. Taken together, we concluded that maspin expression loss might be employed as a potential biomarker for aggressiveness of gastric cancers.

Reportedly, maspin overexpression is associated with better overall survival in esophageal and oral squamous cell carcinoma [56, 57]. Shift from cytoplasmic to nuclear maspin expression was correlated with shorter overall survival in node-negative colorectal cancer and lung cancer [58, 24]. However, Snoeren et al. [59] found that maspin expression was a marker for early recurrence in primary stage III and IV colorectal cancer, and its overexpression was correlated with poor outcome after cancer spread to the local lymph nodes. Our metaanalysis showed that maspin expression was positively linked to the worse prognosis of the patients with gastric cancer. Here, our unpublished data mainly determined the final outcome, which included the cases from Yu et al. [27] and Zheng et al. [28]. However, our bioinformatics data indicated that SERPINB5 mRNA expression was positively associated with overall and progression-free survival rates of the patient with gastric cancer, even stratified by clinicopathological features, opposite with the

	Overall su	ırvival	Progression-free survival		
Clinicopathological features	Hazard ratio	р	Hazard ratio	р	
Sex					
Female	0.53 (0.34-0.83)	0.004	0.5 (0.31-0.81)	0.0042	
Male	0.63 (0.51-0.77)	1.4e-05	0.62 (0.49-0.78)	6.7e-05	
Т					
2	0.52 (0.34-0.79)	0.002	0.51 (0.33-0.78)	0.0019	
3	0.62 (0.41-0.95)	0.026	0.74 (0.53-1.04)	0.086	
4	0.55 (0.21-1.46)	0.23	0.64 (0.29–1.4)	0.26	
Ν					
0	0.41 (0.17-0.95)	0.032	0.4 (0.17-1.02)	0.048	
1–3	0.58 (0.44-0.77)	9.7e-05	0.59 (0.45-0.77)	7.6e-05	
1	0.46 (0.29-0.72)	0.00047	0.47 (0.31-0.72)	0.00038	
2	0.68 (0.43-1.09)	0.11	0.69 (0.44-1.08)	0.1	
3	0.62 (0.36-1.06)	0.079	0.67 (0.39–1.16)	0.15	
М					
0	0.59 (0.44-0.78)	0.00027	0.6 (0.45-0.79)	0.00025	
1	1.79 (0.95–3.35)	0.067	1.71 (0.95–3.1)	0.072	
TNM staging					
Ι	0.25 (0.07-0.88)	0.02	0.31 (0.09–1.13)	0.062	
II	0.28 (0.13-0.58)	3e-04	0.33 (0.16-0.68)	0.0014	
III	0.59 (0.44–0.8)	0.00057	0.59 (0.38-0.93)	0.021	
IV	0.64 (0.42–0.99)	0.042	0.8 (0.52–1.23)	0.31	
Perforation					
-	0.75 (0.47-1.18)	0.21	0.73 (0.47–1.13)	0.15	
Differentiation					
Well-differentiated	0.46 (0.18–1.14)	0.086			
Moderately-differentiated	1.39 (0.73–2.66)	0.32	1.4 (0.75–2.61)	0.29	
Poorly-differentiated	0.72 (0.45–1.14)	0.16	0.72 (0.43–1.21)	0.22	
Lauren's classification					
Intestinal-type	0.55 (0.4–0.75)	0.00013	0.78 (0.55–1.11)	0.17	
Diffuse-type	0.53 (0.37-0.77)	0.00054	0.45 (0.3-0.68)	9e-05	
Mixed-type	0.38 (0.13-1.07)	0.058	0.2 (0.06-0.66)	0.0039	
Her2 positivity					
-	0.63 (0.49–0.81)	0.00039	0.6 (0.46–0.82)	0.00081	
+	0.62 (0.48-0.8)	3e-04	0.54 (0.39–0.75)	0.00016	
Treatment					
Surgery alone	0.65 (0.48-0.88)	0.0044	0.62 (0.46-0.84)	0.0015	
5-FU-based adjuvant	1.63 (1.11–2.4)	0.013	1.66 (1.13–2.45)	0.0091	
Other adjuvant	0.46 (0.19–1.12)	0.079	0.5 (0.23–1.1)	0.079	

Table 2: The prognostic significance of *SERPINB5* mRNA in gastric cancer by Kaplan-Meier plotter

report about pulmonary adenocarcinoma of Lu et al. [54]. The paradoxical phenomenon might be due to the distinct sensitivity of different methodologies: bioinformatics analysis is based on RNA sequencing, but Lu's experiment on RT-PCR.

Several limitations should be noted in our metaanalysis. Firstly, the potential publication bias stems from published results being predominantly positive. Secondly, patient populations in our study are limited because the patients come only from Asia and Romania. Thirdly, all of the survival data are extracted from survival curves, which may introduce subjective bias. Fourthly, this small sample size limits the power to detect the associations in some articles. Fifthly, we add more cases of gastric cancer for our analysis, which also increases the possibility of selection bias.

In conclusion, maspin expression underwent a down-regulation in gastric carcinogenesis as a late event, but versa for its mRNA. It was negatively correlated with depth of invasion, TNM staging and dedifferentiation of gastric cancer at both mRNA and protein levels. Maspin expression might be employed as a good potential marker for worse prognosis of gastric cancer patients, while it was the converse for its mRNA.

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 Feb 10, 2017. The following search terms were used: (maspin OR SERPINB5 OR PI5) AND (gastric OR stomach) AND (cancer OR carcinoma OR adenocarcinoma). Searching was done without restriction on language or publication years. Inclusion criteria for studies: (1) articles to observe the alteration in maspin expression in gastric cancer by immunohistochemistry; (2) papers to compare maspin 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 maspin expression; (4) lack of sufficient information.

Data extraction

Based on the inclusion criteria, two reviewers (Zheng HC and Gong BC) independently extracted information from all eligible publications. The following information was included in each study: name of first author, year of publication, country, ethnicity, antibody company, 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 and their corresponding 95% confidence intervals. Any disagreement was resolved through discussion until the two reviewers reached a consensus.

Quality score assessment

Two reviewers (Zheng HC and Gong BC) 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 *SERPINB5* was analyzed using Oncomine (www. oncomine.org), a cancer microarray database and web-based data mining platform for a new discovery from genome-wide



Figure 6: The prognostic significance of *SERPINB5* mRNA in the patients with gastric cancer. According to the data from KM plotter, *SERPINB5* mRNA expression was positively related to both overall (A) and progression-free (B) survival rates of the patients with gastric cancer. HR, hazard ratio.

expression analyses. We compared the differences in *SERPINB5* 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 325 gastric cancer patients were downloaded from the Cancer Genome Atlas (TCGA) database by TCGA-assembler in R software. We integrated the raw data, analyzed *SERPINB5* expression in gastric cancer, and compared it with clinicopathological and prognostic data of the patients with gastric cancer. Additionally, the prognostic significance of *SERPINB5* 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 maspin 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. Twosided p < 0.05 was considered as statistically significant. SPSS 17.0 software was employed to analyze all data.

ACKNOWLEDGMENTS

This study was supported by Liaoning BaiQianWan Talents Program, Award for Liaoning Distinguished Professor, a Key Scientific and Technological Project of Liaoning Province (2015408001) and National Natural Scientific Foundation of China (81472544; 81672700).

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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