REVIEW

Clinicopathological significance of HSP27 in gastric cancer: a meta-analysis

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Background: Many studies have provided increasing evidence to demonstrate that HSP27 has been involved in the development of gastric cancer; however, they all include few patients and the results remain controversial. Hence, we conducted a meta-analysis to evaluate correlations between HSP27 and the clinicopathological characteristics of gastric cancer.

Methods: An electronic search for relevant articles was conducted in PubMed, Cochrane Library, Web of Science, EMBASE database, Chinese CNKI, and Wan Fang. Data on the relationship between HSP27 expression and lymph node metastasis, serosal invasion, gender, tumor size, differentiation, and TNM stage were extracted. Pooled odds ratios and 95% confidence intervals were estimated by forest plot.

Results: The pooled analyses suggested that HSP27 expression was significantly associated with the incidence of gastric cancer. However, HSP27 expression had no significant relationship with lymph node metastasis, serosal invasion, gender, tumor size, differentiation, and TNM stage.

Conclusion: Our meta-analysis demonstrated that HSP27 may play vital roles in tumorigenesis and deterioration of gastric cancer. However, further high-quality studies are needed to provide more reliable evidence.

Keywords: heat shock protein 27, gastric cancer, meta-analysis

Introduction

Gastric cancer is one of the leading causes of malignancy-related death around the world. It has been reported that gastric cancer is the fifth most common cancer worldwide, and the fatality rate is 75%, accounting for 8.8% of the total deaths due to cancer.[1] Although there is a trend of decreasing mortality rates of stomach cancer attributed to cancer screening, reduced prevalence of risk factors, and improved treatments, the prognosis of gastric patients remains poor.[2,3] Heat shock proteins (HSPs) are ubiquitous, highly conserved proteins, which are induced by heat shock and environmental and physiopathological stresses.[4] Recent evidence suggested that HSPs may have a close relationship with gastric neoplasia.[5–7] Besides, it has been reported that the expression of HSPs also correlated with clinical characteristics in gastric cancer.[8–10]

HSP27 is a member of the small HSPs and is a major molecular chaperone with a protective effect on cells, which has the function of regulating normal cell physiology and the cellular stress response.[11–13] HSP27 is expressed at low levels in normal cells.[14] However, its aberrant expression has been reported in various malignant tumors, such as gastric,[15] colon,[16] hepatocellular,[17] lung,[18] cervical,[19] ovarian,[20] and breast cancer.[21] Moreover, these reports have also indicated the oncogenic potential of HSP27 and its utility as a cancer biomarker. A previous meta-analysis reported that overexpression of HSP27 was closely related to clinicopathological features, including the differentiation

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degree, lymphatic metastasis, clinical stage, squamous cell carcinoma, and tumor size in non-small-cell lung cancer.[22] Although some studies have explored the role of HSP27 overexpression in stomach cancer,[8,15,23] there is still no summary evidence for the association between HSP27 and gastric cancer. Therefore, we conducted this meta-analysis to explore the relationship between the HSP27 expression and clinicopathological characteristics of gastric cancer patients.

Methods
Identification and eligibility of relevant studies

We searched PubMed, Cochrane Library, Web of Science, EMBASE database, Chinese CNKI, and Wan Fang to identify studies that assessed the clinicopathological factors and prognostic value of HSP27 expression in gastric cancer patients using immunohistochemistry (IHC). The search ended in July 1, 2017. Search words were "heat shock protein 27", "HSP27", "gastric cancer", "gastric carcinoma", and "stomach neoplasm". The reference list of included studies was also checked to find out other qualified studies.

Studies were included if the following criteria were met: 1) the study was published in English or Chinese with full text being available; 2) patients in studies were clearly diagnosed with gastric cancer; 3) the definition of HSP27-positive was tested by IHC method; 4) studies included were case–control studies that evaluated the correlation between HSP27 expression and clinicopathological features or prognosis in stomach cancer; 5) studies included at least one primary outcome of interest; and 6) letters, reviews, conference abstracts, and duplicated studies were excluded.

Data extraction

Two reviewers independently screened all literature to determine whether the relevant articles meet the included criteria. Extracted data including the first author's name, publication year, sample size, country, and clinicopathological parameters (expression, lymph node metastasis, serosal invasion, gender, tumor size, differentiation, and TNM stage). Disagreements were resolved by reextraction or third-party adjudication.

Quality assessment

The quality of each included studies was assessed by the Newcastle–Ottawa Scale (NOS) criteria, and we regarded studies with NOS score of ≥6 as a good quality, while studies with NOS score ≤5 were considered as poor quality.

Statistical analysis

STATA 12.0 was used for statistical calculations. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association between positive HSP27 expression and clinicopathological features (lymph node metastasis [yes vs no], serosal invasion [yes vs no], gender [male vs female], tumor size [≤5 cm vs >5 cm], differentiation type [low vs high/moderate], TNM stage [I/II vs III/IV]), meanwhile the expression of HSP27 between cancer tissues and control tissues was also evaluated. The heterogeneity between the studies was evaluated by I^2 test. Fixed effects model was chosen when there was no significant heterogeneity (I^2<50%, P-Het >0.1). If heterogeneity was significant, the random effects model would be used. Potential causes of statistical heterogeneity were explored by subgroup analysis. Publication bias was examined by the Begg's funnel plot test.

Results
Eligible studies

As shown in Figure 1, we identified 538 relevant articles through combined manual and computerized retrieval from PubMed, Cochrane Library, Web of Science, EMBASE database, Chinese CNKI, and Wan Fang. Of these, 517 were excluded after reviewing the titles and abstracts because these articles were duplicated, non-HSP27-related, or did not involve testing of tumor tissues. A total of 21 studies were assessed by reading the full text, and then 12 studies were excluded due to insufficient information and/or lack of cut-off value of HSP27 expression. Finally, 9 eligible articles were included in this meta-analysis.[15,24–31]

The characteristics of the included studies are summarized in Table 1. These studies were published from 2002 to 2015, and a total of 624 gastric cancer patients were enrolled. Sample sizes ranged from 34 to 118 patients. Four of these studies enrolled ≤60 patients and 5 studies included >60 patients. Eight of these studies evaluated patients from China and one from Greece. All of these studies scored ≥6 in methodological assessment, which implied they were of high quality.

Meta-analysis

In this meta-analysis, we assessed the correlation between HSP27 expression and clinicopathological features of gastric carcinoma. As shown in Table 2 and Figure 2, overexpression of HSP27 was associated with the incidence of gastric cancer (OR =4.73, 95% CI =2.22–10.05, P=0.000). However, our result showed that overexpression of HSP27 was
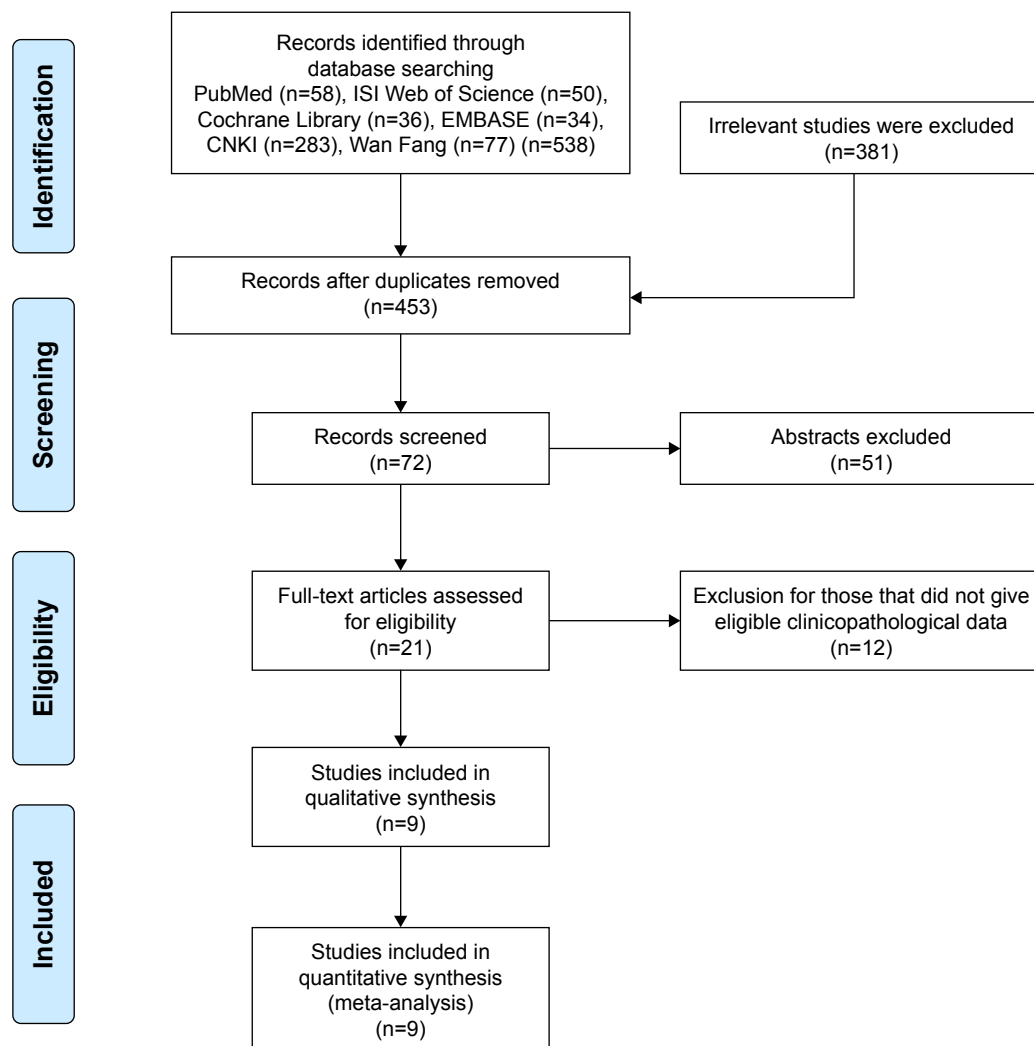
Figure 1 Flowchart of study selection.

not significantly associated with lymph node metastasis (OR =1.32, 95% CI =0.64–2.72, *P*=0.453), serosal invasion (OR =1.31, 95% CI =0.81–2.12, *P*=0.267), gender (OR =0.73, 95% CI =0.50–1.08, *P*=0.120), tumor size (OR =0.56, 95% CI =0.16–1.91, *P*=0.354), differentiation (OR =1.47, 95% CI =0.51–4.22, *P*=0.473), and TNM stage (OR =0.70, 95% CI =0.46–1.08, *P*=0.111).

Publication bias and sensitivity analysis

As shown in Figure 3A, Begg's test suggested that publication bias existed for expression (*P*=0.048). However, as shown in Figure 3B–G, there was no publication bias for lymph node metastasis (*P*=0.902), serosal invasion (*P*=1.000), gender (*P*=1.000), tumor size (*P*=0.296), differentiation (*P*=0.806), and TNM stage (*P*=0.462). Hence, the sensitivity analysis was conducted to evaluate whether individual studies

influenced pooled OR, and the result indicated that no study substantially influenced pooled OR, which indicates that more studies need to be included for further research.

Subgroup analysis

Subgroup analysis was mainly performed on sample size to explore the potential sources of heterogeneity. As seen in Table 3, while in both subgroups divided by sample size, HSP27 expression was correlated to tumor incidence (n≤60: OR =12.15, 95% CI =6.12–24.13, *P*=0.000; n>60: OR =2.51, 95% CI =1.05–6.01, *P*=0.039). However, the heterogeneity of HSP27 expression mainly existed in the bigger sample size subgroup (n>60) (I^2=88.2%). Sample size did not influence the relationship between HSP27 and lymph node metastasis and also tumor size, and there was great heterogeneity in subgroups (lymph node metastasis: n≤60: I^2=79.2%;

Table I Characteristics of studies included in the meta-analysis

Author	Year	Country	No of patients	Expression: cancer (+/−), control (+/−)	Lymph node metastasis: metastasis (+/−), non-metastasis (+/−)	Serosal invasion: yes (+/−), no (+/−)	Gender: male (+/−), female (+/−)	Tumor size: ≤5 cm (+/−), >5 (+/−)	Differentiation: low (+/−), high and moderate (+/−)	TNM: I, II (+/−) III, IV (+/−)	Quality score
Kapranos et al[15]	2002	Greece	86	54/32 68/18	48/23 6/9	NA	25/19 29/13	32/17 22/15	NA	12/12 42/20	9
Li et al[24]	2010	China	45	31/14 12/38	18/11 13/3	21/11 10/3	15/8 16/6	NA	22/5 9/9	NA	8
Hu et al[25]	2015	China	75	48/27 23/52	32/9 16/18	NA	35/18 13/9	23/23 25/4	32/9 16/18	23/21 25/6	9
Li[26]	2015	China	48	31/17 1/13	29/10 2/7	28/10 3/7	NA	16/10 15/7	NA	7/6 24/11	7
Lu et al[27]	2007	China	68	32/36 15/42	10/15 22/21	8/11 24/25	18/19 14/17	NA	4/11 28/25	NA	7
Liu[28]	2014	China	118	71/47 32/86	50/25 32/11	46/16 36/20	57/27 25/9	NA	37/21 46/14	49/18 34/17	9
Tang et al[29]	2009	China	34	18/16 4/30	NA	NA	NA	NA	NA	NA	6
Xiao[30]	2014	China	90	77/13 47/43	51/8 26/5	NA	24/9 53/4	NA	NA	NA	7
Shang et al[31]	2012	China	60	44/16 6/54	30/13 14/3	28/10 16/6	31/12 13/4	NA	30/16 6/8	18/12 17/13	7

Abbreviation: NA, not available.

n>60: I^2=64.6%; tumor size: n>60: I^2=86.8%). When divided by sample size, the subgroup analysis showed that in small sample size group (n≤60), upregulated HSP27 was associated with poor differentiation (OR =3.23, 95% CI =1.31–7.96, P=0.011). While in bigger sample size group (n>60), there was no relationship between differentiation and HSP27 expression (OR =0.90, 95% CI =0.21–3.91, P=0.892). Additionally, the heterogeneity of HSP27 expression mainly existed in the bigger sample size subgroup (n>60) (I^2=84.2%). With these results, the heterogeneity of HSP27 expression and differentiation was most likely caused by the sample size.

Discussion

HSPs have been reported to be overexpressed in a wide range of human tumors, the expression of HSPs was associated with tumor cell growth, differentiation, resistance to apoptosis, and poor prognosis.[32,33] HSP27, an ATP-independent molecular chaperone, is a member of the small HSPs,[34] and it has a protective effect on stress conditions, such as oxidative stress and chemical stress.[13,35] Overexpression of HSP27 is associated with carcinogenesis, such as suppression of apoptosis, increased cytoprotection, and multidrug resistance.[14] Cytoplasmic HSP27 may bind to cytochrome c released from the mitochondria to the cytosol and prevents cytochrome-c-mediated caspase-dependent cell death.[36] HSP27 also inhibits apoptosis by regulating other signaling pathways, including Fas receptor pathway,[37] protein kinase AKT,[38] signal transducer and activator of transcription-3,[39] and the NF-kB signaling pathway.[40] As for cancer therapy resistance, HSP27 can confer cytoprotection by repairing the damaged proteins and DNAs from cytotoxic drug with higher efficiency, protecting the microvasculature inside tumors.[32]

High levels of HSP27 can be found in multiple human malignancies, and the association of HSP27 with gastric cancer and clinicopathologic features has been explored for several years. However, the available data have not yet been fully analyzed. In this paper, we conducted a meta-analysis to investigate the association between HSP27 expression of stomach carcinoma patients and clinicopathologic features.

Combining the outcomes of 624 patients from 9 studies, our analysis revealed that positive HSP27 expression significantly correlated with the incidence of gastric cancer. In addition, statistically significant correlations were not observed between HSP27 expression and clinicopathological features including lymph node metastasis, serosal invasion, gender, tumor size, differentiation, and TNM stage.

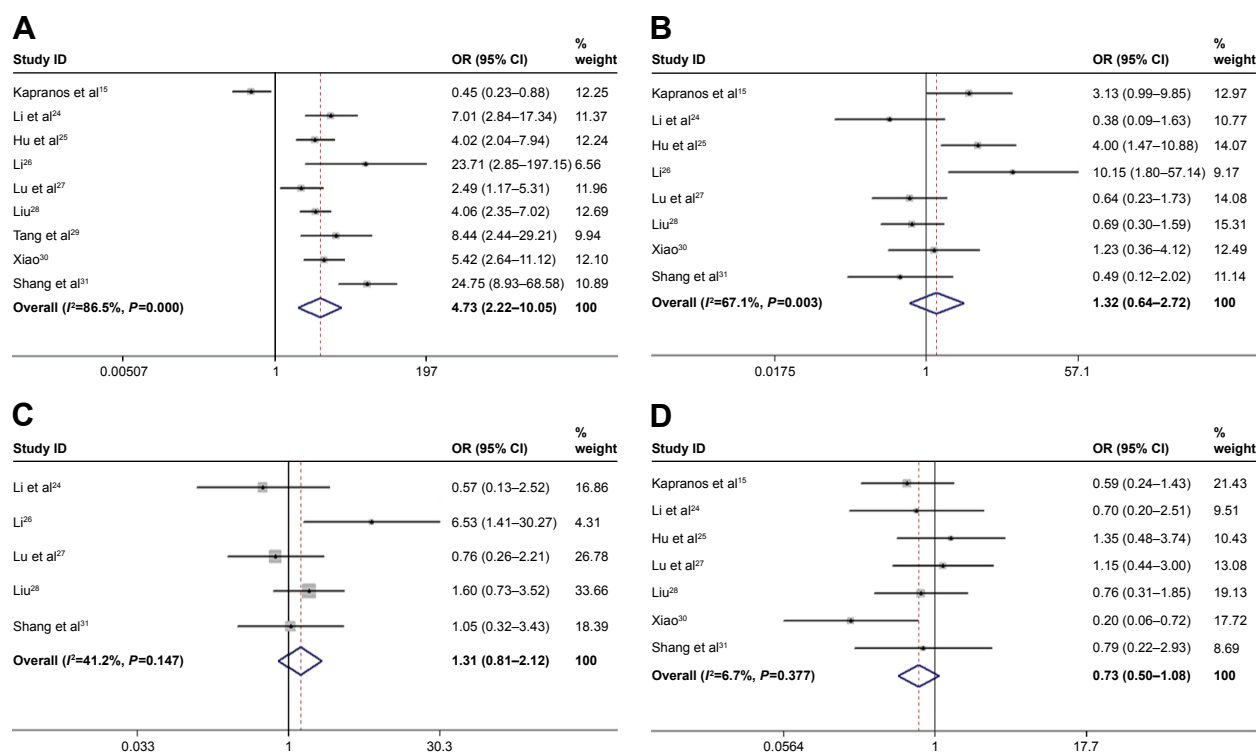**Table 2** HSP27 clinicopathological features for gastric carcinoma

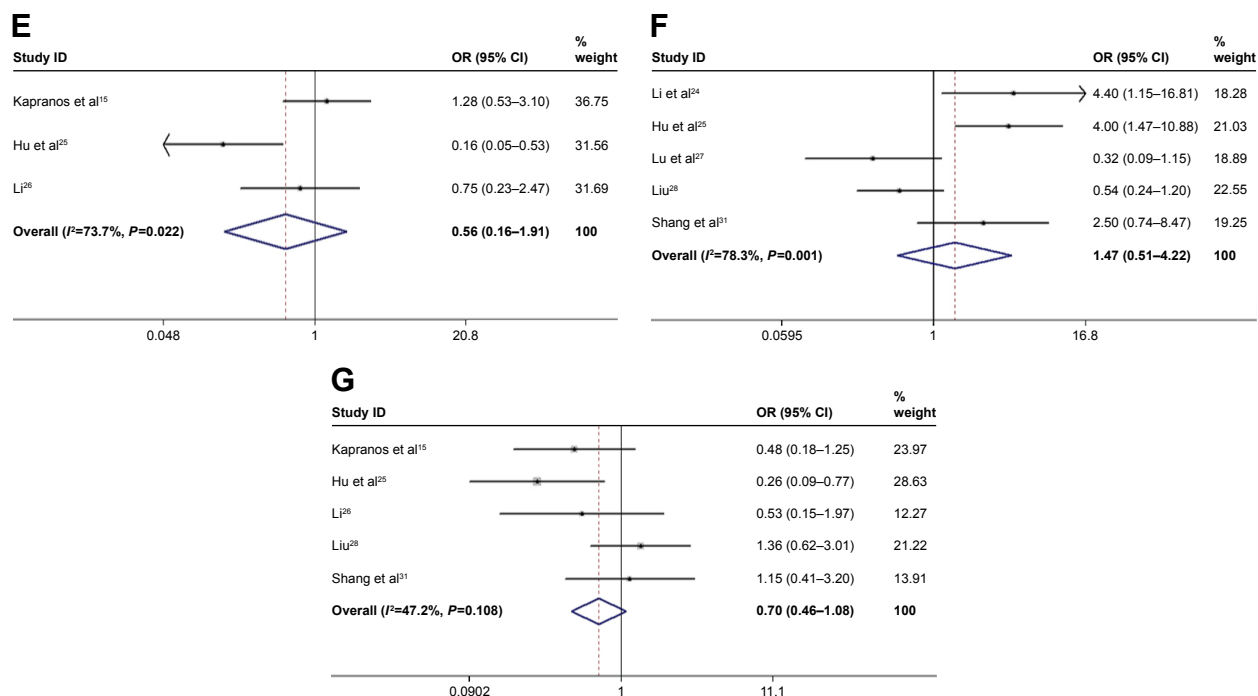| Clinicopathological features	Heterogeneity						
	No of studies	No of patients	Pooled OR (95% CI)	PHet	I^2 (%)	P-value	Model used
Expression	9	624	4.73 (2.22–10.05)	0.000	86.5	0.000	Random
Lymph node metastasis	8	590	1.32 (0.64–2.72)	0.003	67.1	0.453	Random
Serosal invasion	5	339	1.31 (0.81–2.12)	0.147	41.2	0.267	Fixed
Gender	7	542	0.73 (0.50–1.08)	0.377	6.7	0.120	Fixed
Tumor size	3	209	0.56 (0.16–1.91)	0.022	73.7	0.354	Random
Differentiation	5	366	1.47 (0.51–4.22)	0.001	78.3	0.473	Random
TNM stage	5	387	0.70 (0.46–1.08)	0.108	47.2	0.111	Fixed

Abbreviations: Random, random effects model; Fixed, fixed effects model; OR, odds ratio; CI, confidence interval.

In this analysis, five[15,25,26,28,30] of eight, four[25,26,28,31] of five, and three[25,27,31] of four studies suggest that the expression of HSP27 correlated with the lymph node metastasis, TNM stage, and differentiation. However, the overall result showed no statistically significant association between HSP27 expression and these parameters. A previous meta-analysis[22] reported that HSP27 expression was related to differentiation degree, lymphatic metastasis, and clinical stage in non-small-cell lung cancer. Unexpectedly, our results were the opposite. A possible reason is that the results are associated with different kinds of cancer. Without doubt, further high-quality studies are needed to provide more reliable evidence.

In our study, there is a significant heterogeneity in the analysis of HSP27 and several clinicopathological features.

Although we conducted subgroup analysis and sensitivity analysis, the source of heterogeneity has not been fully explained. However, the heterogeneity may be produced in the following aspects. First, all the included studies tested the expression of HSP27 by IHC method, the quality of paraffin section, the antigen retrieval methods, and the use of primary antibody, and the dilutions of the antibodies were different, leading to a potential bias. Second, the cut-off defining a section with positive HSP27 expression is arbitrary, and the calculation error of positive results is unavoidable, which might also result in heterogeneity. In addition, all our findings, except for HSP27 expression, exhibited no publication bias. As eligible articles for meta-analysis were limited, and our review included only fully published studies, in order to
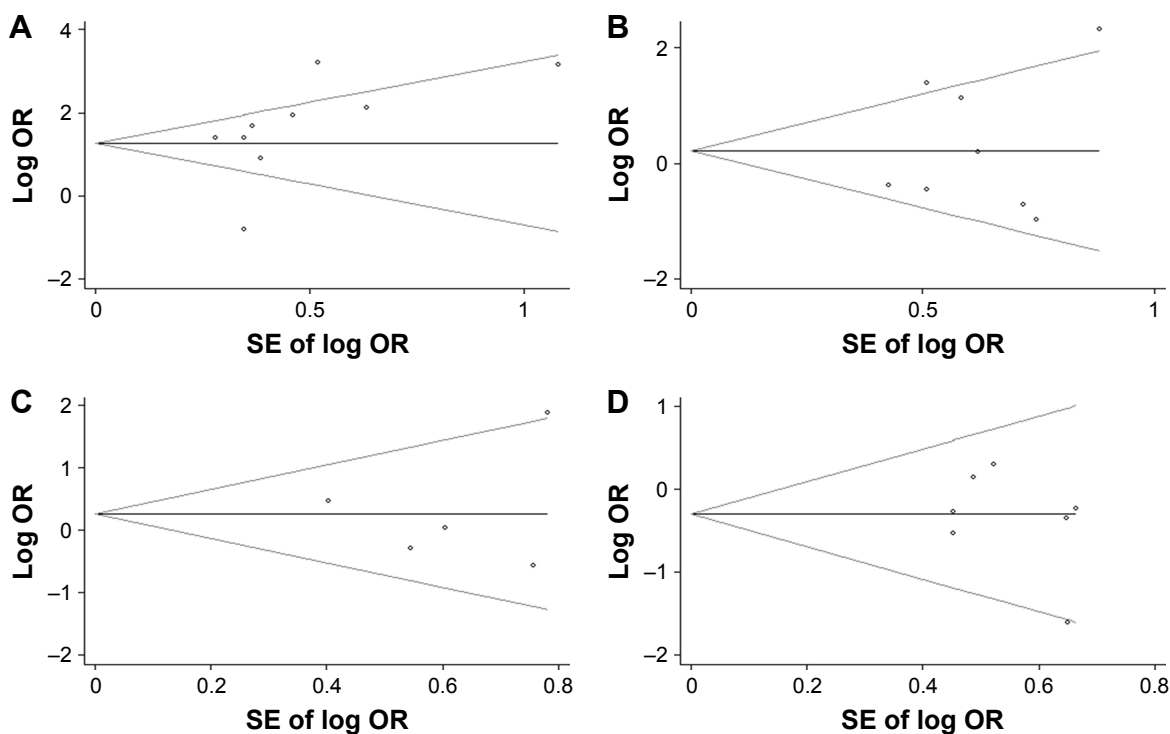

Figure 2 (*Continued*)

E

F

G

Figure 2 Forest plot of studies evaluating the relationship between HSP27 expression and clinicopathological features: (**A**) expression; (**B**) lymph node metastasis; (**C**) serosal invasion; (**D**) gender; (**E**) tumor size; (**F**) differentiation; (**G**) TNM stage.
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

Figure 3 (*Continued*)
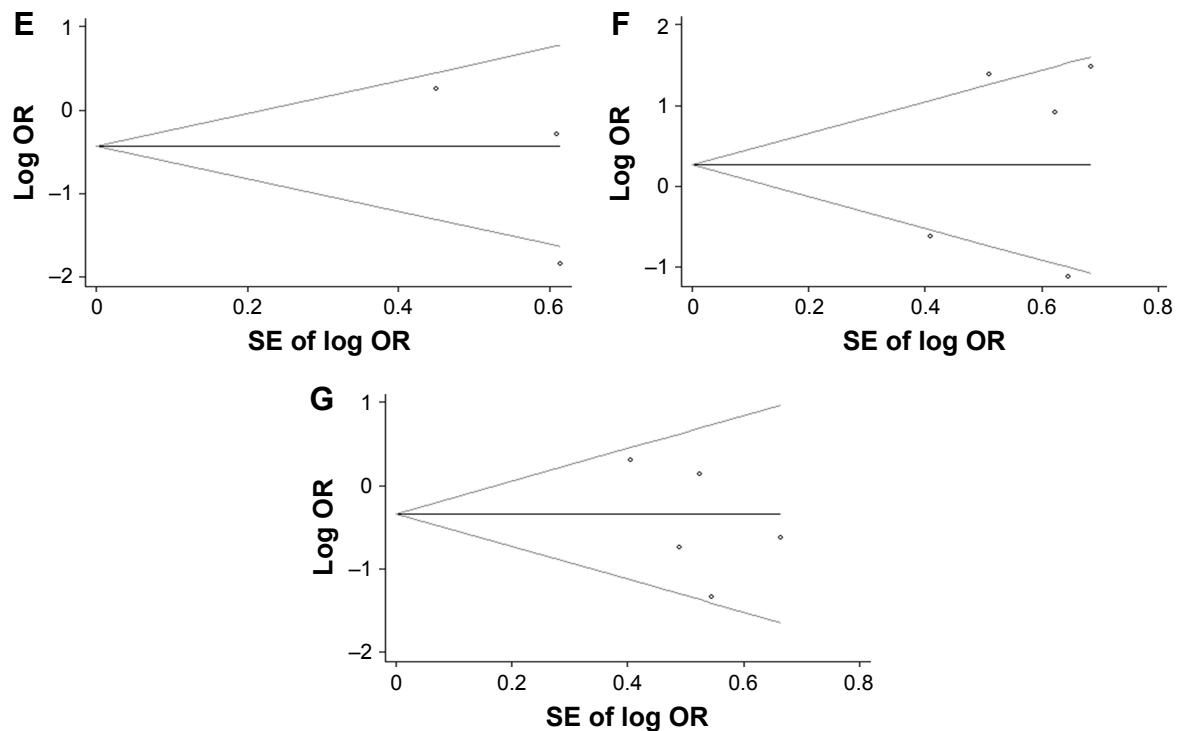
Figure 3 Begg's publication bias plot for HSP27 related studies: (**A**) expression; (**B**) lymph node metastasis; (**C**) serosal invasion; (**D**) gender; (**E**) tumor size; (**F**) differentiation; (**G**) TNM stage.
Abbreviations: SE, standard error; OR, odds ratio.

overcome the publication bias, more studies will be needed for further research.

Limitations

In this meta-analysis, several limitations should be considered: 1) the number of included studies was limited, therefore, the association of HSP27 expression with clinicopathological features still needs to be studied in a larger number of samples; 2) the sample sizes are relatively small; 3) most of the included studies were based on the population from China, so this may not generalize global populations.

Table 3 Subgroup analysis of expression, lymph node metastasis, tumor size, and differentiation

Subgroups	No of studies	No of patients	Pooled OR (95% CI)	PHet	I^2 (%)	P-value
Expression						
Sample size						
≤60	4	187	12.15 (6.12–24.13)	0.260	25.2	0.000
>60	5	437	2.51 (1.05–6.01)	0.000	88.2	0.039
Lymph node metastasis						
Sample size						
≤60	3	153	1.17 (0.17–8.07)	0.008	79.2	0.873
>60	5	437	1.42 (0.66–3.08)	0.023	64.6	0.370
Tumor size						
Sample size						
≤60	1	48	0.75 (0.23–2.45)	–	–	0.632
>60	2	161	0.47 (0.06–3.66)	0.006	86.8	0.473
Differentiation						
Sample size						
≤60	2	105	3.23 (1.31–7.96)	0.541	0.0	0.011
>60	3	261	0.90 (0.21–3.91)	0.002	84.2	0.892

Abbreviations: OR, odds ratio; CI, confidence interval; n, number of sample size.

Conclusion

The available evidence suggests that the incidence of gastric cancer is strongly dependent on the overexpression of HSP27. Clearly, further high-quality research studies with larger sample size are still needed to provide a more representative and convincing statistical analysis in the future.

Disclosure

The authors report no conflicts of interest in this work.

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