RESEARCH ARTICLE

# Heparanase mRNA and Protein Expression Correlates with Clinicopathologic Features of Gastric Cancer Patients: a Meta-analysis

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## Abstract

**Background: Heparanase is believed to be involved in gastric carcinogenesis. However, the clinicopathologic features of gastric cancer with high heparanase expression remain unclear. Aim : The purpose of this study was to comprehensively and quantitatively summarize available evidence for the use of heparanase mRNA and protein expression to evaluate the clinicopathological associations in gastric cancer in Asian patients by meta-analysis. Materials and Methods: Relevant articles listed in MEDLINE, CNKI and the Cochrane Library databases up to MARCH 2015 were searched by use of several keywords in electronic databases. A meta-analysis was performed to clarify the impact of heparanase mRNA and protein on clinicopathological parameters in gastric cancer. Combined ORs with 95%CIs were calculated by Revman 5.0, and publication bias testing was performed by stata12.0. Results: A total of 27 studies which included 3,891 gastric cancer patients were combined in the final analysis. When stratifying the studies by the pathological variables of heparanase mRNA expression, the depth of invasion (633 patients) (OR=4.96; 95% CI=2.38-1.37; *P*<0.0001), lymph node metastasis (639 patients) (OR=6.22; 95%CI=2.70–14.34, *P*<0.0001), and lymph node metastasis (383 patients) (OR=6.85; 95% CI=2.04-23.04; *P*=0.002) were all significant. When stratifying the studies by the pathological variables of heparanase protein expression, this was the case for depth of invasion (1250 patients) (OR=2.76; 95% CI=1.52–5.03; *P*=0.0009), lymph node metastasis (1178 patients) (OR=4.79 ; 95% CI=3.37-6.80, *P*<0.00001), tumor size (727 patients) (OR=2.06 ; 95% CI=1.31-3.23; *P*=0.002) (OR=2.61; 95% CI=2.09-3.27; *P*=0.000), and TNM stage (1233 patients) (OR=6.85; 95% CI=2.04-23.04; *P*=0.002). Egger's tests suggested publication bias for depth of invasion, lymph node metastasis, lymph node metastasis and tumor size of heparanase mRNA and protein expression. Conclusions: This meta-analysis suggests that higher heparanase expression in gastric cancer is associated with clinicopathologic features of depth of invasion, lymph node metastasis and TNM stage at mRNA and protein levels, and of tumor size only at the protein level. Egger's tests suggested publication bias for these clinicopathologic features of heparanase mRNA and protein expression, and which may be caused by shortage of relevant studies. As a result, although abundant reports showed heparanase may be associated with clinicopathologic features in gastric cancer, this meta-analysis indicates that more strict studies were needed to evaluate its clinicopathologic significance.**

**Keywords:** Gastric cancer - heparanase - clinicopathologic features - meta-analysis

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## Introduction

Heparanase is an endo-B-Dglucuronidase that specifically cleaves carbohydrate chains of heparan sulfate proteoglycans (HSPG) (Nadir and Brenner, 2014), the main polysaccharide constituent of the extracellular matrix and basement membrane. Overexpression of heparanase has been found in numerous tumor types and associated with poor prognosis, and because of its peculiar action in tumorgenesis of cancer, heparanase has become a ideal cancer biomarker with many indications and a potential therapeutic target with multiple actions of anti-tumor, anti-angiogenic and anti-inflammatory (Masola et al., 2014; Pisano et al., 2014). As for gastrointestinal cancer, heparanase has been thought to play an important role in the process of invasion and metastasis (Zheng et al., 2009; Wu et al., 2010; Zheng et al., 2010), and even prognosis (Naomoto et al., 2005). However, reports about the clinicopathologic features of high heparanase expression in gastric cancer was not fully same, and conflicting and inconclusive, and even some features of high heparanase expression were missing (Chen et al.,

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2004a; Chen et al., 2004b; Zhang et al., 2012; Zheng et al., 2012). Meta-analysis is becoming more and more popular in evaluating tumor biomarkers about its expressions in cancer with clinicopathological factors (Liu et al., 2013; Han et al., 2014; Liu et al., 2014). In view of the expression of heparanase mRNA and protein in gastric cancer, it is valuable to extract important information of clinicopathological factors and to evaluate the correlation between its expressions and clinicopathological factors by meta-analysis.

## Materials and Methods

Search Strategy and Study Selection Relevant articles studying the relationship between heparanase mRNA and protein and clinicopathologic features of gastric cancer patients published up to July, 2013, were retrieved by online search in PubMed and China National Knowledge Infrastructure. We used the keywords: (''heparanase'' or "HPSE") and (''gastric cancer'' or ''gastric neoplasms'' or ''gastric carcinoma'' or ''stomach cancer'' or ''stomach neoplasms'' or ''stomach carcinoma'') and (''prognostic'' or ''prognosis'' or ''survival'' or ''survive''). All included studies were required to be written in English or Chinese. References of the original studies were also checked, to ensure all eligible studies could be included, heparanase expression of gastric cancer tissues comparing with adajacent non cancerous tissues were statistically calculated by $x^2$ test. Accordingly, The excluding criterion were as follows: review articles, simple commentaries, case reports, or unpublished reports, heparanase expression of gastric cancer tissues comparing with adajacent non cancerous tissues were statistically calculated by student's test.

*Data extraction and quality assessment*

Two authors (Li and Gu) independently extracted information from eligible articles, including year of publication, name of the first author, country, number of patients, years of follow up, TNM stage, patients characteristics, experimental method, cut off value, percentage of heparanase positive expression, analytical method, HR, and 95 % CI from the included articles. We conducted a quality assessment for each eligible study by using reporting recommendations for tumor marker prognostic studies (REMARK). which have been used in previous meta-analysis (McShane et al., 2006).

*Statistical analysis*

Results were expressed with risk ratio (RR) for dichotomous data, and 95% confidence intervals (CI) were counted. $P<0.05$ was required for the overall RR to be statistically significant. In this meta-analysis, HR and 95 % CI were used to calculate the overall effect estimate. Heterogeneity was assessed by the Chi-squared test and $p$ value in our meta-analysis. Using $I^2$ value to evaluate the heterogeneity, fixed-effect model was used if there was $I^2$=0-50%, which means no significant heterogeneity. Otherwise, the random-effects model was applied. Funnel plots and Egger' linear regression test were used to assess evidence for publication bias. All $p$ values were two-side, being statistically significant when $p$ value less than 0.05. All statistical tests for this meta-analysis were performed using REVMAN5.0 software, and publication bias testing was also performed by stata12.0 software.

## Results

*Eligible study characteristics*

A total of 27 studies from including 10 studies about heparanase mRNA expressions and 17 studies heparanase protein expressions (Table 1) were found to meet the criteria for this analysis after the article titles, abstracts and main text were read to identify case reports and clinical outcomes. The total number of patients of heparanase mRNA expressions was 685, including 445 cases heparanase + gastric cancer and a 240 controls; the total number of patients of heparanase mRNA expressions was 1299, including 820 cases heparanase + gastric cancer and a 479 controls. RT-PCR and In Situ Hybridization was a primary method used to evaluate the expressions of heparanase mRNA in gastric cancer specimens, while immunohistochemistry (IHC) was an essential method used to evaluate the expressions of heparanase protein in gastric cancer specimens. Studies were carried out in Japan, China. Table 1 presents the study characteristics for the included trials.

*Meta-analysis results Correlation of heparanase mRNA expression with clinicopathological features*

When stratifying for the different variables by the depth of invasion of gastric cancer, statistical significance was observed. Patients with T3 and T4 gastric cancer had a much higher heparanase expression in 9 studies (633 patients) (OR=4.96; 95% CI=2.38-1.37; $P<0.0001$) than those with T1 and T2 gastric cancer (Figure 1, Table 2). When stratifying for lymph node status of gastric cancer, statistically significant results also illustrated that heparanase expression was associated with lymph node metastasis in 9 studies (639 patients) (OR=6.22; 95% CI=2.70-14.34, $P<0.0001$) (Figure 2, Table 2). When further stratifying for TNM stage, heparanase expression of patients with stages III and IV gastric cancer was much higher than those with stage I and II gastric cancer in 6 studies (383 patients) (OR=6.85; 95% CI=2.04-23.04; $P=0.002$) (Figure 3, Table 2). However, there was no significant relationship between heparanase overexpression and gender, histologic differentiation, distant metastasis, vascular invasion, borrmann type, lymphatic invasion, tumor size of patients with gastric cancer.

*Correlation of heparanase protein expression with clinicopathological features*

When stratifying for the different variables by the depth of invasion of gastric cancer, statistical significance was observed. Patients with T3 and T4 gastric cancer had a much higher heparanase expression in 15 studies (1250 patients) (OR=2.76; 95% CI=1.52-5.03; $P=0.0009$) than those with T1 and T2 gastric cancer (Figure 4, Table 3). When stratifying for lymph node status of gastric cancer, statistically significant results also showed that

**Table 1. TheCorrelation of Heparanase mRNA Expression with Clinicopathological Features**

| References of studies | Nation<br>Positive | Language<br>Negative | Heparanase | Heparanase | Method |
|---|---|---|---|---|---|
| (Inoue et al., 2001) | Japan | English | 42 | 29 | RT-PCR |
| (Tang et al., 2002) | Japan | English | 96 | 20 | In Situ Hybridization |
| (Takaoka et al., 2003) | Japan | English | 35 | 9 | IHC |
| (REN et al., 2003) | China | Chinese | 25 | 27 | In situ hybridization |
| (Chen et al., 2004a) | China | English | 29 | 14 | IHC |
| (Liu et al., 2004) | China | Chinese | 34 | 26 | IHC |
| (Zheng et al., 2004) | China | Chinese | 29 | 21 | RT-PCR |
| (Wang et al., 2005) | China | English | 14 | 16 | RT-PCR |
| (Sun et al., 2005) | China | Chinese | 60 | 37 | IHC |
| (Cai et al., 2004) | China | Chinese | 35 | 12 | RT-PCR |
| (Ru et al., 2006 | China | Chinese | 67 | 51 | In situ hybridization |
| (QIN et al., 2007) | China | Chinese | 39 | 16 | IHC |
| (Ma et al., 2007) | China | Chinese | 98 | 40 | IHC |
| (Liu et al., 2007) | China | Chinese | 48 | 2 | IHC |
| (Huang et al., 2008) | China | Chinese | 39 | 16 | IHC |
| (Wang et al., 2008) | China | Chinese | 41 | 15 | RT-PCR |
| (Liang et al., 2009) | China | Chinese | 49 | 31 | IHC |
| (XI et al., 2009) | China | Chinese | 46 | 44 | In situ hybridization |
| (Cheng et al., 2009) | China | Chinese | 39 | 26 | IHC |
| (Su et al., 2009) | China | Chinese | 39 | 24 | IHC |
| (Zhang et al., 2009) | China | Chinese | 49 | 31 | IHC |
| (Qi et al., 2010) | China | Chinese | 50 | 5 | RT-PCR |
| (Cheng et al., 2010) | China | English | 52 | 50 | IHC |
| (Jiang et al., 2011) | China | Chinese | 40 | 20 | IHC |
| (Zhang et al., 2012) | China | English | 52 | 80 | IHC |
| (Li tao, et al., 2012) | China | Chinese | 51 | 29 | IHC |
| (Zhang et al., 2013) | China | English | 67 | 28 | IHC |

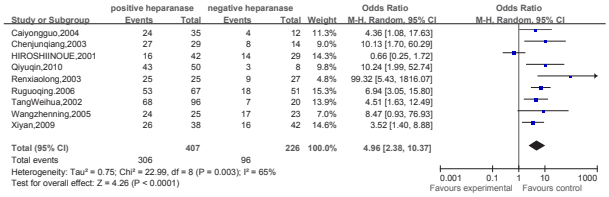


**Figure 1. Forest Plot Analysis Showed that Patients with T3 and T4 Gastric Cancer had a Much Higher Heparanase Expression in 9 Sudies (633 patients) (OR =4.96; 95% CI=2.38-1.37; *P*<0.0001) than those with T1 and T2 Gastric Cancer**

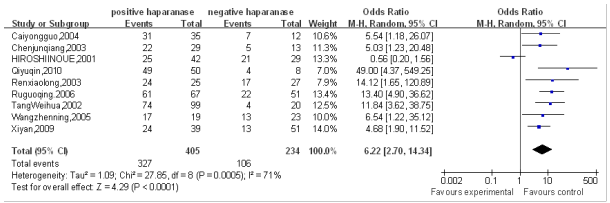


**Figure 2. Forest Plot Analysis Showed that Heparanase Expression was Associated with Lymph Node Metastasis in 9 Studies (639 Patients) (OR=6.22; 95% CI=2.70–14.34, *P*<0.0001)**

heparanase expression was associated with lymph node metastasis in 15 studies (1178 patients) (OR=4.79; 95% CI=3.37-6.80, *P*<0.00001) (Figure 5, Table 3). When further stratifying for TNM stage, heparanase expression of patients with stages III and IV gastric canvcer was much higher than those with stage I and II gastric cancer in 15 studies (1233 patients) (OR=4.66; 95% CI=2.50-8.68; *P*<0.00001) (Figure 6, Table 3). When stratifying

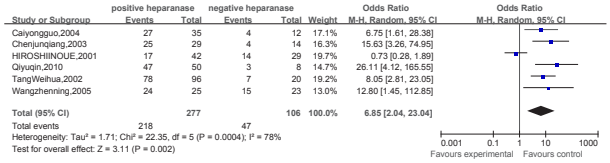


**Figure 3. Forest Plot Analysis Showed that Heparanase Expression of Patients with stages III and IV Gastric Cancer was Much Higher than those with Sage I and II Gastric Cancer in 6 Studies (383 Patients) (OR = 6.85; 95% CI = 2.04–23.04; *P*=0.002)**

for tumor size, heparanase expression of patients with tumor diameter larger than 5 cm was much higher than those with tumor diameter less than 5 cm in 8 studies (727 patients) (OR=2.06; 95% CI=1.31-3.23; *P*=0.002) (Figure 7, Table 3). However, there was no significant relationship between heparanase overexpression and gender, histologic differentiation, distant metastasis, vascular invasion, borrmann type, lymphatic invasion, tumor size of patients with gastric cancer.

*Publication bias*

In order to clarify the clinicopathologic features of depth of invasion, lymph node metastasis, TNM stage and tumor size in gastric cancer. Egger's tests were carried out to analysis publication bias for these clinicopathologic features of heparanase mRNA and protein expression. Results indicated that publication bias were found in depth of invasion, lymph node metastasis, TNM stage and tumor size with heparanase overexpression at mRNA level, and publication bias were found in depth of

**Table 2. The Correlation of Heparanase mRNA Expression with Clinicopathological Features**

| Clinicopathologic Features | Number of patientss | Number of studies | HR (95 % CI) | Heterogeneity $x^2$ | Heterogeneity $I^2$ | Heterogeneity *p* |
|---|---|---|---|---|---|---|
| Gender | 335 | 5 | 0.86 [0.50, 1.47] | 2.77 | 0% | 0.6 |
| Depth of invasion | 633 | 9 | 4.96 [2.38, 10.37] | 22.99 | 65% | 0.003 |
| Differentiation of cell | 373 | 6 | 1.02 [0.55, 1.88] | 8.37 | 40% | 0.14 |
| Lymph node metastasis | 637 | 9 | 6.22 [2.70, 14.34] | 27.85 | 71% | 0.0005 |
| Distant metastasis | 494 | 7 | 4.38 [0.88, 21.76] | 36.44 | 84% | <0.00001 |
| TNM stage | 383 | 6 | 6.85 [2.04, 23.04] | 22.35 | 78% | 0.0004 |
| Tumor size | 208 | 3 | 2.85 [0.74, 10.98] | 5.35 | 63% | 0.07 |
| Vascular invasion | 305 | 3 | 3.03 [0.19, 48.35] | 24.88 | 92% | <0.00001 |

**Table 3. The Correlation of Heparanase Protein Expression with Clinicopathological Features**

| Clinicopathologic Features | Number of patientss | Number of studies | HR (95 % CI) | Heterogeneity $x^2$ | Heterogeneity $I^2$ | Heterogeneity *p* |
|---|---|---|---|---|---|---|
| Gender | 1063 | 12 | 1.12 [0.85, 1.46] | 8.17 | 0% | 0.7 |
| Depth of invasion | 1250 | 15 | 2.76 [1.52, 5.03] | 67.08 | 79% | <0.00001 |
| Differentiation of cell | 1245 | 15 | 1.21 [0.78, 1.87] | 40.02 | 65% | 0.0003 |
| Lymph node metastasis | 1178 | 16 | 4.55 [3.54, 5.85] | 24.53 | 43% | 0.05 |
| Distant metastasis | 621 | 7 | 4.03 [0.74, 21.81] | 36.02 | 83% | <0.00001 |
| TNM stage | 1233 | 15 | 4.66 [2.50, 8.68] | 68.2 | 79% | <0.00001 |
| Tumor size | 727 | 8 | 2.06 [1.31, 3.23] | 12.83, | 45% | 0.002 |

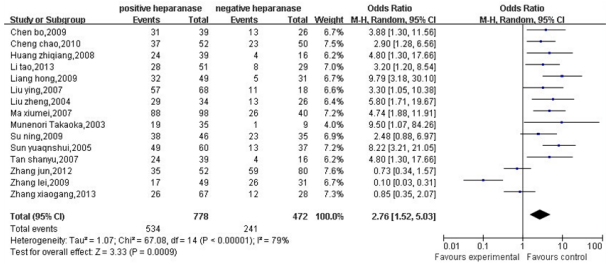


**Figure 4. Forest Plot Analysis Showed that Patients with T3 and T4 Gastric Cancer had a Much Higher Heparanase Expression in 15 Studies (1250 Patients) (OR=2.76; 95% CI=1.52-5.03; *P*=0.0009) than those with T1 and T2 Gastric Cancer**

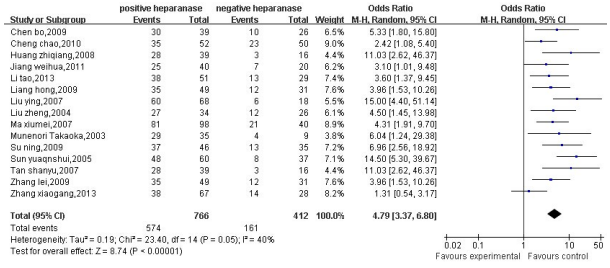


**Figure 5. Forest Plot Analysis Showed that Heparanase Expression was Associated with Lymph Node Metastasis in 15 Studies (1178 Patients) (OR=4.79; 95% CI=3.37-6.80, *P*<0.00001)**

invasion, lymph node metastasis, TNM stage and tumor size with heparanase overexpression at protein level. The reasons may be caused by shortage of relevant studies with less than 10 studies included in mRNA heparanase overexpression, and less than 20 studies included in heparanase protein overexpression.

## Discussion

Abundant clinical studies showed that overexpression of heparanase is correlated with clinicopathological

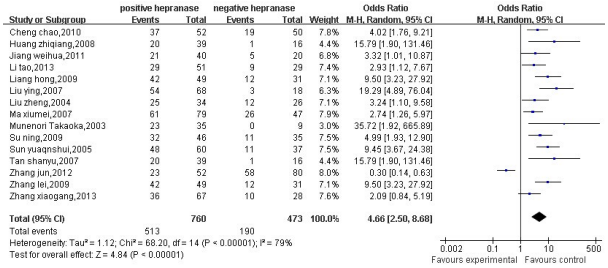


**Figure 6. Forest Plot Analysis Showed that Heparanase Expression of Patients with Stages III and IV Gastric Cancer was Much Higher than those with Stage I and II Gastric Cancer in 15 Studies (1233 Patients) (OR=4.66; 95% CI=2.50-8.68; *P*<0.00001)**

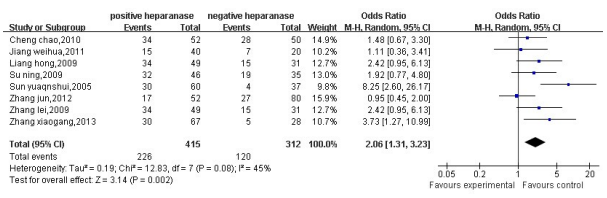


**Figure 7. Forest plot analysis showed that heparanase expression of patients with tumor diameter larger than 5 cm was much higher than those with tumor diameter less than 5 cm in 8 studies (727 patients) (OR = 2.06; 95% CI = 1.31–3.23; *P* = 0.002)**

features, in particular, with metastasis and poor prognosis of a series of cancers including gastric cancer. All clinical data and knockdown experiment (Inoue et al., 2001; REN et al., 2003; Takaoka et al., 2003; Chen et al., 2004b; Wang et al., 2005; XI et al., 2009; Zheng et al., 2009; Zheng et al., 2010 ) in gastric cancer cells in vitro proved that high expression of heparanase to be a potential tumor biomarker and a strong predictor of poor survival. In recent years, meta-analysis has been used to screen and evaluate tumor biomarker and their clinical significances. Plenty of clinical reports suggested that heparanase could be a promising tumor biomarker for metastasis and prognosis

of gastric cancer, and whereas no systematic review of clinical studies about high expression of heparanase in gastric cancer was carried out until now. Hence, it is necessary to review the clinicopathological features of high expression of heparanase systematically by meta-analysis to discover potential tumor biomarkers.

In this meta-analysis, we found high heparanase mRNA expression, as detected by RT-PCR and In Situ Hybridization, and high heparanase protein expression, as detected by immunohistochemistry was confirmed in patients with gastric cancer according to the evidence-based medicine. The pooled statistical data showed that heparanase mRNA and protein, when stratifying for baseline characteristics of patients, including sex, age, tumor size, histo-differentiation, depth of invasion, lymph node status, distant metastasis, vascular invasion, borrmann type, and TNM stage, our present meta-analysis indicated that over expression of heparanase mRNA was associated with depth of invasion, lymph node metastasis and TNM stage, and over expression of heparanase protein was significantly associated with the depth of invasion, lymph node metastasis, TNM stage and tumor size. However, Egger's tests showed that the clinicopathologic features of depth of invasion, lymph node metastasis, and TNM stage and tumor size in gastric cancer showed publication bias for these clinicopathologic features of heparanase mRNA and protein expression. Certainly, these published articles included in this meta-analysis are less than 20, which will lead to bias if egger's tests were adopted to test publication bias. So more serious studies were needed to review clinicopathologic significances of overexpression of heparanase mRNA and protein. Plenty of studies of heparanase mRNA and protein expression reported to be associated with clinicopathological features in different types of cancer including gastric cancer, lung cancer, acute myeloid leukemia, breast, prostate, hepatocellular, pancreatic, colon cancer.

In conclusion, this meta-analysis results of clinicopathologic features showed that overexpression of heparanase mRNA and protein are correlated with depth of invasion, lymph node metastasis, tumor size and TNM stage. Heparanase still might serve as an efficient marker for clinicopathologic features indicator, and could be a new molecular target in gastric cancer therapy. In addition, because of publication bias for these clinicopathologic significances exist suggested by Egger's tests in these published articles, if more serious and eligible studies were included for meta-analysis, it will promote the understanding of clinicopathologic significances of heparanase in gastric cancer.

## Acknowledgements

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