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META-ANALYSIS

# Abnormal β-catenin immunohistochemical expression as a prognostic factor in gastric cancer: A meta-analysis

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## Abstract

**AIM:** To evaluate the effect of β-catenin immunohistochemical expression on the prognosis of gastric cancer (GC).

**METHODS:** We searched Pubmed and Embase to identify eligible studies. The search ended on November 10, 2013, with no lower date limit. The citation lists associated with the studies were used to identify additional eligible studies. We included studies reporting sufficient information to estimate the HR and 95%CI, and information to estimate the OR in the analysis of clinicopathological features. The qualities of these studies were assessed using the Newcastle-Ottawa Quality Assessment Scale. HRs and ORs and their variance were calculated and pooled using Review Manager Version 5.2.

**RESULTS:** A total of 24 studies were identified and comprised 3404 cases. β-catenin expression was significantly correlated with poor overall survival (OS) in GC patients (HR = 1.85, 95%CI: 1.39-2.46), but showed a significant degree of heterogeneity ($I^2$ = 71%, $P$ < 0.0001). Subgroup analysis indicated that an abnormal pattern of β-catenin expression had an unfavorable effect on OS (HR = 1.79, 95%CI: 1.39-2.32). However, accumulation in the nucleus or loss of membrane did not influence the survival of GC patients independently. Moreover, the combined OR of β-catenin indicated that β-catenin expression was associated with Lauren classification (OR = 1.98, 95%CI: 1.19-3.29), lymph node metastasis (OR = 2.00, 95%CI: 1.44-2.77), distant metastasis (OR = 2.69, 95%CI: 1.35-5.38) and grade of differentiation (OR = 2.68, 95%CI: 1.66-4.34). β-catenin expression did not correlate with TNM stage (OR = 1.34 95%CI: 0.96-1.86), the depth of invasion (OR = 1.48, 95%CI: 0.94-2.33) or vascular invasion (OR = 1.11, 95%CI: 0.70-1.76).

**CONCLUSION:** Abnormal β-catenin immunohistochemical expression may be associated with tumor progression and could be a predictive factor of poor prognosis in patients with GC.



**Key words:** β-catenin; Immunohistochemistry; Gastric cancer; Prognosis; Meta-analysis

**Core tip:** β-catenin is involved in the development of multiple tumors. It has been proved that β-catenin is important in cell-to-cell adhesion and the progression of gastric cancer. This meta-analysis demonstrated that abnormal β-catenin expression was associated with poor prognosis in patients with gastric cancer, and may predict invasion and metastasis.

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## INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer globally, and was the second most common cause of death due to malignancies worldwide in 2008[1]. Multiple environmental factors including chronic *Helicobacter pylori* (*H. pylori*) infection, hereditary factors and dietary factors have been implicated in the initiation of gastric carcinogenesis[2,3]. Although the understanding of neoplastic progression has improved in the past decade, the prognosis of patients with advanced GC remains relatively poor. Consequently, it is important to uncover the biological mechanisms underlying progression of the disease and develop strategies to intervene in this process[4].

Epithelial-mesenchymal transition (EMT), a developmental process in which epithelial cells show reduced intercellular adhesion and acquire migratory fibroblastoid properties, is considered to be critical for invasive and metastatic progression in cancer[5]. EMT is associated with the down-regulation of epithelial markers, aberrant upregulation of mesenchymal markers and abnormal translocation of β-catenin in several human cancers including GC[6]. As a central molecule in the int/Wingless family (Wnt) signaling pathway, β-catenin expression is localized in the membrane, cytoplasm and nucleus[7]. β-catenin has a dual role depending on its intracellular localization. Membranous expression of β-catenin is linked to E-cadherin and the actin cytoskeleton, and is responsible for cell-to-cell adhesion and exerting a restrictive effect on tumor growth. Cytoplasmic and nuclear β-catenin are mainly involved in regulation of the Wnt signaling pathway[8]. When a Wnt ligand engages with its receptors, the scaffold protein Axin translocates to the transmembranous receptor complex and inhibits the destruction complex. Thus, cytoplasmic β-catenin escapes degradation, accumulates in the cytoplasm and finally translocates to the nucleus. After localizing to the nucleus, β-catenin activates a target gene expression program with loss of E-cadherin, linking EMT to Wnt signaling. In addition, Wnt signaling is also connected to EMT by activation of snail2 and ZEB1 *via* other Wnt target genes. Taken together, these findings suggest that different forms of β-catenin contribute to a feed-forward loop in invading cancer cells[9].

Deregulated β-catenin is involved in the development of multiple tumors. In the presence of a Wnt signal, activation of β-catenin is found in about 30% of GC patients[10]. Moreover, potential biological mechanisms have been proposed, such as the CagA+ strain of *H. pylori* which is thought to activate β-catenin to promote intestinal transdifferentiation in gastric epithelial cells[11], and accumulating evidence indicates that inflammation induced by COX-2/PGE2 and the Wnt pathway plays a critical role in GC development[12]. These findings provide evidence that β-catenin is important in the development and progression of GC and may be significantly associated with prognosis in patients with GC. When evaluating the expression of variant localization, controversial results have been observed. A recent study by Ayed-Guerfali *et al*[13] showed that nuclear immunohistochemical staining of β-catenin was detected in only 3 of 80 specimens (4%), in contrast to previous reports indicating higher frequencies[14,15]. However, this may suggest that abnormal expression of β-catenin including cytoplasmic and nuclear immunostaining, as well as the absence of membranous staining, is predictive of poor prognosis.

Although a large number of studies have investigated the relationship between β-catenin and GC, the prognostic value of β-catenin remains controversial. Thus, this meta-analysis was performed to evaluate the prognostic significance of β-catenin immunohistochemical expression in patients with GC.

## MATERIALS AND METHODS

### Literature search

We searched the PubMed and Embase databases using the following terms and all possible combinations: "β-catenin", "beta-catenin", "Wnt", "Gastric Neoplasms", "Gastric Cancer", "Gastric Carcinoma", "Gastric Tumor", "Stomach Cancer", "Stomach Carcinoma", "Stomach Neoplasms", "Stomach Tumor", "GC" and "Prognosis." The search ended on November 10, 2013, and no lower date limit was used. The citation lists associated with the studies were used to identify additional eligible studies. The reviews and bibliographies were also manually inspected to find related articles.

### Inclusion and exclusion criteria

The studies were included in our meta-analysis if they met the following inclusion criteria: (1) β-catenin expression examined by immunohistochemistry and evaluated in human GC tissues; (2) Evaluation of the relationships between β-catenin expression and overall survival (OS) or clinicopathological features of GC; (3) Publications in English; and (4) Sufficient information provided to estimate the HR and its 95%CI, and information to estimate the OR in the analysis of clinicopathological features.

The following articles were excluded: (1) letters, case reports, reviews, and conference abstracts without original data; (2) non-English language articles; (3) articles from which the relevant data could not be extracted; and (4) overlapping articles or those with duplicate data.

### Data extraction and assessment

Two investigators (LLF and WZJ) reviewed each eligible study and extracted data. The database recorded the most relevant data comprising author's name, year of publication, antibody source, definition of β-catenin expression, study location, number of patients and tumor characteristics. Study quality was assessed independently by two investigators (LLF and WZJ) according to the Newcastle–Ottawa quality assessment scale[16]. The score assessed

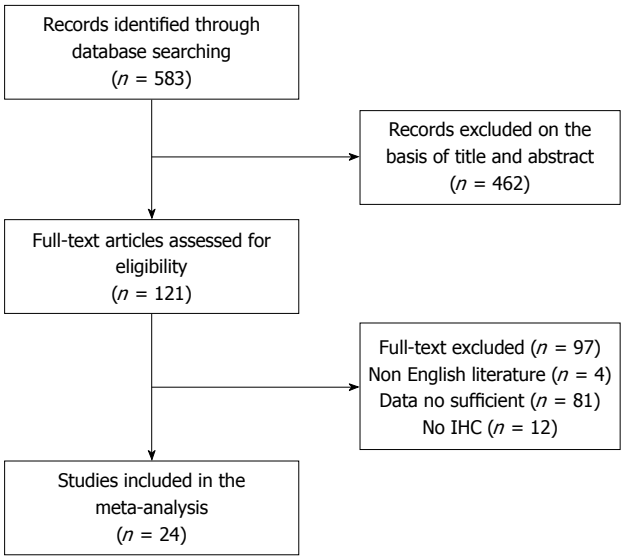


**Figure 1 Flowchart showing selection of studies for inclusion in the meta-analysis.** IHC: Immunohistochemistry.

eight items of methodology, and grouped them into three major classifications: selection, comparability and outcome. A maximum score of 1 was graded for each item, except that related to comparability, which allowed for 2. For quality, scores ranged from 0 (lowest) to 9 (highest), and studies with more than 5 points were rated as qualified.

### Statistical analysis

The impact of β-catenin expression on OS was measured by HR for quantitative aggregation. The most accurate approach was to obtain the HR estimate and 95%CI directly from the paper, or calculate them using the parameters offered in the manuscript[17]. Otherwise, Kaplan-Meier curves were read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/)[18]. Heterogeneity across studies was evaluated using a $\chi^2$-based $Q$ statistical test. The $I^2$ statistic was also calculated for study heterogeneity. $I^2 > 50$ and $P \leqslant 0.10$ indicated a lack of heterogeneity among the studies. For studies with $P > 0.10$, the pooled OR and HR estimates of each study were calculated by the fixed-effects model (the Mantel-Haenszel method). For studies with $P \leqslant 0.10$, the random-effects model (the DerSimonian and Laird method) was used. For the pooled analysis of the correlation between β-catenin expression and clinicopathological features [Lauren classification, tumor-node-metastasis (TNM) stage, the depth of invasion, lymph node metastasis, distant metastasis, grade of differentiation and vascular invasion], ORs and their 95%CIs were combined to estimate the effect.

Sensitivity analysis was also conducted by sequential omission of individual studies to evaluate stability of the results. In addition, publication bias was assessed using funnel plots. HRs and ORs and their variance were calculated and pooled using the RevMan systematic review and meta-analysis software package (Review Manager Version 5.2). A $P$ value < 0.05 was considered statistically significant. An observed HR or OR > 1 indicated a worse prognosis for GC patients with abnormal β-catenin expression and was considered to be statistically significant if the 95%CI did not overlap 1.

## RESULTS

### Study selection and characteristics

As described in Figure 1, a total of 583 articles were identified after searching the databases. After screening the abstract and full-text of these articles, 24 articles were finally included in the quantitative analysis of the prognostic value of β-catenin expression in GC and the relationship between β-catenin expression and clinicopathological features. The characteristics of these 24 publications are summarized in Table 1[13-15,19-40].

### Impact of β-catenin immunohistochemical expression on overall survival in gastric cancer patients

Meta-analysis of the association between β-catenin expression and OS was determined in 15 studies. A forest plot of the individual HR estimates and results from the meta-analysis are shown in Figure 2. In general, aberrant β-catenin expression, which consisted of positive cytoplasmic and nuclear expression and negative membranous expression in GC, demonstrated a significant increase in mortality risk as compared to regular β-catenin expression (combined HR = 1.85, 95%CI: 1.39-2.46). However, a significant degree of heterogeneity was observed ($I^2$ = 71%, $P < 0.0001$).

In order to explain the heterogeneity in OS, we performed a subgroup analysis using the definition of β-catenin expression, study location, number of patients, antibody resources and publication year. Due to the different definition in the included studies, we separated β-catenin expression into four patterns: abnormal β-catenin pattern, nucleus accumulation, cytoplasmic overexpression and loss of membranous expression. The association between abnormal pattern and OS was assessed in five studies, and the pooled HR was 1.79 (95%CI: 1.39-2.32; $I^2$ = 48%, $P$ = 0.10). Furthermore, β-catenin overexpression in the cytoplasm was also associated with poor prognosis (HR = 1.52, 95%CI: 1.05-2.19; $I^2$ = 0%, $P$ = 0.56), but only following the analysis of two limited studies. No significant relationship between OS of GC and the other two patterns of nuclear accumulation (HR = 1.66, 95%CI: 0.90-3.06; $I^2$ = 83%, $P$ = 0.000) and loss of membranous expression (HR = 1.61, 95%CI: 0.88-2.96; $I^2$ = 75%, $P$ = 0.003) was observed (Figure 3).

Moreover, subgroup analysis indicated a significant relationship between β-catenin expression and OS also shown by antibody source from the Transduction Laboratory (HR = 2.36; 95%CI: 1.06-5.27; $I^2$ = 76%, $P$ = 0.000) and publication year ⩽ 2000 (HR = 2.07; 95%CI: 1.13-3.81; $I^2$ = 0%, $P$ = 0.76). Other factors including study location and number of patients did not alter the significant prognostic impact of abnormal β-catenin ex-

**Table 1 Baseline characteristics and methodological assessment of the included trials**

| Ref. | Year | Study location | Patient (M/F) | Luaren classfication | | | Antibody source | Definition of β-catenin expression[1] | NOS |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intestinal | Diffuse | Mixed | | | |
| Ayed-Guerfali *et al*[13] | 2013 | Tunisia | 80 (45/35) | 48 | 32 | | Santa Cruz | Normal/abnormal expression | 7 |
| Sereno *et al*[19] | 2012 | Spain | 44 (33/11) | 22 | 13 | 9 | Transduction Laboratories | Normal/abnormal expression | 6 |
| Hou *et al*[20] | 2012 | China | 158 (105/53) | | | | Santa Cruz | Normal/abnormal expression | 6 |
| Liu *et al*[22] | 2012 | China | 134 (90/44) | | | | Santa Cruz | Nuclear expression | 5 |
| Sun *et al*[21] | 2012 | China | 58 (49/9) | | | | Santa Cruz | Normal/abnormal expression | 5 |
| Ryu *et al*[23] | 2012 | South Korea | 276 (NA) | | | | BD Biosciences | Normal/abnormal expression | 7 |
| Retterspitz *et al*[24] | 2010 | Germany | 94 (46/48) | 0 | 88 | 6 | BD Transduction | Membranous expression | 8 |
| Kim *et al*[25] | 2010 | South Korea | 117 (81/36) | 40 | 75 | 2 | BD Transduction | Nuclear expression | 8 |
| Czyzewska *et al*[26] | 2010 | Poland | 91 (62/29) | 61 | 30 | 0 | Novocastra Laboratories Ltd | Membranous expression | 6 |
| Zali *et al*[28] | 2009 | Iran | 56 (38/18) | 35 | 16 | 5 | Research Diagnostic | Normal/abnormal expression | 8 |
| Kim *et al*[29] | 2009 | South Korea | 598 (396/202) | | | | BD Biosciences | Nuclear expression | 6 |
| Bazas *et al*[30] | 2008 | Ukraine | 150 (89/61) | 117 | 33 | 0 | Dako Cytomation | Cytoplasmic expression | 8 |
| Koriyama *et al*[31] | 2007 | Japan | 149 (NA) | 99 | 50 | 0 | Transduction Laboratories | Normal/abnormal expression | 8 |
| Jung *et al*[32] | 2007 | South Korea | 111 (NA) | 44 | 67 | 0 | Transduction Laboratories | Nuclear expression | 9 |
| Nabais *et al*[33] | 2003 | Portugal | 97 (NA) | 28 | 51 | 18 | Transduction Laboratories | Nuclear and cytoplasmic expression | 7 |
| Zhou *et al*[34] | 2002 | China | 163 (123/40) | 108 | 40 | 15 | Maxim Biotech Inc. | Normal/abnormal expression | 8 |
| Woo *et al*[14] | 2001 | South Korea | 303 (205/98) | 116 | 158 | 29 | Transduction Laboratories | Membranous expression | 9 |
| Shun *et al*[35] | 2001 | Taiwan | 53 (NA) | 30 | 23 | | Transduction Laboratories | Normal/abnormal expression | 6 |
| Grabsch *et al*[36] | 2001 | Germany | 401 (NA) | 255 | 112 | 34 | Transduction Laboratories | Nuclear and cytoplasmic expression | 6 |
| Joo *et al*[37] | 2000 | South Korea | 65 (38/27) | 28 | 25 | 12 | Zymed Laboratories | Normal/abnormal expression | 7 |
| Karatzas *et al*[38] | 2000 | Greece | 36 (NA) | 24 | 12 | | Transduction Laboratories | Normal/abnormal expression | 6 |
| Ohene-Abuakwa *et al*[39] | 2000 | United Kingdom | 41 (NA) | 28 | 7 | 6 | Transduction Laboratories | Normal/abnormal expression | 7 |
| Ramesh *et al*[15] | 1999 | United Kingdom | 40 (NA) | | | | Affinity Research Products Ltd | Normal/abnormal expression | 8 |
| Jawhari *et al*[40] | 1997 | England | 89 (62/27) | 63 | 24 | 2 | Affinity Research Products Ltd | Normal/abnormal expression | 7 |

[1]Different β-catenin location in gastric cancer. NA: Not available; M/F: Male/Female; NOS: Newcastle-Ottawa Quality Assessment Scale.

pression (Table 2).

### Correlation of β-catenin expression with clinicopathological parameters

We evaluated the correlation between β-catenin immunohistochemical expression and the clinicopathological characteristics of GC. The definition of abnormal β-catenin expression was as previously mentioned. As shown in Table 3, we assessed 17 studies to identify the relationship between β-catenin expression and the Lauren classification. Patients with diffuse-type GC had significant abnormal β-catenin expression as compared to patients with intestinal-type GC (OR = 1.98, 95%CI: 1.19-3.29). In addition, β-catenin expression was significantly associated with lymph node metastasis (positive *vs* negative: OR = 2.00, 95%CI: 1.44-2.77), distant metastasis (positive *vs* negative: OR = 2.69, 95%CI: 1.35-5.38) and grade of differentiation (G3/G4 *vs* G1/G2: OR = 2.68, 95%CI: 1.66-4.34). We also found that abnormal β-catenin expression had no significant association with TNM stage (OR = 1.34, 95%CI: 0.96-1.86), the depth of invasion (OR = 1.48, 95%CI: 0.94-2.33) or vascular invasion (OR = 1.11, 95%CI: 0.70-1.76). The meta-analysis of OR in TNM stage, distant metastasis and vascular invasion did not show obvious inter-study heterogeneity ($I^2$ = 0%-44%), whereas analysis of other histological features exhibited heterogeneity ($I^2$ = 44%-74%).

### Statistical analysis

Sensitivity analysis indicated that the pooled HRs were not significantly influenced by omitting any single study. However, in the meta-analysis of clinicopathological parameters, we found that data from Sun *et al*[21] created a significant bias in the pooled ORs of TNM stage, the

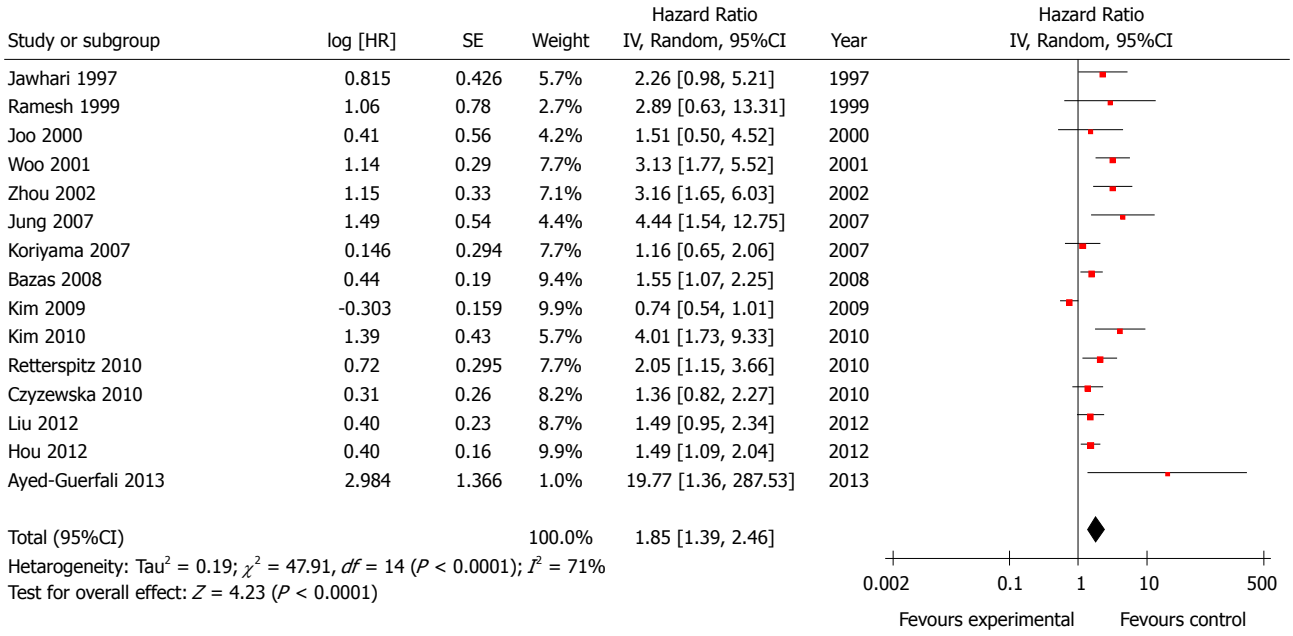


**Figure 2 Meta-analysis of the effects of β-catenin on overall survival of patients with gastric cancer.** Results are presented as individual and pooled HR and 95%CI.

depth of invasion and lymph node metastasis, as well as increased unexpected inter-study heterogeneity. Moreover, Shun's study of early GC was considered unsuitable for the analysis of lymph node metastasis. The funnel plots of publication bias did not exhibit significant asymmetry in the analysis of OS and histopathological features.

## DISCUSSION

In recent years, β-catenin and its associate E-cadherin were proved to be not only static components of adherens junctions, but important mediators of downstream Wnt signaling cascades[8]. As described above, the different localization of β-catenin contributes to cell-cell adhesion or transcriptional activation of responsive target genes. GSK3β, APC, and axin are negative regulators of the Wnt pathway and are functionally assembled in the destruction complex, where β-catenin can be efficiently regulated. This leads to subsequent overexpression of free cytoplasmic β-catenin and exerts a nuclear function without control of tumorigenesis and progression[41,42].

This meta-analysis aimed to examine the association between β-catenin expression, OS and clinicopathological characteristics of GC. When assessing the value of β-catenin expression, researchers tended to separate aberrant β-catenin expression into three patterns: negative β-catenin membranous staining, positive cytoplasmic staining and nuclear staining, and some of the studies included in our analysis combined these three types of expression as the abnormal β-catenin pattern in GC. We assessed the outcomes of patients with GC in 15 studies, and found that β-catenin expression significantly predicted poor OS in GC patients. Subgroup analysis revealed that the combined abnormal pattern of β-catenin (HR = 1.79, 95%CI: 1.39-2.32), instead of an accumulation in the nucleus or loss in the membrane, influenced the survival of GC patients. In addition, positive β-catenin cytoplasmic expression may also be associated with poor prognosis; however, the evidence is limited. We also performed a subgroup analysis using a primary antibody from the Transduction Laboratory (HR = 2.36, 95%CI: 1.06-5.27), to assess the prognostic value of β-catenin expression. The use of antibodies from different resources may have led to potential bias, as the sensitivity of immunohistochemistry usually relies on the condition of the antibody. When evaluating the OR in histopathology, significant correlations were observed between abnormal β-catenin expression and clinicopathological features including Lauren classification, lymph node metastasis, distant metastasis and grade of differentiation, but not TNM stage, the depth of invasion or vascular invasion. These results suggested that β-catenin was expressed more often in diffuse-type GC and undifferentiated tumor, may predict metastasis in patients with advanced GC, and may not be related to tumor stage or invasive route such as blood vessels.

A previous meta-analysis indicated that decreased E-cadherin expression was related to poor OS of gastric carcinoma, as well as being significantly correlated with differentiation, invasion and metastasis[43]. The studies included in our meta-analysis also showed that a decrease in E-cadherin or abnormal β-catenin or both weakened cell-cell adhesion and resulted in cell spread, allowing cancer cell infiltration and metastasis[13,21]. Consistent with the effect on E-cadherin, CagA+ strain of *H. pylori* also has been shown to activate β-catenin to promote intestinal transdifferentiation in gastric epithelial cells[11]. Taking these findings into account, we suggest that abnormal

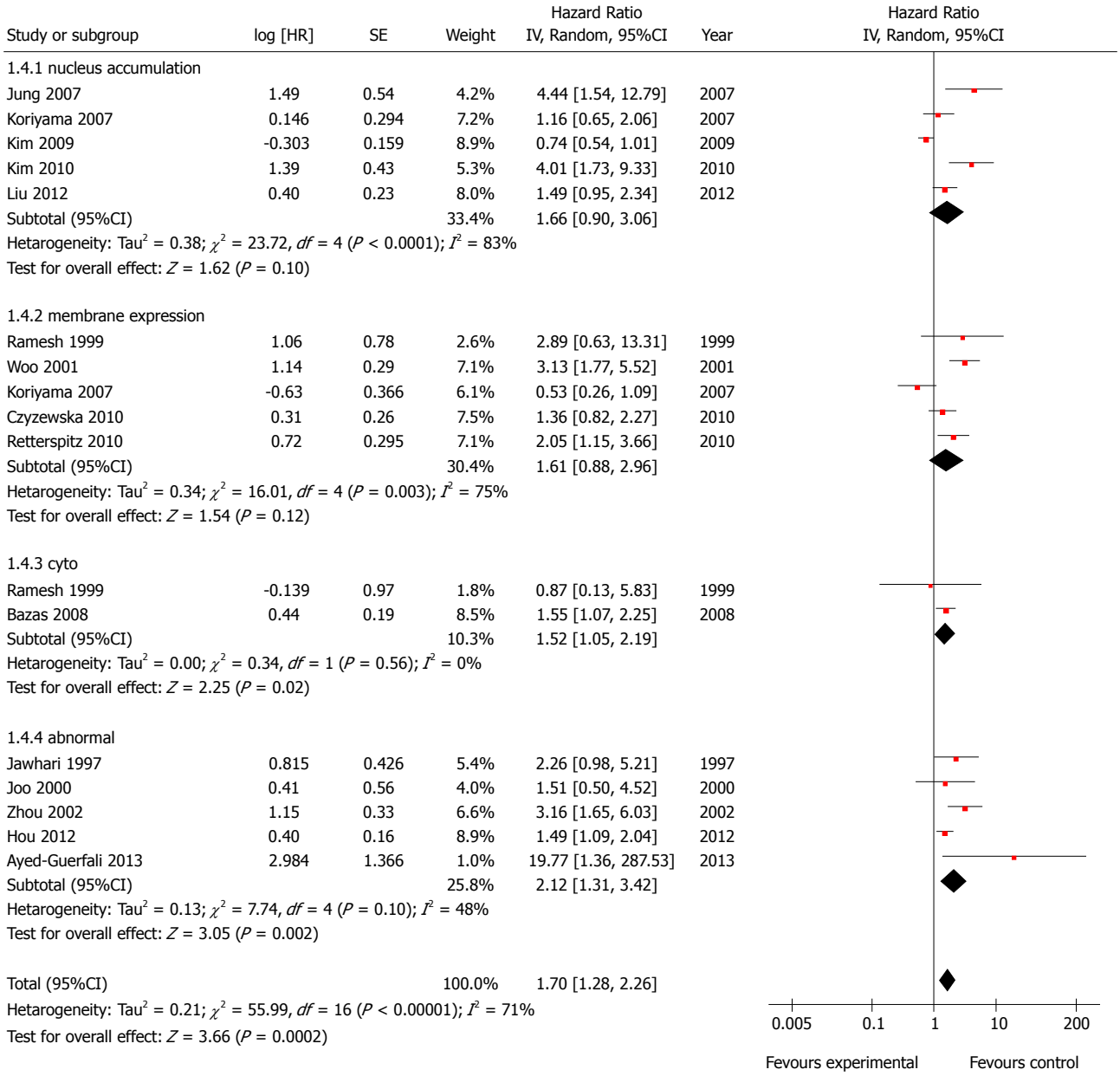


**Figure 3 Subgroup analysis of HR for the association of β-catenin expression with overall survival using different definitions.**

β-catenin expression represents an independent risk factor together with E-cadherin expression for the occurrence and development of GC. However, the role of different β-catenin location in gastric tumor biology remains unclear and should be investigated in future studies.

We found highly significant heterogeneity between the included studies. In the stratified analysis of OS, heterogeneity was not significant in certain subgroup analyses. These findings suggest that the definition of β-catenin, antibody source and number of patients may partly account for this heterogeneity. In our study, most of the included data were derived from articles published after 2000, and this may have led to undetected heterogeneity. Sensitivity analysis did not clarify the source of heterogeneity in the HR analysis, but showed that the OR from Sun *et al*[21] created unexpected heterogeneity. The evaluation of β-catenin staining in this study demonstrated that more than 70% of cell membranes stained positive, unlike other reports which claimed 90% as the cut-off value, and could lead to differential sensitivity. Shun's study[35] on early GC also contributed to heterogeneity in the estimate of OR for lymph node metastasis. It was decided not to incorporate this study in the analysis.

A potential source of bias may be associated with the approach of extrapolating HRs. If HRs were not directly reported in the studies, we calculated them from the data provided in the papers and from the survival curves, assuming that censored observations were identically distributed. Although two of the authors provided graphical representation of the survival curves, this approach did not completely eliminate inaccuracy during extraction of the survival rates. The estimated HR might thus be less reliable

**Table 2 Stratified analysis of pooled hazard ratios**

| Subgroup analysis | Studies (*n*) | Pooled HR (95%CI) | | *P* value | Heterogeneity | |
|---|---|---|---|---|---|---|
| | | Fixed | Random | | $I^2$ (%) | *P* value |
| Definition | | | | | | |
| Abnormal | 5 | | 2.12 (1.31-3.42) | 0.002 | 48 | 0.10 |
| Nucleus accumulation | 5 | | 1.66 (0.90-3.06) | 0.270 | 83 | < 0.0001 |
| Loss of membrane expression | 5 | | 1.61 (0.88-2.96) | 0.0006 | 75 | 0.003 |
| Cytoplasmic expression | 2 | 1.52 (1.05-2.19) | | 0.020 | 0 | 0.56 |
| Study location | | | | | | |
| Asia | 9 | | 1.86 (1.23-2.80) | < 0.0001 | 81 | < 0.00001 |
| Other regions | 6 | 1.70 (1.33-2.19) | | < 0.0001 | 9 | 0.36 |
| No. of patients | | | | | | |
| > 100 | 9 | | 1.82 (1.26-2.64) | 0.002 | 81 | < 0.00001 |
| ⩽ 100 | 6 | 1.81 (1.31-2.49) | | 0.0003 | 3 | 0.40 |
| Publication year | | | | | | |
| > 2000 | 12 | | 1.83 (1.33-2.52) | < 0.00001 | 76 | < 0.00001 |
| ⩽ 2000 | 3 | 2.07 (1.13-3.81) | | 0.020 | 0 | 0.76 |
| Antibody source | | | | | | |
| BD transduction | 3 | | 1.73 (0.64-4.69) | 0.280 | 90 | < 0.0001 |
| Transduction lab | 3 | | 2.36 (1.06-5.27) | 0.040 | 75 | 0.02 |
| Santa cruz | 3 | 1.53 (1.18-1.97) | | 0.001 | 44 | 0.17 |
| Other labs | 6 | 1.75 (1.37-2.25) | | < 0.00001 | 7 | 0.37 |

**Table 3 Meta-analysis of β-catenin expression and clinicopathological features of gastric cancer**

| Clinicopathological features | Studies (*n*) | Cases | Pooled OR (95%CI) | | *P* value | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | Fixed | Random | | $I^2$ (%) | *P* value |
| Lauren classification | 17 | 1793 | | 1.98 (1.19-3.29) | 0.009 | 74 | < 0.00001 |
| TNM stage | 9 | 996 | 1.34 (0.96-1.86) | | 0.080 | 44 | 0.090 |
| The depth of invasion | 10 | 1203 | | 1.48 (0.94-2.33) | 0.090 | 55 | 0.020 |
| Lymph node metastasis | 16 | 2147 | | 2.00 (1.44-2.77) | < 0.0001 | 44 | 0.040 |
| Distant metastasis | 4 | 258 | 2.69 (1.35-5.38) | | 0.005 | 20 | 0.290 |
| Grade of differentiation | 12 | 1372 | | 2.68 (1.66-4.34) | 0.0002 | 58 | 0.006 |
| Vascular invasion | 3 | 774 | 1.11 (0.70-1.76) | | 0.660 | 0 | 0.440 |

TNM: Tumor-node-metastasis.

than when obtained directly from published statistics.

In conclusion, this meta-analysis revealed that β-catenin immunohistochemical expression was associated with poor OS and histopathological features such as Lauren classification, lymph node metastasis, distant metastasis and grade of differentiation in patients with GC. Abnormal β-catenin expression may be a predictive factor of poor prognosis in GC patients, and might predict invasion and metastasis.

## COMMENTS

### Background

Gastric cancer is the second most frequent cause of cancer-related death worldwide. Deregulated β-catenin is involved in the development of multiple tumors. Induced by the process of epithelial-mesenchymal transition, abnormal translocation of β-catenin was found to be essential in several human cancers including gastric cancer.

### Research frontiers

β-catenin has a dual role depending on its intracellular localization. It was proved that membranous expression of β-catenin is responsible for cell-to-cell adhesion, while cytoplasmic and nuclear β-catenin are mainly involved in regulation of the Wnt signaling pathway, contributing to gastric cancer invasion.

### Innovations and breakthroughs

This meta-analysis revealed the prognostic value of β-catenin expression in gastric cancer and identified four patterns: abnormal β-catenin pattern, nucleus accumulation, cytoplasmic overexpression and loss of membranous expression, and examined the association between β-catenin expression and the clinicopathological characteristics of gastric cancer.

### Applications

The results of this study suggest that abnormal β-catenin expression is associated with poor prognosis in patients with gastric cancer, and may predict invasion and metastasis.

### Terminology

β-catenin: β-catenin is a dual function protein, regulating the coordination of cell–cell adhesion and gene transcription. In humans, the β-catenin protein is encoded by the *CTNNB1* gene.

### Peer review

This study evaluated the effect of β-catenin on prognostic value in gastric cancer (GC) patients by conducting a meta-analysis. The findings are significant and reveal that β-catenin immunohistochemical expression is associated with poor OS and histopathological features in GC.

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