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

Li-Fu Li, Zheng-Jie Wei, Hong Sun, Bo Jiang

Li-Fu Li, Zheng-Jie Wei, Hong Sun, Bo Jiang, Guangdong Provincial Key Laboratory of Gastroenterology, Department of Gastroenterology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Author contributions: Li LF and Wei ZJ contributed equally to this study; Li LF designed the study and wrote the manuscript; Li LF and Wei ZJ performed the majority of analyses; Sun H and Jiang B revised the manuscript.

Correspondence to: Bo Jiang, MD, Professor, Guangdong Provincial Key Laboratory of Gastroenterology, Department of Gastroenterology, Nanfang Hospital, Southern Medical University, No. 1838, Guangzhou Avenue North, Guangzhou 510515, Guangdong Province, China. lilifunanfang@foxmail.com

Telephone: +86-20-61641532 Fax: +86-20-61641532

Received: February 18, 2014 Revised: April 3, 2014 Accepted: April 30, 2014 Published online: September 14, 2014

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.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

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.

Li LF, Wei ZJ, Sun H, Jiang B. Abnormal β-catenin immunohistochemical expression as a prognostic factor in gastric cancer: A meta-analysis. World J Gastroenterol 2014; 20(34): 12313-12321 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i34/12313.htm DOI: http://dx.doi.org/10.3748/wjg.v20.
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 Wnt signaling pathway, β-catenin 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 found in about 30% of GC patients[8]. When a Wnt ligand engages with its receptors, 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 expression contribute to a feed-forward loop in invasive 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
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. Otherwise, Kaplan-Meier curves were read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/). Heterogeneity across studies was evaluated using a χ²-based Q statistical test. The I² statistic was also calculated for study heterogeneity. I² > 50 and P ≤ 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 ≤ 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

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 (I² = 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; I² = 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; I² = 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; I² = 83%, P = 0.000) and loss of membranous expression (HR = 1.61, 95%CI: 0.88-2.96; I² = 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; I² = 76%, P = 0.000) and publication year ≤ 2000 (HR = 2.07; 95%CI: 1.13-3.81; I² = 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-
expression (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 (I² = 0%-44%), whereas analysis of other histological features exhibited heterogeneity (I² = 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. created a significant bias in the pooled ORs of TNM stage, the

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

| Ref.          | Year | Study location      | Patient (M/F) | Lauren classification | Antibody source          | Definition of β-catenin expression¹ | NOS |
|---------------|------|---------------------|---------------|-----------------------|--------------------------|------------------------------------|-----|
| Ayed-Guerfali et al.²⁰⁰⁰ | 2013 | Tunisia             | 80 (45/35)    | Intestinal            | Santa Cruz               | Normal/abnormal expression         | 7   |
| Sereno et al.²⁰⁰⁰  | 2012 | Spain               | 44 (33/11)    | Intestinal            | Transduction Laboratories| Normal/abnormal expression         | 6   |
| Hou et al.²⁰⁰⁰   | 2012 | China               | 158 (105/53)  | Mixed                 | Santa Cruz               | Normal/abnormal expression         | 6   |
| Liu et al.²⁰⁰⁰  | 2012 | China               | 134 (90/44)   | Intestinal            | Santa Cruz               | Normal/abnormal expression         | 5   |
| Sun et al.²⁰⁰⁰  | 2012 | China               | 58 (49/9)     | Intestinal            | Santa Cruz               | Normal/abnormal expression         | 5   |
| Ryu et al.²⁰⁰⁰  | 2012 | South Korea         | 276 (NA)      | Intestinal            | BD Biosciences           | Normal/abnormal expression         | 7   |
| Retterspitz et al.²⁰⁰⁰ | 2010 | Germany             | 94 (46/48)    | Intestinal            | BD Transduction          | Membranous expression              | 8   |
| Kim et al.²⁰⁰⁰  | 2010 | South Korea         | 117 (81/36)   | Intestinal            | BD Transduction          | Nuclear expression                 | 8   |
| Czyzewska et al.²⁰⁰⁰ | 2010 | Poland              | 91 (62/29)    | Intestinal            | Novocastra Laboratories  | Membranous expression              | 6   |
| Zali et al.²⁰⁰⁰ | 2009 | Iran                | 56 (38/18)    | Intestinal            | Research Diagnostic      | Normal/abnormal expression         | 8   |
| Kim et al.²⁰⁰⁰  | 2009 | South Korea         | 598 (396/202) | Intestinal            | BD Biosciences           | Nuclear expression                 | 6   |
| Bazas et al.²⁰⁰⁰ | 2008 | Ukraine             | 150 (89/61)   | Intestinal            | Dako Cytomation          | Cytoplasmic expression             | 8   |
| Koriyama et al.²⁰⁰⁰ | 2007 | Japan               | 149 (NA)      | Intestinal            | Transduction Laboratories| Normal/abnormal expression         | 8   |
| Jung et al.²⁰⁰⁰ | 2007 | South Korea         | 111 (NA)      | Intestinal            | Transduction Laboratories| Nuclear expression                 | 9   |
| Nabais et al.²⁰⁰⁰ | 2003 | Portugal            | 97 (NA)       | Intestinal            | Transduction Laboratories| Nuclear and cytoplasmic expression| 7   |
| Zhou et al.²⁰⁰⁰ | 2002 | China               | 163 (123/40)  | Intestinal            | Maxim Biotech Inc.       | Normal/abnormal expression         | 8   |
| Woo et al.²⁰⁰⁰  | 2001 | South Korea         | 303 (205/98)  | Intestinal            | Transduction Laboratories| Membranous expression             | 9   |
| Shun et al.²⁰⁰⁰ | 2001 | Taiwan              | 53 (NA)       | Intestinal            | Transduction Laboratories| Membranous expression             | 6   |
| Grabsch et al.²⁰⁰⁰ | 2001 | Germany             | 401 (NA)      | Intestinal            | Transduction Laboratories| Nuclear and cytoplasmic expression| 6   |
| Joo et al.²⁰⁰⁰  | 2000 | South Korea         | 65 (38/27)    | Intestinal            | Zymed Laboratories       | Normal/abnormal expression         | 7   |
| Karatzas et al.²⁰⁰⁰ | 2000 | Greece              | 36 (NA)       | Intestinal            | Transduction Laboratories| Normal/abnormal expression         | 6   |
| Ohene-Abuakwa et al.²⁰⁰⁰ | 2000 | United Kingdom      | 41 (NA)       | Intestinal            | Transduction Laboratories| Normal/abnormal expression         | 7   |
| Ramesh et al.²⁰⁰⁰ | 1999 | United Kingdom      | 40 (NA)       | Intestinal            | Affinity Research Products Ltd| Normal/abnormal expression         | 8   |
| Jawhari et al.²⁰⁰⁰ | 1997 | England             | 89 (62/27)    | Intestinal            | Affinity Research Products Ltd| Normal/abnormal expression         | 7   |

¹Different β-catenin location in gastric cancer. NA: Not available; M/F: Male/Female; NOS: Newcastle-Ottawa Quality Assessment Scale.
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, \(\beta\)-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\(^\text{[3]}\). As described above, the different localization of \(\beta\)-catenin contributes to cell-cell adhesion or transcriptional activation of responsive target genes. GSK3\(\beta\), APC, and axin are negative regulators of the Wnt pathway and are functionally assembled in the destruction complex, where \(\beta\)-catenin can be efficiently regulated. This leads to subsequent overexpression of free cytoplasmic \(\beta\)-catenin and exerts a nuclear function without control of tumorigenesis and progression\(^\text{[41,42]}\).

This meta-analysis aimed to examine the association between \(\beta\)-catenin expression, OS and clinicopathological characteristics of GC. When assessing the value of \(\beta\)-catenin expression, researchers tended to separate aberrant \(\beta\)-catenin expression into three patterns: negative \(\beta\)-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 \(\beta\)-catenin pattern in GC. We assessed the outcomes of patients with GC in 15 studies, and found that \(\beta\)-catenin expression significantly predicted poor OS in GC patients. Subgroup analysis revealed that the combined abnormal pattern of \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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\(^\text{[8]}\). The studies included in our meta-analysis also showed that a decrease in E-cadherin or abnormal \(\beta\)-catenin or both weakened cell-cell adhesion and resulted in cell spread, allowing cancer cell infiltration and metastasis\(^\text{[3,20]}\). Consistent with the effect on E-cadherin, CagA+ strain of \(H. pylori\) also has been shown to activate \(\beta\)-catenin to promote intestinal transdifferentiation in gastric epithelial cells\(^\text{[11]}\). Taking these findings into account, we suggest that abnormal
**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 fromShun'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

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

| Study or subgroup | log [HR] | SE  | Weight | Hazard Ratio IV, Random, 95%CI | Year |
|-------------------|----------|-----|--------|--------------------------------|------|
| **1.4.1 nucleus accumulation** |          |     |        |                                |      |
| Jung 2007         | 1.49     | 0.54| 4.2%   | 4.44 [1.54, 12.79]             | 2007 |
| Koriyama 2007     | 0.146    | 0.294| 7.2%   | 1.16 [0.65, 2.06]              | 2007 |
| Kim 2009          | -0.303   | 0.159| 8.9%   | 0.74 [0.54, 1.01]              | 2009 |
| Kim 2010          | 1.39     | 0.43 | 5.3%   | 4.01 [1.73, 9.33]              | 2010 |
| Liu 2012          | 0.40     | 0.23 | 8.0%   | 1.49 [0.95, 2.34]              | 2012 |
| **Subtotal (95%CI)** |          |     |        | 33.4%                          | 1.66 [0.90, 3.06] |
| **Heterogeneity: τ² = 0.38; χ² = 23.72, df = 4 (P < 0.0001); I² = 83%** | | | |
| Test for overall effect: Z = 1.62 (P = 0.10) | | | |

| **1.4.2 membrane expression** |          |     |        |                                |      |
| Ramesh 1999         | 1.06     | 0.78| 2.6%   | 1.38 [0.63, 13.31]             | 1999 |
| Woo 2001            | 1.14     | 0.29 | 7.1%   | 3.13 [1.77, 5.52]              | 2001 |
| Koriyama 2007       | -0.63    | 0.366| 6.1%   | 0.53 [0.26, 1.09]              | 2007 |
| Czyzewska 2010      | 0.31     | 0.26 | 7.5%   | 1.36 [0.92, 2.37]              | 2010 |
| Retterspitz 2010    | 0.72     | 0.295| 7.1%   | 2.05 [1.15, 3.66]              | 2010 |
| **Subtotal (95%CI)** |          |     |        | 30.4%                          | 1.61 [0.88, 2.96] |
| **Heterogeneity: τ² = 0.34; χ² = 16.01, df = 4 (P = 0.003); I² = 75%** | | | |
| Test for overall effect: Z = 1.54 (P = 0.12) | | | |

| **1.4.3 cyto** |          |     |        |                                |      |
| Ramesh 1999      | -0.139   | 0.97 | 1.8%   | 0.87 [0.13, 5.83]              | 1999 |
| Bazas 2008       | 0.44     | 0.19 | 8.5%   | 1.55 [1.07, 2.25]              | 2008 |
| **Subtotal (95%CI)** |          |     |        | 10.3%                          | 1.52 [1.05, 2.19] |
| **Heterogeneity: τ² = 0.00; χ² = 0.34, df = 1 (P = 0.56); I² = 0%** | | | |
| Test for overall effect: Z = 2.25 (P = 0.02) | | | |

| **1.4.4 abnormal** |          |     |        |                                |      |
| Jawhari 1997      | 0.815    | 0.426| 5.4%   | 2.26 [0.98, 5.21]              | 1997 |
| Joo 2000          | 0.41     | 0.56 | 4.0%   | 1.51 [0.50, 4.52]              | 2000 |
| Zhou 2002         | 1.15     | 0.33 | 6.6%   | 3.16 [1.65, 6.03]              | 2002 |
| Hou 2012          | 0.40     | 0.16 | 8.9%   | 1.49 [1.09, 2.04]              | 2012 |
| Ayed-Guerfall 2013 | 2.984    | 1.366| 1.0%   | 19.77 [1.36, 287.53]           | 2013 |
| **Subtotal (95%CI)** |          |     |        | 25.8%                          | 2.12 [1.31, 3.42] |
| **Heterogeneity: τ² = 0.13; χ² = 7.74, df = 4 (P = 0.10); I² = 48%** | | | |
| Test for overall effect: Z = 3.05 (P = 0.002) | | | |

| **Total (95%CI)** |          |     |        |                                |      |
|                  | 100.0%   | 1.70| 2.26   | 0.005                          |      |
| **Heterogeneity: τ² = 0.21; χ² = 55.99, df = 16 (P < 0.00001); I² = 71%** | | | |
| Test for overall effect: Z = 3.66 (P = 0.0002) | | | |
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.

**REFERENCES**
1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90 [PMID:...]

---

### Table 2  Stratified analysis of pooled hazard ratios

| Subgroup analysis          | Studies (n) | Pooled HR (95%CI)       | P value | Heterogeneity |
|---------------------------|------------|-------------------------|---------|---------------|
|                           |            | Fixed                   | Random  |               |
| Definition                 |            |                         |         |               |
| Abnormal                  | 5          | 2.12 (1.31-3.42)        | 0.002   | 48            | 0.10          |
| Nucleus accumulation      | 5          | 1.66 (9.03-3.06)        | 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)        | < 0.0001| 76            | < 0.00001     |
| ≤ 2000                    | 3          | 2.07 (1.13-3.81)        | 0.020   | 0             | 0.76          |
| Antibody source           |            |                         |         |               |
| BD transduction lab       | 3          | 1.73 (0.64-4.69)        | 0.290   | 90            | < 0.0001      |
| Transduction lab          | 3          | 2.36 (1.06-5.27)        | 0.040   | 75            | 0.02          |
| Santa cruz                | 3          | 1.53 (1.38-1.97)        | 0.001   | 44            | 0.17          |
| Other labs                | 6          | 1.75 (1.37-2.25)        | < 0.00001| 7             | 0.37          |

TNM: Tumor-node-metastasis.

---

### 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  |               |
| 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 differentation     | 12         | 1372 | 2.68 (1.66-4.34)        | 0.0002  | 58            | 0.036         |
| Vascular invasion           | 3          | 774  | 1.11 (0.70-1.76)        | 0.660   | 0             | 0.440         |

TNM: Tumor-node-metastasis.
β-catenin expression in gastric cancer

21296855 DOI: 10.3322/caac.201017

2. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Cancer 2007; 10:* 75-83 [PMID: 15757615 DOI: 10.1007/s10512-007-0420-0]

3. Brennner H, Ariti V, Sturmer T, Stegmaier C, Ziegler H, Dhom C. Individual and joint contribution of family history and Helicobacter pylori infection to the risk of gastric carcinoma. *Cancer 2000; 88:* 274-279 [PMID: 10640957]

4. Amedei A, Benagiano M, della Bella C, Nicolai E, D’Elios MM. Novel immunotherapeutic strategies of gastric cancer treatment. *J Biomed Biotechnol 2011; 2011:* 437348 [PMID: 22253528 DOI: 10.1155/2011/437348]

5. Micalizzi DS, Farabaugh SM, Ford HL. Epithelial-mesenchymal transition in cancer: parallels between normal development and tumor progression. *J Mammary Gland Biol Neoplasia 2010; 15:* 117-134 [PMID: 20490631 DOI: 10.1007/s10911-010-9178-9]

6. Katoh M. Epithelial-mesenchymal transition in gastric cancer (Review). *Int J Oncol 2005; 27:* 1677-1683 [PMID: 16273224]

7. Scanlon CS, Van Tubergen EA, Inglehart RC, D’Silva NJ. Biomarkers of epithelial-mesenchymal transition in squamous cell carcinoma. *J Dent Res 2013; 92:* 114-121 [PMID: 23128109 DOI: 10.1177/0022034512467735]

8. Schmalhofer O, Brablett S, Brablett T. E-cadherin, β-catenin, and ZEB1 in malignant progression of cancer. *Cancer Metastasis Rev 2009; 28:* 151-166 [PMID: 19153669 DOI: 10.1007/s10555-008-9179-y]

9. Behrens J. Cadherins and catenins: role in signal transduction and tumor progression. *Cancer Metastasis Rev 1999; 18:* 15-30 [PMID: 10505543]

10. Mishra L, Shetty K, Tang Y, Stuart A, Byers SW. The role of TGF-beta and Wnt signaling in gastrointestinal stem cells and cancer. *Oncogene 2005; 24:* 5775-5789 [PMID: 16123810 DOI: 10.1038/sj.onc.1208924]

11. Murata-Kamiya N, Kurashima Y, Teishikata Y, Yamahashi Y, Saito Y, Higashi A, Aburati A, Hikami T, Peer RM, Azuma T, Hatakeyama M. Helicobacter pylori CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncology 2007; 26:* 4617-4626 [PMID: 17237808 DOI: 10.1080/0380575070120251]

12. Oshima H. Oshima M. The role of PGE2-associated inflammatory responses in gastric cancer development. *Semin Immunopathol 2013; 35:* 139-150 [PMID: 23053597 DOI: 10.1007/s00281-012-0353-5]

13. Ayed-Guerfali DB, Hassairi B, Khabir A, Sellami-Boudawara K, Ayed-Guerfali DB, Hassairi B, Khabir A, Sellami-Boudawara K, Koriyama C, Casado E, Feliu J, Gómez C, López M, Barón MG. Expression of APC, β-catenin, and E-cadherin complex in patients with advanced gastric cancer: correlation with tumor progression and prognosis. *Anticancer Res 2010; 30:* 4635-4641 [PMID: 20529814 DOI: 10.1016/j.hec.2011.07.003]

14. Retterspitz MF, Möngig SP, Schreckenberg SC, Schneider PM, Höscher AH, Diens JF, Baldus SE. Expression of [beta]catenin, MUC1, and E-cadherin in diffuse-type gastric adenocarcinoma: correlation with tumor progression and prognosis. *Anti-cancer Res 2010; 30:* 1175-1180 [PMID: 20731820 DOI: 10.2187/nejm20092317]

15. Liu WJ, Ji SR, Sun J, Zhang Y, Liang Z, Zeng HZ. CD146 Expression Correlates with Epithelial-Mesenchymal Transition Markers and a Poor Prognosis in Gastric Cancer. *Int J Mol Sci 2012; 13:* 6399-6406 [PMID: 22754732 DOI: 10.3390/ijms13051399]

16. Ryu HS, Park JY, Kim HH, Kim WH, Lee HS. Combination of epithelial-mesenchymal transition and cancer stem cell-like phenotypes has independent prognostic value in gastric cancer. *Hum Pathol 2013; 42:* 520-528 [PMID: 22018628 DOI: 10.1016/j.humpath.2011.07.003]

17. Kim B, Byun SJ, Kim YA, Kim JH, Lee BL, Kim WH, Chang MS. Cell cycle regulators, APC/β-catenin, NF-kappaB and Epstein-Barr virus in gastric carcinomas. *Pathology 2010; 42:* 58-65 [PMID: 20025482 DOI: 10.3109/00313020903356392]

18. Czyszewska J, Guzinska-Ustymowicz K, Ustymowicz M, Przyuczynik A, Kemona A. The expression of E-cadherin-β-catenin complex in patients with advanced gastric cancer: role in formation of metastasis. *Folia Histochem Cytobiol 2010; 48:* 37-45 [PMID: 20529814 DOI: 10.2478/v10042-010-0017-z]

19. Kamata I, Ishikawa Y, Akishina-Fukasawa Y, Ito K, Akasaka Y, Uzuki M, Fujimoto A, Morita H, Tamao I, Osawa T, Ogata K, Shimokawa R, Igarashi Y, Miki K, Ishii T. Significance of lymphatic invasion and cancer invasion-related proteins on lymph node metastasis in gastric cancer. *J Gastroenterol Hepatol 2009; 24:* 1327-1333 [PMID: 19938308 DOI: 10.1111/j.1440-1746.2009.05810.x]

20. Zali MR, Moaven O, Asadzadeh Aghdaseh H, Ghafarzadegan K, Ahmad KJ, Farzadnia M, Arabi A, Abbaszadegan MR. clinicopathological significance of E-cadherin, β-catenin and p53 expression in gastric adenocarcinoma. *J Res Med Sci 2009; 14:* 239-247 [PMID: 21772990]

21. Kim MA, Lee HS, Lee HE, Kim JH, Yang HK, Kim WH. Prognostic importance of epithelial-mesenchymal transition-related protein expression in gastric carcinoma. *Histopathology 2009; 54:* 442-451 [PMID: 19309396 DOI: 10.1111/j.1365-2559.2009.03247.x]

22. Bazas VM, Lukyanova NY, Demash DV, Galakhov KO, Myasoedov DV. Relation between cell-to-cell adhesion and angiogenesis and clinico-morphological prognostic factors in patients with gastric cancer. *Exp Oncol 2006; 30:* 235-239 [PMID: 18806748]

23. Koriyama C, Akiba S, Itoh T, Sueyoshi K, Minakami Y, Corvalan A, Yonezawa S, Eizuru Y, Uchino Y, Miki I, Shiigi T. Significant of lymphatic invasion and cancer invasion-related proteins on lymph node metastasis in gastric cancer. *J Gastroenterol Hepatol 2009; 24:* 1327-1333 [PMID: 19938308 DOI: 10.1111/j.1440-1746.2009.05810.x]
tric carcinomas. J Korean Med Sci 2007; 22: 855-861 [PMID: 17982235]
33 Nabais S, Machado JC, Lopes C, Seruca R, Carneiro F, Sobrinho-Simões M. Patterns of beta-catenin expression in gastric carcinoma: clinicopathological relevance and mutation analysis. Int J Surg Pathol 2003; 11: 1-9 [PMID: 12598910]
34 Zhou YN, Xu CP, Han B, Li M, Qiao L, Fang DC, Yang JM. Expression of E-cadherin and beta-catenin in gastric carcinoma and its correlation with the clinicopathological features and patient survival. World J Gastroenterol 2002; 8: 987-993 [PMID: 12439911]
35 Shun CT, Wu MS, Lin MT, Chang MC, Lin JT, Chuang SM. Immunohistochemical evaluation of cadherin and catenin expression in early gastric carcinomas: correlation with clinicopathologic characteristics and Helicobacter pylori infection. Oncology 2001; 60: 339-345 [PMID: 11408802]
36 Grabsch H, Takeno S, Noguchi T, Hommel G, Gabbert HE, Mueller W. Different patterns of beta-catenin expression in gastric carcinomas: relationship with clinicopathological parameters and prognostic outcome. Histopathology 2001; 39: 141-149 [PMID: 11493330]
37 Joo YE, Park CS, Kim HS, Choi SK, Rew JS, Kim SJ. Prognostic significance of E-cadherin/catenin complex expression in gastric cancer. J Korean Med Sci 2000; 15: 655-666 [PMID: 11194192]
38 Karatzas G, Karayiannakis AJ, Syrigos KN, Chatzigianni E, Papanikolaou S, Simatos G, Papanikolaou D, Bogris S. Expression patterns of the E-cadherin-catenin cell-cell adhesion complex in gastric cancer. Hepatogastroenterology 2000; 47: 1465-1469 [PMID: 11103788]
39 Ohene-Abuakwa Y, Noda M, Perenyi M, Kobayashi N, Kashi-ma K, Hattori T, Pignatelli M. Expression of the E-cadherin/catenin (alpha-, beta-, and gamma-) complex correlates with the macroscopic appearance of early gastric cancer. J Pathol 2000; 192: 433-439 [PMID: 11113859 DOI: 10.1002/1096-9896(2000)9999:9999<::aid-path723>3.0.co;2-v]
40 Jawhari A, Jordan S, Poole S, Browne P, Pignatelli M, Farthing MJ. Abnormal immunoreactivity of the E-cadherin-catenin complex in gastric carcinoma: relationship with patient survival. Gastroenterology 1997; 112: 46-54 [PMID: 8978342]
41 Barker N. The canonical Wnt/beta-catenin signalling pathway. Methods Mol Biol 2008; 468: 5-15 [PMID: 19099242 DOI: 10.1007/978-1-59745-249-6_1]
42 Huelsken J, Behrens J. The Wnt signalling pathway. J Cell Sci 2002; 115: 3977-3978 [PMID: 12356903]
43 Xing X, Tang YB, Yuan G, Wang Y, Wang J, Yang Y, Chen M. The prognostic value of E-cadherin in gastric cancer: a meta-analysis. Int J Cancer 2013; 132: 2589-2596 [PMID: 23169395 DOI: 10.1002/ijc.27947]

P- Reviewer: Berretta M, Wang Z
S- Editor: Qi Y
L- Editor: Logan S
E- Editor: Ma S
