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Review Article

Aberrant expression of β-catenin in membrane and cytoplasm/nucleus are associated with poor prognosis of gastric cancer: evidence from an updated meta-analysis

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Abstract: The effect of β-catenin expression on the prognosis of gastric cancer (GC) has been investigated by a previous meta-analysis, however, it missed a few studies apparently meeting the inclusion criteria. Recent studies with large sample size further researched this issue, but controversies still remain. To explore the issue clear and draw a firm conclusion to guide clinical practice, the present study updated the meta-analysis by adding these studies. A comprehensive database searching was conducted in the PubMed, EMBASE, and Web of Science in August 2015. After screening, 23 studies with 4212 GC patients were finally included in the meta-analysis. The methodological quality of included studies was assessed by the Newcastle-Ottawa quality assessment scale and the survival data was pooled by STATA 11.0. The results of meta-analysis showed that aberrant expression of β-catenin was associated with a significant increase of mortality risk of GC patients (hazard ratio, 1.63; 95% confidence interval, 1.40-1.90). The subgroup analysis showed that aberrant expression of β-catenin resulted in poor overall survival of GC patients regardless of location of patients, sample size of study, or method of HR estimation. The present study demonstrated that both types of aberrant expression of β-catenin, including overexpression in cytoplasm and/or nucleus and reduced expression in membrane, could be predicative factors of poor prognosis in GC patients.

Keywords: β-catenin, gastric cancer, prognosis, meta-analysis

Introduction

Gastric cancer (GC), according to Globocan 2012 [1], is the fifth most common malignancy globally, but it is the third leading cause of cancer-related deaths. Although recent advances in treatment have improved the prognosis of GC, the overall 5-year survival rate is typically < 20% [2]. This, to some extent, could be blamed to the extensive local invasion and regional lymph node metastasis of GC [3, 4]. Therefore, there is a need to uncover the biological mechanisms underlying the progression of GC, find critical biomarkers and develop strategies to intervene.

β-catenin is a multifunctional protein that plays dual role in the cells. At the cell membrane, it is a key component of the E-cadherin-catenin complex [5], which functions in cell-cell adhesion and displays inhibitory effects against tumor invasion and metastasis [6-8]. However, accumulation of β-catenin in cytoplasm and/or nucleus is the hallmark of the activated Wnt signaling pathway [9, 10], a well-recognized pathway that was associated with the invasion, metastasis of cancers [11-13]. Aberrant expression of β-catenin, including overexpression of β-catenin in cytoplasm and/or nucleus, and reduced expression in membrane, were reported to correlate with progression and poor prognosis of several human tumors [14-18].

A meta-analysis conducted by Li et al. [19] had investigated the effect of β-catenin expression on the prognosis of GC. They found that only

cytoplasmic overexpression of β-catenin expression had an unfavorable effect on overall survival (OS). After then, several studies [20-23] with large sample size further researched this issue. Cui et al. [20] and Di Bartolomeo et al. [21] found that there was no correlation between β-catenin expression and the survival of GC patients. Huang et al. [22] reported that both overexpression of β-catenin in cytoplasm and/or nucleus, and reduced expression in membrane are all prognostic factors for poor survival in GC patients. Until now, controversies still remain. There also is a concern regarding the previous meta-analysis that it missed a few studies apparently meeting the inclusion criteria [24-28]. Adding these missed studies may alter the conclusion and may even avoid misleading clinical practice. Therefore, it is urgent to conduct an updated meta-analysis to clarify the prognostic value of β-catenin in GC patients, drawing a firm conclusion to guide clinical practice.

Materials and methods

The meta-analysis was conducted and reported in accordance with the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) [29].

Inclusion and exclusion criteria

The following criteria should be fulfilled for the included studies: (1) cohort studies with a follow-up period for the survival of GC patients; (2) β-catenin protein expression in the primary GC tissues was examined; (3) the correlation between β-catenin protein expression and the OS of GC patients was evaluated; (4) reported the hazard ratio (HR) and its 95% confidential interval (CI) for OS or had sufficient information to estimate them. Studies were excluded if they were: (1) conference abstracts, editorials, comments, letters, reviews, case reports; (2) articles focusing on the β-catenin expression on animals or cell lines. Only the most complete study was included in the analysis for the studies with duplicate data.

Search strategy

Electronic databases including PubMed, EMBASE, Web of Science were searched using the following terms "β-catenin", "beta-catenin", "CTNNB1" and "gastric cancer". The Mesh terms and variations of each term were used and each database was searched from inception to August 2015. In addition, reference lists of the screened full-text studies were screened to identify additional potentially eligible studies.

Study selection and data extraction

After removing duplicates, two reviewers independently screened the titles and abstracts of studies identified by the search strategy detailed above. And then the full texts of potentially eligible studies were examined to determine whether they were included or excluded.

Using a standard form, two reviewers extracted the following information for included studies: first author andpublication year; location of patients; examination method of β-catenin protein; type of aberrant expression of β-catenin, and patient survival results.

Methodological assessment

The Newcastle-Ottawa quality assessment scale (for cohort study) [29] was used to evaluate the methodological quality of included studies. The scale included eight items of methodology, which were grouped into the three categories of selection, comparability, and outcome. The final score (0-9) was assigned to each study based on them.

Statistical analysis

We used HR with 95% confidence interval (CI) to measure the association between β-catenin expression and the OS of GC patients. The data was obtained directly from the paper or estimated based on the information provided in the article using the methods reported by Tierney et al. [30]. Heterogeneity among studies was assessed by conducting χ^2 test and the I^2 statistics. We pooled the data using a random-effects model if significant heterogeneity was detected ($P<0.1$ or $I^2>50\%$). Otherwise, we used a fixed-effects model.

Subgroup analyses were carried out by location of patients, sample size, type of β-catenin aberrant expression, method of HR estimation and HR calculation. Potential publication bias was evaluated using Egger's test. STATA 11.0 software was used to conduct statistical analysis.

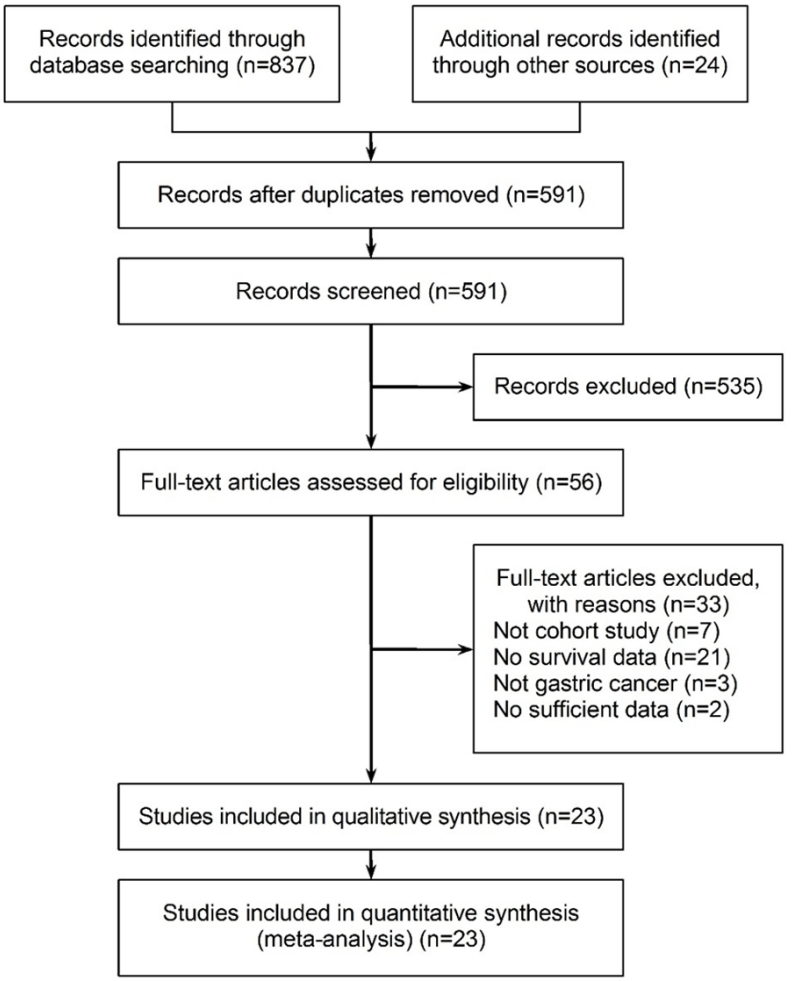

Figure 1. Flow chart of study selection process.

Results

Study selection

We identified 837 articles by database searching and 24 articles by reference screening. After screening the abstract and full-text of these articles, 23 studies [6, 20-28, 31-43] investigating the relationship between β-catenin expression and the OS of GC patients were included in the meta-analysis. The detail of selection process is described in **Figure 1**.

Characteristics and methodological quality of the included studies

Of the 23 included studies, 15 studies [20, 22, 24-26, 28, 32, 34-39, 42, 43] investigated GC patients from Asian countries (including China, Japan and Korea), six studies [6, 21, 31, 33, 40, 41] investigated GC patients from European countries (including Germany, Poland, UK, Italy and Ukraine). The studies were published between 1997 and 2015, and the number of GC tissues they examined ranged from 40 to 598. All the studies used the immunohistochemical method to examine β-catenin expression. The type of aberrant expression of β-catenin differed. Eight studies [24, 31, 32, 35-39] focused on the overexpression of β-catenin in cytoplasm and/or nucleus, while seven studies [21, 26, 28, 33, 40, 42, 43] focused on reduced expression in membrane. HRs with 95% CIs were obtained from the reports in nine studies [20, 21, 23, 24, 26, 32, 38, 39, 41], calculated from available data in nine studies [22, 25, 27, 28, 31, 34, 35, 40, 42], and estimated from Kaplan-Meier curves in five studies [6, 33, 36, 37, 43]. Nine studies used multivariate analysis to calculate HRs [20, 21, 23, 24, 26, 32, 38, 39, 41], and the others used univariate analysis.

The methodological quality of included studies was assessed using the Newcastle-Ottawa quality assessment scale (for cohort study). The total scores they achieved ranged from 6 to 9. The characteristics and methodological quality of included studies are shown in **Table 1**.

Meta-analysis results

HRs with 95% CIs were obtained or estimated from the 23 included studies [6, 20-28, 31-43]. Since significant heterogeneity was detected (I^2=44.1%, P=0.011) among studies, we pooled the data using a random-effects model. The results of meta-analysis showed a statistical significant difference between aberrant expression and normal expression of β-catenin on the OS of GC patients (HR, 1.63; 95% CI, 1.40-

Table 1. Main characteristics of studies included in the meta-analysis

Author	Year	Location; country	No. of specimens	Method	Type of β-catenin aberrant expression	No. of aberrant expression	HR estimation	HR calculation	Quality score
Ayed-Guerfali	2014	Tunisia	80	IHC	NR	49	Reported	Multivariate analysis	7
Bazas	2008	Ukraine	150	IHC	Overexpression in cytoplasm/nucleus	43	Available data calculated	Univariate analysis	6
Cui	2014	China	258	IHC	NR	137	Reported	Multivariate analysis	7
Czyzewska	2010	Poland	91	IHC	NR	48	Kaplan-Meier curve	Univariate analysis	6
Di Bartolomeo	2015	Italy	346	IHC	Reduced expression in membrane	189	Reported	Multivariate analysis	9
Hou	2012	China	158	IHC	Overexpression in cytoplasm/nucleus	36	Reported	Multivariate analysis	6
Huang	2014	China	173	IHC	NR	106	Available data calculated	Univariate analysis	6
Inagaki	2011	Japan	96	IHC	Overexpression in cytoplasm/nucleus	44	Reported	Multivariate analysis	8
Jawhari	1997	UK	87	IHC	Reduced expression in membrane	17	Kaplan-Meier curve	Univariate analysis	6
Joo	2000	Korea	65	IHC	NR	29	Available data calculated	Univariate analysis	6
Jung	2007	Korea	111	IHC	Overexpression in cytoplasm/nucleus	15	Available data calculated	Univariate analysis	7
Kim	2009	Korea	598	IHC	Overexpression in cytoplasm/nucleus	110	Kaplan-Meier curve	Univariate analysis	7
Kim	2010	Korea	117	IHC	Overexpression in cytoplasm/nucleus	12	Kaplan-Meier curve	Univariate analysis	8
Koriyama	2007	Japan	149	IHC	Overexpression in cytoplasm/nucleus	33	Reported	Multivariate analysis	7
Liu	2012	China	134	IHC	Overexpression in cytoplasm/nucleus	81	Reported	Multivariate analysis	6
Ramesh	1999	UK	40	IHC	Reduced expression in membrane	18	Available data calculated	Univariate analysis	9
Retterspitz	2010	Germany	94	IHC	NR	28	Reported	Multivariate analysis	8
Silva	2008	Brazil	490	IHC	NR	445	Available data calculated	Univariate analysis	6
Song	2009	Korea	176	IHC	NR	48	Available data calculated	Univariate analysis	6
Utsunomiya	2000	Japan	82	IHC	Reduced expression in membrane	63	Available data calculated	Univariate analysis	6
Woo	2001	Korea	303	IHC	Reduced expression in membrane	57	Available data calculated	Univariate analysis	6
Yoon	2008	Korea	251	IHC	Reduced expression in membrane	215	Reported	Multivariate analysis	7
Zhou	2002	China	163	IHC	Reduced expression in membrane	73	Kaplan-Meier curve	Univariate analysis	7

IHC, immunohistochemistry; HR, hazard ratio; NR, not reported.

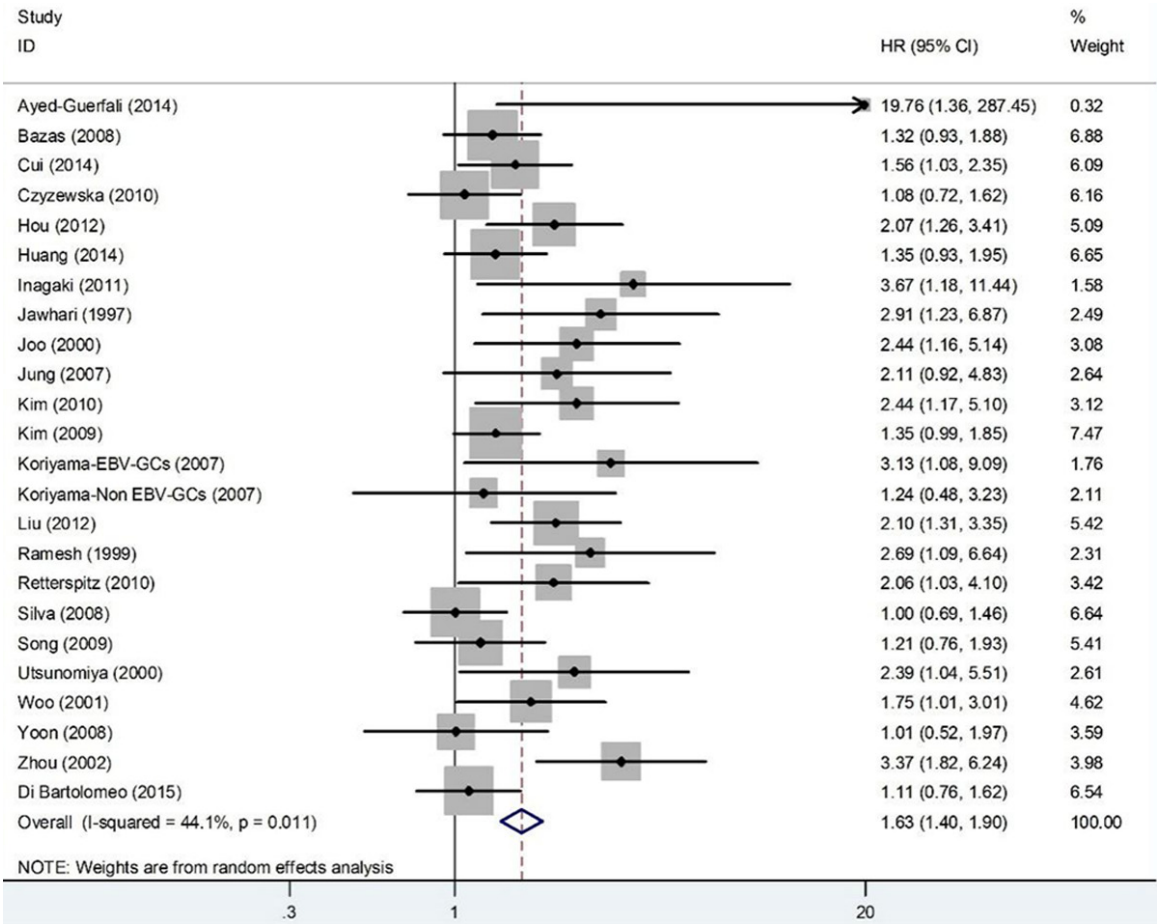

Figure 2. Meta-analysis of β-catenin expression and the overall survival of gastric cancer patients. HR, hazard ratio.

1.90), as shown in **Figure 2**. That is, aberrant expression of β-catenin was associated with a significant increase of mortality risk in GC patients.

Subgroup analysis by location of patients showed that aberrant expression of β-catenin was associated with poor OS in GC patients from European countries (HR, 1.34; 95% CI, 1.10-1.63) and from Asian countries (HR, 1.68; 95% CI, 1.46-1.92), as shown in **Table 2**.

Subgroup analysis by sample size was also conducted. The results pooled from small-sample size (n<100) studies as well as from large-sample size (n>100) studies both showed that aberrant expression of β-catenin was associated with poor OS in GC patients, and the pooled HRs were 2.22 (95% CI 1.48-3.35), and 1.51 (95% CI 1.29-1.77), respectively. As shown in **Table 2**.

The included studies investigated different types of aberrant expression of β-catenin. The subgroup analysis showed that both types of aberrant expression (i.e. overexpression of β-catenin in cytoplasm and/or nucleus and reduced expression in membrane) were associated with poor OS in GC patients. The pooled HRs were 1.65 (95% CI 1.39-1.97), and 1.87 (95% CI 1.27-2.75), respectively. As shown in **Table 2**.

Subgroup analysis showed that method of HR estimation (including directly reported from studies, calculated by available data and estimated from Kaplan-Meier curves) did not alter the significant prognostic impact of aberrant expression of β-catenin. The pooled HRs were 1.71 (95% CI 1.31-2.24), 1.40 (95% CI 1.19-1.66) and 1.86 (95% CI 1.20-2.89), respectively. As shown in **Table 2**.

The HRs calculated by univariate survival analysis were pooled, and the results showed that aberrant expression of β-catenin was associated with poor OS in GC patients (HR, 1.59;

Table 2. Subgroup analysis on the outcome of overall survival

	No. of Studies	No. of specimens	Heterogeneity	Statistical model used	HR (95% CI)
Study location					
Europe	6	808	I^2 = 44.1%; P = 0.111	Fixed	1.34 (1.10, 1.63)
Asia	15	2834	I^2 = 26.5%; P = 0.157	Fixed	1.68 (1.46, 1.92)
Sample size of studies					
<100	8	635	I^2 = 49.6%; P = 0.053	Random	2.22 (1.48, 3.35)
>100	15	3577	I^2 = 39.7%; P = 0.051	Random	1.51 (1.29, 1.76)
Type of β-catenin aberrant expression					
Overexpression in cytoplasm/nucleus	8	1513	I^2 = 19.9%; P = 0.266	Fixed	1.65 (1.39, 1.97)
Reduced expression in membrane	7	1272	I^2 = 60.1%; P = 0.020	Random	1.87 (1.27, 2.75)
HR estimation					
Reported	9	1566	I^2 = 41.8%; P = 0.079	Random	1.71 (1.31, 2.24)
Available data calculated	9	1590	I^2 = 26.6%; P = 0.207	Fixed	1.40 (1.19, 1.66)
Kaplan-Meier curve	5	1056	I^2 = 70.2%; P = 0.009	Random	1.86 (1.20, 2.89)
HR Calculation					
Multivariate analysis	9	1566	I^2 = 41.8%; P = 0.079	Random	1.71 (1.31, 2.24)
Univariate analysis	14	2646	I^2 = 47.8%; P = 0.024	Random	1.59 (1.31, 1.94)

HR, hazard ratio; CI, confidential interval.

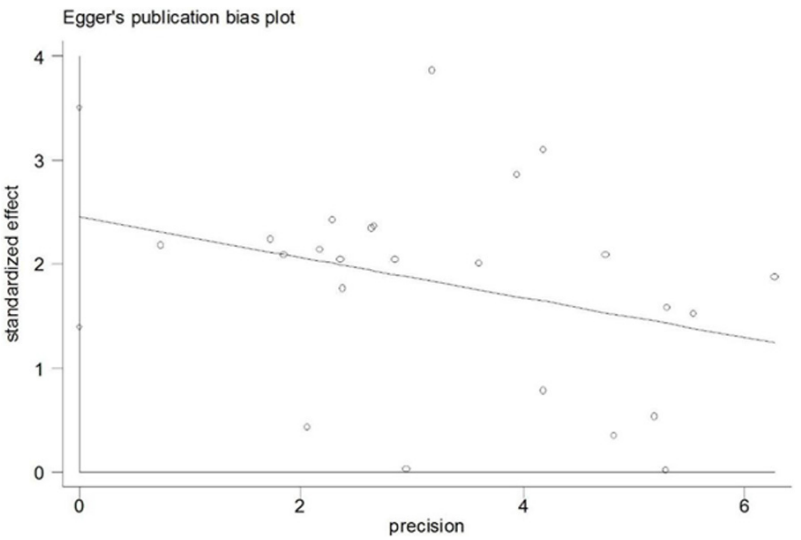

Figure 3. Egger's publication bias plot for the outcome of overall survival.

95% CI, 1.31-1.94). The results pooling HRs calculated by multivariate survival analysis suggested that aberrant expression of β-catenin was an independent prognostic factor for survival in GC patients (HR, 1.71; 95% CI, 1.31-2.24). As shown in **Table 2**.

Egger's test (**Figure 3**) was performed to assess publication bias, and results indicated that there was no publication bias in our meta-analysis (P = 0.171).

Discussion

β-catenin is a multifunctional protein encoded in chromosome 3p21 that expresses in the membrane, cytoplasm and nucleus [44]. At the cell membrane, β-catenin and E-cadherin link to the actin cytoskeleton to constitute E-cadherin-catenin complex [5]. This complex functions in cell-cell adhesion and displays inhibitory effects against tumor invasion and metastasis [5-7]. When one or more components of the E-cadherin-catenin complex were down expressed, the inhibitory effects were removed, and this consequently facilitates tumor progression and metastasis [6, 45, 46]. Reduced expression of β-catenin and/or E-cadherin in the membrane has been reported to correlate with the poor prognosis of a portion of cancers [15, 16, 47-50].

On the other hand, β-catenin is also reported to be an important element of the Wnt signaling pathway [12]. This pathway has been suggest-

ed to plays an important role in proliferation, invasion, and metastasis of cancer cells [10, 51]. In the absence of Wnt ligands, free β-catenin was phosphorylated and then degraded by binding to the glycogen synthase kinase-3β/adenomatous polyposis coli/Axin1 complex [9, 10]. Therefore, β-catenin maintains a low concentration in the cytoplasm. However, when the Wnt signaling is activated by its ligands, glycogen synthase kinase-3β is inactivated, and the phosphorylation and degradation of β-catenin is reduced, which subsequently results in its accumulation in the cytoplasm and translocation to the nucleus [9, 10, 23]. Overexpression of β-catenin in cytoplasm and/or nucleus is associated with activated Wnt signaling pathway as well as the invasion, metastasis and poor prognosis of several cancers [14, 15, 18].

Taken together, both overexpression of β-catenin in cytoplasm and/or nucleus and reduced expression in membrane are associated with tumor progression, and many meta-analyses have reported that aberrant expression of β-catenin correlated with poor prognosis of human cancers, such as non-small cell lung cancer [16], pancreatic cancer [17], hepatocellular carcinoma [18], esophageal carcinoma [15] and colorectal cancer [14].

The correlation between β-catenin expression and the prognosis of GC was also investigated by a meta-analysis [19]. However, it missed a few studies apparently meeting the inclusion criteria, and this may mislead the clinical practice. Moreover, several large-sample studies further researched this issue after the publication of the previous meta-analysis. Adding these studies to update the meta-analysis would explore the issue clear and draw a firm conclusion to guide clinical practice. As an updated meta-analysis, our study analyzed the survival data of 4212 GC patients (from 23 cohort studies), and the results revealed that aberrant expression of β-catenin played an unfavorable role on the survival of GC patients. The subgroup analysis suggested that aberrant expression of β-catenin resulted in poor OS of GC patients regardless of location of patients, sample size of study, type of aberrant expression of β-catenin, or method of HR estimation. We also found that aberrant expression of β-catenin was an independent prognostic factor for survival in GC patients.

There existed significant heterogeneity among the 23 included studies when we pooled the HRs of OS (I^2=44.1%, P=0.011). Subgroup analyses were conducted to explore the potential sources of it. When we grouped the included studies by location of patients, significant heterogeneity was not detected (I^2=44.1%, P=0.111 for group Europe; I^2=26.5%, P=0.157 for group Asia). However, significant heterogeneity still existed when we conducted subgroup analysis by other factors, including sample size of study, type of aberrant expression of β-catenin, and method of HR estimation. This suggested that location of patients may contribute to the heterogeneity in the results.

As a larger sample can yield more accurate results, we conducted subgroup analysis by sample size of studies. The HR pooled from large-sample size (n>100) studies revealed an unfavorable role of aberrant expression of β-catenin, which consisted with the results pooling all the data together. In our study, HRs were obtained from the reports of studies, calculated by available data, or estimated from Kaplan-Meier curves, among which the first way is most reliable. The subgroup analysis showed that different methods of HR estimation resulted in similar results. That is, the results of our meta-analysis were robust. The study also conducted subgroup analysis pooling HRs calculated by multivariate survival analysis and found that aberrant expression of β-catenin is an independent prognostic factor for survival in GC patients

A previous meta-analysis conducted by Li et al. [19] had investigated the effect of β-catenin expression on the prognosis of GC. They searched Pubmed and Embase until 2013, and identified 15 relevant studies [6, 23, 31-43] and found that cytoplasmic overexpression of β-catenin expression, but not accumulation in the nucleus or loss of membrane, had an unfavorable effect on OS. Our study conducted a comprehensive searching up to 2015, and included 23 studies (including 4212 patients), eight [20-22, 24-28] more than that of the previous meta-analysis. We used STATA software instead of Review Manager to pool the HRs. Review Manager is software widely used to conduct meta-analysis, but conversion of raw data is needed when pooling HRs, and this may lead to data loss [52], which could be avoided by STATA. Using STATA, we analyzed the survival

data of 4212 GC patients, and found that both overexpression of β-catenin in cytoplasm and/or nucleus and reduced expression in membrane, were associated with a significant increase of mortality risk of GC patients. Both types of aberrant expression were prognostic factors for survival in GC patients. By conducting subgroup analysis, we also found that aberrant expression of β-catenin was an independent prognostic factor for survival in GC patients. This is a different but a more reliable finding than that of the previous meta-analysis.

Although the results of our meta-analysis were robust, certain limitations should be considered when interpreting the results. Firstly, when assessing the stained type of cancer cells, only five studies [20, 21, 40, 41, 43] reported that they blinded the assessors, which may potentially bias the data. Secondly, eleven studies [6, 22, 24, 25, 28, 31-34, 41, 43] did not report the follow-up details of GC patients, detection bias, therefore, may be introduced to our meta-analysis. Thirdly, because the included studies had different criteria on aberrant expression of β-catenin, we failed to determine the optimal cut-off value for it, and this may limit the translation of our findings to clinical practice.

In conclusion, aberrant expression of β-catenin, including overexpression in cytoplasm and/or nucleus and reduced expression in membrane, is a predicative factor of poor prognosis in GC patients. Further studies should focus on the determination of the optimal cut-off value to define the aberrant expression of β-catenin.

Disclosure of conflict of interest

None.

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