

Original Article

Expression of B7-H4 and gastric cancer progression and prognosis: a meta-analysis

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Received November 28, 2015; Accepted March 25, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Background: Gastric cancer (GC) is one of the most common cancers worldwide. Some studies investigated the association between B7-H4 and GC prognosis. However, the results remained inconclusive. Thus, we performed a meta-analysis. Method: A comprehensive online search was conducted on Pubmed, Embase, Web of Science, Wanfan. The data were extracted by these two authors independently. The strength of association was assessed by calculating OR with 95% CI. Results: Six articles with 704 patients were enrolled in the present study. High expression of B7-H4 was associated with a significantly increased risk of undifferentiated GC (OR=1.72; 95% CI, 1.13-2.60; $I^2=0\%$), lymph node metastasis (OR=4.21; 95% CI, 2.63-6.75; $I^2=1\%$), high clinic stage (OR=4.00; 95% CI, 2.30-6.97; $I^2=47\%$), lymphatic invasion (OR=3.18; 95% CI, 1.58-6.38; $I^2=55\%$), venous invasion (OR=2.11; 95% CI, 1.12-3.95; $I^2=57\%$). However, B7-H4 did not associated with high T stage (OR=1.77; 95% CI, 0.85-3.68; $I^2=60\%$). High expression of B7-H4 was associated with a significantly shorter overall survival (OS) of GC (OR=1.63; 95% CI, 1.30-2.03; $I^2=0\%$). Conclusion: This meta-analysis suggested that high B7-H4 expression might be associated with poor prognosis of GC.

Keywords: Gastric cancer, B7-H4, meta-analysis, association

Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, with around half of all cases occurring in Eastern Asia (mainly China), and is the third leading cause of cancer-related death worldwide [1]. Gastric carcinogenesis is a complex, multistep, and multifactorial process. Several factors such as diet, tobacco smoke, exposure to *Helicobacter pylori* (*H. pylori*), and a history of stomach disorders have been considered potential risk factors [2].

B7-H4, also known as B7x or B7S1, is a member of the B7 family which was expressed on activated antigen presenting cells (APC) [3]. A growing body of literature suggests that B7-H4 on the cell surface binds the putative B7-H4 receptor on activated CD4⁺ and CD8⁺ T cells resulting in the inhibition of effector function via cell cycle arrest, decreased proliferation, and reduced IL-2 production [4]. Overexpression of B7-H4 is seen in various types and stages of ovarian, lung, ductal breast, renal cell, uterine,

and endometrial cancers [5]. In a 4T1 metastatic breast cancer model, B7-H4^{-/-} mice have fewer lung nodules, enhanced survival, and decreased infiltration of immunosuppressive cells (tumor associated macrophages and Tregs) [6], suggesting that B7-H4 plays a role in helping metastasizing cancer cells escape local antitumor immune responses.

The role of B7-H4 in GC is still uncertain. Some studies investigated the association between B7-H4 and GC prognosis. However, the results remained inconclusive [7-12]. Thus, we performed a meta-analysis to clarify the association of B7-H4 and GC prognosis.

Methods

Publication search

A comprehensive online search was conducted on Pubmed, Embase, Web of Science, Wanfang Data from the earliest date to Nov 20, 2015. Free-text words ("Gastric cancer or Gastric car-

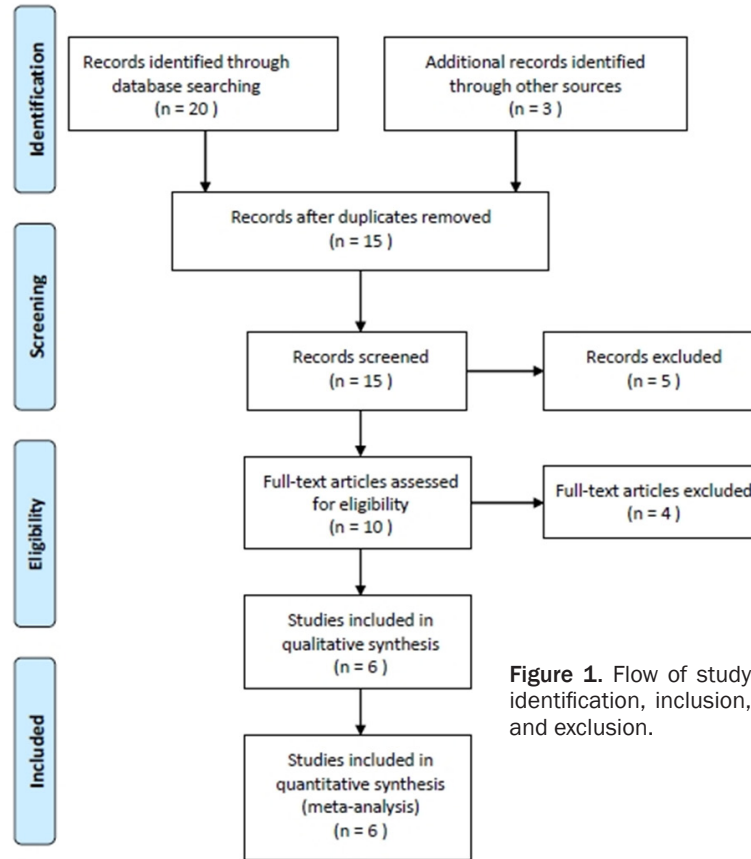


Figure 1. Flow of study identification, inclusion, and exclusion.

cinoma') and ('B7-H4') were searched, with no language or other restrictions. Then studies investigating the association between B7-H4 and GC prognosis were selected through title and abstract. The whole text was reviewed if information in title or abstract is not sufficient to make a decision. Secondary searches of literature were conducted by searching the reference lists of the selected studies and relevant reviews to avoid missing.

Inclusion and exclusion criteria

Case-control or prospective cohort studies were included in our meta-analysis. Patients diagnosed with GC confirmed by pathology were included in case group. Reviews, correspondences, editorial articles and meeting reports were excluded.

Data extraction

Two investigators independently reviewed and extracted data from all the eligible publications. Disagreement was resolved by consen-

sus. Studies in different regions and on different populations were considered as individual ones. The following data were extracted: name, study country, year of publication, source of B7-H4 (blood or tissue), age, gender, number of cases, duration of follow-up, and covariates.

Quality assessment

The included studies were assessed independently by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS employs a star rating system to assess quality from 3 broad perspectives of the study: (1) selection of the study groups, (2) comparability of the groups, and (3) identification of the outcome of interest. Scores ranged from 0 to 9 stars.

Statistical analysis

The strength of association between the B7-H4 and GC prognosis was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The $P > 0.10$ of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model or fixed-effects model. Stratified analysis was performed by country and source of B7-H4. Potential publication bias was examined by Egger's test. All statistical tests were performed with the software Reviewer Manager version 5.2. A P value < 0.05 was considered statistically significant.

Results

Study characteristics

A total of 23 records were found under our search strategy. The complete literature selection process was shown in **Figure 1**. By reviewing title and abstract, we excluded 5 articles. After full text screening, we removed other 4 records. After data extraction from the left 6

Table 1. Characteristics of the included studies

Study	Year	Source of B7-H4	Country	Age	Gender	No. of patients	Follow-up (m)	Quality score	Adjustment for covariates
Arigami	2010	Blood	Japan	68	Mixed	94	25	9	Depth of tumor invasion, Lymph node metastasis
Jiang	2010	Tissue	China	62.2	Mixed	156	120	8	Age, gender, Invasion, Lymph node metastasis
Arigami	2011	Tissue	Japan	65	Mixed	120	40	9	Histological type, Depth of tumor invasion, Lymph node metastasis, Lymphatic invasion, Venous invasion
Geng	2014	Tissue	China	66.4	Mixed	100	>60	8	Differentiation, Lymph node metastasis, Staging, B7-H1, Foxp3
Maskey	2014	Tissue	China	57	Mixed	102	27	7	NA
Shi	2014	Blood	China	61.4	Mixed	132	35	8	Age, gender, Tumor size, Lymph node metastasis, Staging, Depth of tumor invasion

Table 2. The association between B7-H4 and clinicopathological factors

	OR (95% CI)	P value	I ² (%)
Histological type			
Undifferentiated	1.72 (1.13-2.60)	0.01	0
Depth of tumor invasion			
T3-T4	1.77 (0.85-3.68)	0.13	60
Lymph node metastasis			
Positive	4.21 (2.63-6.75)	<0.00001	1
Stage			
III-IV	4.00 (2.30-6.97)	<0.00001	47
Lymphatic invasion			
Positive	3.18 (1.58-6.38)	0.001	55
Venous invasion			
Positive	2.11 (1.12-3.95)	0.02	57

articles, 704 patients were enrolled in the present study. Of the included study, 2 studies were conducted in Japan and 4 in China. As regards to source of B7-H4, 2 studies were conducted in blood and 4 in tissue. The characteristics of studies are presented in **Table 1**.

B7-H4 and clinicopathological factors

The results of the association between B7-H4 and clinicopathological factors are summarized in **Table 2**. High expression of B7-H4 was associated with a significantly increased risk of undifferentiated GC (OR=1.72; 95% CI, 1.13-2.60; $I^2=0\%$; **Figure 2**), lymph node metastasis (OR=4.21; 95% CI, 2.63-6.75; $I^2=1\%$; **Figure 4**), high clinic stage (OR=4.00; 95% CI, 2.30-6.97; $I^2=47\%$; **Figure 5**), lymphatic invasion (OR=3.18; 95% CI, 1.58-6.38; $I^2=55\%$; **Figure 6**), venous invasion (OR=2.11; 95% CI, 1.12-3.95; $I^2=57\%$; **Figure 7**). However, B7-H4 did not associated with high T stage (OR=1.77; 95% CI, 0.85-3.68; $I^2=60\%$; **Figure 3**). Egger's test found no evidence of publication bias ($P>0.05$).

B7-H4 and survival of GC

The results of the association between B7-H4 and survival of GC are summarized in **Table 3**. High expression of B7-H4 was associated with a significantly shorter overall survival (OS) of GC (OR=1.63; 95% CI, 1.30-2.03; $I^2=0\%$; **Figure 8**). In subgroup analysis of country, both patients from Japan (OR=1.49; 95% CI, 1.08-2.06; $I^2=0\%$) and China (OR=1.77; 95% CI, 1.30-2.41; $I^2=0\%$) showed similar results. In subgroup analysis of source of B7-H4, both B7-H4 from blood (OR=1.71; 95% CI, 1.09-2.68; $I^2=0\%$) and tissue (OR=1.60; 95% CI, 1.03-2.07; $I^2=0\%$) also showed similar results. When the results were adjusted by age, gender, depth of tumor invasion, lymph node metastasis, or stage, the results were still positive (**Table 3**). Egger's test found no evidence of publication bias ($P>0.05$).

Discussion

In this study, we included six studies to estimate the association of B7-H4 and gastric cancer progression and prognosis. We found that GC patients with high B7-H4 showed increased risk of undifferentiated GC, lymph node metastasis, high clinic stage, lymphatic invasion, and venous invasion. Therefore, it was possible that GC patients with high B7-H4 might have shorter OS. We thus performed a meta-analysis of B7-H4 and OS in GC patients. The result showed that high expression of B7-H4 was associated with a significantly lower OS of GC. Small inter-study heterogeneity showed in Q test and I^2 and insignificant publication bias suggested the power of our results.

Matsunaga et al. suggested that B7-H4 expression was closely related to the depth of inva-

B7-H4 and gastric cancer

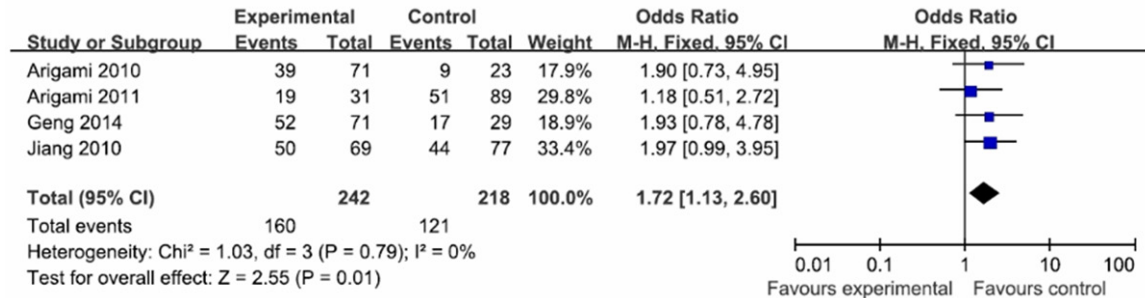


Figure 2. Meta-analysis for the association between B7-H4 and histological type.

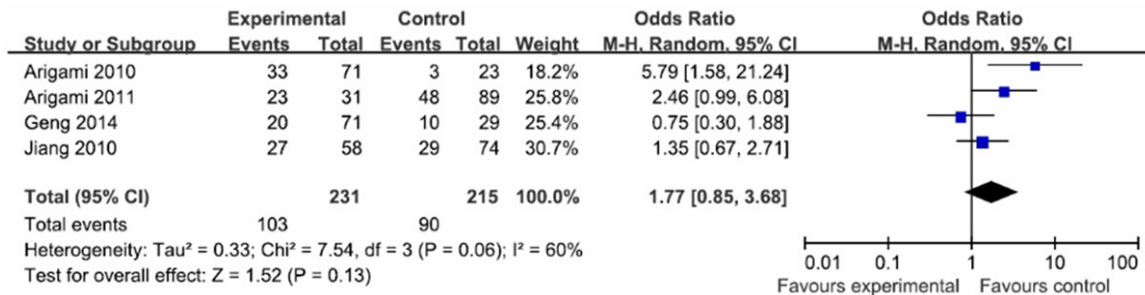


Figure 3. Meta-analysis for the association between B7-H4 and depth of tumor invasion.

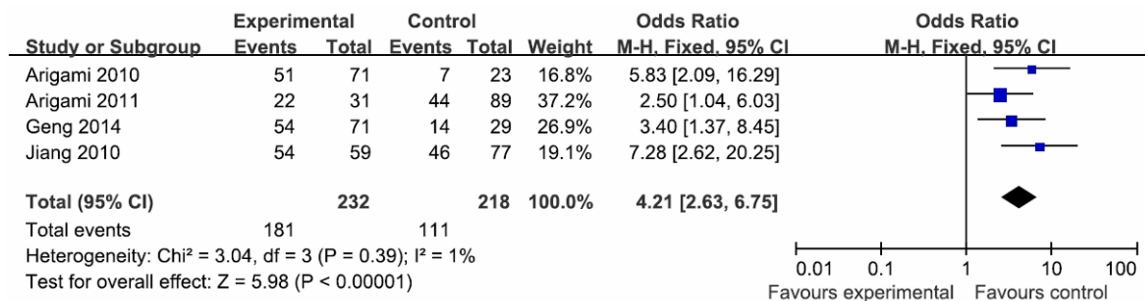


Figure 4. Meta-analysis for the association between B7-H4 and lymph node metastasis.

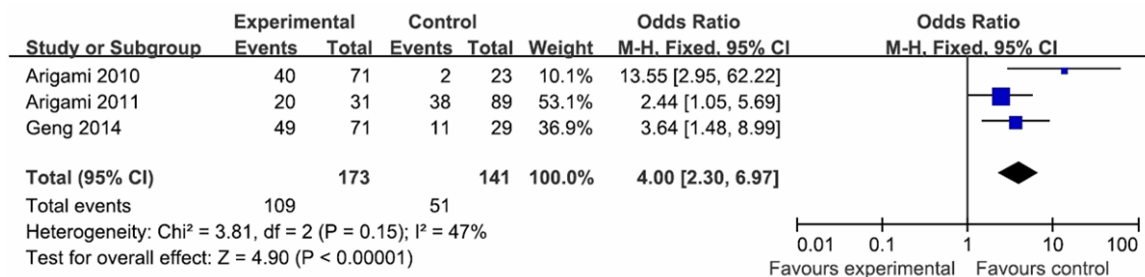


Figure 5. Meta-analysis for the association between B7-H4 and stage.

sion, as well as the presence of lymphatic and venous invasion [13], which was consistent

with our results. In addition, Wang et al. found that high B7-H4 expression was associated

B7-H4 and gastric cancer

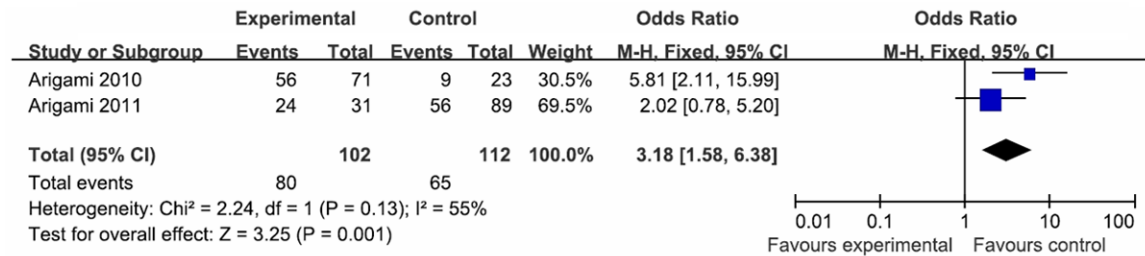


Figure 6. Meta-analysis for the association between B7-H4 and lymphatic invasion.

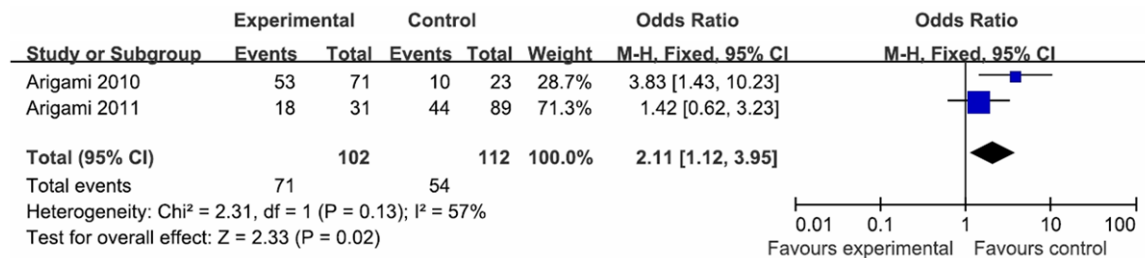


Figure 7. Meta-analysis for the association between B7-H4 and venous invasion.

Table 3. The association between B7-H4 and OS of patients with GC

	OR (95% CI)	P value	I ² (%)
Overall	1.63 (1.30-2.03)	<0.0001	0
Country			
China	1.77 (1.30-2.41)	0.0003	0
Japan	1.49 (1.08-2.06)	0.01	0
Source of B7-H4			
Blood	1.71 (1.09-2.68)	0.02	0
Tissue	1.60 (1.03-2.07)	0.0003	0
Adjust			
Age and gender	1.88 (1.29-2.74)	0.001	0
Depth of tumor invasion	1.57 (1.18-2.09)	0.002	0
Lymph node metastasis	1.63 (1.30-2.03)	<0.0001	0
Stage	1.71 (1.13-2.56)	0.01	0

with advanced TNM stage and lymph node metastasis in esophageal squamous cell carcinoma. Patients with B7-H4 high-expressed tumors had the poorest prognosis, whereas those with both low-expressed tumors had the best survival [14]. Recently, Xu et al. indicated that measurement of sB7-H4 might be useful diagnostic value for malignant effusion [15]. However, recent study investigated the role of B7-H4 in tumor development and show that

B7-H4 expression inhibits tumor growth in two mouse models [16].

To notify, there are several limits in our current study. First of all, although our subgroup analysis showed positive results, our results were based on only five studies. Consequently, the lack of power due to the small number of studies leaves it an open field for future studies. Subsequent studies involving more patients are needed to further confirm our findings. Second, we did not have enough information of individual patients such as age, alcohol consumption, and smoking history, etc. Thus, we could not do subgroup analysis based on these factors.

In conclusion, this meta-analysis suggested that high B7-H4 expression might be associated with poor prognosis of GC.

Disclosure of conflict of interest

None.

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B7-H4 and gastric cancer

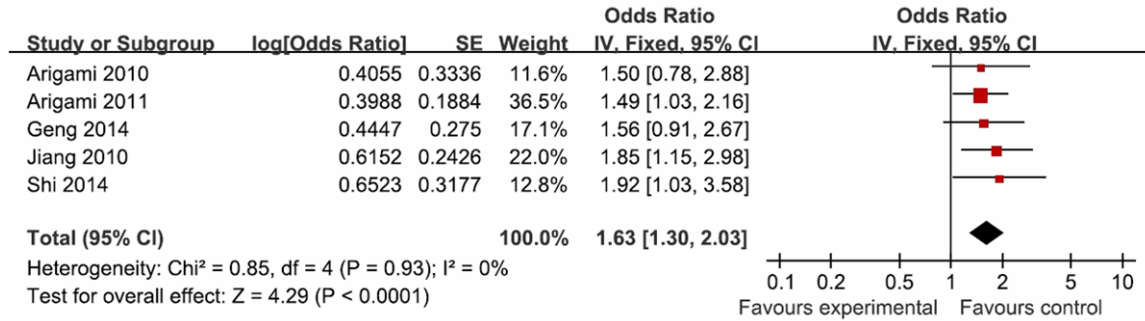


Figure 8. Meta-analysis for the association between B7-H4 and OS of GC patients.

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