International Journal of Surgery 39 (2017) 214–220

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Prognostic and clinical significance of claudin-1 in colorectal cancer: A systemic review and meta-analysis

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HIGHLIGHTS

- The studies of claudin-1 expression in colorectal cancer(CRC) have become more and more, whereas there still exist different arguments about the effects of claudin-1 in colorectal cancer.
- Low expression of claudin-1 is associated with TNM III-IV stage and poor prognosis of CRC patients. Low expression of claudin-1 is not associated with gender, depth of invasion, lymph node involvement, tumors' differentiation of CRC patients.
- Claudin-1 is a candidate novel prognostic biomarker for CRC patients.

ARTICLE INFO

Article history:
Received 10 November 2016
Received in revised form
5 February 2017
Accepted 6 February 2017
Available online 10 February 2017

Keywords:
Claudin-1
Colorectal cancer
Prognosis
Meta-analysis

ABSTRACT

Background: The current reports on the association of claudin-1 expression with colorectal cancer (CRC) result were controversial. Thus, we conducted a meta-analysis to assess the correlation between claudin-1 expression and the clinical parameters and assess the prognostic value of claudin-1 in CRC.

Methods: Systematic searches on PubMed, Embase, Elsevier, CNKI (China National Knowledge Infrastructure), Wanfang data and Cochrane Library prior to August 2016 were performed. The pooled odds ratio (OR) with its 95% confidence interval (95 %CI) was used to assess association between claudin-1 expression and clinical parameters of CRC patients, and to assess association between claudin-1 expression and the prognostic value of CRC patients.

Results: Eight studies with a total of 1146 CRC patients were included. Overall, the pooled results showed that low expression of claudin-1 was associated with TNM III-IV stage of CRC patients (OR: 1.714, 95%CI: 1.215–2.418, $P = 0.002$). Low expression of claudin-1 was also associated with a poor survival in CRC patients (one year survival rate: OR: 2.112, 95%CI: 1.028–4.339, $P = 0.042$; three years survival rate: OR: 1.501, 95%CI: 1.030–2.186, $P = 0.035$; five years survival rate: OR: 1.794, 95%CI: 1.139–2.439, $P = 0.000$). Whereas, low expression of claudin-1 is not associated with gender (OR: 1.259, 95%CI: 0.957–1.657, $P = 0.100$), tumors' differentiation (OR: 1.317, 95%CI: 0.916–1.892, $P = 0.137$), depth of invasion (OR: 1.016, 95 %CI: 0.701–1.472, $P = 0.935$) and lymph node metastasis group (OR: 1.286, 95% CI: 0.982–1.684, $P = 0.06$) of CRC.

Conclusions: Low expression of claudin-1 is associated with TNM III-IV stage and poor prognosis of CRC patients. Low expression of claudin-1 is not associated with gender, tumors' differentiation depth of invasion and lymph node involvement of CRC patients.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignant cancers of digestive system, it is estimated that an annual increase of one million new cases in the world [1,2]. Despite the advancement of medical treatment, approximately a half million of CRC patients die of CRC or primary metastatic disease [3]. It has been

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http://dx.doi.org/10.1016/j.ijsu.2017.02.005
1743-9191/

done in a try to understand the pathogenesis and assess the prognosis of CRC, So, there is an urgent need to find markers to estimate the prognosis of CRC that can stratify patients earlier and better by their risk of CRC recurrence and overall survival (OS) [4,5].

Claudins are major integral cell membrane tight junction proteins which play a vital role in the formation and function of tight junctions and claudin family consists of at least 24 members [6–8]. The main functions of claudin-1 are to regulate paracellular permeability and maintain the cell polarity [8]. These functions are believed to keep inter-cellular adhesion, which prevent the release of cancer cells from the primary cancer nests [9]. Simultaneously, it also decrease the access of tumor cells to nutrients and signaling peptides [10,11]. It is now clear that claudin-1 is frequently reside in various cancers. For example, some studies have demonstrated claudin-1 is frequently up-regulated in pancreatic and thyroid cancers [12–16]. However, some reports showed that claudin-1 also have abnormal expression in CRC [17]. But, the relationship between claudin-1 expression and clinical parameters, such as gender, tumors' differentiation, depth of invasion, lymph node metastasis, TNM stage and OS in CRC, are yet inconsistent. Masatsune et al. reported low claudin-1 expression is associated with lymph node metastasis, tumors' differentiation, extent of poorly-differentiated component, reduced OS [6]. However, Youshida et al. indicated that the expression levels of claudin-1 is not significant differences with gender, depth of invasion, lymph node metastasis and TNM stage [11]. Considering the inconsistent results of current findings, we, therefore, performed a meta-analysis of all eligible studies available to explore the relationship between level-expression of claudin-1 and the CRC.

2. Methods

2.1. Search strategy

We searched PubMed, Embase, Elsevier, CNKI(China National Knowledge Infrastructure), Wanfang data and Cochrane Library for all articles and conference abstracts to identify relevant articles published prior to August 2016. No language restriction was applied. The following key words were used: “colorectal cancer (carcinoma)” or “rectal cancer (carcinoma)” or “colonic cancer (carcinoma)”, “claudin-1” or survival or prognosis. Reference lists of the identified articles were examined and the literature retrieval was performed in duplication by two independent reviewers.

2.2. Inclusion and exclusion criteria

Criteria for eligibility of a study in this meta-analysis were: (1) the patients were diagnosed clearly with CRC and investigated for claudin-1 expression status. (2) study is focused on the relationship between claudin-1 expression and clinicopathologic parameters or/and overall survival rates in CRC; (3) immunohistochemistry (IHC) was used as the main method to determine claudin-1 expression in CRC specimens. (4) Hazard ratios (HR) for overall survival rates according to claudin-1 expression were reported or could be calculated from the published data.

Studies were excluded if (1) studies without original data; animal or laboratory studies; (2) the samples came from lymph nodes or the peritoneal cavity; (3) repeated studies were based on the same database or patients; (4) none of these patients received adjuvant chemoradiation.

2.3. Quality assessment

The quality of each study was assessed using the Newcastle Ottawa Quality Assessment Scale (NOQAS) by two independent reviewers [8]. These scales were used to allocate a maximum of nine points for quality of selection, comparability, exposure, and outcome of study participants. The studies considered to be of high methodological quality (score above 6) were included in this meta-analysis.

2.4. Data extraction

All data were extracted by two independent reviewers. Discrepancies were resolved by discussions and referring to the contents of the articles. We extracted the name of first author, year of publication, region or country where the study was conducted, name of journal, IHC methodology, size of study population and quality score of each study. In studies that reported OR in both univariate and multivariate models, we extracted the latter because these results were more convincing, as there had been adjustment for potential confounders.

2.5. Statistical analysis

The odds ratios (OR) was used to quantitatively determine the association between claudin-1 expression and clinicopathologic parameters of CRC, including age, gender, tumors' differentiation, depth of invasion, lymph node metastasis, TNM-stage, while the OR was used to quantitatively assesses the association between claudin-1 expression and survival rate of CRC. If the OR and 95% confidence intervals (CI) was not provided directly in the study, we can use method reported by Tierney [18]. To calculate these value available data in study. Heterogeneity assumption was evaluated using the chi-squared based Q-test and I^2 test. The mild heterogeneity is I^2 values < 25%, I^2 values between 25 and 50% is a moderate heterogeneity. I^2 values > 50% and *P*-values≥0.1 were considered to have a large heterogeneity [19]. For a large heterogeneity, we can use a fixed-effects model or random-effects model calculate the pooled estimates. A diagnosis of publication bias was provided by Egger test and inverted funnel plots. All statistical tests in this meta-analysis were performed using Stata10.0 software (Stata Corporation, College Station, TX, USA) with two-tail *P* values. *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Search results and study characteristics

The initial search yielded 35 studies. After screening of the titles, abstracts, 18 records were excluded. Among the other 17 articles, 9 articles were excluded, including cell assay only (N = 3), lack of clinical data and statistical analysis (N = 4), abstract only (N = 1), review only (N = 1). Thus a total of eight studies were eventually included in this study based on the predefined criteria [2,6,9,11,17,27–29]. Fig. 1 details the selection process. Among these eight studies, four were from Japan, two were from China, one was from USA, and one was from Egypt. Altogether, these eight studies recruited a total of 1164 CRC, with sample sizes ranged from 50 to 344. Eight articles were published between 2005 and 2013. All the studies used IHC methods for claudin-1 staining. Their basic characteristics and quality are summarized in Table 1.

3.2. Claudin-1 expression and gender

The pooled results of five studies with 976 patients, including 570 males and 406 females, failed to show the significant association between expression of claudin-1 and gender of CRC (OR: 1.259, 95%CI: 0.957–1.657, $P = 0.100$). See Fig. 2. The results of this meta-analysis showed low expression of claudin-1 was not associated with gender.