Clinics and Research in Hepatology and Gastroenterology (2016) 40, 246—253

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

# The prognostic role of Leucine-rich repeat-containing G-protein-coupled receptor 5 in gastric cancer: A systematic review with meta-analysis

**Tianchen Huang**[a,b], **Xinguang Qiu**[a,*], **Jianan Xiao**[b], **Qingbing Wang**[b], **Yanjun Wang**[b], **Yong Zhang**[b], **Dongxiao Bai**[b]

[a] *Department of General Surgery, The First Affiliated Hospital of Zhengzhou University, 28, Jianshe Road, 450052 Zhengzhou, China*
[b] *Anyang cancer hospital, 455000 Anyang, China*

Available online 19 September 2015

**Summary**
*Background and objective:* The prognostic value of Leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5) in gastric cancer remains controversial. To further investigate this relationship, we performed meta-analyses to systematically review the association between LGR5 expression and various clinical parameters in gastric cancer patients.
*Method:* Eligible studies from PubMed, Embase, Web of Science, CNKI (Chinese National Knowledge Infrastructure), Wangfang (Database of Chinese Ministry of Science & Technology) and CBM (China Biological Medicine) databases were evaluated to investigate the association of LGR5 expression with overall survival (OS) and clinicopathological features of gastric cancer.
*Results:* LGR5 overexpression was significantly associated with poor OS in patients with gastric cancer (HR 1.66, 95% CI 1.02—2.69). LGR5 overexpression was also significantly associated with TNM stage (TIII/TIV vs TI/TII: OR 5.42, 95% CI 1.02—28.72) and lymph node metastasis (positive vs negative: OR 2.30, 95% CI 1.06—5.0).
*Conclusions:* Our meta-analysis indicates that LGR5 may be a predictive factor for invasion and metastasis, and poor prognosis in patients with gastric cancer.


## Introduction

Gastric cancer is an aggressive malignancy, and the second most frequent cause of cancer-related deaths worldwide

* Corresponding author.
*E-mail address:* qiuxguang@163.com (X. Qiu).

http://dx.doi.org/10.1016/j.clinre.2015.07.009

[1]. Despite advances in surgical techniques, chemotherapy and radiotherapy, the survival rate of gastric cancer patients remains low, with a 5-year survival rate of < 30% [2]. At the time of diagnosis, the majority of gastric cancer patients are at an advanced stage. Therefore, the identification of prognostic markers, which will facilitate the development of preventive measures and improve the outcome of patients with gastric cancer, is necessary. However, the molecular mechanisms underlying the development of gastric cancer have not been fully elucidated [3]. To improve the clinical care of patients with gastric cancer, the identification of new, biologically relevant prognostic markers is necessary.

Several molecular markers, such as matrix metalloproteinase 2 (MMP-2), E-cadherin, epidermal growth factor (EGF), *p*53 and vascular endothelial growth factor (VEGF), are associated with prognosis in patients with gastric cancer [4—7]. Within the category of biomarkers, Leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5) expression has recently attracted significant attention. Lgr5 is a member of the G-protein-coupled receptor family of proteins and is also thought to be a target of Wnt signaling [8,9]. Overexpression of LGR5 has been reported in various human carcinomas. Furthermore, an increasing number of studies have demonstrated the involvement of LGR5 in tumor development and progression, and LGR5 is considered a prognostic biomarker [10—15].

Several studies have described the relationship between LGR5 expression and prognosis in gastric cancer [16—21]. These reports were inconsistent, however, with several studies drawing statistically insignificant results [17], and in certain cases, completely opposite results [16]. Despite this, LGR5 expression may still represent a meaningful biomarker for the assessment of gastric cancer. Considering the weakness of individual studies, we therefore conducted a systematic review and meta-analysis to assess the prognostic significance of LGR5 in gastric cancer.

## Materials and methods

### Search strategy and selection criteria

This systematic review and meta-analysis was reported and conducted following the PRISMA statement [22]. The criteria for inclusion of a study were as follows:

- patients with distinctive gastric cancer diagnosis by pathology;
- an assessment of the relationships between LGR5 expression and gastric cancer patients;
- publication in English or Chinese;
- assessment of LGR5 expression in primary tumor tissues by immuno-histochemistry (IHC).

A literature search was performed in PubMed, Embase, Web of Science, CNKI (Chinese National Knowledge Infrastructure), Wangfang (Database of Chinese Ministry of Science & Technology), and CBM (China Biological Medicine) databases for clinical studies published before September 2014 (CNKI, Wangfang and CBM databases are the top three Chinese medical databases). Searches were performed using the following terms: gastric cancer, Leucine-rich repeat-containing G-protein-coupled receptor 5 or LGR5. The references of all relevant articles were evaluated to find additional related studies. All studies were carefully examined to avoid the inclusion of duplicate data. Two reviewers (T. Huang and X. Qiu) independently assessed the eligibility of the screened studies. Agreement was reached for the discrepancies by discussion.

### Data extraction and management

Data were independently extracted by two investigators (T. Huang and X. Qiu), using a predefined form. Topics in this form included author's name, year of publication, study location, number of patients and tumor characteristics.

### Methodological assessment

Methodological assessment for each of the included studies was performed by three investigators (T. Huang, J. Xiao and Q. Wang) and scored according to the European Lung Cancer Working Party (ELCWP) scale established by Steels et al. [23]. The score assessed several aspects of methodology, classified into four major groups: scientific design, description of IHC methods, generality of results and analysis of the study data. Each category had a maximal score of 10 points with an overall maximum theoretical score of 40 points. The final scores were expressed as percentages, with higher values reflecting higher methodological quality.

### Statistical analysis

In this meta-analysis, HR and 95% CI values were used to calculate the overall survival estimate. Several studies provided HR and 95% CI explicitly. If HR and 95% CI were not directly reported, these values were calculated from data in the original studies using the methods described by Parmar et al. [24]. Heterogeneity was assessed using Cochran Q and I2 statistics and considered significant at $P < 0.1$. When heterogeneity was significant, we used a random-effect model. Otherwise, a fixed-effect model was used. For analysis of the association of LGR5 expression and clinicopathological features, odds ratios (ORs) and their 95% CIs were applied to estimate the effect. An observed HR or OR > 1 implied worse survival for the group with overexpression of LGR5 or the association between overexpression of LGR5 and malignant clinicopathological characteristics. HR and OR values for studies were pooled using Stata 12.0 software (StataCorp, College Station, TX, USA). Publication bias was evaluated using the Begg's funnel plot [25].

## Results

### Study selection and characteristics

A total of 158 reports were retrieved from the databases described above, using the search strategies described. After exclusion of reports that were out of the scope of our systematic review, 20 reports assessing the clinical value of LGR5 status in patients with gastric cancer were considered eligible for inclusion in the evaluation. Following