1. Introduction

Gastric cancer is one of the most commonly diagnosed cancers and presently the third leading cause of cancer-related deaths in the world. In recent years, although the incidence of gastric cancer has declined, it is still an important disease that threatens human health. In China, gastric cancer is ranked second in incidence and mortality. Generally, when gastric cancer is detected, the patient is already in the advanced stage, accompanied by lymph node metastasis. Surgery, radiotherapy, and chemotherapy are ineffective for patients with advanced gastric cancer. Therefore, the early diagnosis of gastric cancer and the study of its mechanism are greatly important for the prevention and treatment of gastric cancer.

Sex-determining region Y (SRY)-like high-mobility group (HMG) box 2 (SOX2) is a family of transcription factors with a characteristic of HMG DNA binding region, which is highly conserved in eukaryotes. SOX2 is a major member of the SOX gene family; it is expressed in embryonic stem cells and plays an important role in the development of embryos. In the process of human development, SOX2 is mainly involved in the development and differentiation of the gastrointestinal tract during the embryonic stage, which is mainly related to the formation of esophagus and stomach. Recent studies have shown that SOX2 is also a marker of embryonic stem cells and plays a key role in maintaining self-renewal and multi-directional differentiation of embryonic stem cells. It is often used as a molecule of pluripotent cell lineage. In
recent years, SOX2 has been found to be highly expressed in different types of tumors, such as lung cancer, pancreatic cancer, breast cancer, colorectal cancer, and gastric cancer.\(^7\)\(^{-10}\)

However, the role of SOX2 expression in gastric cancer is complicated. In recent studies, low SOX2 expression presents a short survival time and poor prognosis. On the contrary, high SOX2 expression levels showed a better prognosis. Otsubo et al showed that the decrease in SOX2 expression may be associated with the development of gastric cancer and poor prognosis.\(^{11}\) Their research showed that SOX2 inhibits cell growth through cell cycle arrest and apoptosis. Zhang et al detected the SOX2 expression lncRNA in gastric cancer by using quantitative reverse transcription polymerase chain reaction (qRT-PCR), and their result showed that lncRNA SOX2 overexpression serves as a poor prognostic biomarker in gastric cancer.\(^{12}\)

In the present study, a meta-analysis is performed to analyze the relationship between the SOX2 expression and prognostic significance, baseline data (gender, age, and tumor size), related pathological parameters (TNM stage, T stage, and lymphatic metastasis), and Helicobacter pylori infection in gastric cancer patients. This study provides a new direction factor for the diagnosis, treatment, and prognosis of gastric cancer patients.

2. Methods

2.1. Search strategy and study selection

The articles of this meta-analysis literature search were obtained from PubMed, Google Scholar, Cochrane library, SpringerLink, China National Knowledge Infrastructure, Web of Science, and Wanfang databases, which were written in English and Chinese. All related articles until March 12, 2019 were extracted. Search keywords include gastric cancer OR stomach neoplasms OR neoplasm, stomach OR gastric neoplasm OR cancer, gastric OR stomach cancer, AND SOX transcription factors OR SOX2 OR SRY-like HMG box 2 OR transcription factor, SOX-2 OR SRY (sex determining region Y)-Box 2 transcription factor. Articles, which do not satisfy the purpose of the study, are excluded by reading the title and abstract. However, articles that do not provide more detailed information and are used for statistical editing are excluded by reading the article. The statistics of the most comprehensive version of the data repeatedly published in the articles is obtained. This study is a review study in a related field and therefore does not involve ethical review or informed consent of patients.

2.2. Study selection

The inclusion criteria are as follows: gastric cancer tissue protein is detected by immunohistochemistry; human gastric cancer tissue; SOX2 expression, prognosis (such as, overall survival (OS), progression-free survival, and disease-free survival), and clinical pathology data for patients with gastric cancer; data statistics. Studies were excluded if they: do not present SOX2 expression in non-human tumor tissues; provide data only for abstracts, reports, newspapers, letters, and books; comprise reviews, meta-analyses, or proceedings; have small sample sizes (n < 10) to avoid selection bias.

2.3. Data extraction and quality assessment

The extracted data include: OS, baseline data (first author, published time, collection time, antibody information, gender, tumor size, and follow-up), and clinicopathological data (TNM stage, T stage, differentiation, lymphatic metastasis, margins, vascular invasion, and Lauren). Two researchers extracted the data of the included articles separately and negotiated the disputed places.

The quality of the methodology of the included studies was assessed by the Newcastle–Ottawa scale (NOS) recommended by the Cochrane non-randomized studies, methods, and working Group.\(^{13}\) Studies with rating greater than or equal to five were defined as high-quality studies. Quality assessment was independently performed by two investigators. Existing disputes were resolved through negotiation.

2.4. Statistical analysis

SOX2 expression (high vs low) and patient OS were expressed in terms of hazard ratio (HR) and 95% confidence interval (CI). The baseline and clinicopathological data were represented by risk ratio (RR) and 95% CI. An HR > 1 implied a relatively worse prognosis for the group with high SOX2 expression. Meanwhile, an RR > 1 indicated relatively more advanced clinicopathological features and baseline for patients with SOX2 expression. The heterogeneity of the studies was assessed using the Higgins F statistic. An F ≤ 50% indicated low heterogeneity. The fixed-effect model was used for the parameter. An F > 50% indicated high heterogeneity. A random-effect model was selected for the parameter. Begg and Egger tests were used for assessed potential publication bias. Sensitivity analysis was performed to evaluate the stability of results. Stata 12.0 software (Stata Corporation, College Station, TX, USA) was performed for data statistical analyses, and P < .05 was considered statistically significant.

3. Results

3.1. Search results

A total of 472 articles were retrieved according to the retrieval strategy of the study. Finally, a total of 32 articles,\(^{14-45}\) which include 4641 patients and 1991 positive SOX2 expression, were considered; the positive expression rate was 42.83%. The average Newcastle–Ottawa scale is 6.91. More detailed results are shown in Figure 1 and Table 1.

3.2. SOX2 expression and patient prognosis

Thirteen articles,\(^{14,16-18,20-24,30,34,35}\) which include 1482 gastric cancer patients, reported the relationship between the SOX2 expression and patient prognosis. The results showed that the level of SOX2 expression was unrelated to the OS of patients (P = .329, Fig. 2). Among the included articles, five articles\(^{21-24,30}\) reported that high SOX2 expression is a good prognosis for gastric cancer patients. However, eight articles\(^{14,16,18,20,26,34,35}\) reported that high SOX2 expression is a poor prognosis for gastric cancer patients.

3.3. SOX2 expression in cancer group (CG) and adjacent normal group

Sixteen articles\(^{19,23,25,27-29,31-33,36,38,39,41-43,46}\) reported the comparison of SOX in gastric cancer and para-cancerous tissues. The number of positive SOX2 expression in the gastric cancer was 737, and the positive expression rate was 46.30%. A total of 769 cases of SOX2 positive expression were found in the para-cancerous control group, and the positive expression rate was 77.91%. The results showed that the SOX2 expression in gastric cancer was lower than that in the para-cancerous control group (P < .001), as shown in Figure 3.

3.4. H pylori infection

Four articles\(^{21,27,28,40}\) were used to detect the correlation between H pylori infection and SOX2 positive expression. The results showed that the SOX2 expression decreased in gastric cancer
with positive *H pylori* infection (*P* < .001). The results are presented in detail in Figure 4.

### 3.5. SOX2 expression and clinicopathological characteristic

We summarized and analyzed the clinicopathological data of the patients. The clinicopathological data include differentiation (Well/Moderate vs Poor), TNM stage (I/II vs III/IV), T stage (T1/T2 vs T3/T4), lymphatic metastasis (N stage, N0 vs N+), lymphatic invasion (N0 vs N+), margins (R0 vs R1), and vascular invasion (V0 vs V1). The results show that SOX2 expression in low differentiation was significantly statistically lower than well and moderate differentiation (*P* = .047, Fig. 5). In the TNM stage, the expression of III/IV stage was significantly statistically lower than I/II stage (*P* = .012, Fig. 6). In the infiltration of tumor margins, the result showed that the expression of R1 (infiltrated group) was significantly statistically lower than R0 (non-infiltrated group), (*P* = .024, Fig. 7). In lymphatic invasion, the result showed that the expression of N1 (invasion group) was significantly statistically higher than N0 (non-invasion group), (*P* = .032, Fig. 8).

No significant statistics was observed in the T stage (T1/T2 vs T3/T4), lymphatic metastasis (L1 vs L0), lymphatic invasion (N vs P) (Fig. 8 and Figs. S1 and S2, http://links.lww.com/MD/H420).

### 3.6. SOX2 expression and baseline data in CG patients

We perform statistical analysis of the patient’s baseline data, which included gender (male vs female), age (≤60 vs >60), tumor size (<5 cm vs >5 cm), tumor location (Fundus + Cardiac vs Body + Antrum), and Lauren (Intestinal vs Diffuse). However, no difference was observed between different baseline parameters and SOX2 expression (all *P* value > 0.05). The detailed results are shown in Figure S3,
Table 1
The basic information of the including articles.

| N  | Author          | Yr | Region     | Collect time | Methods | Patients | Antibody Concentration | Type | Company                      | Quality score |
|----|-----------------|----|------------|--------------|---------|----------|-------------------------|------|------------------------------|---------------|
| 1  | Vânia Camilo1†[14] | 2014 | Portugal      | NA           | IHC     | 201      | 1:50                    | SP76 clone | Cell Marque, Rockling, CA, USA | 8             |
| 2  | Hiroshi Uozaki1[15] | 2011 | Japan        | 1990–2007    | IHC     | 255      | 1:500                   | PPZ113    | Perseus                      | 7             |
| 3  | Lang Yang1[16] | 2017 | China        | 2010–2013    | IHC     | 915      | 1:200                   | NA       | Cell Signaling Technology, USA | 8             |
| 4  | Ning Li1†[17] | 2015 | China        | 2008–2009    | IHC     | 122      | 1:100                   | NA       | Abcam                       | 7             |
| 5  | Junko Matsuo18[18] | 2012 | Japan        | NA           | IHC     | 69       | 10 mg/mL                | MAB2018   | R and Dystem, Minneapolis, MN | 8             |
| 6  | XUE-LINGLI[19] | 2003 | China        | 1999.10–2001.3 | IHC     | 290      | 1:200                   | NA       | Novocastra                   | 6             |
| 7  | Wei Peng20[20] | 2013 | China        | 1998.3–2011.3 | IHC     | 50       | 1:100                   | NA       | CST                         | 8             |
| 8  | Xin Zhang21[21] | 2011 | China        | 2004.8–2004.12 | IHC     | 64       | 1:100                   | NA       | Chemicon, Temecula, CA       | 7             |
| 9  | Yansu Chen22[22] | 2016 | China        | 1990.5–1995.1 | IHC     | 50       | 1:100                   | NA       | Abcam, Hong Kong, China      | 7             |
| 10 | Simeng Wang23[23] | 2015 | China        | NA           | IHC     | 74       | NA                      | 5024s     | Cell Signaling Technology, Technology | 6             |
| 11 | Helena Link24[24] | 2018 | Germany      | 2002–2014    | IHC     | 203      | 1:50                    | D6D9      | Cell Signaling Technology, Technology | 7             |
| 12 | ISAYA HASHIMOTO25[25] | 2017 | Japan        | 2001.1–2006.6 | IHC     | 529      | 1:3200                  | AB5603    | Abcam, Cambridge, UK          | 8             |
| 13 | Zheng Wang26[26] | 2018 | China        | 2015.6–2016.5 | IHC     | Protein  | NA                      | NA       | NA                          | 6             |
| 14 | Yan-ling Zhang27[27] | 2013 | China        | 2007.1–2008.1 | IHC     | Protein  | 1:100                   | 3579      | Cell Signaling Technology, USA | 7             |
| 15 | Dua Li28[28] | 2011 | China        | 2010.1–2011.1 | IHC     | Protein  | 1:100                   | NA       | SIGMA                       | 6             |
| 16 | Wen-yue Zhang29[29] | 2015 | China        | 2013.12–2014.5 | IHC     | Protein  | NA                      | NA       | BOSTER Biological Technology | 8             |
| 17 | Yong Wang30[30] | 2018 | China        | 2016.2–2018.2 | IHC     | Protein  | NA                      | NA       | CST                         | 5             |
| 18 | Yong-mei Zhang31[31] | 2018 | China        | 2009.1–2010.12 | IHC     | Protein  | 1:100                   | NA       | MXB, China                   | 6             |
| 19 | Shu-jhen Chen32[32] | 2012 | China        | 2009.1–2009.12 | IHC     | Protein  | 1:600                   | bs-0523R  | Bios, China                  | 8             |
| 20 | Feng-rong Hu33[33] | 2011 | China        | 2008.3–2008.9 | IHC     | Protein  | 1:50                    | NA       | ABSENT                      | 6             |
| 21 | Dan Sun34[34] | 2016 | China        | 1998.7–2008.4 | IHC     | Protein  | NA                      | NA       | Chemicon, Temecula, CA, USA | 7             |
| 22 | Yan-ping Zhang35[35] | 2014 | China        | 2007.1–2008.6 | IHC     | Protein  | NA                      | NA       | NA                          | 6             |
| 23 | Hua-rui Xi36[36] | 2012 | China        | 2005.1–2011.8 | IHC     | Protein  | 1:100                   | NA       | CST                         | 5             |
| 24 | Yi Xie37[37] | 2015 | China        | 2013.1–2014.4 | IHC     | Protein  | 1:3000                  | NA       | Abcam, USA                   | 9             |
| 25 | Hua-yuan Yang38[38] | 2011 | China        | 2006.1–2009.12 | IHC     | Protein  | 1:250                   | NA       | Biss, China                  | 6             |
| 26 | Ling Shen39[39] | 2018 | China        | 2016.6–2016.12 | IHC     | Protein  | NA                      | NA       | NA                          | 7             |
| 27 | Lin Zhang40[40] | 2019 | China        | 2016.1–2016.12 | IHC     | Protein  | 1:50                    | NA       | NA                          | 8             |
| 28 | Xin-yi Yang41[41] | 2018 | China        | 2012.01–2014.12 | IHC     | Protein  | NA                      | NA       | CST                         | 7             |
| 29 | Wei Zhang42[42] | 2015 | China        | 2011.3–2014.3 | IHC     | Protein  | NA                      | NA       | NA                          | 8             |
| 30 | Zheng-xing Xie43[43] | 2017 | China        | 2011.1–2016.4 | IHC     | Protein  | NA                      | NA       | Santa Cruz                   | 7             |
| 31 | Chao Lu44[44] | 2017 | China        | 2011.3–2014.4 | IHC     | Protein  | 1:100                   | NA       | Abcam                       | 7             |
| 32 | Yan-qing Niu45[45] | 2014 | China        | 2012.1–2012.12 | IHC     | Protein  | 1:50                    | NA       | NA                          | 6             |

*The quality of the included studies was evaluated using the Newcastle–Ottawa scale. IHC = immunohistochemistry, NA = not mentioned.

Figure 2. Level of SOX2 expression and OS of CG patients. CG = cancer group, OS = overall survival, SOX2 = sex-determining region Y (SRY)-like HMG box 2.
Figure 3. SOX2 expression and differentiation (Well/Moderate vs Poor). SOX2 = sex-determining region Y (SRY)-like HMG box 2.

Figure 4. SOX2 expression and TNM stage (I/II vs III/IV). SOX2 = sex-determining region Y (SRY)-like HMG box 2.
3.7. Sensitivity analysis

Sensitivity analysis was performed to evaluate the stability of results. We performed a sensitivity analysis of the SOX2 expression in gastric cancer and adjacent tumor tissues, as well as information related to patient prognosis (Fig. 9A and B). We found that no study significantly affected either the pooled HRs for OS or the SOX2 expression in different tissues. Although heterogeneity still exists, the results of the filled funnel plot do not require supplementation of new research, thereby indicating that the results are more robust.

3.8. Publication bias

We used funnel plots and Egger and Begg tests to detect publication bias. The results show that all data have low publication bias. The results are presented in detail in Table 2, Figure 10A and B.

4. Discussion

Studies have shown that SOX2 presents deregulation expression in different cancers. In most types of cancer, SOX2 protein can induce aberrant cell growth and tumorigenesis, whereas genetic inactivation impairs self-renewal and tumor growth. Over expression of SOX2 is considered a factor of tumor progression and patient preconditioning. Shima et al showed that SOX2 is a marker of poor prognosis in breast cancer. Ten et al performed an immunohistochemical microarray analysis of 420 esophageal adenocarcinoma cases. Their results showed that loss of SOX2 expression was independently predictive of adverse OS in the multivariable analysis (HR = 1.42, 95% CI: 1.07–1.89). Takeda et al clarified the role of SOX2 in 130 colorectal cancer cases. SOX2 expression was measured by qRT-PCR and western blot analysis in colon cancer cells and colorectal clinical samples. Kaplan–Meier survival curves showed that the group with high SOX2 expression had worse prognosis for relapse-free survival than the group with low SOX2 expression (P = .045). In addition, worse OS may be observed in the high expression group and the low expression group. However, the SOX2 expression and its role is played by exceptions in gastric cancer, acting as tumor suppressor. Several studies have observed that SOX2 is frequently downregulated in gastric cancer tissues. This conclusion was confirmed by Otsubo et al, who suggested that SOX2 is frequently downregulated in gastric cancer tissues and inhibits cell growth through cell cycle arrest and apoptosis in gastric cancer cell experiment, using flow cytometry analysis. They also confirmed that, among the 52 patients with advanced gastric cancers, those with SOX2 methylation had significantly shorter survival time than those without this methylation (P = .0062).

However, SOX2 expression and its role in gastric cancer have similar trends with other tumors. For example, Xin et al showed...
Figure 6. SOX2 expression and margins (R0 vs R1). R0: no distant metastasis; R1: distant metastasis. SOX2 = sex-determining region Y (SRY)-like HMG box 2.

Figure 7. SOX2 expression and *H. pylori* infection. SOX2 = sex-determining region Y (SRY)-like HMG box 2.
that high SOX2 expression provided a survival advantage to patients of gastric carcinoma and that it is associated with metastasis and clinical stages. This conclusion is confirmed by Yansu et al, who conducted experiments on gastric cancer tissues and gastric cancer cells (transwell assay, real-time PCR, and Western blot). Furthermore, Wang et al confirmed the results by conducting mouse experiments. Initially, they proved that lower SOX2 expression in CG relative to matched nontumorous tissues correlates with poor patient prognosis. Then, they confirmed that SOX2 inhibits proliferation, promotes apoptosis, and impedes metastasis in vitro and in vivo. The mechanism is more likely caused by an increase in the expression of interleukin 4 (IL-4) and bone morphogenetic protein-2 (BMP2) factors in gastric cancer. An increase in IL-4 expression causes a decrease in the expression of phosphorylate signal transducers and activators of tranion-6 (p-STAT6), and an increase in BMP2 leads to an increase in the expression of recominant mothers against decapentaplegic homolog 4 (SMAD4) and p-SMAD1/5/8. Both pathways eventually led to a decrease in SOX2 expression and an increase in caudal type homeobox genes 2 (CDX2) expression, which ultimately led to the progression of normal gastric cells toward malignant tumors.

In the present study, we analyze the SOX2 expression protein in gastric cancer by immunohistochemistry through meta-analysis and further analyze the SOX2 expression and patient baseline data, clinicopathological parameters, and patient prognosis.

Our result shows that the SOX2 expression in gastric cancer was lower than that in the para-cancerous control group (\(P < .001\)). Moreover, the included article has lower publication bias. Sensitivity analysis showed that deleting a study did not significantly differ from the total combined effect. However, SOX2 expression has no correlation to the prognosis of patients (\(P = .329\)). Thirteen articles, which involved 1482 CG patients, reported the relationship between SOX2 expression and prognosis. Five of the articles reported that high expression of SOX2 is a good prognosis for gastric cancer patients. However, 8 articles reported that high expression of SOX2 is a poor prognosis for gastric cancer patients. The analysis of patient baseline data revealed that no difference exists between SOX2 expression and patient baseline parameter (Age, ≤60 vs ≥70).
>60; Tumor Location, Fundus + Body vs cardiac + Antrum; Gender, Male vs Female; Tumor size, <5 cm vs >5 cm; Läuren, Intestinal vs Diffuse). In the pathological parameters, the results showed that SOX2 expression was statistically different in the differentiation (Well/Moderate vs Poor), TNM stage (T1/T2 vs T3/T4), lymphatic invasion (N0 vs N+), margins (R0 vs R1) of CG patients (all \( P \) values < 0.05). However, no statistical difference was observed between SOX2 expression and N stage (N0 vs N+), vascular invasion, and lymphatic metastasis (all \( P \) values >0.05).

Four articles reported the relationship between SOX2 expression and \( H \) pylori infection. The results showed that the expression of SOX2 in patients with high expression of \( H \) pylori was lower than that in the \( H \) pylori infection group (\( P < .05 \)). Otsubo et al believed that the mechanism of \( H \) pylori infection triggers its pro-carcinogenic activity through blocking SOX2; SOX2 downregulation leads to an upregulation of CDX2 expression in proportion to the progression of gastric carcinogenesis.[11]

5. Limitations
Despite the large number of articles included, this study still has many limitations. For example, the concentration of SOX2 antibodies used by the experimenters and the criteria for reading SOX2 expression of high expression are different, and the treatments are also inconsistent. These factors affect the quality of this study.
Table 2
Summary of meta-analysis results of various parameters.

| Title                  | Z     | P      | I²(%) | P   | Begg, Pr > |Z| | Egger, P > |t| |
|------------------------|-------|--------|-------|-----|------------|---|---|------------|---|---|---|
| SOX2 (high vs low)     | 6.88  | .000*  | 83.4  | .000| 0.079      |   |   | 0.083      |   |
| OS                     | 0.98  | .329   | 80.0  | .000| 0.462      |   |   | 0.081      |   |
| TNM stage              | 2.57  | .012*  | 83.1  | .000| 0.259      |   |   | 0.071      |   |
| (II/III vs IV/V)       |       |        |       |     |            |   |   |            |   |
| T stage (T1/T2 vs T3/T4) | 1.06 | .290   | 80.7  | .000| 0.053      |   |   | 0.257      |   |
| Lymphatic invasion     | 2.15  | .032*  | 49.5  | .095| 0.462      |   |   | 0.675      |   |
| (N0 vs N+)             | 1.99  | .047*  | 73.8  | .000| 0.837      |   |   | 0.645      |   |
| Differentiation        |       |        |       |     |            |   |   |            |   |
| Margins (R0 vs R1)     | 2.25  | .024*  | 66.2  | .007|            |   |   |            |   |
| Vascular invasion      | 1.41  | .158   | 0     | .569| 1.000      |   |   | 0.938      |   |
| (N vs P)               |       |        |       |     |            |   |   |            |   |
| Lymphatic metastasis   | 0.99  | .324   | 80.4  | .000| 0.822      |   |   | 0.832      |   |
| Tumor location         | 0.34  | .735   | 0     | .520| 0.548      |   |   | 0.492      |   |
| (Fundus + Body vs cardiac + Antrum) | 4.2  | .000*  | 7.2   | .357| 0.734      |   |   | 0.162      |   |
| H pylori infection (- vs +) | 4.2  | .000*  | 7.2   | .357| 0.734      |   |   | 0.162      |   |
| Age (<60 vs >60)       | 0.42  | .678   | 43.1  | .024| 0.012      |   |   | 0.050      |   |
| Sex (male vs female)   | 0.95  | .352   | 3.7   | .410| 0.866      |   |   | 0.193      |   |
| Tumor size (<5 cm vs >5 cm) | 0.32 | .747   | 64.1  | .010| 0.764      |   |   | 0.354      |   |
| Láuren (Intestinal vs Diffuse) | 0.37 | .713   | 0.8   | .428| 0.754      |   |   | 0.855      |   |

H = high-expression of SOX2 as a marker of poor prognosis, L = low-expression of SOX2 as a marker of poor prognosis, N = negative, N0 = no or low expression of SOX2 in Lymph nodes, N1 = high expression of SOX2 in Lymph nodes, OS = overall survival, P = positive, R0: no distant metastasis; R1: distant metastasis. * means the difference was statistically significant (P < .05).

Figure 10. Funnel plot result of SOX2 expression in different expression groups (high vs. low) and prognosis (OS). A: High group versus low group; B: OS. OS = overall survival, SOX2 = sex-determining region Y (SRY)-like HMG box 2.
6. Conclusion
In summary, SOX2 was present in down-regulated expression in gastric cancer and related to differentiation, TNM stage, lymphatic invasion, margins of CG, and H pylori infection. However, no correlation was found between SOX2 expression and prognosis. More studies are required to confirm our conclusion.

Author contributions
Weiwei Hou and Ning Li conducted the study’s conceptualisation, design, and execution. Ning Li performed the collation and analysis of the relevant included study data and writing the manuscript. Yu Pang, Jing Sang, and Yong Sun guided the process of manuscript writing. All were involved in the validation of the final version of the manuscript.

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