EVIDENCE-BASED INTEGRATIVE MEDICINE

Attenuated Effects of Jianpi Qushi Herbs on Patients Receiving FOLFOX4 after Colorectal Cancer Surgery: A Meta-Analysis

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ABSTRACT  Objective: To systematically review the attenuating effects of invigorating Pi (Spleen) and eliminating dampness (Jianpi Qushi, JPQS) herbs on post-operative colorectal cancer patients receiving FOLFOX4 [5-fluorouracil (5-FU) + folinic acid + oxaliplatin] treatment. Methods: China National Knowledge Infrastructure, Wanfang Data, China Science and Technology Journal Database, PubMed/MEDLINE, EMBASE, and the Cochrane Library databases (up to May 2014) were searched in English or Chinese, and clinical trials with specific inclusion criteria were collected. Data were analyzed by using Stata 12. Results: The meta-analysis comprised 8 randomized clinical studies of 449 patients (238 in the treatment group and 211 in the control group). The results showed that JPQS herbs could improve the quality of life for post-operative colorectal cancer patients receiving FOLFOX4 [weighted mean difference (WMD) = 8.883, 95% confidence interval (CI): 5.548 to 12.217]; alleviate the symptoms defined by Chinese medicine (odds ratio (OR) = 5.741, 95% CI: 3.683 to 8.947); and reduce the incidence rate of neutropenia [relative risk (RR) = 0.669, 95% CI: 0.503 to 0.888], decreased hemoglobin (RR = 0.654, 95% CI: 0.464 to 0.922), diarrhea (RR = 0.427, 95% CI: 0.275 to 0.662), nausea and vomiting (RR = 0.502, 95% CI: 0.390 to 0.649), and neurotoxic reactions (RR = 0.752, 95% CI: 0.595 to 0.951); however, the results showed no significant difference in the incidence rate of thrombocytopenia or liver and kidney dysfunction. Conclusion: JPQS herbs can improve the quality of life for patients undergoing FOLFOX4 treatment after colorectal cancer surgery, relieve symptoms, and somewhat reduce the adverse effects of FOLFOX4 regimen.

KEYWORDS  Chinese medicine, Jianpi Qushi, invigorating Pi (Spleen) and eliminating dampness, FOLFOX4, colorectal cancer, meta-analysis

Colorectal cancer (CRC) is one of the most common types of malignant tumor and ranks third highest in incidence rate among all malignant tumors. Chemotherapy is the main means of adjuvant therapy in CRC, although, in recent years, a new therapy scheme has been used that can improve the curative effects and ameliorate the prognosis of the disease, but the adverse reactions are still widespread and seriously affect patients' quality of life (QOL). The FOLFOX4 [5-fluorouracil (5-FU) + folinic acid + oxaliplatin] scheme is the standard adjuvant chemotherapy for CRC. Some studies have shown that the postoperative CRC patients with FOLFOX4 scheme will appear bone marrow suppression, gastrointestinal reactions and other adverse events. Besides, some Chinese medicine (CM) experts think that bone marrow suppression may be caused by Pi (Spleen) deficiency, and the gastrointestinal reactions characterized by diarrhea are more attributed to Pi deficiency and damp abundance. Therefore, invigorating Pi and eliminating dampness (Jianpi Qushi, JPQS) may have an effect on patients in this group. On the other hand, several clinical studies showed that Pi-invigorating recipes can reduce the adverse reactions caused by the FOLFOX4 scheme and improve the QOL for patients. However, there are many rules of treatment in Pi-invigorating compound. Whether treatments based on tonifying Pi, such as JPQS, invigorating Pi and removing toxin, and invigorating Pi...
and activating blood, have also alleviated the toxicity of chemotherapy is unknown because the clinical medications are different. Therefore, in this study we aim to determine whether JPQS herbs have attenuating effects on FOLFOX4 patients after CRC surgery.

METHODS

Search
A comprehensive literature search was carried out using China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Data, PubMed/MEDLINE, EMBASE, and the Cochrane Library database. The following terms were used: "colorectal cancer" or "cancer" or "malignancy(ies)" or "carcinoma" in combination with "Jianpi" or "quality of life" or "chemotherapy" or "FOLFOX4" or "adverse reactions", to identify the studies related to FOLFOX4 and CRC. The reference lists of all eligible articles and reviews were also scanned to identify additional relevant studies. All cancer studies were included to ensure that no results for CRC were overlooked that might have been reported as part of a larger study that included other cancer types. This meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.\(^{(16,17)}\)

Inclusion Criteria
The inclusion criteria were as follows: (1) randomized controlled trial (RCT); (2) postoperative patients with CRC, according to the diagnosis criteria of "Chinese common malignant tumor diagnosis standard",\(^{(18)}\) who were diagnosed by pathological examination. Intervention with the administration of CM decoction with JPQS herbs and chemotherapy (FOLFOX4) to patients (the treatment group) was compared with the administration of chemotherapy alone (the control group). (3) The inclusion of JPQS herbs was according to the "Science of Chinese materia medica (9th version)\(^{(19)}\) which comprised three classes of aromatic drugs for resolving dampness, diuretics for eliminating dampness, and drugs of tonifying qi (Table 1). (4) The outcome indicators were as follows: (i) QOL was scored and evaluated according to the Karnofsky Performance Status (KPS) scale; (ii) the improvement of clinical symptoms was assessed by "Traditional Chinese medicine symptom integral",\(^{(20)}\) it was graded and scored according to the common clinical symptoms of CRC and was cumulative contrasted before and after treatment; (iii) adverse reactions were assessed according to dividing the standard of the World Health Organization's antitumor drugs into acute and subacute toxicity\(^{(21)}\) that involved the inhibition of bone marrow (neutropenia, thrombocytopenia, decrease in hemoglobin), gastrointestinal reactions (nausea and vomiting, diarrhea), neurotoxicity and safety indicators.

<table>
<thead>
<tr>
<th>Table 1. The Main Representative of Three Classes of JPQS Herbs</th>
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<tbody>
<tr>
<td>Function</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Aromatic herbs for resolving dampness</td>
</tr>
<tr>
<td>Diuretics for eliminating dampness</td>
</tr>
<tr>
<td>Herbs for tonifying qi</td>
</tr>
</tbody>
</table>

Exclusion Criteria
The exclusion criteria were as follows: (1) the number of JPQS herbs in the prescription was less than the number of other kinds of CM; and (2) the random assignment method was not mentioned.

Data Extraction
Each full-text report was reviewed to determine its eligibility and all the relevant data were extracted and tabulated independently. The extracted data included the characteristics of the subjects (including number and intervention), study design, published year, and the main components of decoction. Study authors were contacted as needed to obtain detailed data. Any disagreement was resolved by a consensus among the investigators.

Statistical Analysis
Stata 12 was used for data analyses, including the heterogeneity test, meta-analysis, and sensitivity analysis. The odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI) were used as classification variables for the analyses and statistics. A chi-square test was used to analyze the research results into heterogeneity with a significant level of \(\alpha =0.05\), and \(I^2\) was used for quantitative analysis. When heterogeneity was low (\(I^2<50\%\)), the data were analyzed using the fixed-effects model; when heterogeneity was obvious (\(I^2>50\%\)), data were analyzed using the random-effects model; and when heterogeneity was very high (\(I^2>75\%\)), the source of heterogeneity was discussed and the results were not merged. A sensitivity analysis and the stability of the results were applied if the quality of the
research was low. When there were sufficient studies to include in the meta-analysis, a funnel plot was used to analyze potential publication bias.

RESULTS

Results of Search and Study Characteristics

A total of 360 citations were identified through the electronic databases (Figure 1) of which 219 potentially relevant articles were retrieved and assessed in more detail. Among these, 141 were rejected of which 137 were duplication in Chinese database (CNKI, VIP, Wanfang) and 4 were in foreign database (PubMed and Cochrane library). In the remaining, 211 were excluded of which 191 were not related to JPQS herbs, 1 were not related to FOLFOX4 regimen and 20 were excluded due to lack of control data. Seven studies\(^{(22-28)}\) fulfilled the eligibility criteria (Table 2).

QOL

To analyze the patient's QOL, 4 studies of 208 patients were used of which 108 were in the treatment group and 100 were in the control group. The heterogeneity test showed \(\chi^2=11.54, P=0.009\), and \(I^2=74.0\%\) (Figure 2); therefore, the included studies had unacceptable heterogeneity. The combined effects of the weighted mean difference were then determined using a random-effects model (weighted mean difference = 8.883, 95% CI: 5.548 to 12.217, \(P<0.001\)). It was considered that JPQS herbs could improve the QOL for post-operative CRC patients undergoing FOLFOX4 treatment (the quality of evidence was low).

CM Symptom Score

For analysis of CM symptoms, 7 studies of 394 patients were used, of which 209 were in the treatment group and 185 were in the control group. The heterogeneity test showed \(\chi^2=8.60, P=0.197\), and \(I^2=30.2\%\) (Figure 3). Due to the homogeneity of the included studies, the combined effects of the amount

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients assessed</th>
<th>Study design</th>
<th>Intervention</th>
<th>Main components of CM</th>
<th>Endpoint outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2010(^{(22)})</td>
<td>58</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Herba dendrobii, Rhizoma dioscoreae, Semen coicis, Rhizoma atractyloids macrocephalae, Poria, Herba pogostemonis</td>
<td>KPS, symptom score, AEs</td>
</tr>
<tr>
<td>Zhu, 2009(^{(23)})</td>
<td>60</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Radix codonopsis, Rhizoma atractyloids macrocephalae, Polyporus, Poria, Semen coicis</td>
<td>KPS, symptom score, AEs</td>
</tr>
<tr>
<td>Wu, 2011(^{(24)})</td>
<td>40</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Radix codonopsis, Rhizoma atractyloids macrocephalae, Poria, Radix astragali, Rhizoma dioscoreae, Semen coicis</td>
<td>KPS, symptom score, AEs</td>
</tr>
<tr>
<td>Liu, 2005(^{(25)})</td>
<td>64</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Radix astragali, Radix codonopsis, Rhizoma atractyloids macrocephalae, Poria</td>
<td>KPS, symptom score, AEs</td>
</tr>
<tr>
<td>Han, 2012(^{(26)})</td>
<td>60</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Radix astragali, Radix pseudostellariae, Poria, Semen coicis</td>
<td>KPS, symptom score, AEs</td>
</tr>
<tr>
<td>Hu, 2013(^{(27)})</td>
<td>42</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Semen coicis, Rhizome dioscoreae, Rhizoma atractyloids macrocephalae, Radix pseudostellariae, Radix astragali</td>
<td>KPS, symptom score, AEs</td>
</tr>
<tr>
<td>Cao, 2012(^{(28)})</td>
<td>85</td>
<td>parallel-group</td>
<td>F/F+CM</td>
<td>Radix ginseng, Radix codonopsis, Radix astragali, Rhizoma atractyloids macrocephalae, Radix glycyrrhizae</td>
<td>KPS, symptom score, AEs</td>
</tr>
</tbody>
</table>

Notes: F: FOLFOX4, AEs: adverse events
of OR were determined using a fixed-effects model (OR=5.741, 95% CI: 3.683 to 8.947, P<0.001). It was considered that JPQS herbs could alleviate the symptoms of post-operative CRC in patients on FOLFOX4 treatment (the quality of evidence was moderate).

**Adverse Events**

**Bone Marrow Suppression**

For neutropenia evaluation, 6 studies of 357 patients were used, of which 192 were in the treatment group and 165 in the control group. The heterogeneity test showed $\chi^2=8.60$, $P=0.126$, and $I^2=41.9\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined using a fixed-effects model (RR=0.669, 95% CI: 0.503 to 0.888, $P=0.005$). It was considered that JPQS herbs could reduce the incidence rate of neutropenia induced by FOLFOX4 treatment (the quality of evidence was moderate).

For thrombocytopenia evaluation, 5 studies of 297 patients were used, of which 162 were in the treatment group and 135 in the control group. The heterogeneity test showed $\chi^2=0.83$, $P=0.935$, and $I^2=0.0\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined by a fixed-effects model (RR=0.670, 95% CI: 0.345 to 1.301, $P=0.237$); however, it could not be considered that JPQS herbs could reduce the incidence rate of thrombocytopenia induced by FOLFOX4 treatment (the quality of evidence was moderate).
Figure 4. Forest Plot of the RR for Adverse Events Associated with Post-operative CRC Patients

Notes: The subgroup analysis of the association is based on neutropenia, thrombocytopenia, decreased hemoglobin, diarrhea, nausea and vomiting, neurotoxic reactions, liver and renal function.
amount of RR were determined by a fixed-effects model (RR=0.654, 95% CI: 0.464 to 0.922, P=0.015). It was considered that JPQS herbs could reduce the incidence rate of decreased hemoglobin induced by FOLFOX4 treatment (the quality of evidence was moderate).

Gastrointestinal Reaction

For diarrhea evaluation, 5 studies of 297 patients were used, of which 162 were in the treatment group and 135 in the control group. The heterogeneity test showed $\chi^2=1.57$, $P=0.814$, and $I^2=0.0\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined by a fixed-effects model (RR=0.427, 95% CI: 0.275 to 0.662, P<0.001). It was considered that JPQS herbs could reduce the incidence rate of diarrhea induced by FOLFOX4 treatment (the quality of evidence was moderate).

For evaluation of nausea and vomiting, 5 studies of 297 patients were used, of which 162 were in the treatment group and 135 were in the control group. The heterogeneity test showed $\chi^2=4.08$, $P=0.395$, and $I^2=2.0\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined by a fixed-effects model (RR=0.502, 95% CI: 0.390 to 0.648, P<0.001). It was considered that JPQS herbs could reduce the incidence rate of nausea and vomiting induced by FOLFOX4 treatment (the quality of evidence was moderate).

Neurotoxicity

For evaluation of neurotoxic reactions, 5 studies of 307 patients were used, of which 167 were in the treatment group and 140 in the control group. The heterogeneity test showed $\chi^2=4.35$, $P=0.361$, and $I^2=8.0\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined by a fixed-effects model (RR=0.752, 95% CI: 0.595 to 0.951, P=0.017). It was considered that JPQS herbs could reduce the incidence rate of neurotoxic reactions induced by FOLFOX4 treatment (the quality of evidence was moderate).

Safety Indicators

To evaluate liver function, 4 studies of 214 patients were used, of which 118 were in the treatment group and 96 in the control group. The heterogeneity test showed $\chi^2=3.37$, $P=0.338$, and $I^2=11.0\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined by a fixed-effects model (RR=0.757, 95% CI: 0.492 to 1.166, P=0.207). It could not be considered that JPQS herbs could reduce the incidence rate of hypohepatia induced by FOLFOX4 treatment (the quality of evidence was moderate).

To evaluate renal function, 4 studies of 214 patients were used, of which 118 were in the treatment group and 96 in the control group. The heterogeneity test showed $\chi^2=1.89$, $P=0.596$, and $I^2=0.0\%$ (Figure 4). Due to the homogeneity of the included studies, the combined effects of the amount of RR were determined by a fixed-effects model (RR=0.947, 95% CI: 0.639 to 1.404, P=0.786). It could not be considered that JPQS herbs could reduce the incidence rate of renal inadequacy induced by FOLFOX4 treatment (the quality of evidence was moderate).

Publication Bias Evaluation

The evaluation of publication bias was not suitable for this work because there were less than 10 included articles in this systematic review; therefore, the test efficiency of funnel plot was not enough to prompt publication bias.

DISCUSSION

CM is an important part in the combined therapy for CRC and has the advantage of reducing the toxicity of chemotherapy.\(^{(29)}\) The literature and epidemiology show that Pi deficiency and dampness are the basic CM syndromes in patients with CRC; therefore, the basic therapeutic principles in CM are to strengthen Pi and eliminate dampness.\(^{(30,31)}\)

Clinical studies show that JPQS herbs are effective in preventing and curing adverse reactions induced by FOLFOX4 treatment, and can improve the patients' QOL by relieving the clinical symptoms of FOLFOX4 regimen.\(^{(32-37)}\) To provide better evidence of the effects of the combined use of JPQS herbs and FOLFOX4 after CRC surgery, this systematic literature review was performed.

From the studies, the prescriptions were mainly about JPQS herbs, such as Radix codonopsis, Radix astragali, Rhizoma atractyloidis, Poria, Semen coicis,
and *Amomum kravanh*. The meta-analysis showed that the QOL and CM symptom scores of the treatment group were better than those of the control group (*P*<0.05). We considered that JPQS herbs could improve the QOL of post-operative CRC patients receiving FOLFOX4 treatment and alleviate their clinical symptoms. The aspect of adverse events were as follows: (1) The incidence rate of neutropenia and decreased hemoglobin in the treatment group was lower than those in the control group (*P*<0.05), indicating that JPQS herbs could reduce the incidence rate of neutropenia and decreased hemoglobin induced by FOLFOX4 treatment. (2) The incidence rate of diarrhea, neurotoxicity, nausea, and vomiting in the treatment group were lower than those in the control group (*P*<0.05), indicating that JPQS herbs could reduce the incidence rate of diarrhea, neurotoxicity, nausea, and vomiting induced by FOLFOX4 treatment. (3) The difference in the incidence rate of thrombocytopenia had no statistical significance between the treatment and control groups (*P*>0.05). JPQS herbs could not reduce the incidence rate of thrombocytopenia induced by FOLFOX4 treatment. (4) The single effect and combined effect of individual studies showed that liver and kidney dysfunction between the treatment and control groups had no statistical significance (*P*>0.05); therefore, JPQS herbs have no obvious effect on reducing the incidence rate of liver and kidney dysfunction induced by FOLFOX4 treatment.

Most domestic researches used the KPS scale to evaluate the QOL. Meta-analysis showed that for herbs could indeed improve the behavior ability of patients; however, there are many kinds of scales for the evaluation of QOL for patients with CRC, mainly, the QOL questionnaire from the European Organization for Research and Treatment of Cancer (EORTC QLQ C-30 or CR38). EORTC QLQ-C30 is a core scale in the scale system for cancer patient survival, and can be used to assess the QOL of all cancer patients. The parameters involve the daily functioning of cancer patients, symptom score (fatigue, pain, nausea, vomiting), state of health, as well as several single symptoms. EORTC QLQ-CR38 is formulated on the basis of QLQ-C30 as related to the CRC questionnaire. But because the onset characteristics and intervention of CRC in China compared with those in Europe and the United States have significant differences, and some scholars have begun to develop Quality of Life Questionnaire of Chinese Medicine for Postoperative Patients with Colorectal Cancer (QLQ-CMPPCC) in accordance with the national conditions.

Compared with the amount of QLQ mentioned above, the KPS scale does not include the patient's subjective feelings, psychological status and social status, which can be regarded as only part of their QOL, and cannot fully reflect the characteristics of CM. The use of KPS scores, strictly speaking, showed that JPQS herbs can improve only the patient's capacity for action. Their use to evaluate the QOL for the patient is not comprehensive. The standard table used to score the CM symptoms for CRC includes abdominal pain, diarrhea, constipation, anorexia, fatigue, weight loss, nausea, and vomiting. Through the meta-analysis, it was found that JPQS herbs had specific effects that improved CM symptoms; however, domestic clinical research over the past 10 years compared only overall integration of CM symptoms—there was a lack of comparison for individual symptoms. To assess whether the difference in symptoms before and after treatment was statistically significant, integral evaluation of CM symptoms should be compared with overall and individual symptom scores so that it is more accurate. The effects of JPQS herbs on individual symptoms will be evaluated in greater depth.

For patients with CRC, chemotherapy drugs can inhibit the synthesis and replication of cancer cell DNA so as to increase the generation of antitumor activity and reduce cytotoxicity. Although FOLFOX4 has an anti-tumor effect, there are still some adverse reactions, which are reflected mainly by bone marrow suppression, gastrointestinal reactions, and neurotoxicity. Research has shown that Chinese herbal medicine plays a role in preventing adverse reactions to cancer chemotherapy. The studies also found that JPQS herbs have specific effects on bone marrow suppression and have obvious effects on the incidence of diarrhea, neurotoxicity, nausea, and vomiting caused by a FOLFOX4 scheme after CRC surgery.

CM pharmacology research shows that JPQS herbs, such as *Astragali radix*, *Rhizome Atractylodis*, and *Porzia*, promote bone marrow cell division and differentiation, and promote blood cell formation,
development, and maturation. The results of the meta-analysis showed that the difference in neutropenia and decreased hemoglobin had statistical significance but the difference in thrombocytopenia had no significant statistical difference. Studies have shown that the cause of poor outcomes in thrombocytopenia is most likely because there is no current standard to evaluate uniform effects. Researches mainly use self-efficacy criteria and the difference is large; therefore, a standard should be created for curative effects as soon as possible.

Li believes that amino antitumor drugs (5-aminolevulinic acid) can mechanically inhibit or stimulate the appetite through central or peripheral nerve, and that the platinum metallic antitumor drugs reduce a patient's sensitivity to taste, cause anorexia, gastrointestinal reactions, and decreased food intake, which results in patients' bodies being accelerated to cachexia, eventually leading to severe malnutrition. Other studies have shown that nearly all drugs result in this reaction, and nausea and vomiting after treatments are painful to patients and affect their QOL. CM believes that nausea and vomiting, diarrhea, and other gastrointestinal reactions caused by chemotherapy drugs are because of damage to the Pi and Wei (Stomach), the middle energizer, and to gas imbalance. Treatment should invigorate Pi and eliminate dampness and regulate the qi and Wei, the suggestions of which are consistent with those of this study.

Patients after FOLFOX4 scheme appeared neurotoxicity reactions with sensory disorder and there is a lot of experience in the field of CM, the lack of in-depth analysis of CM leads to a different understanding of its pharmacological mechanisms. In this study, we found that JPQS herbs had specific curative effects on neurotoxic reactions caused by FOLFOX4 treatment. We hope to be able to carry out more in-depth studies to explore the pharmacological mechanisms of action for effective prescriptions.

There were several potential limitations of this study. First, there was the possibility of information and selection bias, and unidentified confounders cannot be completely excluded because all of the included studies were observational. Second, different evaluation standards of thrombocytopenia might have caused a measurement bias. Third, there might be reporting bias because positive results in the study were not unified and the sample size was small. Finally, we restricted our search strategy to articles published in English or Chinese. Articles with potentially high-quality data published in other languages were not included because of anticipated difficulties in obtaining accurate medical translations.

In conclusion, we found in our study that JPQS herbs played an active role in QOL and CM symptoms of postoperative CRC patients with FOLFOX4. At the same time, adverse events caused by FOLFOX4 could be partly reduced by JPQS herbs, mainly reflected in the following three aspects: (1) in terms of the inhibition of bone marrow, JPQS herbs could reduce the occurrence of neutropenia and decreased hemoglobin; (2) during the process of FOLFOX4 treatment, the incidence of gastrointestinal reaction in the treatment group was lower than that in control group; (3) JPQS herbs offered protection to neurotoxic reactions induced by FOLFOX4 treatment. However, this study suggests that JPQS herbs have no effect on chemotherapy-induced thrombocytopenia or damage to the liver or kidney. The meta-analysis results are not immutable, and with additional and improved research methods, the results of additional studies and subsequent meta-analyses will be more objective and reliable.

Conflict of Interest
The authors have no conflict of interest.

Author Contributions
Conception and design: Shi Q; financial support: Hou FG; provision of study materials or patients: Hou FG, Ren JL; collection and assembly of data: Li W, Le QQ; data analysis and interpretation: Shi Q; manuscript writing: Shi Q.

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