Comparative effectiveness and safety of traditional Chinese medicine supporting Qi and enriching blood for cancer related anemia in patients not receiving chemoradiotherapy: a meta-analysis and systematic review

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Abstract: A systematic review and meta-analysis of previous randomized controlled trials of traditional Chinese medicine (TCM) supporting Qi and enriching blood in the treatment of cancer related anemia (CRA) in patients not receiving chemoradiotherapy were conducted. A total of 13 randomized controlled trials were included. Compared with the control group, better improvement was found for the level of hemoglobin (mean difference=4.57, 95% CI [1.38, 7.76], P=0.005) and overall therapeutic effect (risk ratio [RR]=1.31, 95% CI [1.18, 1.46], P<0.000) in the TCM groups. The incidence of related adverse events was not increased in the TCM groups (RR=0.54, 95% CI [0.29, 0.99], P=0.05). However, due to the relatively low quality and the small sample sizes of the included studies, the results should be interpreted with a degree of caution. Nevertheless, TCM with the role of supporting Qi and enriching blood may be a safe and effective treatment for CRA in patients not receiving chemoradiotherapy and might be considered as an alternative treatment to conventional western medicine including iron supplements and erythropoietin.

Keywords: traditional Chinese medicine, supporting Qi and enriching blood, cancer related anemia, randomized controlled trial, meta-analysis

Introduction

As a common complication of tumors, the incidence of cancer related anemia (CRA) ranges from 30% to 90%,1 which can be divided into nonchemotherapy- and chemotherapy-induced CRA. Without doubt, the lifestyle quality of these patients is decreased by this condition.2 Studies have shown that continuous anemia can cause tachycardia, palpitations, fatigue, respiratory disorders, and other symptoms.3 Therefore, the management of anemia in cancer patients is clinically important even though survival is the primary treatment goal. Current mainstream treatment methods include blood transfusions, iron supplements, and erythropoietin (EPO) therapy. However, these treatment methods have some disadvantages; blood transfusion is hampered by a relative shortage of blood donation and the potential survival risk to CRA patients due to transfusion-related complications such as anaphylaxis, iron overload, hemolysis, allogeneic immune response, thrombosis, posttransfusion cardiogenic pulmonary edema, and transfusion-induced viral infections. A careful inspection of a large patient database revealed that cancer patients who received red cell transfusions were more...
at risk of having venous thrombosis, arterial thrombosis, or of dying. Cancer patients who underwent surgery and who received red cell transfusions also had an increased mortality. Iron supplements are usually given for the management of iron deficiency anemia. However, hemochromatosis or cell injury can occur due to indiscriminate use of oral iron, and a poor medication compliance rate in these patients was reported, owing to the high frequency of gastrointestinal side effects. EPO is known to be very effective in improving the hematological response and reducing the need for blood transfusions.

CRA has increasingly aroused general concern due to its high morbidity and potential influence on the quality of life of CRA patients, with an effective and safe therapeutic method for this condition being of obvious clinical significance. CRA is essentially a type of blood deficiency syndrome, and thus may be treated with traditional Chinese medicine (TCM). In fact, the knowledge and theoretical studies on blood deficiency in TCM are quite mature and have a profound theoretical and practical basis. Based on the relationship between Qi and blood and the relationship between Zangfu and blood generation, TCM formulas supporting Qi and enriching blood have been used to treat blood deficiency syndrome for a long time. In a recent meta-analysis, Zhu et al reported that Huangqi injection could significantly enhance the efficacy of androgens for aplastic anemia. Another study has also reported the therapeutic effect and safety profile of TCM formulas supporting Qi and enriching blood in the management of CRA, but the sample sizes in these studies were relative small. Thus we performed this meta-analysis to review systematically randomized controlled trials of TCM supporting Qi and enriching blood for the treatment of CRA in order to clarify in detail the effect and safety of TCM for its treatment.

Materials and methods

Search strategy

We performed an electronic search of PubMed, EMBASE, Cochrane, Chinese biological medicine, Chinese Scientific Journal Database, China Wanfang database, and China National Knowledge Infrastructure databases for previous studies on the therapeutic effects and safety of TCM for CRA, with no limitations on language or the publication year, using the following search keywords: “Traditional Chinese medicine supporting Qi and enriching blood” or “Chinese herbology supporting Qi and enriching blood” or “Chinese medicine supporting Qi and enriching blood” and “Chinese medicine supporting Qi and enriching blood” or “Cancer related anemia” or “malignant tumor anemia.” A Google Scholar search was also performed using these search terms.

Eligibility criteria

Randomized controlled trials that provided data on the therapeutic effect and safety of supporting Qi and enriching blood TCMs in patients with CRA compared to a control group who received conventional treatment were eligible for this meta-analysis. In addition, the involved subjects should be solid tumor patients with a hemoglobin level $<110$ g/L. Studies in which patients received radiotherapy or chemotherapy during treatment or suffered with a disease that may affect the level of hemoglobin, such as aplastic anemia, were excluded.

Data extraction

Two reviewers (Zhibo Dang and Xiaoli Liu) independently extracted the following data from each study: first author’s surname, publication year, country, the study design, number of patients in the control and TCM groups, male or female, the level of hemoglobin before and after the treatment, the overall therapeutic effect, and any adverse events.

Outcome measurement indexes

Primary outcome indexes

The level of hemoglobin was set as the primary outcome index.

Secondary outcome indexes

The overall therapeutic effect and adverse events were set as the secondary outcome indexes.

Statistical analysis

All statistical analyses were carried out using RevMan (ver 5.3). An OR was employed for the statistical analysis of the counting data and standardized mean difference or weighted mean difference (MD) were used to analyze statistically the measurement data. Statistical heterogeneity between studies was evaluated using a chi-squared test; $P>0.1$ and $I^2<50\%$ were taken to be of low heterogeneity, and a fixed effect model was used. $P<0.1$ and $I^2>50\%$ were considered to have statistical heterogeneity; therefore, a random effect model was employed. The heterogeneous source was analyzed and subgroup analysis carried out for factors that may lead to heterogeneity. If heterogeneity arose from low-quality research, sensitivity analysis was carried out. If there was still significant heterogeneity between the two groups, descriptive analysis was used. A $P$-value $<0.05$ was considered to be statistically significant, and all tests were two-sided.
Assessment of publications
The methodology excellence of the included studies was evaluated following the guidelines laid down in the Cochrane Handbook for Systematic Reviews. The following factors were taken into account: allocation concealment; blinding of participants; personnel and outcome assessments; incomplete outcome data; random sequence generation; selective reporting; and other potential sources of bias.

Results
Publication selection
A total of 422 papers were obtained from the initial retrieval, of which 260 were excluded due to duplicate publication. A total of 96 papers were obtained after reviewing the title and summary according to the exclusion and inclusion criteria, and 13 were eventually included after a full-text review, which included a total of 1,198 patients (Figure 1). In these 13 studies, a different prescription was used in each study, but all of them were typical TCM formula used to improve the Qi and blood deficiency, which is termed anemia in western medicine. In the control group, EPO therapy was used in seven studies, iron supplements were used in three studies, and only antitumor and supportive therapies were used in two studies. One study used either EPO or iron supplements in the control group, but the authors did not clearly clarify which patients used EPO or iron supplement therapy. Eleven studies reported the results of hemoglobin levels and ten studies reported the results of the overall therapeutic effect. All these studies were conducted in Asian patients, one in Japan and the others in P.R. China (Table 1).

Quality assessment of the selected publications
The methodology quality of the included studies was relatively low. Five of the studies reported random methods, but all of these studies did not report allocation concealment, blinding of participants, personnel, or the outcome assessments. The outcome data in all of the studies were complete, and there was no selective reporting or bias (Figure 2).

Hemoglobin
A total of eleven studies\textsuperscript{11–21} reported changes in hemoglobin levels. A \( P \)-value <0.001 and \( I^2 = 97\% \) indicated that there was...
significant heterogeneity among the studies; thus a random
effect model was employed. In the pooled results, the level
of hemoglobin in the TCM group was greater than that in
the control group (MD=4.57, 95% CI [1.38, 7.76], \( P=0.005; \)
\( I^2=97\% \)) (Figure 3).

### Subgroup analysis according to the therapeutic period and therapy method in the control group

In order to analyze further the source of significant heteroge-
nity, subgroup analysis by the follow-up period and therapy
method in the control group were separately performed.

First, subgroup analysis was performed according to the
different therapeutic period. In the eleven studies, which
reported changes in hemoglobin levels, the therapeutic
period ranged from 3 weeks to 3 months and was divided
into three subgroups: \( \leq 30 \) days for subgroup 1; 31 days to
2 months for subgroup 2; and \( >2 \) months for subgroup 3.
However, significant heterogeneity was still found in these
subgroups; the level of hemoglobin in the TCM group was
significantly greater than that in the control group for
subgroup 1 (MD=8.72, 95% CI [4.62, 12.83], \( P<0.000; \)
\( I^2=97\% \)) and subgroup 3 (MD=2.92, 95% CI [1.61, 4.22],
\( P<0.000; \) \( I^2=0\% \)), but was significantly lower for subgroup
2 (MD=-3.77, 95% CI [−17.75, 10.21], \( P=0.60; \) \( I^2=97\% \)) (Figure 4A).

Second, subgroup analysis was performed according to
the therapy method in the control group. In the eleven
studies that reported changes in hemoglobin levels, EPO
therapy was employed as the control in six studies, and iron
supplements were used in three studies; thus we divided
them into EPO and iron supplements subgroups. In a further
subgroup analysis, we found that the levels of hemoglobin
in the TCM group was significantly higher than that in the
control group for both subgroups (EPO subgroup: MD=3.85,
95% CI [2.18, 5.52], \( P<0.000; \) \( I^2=86\% \); iron supplements
subgroup: MD=6.68, 95% CI [−14.49, 27.85], \( P=0.54; \)
\( I^2=99\% \)) (Figure 4B).

### Sensitivity analysis

We found that the pooled results for comparison of hemo-
oglobin levels between the two groups did not show obvious
changes after excluding studies that reported hemoglobin
levels one by one, and all of these results achieved statistical
significance, thus indicating that the pooled results data
had good stability.

### Table 1 The basic characteristics of the included literature

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Publication time</th>
<th>Number of cases (human)</th>
<th>Gender (male/ female)</th>
<th>Intervention measures</th>
<th>Outcome measures</th>
<th>Course of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akase et al(^1)</td>
<td>2003</td>
<td>10/15</td>
<td>Unreported</td>
<td>Danggui Shaoyao Powder + EPO</td>
<td>Chalybeate + EPO</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Cheng et al(^4)</td>
<td>2009</td>
<td>33/32</td>
<td>Unreported</td>
<td>Shenfu injection + conventional therapy</td>
<td>Conventional therapy</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Gu et al(^6)</td>
<td>2010</td>
<td>63/50</td>
<td>62/51</td>
<td>Modified Bazhen decoction</td>
<td>EPO</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Cai and Zhu(^12)</td>
<td>2016</td>
<td>45/44</td>
<td>48/41</td>
<td>YXS + conventional therapy</td>
<td>Conventional therapy</td>
<td>30 days</td>
</tr>
<tr>
<td>Cai and Wang(^13)</td>
<td>2016</td>
<td>60/60</td>
<td>64/56</td>
<td>Tonifying blood and nourishing Qi decoction</td>
<td>Conventional therapy</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Du et al(^15)</td>
<td>2015</td>
<td>43/43</td>
<td>45/41</td>
<td>Self-made Chinese herbal decoction</td>
<td>Conventional therapy</td>
<td>3 months</td>
</tr>
<tr>
<td>Ling et al(^17)</td>
<td>2016</td>
<td>50/50</td>
<td>71/29</td>
<td>Shen Bai Fu Zheng granule + EPO</td>
<td>EPO</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Liu and Xiao(^22)</td>
<td>2015</td>
<td>44/44</td>
<td>40/48</td>
<td>Self-made warming kidney and invigorating spleen and enriching blood decoction</td>
<td>Folic acid and ferrous succinate</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Liu(^18)</td>
<td>2015</td>
<td>46/46</td>
<td>60/32</td>
<td>Self-made warming kidney and invigorating spleen and enriching blood decoction</td>
<td>EPO</td>
<td>30 days</td>
</tr>
<tr>
<td>Lv et al(^19)</td>
<td>2016</td>
<td>56/56</td>
<td>Unreported</td>
<td>Self-made decoction + EPO</td>
<td>Conventional therapy</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Wang and Li(^20)</td>
<td>2015</td>
<td>40/40</td>
<td>43/37</td>
<td>Tonifying kidney strengthening spleen and enriching blood decoction + conventional therapy</td>
<td>EPO</td>
<td>30 days</td>
</tr>
<tr>
<td>Zhang(^23)</td>
<td>2007</td>
<td>50/50</td>
<td>52/48</td>
<td>Self-made decoction + EPO</td>
<td>EPO</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Zi(^21)</td>
<td>2016</td>
<td>64/64</td>
<td>73/55</td>
<td>Shengxue tiaoyuan granule + EPO</td>
<td>EPO</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

Notes: ① hemoglobin; ② curative effects; ③ untoward effects.

Abbreviations: EPO, erythropoietin; YXS, Yixuesheng capsule; T/C, treatment/control group.
The overall therapeutic effect and adverse events

A total of ten studies \(^1\)–\(^\text{14,17,23}^\) reported the results of the overall therapeutic effects. In these studies, the therapeutic effects were summarized as “obvious effect”, “moderate effect”, “mild effect”, and “no efficacy” according to symptoms such as dizziness and facial pallor. However, the former three were classified as “effective” in this review in order to reduce the bias due to no standard criteria for the subjective therapeutic effect. A result of \(P=0.03\) and \(I^2=51\%\) indicated significant heterogeneity; thus, a random effect model was employed. For the pooled results, a significant improvement in the overall therapeutic effect was found in the TCM group compared to the control group (risk ratio [RR] = 1.31, 95% CI [1.18, 1.46], \(P<0.000; I^2=51\%)\ (Figure 5A).

A subgroup analysis was also performed according to EPO or iron supplement therapy in the control group, and we found the overall therapeutic effect was significantly better in the TCM group than in the control group for both subgroups (EPO subgroup: RR = 1.43, 95% CI [1.30, 1.58], \(P<0.000; I^2=27\%\); iron supplement subgroup: RR = 1.30, 95% CI [1.09, 1.56], \(P=0.044; I^2=0\%)\), and the heterogeneity was obviously decreased (Figure 5B).

A total of four studies reported the results of adverse events, with a result of \(P=0.14\) and \(I^2=45\%\) indicating low heterogeneity, and a fixed effect model was employed. In the pooled results, the incidence of adverse events was significantly reduced in the TCM group compared to that in the control group (RR = 0.54, 95% CI [0.29, 0.99], \(P=0.05; I^2=45\%)\ (Figure 5C).

Discussion

As a disease caused by the tumor itself or the treatment, CRA has been reported to be improved or cured by TCM by supporting Qi and enriching the blood. In this meta-analysis, we systematically reviewed studies on the therapeutic effect and safety of TCM formulas for the treatment of CRA in patients not receiving chemoradiotherapy, and a significant improvement in the hemoglobin level was found after TCM treatment compared with that in the control group (MD = 4.57, 95% CI [1.38, 7.76], \(P=0.005; I^2=97\%)\). Promising results were also found for the overall therapeutic effect (RR = 1.31, 95% CI [1.18, 1.46], \(P<0.000; I^2=51\%)\). This finding was expected because the evaluation parameters for the overall therapeutic effect in these studies, including symptoms such as facial pallor and dizziness, would theoretically be improved after an increase in hemoglobin levels. However, the significant improvement in hemoglobin levels and the overall therapeutic effect in the TCM group should be cautiously interpreted due to substantial heterogeneity. Therefore, subgroup analysis was performed to explore the source of the heterogeneity, but an opposite changing trend of heterogeneity was found, that had significantly higher heterogeneity in the therapeutic period or in the control method subgroups for hemoglobin levels and obviously decreased heterogeneity for the overall therapeutic effect.
an immunomodulatory effect, which can effectively enhance the activity of NK cells, promoting the transformation of T lymphocytes and thus playing an anticancer role. It has been proven that the combination of Astragalus polysaccharide with chemotherapy drugs improves the quality of life and survival time of patients with progressive non-small cell lung cancer.28 Angelica is a major Chinese hematinic medicine, which can repair the hematopoietic function by stimulating the cells and molecules associated with hematopoesis.29 Therefore, a rational combination of these Chinese medicines could theoretically enhance the antitumor effect and improve blood deficiency, and eventually show a significant therapeutic effect on CRA. In the present study, this assertion was proven by the obvious improvement in hemoglobin levels and the overall therapeutic effect in the TCM group compared to that in the control group.

A significant reduction in the incidence of adverse events was also found in the TCM group compared to that in the control group. A total of 14 cases of adverse events were found in this study, including 3 cases of skin rashes or incidence of hypertension; 2 cases of anorexia, allergies or nausea; and 1 case of liver dysfunction or fatigue. All of these adverse events occurred in studies that employed TCM. In the control group, a total of 14 cases of adverse events were found in this study, including 3 cases of skin rashes or incidence of hypertension; 2 cases of anorexia, allergies or nausea; and 1 case of liver dysfunction or fatigue. All of these adverse events occurred in studies that employed TCM. In the control group, the incidence of adverse events was significantly lower in the TCM group compared to that in the control group.

**For example, Chinese medicine polysaccharide can activate T and B lymphocytes, macrophages, natural killer cells, cytotoxic T cells, dendritic cells, and other immune cells and can stimulate the production of a variety of cytokines including IL-1, IL-2, IL-6, interferon, and tumor necrosis factor that enhance the body’s immune function.**24 On the other hand, Chinese hematonic medicine is sweet, warm, and nurturing. The commonly used hematonic medicines such as Angelica, Radix paeonia alba, Radix rehmanniae preparata, and donkey-hide gelatin have been reported to promote the production of red blood cells and hemoglobin.26 In the published studies, the Chinese medicine used in the TCM group included traditional prescription, Chinese patent medicine, and self-prescription medicine, which covered all types of TCM used for the treatment of CRA. The most commonly used Chinese medicines in the studies were Codonopsis pilosula, Astragalus, and Angelica. In animal experiments, subcutaneous injection of Codonopsis pilosula decoction obviously increased the number of rabbit red blood cells and hemoglobin levels.27 Astragalus polysaccharide has an immunomodulatory effect, which can effectively enhance the number of red blood cells and hemoglobin. The decoction of Codonopsis pilosula obviously increased the number of rabbit red blood cells and hemoglobin.

**Figure 3** Forest plots of hemoglobin level changes in the enrolled RCT studies, and I^2=97% indicated a significant heterogeneity among the studies (P<0.001).

**Abbreviation:** RCT, randomized controlled trial.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>Experimental SD</th>
<th>Experimental Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akase T 2003</td>
<td>107</td>
<td>5</td>
<td>101</td>
<td>121</td>
<td>2</td>
<td>14</td>
<td>9.0</td>
<td>-14.00 (-17.28, -10.72)</td>
</tr>
<tr>
<td>Cheng Z 2009</td>
<td>108</td>
<td>5</td>
<td>103</td>
<td>104</td>
<td>8</td>
<td>18</td>
<td>9.0</td>
<td>4.00 (0.75, 7.25)</td>
</tr>
<tr>
<td>Gu Y 2010</td>
<td>100.9</td>
<td>10.5</td>
<td>102</td>
<td>91.9</td>
<td>9.56</td>
<td>50</td>
<td>8.8</td>
<td>9.00 (5.29, 12.71)</td>
</tr>
<tr>
<td>Ling Z 2016</td>
<td>82.45</td>
<td>1.79</td>
<td>50</td>
<td>80.14</td>
<td>1.74</td>
<td>50</td>
<td>9.9</td>
<td>2.31 (1.62, 3.00)</td>
</tr>
<tr>
<td>Liu X 2015</td>
<td>125.34</td>
<td>8.97</td>
<td>46</td>
<td>101.49</td>
<td>8.61</td>
<td>46</td>
<td>8.8</td>
<td>23.85 (20.26, 27.44)</td>
</tr>
<tr>
<td>Lv X 2016</td>
<td>82.9</td>
<td>3.6</td>
<td>56</td>
<td>76.5</td>
<td>3.4</td>
<td>56</td>
<td>9.8</td>
<td>6.40 (5.10, 7.70)</td>
</tr>
<tr>
<td>Du X 2016</td>
<td>80.23</td>
<td>4.15</td>
<td>43</td>
<td>77.52</td>
<td>2.33</td>
<td>43</td>
<td>9.8</td>
<td>2.71 (1.29, 4.13)</td>
</tr>
<tr>
<td>Wang X 2017</td>
<td>116.65</td>
<td>7.3</td>
<td>40</td>
<td>106.46</td>
<td>6.8</td>
<td>40</td>
<td>9.1</td>
<td>10.22 (7.13, 13.31)</td>
</tr>
<tr>
<td>Cai G 2006</td>
<td>108.37</td>
<td>14.46</td>
<td>45</td>
<td>112.38</td>
<td>15.04</td>
<td>44</td>
<td>7.3</td>
<td>-4.01 (-10.14, 2.12)</td>
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<tr>
<td>Cai H 2016</td>
<td>80.7</td>
<td>4.4</td>
<td>60</td>
<td>78.4</td>
<td>4.6</td>
<td>60</td>
<td>9.7</td>
<td>2.30 (0.69, 3.91)</td>
</tr>
<tr>
<td>Zi J 2016</td>
<td>107.92</td>
<td>10.23</td>
<td>64</td>
<td>101.18</td>
<td>10.93</td>
<td>64</td>
<td>8.8</td>
<td>6.74 (3.07, 10.41)</td>
</tr>
</tbody>
</table>

Total (95% CI) 510 498 100 4.57 (1.38, 7.76)
**A**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>Control Mean</th>
<th>Total Weight</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
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<td><strong>Subgroup 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Gu Y 2010</td>
<td>10.9</td>
<td>10.5</td>
<td>63</td>
<td>91.9</td>
<td>9.56</td>
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<tr>
<td>Ling Z 2016</td>
<td>82.45</td>
<td>1.79</td>
<td>50</td>
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<tr>
<td>Liu X 2015</td>
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<td>101.49</td>
<td>8.61</td>
</tr>
<tr>
<td>Lv X 2016</td>
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<td>3.6</td>
<td>56</td>
<td>76.5</td>
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<tr>
<td>Wang X 2017</td>
<td>116.65</td>
<td>7.3</td>
<td>40</td>
<td>106.43</td>
<td>6.8</td>
</tr>
<tr>
<td>Cai H 2016</td>
<td>80.7</td>
<td>4.4</td>
<td>60</td>
<td>78.4</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>315</td>
<td>302</td>
<td>56.1</td>
<td>8.72</td>
<td>6.12 (12.83)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=24.59$, $P=0.00001$; $I^2=97$

Test for overall effect: $Z=4.17$ ($P=0.0001$)

| **Subgroup 2**   |                  |              |              |                                    |                                    |
| Akase T 2003     | 107              | 5            | 10           | 121                                | 12                                    |
| Cai G 2016       | 108.37           | 14.46        | 45           | 112.38                             | 15.04                                 |
| Zhi J 2016       | 107.92           | 10.23        | 64           | 101.18                             | 10.93                                 |
| **Subtotal (95% CI)** | 119              | 121          | 25.1         | $-3.77$ ($-17.75, 10.21$)          |

Heterogeneity: $\chi^2=147.26$, $df=2$ ($P=0.0001$); $I^2=97$

Test for overall effect: $Z=5.33$ ($P=0.005$)

| **Subgroup 3**   |                  |              |              |                                    |                                    |
| Cheng Z 2009     | 108              | 3            | 33           | 104                                | 8                                    |
| Du X 2016        | 80.23            | 4.15         | 43           | 77.52                              | 2.33                                 |
| **Subtotal (95% CI)** | 76               | 75           | 18.8         | 2.92                              | 1.61 (4.22)                          |

Heterogeneity: $\chi^2=0.00$, $df=1$ ($P=0.48$); $I^2=0$

Test for overall effect: $Z=4.39$ ($P=0.001$)

| **Total (95% CI)** |                  |              |              |                                    |                                    |
|                    |                  |              |              |                                    |                                    |
| Total              | 510              | 498          | 100          | 4.57                              | 1.38 (7.76)                          |

Heterogeneity: $\chi^2=26.62$, $df=10$ ($P=0.0001$); $I^2=97$

Test for overall effect: $Z=2.81$ ($P=0.005$)

Test for subgroup differences: $\chi^2=8.00$, $df=2$ ($P=0.02$); $I^2=75.0$

**B**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>Control Mean</th>
<th>Total Weight</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPO group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng Z, Wu JL 2009</td>
<td>108</td>
<td>5</td>
<td>33</td>
<td>104</td>
<td>8</td>
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<tr>
<td>Ling Z 2016</td>
<td>82.45</td>
<td>1.79</td>
<td>50</td>
<td>80.14</td>
<td>1.74</td>
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<tr>
<td>Lv X 2016</td>
<td>82.9</td>
<td>3.6</td>
<td>56</td>
<td>76.5</td>
<td>3.4</td>
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<tr>
<td>Du X 2016</td>
<td>80.23</td>
<td>4.15</td>
<td>43</td>
<td>77.52</td>
<td>2.33</td>
</tr>
<tr>
<td>Cai H 2016</td>
<td>80.7</td>
<td>4.4</td>
<td>60</td>
<td>78.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Zhi J 2016</td>
<td>107.92</td>
<td>10.23</td>
<td>64</td>
<td>101.18</td>
<td>10.93</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>306</td>
<td>305</td>
<td>67.9</td>
<td>3.85</td>
<td>2.18 (5.52)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=3.33$, $df=5$ ($P=0.0001$); $I^2=86$

Test for overall effect: $Z=4.51$ ($P<0.00001$)

| **Iron supplement** |                  |              |              |                                    |                                    |
| Akase T 2003       | 107              | 5            | 10           | 121                                | 2                                    |
| Liu X 2015         | 125.34           | 8.97         | 46           | 101.49                             | 8.61                                 |
| Wang X 2017        | 116.65           | 7.3          | 40           | 106.43                             | 6.8                                  |
| **Subtotal (95% CI)** | 96               | 99           | 32.1         | 6.68                              | $-14.49$ (27.85)                      |

Heterogeneity: $\chi^2=347.03$, $df=2$ ($P=0.00001$); $I^2=98$

Test for overall effect: $Z=6.82$ ($P=0.054$)

| **Total (95% CI)** |                  |              |              |                                    |                                    |
|                    |                  |              |              |                                    |                                    |
| Total              | 402              | 404          | 100          | 4.86                              | 1.37 (8.34)                          |

Heterogeneity: $\chi^2=26.69$, $df=8$ ($P=0.00001$); $I^2=97$

Test for overall effect: $Z=2.73$ ($P=0.006$)

Test for subgroup differences: $\chi^2=0.07$, $df=1$ ($P=0.79$); $I^2=0$

Figure 4 Subgroup analysis was performed with the follow-up period and therapy method in the control group for finding the source of significant heterogeneity.

Notes: (A) Analysis of changes in hemoglobin levels in the follow-up period subgroups 1 (≤30 days), 2 (31 days to 2 months), and 3 (>2 months). (B) Analysis of changes in hemoglobin levels between 1) TCM vs EPO and 2) TCM vs iron supplement subgroups.

Abbreviations: EPO, erythropoietin; TCM, traditional Chinese medicine.
Figure 5 Analysis of the overall therapeutic effects in this meta-analysis (A) in 10 included studies; (B) in iron supplement and EPO control studies; (C) analysis of adverse events in the pooled results.

Abbreviation: EPO, erythropoietin.
size of these studies was relatively small, and all of them were limited to Asian populations and regions. A further subgroup analysis was not possible and the pooled results may not be acceptable for other populations in other world regions. Third, there is a lack of uniform efficacy evaluation criteria; hence, the pooled results may have some bias owing to roughly dividing the subjective therapeutic effect into “effective” and “not effective”. Finally, since the meta-analysis excluded all reports on patients under chemotherapy or radiotherapy, treatment-related anemia remained outside the scope of our study.

Conclusion
An analysis of current data shows that TCM formulas supporting Qi and enriching blood may be a safe and effective treatment of CRA in patients not receiving chemoradiotherapy and could be considered as an alternative treatment to conventional therapy. There is a certain clinical significance when the risk and cost of blood transfusions, iron supplements, and EPO injections are considered. However, due to the relatively low quality and the small sample sizes of the included studies, the results should be interpreted cautiously. A well-designed, multicenter, and large-sample study is needed to confirm the therapeutic effect and safety of TCM formulas in supporting Qi and enriching the blood for the treatment of CRA in patients not receiving chemoradiotherapy.

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Author contributions
ZY was responsible for the conception and design of the study. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

References