Ginkgo leaf extract and dipyridamole injection for chronic cor pulmonale: a PRISMA-compliant meta-analysis of randomized controlled trials

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Ginkgo leaf extract and dipyridamole injection (GLED), a kind of Chinese herbal medicine preparation, has been considered as a promising supplementary treatment for chronic cor pulmonale (CCP). Although an analysis of the published literature has been performed, the exact effects and safety of GLED have yet to be systematically investigated. Therefore, a wide-ranging systematic search of electronic databases from which to draw conclusions was conducted. All randomized controlled trials concerning the GLED plus conventional treatments for CCP were selected in the present study. Main outcomes were treatment efficacy, blood gas and hemorrheology indexes, and adverse events. Data from 28 trials with 2457 CCP patients were analyzed. The results indicated that, compared with conventional treatments alone, the combination of conventional treatments with GLED obviously improved the markedly effective rate (RR = 1.44, 95% CI = 1.31–1.58, P < 0.00001) and total effective rate (RR = 1.28, 95% CI = 1.18–1.38, P < 0.00001). Moreover, the hemorrheology (PaO2, P < 0.00001; PaCO2, P < 0.00001; SaO2, P < 0.00001; pH value, P = 0.05) and blood gas indexes (PV, WBHSV, WBMSV, WBLSV, hematocrit and FBG, P < 0.01) of CCP patients were also significantly ameliorated after the combined therapy. The frequency of adverse events did not differ significantly between the two groups (P > 0.05). In summary, evidence from the meta-analysis suggested that the combination of conventional treatments and GLED appeared to be effective and relatively safe for CCP. Therefore, GLED mediated therapy could be recommended as an adjuvant treatment for CCP.

Introduction

Chronic cor pulmonale (CCP), a common type of heart disease, has become a rising major public problem that threatens people’s health and quality of life around the world [1]. Although the term “cor pulmonale” is popular in the medical literature, there is presently no consensual definition [1–3]. World Health Organization (WHO) defined CCP as “hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, and may further leading to heart failure” [4]. Pulmonary hypertension resulting from disorders of the respiratory system and/or from chronic hypoxaemia is the main pathological mechanism of CCP [1,5,6]. Currently, the conventional treatment, including antibiotics, vasodilators, expectorants, antiasthmatic drugs, diuretics and antiarrhythmic drugs etc. is the main clinical therapy for CCP [1]. However, it is universally acknowledged that long-time use of western medicine sometimes may cause drug resistance and toxic side effects, and therefore its clinical efficacy is still unsatisfactory [1,2]. Many researchers in China and some other Asian countries indicated that the combination of Chinese and Western medicine for CCP might be the potential trend of clinical treatment development in future [7–12].
Ginkgo leaf extract and dipyridamole injection (GLED) is a compound Chinese herbal medicine, which mainly consists of ginkgo flavone glycosides (24–25%), terpene lactones [ginkgolides (3.1%) and bilobalide (2.9%)] and dipyridamole (10%) [13–15]. Ginkgo leaf extract has been proved to be an antioxidant and free radical scavenger, an inhibitor of the platelet-activating factor, a vasodilator, and a regulator of metabolism [14–17]. The therapeutic effect mechanism of GLED on CCP included its ability to scavenge free radicals, reduce inflammation and platelet aggregation while regulating vasodilation and glucose and lipid metabolism [16]. Furthermore, GBE affects vasomotor functions by modulating the synthesis of vasoactive substances including nitric oxide and endothelin [16]. GLED is a combination of Ginkgo leaf extract and dipyridamole (a kind of anti-thrombus and vasodilator drug) [18], and has the pharmacological characteristics of both. GLED has been considered as a promising supplementary treatment option for cardiovascular disease, peripheral vascular disease and pulmonary disease due to its unique biological characteristics [13–17]. Tan et al. [14] reported that GLED (10–40 ml/day per day via intravenous infusion) could relieve the incidence of angina pectoris and improve the hemorheology index of patients with coronary artery disease. Xue et al. [15] showed that the clinical application of GDI (10–40 ml/day per day via intravenous infusion) not only obviously enhanced the overall response rate of conventional treatments, but also effectively improved the blood viscosity and blood lipid level of ischemic stroke patients.

Currently, its application in CCP is garnering much attention [14,19–23]. Several clinical trials reported that conventional treatments combined with GLED exhibits more prominent therapeutic effects for CCP than conventional treatments alone [24–51]. However, the scientific evidence has not been systematically reviewed. In the present study, we conducted a meta-analysis to investigate the clinical efficacy and safety of GLED for CCP, in order to provide the best available evidence for clinical practice and further research planning on CCP treatment.

**Materials and methods**

This systematic review and meta-analysis was performed following the PRISMA guidelines and Cochrane Handbook. Ethics approval was not necessary due to the nature of the study (i.e. meta-analysis).

**Search strategy**

Literatures were searched across nine electronic databases, including PubMed, Embase, Web of Science, Cochrane Library, Medline, Chinese Scientific Journal Database (VIP), Wanfang database, China National Knowledge Infrastructure (CNKI) and Chinese Biological Medicine Database (CBM), before December 2019, with key terms “ginkgo biloba” or “ginkgo leaf extract” or “ginkgo dipyidamolum” and “dipyridamole injection” or “Ginkgo leaf extract and dipyridamole injection” or “yinxingdamo injection” and “pulmonary heart disease” or “chronic cor pulmonale” or “cor pulmonale” or “fei yuan xing xin zang bing” or “fei xin bing” (Supplementary Table S1). Language is limited with English and Chinese.

**Eligibility criteria**

Inclusion criteria:

1. Randomized controlled trials (RCTs) concerning patients diagnosed with CCP were included;

2. Articles involving more than 50 CCP patients;

3. There were no other medicines in combination with the conventional treatments in the experimental group, except for GLED, compared with the conventional treatments as a control;

4. One or more outcome measures, including the therapeutic effect, or hemorheology or blood gas indexes, or adverse events must be included in each study.

Exclusion criteria:

1. Studies not focus on GLED were excluded;

2. Inappropriate criteria in experimental or control group were excluded;

3. Articles without sufficient available data were excluded;

4. Non-RCTs, literature reviews, meta-analysis, meeting abstracts and case reports, repeated studies and experimental model researches were excluded.
Data extraction and quality assessment

Data were extracted by two reviewers (Guo, Y. J. and Xu, X.) independently according to the same inclusion and exclusion criteria; disagreements were adjudicated by the third investigator (Yue, H. M.). The extracted characteristics comprised the following items: (a) first authors' names, (b) years of publication, (c) NYHA heart function classification, (d) number of cases, (e) patient ages, (f) intervening measure, (g) dosage of GLED, (h) duration of treatment, (i) manufacturer of GLED and (j) study parameter types. The quality of included trials was evaluated according to Cochrane Handbook [52,53].

Outcome definition

Treatment efficacy was evaluated in terms of markedly effective rate (MER) and the total effective rate (TER), blood gas and hemorrheology indexes. The hemorrheology indexes covered the following indicators: plasma viscosity (PV), whole blood high-shear viscosity (WBHSV), whole blood medium-shear viscosity (WBMSV), whole blood low-shear viscosity (WBLSV), hematocrit, erythrocyte aggregation index (EAI) and content of fibrinogen (FBG). The blood gas indicators [partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂), saturation of hemoglobin with oxygen (SaO₂) and pH value] of CCP patients were also determined and compared between the GLED and non-GLED groups.

Statistical analysis

Statistical analysis was performed using the Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 13.0 (Stata Corp., College Station, TX, U.S.A.) statistical software. Dichotomous data were represented by the risk ratio (RR) with the respective 95% confidence interval (CI), whereas continuous variables were expressed as mean difference (MD) with 95% CI. P < 0.05 indicates difference with statistical significance. Cochrane's Q-test and I² statistics were used to assess heterogeneity between studies; P < 0.1 or I² > 50% indicates statistical heterogeneity [54]. A fixed-effects model was used to pool the estimates when heterogeneity was absent. Otherwise, a random effects model was selected.

Publication bias was evaluated by Begg's and Egger's regression tests [55]. If publication bias existed, a trim-and-fill method should be applied to coordinate the estimates from unpublished studies, which were compared with the original pooled RR [56]. Sensitivity analysis was conducted to investigate the influence of different GLED dosages, duration of treatment, sample sizes of involved studies, and manufacturer of GLED on clinical efficacy.

Results

Search results

A total of 1722 articles were identified with initial retrieve. A total of 1395 papers were excluded due to duplication. After title and abstract review, 246 articles were further excluded because they were not clinical trials (n = 171) or were unrelated studies (n = 59) or were reviews and meta-analysis (n = 7) or were meeting abstracts and case report (n = 9), leaving 81 studies as potentially relevant. After detailed assessment of full texts, articles were not RCTs (n = 16), publications with inappropriate criteria of experimental or control group (n = 29) and trials with insufficient data (n = 8) were excluded. Finally, 28 trials [24–51] involving 2457 CCP patients were included in this analysis (Figure 1).

Patient characteristics

After selection, all included trials were performed in different hospital of China. In total, 1214 CCP patients were treated by conventional treatments in combination with GLED adjuvant therapy, while 1243 patients were treated by conventional treatments alone. Detailed information of the involved studies and CCP patients is shown in Table 1. All included trials except two [36,43] clearly introduce the duration of treatment. Fourteen studies [24–31,34,35,41,45,46,50] specifically describe the manufacturer of GLED and the remaining 14 studies [32,33,36–40,44,47–49,51] lacked clear description of production information (Supplementary Table S2).

Quality assessment

The assessment of bias risk is shown in Figure 2. Twenty-seven studies were determined as low risk, while one trial [26] did not provide a clear description of the randomization process. All included trials did not provide clear description of performance and detection risks. The attrition risks of involved trials were low. Three trials [25,43,48] were considered as high reporting risk owing to lack of primary outcomes (MER or TER) and 15 studies [25,26,28,32,35,37–39,42–51] were considered as unclear reporting risk due to lack of safety assessment.
TER and MER

Twenty-five clinical trials [24,26–42,44–47,49–51] involving 2,153 cases compared the MER and/or TER between the two groups (Figures 3 and 4). Our pooled results showed that CCP patients underwent combined therapy had significantly increased MER (RR = 1.44, 95% CI = 1.31–1.58, $P < 0.00001$) and TER (RR = 1.28, 95% CI = 1.18–1.38, $P < 0.00001$) compared with conventional treatments alone. MER ($P = 0.92, I^2 = 0\%$) was not heterogeneous among the studies, so fixed-effect model was used to analyzing its RR. Otherwise, random-effect model was used.

Review of authors’ judgments about each risk of bias item for included studies. Note: Each color represents a different level of bias: red for high-risk, green for low-risk, and yellow for unclear-risk of bias.
Table 1: Clinical information from the eligible trials in the meta-analysis

| Included studies | NYHA classification | Patients Con/Exp | Intervening measure (Exp/Con) | Dosage of GLED | Duration |
|------------------|---------------------|-----------------|------------------------------|----------------|----------|
| Fan, J. 2011     | II-IV               | 40/40           | CT+GLED (iv) VS CT           | 20 ml/day      | 14 days  |
| Gan, L. 2015     | II-IV               | 43/43           | CT+GLED (iv) VS CT           | 20 ml/day      | 10—14 days |
| Gao, L. S. 2006  | NG                  | 48/48           | CT+GLED (iv) VS CT           | 20 ml/day      | 7 days    |
| Gao, L. Y. 2009  | NG                  | 40/40           | CT+GLED (iv) VS CT           | 20 ml/day      | 14 days    |
| He, F. Z. 2009   | III-IV              | 35/36           | CT+GLED (iv) VS CT           | 20 ml/day      | 14 days    |
| He, H. 2019      | NG                  | 31/31           | CT+GLED (iv) VS CT           | 20 ml/day      | 12 days    |
| He, K. X. 2012   | III-IV              | 31/31           | CT+GLED (iv) VS CT           | 20 ml/day      | 7—14 days |
| Hu, Z. W. 2013   | NG                  | 40/40           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Jia, X. H. 2009  | NG                  | 48/48           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Li, W. M. 2009   | NG                  | 51/52           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Liu, R. P. 2009  | II-IV               | 31/30           | CT+GLED (iv) VS CT           | 20 ml/day      | 14 days    |
| Liu, W. M. 2008  | III-IV              | 48/48           | CT+GLED (iv) VS CT           | 20 ml/day      | 15 days    |
| Liu, L. Q. 2012  | NG                  | 64/64           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Liu, R. P. 2009  | NG                  | 50–79 (range)   | 51–79 (range)                | 20 ml/day      | 10 days    |
| Li, W. M. 2009   | NG                  | 49–92 (range)   | 45–95 (range)                | 20 ml/day      | 14 days    |
| Li, X. D. 2016   | III-IV              | 60.89 ± 3.87 (mean) | 61.02 ± 3.76 (mean) | 20 ml/day      | 7—14 days |
| Tao, L. 2015     | II-IV               | 54/54           | CT+GLED (iv) VS CT           | 20 ml/day      | 14 days    |
| Wang, B. C. 2011 | III-IV              | 28/28           | CT+GLED (iv) VS CT           | 20 ml/day      | 15 days    |
| Wang, L. H. 2014 | II-IV               | 56/56           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Wang, Y. 2017    | II-III              | 36/36           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Xie, J. 2012     | NG                  | 50/50           | CT+GLED (iv) VS CT           | 20 ml/day      | 10 days    |
| Xu, C. H. 2008   | NG                  | 40/48           | CT+GLED (iv) VS CT           | 20 ml/day      | 7 days     |
| Yang, J. L. 2010 | III-IV              | 30/30           | CT+GLED (iv) VS CT           | 20 ml/day      | 7—10 days |
| Yang, Y. P. 2011 | III-IV              | 35/35           | CT+GLED (iv) VS CT           | 20 ml/day      | 14 days    |
| Yin, Y. W. 2008  | III-IV              | 29/36           | CT+GLED (iv) VS CT           | 20 ml/day      | 15 days    |
| Zhong, G. N. 2015| III-IV              | 60/60           | CT+GLED (iv) VS CT           | 20 ml/day      | 12 days    |
| Zhou, B. 2012    | III-IV              | 43/43           | CT+GLED (iv) VS CT           | 25 ml/day      | 28 days    |
| Zhou, C. Y. 2015 | III-IV              | 25/30           | CT+GLED (iv) VS CT           | 20-30 ml/day   | 10 days    |
| Zou, D.H. 2009   | III-IV              | 100/100         | CT+GLED (iv) VS CT           | 20 ml/day      | 28 days    |

Notes: Con, control group (conventional treatments alone group); Exp, experimental group (conventional treatments and GLED combined group).
*The compositions and concentrations of GLED in all included trials are the same (every 10 ml GDI contained 9.0–11.0 mg total flavonoids and 3.6–4.4 mg dipyridamole).

Abbreviations: CT, conventional treatments; NG, not given; NYHA, New York Heart Association; GLED, Ginkgo leaf extract and dipyridamole injection; iv, intravenous injection.

Blood gas analysis
Eight trials [27,29,30,33,35,38,39,49] with 722 participants measured the PaO2 and PaCO2, two trials [27,29] involving 142 CCP patients evaluated the SaO2, and three trials [27,35,39] including 316 patients reported data on pH value (Figure 5). Results showed that the blood gas indexes of CCP patients received combined therapy was obviously improved compared with those treated by conventional treatments alone, indicated by significantly increased PaO2 (MD = 1.14, 95% CI = 0.89–1.39, P < 0.00001), SaO2 (MD = 5.34, 95% CI = 3.65–7.04, P < 0.00001) and PH value (MD = 0.11, 95% CI = 0.00–0.22, P = 0.05), and obviously decreased PaCO2 (MD = -0.52, 95% CI = -0.73–0.32, P < 0.00001). PH value (P = 0.99, I² = 0%) was heterogeneous among the studies, so random-effect model was used to analyzing its RR. Otherwise, fixed-effect model was used.
Hemorrheology assessment

The hemorrheology of CCP patients was measured between GLED and non-GLED groups in 13 controlled studies [25–27,29,31,34,36,37,39,41,43,44,48] with 1,192 CCP patients (Figure 6). In this analysis, our results showed that the hemorrheology of CCP patients received combined therapy was significantly ameliorated compared with those treated by conventional treatments alone, indicated by significantly decreased PV (MD = -0.21, 95% CI = -0.32–0.11, P < 0.0001), WBHSV (MD = -1.07, 95% CI = -1.41–0.74, P < 0.0001), WBMSV (MD = -1.91, 95% CI = -3.22–0.59, P = 0.004), WBLSV (MD = -2.17, 95% CI = -3.25–1.10, P < 0.0001), hematocrit (MD = -0.06, 95% CI = -0.09–0.04, P < 0.0001) and FBG (MD = -0.69, 95% CI = -1.01–0.37, P < 0.0001), whereas analysis of EAI (MD = -0.36, 95% CI = -0.75–0.03, P = 0.07) did not differ significantly between the two groups. There was significant heterogeneity among the studies. Therefore, a random-effects model was conducted to pool data and so any conclusions need to be made with caution.

Adverse events assessment

Among all included studies, 18 trials [25,26,28,32,35,37–39,42–51] did not report adverse events. Ten trials [24,27,29–31,33,34,36,40,41] involving 795 CCP patients described specific adverse events that occurred in GLED treatment. The most common side effects of GLED treatment were including nausea, headache, dizziness, abdominal distention, pruritus and skin rash, which usually subsided after symptomatic treatment. No severe adverse event occurred during GLED treatment, and the occurrence of these adverse reactions in the two groups did not differ obviously (Figure 7, RR = 2.21, 95% CI = 0.95–5.15, P = 0.07). Statistics showed no statistically significant heterogeneity (P = 0.42, I² = 0%), so fixed-effect model was used to carry out the meta-analysis.
Figure 4. Comparisons of TER between experimental and control group
Forest plot of the comparison of TER between the experimental and control group. Control group, conventional treatments alone group; Experimental group, conventional treatments and GLED combined group. The random effects meta-analysis model (Mantel–Haenszel method) was used.

Publication bias
Publication bias was assessed by funnel plots, Begg’s and Egger’s regression tests (Figure 8). Analysis results indicate that publication bias was existed in MER and TER. To determine if the bias affect the results of pooled analysis, we conducted trim and filled analysis. The adjusted RR indicated same trend with the result of the primary analysis (Figure 8, MER: before: \( P < 0.001 \), after: \( P < 0.001 \); TER: before: \( P < 0.001 \), after: \( P < 0.001 \)), reflecting the reliability of our primary conclusions.

Sensitivity analysis
Sensitivity analysis was performed to explore an individual study’s influence on the pooled results by deleting one single study each time from pooled analysis. As Figure 9 signified, the results revealed that no individual studies significantly affected the primary indicators (MER and TER), which indicated statistically robust results.

We also conducted subgroup analysis to explore the source of heterogeneity in MER and TER with respect to GLED dosages, duration of treatment, sample sizes of involved studies, and manufacturer of GLED. As shown in Table 2, our analysis showed that these variables except manufacturer of GLED did not have a significant impact on the therapeutic efficacy of GLED for CCP.

Discussion
Ginkgo biloba, a “living fossil,” have been used as traditional herbal medicine for thousands of years in China [16]. As an important Ginkgo biloba extract preparation, it has been proven that the pharmacological effects of GLED include regulating vasomotor, improving hemorheology, enhancing immunity, relieving inflammation and scavenging...
Figure 5. Comparisons of blood gas indexes between experimental and control group

Forest plot of the comparison of the blood gas indexes including PaO2 (A), PaCO2 (B), SaO2 (C) and PH value (D) between the experimental and control group. Control group, conventional treatments alone group; Experimental group, conventional treatments and GLED combined group.
### Figure 6. Comparisons of hemorrheology indexes between experimental and control group

Forest plot of the comparison of the hemorrheology indexes including PV (A), WBHSV (B), WBMSV (C), WBLSV (D), hematocrit (E), EAI (F) and FBG (G) between the experimental and control group. Control group, conventional treatments alone group; Experimental group, conventional treatments and GLED combined group. The random effects meta-analysis model (Mantel–Haenszel method) was used.

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Figure 7. Comparisons of total adverse effects between experimental and control group

Forest plot of the comparison of total adverse effects between the experimental and control group. Control group, conventional treatments alone group; Experimental group, conventional treatments and GLED combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

Figure 8. Funnel plot of MER (A) and TER (B)

Figure 9. Sensitivity analysis for MER (A) and TER (B)

Free radicals \[14,15,57\]. It has been clinically applied as an effective complementary drug for lung and heart disease \[14,15,58–60\]. Even though there was statistical analysis of published literatures, a comprehensive and systematic evaluation of GLED for the treatment of CCP is still rare. In this analysis, we conducted a wide range of online search
Table 2 Subgroup analyses of MER and TER between the experimental and control group

| Parameter                  | Experimental group, No. of patients (n) | Control group, No. of patients (n) | Analysis method | Heterogeneity | Risk ratio (RR) | 95% CI          | P-value |
|----------------------------|----------------------------------------|-----------------------------------|-----------------|---------------|----------------|----------------|---------|
|                           |                                        |                                   |                 |               |                |                 |         |
| MER                        |                                        |                                   |                 |               |                |                 |         |
| Dosage of GLED (DG)        |                                        |                                   |                 |               |                |                 |         |
| 20< DG ≤ 40 ml/day        | 189                                    | 188                               | Fixed           | 16            | 0.31           | 1.32            | 1.08–1.61 | 0.006  |
| 15≤ DG ≤ 20 ml/day        | 774                                    | 760                               | Fixed           | 0             | 0.98           | 1.49            | 1.34–1.66 | <0.00001|
| Duration of treatment     |                                        |                                   |                 |               |                |                 |         |
| ≥14 days                  | 364                                    | 362                               | Fixed           | 0             | 0.70           | 1.38            | 1.19–1.60 | <0.0001 |
| <14 days                  | 520                                    | 501                               | Fixed           | 0             | 0.69           | 1.48            | 1.31–1.68 | <0.00001|
| Manufacturer of the GLED  |                                        |                                   |                 |               |                |                 |         |
| I                         | 70                                     | 70                                | Fixed           | 0             | 0.82           | 1.77            | 0.99–3.16 | 0.05   |
| II                        | 92                                     | 91                                | Fixed           | 0             | 0.42           | 1.34            | 1.02–1.76 | 0.03   |
| III                       | 322                                    | 323                               | Fixed           | 0             | 0.87           | 1.47            | 1.26–1.70 | <0.0001 |
| IV                        | 30                                     | 25                                | Fixed           | 0             | 0.53           | 1.42            | 1.27–1.58 | <0.00001|
| Study sample size         |                                        |                                   |                 |               |                |                 |         |
| >80                       | 596                                    | 582                               | Fixed           | 0             | 0.97           | 1.48            | 1.25–1.75 | <0.00001|
| ≤80                       | 397                                    | 391                               | Fixed           | 0             | 0.97           | 1.48            | 1.25–1.75 | <0.00001|
| TER                        |                                        |                                   |                 |               |                |                 |         |
| Dosage of GLED            |                                        |                                   |                 |               |                |                 |         |
| 20< DG ≤ 40 ml/day        | 283                                    | 265                               | Fixed           | 49            | 0.08           | 1.27            | 1.16–1.39 | <0.0001 |
| 15≤ DG ≤ 20 ml/day        | 777                                    | 773                               | Random          | 76            | <0.00001      | 1.30            | 1.18–1.44 | <0.00001|
| Duration of treatment     |                                        |                                   |                 |               |                |                 |         |
| ≥14 days                  | 486                                    | 467                               | Random          | 69            | 0.0004        | 1.27            | 1.14–1.41 | <0.0001 |
| <14 days                  | 495                                    | 486                               | Random          | 74            | <0.00001      | 1.29            | 1.14–1.48 | 0.0001 |
| Manufacturer of the GLED  |                                        |                                   |                 |               |                |                 |         |
| I                         | 70                                     | 70                                | Fixed           | 0             | 0.70           | 1.43            | 1.18–1.74 | 0.0003 |
| II                        | 92                                     | 91                                | Fixed           | 0             | 0.59           | 1.19            | 1.04–1.36 | 0.01   |
| III                       | 322                                    | 323                               | Fixed           | 31            | 0.18           | 1.26            | 1.16–1.98 | <0.0001 |
| IV                        | 30                                     | 25                                | Fixed           | 0             | 0.11           | 1.11            | 0.91–1.35 | 0.29   |
| Study sample size         |                                        |                                   |                 |               |                |                 |         |
| >80                       | 519                                    | 496                               | Random          | 67            | 0.0001        | 1.30            | 1.16–1.45 | <0.00001|
| ≤80                       | 571                                    | 567                               | Random          | 75            | <0.00001      | 1.26            | 1.13–1.40 | <0.00001|

Notes: Con, control group (conventional treatments alone group); Exp, experimental group (conventional treatments and GLED combined group); I, Shanxi Pude Pharmaceutical Co., Ltd.; II, Hubei Minkang Pharmaceutical Co., Ltd.; III, Guizhou Yibai Pharmaceutical Co., Ltd.; IV, Tonghua Guhong Pharmaceutical Co., Ltd.

Abbreviations: GLED: Ginkgo leaf extract and dipyridamole injection; MER: Markedly effective rate; TER: Total effective rate.

According to strict eligibility criteria, by which to provide an internationally accessible systematic review of the clinical efficacy and safety of GLED for the CCP.

The meta-analysis was carried out in 25 articles [24,26–42,44–47,49–51] to evaluate the therapeutic effects of GLED for CCP. Compared with conventional treatments alone, GLED combined with conventional treatments was associated with obviously higher MER and TER. Moreover, because of chronic hypoxia, patients with CCP will suffer from oxygen free radicals metabolism imbalance, increased blood viscosity and pulmonary artery pressure, and further lead to the right heart dysfunction and even failure [1–4]. Our analysis results showed that the blood gas and hemorheology indexes of patients were also significantly ameliorated after conventional treatments and GLED combined therapy. All these results indicated that GLED can improve the cardiopulmonary function of CCP patients effectively, which may be related with its action on regulating the blood viscosity and blood gas indexes. To further confirm whether some variable factors affect the therapeutic effects of GLED for CCP. We used four clinical variables (GLED dosages, duration of treatment, sample sizes of involved studies, and manufacturer of GLED) to interact with two outcome indicators (MER and TER) and found that the MER and TER might be associated with manufacturer of GLED. However, given that only one study [50] reported the use of GLED produced by Tonghua Guhong Pharmaceutical Co., Ltd., therefore it is not enough to draw a definitive conclusion at present.

Safety is the top priority of a therapeutic strategy, and special attention should be paid to adverse drug events. The most common side effects during GLED therapy were nausea, headache, dizziness, abdominal distention, pruritus...
and skin rash, and the total adverse events did not differ significantly between the two groups. Therefore, GLED is a relatively safe auxiliary medicine for CCP. However, evidence was limited to make a conclusion on safety evaluation because only 10 studies mentioned the adverse events.

There are some limitations in our analysis. First, as an important Chinese herb preparation, GLED was mainly applied in China or other Asian countries, which may bring the unavoidable regional bias and subsequently influence the clinical application of GLED worldwide. Second, the duration of treatment ranged from 7 to 28 days among the included studies. All of the trials assessed the efficacy immediately after the termination of the treatment period. Therefore, the long-term effect of GLED for CCP still needs methodologically rigorous trials to verify. Third, the main pathological features of CCP are pulmonary artery pressure, progressive of right ventricular hypertrophy and cardiopulmonary functional insufficiency. Many key variables, such as number of exacerbation, heart and lung function, quality of life, which closely related to survival, are not evaluated in these studies. Therefore, it is not yet possible to draw a conclusion on important outcomes. Moreover, GLED is a mixture that consists of more than one effective component, in this case, the mechanism of GLED may be complex and has multiple targets, and also this limits the usage of it. Fourthly, the administration conditions (extract/distill methods, storage conditions, dripping speed, GLED dosages and manufacturer, et al.) might be related with the efficacy of GLED mediated therapy [61,62]. In order to achieve the clinical therapeutic effect and reduce the incidence of adverse reactions of GLED mediated therapy to the greatest extent, it is necessary to strengthen the supervision of clinical medication to standardize the rational medication. The GLED in all included trials was approved by Chinese State Food and Drug Administration (SFDA), and granted the Manufacturing Approve Number issued by Chinese SFDA (Supplementary Table S2). Based on currently available literatures, we have conducted subgroup analysis according to different GLED dosages and manufacturer. However, there are insufficient data to perform a statistical analysis to evaluate the impacts of other variable factors (extract/distill methods, storage conditions and dripping speed, et al.) on the treatment effect of GLED. We will keep following up with upcoming clinical trials to obtain relevant data when available. Finally, allocation concealment and blind method were not clear in most included studies, which may results in exaggerated estimates of treatment effect. Given the limitations mentioned above, all the findings from our study should be dealt with some caution.

Conclusion and prospect
In summary, our meta-analysis suggested that GLED could have potential therapeutic effects and be relatively safe for the treatment of CCP. Clinical application of GLED not only obviously enhanced the therapeutic effects of conventional treatments, but also useful in lowering plasma viscosity, blood viscosity, hematocrit, alleviating and improving PaO2 and SaO2 of CCP patients. However, due to the publication bias and low quality of some included trials increases risks and bias, the clinical efficacy and safety of GLED-mediate therapy for CCP still needs more high-quality, multi-center large randomized trials to verify.

Traditional Chinese medicine plays an increasingly important role in various disease treatments (such as malaria and 2019 novel coronavirus, etc.) [16,63]. Ginkgo leaf extract has been used for pharmaceutical and medicinal purpose in China for several hundred years to treat various diseases [16]. The extremely low rate of side effects and good tolerance together with its pharmacological mechanism will make GLED a promising therapeutic drug in cardiovascular disease, peripheral vascular disease and pulmonary disease worldwide [16].

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
Q.J. conceived and designed the methods. Q.J. G.Y.J. and Y.H.M. extracted the original data and drafted the manuscript. G.Y.J. X.X. and Y.Y.P. performed statistical analysis. Q.J. and G.Y.J. interpreted results. Q.J. and Y.Y.P. revised the manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Abbreviations
CCP, chronic cor pulmonale; CI, confidence interval; EAI, erythrocyte aggregation index; FBG, content of fibrinogen; GLED, Ginkgo leaf extract and dipyridamole injection; MD, mean difference; MER, markedly effective rate; NYHA, New York Heart Association; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PRISMA, Preferred Reporting Items for
References

1. Shi, L., Xie, Y., Liao, X., Chai, Y. and Luo, Y. (2015) Shenmai injection as an adjuvant treatment for chronic cor pulmonale heart failure: a systematic review and meta-analysis of randomized controlled trials. *BMC Complement. Altern. Med.* **15**, 418, [https://doi.org/10.1186/s12906-015-0393-2](https://doi.org/10.1186/s12906-015-0393-2).

2. Liu, Y., Huang, Y., Zhao, C., Qin, X., Zhu, Q., Chen, S. et al. (2014) Salvia miltiorrhiza injection on pulmonary heart disease: a systematic review and meta-analysis. *Am. J. Chin. Med.* **42**, 1315–1331, [https://doi.org/10.1142/S0129049614500827](https://doi.org/10.1142/S0129049614500827).

3. Roberts, W.C., Shafii, A.E., Grayburn, P.A., Ko, J.M., Weissenborn, M.R., Rosenblatt, R.L. et al. (2015) Clinical and morphologic features of acute, subacute and chronic cor pulmonale (pulmonary heart disease). *Am. J. Cardiol.* **115**, 697–703, [https://doi.org/10.1016/j.amjcard.2014.12.002](https://doi.org/10.1016/j.amjcard.2014.12.002).

4. Weitzenblum, E. and Choaouat, A. (2009) Cor pulmonale. *Chron. Respir. Dis.* **6**, 177–185, [https://doi.org/10.1177/1479972309104664](https://doi.org/10.1177/1479972309104664).

5. Weitzenblum, E. (2003) Chronic cor pulmonale. *Heart* **89**, 225–230, [https://doi.org/10.1136/heart.89.2.225](https://doi.org/10.1136/heart.89.2.225).

6. Shujaat, A., Minkin, R. and Eden, E. (2007) Pulmonary hypertension and chronic cor pulmonale in COPD. *Int. J. Chron. Obstruct Pulmon Dis.* **2**, 273–282.

7. Chen, M.Z. and Gao, C.Y. (1985) The effects in chronic cor pulmonale treated with traditional Chinese medicine and western medicine. *Chin. J. Integrated Tradit. West Med.* **5**, 463–465.

8. Huang, Y., Li, L., Li, X., Fan, S., Zhuang, P. and Zhang, Y. (2018) Ginseng Compatibility Environment Attenuates Toxicity and Keeps Efficacy in Cor Pulmonale Treated by Fuzi Beimu Incompatibility Through the Coordinated Crosstalk of PKA and Epac Signaling Pathways. *Front. Pharmacol.* **9**, 634, [https://doi.org/10.3389/fphar.2018.00634](https://doi.org/10.3389/fphar.2018.00634).

9. Liu, S.M. and Tang, T.Q. (1994) Clinical and experimental studies of faiyanying in treating pulmonary arterial hypertension in cor pulmonale. *Chin. J. Integrated Tradit. West Med.* **14**, 469–473.

10. Che, H. and Luo, K. (2000) Effects of huang qi wu wu decoction on plasma proteins in 70 cases of chronic pulmonary heart disease. *J. Tradit. Chin. Med.* **20**, 254–257.

11. Li, J.S., Wang, H.F., Bai, Y.P., Li, S.Y., Yu, X.Q. and Li, Y. (2012) Ligustrazine injection for chronic pulmonary heart disease: a systematic review and meta-analysis. *Evid. Based Complement. Alternat. Med.* **2012**, 792762.

12. Li, P. (2006) Clinical observation on shufei granule in improving right ventricular function of patients with chronic pulmonary heart disease. *Chin. J. Integrated Tradit. West Med.* **26**, 732–735.

13. Zeng, X., Liu, M., Yang, Y., Li, Y. and Asplund, K. (2005) Ginkgo biloba for acute ischaemic stroke. *Cochrane Database Syst. Rev.* **4**, CD003691.

14. Tan, D., Wu, J.R., Cui, Y.Y., Zhao, Y., Zhang, D., Liu, S. et al. (2018) Ginkgo Leaf Extract and Dipyridamole Injection as Adjuvant Treatment for Angina Pectoris: A Meta-Analysis of 41 Randomized Controlled Trials. * Chin. J. Integr. Med.* **24**, 930–937, [https://doi.org/10.1007/s11655-018-2557-6](https://doi.org/10.1007/s11655-018-2557-6).

15. Xue, P., Ma, Z. and Liu, S. (2019) Efficacy and Safety of Ginkgo Leaf Extract and Dipyridamole Injection for Ischemic Stroke: A Systematic Review and Meta-Analysis. *Front. Pharmacol.* **10**, 1403, [https://doi.org/10.3389/fphar.2019.01403](https://doi.org/10.3389/fphar.2019.01403).

16. Tian, J., Liu, Y. and Chen, K. (2017) Ginkgo biloba Extract in Vascular Protection: Molecular Mechanisms and Clinical Applications. *Curr. Pharm. Sci.* **15**, 532–548, [https://doi.org/10.2174/157011115666170713095545](https://doi.org/10.2174/157011115666170713095545).

17. Cao, H., Tan, D., Wang, K., Duan, X., Wu, J., Liu, X. et al. (2019) Comparative effectiveness of Ginkgo injections for treating vertebralbasilar insufficiency: A systematic review and network meta-analysis. *J. Clin. Pharmacol. Ther.* **45**, 256–263.

18. Ciaciarelli, M., Zerbinati, C., Violi, F. and Iuliano, L. (2015) Dipyridamole: a drug with unrecognized antioxidant activity. *Curr. Top. Med. Chem.* **15**, 822–829, [https://doi.org/10.2174/1568026615666150220111942](https://doi.org/10.2174/1568026615666150220111942).

19. Song, Q.J., Wang, S.H., Yang, J., Sun, J., Yan, Q., Zhu, M. et al. (2006) Effect of ginkgo biloba extract and dipyridamole on transcription and translation of inducible NO synthbase in rabbits after myocardial ischemia-reperfusion injury. *Chin. J. Integr. Tradit. Med.* **26**, 240–243.

20. Wang, J., Wang, H.H., Zhou, P.P. and Jiang, Y.X. (2015) Regulation Mechanism of Ginkgo-Dipyridamolium for Calcium Homeostasis on Cardioprotective Effect During Ischemia Reperfusion Injury. *J. Chin. Med. Mater.* **38**, 2557–2562.

21. Liu, S., Wu, J.R., Zhang, D., Wang, K.H., Zhang, B., Zhang, X.M. et al. (2018) Comparative efficacy of Chinese herbal injections for treating acute cerebral infarction: a network meta-analysis of randomized controlled trials. *BMC Complement. Altern. Med.* **18**, 120, [https://doi.org/10.1186/s12906-018-1718-9](https://doi.org/10.1186/s12906-018-1718-9).

22. Zhang, H., Li, Y.J. and Yang, R. (2010) Tissue Doppler imaging observation on effect of long-term use of ginkgo biloba tablet on left ventricular function in patients with chronic heart failure. *Chin. J. Integrated Tradit. West Med.* **30**, 478–481.

23. Xu, Z., Wu, W., Lan, T. and Zhang, X. (2009) Protective effects of extract of Ginkgo biloba on adriamycin-induced heart failure and its mechanism: role of ghrelin peptide. *China J. Chin. Mater. Med.* **34**, 2786–2789.

24. Fan, J. (2011) Clinical observation of ginkgo dipyridamolium for the treatment of heart failure caused by pulmonary heart disease. *Chin. J. Aesthetic Med.* **20**, 279.

25. Gan, L. (2015) Efficacy of ginkgo leaf extract and dipyridamolium injection for the treatment of pulmonary heart disease and the influence upon hemorheology. *Chin. J. Integr. Med. Cardio Cerebrovasc Dis.* **13**, 1137–1138.

26. Gao, L.S., Zhang, H.Y. and Huang, Z.W. (2006) Therapeutic efficacy of ginkgo dipyridamolium for the treatment of pulmonary heart disease and the impact on hemorheology. *J. Chin. Microcircul.* **10**, 296.

27. Gao, L.Y., Yang, X., Yuan, H.L. and Liu, X.J. (2009) Observation of clinical efficacy in yinxiangdama injection in treating chronic pulmonary heart disease. *J. Emerg. Tradit Chin. Med.* **18**, 331–332.
28 He, F.Z. and Li, H. (2009) Clinical observation of yinxingdamo injection for 36 patients with acute exacerbation of chronic pulmonary heart disease. *J. Clin. Pul. Med.* **14**, 660
29 He, H., Zhang, J.L. and He, Y.Z. (2019) Therapeutic efficacy of Low molecular weight heparin calcium combined with ginkgo dipyidamolum for the treatment of acute exacerbation of chronic pulmonary heart disease. *Jiangxi Med.* **54**, 126–128
30 He, K.X., Yang, T.E. and Zhang, J.Y. (2012) Clinical efficacy analysis of ginkgo leaf extract and dipyridamol injection for the treatment of cor pulmonale. *Nat. Med. Front China* **7**, 14–15
31 Hu, Z.W., Cai, T.J., Wu, J.C. and He, M. (2013) Clinical analysis of yinxingdamo injection for 40 patients with acute exacerbation of chronic cor pulmonale. *J. Clin. Pul. Med.* **18**, 144–145
32 Jia, X.H. (2009) Clinical study on the treatment of acute attack of chronic cor pulmonale. *China Foreign Med. Treat* **28**, 45
33 Ji, N.P. and Jin, J.N. (2010) Effect of ginkgo leaf extract and dipyridamole injection for the treatment of acute exacerbation of chronic cor pulmonale. *Inner Mongol. J. tradit Chin. Med.* **29**, 20–21
34 Liang, Y.M. (2007) Ginkgo leaf extract and dipyridamole injection for the treatment of acute exacerbation of chronic cor pulmonale. *Prim. Med. Pharm.* **8**, 3843–3846
35 Liu, H.Q. (2012) Clinical efficacy analysis of ginkgo-dipyidamolum injection in the treatment of chronic pulmonary heart diseases. *Clin. Med. Engin.* **19**, 1718–1719
36 Liu, R.P. (2009) Clinical effects of ginkgo-damole combined with regtin in treating pulmonary heart disease with heart failure. *Chin. J. Clin. Rat. Drug Use* **2**, 1–2
37 Li, W.M., Yu, T., Yang, W. and Wang, Y. (2009) The therapeutic effect of ginkgo dipyridamol in jection in treating patients with acute exacerbation of chronic cor pulmonale. *Sichuan Med. J.* **30**, 927–928
38 Li, X.D. (2016) Effect analysis ginkgo leaf extract and dipyridamole injection for the treatment of cor pulmonale. *J. Today Health* **15**, 120
39 Tao, L. (2015) Therapeutic efficacy analysis of ginkgo dipyridamol injection for the treatment of acute exacerbation of chronic pulmonary heart disease. *J. Inner Mongolia Med. Univer.* **37**, 56–57
40 Wang, B.C. (2011) Efficacy of ginkgodipyidamlum for acutely exacerbations of chronic obstructive pulmonary disease with chronic pulmonary heart disease. *China Modern Med.* **18**, 52–53
41 Wang, L.H. and Wang, L. (2014) Ginkgo leaf extract and dipyridamole injection in treating 56 cases of chronic pulmonary heart disease. *Western J. Tradit Chin. Med.* **27**, 101–103
42 Wang, Y. and Fu, L.P. (2017) Efficacy analysis of yinxingdamo for the treatment of cor pulmonale. *Good Health All* **11**, 166
43 Xie, J. and Hu, X.L. (2012) Curative effect observation of ginkgo dipyridamol injection for the treatment of acute exacerbation of chronic pulmonary heart disease. *Jilin Med. J.* **33**, 3661–3662
44 Xu, C.H. and Zhang, L.W. (2008) Efficacy of ginkgo dipyridamol injection for the treatment of acute exacerbation of chronic pulmonary heart disease and its influence on hemorheology. *China Med. Herald* **5**, 70–71
45 Yang, Y.J. (2010) The clinical efficacy observation of yinxingdamo for 30 patients with acute exacerbation of chronic pulmonary heart disease. *J. Prim. Med. Pharm.* **17**, 45–46
46 Yang, Y.P. (2011) Therapeutic efficacy observation of ginkgo leaf extract and dipyridamole injection for 35 patients with acute exacerbation of chronic cor pulmonale. *Guide China Med.* **9**, 85–90
47 Yin, Y.W. and Kong, L.X. (2008) Therapeutic efficacy observation of ginkgo leaf extract and dipyridamole for 36 patients with acute exacerbation of cor pulmonale. *J. Gen. Intern. Med.* **20**, 2093
48 Zhong, G.N. (2015) Clinical efficacy observation of Yinxingdamo Injection for the treatment of acute exacerbation of chronic pulmonary heart disease. *Med. J. Inner Mongolia Med. Univer.* **37**, 102–103
49 Zhou, B. (2012) Clinical efficacy observation of ginkgo leaf extract and dipyridamole injection for the treatment of cor pulmonale. *China Foreign Med. Treat.* **31**, 127
50 Zhou, C.Y. (2015) Therapeutic effect observation of ginkgo leaf extract and dipyridamole injection for patients with acute exacerbation of chronic pulmonary heart disease. *Contemp Med. Forum* **13**, 134–135
51 Zou, D.H. (2009) Comparing observation of therapeutic effects of yinxingdamo injection for 100 patients with acute exacerbation of chronic pulmonary heart disease. *China Med. Herald* **6**, 38–39
52 Zeng, X., Zhang, Y., Kwong, J.S., Zhang, C., Li, S., Sun, F. et al. (2015) The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J. Evid. Based Med.* **8**, 2–10, https://doi.org/10.1111/jebm.12141
53 Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D. et al. (2011) The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928, https://doi.org/10.1136/bmj.d5928
54 Jackson, D., White, I.R. and Riley, R.D. (2012) Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat. Med.* **31**, 3805–3820, https://doi.org/10.1002/sim.5453
55 Lin, L., Chu, H., Murad, M.H., Hong, C., Qu, Z., Cole, S.R. et al. (2018) Empirical Comparison of Publication Bias Tests in Meta-Analysis. *J. Gen. Intern. Med.* **33**, 1260–1267, https://doi.org/10.1007/s11606-018-4425-7
56 Shi, L. and Lin, L. (2019) The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. *Medicine (Baltimore)* **98**, e15987, https://doi.org/10.1097/MD.0000000000015987
57 Tao, Z., Jin, W., Ao, M., Zhai, S., Xu, H. and Yu, L. (2019) Evaluation of the anti-inflammatory properties of the active constituents in Ginkgo biloba for the treatment of pulmonary diseases. *Food Funct.* **10**, 2209–2220, https://doi.org/10.1039/C8FO2506A
58 Qi, J., Liu, Y., Li, O. and Chen, X. (2010) Effect of ginkgo biloba extract against pulmonary fibrosis and its mechanisms. *China J. Chin. Materia Med.* **35**, 3043–3047
59 El-Boghdady, N.A. (2013) Increased cardiac endothelin-1 and nitric oxide in adriamycin-induced acute cardiotoxicity: protective effect of Ginkgo biloba extract. *Indian J. Biochem. Biophys.* **50**, 202–209

60 Tao, Z., Jin, W., Ao, M., Zhai, S., Xu, H. and Yu, L. (2019) Evaluation of the anti-inflammatory properties of the active constituents in Ginkgo biloba for the treatment of pulmonary diseases. *Food Funct.* **10**, 2209–2220, [https://doi.org/10.1039/C8FO02506A](https://doi.org/10.1039/C8FO02506A)

61 Yan, H.Y., Liu, F.X., Xu, J.W., Zhao, X., Shi, Y.P., Yan, X.L. et al. (2019) Clinical Safety Evaluation and Risk Management of Ginkgo Leaf Extract and Dipyridamole Injection. *Drug Eval.* **16**, 12–15

62 Pan, D., Li, L., Lu, D.D., Dou, N.N., Chen, K.X. and Zhao, K.X. (2017) The pharmaceutical care of ginkgo dipyridolum injection. *China Med. Herald* **14**, 27–30

63 Wang, Z., Chen, X., Lu, Y., Chen, F. and Zhang, W. (2020) Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci. Trends,* [Epub ahead of print], [https://doi.org/10.5582/bst.2020.01030](https://doi.org/10.5582/bst.2020.01030)