Add-On Effect of Chinese Herbal Medicine on Mortality in Myocardial Infarction: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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In China, Chinese herbal medicine (CHM) is widely used as an adjunct to biomedicine (BM) in treating myocardial infarction (MI). This meta-analysis of RCTs evaluated the efficacy of combined CHM-BM in the treatment of MI, compared to BM alone. Sixty-five RCTs (12,022 patients) of moderate quality were identified. 6,036 patients were given CHM plus BM, and 5,986 patients used BM only. Combined results showed clear additional effect of CHM-BM treatment in reducing all-cause mortality (relative risk reduction (RRR) = 37%, 95% CI = 28%–45%, \(I^2 = 0.0\%\)) and mortality of cardiac origin (RRR = 39%, 95% CI = 22%–52%, \(I^2 = 22.8\%\)). Benefits remained after random-effect trim and fill adjustment for publication bias (adjusted RRR for all-cause mortality = 29%, 95% CI = 16%–40%; adjusted RRR for cardiac death = 32%, 95% CI = 15%–46%). CHM is also found to be efficacious in lowering the risk of fatal and nonfatal cardiogenic shock, cardiac arrhythmia, myocardial reinfarction, heart failure, angina, and occurrence of total heart events. In conclusion, addition of CHM is very likely to be able to improve survival of MI patients who are already receiving BM. Further confirmatory evaluation via large blinded randomized trials is warranted.

1. Background

1.1. Myocardial Infarction: Disease Burden and Therapeutic Options. Incoronal artery disease, a critical reduction of the blood supply to the heart may result in myocardial infarction (MI), a phenomenon owing to the formation of an area of necrosis in heart muscles caused by inadequate supply of blood to the muscles, usually as a result of occlusion of a coronary artery. About a quarter of MI patients will die from it due to complications including cardiogenic shock, cardiac perforation, embolism, heart failure, papillary muscle rupture, rhythm disturbances, or autoimmune pericarditis. Current evidence on biomedicine (BM) treatment suggests that aspirin, thrombolytics with or without adding low-molecular-weight heparin, beta-blockers, ACE inhibitors, and nitrates are beneficial for improving outcomes in people with MI. Invasive procedures including coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA, balloon angioplasty) were also found to be useful. However, their efficacy in preventing death is not without limitations. For instance, beta-blockers have no short-term effect on mortality, and they may increase the risk of cardiogenic shock. Thrombolytics may cause stroke and major bleeding while reducing mortality, and those who are treated will receive no additional benefits from nitrates [1].

Despite these therapeutic advances, coronary artery disease remained to be the foremost leading cause of death in both low- and middle income countries as well as high-income countries, contributed 11.8% and 17.3% of total deaths, respectively [2]. Researchers are evaluating the potential benefits and harms of add-on treatments like
vasodilators and positive inotropes on mortality [3]. Chinese herbal medicine (CHM) is another novel candidate as an add-on treatment.

1.2. Chinese Herbal Medicine for Treating Myocardial Infarction. In China, CHM is widely prescribed in both outpatient and inpatient settings [4]. Amongst community health clinics, 75% provide both BM and traditional Chinese medicine (TCM) treatments. TCM hospitals comprised 13.8% of all hospitals, and 90% of the BM hospitals are annexed with TCM departments [5]. Given the omnipresence of TCM services within the Chinese healthcare system, it is not uncommon for clinicians to prescribe CHM as an adjunct to BM treatment in the management of potentially life-threatening conditions including MI [6]. One of the most researched single herbs is *Radix Astragali*, which exerts its therapeutic effectiveness by inhibiting cardiac fibrosis, reducing infarct size, and increasing capillary and arteriole densities [7]. Commonly used Chinese proprietary medicines include Shexiangbaoxin tablets and Tongxinluo capsules. Shexiangbaoxin tablets are found to slow MI pathogenesis by inhibiting hypertrophy related metabolites [8]. On the other hand, Tongxinluo capsules act by promoting local blood supply and thus limit infarct size [9]. CHM injections based on sheng mai san are also widely prescribed. It reduces infarct size via the activation of protein kinase C, opening of the mitochondrial KATP channels, and lowering the concentration of 5-hydroxytryptamine, norepinephrine, methionine-enkephalin, and leucine-enkephalin [10, 11].

1.3. Synthesizing Chinese Herbal Medicine Trials: Focusing on Objective Outcomes. The average effect of these CHM formulae as an adjunct to BM could be estimated using random effect meta-analyses of randomized controlled trials (RCTs) [12]. One of the major caveats in conducting systematic reviews on CHM is that existing RCTs are often prone to high risks of bias, thus limiting their usefulness in elucidating treatment effectiveness [13]. However, results from a recent metaepidemiological study have provided an alternative perspective on this issue. It is suggested that objective outcomes are less susceptible to bias associated with inadequate allocation concealment and blinding [14, 15]. Accordingly, by focusing on objective outcomes like mortality, we may partially overcome limitations imposed by the relatively high risk of bias amongst CHM trials.

1.4. Aim of This Paper. Taking into account the methodological considerations above, we performed a systematic review and meta-analysis of RCTs on the efficacy and safety of CHM for MI as an add-on to BM treatment, with a focus on objective critical outcomes including death, recurrent myocardial infarction, and other post-MI cardiac consequences.

2. Methods

2.1. Criteria for Considering Studies for This Paper. We included RCTs comparing the efficacy and safety of CHM plus BM versus BM alone. CHM is defined as any preparation containing at least one herb or its extraction referenced in the 2010 Chinese Pharmacopeia [16]. We included RCTs which enrolled adult MI patients regardless of gender, age, ethnicity, or comorbidities. We focused on the primary outcomes of (i) mortality of cardiac origin and (ii) all-cause mortality. We also consider the following as secondary outcomes: (i) recurrence of MI and (ii) other nonfatal, post-MI cardiac outcomes including cardiac arrhythmia, heart failure, cardiac rupture, cardiogenic shock, and angina. Adverse events reported by authors were also summarized. We imposed no restrictions on language and publication status.

2.2. Search Methods for Identification of Studies. We searched 8 electronic databases since their inception to July 2010, including CENTRAL, MEDLINE, EMBASE, CINAHL, AMED, Chinese Biomedical Database (CBM), Chinese Medical Current Contents (CMCC), and Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS) (Figure 1). Search strategies are shown in Appendix 1 in the Supplementary Materials available online at http://dx.doi.org/10.1155/2013/675906.

2.3. Data Collection and Analysis

2.3.1. Selection of Studies, Data Extraction, and Risk of Bias Assessment. Two reviewers (Y. Qin and C. Mao) independently screened the titles and abstracts to assess their eligibility. Full texts of potentially eligible citations were retrieved for detailed examination. Selection discrepancies were settled through discussions between these two authors. The remaining disagreements were resolved by consulting another author (J. L. Tang). For included RCTs, comprehensive information on patients, CHM interventions, and baseline and control treatments, as well as outcomes, was extracted. Risks of bias amongst included RCTs were evaluated by the Cochrane collaboration’s risk of bias assessment tool [17]. The assessment composed of a description and a judgement for each entry in a risk of bias table, including (i) sequence generation, (ii) allocation sequence concealment, (iii) incomplete outcome data, (iv) selective outcome reporting, and (v) other potential sources of bias. Blinding was assessed for the primary outcome of all-cause morality.

2.3.2. Data Analysis. Analyses were conducted using Stata 11 and R software. Dichotomous efficacy outcomes were expressed as relative risk reduction (RRR) and relative risk (RR), while RR was used for adverse events. 95% confidence intervals (CIs) were calculated for all estimates. We performed random-effect meta-analysis separately for each outcome. For primary outcomes of all-cause mortality and cardiac death, funnel plots were drawn for assessing publication bias. In case of asymmetry, random trim and fill analysis were performed as a sensitivity analysis [18]. Tests for heterogeneity were performed with chi-squared tests, at a significance level of $P = 0.1$. $I^2$ statistic was calculated to estimate variation across studies. We regarded $I^2 < 25\%$ as an indicator of low heterogeneity level, 25–50% as moderate level, and higher than 50% as high level [19]. Heterogeneity
Citations identified through electronic database search \( (n = 15866) \)
- From Chinese databases \( (n = 10856) \)
- From international databases \( (n = 5010) \)

Duplicates excluded \( (n = 3200) \)

Titles and abstracts screened \( (n = 12666) \)
- Excluded after review of titles and abstracts \( (n = 10006) \)
  - Did not report specified outcomes \( (n = 3201) \)
  - Not RCTs \( (n = 6805) \)

Full-text articles assessed for eligibility \( (n = 2660) \)
- Excluded after examining the full text \( (n = 2597) \)
  - Did not report specified outcomes \( (n = 1039) \)
  - Not RCTs \( (n = 1502) \)
  - Studies on patients without the diagnosis of MI \( (n = 56) \)

Articles included in this systematic review \( (n = 63) \)

**Figure 1:** Flow chart of literature search and study selection.

was explored with random-effect metaregression using baseline risk, mean age, route of drug administration (oral versus intravenous), and treatment duration as covariates, taking into account the sample size requirement of including not more than 1 covariate for every 10 studies [20]. We expected that higher baseline risk and mean age could be associated with a smaller effect [1], while intravenous administration and longer treatment duration could be associated with a larger effect.

### 3. Results

#### 3.1. Literature Search

As shown in Figure 1, our search in electronic bibliographical databases yielded 12,666 citations after removal of duplications, of which 2,660 were classified as potentially relevant and were subjected to a full-text assessment. A total of 65 RCTs published in 63 articles met the inclusion criteria. Details of these studies are presented in Table 1.

#### 3.2. Study Characteristics

A total of 6,036 patients were enrolled in the CHM plus BM group, and 5,986 patients were allocated to the BM only group. The average size of the trials was 185 participants (ranging from 28 to 2735 participants per trial). Fifty trials reported treatment duration and the average duration was 68.9 days, ranging from 3 to 1440 days. Forty-nine trials reported the length of follow up. The average follow-up length was 7.1 months, ranging from 0.1 to 84 months.

For diagnostic criteria, 36 (55.4%) studies applied the 1979 World Health Organization criteria, which enrolled patients with at least two of the following three presentations: chest pain or discomfort, an elevation in CK-MB levels, or an ECG with significant ST-segment elevations [84]. Four adopted criteria from the Chinese Society of Cardiology [85] and one used criteria from the European Society of Cardiology [86]. Twelve applied author-defined diagnostic criteria, and the remaining 12 did not report criteria used.

Thirty-one standardized Chinese herbal formulae were examined in 63 (96.9%) of the 65 included studies, while the other two studies used an individualized approach. 32 (50.0%) preparations were administered orally, 30 (46.9%) were prescribed as herbal injections, and 2 (3.12%) trials used both intravenous and oral treatments. Eight formulae were evaluated by three or more trials. In total, these formulae were assessed in 38 studies, constituting 58.5% of all included trials.

(i) Nine (13.8%) trials studied Shenmai injection, which contains ginsenoside, ginseng polysaccharide, Ophiopogon polysaccharides, and Ophiopogon flavonoids extracted from *Panax ginseng* and *Ophiopogon japonicas*.

(ii) Five (7.7%) evaluated Huangqi injection manufactured by extracting astragalosides from *Radix Astragali*.

(iii) Another five (7.7%) assessed Shexiangbaoxin tablets, which consisted of Moschus, *Radix Ginseng*, *Borneolum Syntheticum*, *Venenum Bufonis*, *Cortex Cinnamomi*, *Calcus Bovis*, and *Styrax*.

(iv) Four (6.2%) tested Shengmai injection, which is a mixture of extracts from *Panax ginseng*, *Radix Ophiopogonis*, and *Schisandra chinensis Baill*.

(v) Another four (6.2%) evaluated Tongxinluo capsules, consisting of *Radix Ginseng*, *Scorpio*, *Hirodu*, *Eupolyphaga seu Stelephaga*, *Scolopendra*, *Peristram Cicadae*, *Radix Paoniae Rubra*, and *Borneolum Syntheticum*.

(vi) Three trials (4.6%) assessed Shenfu injection, which contains Ginsenoside and Aconitine extracted from *Panax ginseng* and *Aconitum carmichaelii*.

(vii) Another three evaluated Suxiao jiuxin pill (4.6%), consisting of *Ligusticum chuanxiong* Hort. And *Borneolum syntheticum*.
| First author | Year | No. of patients in the treatment group | No. of patients in the control group | Diagnostic criteria | Intervention | Control | Duration of treatment (days) | Duration of followup (months) |
|--------------|------|----------------------------------------|--------------------------------------|---------------------|-------------|---------|-----------------------------|-----------------------------|
| CHD Group [21] | 1981 | 138 | 138 | Not reported | Kangxingeng heji + BM | BM | N/A | N/A |
| Kou [22] | 1983 | 133 | 135 | WHO criteria | Yiqihuxue decoction and In + Xuejie powder + BM | BM | N/A | N/A |
| Chen [23] | 1984 | 112 | 112 | WHO criteria | Yiqihuxue decoction + Yiqihuxue In + BM | BM | 35 | N/A |
| Liang [24] | 1989 | 74 | 74 | Author defined | Tuoqingyanyu su + BM | BM | N/A | N/A |
| Xia [25] | 1993 | 23 | 10 | Not reported | Dushen tang + thrombolysis | Thrombolysis | 3 | N/A |
| Li [26] | 1994 | 60 | 64 | WHO criteria | Wenyanghuoxue decoction + BM | BM | 14 | 0.1 |
| Li [27] | 1994 | 18 | 15 | WHO criteria | Huangqi In + polarized solution | BM | 28 | 1 |
| Yang [28] | 1997 | 66 | 80 | WHO criteria | Shexiangbaoxin tablets + BM | BM | 360 | 12 |
| Zhang [29] | 1998 | 76 | 59 | WHO criteria | JianXin tablet + BM | BM | 30 | 1 |
| Guo [30] | 1999 | 243 | 259 | WHO criteria | Shenmai In + thrombolysis | Thrombolysis | 14 | 1.25 |
| Li [31] | 1999 | 51 | 50 | WHO criteria | Ligustrazine + compound danshen In + Chinese medicinal formulae + thrombolysis | Thrombolysis | 28 | 1 |
| Zhang [32] | 1999 | 52 | 47 | WHO criteria | Yiqihuxuetongguo decoction + BM | BM | 28 | 1 |
| Guo [33] | 2000 | 143 | 159 | WHO criteria | Shuxiao juxin pills + thrombolysis | Thrombolysis | 14 | 1.25 |
| Han [34] | 2000 | 38 | 44 | WHO criteria | Huangqi In + thrombolysis | BM | 7 | 0.25 |
| Li [35] | 2000 | 28 | 19 | WHO criteria | Zhupi decoction + BM | BM | 360 | 12 |
| "Li QZ(a) [36]" | 2000 | 66 | 72 | WHO criteria | Suxiao juxin pills + BM | BM + Propranolol | 360 | 12 |
| "Li QZ(b) [36]" | 2000 | 66 | 72 | WHO criteria | Suxiao juxin pills + BM | BM | 14 | 0.5 |
| Lu [37] | 2000 | 21 | 21 | WHO criteria | Shuizhi In + BM | BM | 14 | N/A |
| Yin [38] | 2000 | 15 | 13 | WHO criteria | Shenma In + Herba Erigerontis In + BM + thrombolysis | BM + Thrombolysis | 14 | N/A |
| Wu [39] | 2001 | 54 | 49 | WHO criteria | Huangqi In + Dan - Shen In + BM | BM | 14 | 0.75 |
| Bai [40] | 2002 | 62 | 60 | WHO criteria | Shenmai In + BM | BM | 14 | N/A |
| Shi [41] | 2002 | 58 | 56 | Author defined | Breviscapinum + BM + thrombolysis | BM + Thrombolysis | 20 | 0.67 |
| Guan [42] | 2003 | 30 | 30 | WHO criteria | Xingling In + BM | BM | 15 | 1 |
| Zhang [43] | 2003 | 45 | 45 | Not reported | Shenfu decoction + Xuefuzhupi decoction + BM | BM | 28 | N/A |
| Han [44] | 2004 | 46 | 52 | WHO criteria | Shexiangbaoxin tablets + BM + thrombolysis | BM + Thrombolysis | 28 | 1 |
| Li [45] | 2004 | 32 | 18 | WHO criteria | Shexiangbaoxin tablets + BM + thrombolysis | BM + Thrombolysis | 90 | 3 |
| Liu [46] | 2004 | 41 | 96 | WHO criteria | Shenmai In + BM | BM | 15 | N/A |
| First author | Year | No. of patients in the treatment group | No. of patients in the control group | Diagnostic criteria | Intervention | Control | Duration of treatment (days) | Duration of followup (months) |
|--------------|------|--------------------------------------|-------------------------------------|---------------------|--------------|---------|----------------------------|-----------------------------|
| Yang [47]    | 2004 | 45                                   | 45                                  | Not reported         | Huangqi In + thrombolysis | Thrombolysis | 7                          | 6                           |
| Chen [48]    | 2005 | 35                                   | 34                                  | Not reported         | Huangqi In + thrombolysis | Thrombolysis | 10                         | 12                          |
| Deng [49]    | 2005 | 38                                   | 35                                  | Author defined       | Xingnaojing In + BM       | BM           | 21                         | 24                          |
| He [50]      | 2005 | 23                                   | 23                                  | Not reported         | Kaixin capsule + BM + thrombolysis | BM + thrombolysis | 5                          | 0.17                        |
| Li [51]      | 2005 | 83                                   | 83                                  | Not reported         | Diaohuangqi In + BM       | BM           | 28                         | 2                           |
| Liu [52]     | 2005 | 30                                   | 22                                  | WHO criteria         | Treatment based on TCM syndrome differentiation + thrombolysis | Thrombolysis | 28                         | 1                           |
| Miao [53]    | 2005 | 64                                   | 62                                  | WHO criteria         | Shengmai In + BM + thrombolysis | BM + thrombolysis | 15                         | 2                           |
| Yang [54]    | 2005 | 45                                   | 45                                  | Criteria from the Chinese Society of Cardiology | Shexiangboxin tablets + BM | BM           | N/A                        | 3                           |
| Ding [55]    | 2006 | 15                                   | 15                                  | WHO criteria         | Shengmai In + BM          | BM           | N/A                        | N/A                         |
| Du (a) [56]  | 2006 | 1364                                 | 1371                                | Not reported         | Xuezhikang capsules + BM  | BM + placebo | N/A                        | 84                          |
| Du (b) [56]  | 2006 | 1070                                 | 1065                                | Guideline from the European Society of Cardiology | Xuezhikang capsules + BM  | BM + placebo | 1440                       | 48                          |
| Li [57]      | 2006 | 31                                   | 32                                  | WHO criteria         | Shenfu In + BM            | BM           | 14                         | N/A                         |
| Ma [58]      | 2006 | 25                                   | 25                                  | Criteria from the Chinese Society of Cardiology | Yuxingeng decoction + BM | BM           | 28                         | 1                           |
| Qi [59]      | 2006 | 48                                   | 46                                  | WHO criteria         | Tanshinone II A sulfoacid In + BM + thrombolysis + PCI | BM + thrombolysis + PCI | 14                         | 0.5                         |
| Shen [60]    | 2006 | 83                                   | 82                                  | Author defined       | Shenfu In + BM            | BM           | N/A                        | 0.25                        |
| Wang [61]    | 2006 | 228                                  | 162                                 | WHO criteria         | Shenmai In + BM           | BM           | N/A                        | 0.25                        |
| Wei [62]     | 2006 | 31                                   | 37                                  | WHO criteria         | Shenfu In + BM + thrombolysis | BM + thrombolysis | 7                          | 0.25                        |
| Wu [63]      | 2006 | 19                                   | 21                                  | WHO criteria         | Shenmai In + BM           | BM           | 20                         | 1                           |
| Yang [64]    | 2006 | 48                                   | 49                                  | Not reported         | Xuezhikang capsules + BM  | BM + placebo | N/A                        | 72                          |
| Chen [65]    | 2007 | 30                                   | 30                                  | WHO criteria         | Tongxinluo capsule + BM   | BM           | 56                         | 2                           |
| First author | Year | No. of patients in the treatment group | No. of patients in the control group | Diagnostic criteria | Intervention | Control | Duration of treatment (days) | Duration of followup (months) |
|--------------|------|--------------------------------------|-------------------------------------|---------------------|-------------|---------|---------------------------|-------------------------------|
| Li [66]      | 2007 | 45                                    | 45                                  | Author defined      | Guanxinning In + BM | BM      | 15                        | 6                             |
| Liang [67]   | 2007 | 90                                    | 68                                  | WHO criteria        | Shengmai In or Shenmai In + treatment based on TCM syndrome Differentiation + BM + thrombolysis | BM      | N/A                       | N/A                           |
| Pan [68]     | 2007 | 20                                    | 20                                  | WHO criteria        | Tongxinluo capsule + BM | BM      | N/A                       | 1                             |
| Zhai [69]    | 2007 | 38                                    | 30                                  | Criteria from Chinese Society of Cardiology | Shenmai In + BM | BM      | 10                        | N/A                           |
| Ding [70]    | 2008 | 23                                    | 23                                  | Author defined      | Shengmai In + BM | BM      | N/A                       | N/A                           |
| Lan [71]     | 2008 | 130                                   | 128                                 | WHO criteria        | Xinmaitong capsules + BM | BM      | 30                        | 1                             |
| Yu [72]      | 2008 | 100                                   | 96                                  | Author defined      | Shexiang Baoxin tablets + BM | BM      | 10                        | 1                             |
| Yu [73]      | 2008 | 32                                    | 32                                  | Author defined      | Yinxingdamo In + BM + thrombolysis | BM + thrombolysis | 14                        | 0.5                           |
| Zhang [74]   | 2008 | 27                                    | 27                                  | WHO criteria        | Shenmai In + Shuxuening In + BM | BM      | 28                        | N/A                           |
| Gao [75]     | 2009 | 60                                    | 60                                  | WHO criteria        | Danhong In + BM | BM      | N/A                       | 0.5                           |
| Lin [76]     | 2009 | 25                                    | 25                                  | Author defined      | Compound danshen dripping pills + BM | BM      | N/A                       | 1                             |
| Liu [77]     | 2009 | 16                                    | 16                                  | Author defined      | Tanshinone II A sulfoacid In + BM | BM      | 7                         | 3                             |
| Song [78]    | 2009 | 36                                    | 34                                  | Author defined      | Tongxinluo capsule + Shenmai In + Gegensu In + BM | BM      | 28                        | N/A                           |
| Yuan [79]    | 2009 | 38                                    | 38                                  | WHO criteria        | Shenmai In + thrombolysis | Thrombolysis + BM | 10                        | 1                             |
| Zhao [80]    | 2009 | 50                                    | 48                                  | Not reported        | Tongxinluo capsule + BM + thrombolysis | BM + thrombolysis | N/A                       | 12                            |
| Zuo [81]     | 2009 | 80                                    | 80                                  | Criteria from Chinese Society of Cardiology | Breviscapinun + BM | BM      | 14                        | 1                             |
| Guo [82]     | 2010 | 48                                    | 45                                  | Not reported        | Compound Danshen tablet + BM | BM      | N/A                       | 12                            |
| Xu [83]      | 2010 | 32                                    | 30                                  | Author defined      | Treatment based on TCM syndrome differentiation + BM | BM      | 28                        | 1                             |

BM: routine biomedical treatment as defined by the investigators; In: injection; N/A: not reported.
*Two RCTs reported in one publication.
(viii) Finally, three (4.6%) studies tested Xuezhikang capsule, which comprise partially purified extract of fermented Monascus purpureus.

3.3. Risk of Bias. Among these 65 RCTs, only 7 were at low risk for bias for allocation sequence generation. Twelve were at high risk and the remaining RCTs did not report their sequence generation procedure clearly. All but one had high risk of bias in terms of allocation concealment and none of the included studies report the use of blinding. However, we regarded the risks of bias associated with lack of blinding and allocation concealment to be minimal, as the primary outcomes were of objective nature. Two of the included studies had high risk of bias for incomplete data and one for selective outcome reporting. Six are at high risk of bias due to other reasons. In summary, we consider the overall risk of bias amongst our included studies to be moderate (Figure 2). The detailed risk of bias assessment results is presented in Appendix 2 in the supplementary materials.

3.4. Effects of Interventions

3.4.1. Impact on Fatal Outcomes. In this comparison (Table 2), a total of 44 RCTs reported total all-cause mortality. Pooled results demonstrated superiority of combined treatment in preventing all-cause mortality (RRR = 37%, 95% CI = 28%–45%). Funnel plot indicates the presence of publication bias. After applying trim and fill procedure (Figure 3), the RRR remained to be significant (RRR = 29%, 95% CI = 16%–40%, Table 2). Ten RCTs reported death of cardiac origin, and pooled findings also favor combined treatment (RRR = 39%, 95% CI = 22%–52%). Funnel plot indicates the presence of publication bias. After applying trim and fill procedure, the RRR remained to be significant (RRR = 32%, 95% CI = 15%–46%).

Pooled results from another four RCTs reporting the occurrence of fatal cardiogenic shock also favored combined treatment (RRR = 28%, 95% CI = 5%–45%). Respectively nine, six, five, and three RCTs reported outcomes on sudden cardiac death, fatal myocardial reinfarction, fatal heart failure, and fatal cardiac arrhythmia. In these four comparisons, all pooled findings favored combined treatment (sudden cardiac death: RRR = 24%, 95% CI = 6%–45%; fatal cardiac reinfarction: RRR = 54%, 95% CI = 12%–81%; fatal heart failure: RRR = 52%, 95% CI = 9%–79%; fatal cardiac arrhythmia: RRR = 29%, 95% CI = 84%–222%), but the estimates were statistically insignificant. Except for fatal myocardial reinfarction ($I^2 = 37.3\%$), no significant heterogeneity existed in the comparisons mentioned above. However, given the small number of RCTs reporting this outcome, we were unable to explore heterogeneity using metaregression.

3.4.2. Impact on Nonfatal Cardiovascular Events. In this comparison (Table 2), a total of 11 RCTs reported overall, undifferentiated nonfatal heart events. Pooled results demonstrated superiority of combined treatment in preventing this outcome (RRR = 48%, 95% CI = 40%–56%). Twenty-three RCTs evaluated myocardial reinfarction, and the pooled result favors combined treatment (RRR = 52%, 95% CI = 39%–61%). The pooled results from 14 and 24 RCTs have also favored combined treatment, respectively, in preventing cardiogenic shock (RRR = 37%, 95% CI = 15%–53%) and in alleviating angina symptoms (RRR = 53%, 95% CI = 46%–61%). Three RCTs investigated nonfatal cardiac rupture as an outcome. The pooled finding supports combined treatment but the estimate was statistically insignificant (RRR = 56%, 95% CI = 67%–89%). No significant heterogeneity existed in all meta-analyses mentioned above.

Respectively, thirty and twenty-eight RCTs reported outcomes of cardiac arrhythmia and heart failure. In these two groups of studies, pooled findings all favored combined treatment, but high level of heterogeneity existed in both estimates (cardiac arrhythmia: RRR = 41%, 95% CI = 27%–52%, $I^2 = 76.2\%$; heart failure: RRR = 48%, 95% CI = 36%–58%, $I^2 = 47.9\%$).

3.4.3. Metaregression. We explored these heterogeneities by performing multivariate metaregression analyses using mean age, treatment duration, route of administration (oral versus intravenous), and baseline risk as covariates. None of the four covariates is significantly associated with cardiac arrhythmia (for baseline risk regression coefficient ($\beta$) = 0.46, $P = 0.41$; for mean age $\beta = 0.00$, $P = 0.96$; for duration of treatment $\beta = 0.00$, $P = 0.95$; for route of administration $\beta = 0.21$, $P = 0.63$), or heart failure (for baseline risk $\beta = 0.67$, $P = 0.39$;
| Events                              | No. of studies | No. of events/total no. | Combined effect | Test for heterogeneity | Adjusted combined effect (trim and fill) |
|------------------------------------|----------------|------------------------|----------------|------------------------|----------------------------------------|
|                                    |                | CHM + BM group         | BM group       | RR (95% CI)            | RR (95% CI)                            | P value* | 𝑥² statistic | P value* | RR (95% CI) | RRR (95% CI) | P value* |
| Fatal events                       |                |                        |                |                        |                                        |          |              |          |              |              |          |
| All-cause mortality                | 44             | 308/5107               | 521/5112       | 0.63 (0.55–0.72)       |                                       | <0.001   | 37.47        | 0.709     | 0.0          | 0.71 (0.60–0.84) | 0.71     |
| Mortality of cardiac origin        | 10             | 142/2820               | 227/2796       | 0.61 (0.48–0.78)       |                                       | <0.001   | 11.66        | 0.233     | 22.8         | 0.68 (0.54–0.85) | 0.68     |
| Fatal myocardial infarction        | 6              | 20/2660                | 37/2687        | 0.46 (0.19–1.12)       |                                       |          | 0.086        | 7.98      | 0.157        | 29% (16%–40%)     | 0.001   |
| Fatal cardiac arrhythmia           | 3              | 4/162                  | 5/160          | 0.71 (0.16–3.22)       |                                       |          | 0.662        | 2.21      | 0.331        | 32% (15%–46%)     | 0.001   |
| Fatal heart failure                | 5              | 8/410                  | 18/444         | 0.48 (0.21–1.09)       |                                       |          | 0.078        | 0.06      | 1.000        | —             | —       |
| Fatal cardiogenic shock            | 4              | 37/330                 | 58/332         | 0.72 (0.55–0.95)       |                                       |          | 0.019        | 2.42      | 0.490        | —             | —       |
| Sudden cardiac death               | 9              | 61/2775                | 81/2795        | 0.76 (0.55–1.06)       |                                       |          | 0.104        | 3.13      | 0.926        | —             | —       |
| Nonfatal events                    |                |                        |                |                        |                                        |          |              |          |              |              |          |
| Undifferentiated total heart events| 11             | 209/2762               | 407/2761       | 0.52 (0.44–0.60)       |                                       | <0.001   | 8.99         | 0.533     | 0.0          | 0.52 (0.44–0.62) | 0.52     |
| Myocardial infarction              | 23             | 103/2377               | 215/2343       | 0.48 (0.39–0.61)       |                                       | <0.001   | 9.95         | 0.987     | 0.0          | 0.53 (0.43–0.66) | 0.53     |
| Cardiac arrhythmia                 | 30             | 398/1730               | 640/1696       | 0.59 (0.48–0.73)       |                                       | <0.001   | 121.94      | 0.000     | 76.2         | 0.72 (0.58–0.89) | 0.72     |
| Heart failure                      | 28             | 249/1825               | 496/1835       | 0.52 (0.42–0.64)       |                                       | <0.001   | 51.86        | 0.003     | 47.9         | 0.60 (0.50–0.72) | 0.60     |
| Cardiac rupture                    | 3              | 2/122                  | 7/134          | 0.44 (0.11–1.67)       |                                       |          | 0.224        | 0.60      | 0.740        | —             | —       |
| Cardiogenic shock                  | 14             | 63/1015                | 110/1030       | 0.63 (0.47–0.85)       |                                       | 0.002    | 10.65        | 0.640     | 0.0          | 0.75 (0.57–0.98) | 0.75     |
| Angina                             | 24             | 177/1047               | 297/1001       | 0.47 (0.39–0.56)       |                                       | <0.001   | 22.20        | 0.508     | 0.0          | 0.58 (0.48–0.69) | 0.58     |
| Adverse events                     |                |                        |                |                        |                                        |          |              |          |              |              |          |
| Undifferentiated total events      | 2              | 43/2434                | 39/2436        | 1.16 (0.59–2.27)       |                                       |          | 0.664        | 2.19      | 0.138        | —             | —       |
| Bleeding                           | 9              | 81/706                 | 81/745         | 0.97 (0.73–1.28)       |                                       |          | 0.816        | 4.89      | 0.769        | —             | —       |

*Test for overall effect; *chi-square test for heterogeneity.
BM: biomedical treatment; CHM: Chinese herbal medicine treatment; RR: relative risk; RRR: relative risk reduction; 95% CI: 95% confidence interval.
events. Benefts in preventing heart failure and angina were myocardial reinfarction, and the occurrence of total heart lowering the risk of cardiogenic shock, cardiac arrhythmia, analyses demonstrated that CHM is an effective add-on for failure, and sudden cardiac death. For nonfatal outcomes, our including myocardial reinfarction, cardiac arrhythmia, heart of combined treatment on other reviewed fatal outcomes. Our analyses did not demonstrate the therapeutic benefts of combined treatment on other reviewed fatal outcomes. The direction of effect did not change after the adjustment, and the 95% CI boundary of the trim- and ft-adjusted RRR for all-cause and cardiac mortality was 16% and 15%, respectively. Conservatively speaking, CHM appeared to offer a protective add-on efect against mortality after adjusting for the publication bias, a common problem amongst the clinical research literature on CHM [87].

Combined treatment is also found to be more effective than BM alone in lowering the risk of fatal cardiogenic shock. Our analyses did not demonstrate the therapeutic benefts of combined treatment on other reviewed fatal outcomes including myocardial reinfarction, cardiac arrhythmia, heart failure, and sudden cardiac death. For nonfatal outcomes, our analyses demonstrated that CHM is an effective add-on for lowering the risk of cardiogenic shock, cardiac arrhythmia, myocardial reinfarction, and the occurrence of total heart events. Benefits in preventing heart failure and angina were also observed but these ndings are less robust given the subjective nature of the outcome, and metaregression did not shed light on potential sources of heterogeneity. We have considered including allocation concealment and blinding as covariates in our metaregressions but numbers of trials with low risk in these domains are too small for conducting such analysis. The efect of combined treatment on these two outcomes would need to be further evaluated with methodology stronger trials. In addition, more comprehensive reporting on BM treatment details and adverse events is expected in future studies, preferably with reference to the CONSORT statement.

Comprehensiveness of search is the major strength of this systematic review. The use of both international and Chinese databases allowed us to locate a much higher number studies compared to seven existing reviews on the topic [88]. We also attempted to synthesize results from trials evaluating heterogeneous CHM using random-effect model. This allowed us to estimate the average efect of adding CHM on top of conventional therapies [12]. The use of the trim and ft method has also partly circumvented the problem of publication bias. Nevertheless, the robustness of our conclusion depends on the assumption that the objective nature of outcomes was less affected by two major sources of bias: allocation concealment and blinding. While this assumption is tested in metaepidemiological studies [89, 90], the generalizability of these ndings warrants further investigations.

3.4.4. CHM and BM versus BM Alone for MI: Adverse Events. In this comparison (Table 2), nine RCTs reported bleeding as adverse events, but the pooled estimate was statistically insignificant (RR = 0.97, 95% CI = 0.73, 1.28). Two RCTs reported general, undifferentiated adverse events, pooled estimate is heterogeneous and statistically insignificant (RR = 1.16, 95% CI = 0.59, 2.27, I2 = 54.4%).

4. Discussion

This systematic review on the add-on efect of CHM on BM in the treatment of MI summarized ndings from 12,022 patients reported in 65 RCTs. The overall risk of bias amongst included studies was moderate. Despite the lack of allocation concealment and blinding in the majority of included trials, its impact on risk of bias was less critical as we focused on objective outcomes. Random-effect meta-analyses demonstrated that combined treatment is superior to BM alone in reducing the risk of all-cause mortality and death of cardiac origin. Funnel plots indicated the presence of publication bias for both outcomes, and trim and ft procedures were conducted as sensitivity analyses. The directions of efect did not change after the adjustment, and the 95% CI of the estimates overlapped with the unadjusted values. The lower 95% CI boundary of the trim- and ft-adjusted RRR for all-cause and cardiac mortality was 16% and 15%, respectively. Conservatively speaking, CHM appeared to offer a protective add-on efect against mortality after adjusting for the publication bias, a common problem amongst the clinical research literature on CHM [87].

5. Conclusion

Based on RCTs of moderate quality, this systematic review demonstrated consistent, add-on benefts of using CHM on top in BM treatment for preventing all-cause and cardiac mortality amongst MI patients. These ndings are in line with the results from seven existing systematic reviews of smaller scope and lower methodological quality. This tentative conclusion warrants further scrutiny using rigorously designed RCT, and a more comprehensive approach in reporting BM treatment details and adverse events is warranted.

Authors’ Contribution

V. C. H. Chung and M. Chen are the co-irst authors of this paper.

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