Combination of traditional Chinese medicine and EGFR-TKIs in the treatment of non-small cell lung cancer: a systematic review and meta-analysis

xinbing Sui[1], mingming zhang[1], Xuemeng Han[1], Ruonan Zhang[1], liuxi Chen[1], ying Liu[1], yu xiang[1], and Tian Xie[1]

[1]Affiliation not available

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Abstract

Traditional Chinese Medicines (TCMs) is used in China as part of the treatment for non-small-cell lung cancer (NSCLC) and often includes prescription in combination with conventional therapies based on syndrome differentiation. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) represent the first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). In China, EGFR-TKIs may be combined with TCMs with the aim of reducing the side effects and/or augmenting the efficacy of the EGFR-TKIs. However, the relationship between TCMs and EGFR-TKIs remain unclear. So, this meta-review evaluates the clinical evidence of TCMs combined with EGFR-TKIs in the treatment of NSCLC. Seven electronic databases were searched for randomized controlled trials of EGFR-TKI combined with TCMs compared to the EGFR-TKIs alone. Fifty-seven randomized controlled trials were involved in this study, and all the data were analyzed by Stata software (version 12.0). This study suggested that the objective response rate (ORR) of the group with TCMs combined with EGFR-TKIs-based regimens was higher than the group of EGFR-TKIs alone (RR 1.39, 95% CI [1.29, 1.50]). Further sensitivity analysis of specific plant-based TCMs showed that Huangqi, Baishu, Fuling, Gancao, Maidong, Baihuashecao, Shashen, Renshen and Dangshen, had significantly higher contributions to the results. Therefore, TCMs may have the potential to improve the efficacy of EGFR-TKIs for NSCLC.

1. Introduction

Lung cancer remains the most common cancer worldwide and the leading cause of cancer-related deaths [1]. There are two main types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While NSCLC accounts for approximately 85% of all lung cancer cases [2]. If patients are NSCLC, they are often diagnosed at an advanced stage and some new oncogene-targeted drugs and treatment regimens have been applied in clinical practice of NSCLC and achieved remarkable results. EGFR mutated NSCLC patients are sensitive to small molecule receptor tyrosine kinase inhibitors (TKIs), which occur in 60-70% of patients[3, 4]. However, unfortunately, acquired drug resistance inevitably develops, leading to disease progression. Therefore, how to augment the efficacy and/or prevent the resistance of EGFR-TKIs are an imperative issue.

Natural product-based TCMs are widely used in China and have long been combined with traditional therapies to treat cancer patients[5]. Currently, the treatment of lung cancer by combination of TCMs and traditional therapy has become one of the most important means recognized in China. This treatment may assist in reducing the side effects, enhancing cytotoxic effects, preventing or overcoming resistance to anticancer drugs, and/or improving the quality of life of patients [6-8]. However, the relationship between TCMs and EGFR-TKIs remain less well elucidated.

In this article, we compared the objective tumor response rate (ORR) between EGFR-TKIs alone and EGFR-TKIs combined with TCMs in NSCLC. As a result, data of our study showed that the ORR was significantly higher in the TCM plus EGFR-TKIs group than in the EGFR-TKIs alone group. Further research of specific plant-based TCMs showed that Huangqi, Baishu, Fuling, Gancao, Maidong, Baihuashecao, Shashen, Dangshen and Renshen, had significant higher contributions to results. Taken together, our meta-analysis provides evidence that TCMs have the potential to enhance the efficacy of EGFR-TKIs in the treatment of NSCLC.

2. Materials and Methods

2.1 Search methods

From July 2009 to February 2019, related studies were found by searching the databases of EMBASE, PubMed, Web of Science, MEDLINE, and Cochrane library database, meanwhile, we also consulted some Chinese periodicals, such as China Academic Journals (CNKI), Wanfang and Weipu. The key words are as follows: (a) Disorder: Non-small cell lung cancer and related terms; (b) Intervention: traditional Chinese medicine, Chinese herbal medicine and related terms; (c) Study type: randomized controlled trial and related terms. The experimental and control groups included in this analysis were the intervention and EGFR-TKIs groups, respectively. All NSCLC cases were confirmed by histopathological examination. Two independent reviewers independently searched the literature and extracted the data.

2.2 The type of results measured

According to Response Evaluation Criteria in Solid Tumors (RECIST), the objective efficacy evaluation standard for solid tumors, it can be divided into: complete response (CR): all measurable tumor lesions disappear completely and maintain for more than 4 weeks; Partial response (PR): the sum of the products of the largest diameter and the largest perpendicular diameter of each lesion was reduced by no less than 50% and maintained for more than 4 weeks without the appearance of new lesions. Stable disease (SD): 50% decrease or more than 25% increase in the sum of the products of the largest diameter and the largest perpendicular diameter of each lesion; Progressive disease (PD): at least 25% increase in the product of the largest diameter and the largest perpendicular diameter in at least one lesion or new lesion. ORR was the primary clinical outcome. CR plus PR were combined into the data pool as ORR.

2.3 Types of research

All studies comparing RCT of TCMs plus EGFR-TKIs with EGFR-TKIs alone were selected and assessed for inclusion in our study.

2.4 Eligibility criteria

Patients in this study should meet the following criteria: Pathological diagnosis of NSCLC stage III/IV; One or more two-dimensional measurable lesions; $18 < \text{age} < 80$; Karnofsky performance status (KPS) score [?] 60 or Zubrod-ECOG-WHO (ZPS) score [?] 2; Average life expectancy [?]3 months; normal heart, bone marrow, lung, liver and kidney function.

2.5 Data extraction

The Stata software application (version 12.0; StataCorp, College Station, TX) was used for data synthesis and analysis. Risk ratios (RR) and 95% confidence intervals (CI) were calculated; pooled RR and 95% CI were calculated using a fixed-effects model if the homogeneity assumption was not rejected ($P > 0.1$, $I^2 <$ 50%). If not, used the random effects model. Chi-square-based Q statistic was used for subgroup analysis based on between-trial heterogeneity, and statistical significance was considered when the p-value was less than 0.05 or I^2 was greater than 50%.

2.6 Bias detection

All statistics were analyzed using Stata 12.0 version (Stata Corporation, College Station, TX, United States). Funnel plot is a method to identify the existence of publication bias by visual observation. This method takes

the effect size as the abscissa and the y-coordinate is the standard error. The dispersion of small samples is large, so it is often at the bottom of the funnel plot, while that of large samples is small, so it is at the top.

3. Results

3.1 Literature Search

As shown in Figure 1, these were the detailed steps for our literature retrieval. According to the retrieval method, 11,676 potential related citations were retrieved. After screening, this meta-analysis included 57 studies [9-65]. All studies conformed to the requirements of EGFR-TKIs regimen combined with TCMs intervention*versus* EGFR-TKIs regimen solely. ORR was provided in a similar manner. The 57 studies were classified as capsules (7 studies), granule group (2 studies), decoction group (22 studies), TCM differentiation group (5 studies) and injection group (21 studies), there were a total of 4266 individuals, 2161 in the experimental group and 2105 in the control group. Table 1 summarizes the clinical characteristics of all participants, including TCM intervention dose, sample size, duration, dose, and cycle of EGFR-TKIs regimen.

3.2 Risk of Bias Assessment

We used RoB2.0 to assess the risk of bias in these articles. Except 2 articles (Kang X, et al; Lu S, et al), other studies have shown that with randomization, so the risk of deviation (SG) from sequence generation was assessed as "low". The experimental groups in the two studies were not randomized, so the risk of SG bias in this group was assessed as "high". Three studies (Zhang L, et al; Hou J, et al; Li Y, et al) described allocation concealment (AC), participant blindness (BPt), and these were decided "low risk". The other 54 studies did not describe the treatment course of AC and were therefore considered to be at "unclear risk". In cancer trials, it is difficult to blind participants. For selective outcome reporting (SOR), the study was assessed as "low-risk" only if the objectives and outcome measures described in the methods section are in the results section. Our results show TRR symmetry in funnel plots of the 57 studies, indicating a lower risk of publication bias.

3.3 Tumor response according to RECIST criteria

Fifty-seven studies used RECIST criteria to assess TRR. A meta-analysis of CR and TRR was performed. RR [?] 1 (IV model, fixed, 95% confidence interval), it is beneficial for the test group. Based on the different dosage forms of medicine, they were divided into 6 groups for meta-analysis: total (57 studies); capsule group (7 studies); granule group (2 studies); decoction group (22 studies); TCM syndrome group (5 studies); injection group (21 studies).

Total group. In 57 studies (n = 4266, Table 1), ORR improved significantly in the experimental arm (RR 1.39, 95% CI [1.30, 1.50]); P=0.621 > 0.05, I^2 = 0%), indicating low heterogeneity, the fixed effect model was used for calculating OR value of combined effect size (Figure 2).

Capsule group. Seven studies were included in the capsule group (n = 547, Table 1). TRR improved significantly (RR 1.30 [1.05-1.63], I^2 = 0%). And the TRR funnel plot is symmetric. Two studies were included in the granule group (n = 73, Table 1). There may be effective improvements for TRR (RR 0.81 [0.40-1.67], I^2 = 0%). TRR funnel plot is slightly asymmetric, maybe the sample size is too small.

Decoction group. Twenty-two studies were included in the decoction group (n = 1629, Table 1). Significant improvement in TRR (RR 1.34 [1.19-1.50], I^2 = 0%). The TRR funnel plot is obviously symmetrical.

TCM syndrome group. Five studies were included in the TCM syndrome group (n = 372, Table 1). There was also a significant improvement in TRR (RR 1.51 [1.17-1.93], I^2 = 0%). The TRR funnel plot is symmetric.

Injection group. Twenty-one studies were included in the injection group (n = 1645, Table 1). TRR improved significantly (RR 1.48 [1.32-1.66], I^2 = 0%). The TRR funnel plot is symmetric.

To put it briefly, the curative effect of adjuvant treatment of lung cancer with traditional Chinese medicine was observed in the order: TCM syndrome group > injection group > decoction group > capsule group > granule group.

3.4 Bias in Meta-analysis

In Funnel plot (Figure 3), we can clearly see that our sample studies are large(57 studies)and the estimated effect size varies less. Therefore, the estimated effect size points are scattered at the top of the funnel plot, and funnel plots can be roughly symmetrical. So, the bias of our studies is relatively small.

3.5 The Effects of Multi-Ingredient TCM

In the 57 studies with 46 prescriptions, we made an analysis on the use of single and multiple traditional Chinese medicine (Figure 4 and table 2).

Level 1: Single TCMs. One hundred fifty-one ingredients in the formulation have been included in this study. Of these, 27 ingredients were used in five or more formulations. The name of each ingredient was displayed in pin yin. According to their frequency of use in prescription, Here is a list of TCMs: Huangqi (n = 26), baishu (n = 21), fuling (n = 21), gancao (n = 19), maidong (n = 14), baihuashecao (n = 13), shashen (n = 13), and renshen (n = 10) (Figure 4).

Level 2: Combinations of two TCMs. In this level, a total of 22 pairs of TCMs were used more than 7 times, including huangqi + baishu (n = 18), huangqi + fuling (n = 14), huangqi + gancao (n = 12), baishu + fuling (n = 17), baishu + gancao (n = 13), huangqi + baihuashecao (n = 12), huangqi+ maidong (n = 11), huangqi + shashen (n = 11), baishu + maidong (n = 11), fuling + gancao (n = 11), fuling + baihuashecao (n = 11), baishu + baihuashecao (n = 10), fuling + maidong (n = 10), maidong + shashen (n = 10) (Table 2).

Other levels: Combinations of three and more TCMs. These combinations of TCMs are used no less than five times in 46 prescriptions and they were shown in Table 2.

3.6 Potential Synergistic Effects Selection for TCMs

TCMs were divided into qi-tonifying herbals (Huangqi, Baishu, Gancao, Dangshen, Renshen, Shanyao), Yin-nourishing berbals (Shashen, Tiandong, Maidong, Baihe, Nvzhenzi), heat-clearing phlegm-transforming herbals (Zhebeimu, Gualou, Jiegeng) in turn from high frequency to low frequency (Table 2). Moreover, when two drugs are combined, two qi-tonifying drugs are the most, the second are qi-tonifying drugs + clearing damp herbals. For more combinations, the combination of qi-tonifying and clearing damp berbals is the most common.

4. Discussion

At present, western medicine is the main treatment for lung cancer. Western medicine plays a role in directly fighting against cancer cells. While, traditional Chinese medicines (TCMs) for cancer treatment often plays a multi-target or multi-effect therapeutic role[66]. There are many aspects in the treatment of cancer with TCMs, such as enhancing the inhibitory effect on cancer cells, inhibiting the angiogenesis of tumors, and reversing the effect of drug resistance targeting. Shu Q, *et al*[67] found that aqueous extract of Taxus chinensis in combination with erlotinib inhibits the proliferation of cancer cells by inhibiting the expression of P-EGFR, P-ERK, and P-JNK proteins in the EGFR/MAPK signaling pathway. Kou J, *et al*[68] found that Xiaoaiping combined with hyperthermia could inhibit the proliferation of gefitinib-resistant human lung adenocarcinoma A549 cell line by reducing the expression of vascular endothelial growth factor and mediating angiogenesis. Gao F,*et al* [69] found that β-elemene can reverse PC9/ZD resistance, which probably is related with its down-regulation of p-Erk and p-Akt protein expression.

Molecular targeted therapy has been recognized as one of the effective methods to treat some cancer types. The Food and Drug Administration has tested and approved EGFR-TKIs as molecularly targeted agents for the treatment of non-small cell lung cancer, mainly including the First-generation drug gefitinib (Iressa,

2003) and Erlotinib (Tarceva, 2004); The Second generation drug Afatinib (Afatinib, Gilotrif, 2013), and the third generation of drugs for Osimertinib (Osimertinib, Tagrisso, 2015). At present, thousands of studies have demonstrated the effectiveness of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as molecular targeted agents[70, 71]. Many studies have now shown that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have multidrug resistance mechanisms in EGFR-mutated non-small cell lung cancer (NSCLC). Nevertheless, relapsed drug resistance in EGFR-TKIs remains a major clinical challenge due to heterogeneous mechanisms [72]. Because of the high cost of treatment and the lack of relevant clinical research results, in particular, there are few research cases of combined application of TCM. To explore the clinical basis of adding TCMs to EGFR-TKIs in the treatment of non-small cell lung cancer, our study evaluated 57 studies that were classified as capsule group (7studies), granule group (2 studies), decoction group (22 studies), TCM differentiation group (5 studies) and injection group (21 studies), which had 4266 experimental subjects, 2161 in the experimental group and 2105 in the control group. In this study, TCM or TCM plus EGFR-TKIs in the treatment of NSCLC get the better of EGFR-TKIs solely in terms of short-term efficiency and long-term survival rate, reflecting the synergistic effect of TCM-assisted EGFR-TKIs treatment. The principle of treatment is to strengthen the body and remove pathogenic factors. The diseases of zang-fu organs are mainly located in the lung, spleen and stomach, and heart and kidney. The treatment mostly adopts flexible compatibility and cutting methods, which can be roughly divided into the following categories: (1) Tonifying qi and yin: shashen, maidong, huangqi, renshen and so on; (2) Heat-clearing and detoxifying: baihuashecao, daqingye, shancigu, lianqiao and so on; (3) Dispelling wind and arresting itching: fangfeng, jiangcan, chantui, baixianpi, difuzi and so on; (4) Promoting circulation and removing stasis: danshen, chishao, yujin, taoren, honghua, eshu and so on; (5) Clearing damp phlegm: chenpi, banxia, fuling, baishu and so on.

Taken together, we have demonstrated that particular combinations of TCMs with EGFR-TKIs have a greater effect on TRR than EGFR-TKIs alone. Among them, it is worth noticing combination of Maidong, Baihuashecao, Shashen, Renshen and Dangshen. Therefore, TCM may have the potential to improve the efficacy of EGFR-TKI in the treatment of lung cancer. However, the limitations of this study are also obvious, such as almost all the selected studies are in Chinese literature, the lack of rigorous design and implementation, and the low quality of research, which affect the accuracy and reliability of the conclusions of this study to a certain extent.

5. Declaration of Conflicting Interests

The authors declare no conflict of interest.

Nothing in this manuscript has been published previously and has not been considered elsewhere. All authors read and approved the final version of the manuscript before submission.

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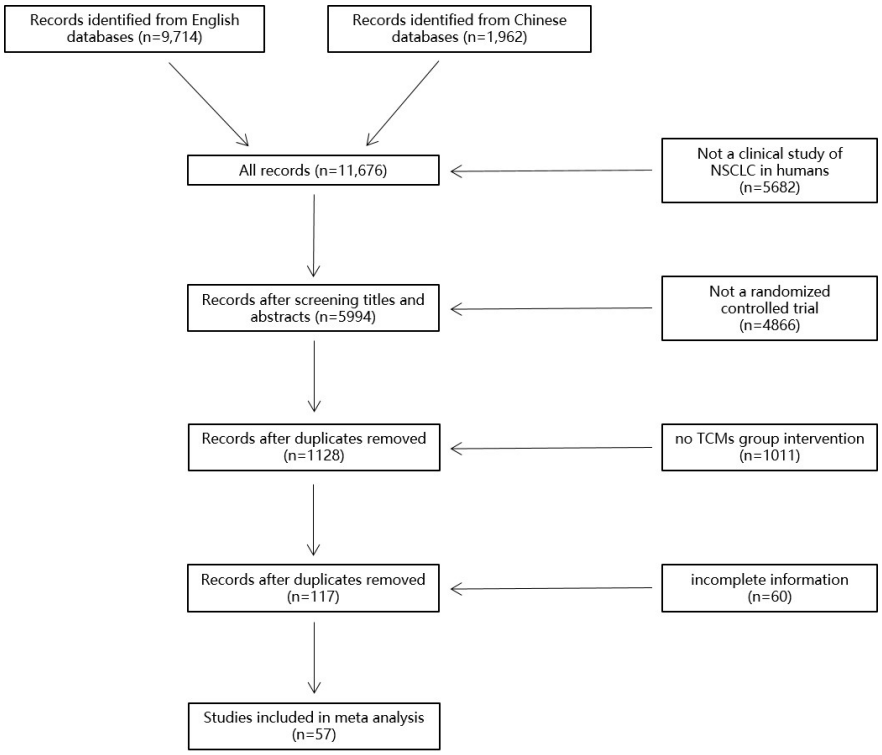

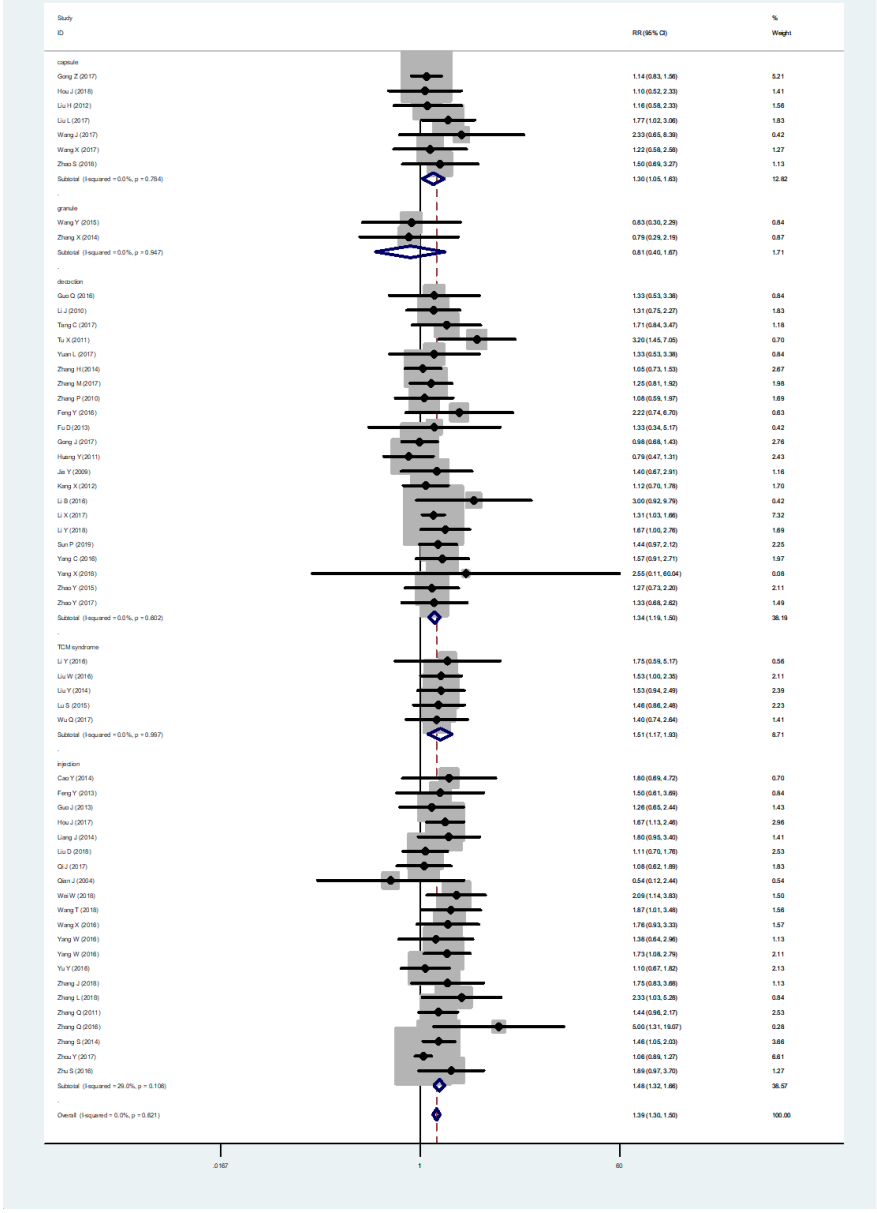

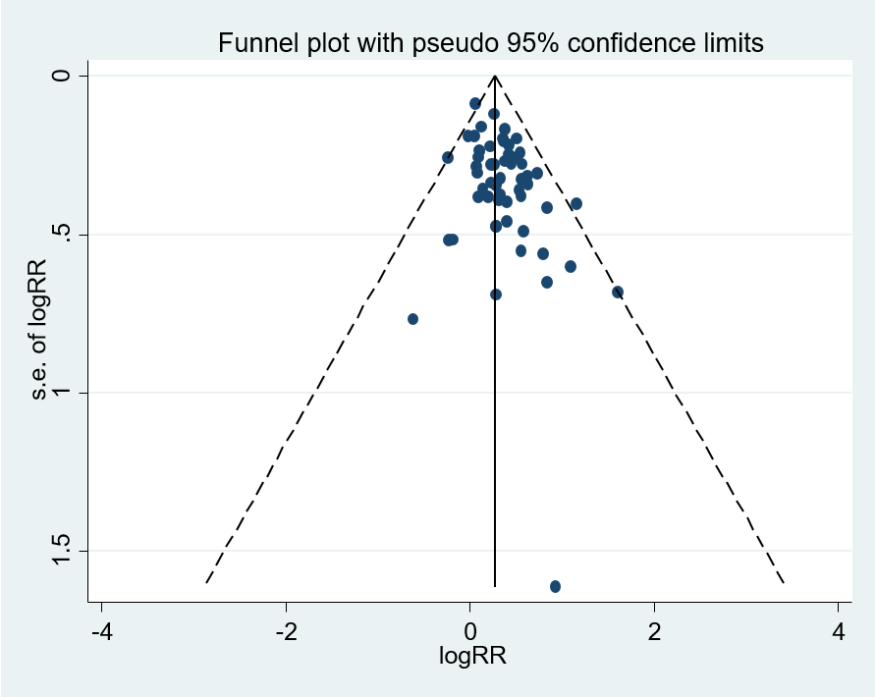

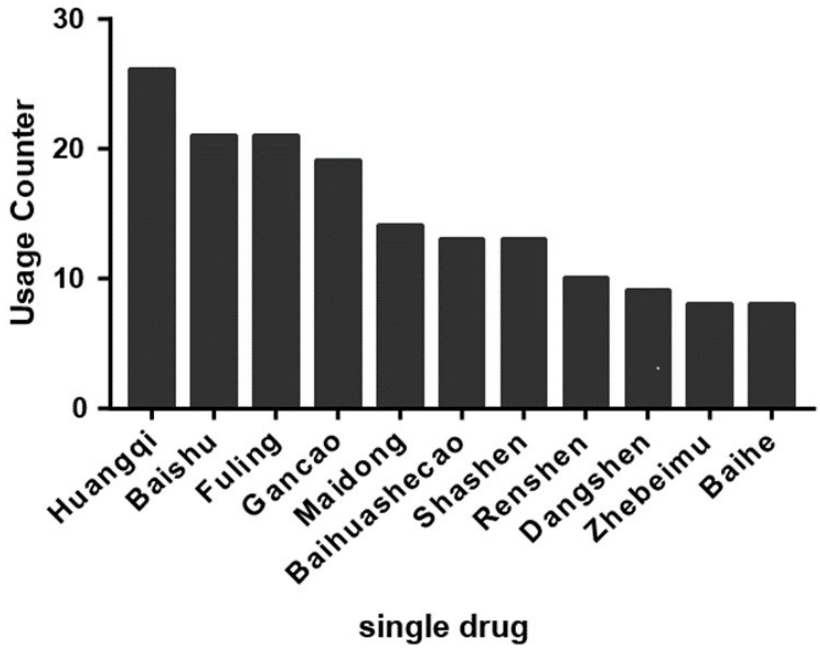

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