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Contents

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Contents

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EDITORIAL

Evolving role of salvage reirradiation: Is global harmonization required before treatment guidelines can be developed?

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Abstract

Up to 90% of patients initially treated with curative-intent radiotherapy (RT) will experience locoregional failure. Historically, reirradiation (ReRT) was offered purely with palliative intent, if considered at all, due to concerns surrounding toxicity, tolerance of normal tissues, and choice of appropriate dose schedule. With technological advancements in RT delivery, coupled with longer survival in many malignancies secondary to improvements in systemic therapy, a small subset of patients presenting with localized recurrence is increasingly being offered salvage ReRT. However, this is largely on an ad hoc basis, guided mainly by small retrospective, single-institution reports. The patient population retreated, RT modality, dose received, degree of attrition and follow-up are extremely variable. The opportunity presently exists to apply lessons learned from the harmonization of the research efforts within the bone metastases community to the salvage ReRT situation: the adoption of common endpoints, minimum features to be incorporated into clinical trial design, and methods of data analysis and reporting. The ReRT data available must be harmonized so that valid, clinically applicable conclusions can be drawn. Collaboration in the form of an international registry of prospectively collected outcomes of patients reirradiated for cure for a variety of tumour sites would further support the evolution of Radiation Oncology towards personalized medicine, and away from the current "one-dose-fits-all" approach.

Key words: Reirradiation; Salvage; Treatment planning; Toxicity; Registry; Dose; Radiotherapy

Core tip: Given the heterogeneity of the available reirradiation evidence, an international registry would provide a foundation on which to base consensus recommendations regarding many of the outstanding

questions surrounding patient selection and treatment planning. Inter-centre collaboration will be required to build a critical mass of data sufficient for robust statistical analysis; however, in order to achieve this, global harmonization is needed. Standardized nomenclature would facilitate consistent coding of treated volumes, doses, toxicity rates, and quality of life outcomes. A registry would also assist in determining the feasibility of both phase Ⅱ prospective studies and meta-analysis of currently available data.

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INTRODUCTION

Depending on the type and stage of cancer at first presentation, up to 90% of patients initially treated with curative-intent radiotherapy (RT) will experience locoregional failure[1]. For example, in breast cancer, despite local radiation, locoregional recurrences occur in up to 14% at 18 years[2], and after RT for non-melanoma skin cancer, in-field recurrence has been reported in up to 16%[3]. Pelvic recurrence occurs in 20%-40% of patients after radical radiation or surgery for gynecologic cancer[4]. In lung cancer, approximately one-third of those treated with radical chemoRT will develop a locoregional recurrence within five years[5,6]. Likewise, locoregional failure is the dominant pattern of failure after radical chemoRT for both head and neck cancer[7] and glioblastoma multiforme, with the latter recurring more than 90% of the time despite optimal up-front treatment[8].

At the time of local recurrence, treatment options may include resection, systemic therapy, laser or radiofrequency ablation, cryotherapy, hyperthermia, or photodynamic therapy. However, these options are not universally available; each has different and often stringent eligibility criteria; strength of supporting evidence varies; and in some, proof of long-term efficacy is lacking. Reirradiation (ReRT) with repeat conventional external beam RT, highly conformal RT such as stereotactic body RT (SBRT) (Table 1), proton therapy, heavy ions or brachytherapy may also be considerations in those experiencing recurrence who have exhausted or are not eligible for other forms of therapy.

RERT: THE CASE FOR HARMONIZATION

Historically, the use of ReRT has been limited by concerns surrounding toxicity, tumour radioresistance, and lack of robust evidence[1,9,10]. The complexity of delivering RT a second time to the same volume has been exacerbated by a dearth of individual radiation oncologist experience, a lack of confidence in the ability to reproduce the previous treatment's dosimetric parameters, a scarcity of adequate data on recovery of normal organs after radiation injury, and the absence of guidelines supporting approaches to optimal RT planning. In a 2008 Canadian national survey, the majority of respondents reported a lack of departmental guidelines and "enthusiasm" for instituting ReRT[1]. Controversy surrounds the choice of appropriate prescription in the context of the initial dose and field arrangement, and the best combination of steps to limit further damage to normal structures which have already received maximum or near-tolerance doses. Consequently, repeat RT in past was primarily done with palliative intent[11]. This is echoed by results of the 2008 survey, in which only 32% of respondents would offer ReRT for salvage but 99% would institute ReRT if quality of life could be improved[1].

The situation where both RT courses are delivered with palliative intent has been extensively studied in the setting of bone metastases. However, it required significant international effort over more than a decade to bring the Radiation Oncology community to the point of being able to answer even the most fundamental question of optimal ReRT dose. Prior to 2002, differences in endpoint definition and measurement, timing of follow-up, and interval to retreatment, for example, plagued cross-trial comparisons[12]. An update of the International Bone Metastasis Consensus Working Party recommendations in 2012 again encouraged investigators to adopt a common set of endpoints, described minimum features which should be incorporated into the design of future trials, and suggested methods of data analysis and reporting[13]. Together with the results of multiple meta-analyses[14-19], the steady evolution towards consensus has culminated in the recent publication of a phase Ⅲ randomized controlled trial. This has finally provided level Ⅰ evidence supporting a specific approach for treatment planning and dosing for external beam ReRT for bone metastases[20].

Given technological advancements in diagnostic imaging and RT delivery, coupled with longer survival in many malignancies secondary to improvements in systemic therapy, a small subset of patients presenting with localized recurrence is increasingly being offered ReRT for salvage (*i.e.*, with curative intent). At present, this is on an ad hoc basis, guided by data mainly from retrospective single-institution series which commonly span twenty years or more. Conclusions are limited by small patient numbers, attrition, heterogeneous baseline characteristics, and the presence of selection and referral bias. Descriptions of the patient population retreated, RT modality and dose received, endpoints reported and follow-up are extremely variable. Consequently, whether ReRT is offered, and how it is implemented, remains highly dependent on the specific radiation oncologist and may be limited by resource availability[9]. The opportunity presently exists to apply lessons learned from the harmonization of the research efforts within the

Table 1 Selected results of reirradiation: Both courses external beam radiotherapy unless otherwise specified

Site of ReRT	Symptom overall response rate	Symptom response duration	Overall radiologic response rate	Radiologic response duration	Overall survival	Toxicity	% not completing ReRT	ReRT-related death
Head and Neck[24]	NR	NR	NR	NR	44% at 1 yr	23% grade 3+ late at 1 yr	13%	6.7%
Thoracic[21]	Average 69.2%	0.5-5 mo	55%-77% (0-11% CR; 7%-44% PR)	NR	9%-59% at 1 yr	Esophagitis 17.2% Pneumonitis 12.3% Skin 4.1% Fracture 0.5% Myelopathy 0.5%	4.5%	1.6%
Breast[25]	100% (56% PR; 44% CR)	"For a long time of the patients' lifetime in the majority"	NR	NR	61% at 1 yr	No grade 3-4 acute or late toxicity	NR	NR
[1]Pancreas[26]	57% at 1-2 mo	NR	"Tumour stabilization but… not…reduction in tumour size"	NR	Med surv after ReRT 8.8 mo (95%CI: 1.2-16.4 mo)	28% acute grade 2 toxicity (fatigue, abdominal pain, anorexia, nausea, diarrhea) No acute grade 3+ toxicity 6% grade 3 late toxicity	0%	NR
[1,3]Cervix[27]	71% achieved ⩾ 50% reduction from baseline at 1-2 mo	NR	35% CR, 30% PR, 17% SD, 17% PD at 4 mo	NR	43% at 2 yr	35% mild acute toxicity 13% late grade 4 toxicity (all rectovaginal fistulae requiring colostomy)	NR	NR
[1]Abdomen/pelvis[28]	95% - pain 75% - bleeding	NR	100%	NR	52% at 1 yr	0% grade 3-5 acute or late toxicity Acute 22% grade 1-2 pain 14% grade 1-2 skin reaction 8% grade 1-2 diarrhea 15% grade 1-2 nausea 4% grade 2 vomiting 4% grade 1 dysuria 4% grade 1 dysphagia Late 4% grade 2 pain 4% grade 2 skin reaction 4% grade 1 diarrhea 15% grade 1-2 dysuria 19% grade 1-2 nerve complaints 11% grade 1-2 limb dysfunction	NR	NR
Bone metastases[18,19]	58%-68% (16%-28% CR; 28%-50% PR)	1-9.7 mo	NR	NR	Median 3-6 mo	30% (nausea, vomiting, fatigue, diarrhea)	NR	NR
Bone metastases[20]	45%-51% of per protocol patients at 2 mo[2] (11%-14% CR; 31%-40% PR)	NR	NR	NR	NR	Acute[2] skin 14%-24% Anorexia 56%-66% Vomiting 13%-23% Diarrhea 23%-31% Late[2] Fracture 5%-7%	NR	0%

									Spinal cord compression 1%-2% Myelopathy 0%

[1]EBRT followed by SBRT; [2]Depending on dose; [3]7/23 patients in this series did not have EBRT up front but results not reported separately. CR: Complete response; EBRT: External beam radiotherapy; Med surv: Median survival; NR: Not reported; PD: Progressive disease; PR: Partial response; ReRT: Reirradiation; SBRT: Stereotactic body radiotherapy; SD: Stable disease.

bone metastases community to the salvage ReRT situation.

In future publications, eligibility for retreatment should be defined prospectively; this may be symptom or radiologic progression or both. Baseline characteristics such as current symptom burden (and methodology of measurement), performance status, and previous treatment modalities should be documented. Controversy exists as to whether a favourable response to initial RT over a long disease-free interval should be required before considering ReRT. Information on toxicity experienced after first RT should be reviewed. Comprehensive restaging and pathologic confirmation is encouraged as outcomes after ReRT for a new primary will differ from those expected after treatment for in-field recurrence.

Initial and ReRT techniques, energies, field sizes, calculation algorithms, prescription points, doses, planning techniques, and volumes have varied significantly as can be expected from differing treatment indications, intents, geographic locations, and years[21]. Many past studies did not include all RT details, with the lack of information often due to treatment planning software changes and evolution of RT delivery techniques[21]. When reported, total dose over both courses was often the arithmetic cumulative dose, which does not take into account dose per fraction or overall treatment time. In comparison, biologically equivalent dose (BED) and equivalent dose in 2 Gy fractions (EQD2) provide the ability to compare different dose fractionation schedules. Data sufficient to calculate BED or EQD2 are not found in most studies, so conclusions which can be drawn at present regarding ReRT schedules are limited.

The rationale for ReRT dosing and cumulative allowed organ at risk tolerance doses should be stated, as should the radiobiological justification for minimum interval between RT courses. Prospective data on utilization of and outcomes after highly conformal techniques such as SBRT after conventional RT are urgently needed, including cost-effectiveness, as these approaches are steadily migrating into the clinical setting. While in theory, these technologies should allow optimal tumour localization and therefore normal tissue sparing, they also deposit extensive low dose wash resulting in higher integral doses. The methods of constructing a composite plan (*i.e.*, rigid *vs* deformable registration) and the resulting dosimetric parameters should be available and cumulative tumour and normal tissue BEDs reported.

Once such additional volumetric data are available (*e.g.*, median degree of overlap of 50% or 90% isodose lines), correlations can be explored with outcomes such as symptom response, progression and especially toxicity. Further understanding of organ tolerance to ReRT is essential, as traditional recommendations based on the Emami[22] or QANTEC[23] guidelines may not be entirely generalizable to commonly used intensity-modulated and arc-based techniques. Construction of a prognostic score including demographic, disease and treatment-factors which render a patient likely to respond, and/or unlikely to complete a second course of RT, which can be easily applied in clinic is urgently needed.

Follow-up intervals as measured from a common starting point, endpoints assessed and investigations performed should be guided by standard practice for up-front curative-intent RT in the specific primary site, and patients should be monitored long-term by their radiation oncologist for outcomes and side effects[21]. Symptom improvement and progression rates and duration must be reported, notwithstanding that measurement of these can be confounded by progressive disease and comorbidities. The use of a validated patient-reported quality of life scale prior to ReRT and at regular follow-up intervals should be strongly considered. There is little data currently available on the important parameter of duration of symptom control in relation to overall survival which would be illustrative for patients during consent discussions.

Given the heterogeneity within the population of patients reirradiated for cure, an international registry would provide a foundation on which to base consensus recommendations regarding many of the outstanding questions regarding patient selection and treatment planning. Inter-centre collaboration will be required to build a critical mass of data sufficient for robust statistical analysis; however, in order to achieve this, global harmonization is needed. Standardized nomenclature would facilitate consistent coding of treated volumes, BEDs, toxicity measurement, systemic therapy use, quality of life outcomes, and duration of follow-up. Parameters such as the minimum recommended interval between courses for different indications and sites, along with guidelines around tolerance doses for critical organs at risk could be derived. Even the definition of ReRT could be conclusively addressed, given the lack of clarity at present due to the increasing sequential use of different RT modalities. A registry

would also assist in determining the feasibility of development of phase Ⅱ prospective studies and meta-analysis of currently available data.

CONCLUSION

Given the evolving technological climate and number of patients who are being considered for salvage ReRT, the data available must be harmonized so that valid conclusions can be available for translation to the clinic. In order to properly consent patients, physicians require information about the potential benefits as well as the potential risks in relation to other available treatment modalities. International collaboration in the form of a registry of prospectively collected data on patients reirradiated for cure for a variety of tumour sites would further support the evolution of Radiation Oncology towards personalized medicine, and away from the current "one-dose-fits-all" approach.

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MINIREVIEWS

Systematic reviews and meta-analyses: Why are they clinically significant?

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Abstract

This review aims to clarify the clinical significance of systematic reviews and meta-analyses by illustrating several classical examples. Firstly, systematic reviews can provide the highest level of evidence for clinical decisions. Secondly, systematic reviews can propose unresolved issues and future directions. Thirdly, systematic reviews can avoid harm to the human body. Fourthly, systematic reviews can prevent a waste of resources. Generally speaking, clinical researchers should be encouraged to perform systematic reviews and meta-analyses.

Key words: Systematic reviews; Meta-analyses; China; Publication; Science citation index

Core tip: Systematic reviews and meta-analyses are very important for clinicians and investigators because they can provide the highest level of evidence for clinical decisions, propose unresolved issues and future directions, avoid harm to the human body and prevent a waste of resources.

Qi XS, Yang ZP, Bai M, Wang YJ. Systematic reviews and meta-analyses: Why are they clinically significant? *World J Meta-Anal* 2015; 3(3): 139-141 Available from: URL: http://www.wjgnet.com/2308-3840/full/v3/i3/139.htm DOI: http://dx.doi.org/10.13105/wjma.v3.i3.139

INTRODUCTION

In recent years, the number of systematic reviews and meta-analyses has been steadily on the rise. By searching the PubMed database, about 500 relevant papers were published around the world in 1994 but more than 6000 relevant papers were published

in 2009[1]. Currently, systematic reviews and meta-analyses are also very hot in China. According to the statistics produced by *Ding Xiang Yuan* reporters, China contributed over 1000 meta-analysis papers in 2012[2]. There was a 40-fold increase in the annual number of meta-analyses in the genomic era for China from 2003 to 2011[3].

Investigators who perform original research need lots of time and costs for collecting clinical data and/or doing the experiments. By comparison, meta-analysis authors spend less time and fewer costs on synthesizing previously published data into a new result. It is said that a doctor wrote dozens of meta-analyses in Science Citation Index (SCI) journals with an accumulated impact factor > 200 in one year[4]. Ironically, the spectrum of his or her meta-analyses was very wide, including breast diseases, colon cancer, orthopedics, etc. As a criticism of the fact, publishing a meta-analysis in SCI journals is often regarded as opportunistic behavior. Some experts working at famous institutions strongly discourage their students from doing meta-analyses[5]. Herein, we highlight the significance of meta-analyses to correct such a distortion and encourage more investigators to perform meta-analyses.

SYSTEMATIC REVIEWS CAN PROVIDE THE HIGHEST LEVEL OF EVIDENCE FOR CLINICAL DECISIONS

According to the system produced by the Oxford Centre for Evidence-Based Medicine (March 2009), evidence for therapy/prevention and etiology/harm studies is divided into five levels[6]. They include level 1 (randomized controlled trials), level 2 (cohort studies), level 3 (case-control studies), level 4 (case series) and level 5 (expert opinion). Level 1 is further classified into level 1a (systematic review of randomized controlled trials) and 1b (individual randomized controlled trials). Similarly, systematic reviews of cohort and case-control studies are also classified as levels 2a and 3a, respectively. In the updated system produced by the Oxford Centre for Evidence-Based Medicine (2011), evidence for treatment benefit studies is also divided into five levels[7]. Systematic reviews of randomized trials provide the top level of evidence. On the other hand, the number of citations potentially reflects the hierarchy of evidence. Meta-analyses can receive the largest number of citations, followed by randomized controlled trials, cohort or case-control studies, nonsystematic review articles, decision and cost-effectiveness analyses and case reports[8].

SYSTEMATIC REVIEWS CAN PROPOSE UNRESOLVED ISSUES AND FUTURE DIRECTIONS

Systematic reviews are indispensable before initiating new clinical research[9,10]. Since August 2005, the *LANCET* editors have required authors to summarize previously published findings and explain the impact of their findings on existing knowledge[11]. In this renowned journal, the guidelines for authors obviously propose how the authors of clinical trials should do an updated systematic review if a recent systematic review is unavailable[12].

This consideration is also appropriate for every clinical researcher. In 2011, we published a meta-analysis to explore the significance of screening for JAK2 V617F mutation in patients with Budd-Chiari syndrome[13]. The prevalence of JAK2 V617F mutation was 37% and positive JAK2 V617F mutation could predict the presence and development of myeloproliferative neoplasms in such patients[13]. However, most available studies were conducted in the West and only one study was conducted in Asia (India). Given the ethnical differences between China and the West and the absence of related data from China, further evaluation of the prevalence of JAK2 V617F mutation in Chinese patients is warranted. In 2012, we reported the results of a clinical study in which the prevalence of JAK2 V617F mutation in Chinese patients with Budd-Chiari syndrome was only 4.3%[14]. This finding suggested a difference in the etiological distribution of Budd-Chiari syndrome between China and the West. Thus, we further performed a large-scale observational study to more comprehensively analyze the thrombotic risk factors for Budd-Chiari syndrome in Chinese patients[15]. Except for JAK2 V617F mutation and myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, factor Ⅴ Leiden mutation and prothrombin G20210A mutation were rarely found in our patients. These results were immediately confirmed by other peers[16,17].

SYSTEMATIC REVIEWS CAN AVOID HARM TO THE HUMAN BODY

Gilbert *et al*[18] performed a systematic review of observational studies and recommendations from textbooks about the association between infant sleeping position and sudden infant death syndrome. In books on infant care, the recommendation regarding whether the infants should be on a back or front sleeping position was controversial before 1989 but only a back sleeping position was recommended after that. In the meta-analysis, 25 individual studies published between 1965 and 2004 were identified. Indeed, the cumulative meta-analysis of the first two published studies (the first study was published in 1965 and the second one was published in 1970) demonstrated that the front sleeping position led to a statistically significant increase in the incidence of sudden infant death syndrome (cumulative odds ratio = 2.93, 95%CI: 1.15-7.47). In other words, if a meta-analysis was performed soon after the first two papers were published, the debate regarding the sleeping position would have disappeared, thereby

preventing more than 10000 infant deaths in the United Kingdom and more than 50000 in Europe, the United States and Australasia.

SYSTEMATIC REVIEWS CAN PREVENT A WASTE OF RESOURCES

Lau *et al*[19] performed a meta-analysis of clinical trials to compare the benefit of intravenous streptokinase *vs* placebo or no therapy for acute myocardial infarction. In the meta-analysis, 33 individual studies published between 1959 and 1988 were identified. Indeed, in the cumulative meta-analysis of the first four published studies with 962 patients, the benefit of intravenous streptokinase for acute myocardial infarction became statistically significant (P = 0.023) but the 95%CI was relatively wide. In the cumulative meta-analysis of the first 15 published studies with 4314 patients, the benefit remained significant (P < 0.001) and the odds ratio became steadier with a narrower 95%CI. Accordingly, the 18 trials published since then were unnecessary. More importantly, the additional 32660 participants should not have been enrolled because the participants assigned to the placebo/no therapy group would not have received intravenous streptokinase.

Another similar example was a meta-analysis to evaluate the risk of lung cancer in never-smoking women exposed to passive smoking by spouses[20]. Taylor *et al*[20] identified a total of 51 studies between 1981 and 2006. In the cumulative meta-analysis of the first 10 studies published before 1986, the association of passive smoking and lung cancer was significant. In the cumulative meta-analysis of the first 20 studies published before 1989, the statistical significance became steadier. Thus, the subsequent 31 studies may have been wasteful.

CONCLUSION

The importance of systematic reviews and meta-analyses in the contemporary era of evidence-based medicine needs to be clearly recognized. Clinical researchers should be accustomed to publishing their own data after the related evidence is systematically reviewed.

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Development of the Documentation and Appraisal Review Tool for systematic reviews

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Author contributions: Diekemper RL was the primary developer of the tool and she participated in the testing of the tool and drafting parts of the paper; Ireland BK came up with the concept of developing the tool and was a co-developer of the tool and participated in the testing of the tool and drafting parts of the paper; Merz LR was a co-developer of the tool and participated in the testing of the tool and drafting parts of the paper.

Conflict-of-interest: All of the authors report that they receive no financial compensation for DART. Diekemper RL uses DART for assessing the quality of systematic reviews used to inform guideline recommendations for CHEST guidelines. Due to her role as a developer of DART, the tool has been adopted by CHEST for use in guideline development. Ireland BK reports that as a consultant who frequently conducts systematic reviews and overviews of reviews, she is interested in an effective and efficient tool for evaluating the quality of systematic reviews. Merz LR has no conflicts of interest to disclose.
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Abstract

AIM: To develop a tool to more explicitly assess and document the quality of systematic reviews.

METHODS: We developed the Documentation and Appraisal Review Tool (DART) using epidemiologic principles of study design and the following resources: the modified Overview Quality Assessment Questionnaire (modified OQAQ), Assessment of Multiple Systematic Reviews (AMSTAR), the Cochrane Handbook, and the standards promoted by the Agency for Healthcare Research and Quality, and the Institutes of Medicine (IOM). We designed the DART tool to include the following: more detail to provide guidance and improve standardization of use, an approach to assess quality of systematic reviews addressing a variety of research designs, and additional space for recording notes to facilitate recall. DART underwent multiple rounds of testing with methodologists of varying levels of training and experience. Based on the results of six phases of pilot testing, we revised DART to improve performance, clarity and consistency. Pilot testing also included comparisons between DART, and the two most commonly used tools to evaluate the quality of systematic reviews, the modified OQAQ and AMSTAR.

RESULTS: Compared to AMSTAR and modified OQAQ, DART includes two unique questions and several questions covered by modified OQAQ or AMSTAR but not both. Modified OQAQ and DART had the highest reporting consistency. Four AMSTAR questions were unclear and elicited inconsistent responses. Identifying reviewer rationale was most difficult using the modified OQAQ tool, and easiest using DART. DART allows

for documentation of reviewer rationale, facilitating reconciliation between reviewers and documentation for future updates. DART also provides a comprehensive, systematic approach for reviewers with limited experience with systematic review methodology, to critically analyze systematic reviews. In addition, DART is the only one of the three tools to explicitly include quality review for biases specific to observational studies. This is now more widely recognized as important for assessing risk in order to generate recommendations that balance benefit to harm. The tool also includes the assessment of standards recommended by the March 2011 IOM Standards for Systematic Review.

CONCLUSION: This comprehensive tool improves upon existing tools for assessing the quality of systematic reviews and guides reviewers through critically analyzing a systematic review.

Key words: Quality assessment tool; Methodology; Healthcare research; Systematic review; Meta-analysis; Guidelines

Core tip: Systematic reviews and meta-analyses are commonly used to inform the recommendations presented in evidence-based clinical practice guidelines. The purpose of this study was to evaluate the Documentation and Appraisal Review Tool (DART) for its comprehensiveness, identify areas addressed by DART that were not addressed by two other validated tools [Overview Quality Assessment Questionnaire (OQAQ) and Assessment of Multiple Systematic Reviews (AMSTAR)], and to test its performance in eliciting consistent responses. We found that our tool was more comprehensive and included several questions not included in the other tools. We also found that DART elicited the most consistent responses when compared to OQAQ and AMSTAR.

Diekemper RL, Ireland BK, Merz LR. Development of the Documentation and Appraisal Review Tool for systematic reviews. *World J Meta-Anal* 2015; 3(3): 142-150 Available from: URL: http://www.wjgnet.com/2308-3840/full/v3/i3/142.htm DOI: http://dx.doi.org/10.13105/wjma.v3.i3.142

INTRODUCTION

Systematically collected and critically evaluated evidence forms the backbone of evidence-based clinical practice guidelines, hospital order sets, and quality measurement. Grant *et al*[1] define a systematic review as a systematic search, appraisal and synthesis of research evidence, often adhering to guidelines for conducting a review. Systematic reviews are the most comprehensive and valid method of collecting and synthesizing the published and unpublished record of clinical science, making them a preferred source of evidence and encouraging increased production. In 2010, Bastian *et al*[2] estimated 11 systematic reviews are published each day.

The consistent application of well-defined processes is essential to creating valid systematic reviews. These processes include (1) development of specific clinical question(s) using an analytic framework and standard format to articulate the question(s); (2) use of comprehensive and systematic methods to search for evidence; (3) unbiased process for selecting relevant research; (4) critical evaluation of the quality of included studies; (5) the extraction and synthesis of data from the included studies; and (6) the use of a pre-specified system to evaluate the body of evidence[3]. Even though these processes for sound systematic review are well described, and reporting checklists like Preferred Reporting Items for systematic reviews and meta-analyses[4] are available to authors to ensure a higher quality systematic review, the quality of published systematic reviews is not uniformly high. In 2002, Shea *et al*[5] evaluated the quality of Cochrane and other systematic reviews published in paper based journals, using the Oxman and Guyatt scale and the Sacks checklist. They found the average quality low for both types of reviews.

The Institute of Medicine (IOM) recognized that variation in the quality of systematic reviews still exists and convened a panel in 2010 to develop national standards for the design and implementation of systematic reviews. In 2011, the IOM panel released a list of 21 recommended standards for conducting systematic reviews[3]. If implemented properly and consistently, these standards could greatly reduce the variability and improve the overall quality of systematic reviews.

Currently, providers and policy makers wanting to incorporate the findings from existing systematic reviews into care decisions, protocols, and guidelines need assistance in evaluating the quality of systematic reviews. Several tools have been developed and evaluated and two have been validated for content[5,6]. We reviewed published user experience with these two, the modified Overview Quality Assessment Questionnaire (modified OQAQ)[5] and the Assessment of Multiple Systematic Reviews (AMSTAR)[6]. Most current users report implementation of AMSTAR because methods for evaluating systematic reviews have advanced since the development of OQAQ, however some also report modifying AMSTAR because it did not meet all their needs[7,8]. The Agency for Healthcare Research and Quality (AHRQ) recommends that its Evidence-based Practice Centers (EPCs) supplement the use of AMSTAR with additional considerations when incorporating existing systematic reviews into their reviews[8].

We examined both tools for use in evaluating systematic reviews of clinical interventions in a health system setting. Neither met all our needs (Table 1), and so we first set out to enhance one of the existing assessment tools. However, ultimately we determined the need to develop a comprehensive tool that improves

Table 1 Assessment of existing systematic review quality assessment tools

Need	Modified OQAQ	AMSTAR
Standardized quality assessment process across multiple reviewers with varying levels of experience	Insufficient detail to evaluate disputes	Confusing questions leading to inconsistent responses by same reviewer as well as between reviewers
Single tool to assess a variety of included research designs including randomized trials and observational studies	Insufficient detail on methods	Insufficient detail on methods
Detailed record of the review to facilitate updates of the evidence review	Insufficient detail for replication	Confusing questions leading to inconsistent responses by same reviewer and insufficient detail for replication
Training tool for junior epidemiologists and interns in systematic review methods	Insufficient detail on methods	Insufficient detail on methods

OQAQ: Overview Quality Assessment Questionnaire; AMSTAR: Assessment of Multiple Systematic Reviews.

upon existing tools for assessing the quality of systematic reviews and that guides reviewers through critically analyzing a systematic review. Here we describe the development of a tool designed to more explicitly document the quality assessment of systematic reviews: the Documentation and Appraisal Review Tool (DART) for Systematic Reviews (Table 2). To download the complete tool, please go to http://www.theevidencedoc.com.

MATERIALS AND METHODS

Design

DART was developed using epidemiologic principles of study design, the AMSTAR tool[6], and the Cochrane Handbook for Systematic Reviews of Interventions (version 4.2.6)[9] as guides. Once completed, we compared our tool to the validated systematic review tools, modified OQAQ and AMSTAR, and to tools developed by some of the AHRQ EPCs to ensure that the tool was as comprehensive as possible. All questions in the DART tool include the following: more detail to provide guidance and improve standardization of use, an approach to assess quality of systematic reviews addressing a variety of research designs, and additional space for recording notes to facilitate recall.

First round testing

An internal group of six methodologists then reviewed and pilot-tested the tool. The group was given systematic reviews of varying quality and asked to use the tool to critically analyze the reviews. The group met weekly for several weeks, testing a different systematic review with the tool each week. This exercise resulted in several revisions. By the end of phase Ⅱ, we determined that the tool was designed well enough to elicit consistent responses and agreement regarding the overall quality of the studies reviewed.

Comparison of test performance to validated tools

The second round of testing focused on the review of systematic reviews using DART in addition to the modified OQAQ and AMSTAR, two widely accepted, validated tools for assessing the quality of systematic reviews. The goal of this round of testing was to compare the performance of DART to the modified OQAQ and AMSTAR to determine if we met our design goals. Four internal reviewers with varying levels of training and experience, ranging from a student enrolled in a Masters of Public Health program to a faculty epidemiologist with over 30 years of experience used the three tools to independently assess the quality of several published systematic reviews. The reviewers then used a modified nominal group technique to brainstorm the strengths, weaknesses, and suggestions for improvement of DART. The reviewers also compared the performance of the three tools and identified variation in the responses to the quality assessment questions. The three tools were then mapped against each other to identify and characterize areas of overlap between the questions (Table 3), in order to determine if design goals for DART were met.

Refinement

After evaluating results from the content mapping and comparing performance and utility of DART for reviewers with different levels of experience, the tool was once again revised. A third round of pilot testing was performed using the revised tool to appraise the quality of different systematic reviews.

Comparison to IOM standards for systematic reviews

As a final review of our tool, we compared content to the March 2011 Standards for Systematic Reviews from the IOM to ensure that the tool included an evaluation component for each IOM standard[3].

Final testing

Final modification of the tool was completed in April 2011, followed by more rounds of internal pilot testing to evaluate consistency of responses for each question when the same reviewer appraised the systematic review at different points in time (intra-observer reliability) and when used by different reviewers (inter-observer reliability).

RESULTS

Assessing comparability of content of the three tools

In order to determine if we met our design goals, we

Table 2 Documentation and Appraisal Review Tool for systematic reviews

Title of Systematic Review:				
Author:				
Publication date:		Article tracking number:		
Reviewer:		Date completed:		
1 Did the authors develop the research question(s) and inclusion/exclusion criteria before conducting the review?				Use this space to document the rationale for your answer
a	It was clear the authors developed the research question(s) and inclusion criteria before conducting the review and that they stated the question(s) clearly	Yes		
b	Not described or cannot tell	No		
2 Did the authors describe the search methods used to find evidence (original research) on the primary question(s)?				Use this space to document the rationale for your answer
a	Key words and/or MESH terms were stated and where feasible the search strategy was provided	Yes		
b	Not described or cannot tell	No		
3 Was the search for the evidence reasonably comprehensive? Were the following included?				Use this space to document the rationale for your answer
a	Search included at least two electronic sources	Yes	No	
b	Authors chose the most applicable electronic databases (*e.g.*, CINAHL for nursing journals, EMBASE for pharmaceutical journals, and MEDLINE for general, comprehensive search) and only limited search by date when performing an update of a previous systematic review	Yes	No	
c	Search methods are likely to capture all relevant studies (*e.g.*, includes languages other than English; gray literature such as conference proceedings, dissertations, theses, clinical trials registries and other reports) and authors hand-searched journals or reference lists to identify published studies which were not electronically available	Yes	No	
4 Did the authors do the following when selecting studies for the review?				Use this space to document the rationale for your answer
a	Provide in the inclusion criteria: population, intervention, outcome and study design?	Yes	No	
b	State whether the selection criteria were applied independently by more than one person?	Yes	No	
c	State how disagreements were resolved during study selection?	Yes	No	
d	Provide a flowchart or descriptive summary of the included and excluded studies?	Yes	No	
e	Include all study designs appropriate for the research questions posed?	Yes	No	
5 Were the characteristics of the included studies provided? (in an aggregated form such as a table, data from the original studies were provided on the participants, interventions and outcomes)				Use this space to document the rationale for your answer
a	Yes			
b	Partially			
c	No			
6 Did the authors make any statements about assessing for publication bias?				Use this space to document the rationale for your answer
a	The authors did assess for publication bias and if publication bias was detected they stated how it was handled	Yes		
b	The authors did assess for publication bias but did not state how it was handled if it was detected	Partially		
c	Not described or cannot tell	No		
7 Did the authors do the following to assess the overall quality of the individual studies included in the review?				Use this space to document the rationale for your answer
a	Was the quality assessment specified with adequate detail to permit replication?	Yes	No	
b	Was the quality assessment conducted independently by more than one person?	Yes	No	
c	Did the authors state how disagreements were resolved during the quality assessment?	Yes	No	
8 Did the authors appropriately assess for quality by appropriately examining the following sources of bias in all of the included studies?				Use this space to document the rationale for your answer
All studies:				
a	Confounding (assessed comparability of study groups at start of study, was randomization successful?)	Yes	No	
b	Sufficient sample size (only applicable to studies that summarize their results in a qualitative manner; it's not a concern for pooled results)	Yes	No	
c	Outcome reporting bias (assessed for each outcome reported using a system such as the ORBIT classification system)	Yes	No	
d	Follow up (assessed for completeness and any differential loss to follow-up)	Yes	No	
For Randomized Controlled Trials only:				
e	Randomization	Yes	No	
f	Allocation concealment	Yes	No	
g	Blinding	Yes	No	

For Case-Control and Cohort Studies only:				
h	Selection bias	Yes	No	
i	Information bias--recall and completeness to follow-up	Yes	No	
For Quasi-Experimental Studies only:				
j	Differences between the first and second study measurement point - such as changes or improvements in other interventions, changes in measurement techniques or definitions, or aging of subjects	Yes	No	
k	Selection bias	Yes	No	
For Diagnostic Accuracy Studies only:				
l	Selection (spectrum) bias - were subjects selected to be representative of patients to whom the test will be applied in clinical practice, and to represent the broadest spectrum of disease?	Yes	No	
m	Verification bias - were all patients subjected to the same reference standard of diagnosis, and was it measured blindly and independently of the test?	Yes	No	
9 Did the authors use appropriate methods to extract data from the included studies?				Use this space to document the rationale for your answer
a	Were standard forms developed and piloted prior to the systematic review conduct?	Yes	No	
b	Did the authors ensure that data from the same study but that appeared in multiple publications were counted only once in the synthesis?	Yes	No	
c	Was data extraction performed by more than one person?	Yes	No	
10 Did the authors assess and account for heterogeneity (differences in participants, interventions, outcomes, trial design, quality or treatment effects) among the studies selected for the review?				Use this space to document the rationale for your answer
a	The authors stated the differences among the studies and how they accounted for those differences	Yes		
b	The authors stated the differences but not how they accounted for them	Partially		
c	Not described or cannot tell	No		
11 Did the authors describe the methods they used to combine/synthesize the results of the relevant studies (to reach a conclusion) and were the methods used appropriate for the review question(s)?				Use this space to document the rationale for your answer
a	Methods were reported clearly enough to allow for replication. The overview included some assessment of the qualitative and quantitative heterogeneity of the study results and the results were appropriately combined/synthesized. For meta-analyses, an accepted pooling method (*i.e.*, more than simple addition) was used. Or the authors state that the evidence is conflicting and that they can't combine/ synthesize the results	Yes		
b	The methods were reported clearly enough to allow for replication but they were not combined appropriately	Partially		
c	Not described or cannot tell	No		
12 Did the authors perform sensitivity analyses on any changes in protocol, assumptions, and study selection? (For example, using sensitivity analysis to compare results from fixed effects and random effects models)				Use this space to document the rationale for your answer
a	Sensitivity analyses were used when appropriate on all changes in a priori design	Yes		
b	Sensitivity analyses were only used on some changes in a priori design	Partially		
c	Not described or cannot tell	No		
13 Are the conclusions of the authors supported by the reported data with consideration of the overall quality of that data?				Use this space to document the rationale for your answer
a	The conclusions are supported by the reported data and reflect both the scientific quality of the studies and the risk of bias in the data obtained from those studies	Yes		
b	The authors failed to consider study quality and/or their conclusions were not supported by the data, or cannot tell	No		
14 Were conflicts of interest stated and were individuals excluded from the review if they reported substantial financial and intellectual COIs?				Use this space to document the rationale for your answer
a	COIs were reported for each team member and individuals were excluded if they had substantial COIs	Yes		
b	COIs were reported but it was not clear whether individuals were excluded based on their COIs	Partially		
c	COIs were not reported and individuals were not excluded based on their COIs	No		
15 On a scale of 1-10, how would you judge the overall quality of the paper?				
Rating	Overall Comments			
Good (8-10)				
Fair (5-7)				
Poor (< 5)				

COIs: Conflicts of interests.

Table 3 Comparison of Documentation and Appraisal Review Tool to modified Overview Quality Assessment Questionnaire and Assessment of Multiple Systematic Reviews

DART questions	Corresponding AMSTAR question(s)	Corresponding modified OQAQ question(s)
(1) Did the authors develop the research question(s) and inclusion/exclusion criteria before conducting the review?	(1) Was an "a priori" design provided?	Not addressed
(2) Did the authors describe the search methods used to find evidence (original research) on the primary question(s)?	(3) Was a comprehensive literature search performed?	(1) Were the search methods used to find evidence on the primary question stated?
(2a) Are key words and/or MESH terms stated?	(3) Was a comprehensive literature search performed?	Not addressed
(3) Was the search for the evidence reasonably comprehensive?	(3) Was a comprehensive literature search performed?	(2) Was the search for evidence reasonably comprehensive?
(3a) Does the search include at least 2 databases?	(3) Was a comprehensive literature search performed?	Not addressed
(3b) Did the authors choose the most applicable electronic databases and only limit the search by date when performing an update?	Not addressed	Not addressed
(3c) Are search methods likely to capture all relevant studies and did the authors hand-search journals or reference lists to identify published studies which were not electronically available?	(3) Was a comprehensive literature search performed?	Not addressed
	(4) Was the status of publication (*i.e.*, grey literature) used as an inclusion criterion?	
(4a) Did the authors provide in the inclusion criteria: Population, intervention, outcome, and study design, when selecting studies for the review?	Not addressed	Not addressed
(4b) Did the authors state whether the selection criteria were applied by more than one person?[1]	(2) Was there duplicate study selection and data extraction?[1]	Not addressed
(4c) Did the authors state how disagreements were resolved during study selection?[1]	(2) Was there duplicate study selection and data extraction?[1]	Not addressed
(4d) Did the authors provide a flowchart or descriptive summary of the included and excluded studies?	(5) Was a list of studies (included and excluded) provided?	Not addressed
(4e) Did the authors include all study designs appropriate for the research questions posed?	Not addressed	Not addressed
(5) Were the characteristics of the included studies provided? (in an aggregated form such as a table, data from the original studies were provided on the participants, interventions and outcomes)	(6) Were the characteristics of the included studies provided?	Not addressed
(6) Did the authors make any statements about assessing for publication bias?	(10) Was the likelihood of publication bias assessed?	Not addressed
(7a) Was the quality assessment specified with adequate detail to permit replication?	(7) Was the scientific quality of the included studies assessed and documented?	(5) Were the criteria used for assessing the validity of the included studies reported?
(7b) Was the quality assessment conducted independently by more than one person?	Not addressed	Not addressed
(7c) Did the authors state how disagreements were resolved during the quality assessment?	Not addressed	Not addressed
(8) Did the authors appropriately assess for quality by appropriately examining the following sources of bias in all of the included studies: confounding, sufficient sample size, outcome reporting bias, follow-up, randomization, allocation concealment, blinding, selection bias, information bias, verification bias, and differences between the first and second study measurement point?	(7) Was the scientific quality of the included studies assessed and documented? (partial match)	(6) Was the validity of all studies referred to in the text assessed using appropriate criteria? (partial match)
(9) Did the authors use appropriate methods to extract data from the included studies?	Not addressed	Not addressed
(9a) Were standard forms developed and piloted prior to the systematic review conduct?	Not addressed	Not addressed
(9b) Did the authors ensure that data from the same study that appeared in multiple publications were counted only once in the synthesis?	Not addressed	Not addressed
(9c) Was data extraction performed by more than one person?	(2) Was there duplicate study selection and data extraction?	Not addressed
(10) Did the authors assess and account for heterogeneity (differences in participants, interventions, outcomes, and trial design, quality or treatment effects) among the studies selected for the review?	(9) Were the methods used to combine the findings of studies appropriate?	(7) Were the methods used to combine the findings of the relevant studies reported?

		(8) Were the findings of the relevant studies combined appropriately?
(11) Did the authors describe the methods they used to combine/synthesize the results of the relevant studies (to reach a conclusion) and were the methods used appropriate for the review question(s)?	(9) Were the methods used to combine the findings of studies appropriate?	(7) Were the methods used to combine the findings of the relevant studies reported?
		(8) Were the findings of the relevant studies combined appropriately?
(12) Did the authors perform sensitivity analyses on any changes in protocol, assumptions, and study selection? (For example, using sensitivity analysis to compare results from fixed effects and random effects models)	Not addressed	Not addressed
(13) Are the conclusions of the authors supported by the reported data with consideration of the overall quality of that data?	(8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (partial match)	(9) Were the conclusions made by the author(s) supported by the data reported? (partial match)
(14) Were conflicts of interest stated and were individuals excluded from the review if they reported substantial financial and intellectual COIs?	(11) Was the conflict of interest stated? (partial match)	Not addressed
(15) On a scale of 1-10, how would you judge the overall quality of the paper?	Not addressed	(10) Overall quality

[1]Separate questions in DART, but concepts not separated in AMSTAR. DART: Documentation and Appraisal Review Tool; OQAQ: Overview Quality Assessment Questionnaire; AMSTAR: Assessment of Multiple Systematic Reviews; COIs: Conflicts of interests.

mapped OQAQ and AMSTAR to DART and displayed the results in Table 3. Table 3 shows that our tool includes several questions that are unique and not included in the modified OQAQ or AMSTAR, with several other questions covered by one or the other but not both tools.

Assessing consistency of performance of the three tools

Throughout the iterations of development, testing and group discussion and review of performance, we learned that the modified OQAQ and DART consistently produced similar overall assessments of quality. However, during these discussions we had more difficulty remembering or locating reviewer rationale for the responses using the modified OQAQ tool. DART has sufficient space to record page and line details to facilitate recall. This was important when resolving disputes. We also discovered that the AMSTAR tool had questions that were confusing and difficult to implement consistently. They are the following: (1) Question 4: Was the status of publication (*i.e.,* grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports from the systematic review, based on their publication status, language, *etc.* This question was confusing since it seemed to equate an accurate description of the extent of the search with the actual execution of a thorough search; (2) Question 5: Was a list of studies (included and excluded) provided? This question was interpreted as being too specific by requiring lists, and did not allow for a good flow chart; it seemed to require more detail than most journal space would allow; (3) Question 7: Was the scientific quality of the included studies assessed and documented? A priori methods of assessment should be provided [*e.g.,* for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria]; for other types of studies alternative items will be relevant. This question did not provide sufficient detail to execute consistently. We found it more useful to specify the most important sources of bias by study type for consistent reporting both within and across reviewers; and (4) Question 11: Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. The answer to this question was always no. Systematic review authors often mention their personal sources of support, but we did not find an example where potential sources of support were provided for the included studies. This needs to either be two questions, or allow for partial scoring.

DART was the only one of the three tools to explicitly include quality review for biases specific to observational studies. Since the importance of including evidence from observational data is now more widely recognized, particularly for assessing risk in order to generate recommendations that balance benefit to harm, we believe it is important to include careful assessment of the potential for biased measurement unique to this design.

DISCUSSION

We are aware that a revision of the AMSTAR tool exists and is known as R-AMSTAR[7]. The primary goal for revising AMSTAR was to produce an overall quantitative estimate of the quality of the systematic review. The performance of R-AMSTAR has been compared to the original tool using systematic reviews from the field of assisted reproduction for subfertility[10]. In that comparison study, R-AMSTAR was noted to provide more guidance to the reviewer than AMSTAR, but was

more difficult to apply consistently. Popovich *et al*[10] reported that the R-AMSTAR criteria were difficult to apply because of subjectivity of some of the domains, especially domain 8. That question "Was the scientific quality of the included studies used appropriately in formulating conclusion?" provided four criteria, which Popovich *et al*[10] report as being difficult to distinguish. Their kappa statistics also showed poor inter-rater reliability for this domain.

We designed the DART quality assessment tool to address limitations we discovered when using the modified OQAQ and AMSTAR tools. The specific improvements are: (1) Space for enhanced recording detail to facilitate reconciliation between reviewers and provide detailed reference for use in future updates; (2) An evaluation of major biases relevant to observational study designs and the assessment of standards recommended by the March 2011 IOM Standards for Systematic Review[3]; (3) Additional detail and guidance for junior epidemiologists, clinicians and other members of the review panel with less experience in systematic review methods; and (4) Consistent overall quality assessment of systematic reviews using a qualitative ranking that categorizes studies as good, fair or poor at the end of a detailed assessment.

In order to facilitate the use of systematic reviews, the American College of Chest Physicians (CHEST) adopted DART to assess the quality of systematic reviews included in their evidence reviews. CHEST guideline authors used DART to assess the quality of systematic reviews and meta-analyses included in the "Diagnosis and Management of Lung Cancer: CHEST Evidence-Based Clinical Practice Guideline (3rd Edition)"[11], and subsequent guidelines. DART has been used for other CHEST guidelines and it is discussed in the article Methodologies for the Development of CHEST Guidelines and Expert Panel Reports[12].

This paper describes the development of DART for systematic reviews. The next step is to quantify the performance of components of the tool through validation testing, assessing inter-rater agreement scores. Based on our preliminary evaluation with the modified OQAQ and AMSTAR, intra-rater reliability should also be tested when assessing the same systematic review at a later point in time, since updated evidence reviews are essential to ensuring that the best current evidence informs clinical guidelines and policy. The ability to facilitate accurate recall of prior reviews will improve the efficiency of that process.

The authors now have considerable experience and familiarity with DART and can complete the assessment form quickly. It is therefore important to use an external validation process to test performance in persons with a wide variety of backgrounds and without prior experience with the tool in order to evaluate inter and intra rater consistencies in response and time for completion.

Well-executed systematic reviews now form the foundation of evidence-based clinical practice guidelines. Even though the IOM has developed rigorous standards for conducting systematic reviews, there is still wide variation in how they are conducted and reported. Given this variation and the new reliance on systematic reviews, comprehensive tools are needed to assess the quality of systematic reviews. By creating the DART for Systematic Reviews we attempted to fill this gap.

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COMMENTS

Background

Systematic reviews are the foundation for evidence-based guidelines. Rigorous standards exist, but there is wide variation in implementation, highlighting the need for a more comprehensive quality assessment tool for systematic reviews.

Research frontiers

As the publication of systematic reviews increases, variability in the quality still exists. Users of systematic reviews need a way to assess the quality of systematic reviews that includes all relevant study designs. Since the importance of including evidence from observational data is now more widely recognized, especially to assess potential for harm, a single tool is needed that includes careful assessment of the potential for biased measurement unique to this design as well as for randomized trials.

Innovations and breakthroughs

The authors designed the the Documentation and Appraisal Review Tool (DART) quality assessment tool to address limitations they discovered when using the modified Overview Quality Assessment Questionnaire and Assessment of Multiple Systematic Reviews tools. The specific improvements include: the ability to record rationale for each criteria; criteria for assessing observational studies and for assessing standards recommended by the Institute of Medicine in 2011; additional guidance to assist less experienced reviewers in assessing the quality of systematic reviews; and consistent overall quality assessment of systematic reviews using a qualitative ranking.

Applications

DART provides a comprehensive, systematic approach for reviewers with limited experience with systematic review methodology, to critically analyze systematic reviews. It also provides a complete record of judgments and decisions made during the assessment to assist reconciliation between reviewers during the current review and for use in future updates.

Terminology

The terminology used in this article reflects the vocabulary familiar to an audience using systematic reviews for decision-making.

Peer-review

The peer reviewers did not report having any concerns about the paper. Reviewer comments included the following: Systematic reviews are the foundation for evidence-based guidelines and are increasing. The article discusses the development of a comprehensive tool that improves upon existing tools for assessing the quality of systematic reviews and that guides reviewers through critically analyzing a systematic review. It has significance to appraise a systematic review.

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Effectiveness of 7-valent pneumococcal conjugate vaccine: A meta-analysis of post-marketing studies

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Abstract

AIM: To investigate the 7-valent pneumococcal conjugate vaccine (PCV7) effectiveness.

METHODS: A systematic literature review of studies which evaluated the effectiveness of PCV7 vaccine was performed searching the keyword "heptavalent pneumococcal conjugate vaccine" in PubMed and Scopus until March 16, 2013. The selection of potential eligible articles was done by two researchers independently on the basis of abstract and title and only post-marketing studies were included in the systematic review. Data extraction was carried out by two researchers with respect to invasive pneumococcal diseases due to both all and vaccine serotypes in pre-vaccine and post-vaccine periods in children less than 5 years. Results of studies which were considered suitable for meta-analysis were combined by means of relative risk (RR) with 95%CI. Vaccine effectiveness was calculated as (1-RR) × 100. Heterogeneity was assessed by I^2 and a random effects model was used to combine data in the case of heterogeneity. RevMan 5 was used to pool data.

RESULTS: On the whole, 757 eligible papers were identified from the literature search in PubMed and Scopus. Of them, 62 were finally considered in the systematic review and 38 were included in the meta-analysis. In all post-marketing studies included in the systematic review the incidence of invasive pneumococcal diseases due to vaccine serotypes declined significantly with the exception of few studies showing stability or a slight, but not significant, increase. Furthermore most of studies highlighted also a reduction in the incidence of invasive pneumococcal diseases due to all serotypes. With regards to meta-analysis, a random effects model was used to combine data because of the high heterogeneity. Data combination showed that the effectiveness of PCV7 in reducing invasive pneumococcal diseases due to vaccine serotypes and to all serotypes was 84% (95%CI: 74%-90%) and 53% (95%CI: 46%-59%) respectively. These results are confirmatory with respect to the efficacy of PCV7 against invasive pneumococcal diseases

due to vaccine serotypes.

CONCLUSION: PCV7 implementation determines a significant decrease of invasive pneumococcal diseases.

Key words: Streptococcus pneumoniae; Pneumococcal infections; Pneumococcal vaccines; Treatment outcome; Meta-analysis

Core tip: This systematic review and meta-analysis was performed with the aim to collect data from post-marketing studies on 7-valent pneumococcal conjugate vaccine (PCV7) and to provide evidence about the impact of the vaccine in the real world. Eligible articles were identified through a search on PubMed and Scopus. The meta-analysis showed that PCV7 is able to reduce invasive pneumococcal diseases due to both vaccine serotypes and to all serotypes. The effectiveness was 84% (95%CI: 74%-90%) and 53% (95%CI: 46%-59%) respectively. These data may be taken into consideration in order to foresee the impact under real conditions of PCV13 which has replaced PCV7 from 2010 onwards.

de Waure C, Specchia ML, Capizzi S, Aljicevic M, Dujovic M, Malaj A, Ricciardi W. Effectiveness of 7-valent pneumococcal conjugate vaccine: A meta-analysis of post-marketing studies. *World J Meta-Anal* 2015; 3(3): 151-162 Available from: URL: http://www.wjgnet.com/2308-3840/full/v3/i3/151.htm DOI: http://dx.doi.org/10.13105/wjma.v3.i3.151

INTRODUCTION

Streptococcus pneumoniae (*S. pneumoniae*) is a leading cause of severe bacterial infectious disease and World Health Organization has estimated that this bacteria causes 1.4-1.6 million child deaths annually[1,2], in that around 11% of all deaths in children < 5 years[3]. More than 90 serotypes of *S. pneumoniae* exist. These strains may cause invasive pneumococcal disease (IPD). The highest incidence of IPD is seen in children < 2 years old. In order to prevent disease caused by *S. pneumoniae,* two types of vaccines, polysaccharide (PPV) and conjugate (PCV) exist, even though the PPV vaccine is ineffective in children < 2 years old[4].

The PCV vaccines consist of capsular PPVs bound to proteins which are highly immunogenic and enhance an immune response by recruiting type 2 helper T cells, which allows for immunoglobulin type switching and production of memory B cells. The main drawbacks of PCV vaccines are that they only provide protection against a subset of serotypes covered by the PPV vaccines[5-7]. In fact, PCV vaccines encompass the 7-valent vaccine (PCV7), the PCV10 and the PCV13. Currently, PCV13 is used in prevention campaigns. Its marketing authorization in the European Union goes back to December 2009[8]. PCV13 has replaced PCV7 from 2010 onward.

The PCV7, providing protection against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, was introduced into routine childhood immunization program in the United States in 2000 and was shown to reduce the incidence of IPD by all and vaccine-serotypes[9,10]. Notwithstanding, some studies have described significant rises in non-vaccine serotypes after the implementation of universal PCV7 programs[11-14]. Based on the favourable United States experience and the proof of vaccine efficacy[15] a number of countries have introduced PCV7[16]. Worldwide the vaccine has been provided with different schedules. In Europe both the 2 + 1 and 3 + 1 schedules have been used[16].

In the light of monitoring the health impact of technologies and policies, data from the real practice should be collected and analysed. Because of the recent introduction and implementation of PCV13, many data from real practice are only available for PCV7 even though evidence is being produced on PCV13 also[17-23]. Notwithstanding, this evidence should be considered early and is still scant in order to make a meta-analysis. Furthermore, it is mostly related to the transition period between the use of PCV7 and the introduction of PCV13 which took place from 2010 onward with different time schedules across countries. Based on this premises, the objective of this study was to perform a systematic review and a meta-analysis of post-marketing studies on the effectiveness of PCV7 in comparison with no vaccination in preventing IPD in children less than 5 years of age worldwide. The final aim was to provide evidence about PCV7 effectiveness under real conditions and to foresee the potential impact of PCV13 on the basis of results. The systematic review was performed according to PRISMA Statement published by Moher *et al*[24].

MATERIALS AND METHODS

Selection of articles

A literature search was conducted using PubMed and Scopus search engines. The following search strategy was used: "heptavalent pneumococcal PCV vaccine" (Substance Name) NOT ["Clinical Trial" (Publication Type) OR "Clinical Trials as Topic" (Mesh) OR "Controlled Clinical Trial" (Publication Type) OR "Clinical Trial, Phase Ⅳ" (Publication Type) OR "Clinical Trial, Phase Ⅲ" (Publication Type) OR "Clinical Trial, Phase Ⅱ" (Publication Type) OR "Clinical Trial, Phase Ⅰ" (Publication Type)]. The search covered the period up to March 16, 2013, without starting date, and was limited to English-language publications.

The selection of potential eligible articles was done by two researchers independently on the basis of title and abstract. Full text of eligible articles was collected for the final judgment on inclusion. Disagreements were solved through consensus or the consultation of a third researcher.

We defined a priori criteria for the inclusion of studies

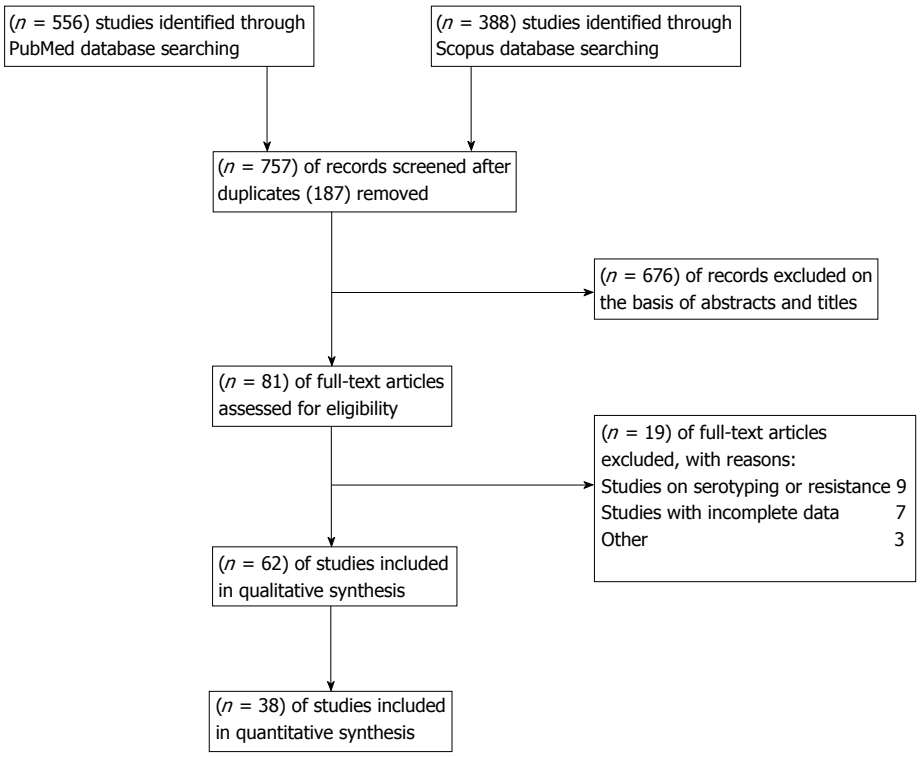

Figure 1 Flow-chart of studies selection.

in this meta-analysis, selecting studies dealing with the incidence of IPD in children less than 5 years of age in the period before and after the introduction of PCV7. Only articles releasing data on IPD incidence in pre- and post-vaccination periods were included in the quantitative assessment.

Data extraction

The following data were recorded from each study: first author, journal, published year, country, study population, IPD case definition, crude number or incidence of IPD before and after the introduction of PCV7. Data on IPD caused by all serotypes and due to vaccine serotypes, if available, were collected. Data extraction was performed by two researchers independently and disagreements were solved through consensus or the consultation of a third researcher.

Statistical analysis

Studies were included in the meta-analysis if they provided crude data or if it was possible to get them through computation.

The relative risk (RR) with 95%CI was used to combine data. Vaccine effectiveness was calculated as (1-RR) × 100. RevMan 5 was used to combine data and a fixed effects model was applied in the case of absence of heterogeneity (I^2 < 50%). On the other way around, a random effects model was used. Studies which were not considered in the meta-analysis were described qualitatively in Table 1. Finally, publication bias was assessed by means of funnel plots.

RESULTS

On the whole, 556 articles were yielded from PubMed and 388 from Scopus but 187 papers were shared by the two databases for a total of 757 papers. Of them, 62 were finally considered in the systematic review (Figure 1)[25-86]. Their characteristics and results are shown in Table 1.

With respect to meta-analysis, 38 articles provided data on IPD due to all serotypes while 22 allowed the collection of data on IPD due to vaccine serotypes. Data combination showed a vaccine effectiveness of 84% for IPD due to vaccine serotypes (RR = 0.16, 95%CI: 0.10%-0.26; I^2 = 95%, Figure 2) and 53% (RR = 0.47, 95%CI: 0.41-0.54; I^2 = 95%, Figure 3) for IPD related to all serotypes. Publication bias could not be excluded with respect to the assessment of effectiveness against IPD due to vaccine serotypes while may be excluded as regards IPD due to all serotypes (Figures 4 and 5).

DISCUSSION

Our study aimed to review and combine data of post-marketing studies on PCV7 worldwide.

The analysis and data combination allowed us to investigate the effectiveness of PCV7 and its impact in terms of public health. Results are indeed useful for supporting decision-makers in the field of vaccinations. In particular, findings of the meta-analysis showed that the effectiveness of PCV7 in reducing IPD due to vaccine serotypes is 84%. The effectiveness is estimated to be 53% with respect to IPD due to all serotypes.

Table 1 Summary of studies characteristics and results

Ref.	Country	Study period	Invasive pneumococcal disease definition	Main results
Albrich *et al*[25]	United States	1997-2004	Isolation of *S. pneumoniae* from sterile body fluid	1
Ampofo *et al*[26]	United States	1997-2010	Isolation of *S. pneumoniae* from sterile body fluid	The proportion of children younger than 2 yr with IPD decreased (54% *vs* 43% with respect to all serotypes and 56% *vs* 43% for vaccine serotypes), while the proportion of disease among children aged 2-4 slightly increased (27% *vs* 29% with respect to all and vaccine serotypes)
Aristegui *et al*[27]	Spain	1998-2003	Isolation of *S. pneumoniae* from sterile body fluid	1
Barricarte *et al*[28]	Spain	2001-2005	Isolation of *S. pneumoniae* from sterile body fluid	The overall effectiveness in reducing IPD was 31% (OR = 0.69, 95%CI: 0.37-1.27) and 88% (OR = 0.12, 95%CI: 0.02-0.91) for all serotypes and vaccine serotypes respectively
Benito-Fernández *et al*[29]	Spain	2000-2005	Isolation of *S. pneumoniae* from sterile body fluid	1
Ben-Shimol *et al*[30]	Israel	1989-2010	Isolation of *S. pneumoniae* from sterile body fluid	In 2009 and 2010, IPD incidence (due to vaccine serotypes) were 15.9 per 100000 and 5.4, per 100000 respectively (a 43% and 81% decrease compared to 2003-2007)
Bjornson *et al*[31]	Canada	2001-2005	Isolation of *S. pneumoniae* from sterile body fluid	1
Calbo *et al*[32]	Spain	1999-2004	Isolation of *S. pneumoniae* from sterile body fluid	The IPD incidence significantly decreased from 96.9 cases per 100000 person-years to 90.6 cases per 100000 person-years (7% reduction)
Carstairs *et al*[33]	United States	2000-2002	Isolation of *S. pneumoniae* from sterile body fluid	1
Casado-Flores *et al*[34]	Spain	2001-2006	Isolation of *S. pneumoniae* from sterile body fluid	1
CDC[35]	United States	1998-2005	Isolation of *S. pneumoniae* from sterile body fluid	1
De Serres *et al*[36]	United States	2001-2009	Isolation of *S. pneumoniae* from sterile body fluid	Effectiveness of PCV7 against IPD due to vaccine serotypes was 97% (95%CI: 92%-98%) among healthy children and 88% (95%CI: 78%-94%) among children with comorbid conditions. The incidence of IPD due to non-vaccine serotypes increased from 6.8 per 100000 (1998-1999) to 10.3 per 100000 in 2007 (51% increase)
De Wals *et al*[37]	Canada	2007-2010	Isolation of *S. pneumoniae* from sterile body fluid	A decrease in the frequency of IPD caused by vaccine serotypes was observed
Dias *et al*[38]	Portugal	1999-2004	Isolation of *S. pneumoniae* from sterile body fluid	1
Vestrheim *et al*[39]	Norway	2004-2008	Isolation of *S. pneumoniae* from sterile body fluid	1
Dubos *et al*[40]	France	2000-2005	Isolation of *S. pneumoniae* from sterile body fluid	A decrease of 82% (95%CI: 52%-95%) of cases was observed (from 8.9 cases per 100000 in 2001 to 1.8 per 100000 in 2005) in children < 2 yr
Fenoll *et al*[41]	Spain	1996-2001 2005-2006	Isolation of *S. pneumoniae* from sterile body fluid	A decrease of the incidence of IPD due to vaccine serotypes from 5.2 per 100000 in 1996-2001 to 2.4 per 100000 in 2005-2006 was observed
Flannery *et al*[42]	United States	1998-2002	Isolation of *S. pneumoniae* from sterile body fluid	1
Giele *et al*[43]	Australia	1996-2005	Isolation of *S. pneumoniae* from sterile body fluid	1
Schutze *et al*[44]	Arkansas	1998-2003	Isolation of *S. pneumoniae* from sterile body fluid	A decrease of IPD from 44.2 per 100000 person-years to 8.30 per 100000 person-years was observed in children < 2 yr
Guevara *et al*[45]	Spain	2001-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Haddy *et al*[46]	United States	1999-2002	Isolation of *S. pneumoniae* from sterile body fluid	1
Hanna *et al*[47]	Queensland	1999-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Hanquet *et al*[48]	Belgium	2002-2008	Isolation of *S. pneumoniae* from sterile body fluid	1
Harboe *et al*[49]	Denmark	2000-2008	Isolation of *S. pneumoniae* from sterile body fluid	In children < 2 yr, the overall incidence decreased from 54 to 23 cases per 100000 (IRR = 0.43, 95%CI: 0.29-0.62) and from 36.7 to 7.7 (IRR = 0.20, 95%CI: 0.09-0.38) for vaccine serotypes. A non-significant increase was observed in children aged 2-4 yr
Hennessy *et al*[50]	United States	1995-2003	Isolation of *S. pneumoniae* from sterile body fluid	1
CDC[51]	United States	1998-2003	Isolation of *S. pneumoniae* from sterile body fluid	A decrease of IPD due to vaccine serotypes from 80 cases per 100000 to 4.6 per 100000 was observed (decrease of 94% (95%CI: 92%-96%) from 1998-1999 to 2003
Hsu *et al*[52]	United States	1998-2005	Isolation of *S. pneumoniae* from sterile body fluid	1

Hsu *et al*[53]	United States	1990-1991 2001-2003	Isolation of *S. pneumoniae* from sterile body fluid	1
Hsu *et al*[54]	United States	2001-2007	Isolation of *S. pneumoniae* from sterile body fluid	IPD incidence was stable during the 6 yr period, although IPD due to vaccine serotypes decreased
Ingels *et al*[55]	Denmark	2000-2010	Isolation of *S. pneumoniae* from sterile body fluid	1
Wenger *et al*[56]	United States, Alaska	1986-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Johnson *et al*[57]	South Australia	2002-2009	Isolation of *S. pneumoniae* from sterile body fluid	1
Kellner *et al*[58]	Canada	1998-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Kyaw *et al*[59]	United States	1996-2004	Isolation of *S. pneumoniae* from sterile body fluid	1
Leal *et al*[60]	Alberta	1998-2010	Isolation of *S. pneumoniae* from sterile body fluid	1
Liao *et al*[61]	Taiwan	2000-2008	Isolation of *S. pneumoniae* from sterile body fluid	The overall incidence of IPD decreased by 33% (95%CI: 0%-72.2%)
Messina *et al*[62]	United States	1999-2001 2003-2005	Isolation of *S. pneumoniae* from sterile body fluid	1
Muñoz-Almagro *et al*[63]	Spain	1997-2006	Isolation of *S. pneumoniae* from sterile body fluid	1
Patrzalek *et al*[64]	Poland	2005-2010	Isolation of *S. pneumoniae* from sterile body fluid	1
Pérez *et al*[65]	Spain	1998-2008	Isolation of *S. pneumoniae* from sterile body fluid	1
Pérez-Trallero *et al*[66]	Spain	1996-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Pilishvili *et al*[67]	United States	1998-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Poehling *et al*[68]	United States	1997-2004	Isolation of *S. pneumoniae* from sterile body fluid	1
[69]	Canada	2002-2005	Isolation of *S. pneumoniae* from sterile body fluid	1
Ramani *et al*[70]	United States	1994-2001	Hospital discharges for IPD	A significant decrease was observed only for children aged < 1 yr (from 40 per 100000 to 23 per 100000 person years). All other age groups did not show a significant change in discharge rates for IPD
Rendi-Wagner *et al*[71]	Austria	2001-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Rodenburg *et al*[72]	Netherlands	2004-2008	Isolation of *S. pneumoniae* from sterile body fluid	1
Rückinger *et al*[73]	Germany	1997-2003 2007-2008	Isolation of *S. pneumoniae* from sterile body fluid	1
de Sevilla *et al*[74]	Spain	2007-2009	Isolation of *S. pneumoniae* from sterile body fluid	An increase of 44% of IPD (95%CI: 10%-89%) was shown
Shafinoori *et al*[75]	United States	1998-2004	Isolation of *S. pneumoniae* from sterile body fluid	A significant 68% and 70% decrease of IPD in children < 2 yr and aged 2 to 4 yr respectively was observed
Shah *et al*[76]	United States	1999-2003	Hospital discharges for IPD	A significant decrease from 12.03 per 100000 person-years in 1999 to 5.60 per 100000 person-years in 2003 was shown
Techasaensiri *et al*[77]	United States	1999-2008	Isolation of *S. pneumoniae* from sterile body fluid	The incidence of IPD significantly decreased in children < 2 yr
Tsai *et al*[78]	United States	1994-1999 2001-2004	Hospital discharges for pneumococcal meningitis	The average annualized rates of hospitalizations decreased from 7.7 per 100000 to 2.6 per 100000 in children < 2 yr and from 0.9 per 100000 to 0.5 per 100000 in children aged 2-4 (a reduction of 66%, 95%CI: 56.3%-73.5% and of 51.5%, 95%CI: 28.9%-66.9% respectively)
Tsigrelis *et al*[79]	United States	1995-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Tyrrell *et al*[80]	Canada	2000-2006	Isolation of *S. pneumoniae* from sterile body fluid	IPD due to vaccine serotypes decreased of 61% in children < 2 yr (from 96.7 per 100000 person-years to 25.8 per 100000 person-years) and of 57% in children from 2 to 4 yr (from 24.5 per 100000 person-years to 10.6 per 100000 person-years)
Van der Linden *et al*[81]	Germany	1997-2010	Isolation of *S. pneumoniae* from sterile body fluid	IPD incidence decreased from 2.4 per 100000 to 0.3 per 100000
Vestrheim *et al*[82]	Norway	2002-2007	Isolation of *S. pneumoniae* from sterile body fluid	1
Weatherholtz *et al*[83]	United States	1995-2006	Isolation of *S. pneumoniae* from sterile body fluid	Rates of IPD due to vaccine serotypes among children aged < 1 yr, 1-2 yr, and 2-5 yr decreased from 210, 263, and 51 cases per 100000 respectively in to 0 case per 100000
Whitney *et al*[84]	United States	1998-2001	Isolation of *S. pneumoniae* from sterile body fluid	1

Winters *et al*[85]	Canada	2002-2005	Isolation of *S. pneumoniae* from sterile body fluid	The incidence of IPD decreased from 54 per 100000 person-years to 16 per 100000 person-years (decrease of 70%). An even stronger decrease was observed in children < 1 yr, where the incidence decreased from 135 per 100000 to 15 per 100000 person-years (decrease of 89%)
Yildirim *et al*[86]	United States	2007-2010	Isolation of *S. pneumoniae* from sterile body fluid	IPD cases due to vaccine serotypes decreased

[1]Studies included in the meta-analysis. IPD: Invasive pneumococcal disease; CDC: Centers for Disease Control and Prevention; IRR: Incidence rate ratio; PCV7: 7-valent pneumococcal conjugate vaccine; *S. pneumoniae*: *Streptococcus pneumoniae*.

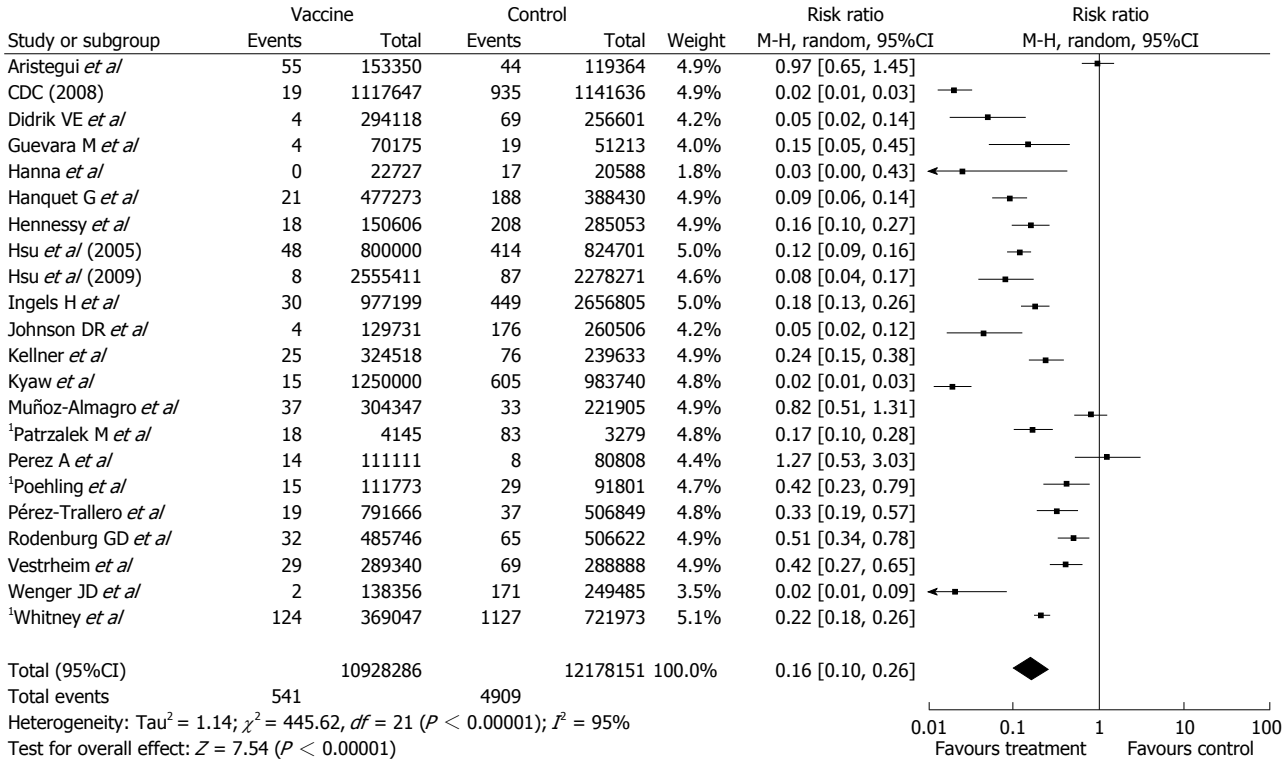

Figure 2 Data combination for invasive pneumococcal disease due to vaccine serotypes. [1]Data available not for the entire age group < 5 years. CDC: Centers for Disease Control and Prevention.

The results of our study are aligned with the evidence on the efficacy of PCV7 demonstrated in randomized clinical trials (RCT). In fact, a meta-analysis of RCT conducted by Pavia *et al*[15] showed an efficacy of 89% in preventing IPD due to vaccine serotypes, and of 63%-74% in preventing IPD due to all serotypes. Indeed, as IPD due to vaccine serotypes, effectiveness data have confirmed efficacy data. With this respect it is important to point out that the assessment of efficacy of interventions is critical in order to decide upon their adoption and is addressed through explanatory clinical trials[87]. Notwithstanding, the proof of efficacy is not always sufficient because it is also important to have evidence about how interventions work under more natural field conditions rather than in controlled clinical trials[87,88]. Indeed, overall effectiveness of interventions should be assessed by different study designs able to maximize external validity[87].

As far as PCV7 is concerned, all post-marketing studies showed that the incidence of IPD due to vaccine serotypes declined significantly after the implementation of vaccination, with the exception of few studies[36,27,49,63,65] showing a stability or a slight increase. As a consequence, the implementation of vaccination has definitively contributed in consistently preventing IPD in children up to 5 years of age with a strong impact on population health and costs due to hospitalizations[89,90]. In fact, a relevant reduction of IPD due to all serotypes was also shown by the meta-analysis even though, comparing with IPD due to vaccine serotypes, more studies highlighted a stability or an increase in the overall incidence of IPD[26,32,38,45,48,52,63,65,66,70-72,74,79]. In particular two studies[64,75] showed a significant increase although due to non-vaccine serotypes and in a context of low vaccination coverage. The increase in the incidence of non-vaccine serotypes is a well-known phenomenon which may be counteracted by the extension of serotypes coverage. In this view the availability and the implementation of PCV13 is useful in order to further reduce the incidence of IPD. In fact, the post-licensure assessment already carried out by Andrews *et al*[23] estimated that the effectiveness of at least 2 doses of

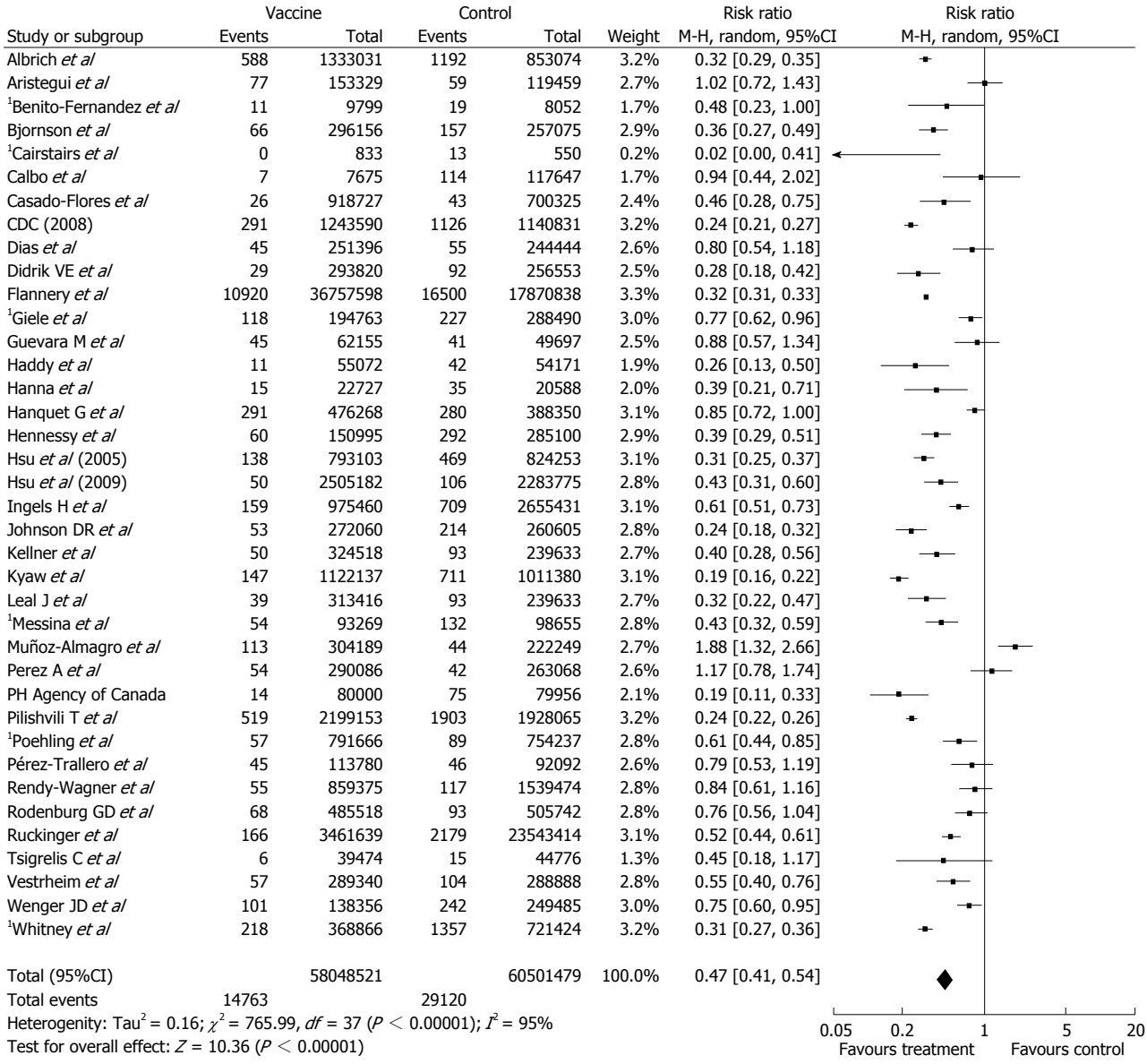

Figure 3 Data combination for invasive pneumococcal disease due to all serotypes. [1]Data available not for the entire age group < 5 years. CDC: Centers for Disease Control and Prevention.

PVC13 before 12 mo of age or of 1 dose from 12 mo onwards was 90% (95%CI: 34%-98%) against PCV7 serotypes. This result is aligned with data from our and Pavia *et al*[15] meta-analyses. Furthermore, PCV13 was shown to have an effectiveness of 73% (95%CI: 55%-84%) against the additional serotypes included in the vaccine[23]. PCV13 may indeed provide an added value in comparison to PCV7. In fact, already available population-based studies showed that IPD decreased of a percentage from 18% to 42% when PCV13 era is compared to PCV7 one[18,20,21]. The decline is more important in children less than 2 years of age in which the decrease in all IPD varies from 50% to 60%[18,20,21].

This study presents some limitations. The research was limited to only two specialized searching engines and, consequently, selection bias may be not excluded. Papers included in the review were heterogeneous with respect to countries and study design as also highlighted by the test of heterogeneity. Crude data were not obtainable from all the papers selected and only children < 5 years of age, independently by their health status, were considered in the analysis. Furthermore, neither a quality assessment nor stratified analyses in order to investigate heterogeneity were performed.

Strengths of this study are represented by the objective itself, because we focused on effectiveness instead of efficacy, and the large number of papers included in the analysis.

The consistent decrease of IPD due to vaccine serotypes after the PCV7 implementation is important as the new PCV13 is being implemented. In fact, it is expected that it will have the same effectiveness in preventing IPD due PCV7 vaccine serotypes and it will also have an important impact on cases due to new vaccine

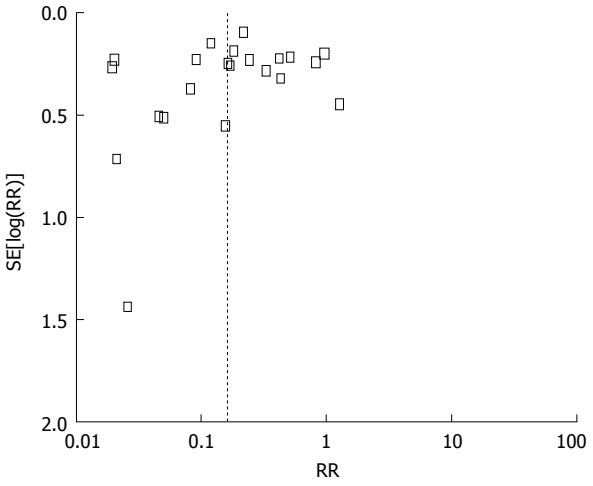

Figure 4 Funnel plot of studies on invasive pneumococcal disease due to vaccine serotypes. RR: Relative risk.

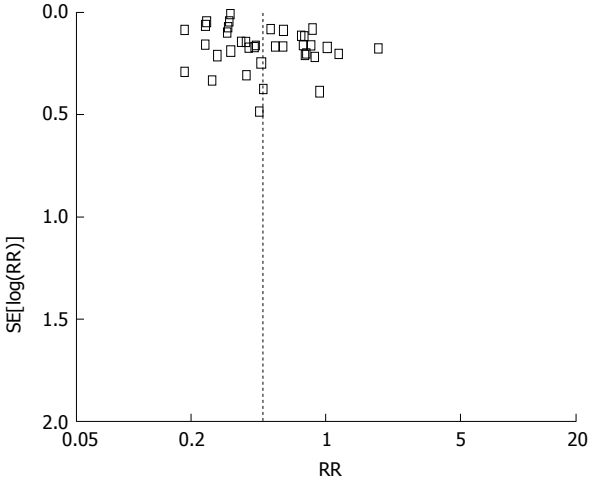

Figure 5 Funnel plot of studies on invasive pneumococcal disease due to all serotypes. RR: Relative risk.

serotypes[91,92].

COMMENTS

Background

Streptococcus pneumoniae (*S. pneumoniae*) is a leading cause of severe bacterial infectious disease, causing 1.4-1.6 million child deaths annually, in that around 11% of all deaths in children < 5 years. Two types of vaccines against *S. pneumoniae* exist, polysaccharide (PPV) and conjugate (PCV), even though the PPV vaccine is ineffective in children < 2 years old. PCV vaccines encompass the 7-valent vaccine (PCV7), the PCV10 and the PCV13. Currently, PCV13 is used in prevention campaigns. Its marketing authorization in the European Union goes back to December 2009 and it has replaced PCV7 from 2010 onward. Because of the recent introduction and implementation of PCV13, consistent data from real practice are only available for PCV7 and their assessment is of utmost importance in order to monitor the health impact of the vaccine.

Research frontiers

The monitoring of the overall health impact of technologies and policies is a key issue in medicine. It is mainly based on post-marketing studies on the effectiveness of interventions carried out through the collection and analysis of data from the real practice. In this context, the objective of the authors study was to perform a systematic review and a meta-analysis of post-marketing studies on the effectiveness of PCV7 worldwide.

Innovations and breakthroughs

The authors' findings showed that the effectiveness of PCV7 in reducing invasive pneumococcal disease (IPD) is 84% with respect to IPD due to vaccine serotypes and 53% with respect to IPD due to all serotypes. Concerning IPD due to vaccine serotypes, effectiveness data have confirmed efficacy data previously reported in a meta-analysis of randomized clinical trial conducted by Pavia *et al*. However, with this respect, it is important to emphasize that efficacy trials test the expected results of an intervention under ideal circumstances whereas effectiveness studies measure the beneficial effects under "real world" clinical settings. Indeed, the results of their meta-analysis represent and advance in the knowledge of PCV7 impact.

Applications

Given the consistent decrease of IPD due to vaccine serotypes after the PCV7 implementation, results of their systematic review and meta-analysis allow forecasting that the new PCV13, which is being implemented, will further decrease the number of IPD. In fact PCV13 effectiveness is expected to be the same as PCV7 in preventing IPD due to both PCV7 vaccine serotypes and new vaccine serotypes.

Terminology

IPD is defined as the isolation of *S. pneumoniae* from a sterile site/body fluid.

Peer-review

The authors performed an interesting and well-written meta-analysis on a highly relevant topic.

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META-ANALYSIS

Is the traditional Chinese medicine helpful for patients with hematologic malignant diseases? A meta-analysis of randomized controlled trials

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Abstract

AIM: To evaluate the efficacy of traditional Chinese medicine (TCM) for the treatment of hematologic malignant diseases.

METHODS: We searched the Cochrane CENTRAL, PubMed, Embase, Web of Science, AMED, CNKI, Wanfang Platform; China Sinomed and the clinical trial registry web sites and Googlescholar electronically up to June 19th, 2014 and hand searched related publications. Only randomized controlled trials (RCTs) researching on whether TCM as the adjuvant treatment improved the effect for hematologic malignant diseases were included. Two reviewers extracted data and evaluated the studies independently. Pooled risk ratios (RR) were calculated as outcome measures. Our primary outcomes were the overall response (OR) rate.

RESULTS: We retrieved 13143 references and included 11 RCTs involved 891 participants after screening. Because the non-significant heterogeneity we used the fixed effect model to combine data and TCM had a significantly higher OR and CR (complete response) rates than the control [RR = 1.17, 95%CI: (1.10, 1.25), $P < 0.00001$; RR = 1.24, 95%CI: (1.11, 1.37), $P < 0.0001$, respectively]. Only three studies included in the survival rate analysis. We combined them with random effects model and there was no significant difference between the TCM and control arms. Because

of the low heterogeneity we used the fixed effect model to combine the non-hematologic adverse effects (AEs) data. Our results showed that TCM significantly decreased non-hematologic AEs rates we researched, the gastrointestinal reaction [RR = 0.50, 95%CI: (0.37, 0.68), $P < 0.0001$], liver and/or kidney injury [RR = 0.37, 95%CI: (0.26, 0.53), $P < 0.00001$] and heart injury [RR = 0.24, 95%CI: (0.09, 0.68), $P = 0.007$]. Additionally, TCM had a trend to decrease the infection rate [RR = 0.16, (0.02, 1.12), $P = 0.07$], but not statistically significantly.

CONCLUSION: TCM increases OR and CR rates for hematologic malignances and reduces treatment associated serious non-hematologic AEs. Therefore, TCM should be included in the treatment of hematologic malignances.

Key words: Hematologic malignant disease; Leukemia; Lymphoma; Chinese medicine

Core tip: We pooled all the studies complied to our inclusion criteria that were retrieved by extensively searching the related databases, journals and websites. Our result suggested that adding traditional Chinese medicine (TCM) increased overall response and complete response rates for malignant hematologic diseases treatment. Although it was based on the evidence of low level of GRADE quality, our result demonstrated that TCM reduced treatment associated serious non-hematologic adverse effects (AEs). Furthermore, considering the rare AEs and drugs interactions, TCM should be included in the hematologic malignances treatment, at least for adult acute leukemia.

Qian CL, Yan F, Song YZ, Li D, Dong KZ, Zhu YM. Is the traditional Chinese medicine helpful for patients with hematologic malignant diseases? A meta-analysis of randomized controlled trials. *World J Meta-Anal* 2015; 3(3): 163-180 Available from: URL: http://www.wjgnet.com/2308-3840/full/v3/i3/163.htm DOI: http://dx.doi.org/10.13105/wjma.v3.i3.163

INTRODUCTION

The incidence and mortality of malignant tumors have increased greatly in recent years[1]. Albeit the treatment methods of malignant diseases progress quickly the general prognosis of this kind of diseases is poor[1]. Whereby the hematologic malignancies have a particular high-grade malignancy and are systemic diseases that are common to involve multiple systems and organs. Hence, the systemic chemotherapy with western medicine becomes the standard treatment of these kind of diseases[2]. However, the same as other malignant diseases, even in nowadays, the response and survival rates are still not ideal[3,4]. As well as the chemotherapy always causes serious adverse effects (AEs), such as Ⅲ-Ⅳ grade bone marrow suppression, serious nausea and vomiting, hepatic and renal dysfunction and heart injury etc. Attempts to improve therapy by intensifying the number of chemotherapeutic agents or their doses lead only to increase side effects[5]. Even the targeted molecular therapy developed in recent years also causes obvious side effects. For example, the rituximab increases the response rate and survival time for B cell lymphoma[6,7], alternatively, it will obviously suppress the bodies' normal immune response to pathogens for a long period of more than one year. As a result of it, patients who received it are sensitive to infection and sometimes it is fatal[8,9]. And furthermore, in most conditions, these new medicines need to be administered with chemotherapy together not to mention the tumor cells will become resistant to the therapy after treated for a period[10].

On the other hand, many studies reported that adding traditional Chinese medicine (TCM) into the malignant diseases treatment strategy not only increased the response rate but also significantly lowered the treatment associated AEs rate[11-14]. There are a variety of herbs being used in different combinations and forms, such as oral administration and intravenous injection for hematologic malignancies yet. Many randomized controlled studies have shown that TCM as the adjuvant agent improved the malignant hematologic diseases response and reduced the AEs associated with chemotherapy[15]. But most of the published studies were small sample sized and the results were not consensus. So we wrote the meta-analysis to evaluate the efficacy of TCM for the treatment of hematologic malignant diseases.

MATERIALS AND METHODS

This meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement issued in 2009 (Table 1).

Inclusion criteria

We only included randomized controlled trials (RCTs) that researched on whether TCM as the adjuvant treatment improved the effect for malignant hematologic diseases. There was no age, sex, race, complicated diseases or language limits of the study. Our primary outcomes were the overall response (OR) rate calculated by summating the complete response (CR), partial response and stable disease rates. The survival and serious AEs rates and the change of quality of life were our secondary outcomes. The diagnosis must be confirmed by pathological sections or bone marrow smears.

Since some TCMs for acute promyelocytic leukemia treatment, such as the compound Huang Dai Tablets, have been administered as the primary maintenance treatment, not the adjuvant treatment and their active ingredients has been recognized as Tetraarsenic tetra-

Table 1 The Preferred Reporting Items for Systematic Review and Meta-Analysis checklist

Section/topic	*n*	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	3-4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (*e.g.*, Web address), and, if available, provide registration information including registration number	
Eligibility criteria	6	Specify study characteristics (*e.g.*, PICOS, length of follow-up) and report characteristics (*e.g.*, years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (*e.g.*, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	5-6, Table 2
Study selection	9	State the process for selecting studies (*i.e.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6-7
Data collection process	10	Describe method of data extraction from reports (*e.g.*, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	7
Data items	11	List and define all variables for which data were sought (*e.g.*, PICOS, funding sources) and any assumptions and simplifications made	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6-7
Summary measures	13	State the principal summary measures (*e.g.*, risk ratio, difference in means)	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g.*, I^2) for each meta-analysis	7

PICOS: Participants, interventions, comparisons, outcomes, and study design.

sulfide we did not include these studies. The efficacy and safety of this kind of TCM is the focus of our next study.

Searching method

YS and CQ searched the following databases independently, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, PubMed, Embase, Web of Science, Allied and Alternative Medicine (AMED), Googlescholar, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform; China biomedical literature service system (Sinomed); and the well-known clinical trial registry sites (http://www.clinicaltrial.gov/; http://apps.who.int/trialsearch/). The electronic search was up to June 19th, 2014. The detailed searching strategy for PubMed was recorded in Table 2.

We specified three searching themes: First, we searched TCM related words, we used the terms "complementary medicine", and the free words "tradition or tradition* or china or chinese or herb or herbal or complement* or tcm or 'zhong yi' or chm or ethno* or folk or home or indigenous or primitive or materia* or nosod* or east or eastern or orient or oriental or Asian or Korea* or Tibet* or herbaceous or plant or plants or botan* or kampo or mongol* or phytogenic or phytotherapy or alternative"; Second, we searched hematologic diseases related words, we used the terms "leukemia" or "lymphoma" or "multiple myeloma", and the free words "hemotolog* or anemia or thrombocytopen* or pancytope* or 'bone marrow'or transplant or 'stem cell' or 'leukemia or lymphoma' or cancer or dysplas* or malignant or hyperplas* or hypoplas* or myelom* or Hodgkin or non-Hodgkin or blast or blasts or 'progression free survival (PFS)' or 'disease free survival (DFS)' or 'overall survival (OS)' or OS or PFS or DFS or chemotherapy or (chemical treatment) or radiotherapy or irradia* or oncolog* or monoclon*"; and third, we used the Cochrane highly sensitive search filters to retrieve randomized trials in Medline and Embase[16].

We also hand searched other journals that might publish relative clinical trials, PubMed related articles, reference lists of retrieved articles. Considering there might be some ongoing studies which did not register in the clinical trial registry sites and some finished studies which did not published, we contacted some researchers, relative manufacturers and specialists for further information of unpublished trials. Our study did not set limits of ages, sexes, races, published languages and

Table 2 The PubMed searching strategy

(1) "Complementary therapies" (Mesh)
(2) Tradition or tradition* OR china or chinese OR herb or herbal OR complement* or tcm or "zhong yi" or chm or ethno* or folk or home or indigenous or primitive or materia* or nosod* or east or eastern or orient or oriental or asian or Korea* or Tibet* or herbaceous or plant or plants or botan* or kampo or mongol* or phytogenic or phytotherapy or alternative
(3) Medicine or medicinal or medical or remed* or therapy or therapies or therapeutic or therapeutics or therapist or treat or treatment or drug or drugs
(4) (2) and (3)
(5) (1) or (4)
(6) Leukemia or lymphoma or "multiple myeloma" (mesh)
(7) Hemotolog* or anemia or thrombocytopen* or pancytope* or "bone marrow" or transplant or "stem cell"
(8) Leukemia OR lymphoma OR cancer OR dysplas* OR malignant OR hyperplas* OR hypoplas* or myelom* or Hodgkin or non-hodgkin or blast or blasts or "progression free survival" or "disease free survival" or "overall survival" or OS or PFS or DFS or chemotherapy or (chemical treatment) or radiotherapy or irradia* or oncolog* or monoclon*
(9) (7) and (8)
(10) (6) or (9)
(11) (((((Randomized controlled trial [Publication type]) OR controlled clinical trial [Publication type]) OR (randomized or placebo[Title/Abstract])) OR drug therapy [MeSH Subheading]) OR (randomly or groups or trial [Title/Abstract])) OR rct
(12) Animals [mh] NOT humans [mh]
(13) (11) not (12)
(14) (5) and (10) and (13)
(15) (Cancer or carcinoma or sarcoma)[ti]
(16) Carcinoma[mesh] or sarcoma[mesh]
(17) (14) not (15) or (16)

Table 3 Characteristics of Dian Rong 2009 study

Methods	A randomized double blind placebo controlled Ⅰ multicenter study
Participants	Refractory acute leukemia patients
Interventions	TCM group: Combine Chinese interventions with standard chemotherapy of western medicine Control group: Standard chemotherapy with western medicine
Outcomes	The primary outcome: the response rate

TCM: Traditional Chinese medicine.

regions.

Data extraction, evaluation and analysis

YS and CQ extracted data from the retrieved studies. Then they independently used the Cochrane Collaboration tool for assessing risk of bias[17] to assess the quality of the trials (Tables 3-24). The tool comprised of seven specific domains (named sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other issues). We only included studies in "low risk" of bias in the randomization sequence generation and did not show high risks in any other domains. We used the funnel plot to detect the publication bias. If it was symmetrical we considered there was no publication bias, or else, we considered there was publication bias. If there was some disagreement between the two authors, they would resolve it by discussion.

We analyzed the included data with the Revman software (Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). We used the relative risk (RR) to evaluate the outcomes. If there was not significant heterogeneity between the included studies (detected by the P value of the χ^2 test over 0.10 and $I^2 \leqslant 25\%$) we used the Mantel-Haenszel fixed effect model to analyze data. If there was significant heterogeneity (detected by the P value was less than 0.10 and/or $I^2 \geqslant 50\%$) we detected if there was clinical heterogeneity. In the condition of absence of clinical heterogeneity we pooled data with random effects model. If $P \geqslant 0.10$ and $25\% \leqslant I^2 \leqslant 50\%$, we decided to choose the fixed effect or random effects models to combine data by discussion. Considering there might be clinical heterogeneity between different diseases we performed subgroup analyses (studies were divided into four subgroups: the adult acute leukemia, chronic myelogenous leukemia, lymphoma and pediatric acute myeloid leukemia subgroups). We also used sensitivity analyses to assess the association of the quality of included studies and the clinical characteristics. A two-sided P value of less than 0.05 was considered as a significant difference. We also used the GRADE grid to evaluate the quality of evidence on the primary outcome.

Statistical analysis

Technical appendix, statistical code, and dataset available from the corresponding author at yandgics@126.com. The article was reviewed by the statistician Xiaoxiao Wang. In her opinion, the RR rate was suitable, the heterogeneity of the included articles was effectively detected and the appropriate pooling methods (the random effects model or fixed effect model) was chosen for the systematic review. He also supported using the funnel plot to detect the publication bias.

RESULTS

We searched 13143 references in total. There were 367 papers retained after we examined the titles and abstracts. We excluded 347 references in the further assessment with the reason of that focused on the solid

Table 4 Risk assessment of Dian Rong 2009 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Central randomized Comment: Probably done. Several studies published by this research group reported reliable randomization method
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: A double-blind and placebo controlled Comment: Probably done. Several studies published by this research group reported reliable method to warrant the double blindness
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival time are objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 5 Characteristics of Xiu Mei 1997 study

Methods	A randomized controlled study
Participants	Non-Hodgkin lymphoma patients
Interventions	TCM group: Standard chemotherapy + traditional Chinese medicine Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

tumors but not the hematologic malignancies, were not real RCTs, did not report the primary outcome of our study or clearly described the randomization methods, and had other reasons that did not conform our inclusion criteria[18-20]. Finally all the reviewers agreed 11 studies[15,21-35] involved 891 participants should be included for meta-analysis (Figure 1).

Characteristics of included trials

The 11 included studies all compared the OR rate between the addition of TCM or not in the treatment of hematologic malignant diseases, such as acute leukemia, lymphoma, *etc.* Seven studies[15,21,24-31,33,34] researched the effect of adding TCM to the standard treatment for adult acute leukemia patients. Among the 7 studies, Mao Sheng 2007, Chuan Xin 2013, Ji Hong 2011, Rui Rong 2004 and Wen Jiang 2010[26,27,29,30,32,34] focused on acute myeloid leukemia. [Wang, 2007 #18; Wang, 2007 #9; Xu, 2010 #11; Zhu, 2011 #21]. The rest two studies did not restrict the type of the acute leukemia (lymphoblastic or non-lymphoblastic). Only one study Chuan Xin 2013[32] focused on pediatric acute myeloid leukemia patients while no study focused on pediatric acute lymphoblastic leukemia patients. Also only one study Xiu Mei 1997[35] focused on lymphoma patients. Two studies (sHai Yan 2007 and sWei Hong 2013)[22,23] focused on chronic myelogenous leukemia patients. But the basic treatment of the two studies were the hydroxyurea and/or a-interferon treatment but not the tyrosine kinase inhibitors which was the standard treatment recently[36]. Hence we did a sensitivity analysis of excluding the two studies. There was not study included was about the multiple myeloma (MM) or myelodysplastic syndrome (MDS). Only the study Dian Rong 2009[15] published one article in English, all of the rest studies were published in Chinese. Only one study reported the quality of life hence we did not analyze this outcome. There was not significant difference in the demographic characteristics of the two treatment groups in the 11 included studies (Table 25).

Quality of included trials

Five studies (Dian Rong 2009; Ying Fei 2005; Su Juan 2005; Mao Sheng 2007; Rui Rong 2004)[15,21,24-29,31,33] were multi-center double-blind RCT studies. The rest six studies[22,23,30,32,34,35] were single center studies and did not use the blind method. All of the included studies were not large sampled with the largest sample size (Xiu Mei 1997)[35] was 167 and the smallest sample size was 18 (sHai Yan 2007)[22]. All of the included studies did not use the intention to treat strategy to analyze results. There was no other factors influenced the quality of included studies. The funnel plot of the primary outcome was symmetric (Figure 2 and Tables 3-24, 26).

Efficacy analysis

Studies in both the OR and CR meta-analyses did not show significant heterogeneity so we combined data with the fixed effect model. The efficacy analyses showed the TCM arm had a significantly higher OR rate than the control arm (RR = 1.17 with a 95%CI: (1.10, 1.25), $P < 0.00001$) (Figure 3). The higher response rate was also statistically significant in the sensitivity analysis of excluding the two chronic myelogenous studies (RR = 1.17, 95%CI: (1.09, 1.26), $P < 0.00001$). As for the CR rate, the TCM arm was significantly higher than the control group as well [RR = 1.24, 95%CI: (1.11, 1.37), $P < 0.0001$] (Figure 4). And also it was

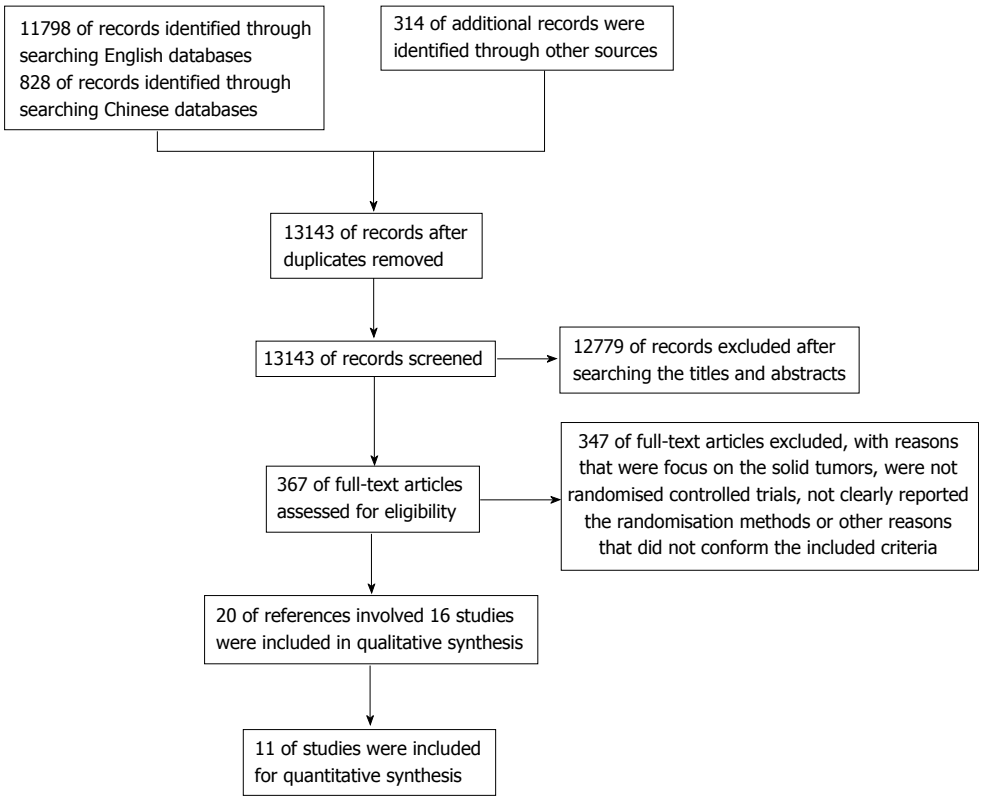

Figure 1 Study selection.

Table 6 Risk assessment of Xiu Mei 1997 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The random sequence produced by rolling the dice Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 7 Characteristics of Ji Hong 2011 study

Methods	A randomized controlled study
Participants	Initial treat old AML patients
Interventions	TCM group: HAG + TCM Control group: HAG
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine; AML: Acute myeloid leukemia; HAG: Homoharringtonine + cytoarabine + granulocye colony stimulating factor.

not changed in the sensitivity analysis that excluded the two chronic myelogenous leukemia studies [RR = 1.21, 95%CI: (1.08, 1.35), P = 0.0007]. However, the Summary of findings (SoF) table showed the quality of the evidence was low (Table 27). There were three studies[15,21,25-27,35] reported the survival rate. The pooled results of the three studies did not show significant difference between the TCM arm and the control arm [RR = 1.22, 95%CI: (0.77, 1.94), P = 0.40] (Figure 5). Studies included in this analysis reported the survival rate of different period and the heterogeneity was significant. As a result of it, we used the random effects model to pool data.

Table 8 Risk assessment of Ji Hong 2011 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: 7 participants in 53 randomized lost to follow-up Comment
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 9 Characteristics of Ying Fei 2005 study

Methods	A multicenter double-blinded randomized controlled study
Participants	Initial treat leukemia patients
Interventions	TCM group: standard chemotherapy + Shen Qi Fu Zheng Ye Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

Serious AEs analysis

Our study demonstrated the TCM arm had a significantly less non-hematologic serious AEs rates in the gastrointestinal reaction [RR = 0.50, 95%CI: (0.37, 0.68), $P < 0.0001$], liver and/or kidney injury [RR = 0.37, 95%CI: (0.26, 0.53), $P < 0.00001$] and heart injury [RR = 0.24, 95%CI: (0.09, 0.68), $P = 0.007$] analyses (Figure 6). Additionally, the TCM showed a trend of reducing the infection rate [RR = 0.16, 95%CI: (0.02, 1.12), $P = 0.07$] but it was not statistically significant (Figure 7). The rates of Ⅲ-Ⅳ grade agranulocytosis and thrombocytosis were not different between adding TCM in the treatment method and not adding it [RR = 0.52, 95%CI: (0.14, 1.84), $P = 0.31$; RR = 0.52, 95%CI: (0.14, 1.91), $P = 0.33$, respectively] (Figure 7). Most of the included studies did not report the myelosuppression recovery time. So we did not analyze this outcome. In the non-hematologic serious AEs analyses, studies were pooled with the fixed effect model while in the hematologic AEs analyses, studies were pooled with the random effects model because of the significant heterogeneity. Because there were only two to three studies included in the serious AEs meta-analyses, we did not perform subgroup analysis to detect the clinical heterogeneity.

DISCUSSION

Oncologists begin to pay attention to the effect of TCM for the malignant diseases treatment in nowadays.

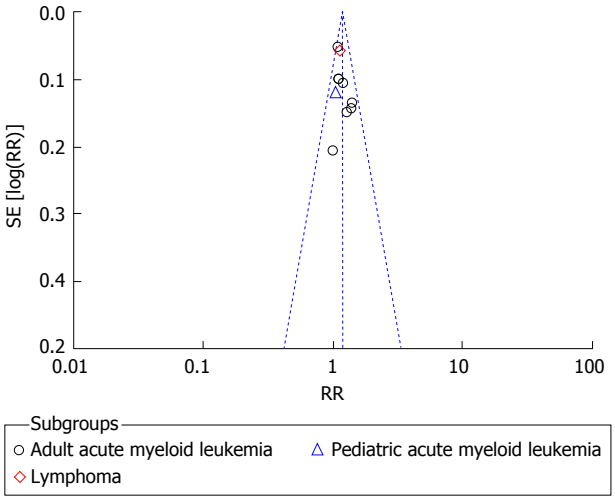

Figure 2 Funnel plot of the overall response meta-analysis. RR: Risk ratios.

Several meta-analyses revealed that TCM could improve response rate for some kinds of solid tumors[11-13]. There were also several RCTs showed that some TCM could increase the OR rate and decrease the AEs rate for hematologic malignancies. But the results published were not consistent[15,34]. At the same time there is not large sample sized RCT reported. As is generally accepted, meta-analysis attempts to identify all studies that would meet the eligibility criteria, subjectively assess the validity of the findings of the included studies and systematically present and synthesize the characteristics and findings of the included studies[37]. Therefore, it increases the sample size and reports a more reliable result. In The Oxford 2011 Levels of Evidence Table, meta-analysis of RCT has become the highest level of evidence[38]. In consequence, meta-analysis is a good method to evaluate the efficacy and safety of TCM for hematologic malignancies.

Response rate of TCM

Our results showed that TCM significantly increased the OR and CR rates. Although the GRADE SoF tables (Table

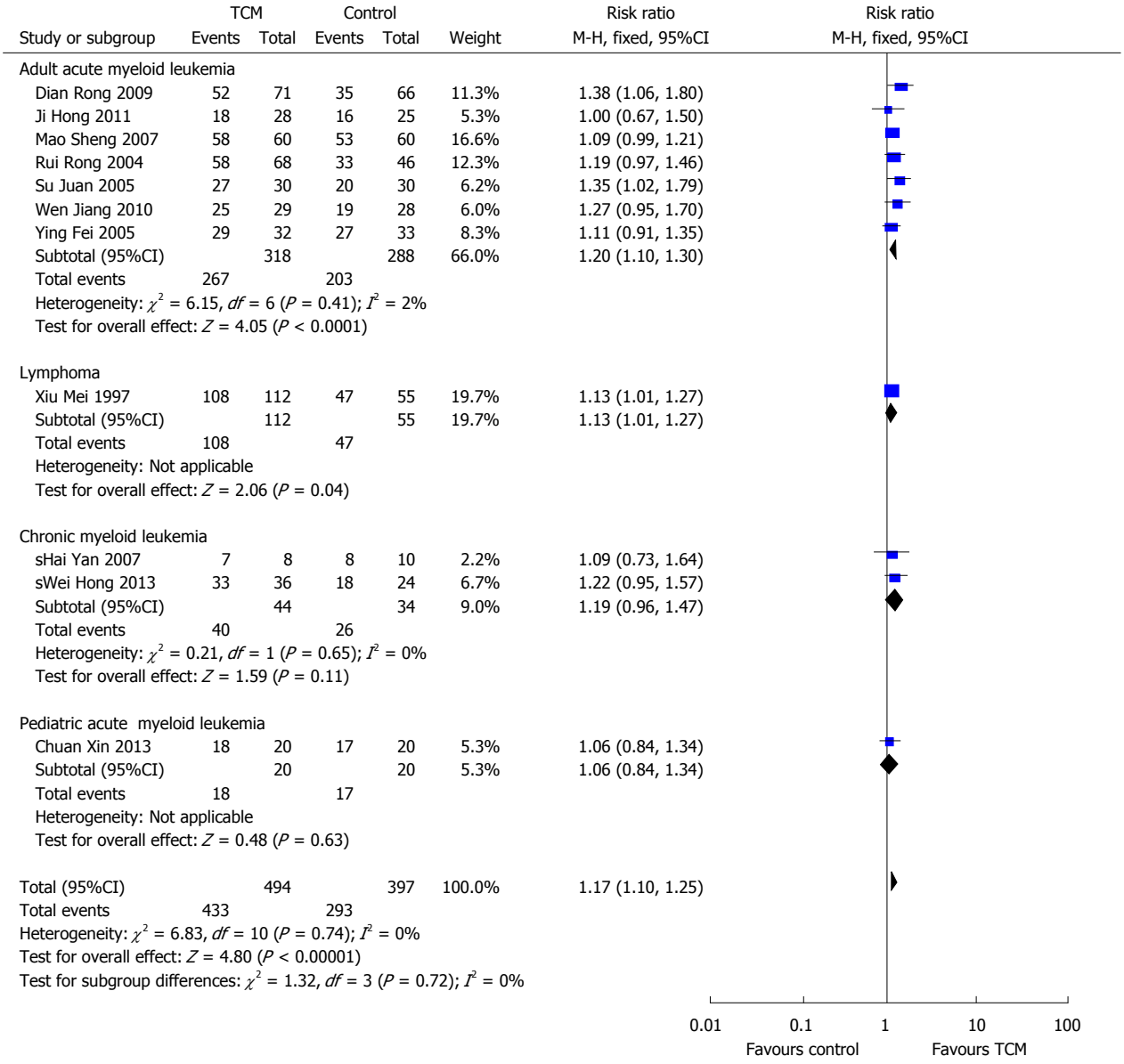

Figure 3 Overall response meta-analysis. TCM: Traditional Chinese medicine.

Table 10 Risk assessment of Ying Fei 2005 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Generate randomization sequence by drawing lots Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

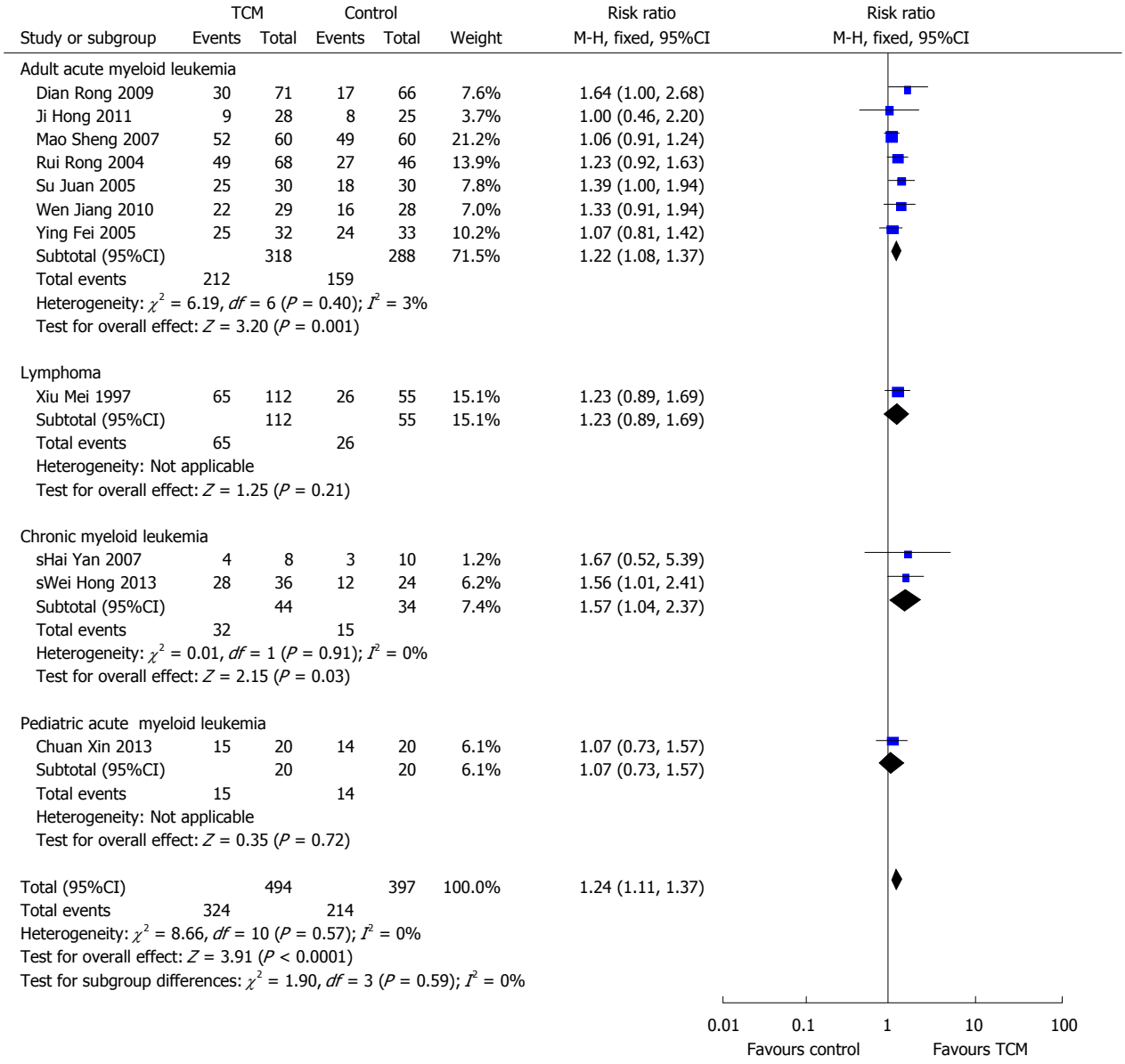

Figure 4 Complete response meta-analysis. TCM: Traditional Chinese medicine.

Table 11 Characteristics of Wen Jiang 2010 study

Methods	A randomized placebo controlled study
Participants	Initial treat acute leukemia patients
Interventions	TCM group: Standard chemotherapy + Shen Qi Qing Re Ke Li
	Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

27) showed the evidence quality of the two meta-analyses was low and the recommendation strength was weak (data not show), the TCM causes little side effects and it is economical. Furthermore, even though we included studies of different diseases there was not significant heterogeneity in the meta-analyses. So we could pooled data with the fixed effect model which made the result more reliable. Subsequently, it is suggested that TCM, as an adjuvant treatment method, can improve the efficacy of hematologic malignant diseases treatment.

However, there were two studies included in the chronic myelogenous leukemia subgroup prescribed the hydroxyurea or interferon as the fundamental treatment rather than the tyrosine kinase inhibitors which should be the first choice[36] nowadays. We excluded the two studies in the sensitivity analyses and then we got the same result that the TCM arm had significantly higher response rates (both OR and CR) than the control arm. The results of the sensitivity analyses strengthened the evidence that the response rate could be increased by adding TCM for hematologic malignancies. But there was only one study included in the pediatric acute myeloid leukemia and lymphoma subgroups and no studies on MM and MDS. As it was shown in the efficacy forest, the better effect of the TCM was mainly contributed by

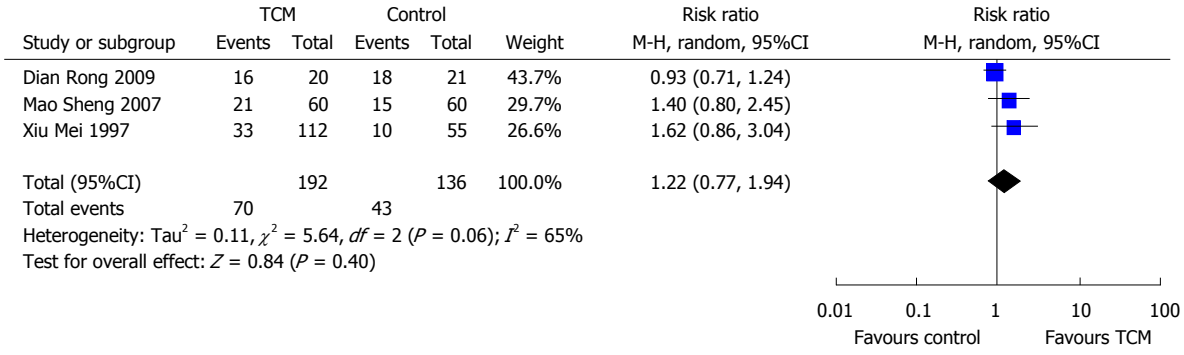

Figure 5 Survival rate meta-analysis. TCM: Traditional Chinese medicine.

Table 12 Risk assessment of Wen Jiang 2010 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 13 Characteristics of Su Juan 2005 study

Methods	A multicenter randomized controlled study
Participants	Acute leukemia
Interventions	TCM group: Standard chemotherapy + TCM Qing Re Jie Du Kang Bai Fang Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

Table 14 Risk assessment of Su Juan 2005 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

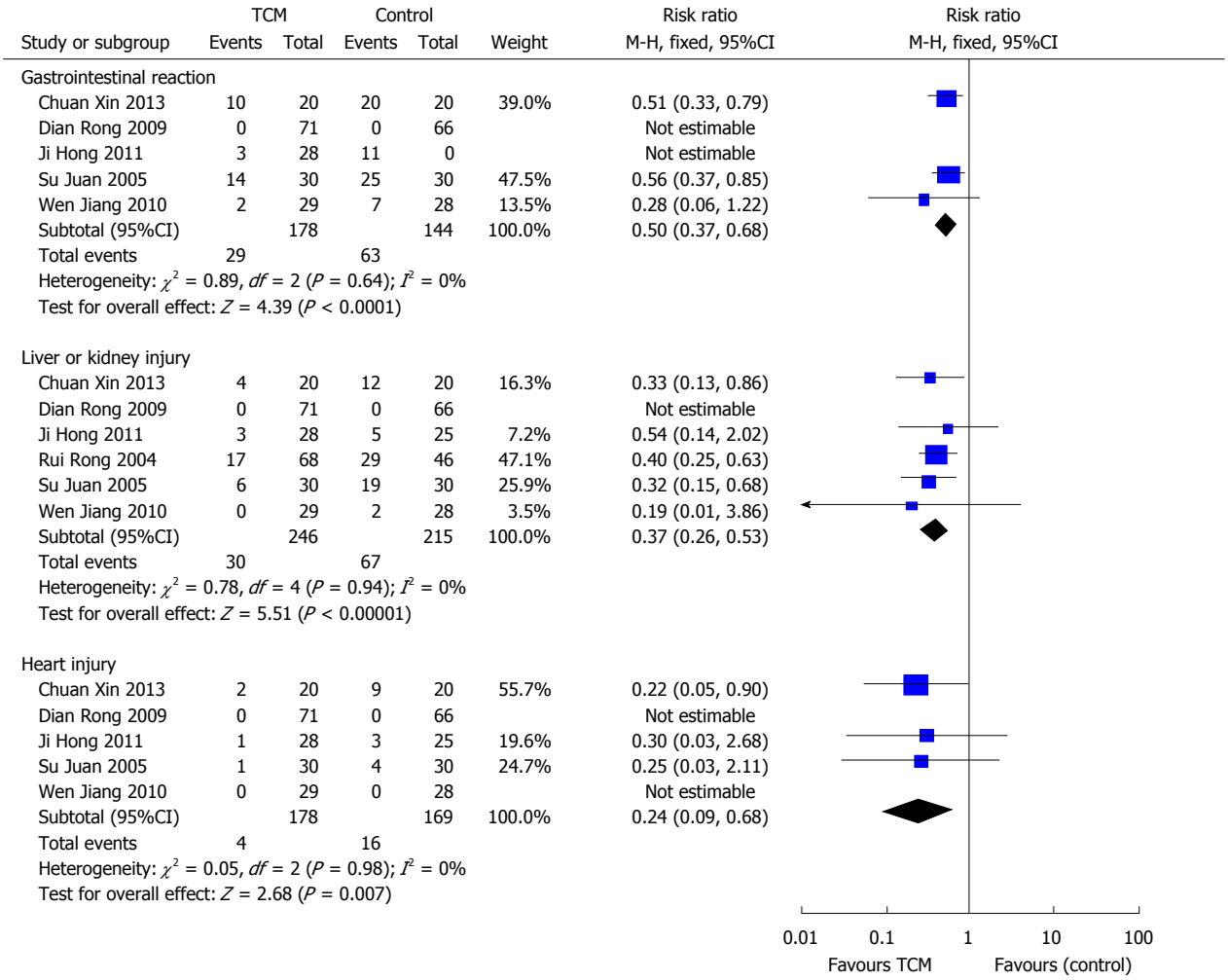

Figure 6 Non-hematologic serious adverse effects meta-analysis. TCM: Traditional Chinese medicine.

Table 15 Characteristics of Mao Sheng 2007 study

Methods	A multicenter double-blinded randomized placebo controlled study
Participants	Acute myeloid leukemia patients with micro residual disease
Interventions	TCM group: Standard chemotherapy + Yi Qi Jie Du Huo Xue Fang Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

the adult acute leukemia subgroup. For this reason we concluded TCM can be used as the adjuvant treatment for acute myeloid leukemia and there was in lack of studies on other hematologic malignant diseases, including chronic myelogenous leukemia.

Survival rate of TCM

There were only three studies with significantly heterogeneity involved 328 participants included in the survival rate meta-analysis. We did not show the difference between adding the TCM or not for treatment of malignant hematologic diseases. The result might because the small number of included studies was not enough to show a statistical significance or the addition of TCM can not change the survival rate. We need more high quality studies to clarify the problem. As a result of it, the data included was not enough to draw a conclusion of besides increasing the response rates, whether the addition of TCM can further improve patients survival rate.

Serious AEs rate of TCM

It is well known in the solid tumors treatment, TCM can decrease the AEs of chemotherapy[39], our results also showed that TCM significantly decreased the serious non-hematologic AEs and had a trend to reduce the serious infection rate. The result enhanced the role of TCM for hematologic malignant diseases treatment. Decreasing the serious non-hematologic AEs makes the chemotherapy safer and improves patients' tolerance

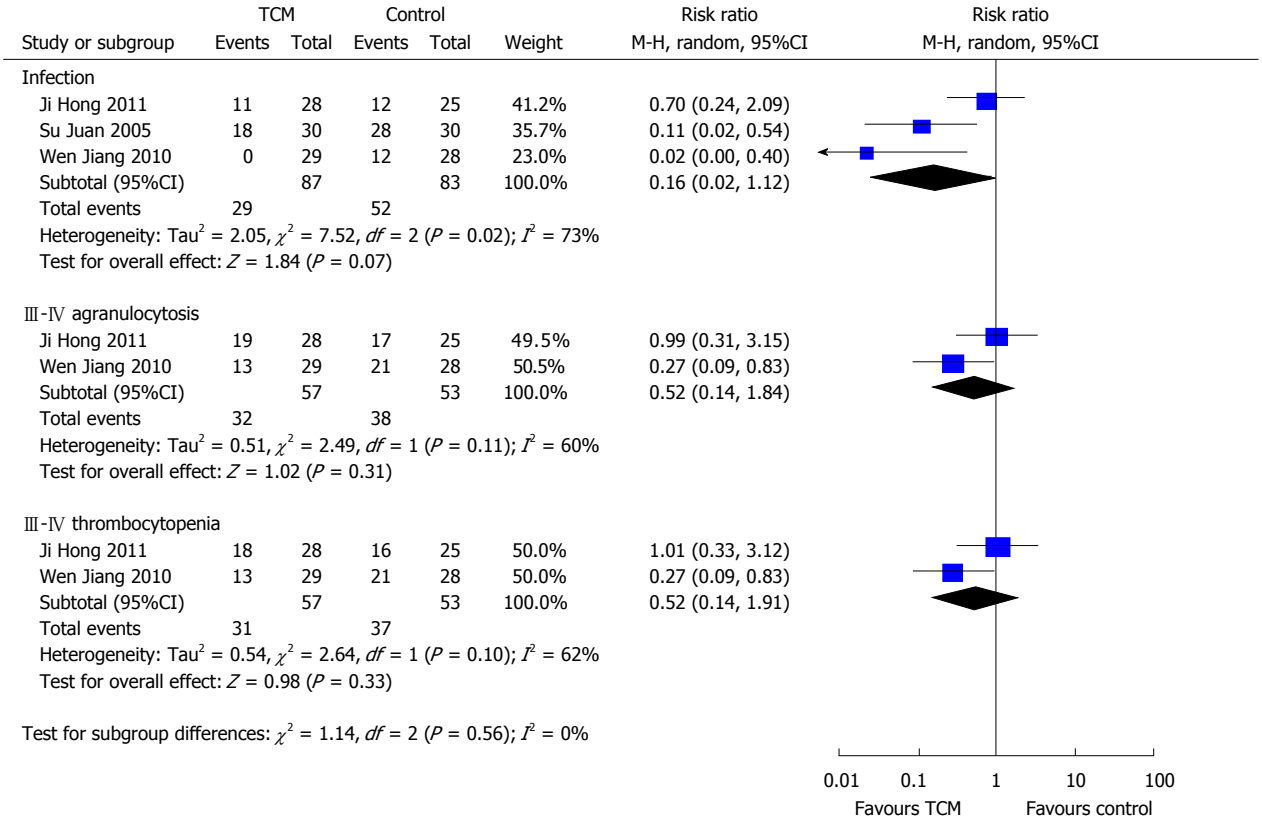

Figure 7 Hematologic serious adverse effects meta-analysis. TCM: Traditional Chinese medicine.

Table 16 Risk assessment of Mao Sheng 2007 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 17 Characteristics of Rui Rong 2004 study

Methods	A multicenter double-blinded randomized placebo controlled study
Participants	Acute myeloid leukemia
Interventions	TCM group: Standard chemotherapy + Yi Qi Yang Yin Qing Re Fa Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

and adherence. This point is especially important for hematologic malignant diseases because most of such patients do not have the opportunity of surgical operation and rely on chemotherapeutic treatment. Additionally, the chemotherapy usually has better effect for hematologic malignant diseases than solid tumors. Infection is the most common cause of death among patients with acute leukemia accounting for up to 75% of mortality[40]. In our study, we showed a trend of reducing infection rate but it was not statistically significant. Since the three included studies all showed better effect of TCM and two were statistically significant we inferred the reason might be there were not enough studies included. More data was

Table 18 Risk assessment of Rui Rong 2004 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 19 Characteristics of Chuan Xin 2013 study

Methods	A randomized controlled study
Participants	Child acute myeloid leukemia patients
Interventions	TCM group: Standard chemotherapy + traditional Chinese medicine Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

Table 20 Risk assessment of Chuan Xin 2013 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 21 Characteristics of sWei Hong 2013 study

Methods	A randomized controlled study
Participants	Chronic myeloid leukemia patients
Interventions	TCM group: A-interferon or hydroxyurea + TCM Control group: A-interferon or hydroxyurea
Outcomes	The primary outcome: The response rate

TCM: Traditional Chinese medicine.

needed to confirm whether it was the truth. There were only two studies included in the serious hematologic AEs meta-analyses and we were in need of more studies to clarify this question.

Comparison with other studies

Our study result was consistent with several meta-analyses on the solid tumors[11-14]. In the studies, the authors showed that the Chinese herbal medicine (CHM) can increase the response and survival more than one year rates. Among the diseases studied, the non small cell lung cancer (NSCLC) is also sensitive to chemotherapeutic agents that is something like the hematologic malignancies. Our study also showed that TCM increased the response rate but failed to show that TCM increased the survival rate. This might be because there were not enough participants involved in our meta-analysis or the different clinical features of the diseases we researched. In the NSCLC study, authors

Table 22 Risk assessment of sWei Hong 2013 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The random number table was used to generate the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 23 Characteristics of sHai Yan 2007 study

Methods	A randomized controlled study
Participants	Chronic myeloid leukemia patients
Interventions	Traditional Chinese medicine group: Hydroxyurea + traditional Chinese medicine Control group: Hydroxyurea
Outcomes	The primary outcome: The response rate

Table 24 Risk assessment of sHai Yan 2007 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The random number table was used to generate the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

demonstrated the CHM decreased the morbidity of serious agranulocytosis and thrombocytosis which was not revealed in our study. As well, this might be caused by the lack of studies included or the different clinical features of the diseases. The consistency of our study with other studies strengthened our results.

Limitation of the meta-analysis

We have tried our best to make our research more reliable but we still have some limitation. First, none of included studies were performed out of China and all of the included studies except one were published in Chinese. As the funnel plot was symmetric, the publication bias was unavoidable. Second, six of the included studies were small sample sized and did not mention any blindness methods that had the risk of compromising concealment allocation[41]. Third, except the acute leukemia subgroup, there were rare studies of other hematologic malignant diseases included in the meta-analyses. Thus the efficacy result mainly reflected the efficacy of TCM for acute leukemia. According to our result, it was not clear whether the TCM usage had the same efficacy for other hematologic malignant diseases. Finally, all of the included studies were not large sample sized. Only 5 studies used the central randomization method. As a result of it, the quality of evidence of our study was compromised and the GRADE recommendation level was low. Because of these limitations the reliability might be influenced and the

Table 25 Characteristics of included studies

Studies	Age	Sex (male:female)	Race	Disease	No. of participants (TCM:control)	Intervention		Published language
						TCM	Control	
Dian Rong 2009[15,21,25,31,33]	TCM 39.52 ± 18.87 Control 37.94 ± 18.55	TCM 50:21 Control 39:27	Chinese	Acute leukemia	71:66	Compound Zhe Bei granule + standard chemotherapy	Placebo + standard chemotherapy	English
Mao Sheng 2007[26,27]	TCM 35.63 ± 6.46 Control 36.57 ± 7.38	TCM 33:27 Control 31:29	Chinese	Acute myeloid leukemia	60:60	Yi Qi Jie Du Huo Xue decoction + standard western mechicine	Standard western mechicine	Chinese
sHai Yan 2007[22]	TCM 18-65 Control 19-63	TCM 5:3 Control 7:3	Chinese	Chronic myelogenous leukemia	8:10	Qu Du Hua Yu decoction + hydroxyurea	Hydroxyurea	Chinese
sWei Hong 2013[23]	TCM 25-60 Control 25-65	TCM 22:14 Control 17:7	Chinese	Chronic myelogenous leukemia	22:17	TCM + interferon-α	Interferon-α	Chinese
Chuan Xin 2013[32]	TCM 4.30 ± 1.81 Control 4.95 ± 2.04	TCM 12:8 Control 10:10	Chinese	Pediatric acute myeloid leukemia	20:20	TCM + standard chemotherapy	Standard chemotherapy	Chinese
Ji Hong 2011[34]	TCM 60-71 Control 61-72	TCM 16:16 Control 15:13	Chinese	Elderly acute myeloid leukemia	32:28	TCM + HAG chemotherapy	HAG chemotherapy	Chinese
Rui Rong 2004[29]	TCM 12-78 Control 11-76	TCM 40:28 Control 27:19	Chinese	Acute myeloid leukemia	68:46	TCM + standard chemotherapy	Standard chemotherapy	Chinese
Su Juan 2005[24]	TCM 32.5 ± 12.45 Control 31.53 ± 12.41	TCM 16:14 Control 17:13	Chinese	Acute leukemia	30:30	Qing Re Jie Du kang Bai decoction + standard chemotherapy	Standard chemotherapy	Chinese
Wen Jiang 2010[30]	TCM 47-78 Control 46-79	TCM 17:12 Control 15:13	Chinese	Acute myeloid leukemia	29:28	Shen Qi Qing Re Ke Li + HAG chemotherapy	HAG chemotherapy	Chinese
Xiu Mei 1997[35]	TCM 6-73 Control 6-71	TCM 72:40 Control 36:19	Chinese	Non-Hodgkin lymphoma	112:55	TCM + standard chemotherapy	Standard chemotherapy	Chinese
Ying Fei 2005[28]	TCM 13-72 Control 15-71	TCM 22:10 Control 25:8	Chinese	Acute leukemia	32:33	Shen Qi Fu Zheng injection + standard chemotherapy	Standard chemotherapy	Chinese

TCM: Traditional Chinese medicine; HAG: Homoharringtonine + cytoarabine + granulocye colony stimulating factor.

Table 26 Quality assessment of included studies

Studies	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias) All outcomes	Blinding of outcome assessment (detection bias) All outcomes	Incomplete outcome data (attrition bias) All outcomes	Selective reporting (reporting bias)	Other bias
Dian Rong 2009[15,21,25,31,33]	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear
Mao Sheng 2007[26,27]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
sHai Yan 2007[22]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
sWei Hong 2013[23]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Chuan Xin 2013[32]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Ji Hong 2011[34]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
Rui Rong 2004[29]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Su Juan 2005[24]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Wen Jiang 2010[30]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Xiu Mei 1997[35]	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Ying Fei 2005[28]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear

Table 27 Summary of findings of the overall response and complete response outcomes

Outcomes	Illustrative comparative risks[1] (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Overall response rate				
Overall response rate	Study population		RR = 1.14	974	++--	
	761 per 1000	867 per 1000 (784-959)	(1.03-1.26)	(12 studies)	Low	
	Moderate					
	775 per 1000	883 per 1000 (798-976)				
Complete response rate	Study population		RR = 1.21	974	++--	
	579 per 1000	701 per 1000 (579-846)	(1-1.46)	(12 studies)	Low[2,3]	
	Moderate					
	579 per 1000	701 per 1000 (579-845)				
Overall response rate for malignant hematologic disease Patient or population: Patients with malignant hematologic disease Settings: Intervention: Overall response rate						

[1]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI); [2]Not all studies included were high quality randomized controlled trial; [3]Most studies showed better effect when traditional Chinese medicine was added while some studies did not show statistically significant better effect. GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.

results should be interpreted with caution. As there were some limitations, we extensively searched the related databases, publications and websites, strictly screened and evaluated retrieved articles and analyzed the pooled data. Our study assessed the evidence available recently so it is still significant for evaluating the role of TCM for hematologic malignancies.

Because TCM causes little AEs, has little interaction with other drugs or treatment methods it can be safely prescribed in most of the malignant diseases treatment. It is especially popular among the complementary and alternative medicine usage in the palliative care of cancer patients[42]. But recently, it plays more important role in the tumor treatment. Our meta-analysis demonstrated that TCM not only had the advantage of reducing the chemotherapy associated serious non-hematologic AEs and had a trend to reduce the serious infection rate, but also significantly increased the response rate. Our result suggests TCM is helpful for hematologic malignant diseases treatment. Although we failed to show a better survival rate of TCM compared with control, we believed to recommend adding TCM to the hematologic malignancies treatment as an adjuvant therapy is reasonable, at least for adult acute leukemia.

Conclusion and implications for research

TCM increases the OR and CR rate for acute leukemia treatment and reduced the treatment associated serious non-hematologic AEs. Therefore, we recommend including TCM in the hematologic malignancies treatment, at least for adult acute leukemia treatment.

Except adult acute leukemia, we need more high quality studies on other hematologic malignant diseases, pediatric patients and in other regions apart from China. We are also in need of studies of TCM on the survival, infection and hematologic AEs rates for hematologic malignancies treatment.

COMMENTS

Background

Albeit as the standard treatment, the chemotherapy always causes serious adverse effects (AEs) and its efficacy is still not satisfactory. Recently, many studies showed that traditional Chinese medicine (TCM) can improve the effect of the standard treatment and reduce the AEs.

Research frontiers

In recent years, more and more researchers begin to pay attention to the effect of TCM for malignant diseases. Many studies showed that TCM can increase the efficacy of the standard treatment and decrease the AEs.

Innovations and breakthroughs

Although there were many clinical studies published on the TCM for hematologic malignances, as far as we know, there was no systematic review published on this issue. As far as we know, the authors first summarized the evidence now available on it with systematic review and demonstrated a subjective result. The result confirmed the effectiveness of TCM for hematologic malignances and could be used in the clinical practice.

Applications

The result showed that TCM can increase the overall response and complete response rates. In addition, TCM also reduced the non-hematologic serious AEs. The authors consider TCM should be used for hematologic malignances treatment.

Peer-review

The manuscript is quite interesting.

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META-ANALYSIS

Sleep-associated movement disorders and the risk of cardiovascular disease: A systematic review and meta-analysis

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Author contributions: Fang Z, Liu YW and Zhang FX designed the review; Fang Z, Zhao LY and Xu Y collected the data; Fang Z and Liu YW analyzed the data and wrote the paper.

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Abstract

AIM: To investigate whether an association exists between sleep-associated movement disorders and cardiovascular disease (CVD).

METHODS: Several studies have observed the relationship of sleep-associated movement disorders such as restless legs syndrome (RLS) and periodic limb movements during sleep with CVD, but the results were still contradictory. We performed an extensive literature search on PubMed, Medline and Web of Science published from inception to December 2014. Additional studies were manually searched from bibliographies of retrieved studies. Meta-analyses were conducted with Stata version 12.0 (Stata Corp, College Station, Texas). Pooled odds ratios (ORs) and 95%CIs were calculated to assess the strength of association using the random effects model. Sensitivity and subgroup analyses were performed to explore the underlying sources of heterogeneity. The publication bias was detected using Egger's test and Begg's test.

RESULTS: A total of 781 unique citations were indentified from electronic databases and 13 articles in English were finally selected. Among these studies, nine are cohort studies; two are case-control studies; and two are cross-sectional studies. The results showed that the summary OR of CVD associated with sleep-associated movement was 1.51 (95%CI: 1.29-1.77) in a random-effects model. There was significant heterogeneity between individual studies (P for heterogeneity = 0.005, I^2 = 57.6%). Further analysis revealed that a large-scale cohort study may account for this heterogeneity. A significant association was also found between RLS and CVD (OR = 1.54, 95%CI: 1.24-1.92). In a fixed-effects model, we determined a significant relationship between sleep-associated

movement disorders and coronary artery disease (CAD) (OR = 1.34, 95%CI: 1.16-1.54; *P* for heterogeneity = 0.210; I^2 = 30.0%). Our meta-analysis suggests that sleep-associated movement disorders are associated with prevalence of CVD and CAD.

CONCLUSION: This finding indicates that sleep-associated movement disorders may prove to be predictive of underlying CVD.

Key words: Sleep-associated movement disorders; Restless legs syndrome; Cardiovascular disease; Meta-analysis; Periodic limb movements during sleep

Core tip: We conducted a meta-analysis of 13 relevant studies to investigate the association between sleep-associated movement disorders and cardiovascular disease (CVD). The present study suggested that sleep-associated movement disorders are associated with prevalence of CVD. This finding indicates that sleep-associated movement disorders may prove to be predictive of underlying CVD.

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INTRODUCTION

Sleep-associated movement disorders are a group of movement disorders which occur during sleep in relation to episodes of arousal and sleep disorder. They are characterized by the persistence of muscle tone or the emergence of motor activity. Among of them, restless legs syndrome (RLS) and periodic limb movements during sleep (PLMS) are the two most common disorders encountered in adult. RLS affects approximately 5%-10% of the general population and up to 80% of RLS patients may have PLMS[1,2]. RLS and PLMS can result in similar clinical problems due to sleep disruption[3]. Recently, several studies indicate that untreated RLS with PLMS may contribute partly to secondary causes of uncontrolled hypertension and cardiovascular disease (CVD), while some studies demonstrated negative results[4,5]. Therefore, the objective of the present study was to provide a systematic review and meta-analysis of the available evidence on the association between sleep-associated movement disorders and CVD in general populations.

MATERIALS AND METHODS

This meta-analysis was based on the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group[6].

Data sources and search strategy

We performed a literature search of PubMed, Medline and Web of Science using key words of "periodic limb movements", "RLS", "heart disease", "CVD", "coronary artery disease (CAD)" and "sleep-associated movement disorders" published from inception to December 2014. Additional studies were manually searched from references of related studies or reviews and the language was limited in English. Review articles, abstracts, correspondence, conference proceedings and book chapters were excluded, and only one instance of the study found in multiple journals was included.

Inclusion and exclusion criteria

Prospective cohort, case-control, and cross-sectional studies based in general populations that assessed the association of sleep-associated movement disorders with CVD were eligible for this systematic review. Exclusion criteria were as follows: (1) duplicated studies; (2) no controls; and (3) no detail risk estimates and 95%CIs. We included only published full-text that assessed sleep-associated movement disorders and CVD, or that provided sufficient data to calculate risk estimates of CVD associated with sleep-associated movement disorders. Unpublished reports, abstracts, comments, reviews, case report or editorials were not considered in this review. CVD in our investigation were defined as CAD, heart failure (HF) and stroke, not including hypertension.

Data extraction

Two reviewers independently extracted eligible data by screening the titles and abstracts of the search results and evaluating the remaining full-text articles. Disagreements were discussed till consensus was achieved. The following data were extracted: the first authors' name, publication year, country where the study was conducted, study type, RLS or PLMS, number of samples, crude or adjusted risk estimates and 95%CIs. Different study types were divided into prospective cohort, case-control, and cross-sectional studies.

Statistical analysis

Summary odds ratios (ORs) and 95%CIs were used to measure the association strength between sleep-associated movement disorders and CVD risk. Cochran's Q statistic and the I^2 statistic were used to quantify between-study heterogeneity. The heterogeneity was considered as significant with a conservative *P* value of 0.10 and a value of I^2 exceeding 56%. We pooled ORs, relative risks and hazard ratios (HRs) with the random-effects model when a significant heterogeneity exists, otherwise, with the fixed-effect model[7]. We also performed subgroup analyses to explore the underlying confounding factor. Sensitivity analyses were carried out to test the reliability of results. We checked for funnel

Table 1 Characteristics of the eligible studies included in the meta-analysis

Ref.	Year	Country	Study type	Total	Source of patients	CVD-OR (95%CI)	CAD-OR (95%CI)
Hanly *et al*[10]	1996	Canada	Cohort	32	PLMS	8.73 (0.94-81.49)	-
Ulfberg *et al*[11]	2001	Sweden	Case-control	4000	RLS	2.50 (1.40-4.30)	-
Ohayon *et al*[12]	2002	5 European countries	Cross-sectional	18980	PLMS/RLS	1.47 (1.12-1.81)	-
Winkelman *et al*[13]	2006	United States	Cohort	2821	RLS	2.07 (1.31-3.27)	
Elwood *et al*[14]	2006	United Kingdom	Cohort	1871	RLS	1.38 (1.06-1.81)	1.24 (0.89-1.74)
Winkelman *et al*[15]	2008	United States	Cross-sectional	3433	RLS	2.07 (1.43-3.00)	2.05 (1.38-3.04)
Walters *et al*[16]	2010	United States	Cohort	267	RLS	2.46 (0.97-6.28)	-
Koo *et al*[17]	2011	United States	Cohort	2911	PLMS	1.28 (1.08-1.51)	1.23 (1.01-1.50)
Li *et al*[18]	2012	United States	Cohort	70977	RLS	1.46 (0.97-2.18)	1.46 (0.97-2.18)
Winter *et al*[19]	2012	United States	Cohort	48938	RLS	1.06 (0.90-1.26)	-
Lindner *et al*[20]	2012	Hungary	Cohort	150	PLMS	1.85 (0.46-7.51)	1.15 (0.35-3.81)
Mirza *et al*[21]	2013	United States	Case-control	584	PLMS	1.62 (1.14-2.30)	-
Szentkirályi *et al*[22]	2013	German	Cohort	4308	RLS	0.94 (0.42-2.10)	0.53 (0.12-2.27)

RLS: Restless legs syndrome; PLMS: Periodic limb movements during sleep; CVD: Cardiovascular disease; CAD: Coronary artery disease.

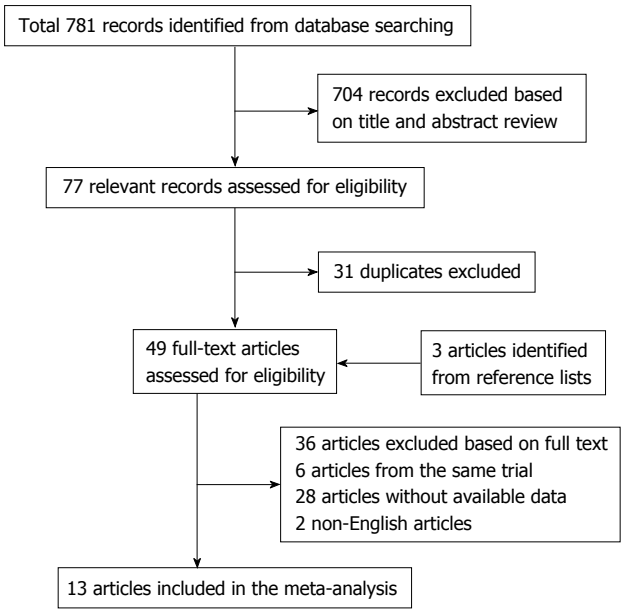

Figure 1 Flow diagram of the study selection process.

plot asymmetry, Begg's test and Egger's test to assess potential publication bias, and the significant *P* value was < 0.05[8,9]. The "trim and fill" procedure was utilized to further evaluate the possible effect of publication bias in the present meta-analysis[7]. All analyses were calculated with Stata version 12.0 (Stata Corp, College Station, Texas).

RESULTS

Characteristics of eligible studies

A total of 781 unique citations were identified: 279 from PubMed, 283 from Medline and 219 from Web of Science. The flow of study identification was shown in Figure 1[10-22]. Table 1 shows characteristics of eligible studies and the effect of sleep-associated movement disorders on the risk for CVD and CAD. Among these studies, nine are cohort studies; two are case-control studies; and two are cross-sectional studies. All participants were investigated from either European countries or United States. The sample sources of cases in nine studies were RLS patients and five were PLMS patients, including one study investigating both PLS and PLMS patients. The risk estimates and 95%CIs of most studies were extracted directly from original articles except for those of seven studies were recalculated by merging raw data[12-14,17,19,20,22].

Associations of sleep-associated movement disorders with CVD and CAD

Several studies indicated that sleep-associated movement disorders were associated with a significant increased risk for CVD; while others showed inconsistent findings (Figure 2). In a random-effects model, the summary OR of CVD associated with sleep-associated movement was 1.51 (95%CI: 1.29-1.77), with the evidence of heterogeneity (*P* for heterogeneity = 0.005, I^2 = 57.6%) (Figure 2). In subgroup analysis by study type, the summary OR was 1.36 for nine cohort studies (95%CI: 1.14-1.62; *P* for heterogeneity = 0.055; I^2 = 47.5%) (Figure 2). Figure 3 listed that a significant association was also found between RLS and CVD (OR = 1.54, 95%CI: 1.24-1.92). In a fixed-effects model, we determined a significant association of sleep-associated movement disorders with CAD (OR = 1.34, 95%CI: 1.16-1.54; *P* for heterogeneity = 0.210; I^2 = 30.0%) (Figure 4).

Sensitive analysis and publication bias evaluation

Sensitive analysis was performed by sequentially excluding each study to test the stability of the results in the present meta-analysis. After removing a study performed by Winter *et al*[19] which allowed the assessment of incident CVD cases, we found no significantly heterogeneity existed between overall studies (*P* = 0.112, I^2 = 34.8%). In addition, there was no significantly influence on the pooled OR of the CVD risk (OR = 1.49, 95%CI: 1.35-1.64). Therefore, the different study design may be a possible origin of heterogeneity. Then we conducted the funnel plot and

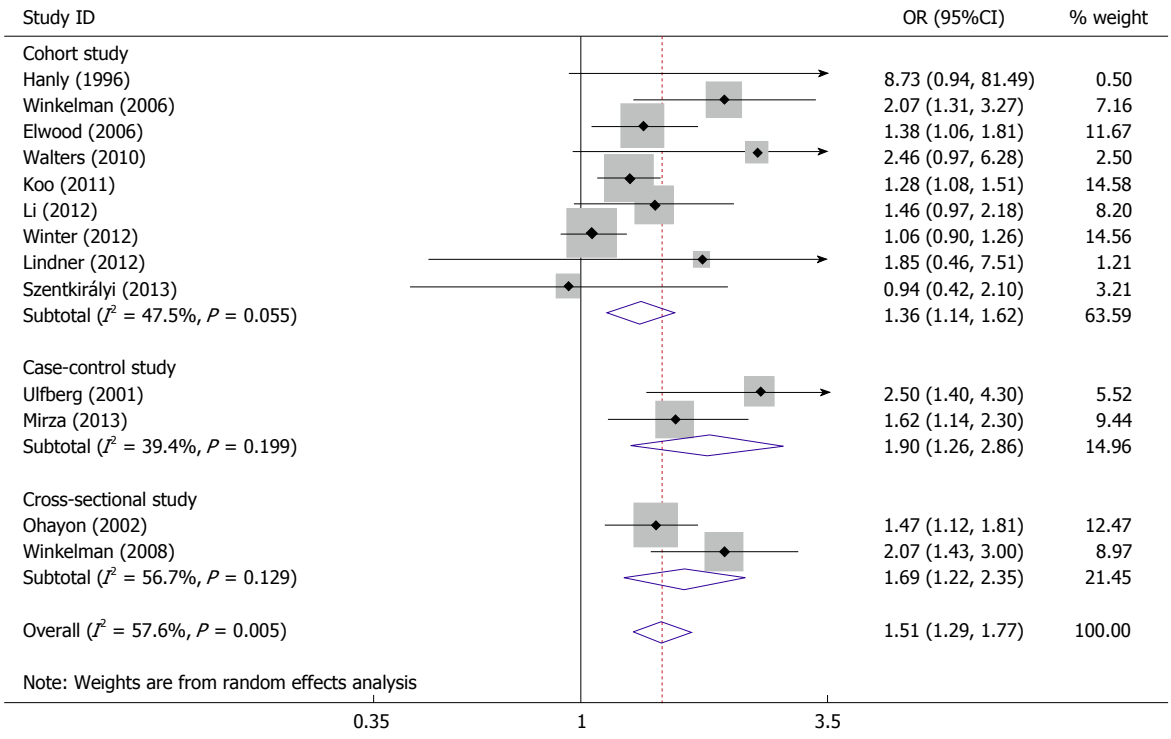

Figure 2 Forest plot (random effects model) of overall cardiovascular disease risk associated with sleep-associated movement disorders.

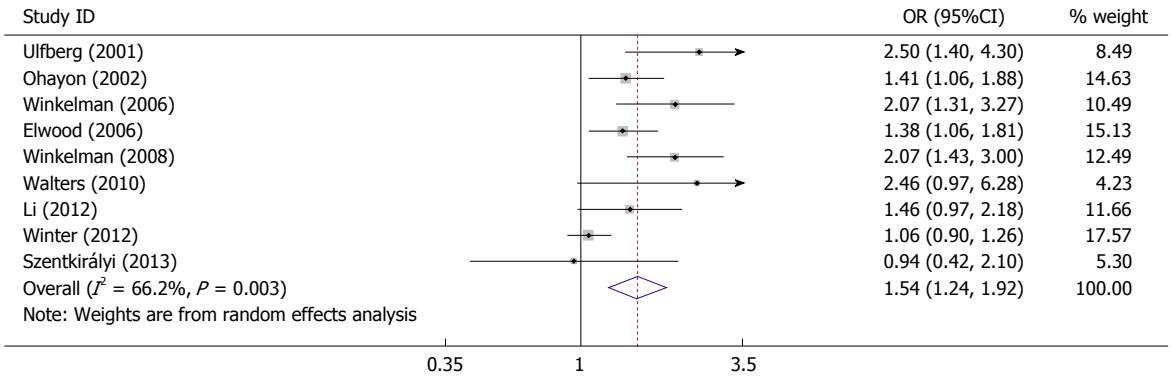

Figure 3 Forest plot (fixed effects model) of overall cardiovascular disease risk associated with restless legs syndrome.

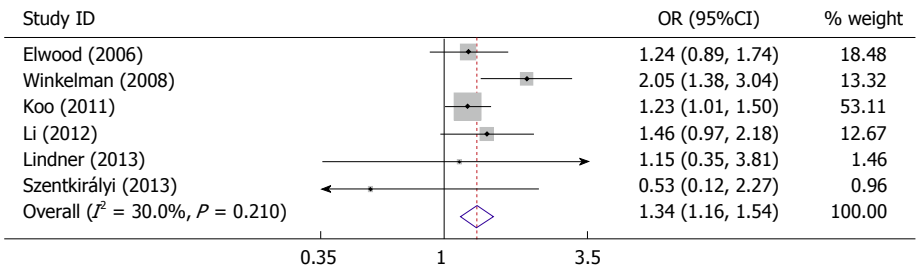

Figure 4 Forest plot (random effects model) of overall coronary artery disease risk associated with sleep-associated movement disorders.

Egger's test to assess the publication bias of literatures. Visual assessment of the Begg funnel plot revealed asymmetry (Figure 5A). This indicates the potential publication bias, although the Begg's test showed no statistically significance (Z = 1.53, P = 0.127). In order to identify and correct for funnel plot asymmetry arising from publication bias, we continued the analysis using the trim and fill method. The other four hypothetical studies were filled to produce a symmetrical funnel plot (Figure 5B). After that, the meta-analysis still showed a statistically significant association between sleep-associated movement disorders and CVD (OR = 1.39,

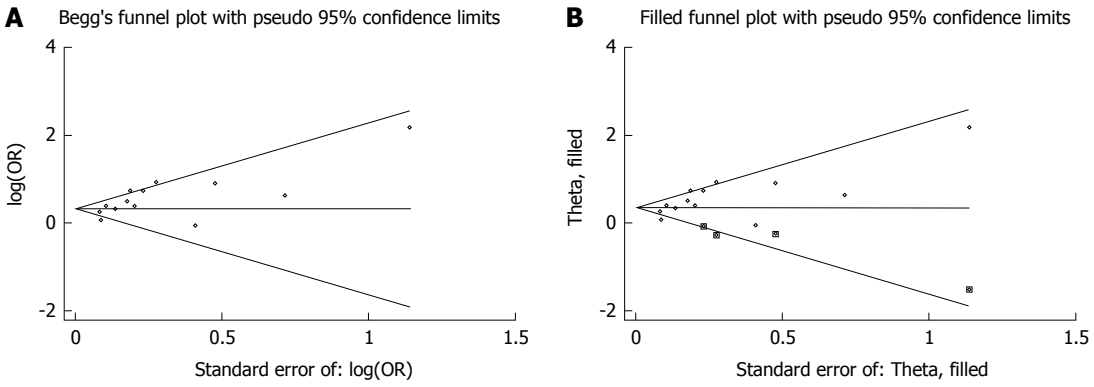

Figure 5 Funnel plots without and with trim and fill. A: Funnel plot without trim and fill; B: Funnel plot with trim and fill.

95%CI: 1.19-1.63).

DISCUSSION

Plenty of evidences have revealed screening, identification, and treatment of sleep disorders were important among patients with CVD. Several studies showed RLS were associated with hypertension and heart disease, because RLS may contribute to a high cardiovascular burden[1,11,12]. In 2001, Ulfberg *et al*[11] found an association of RLS with both self-reported hypertension and heart problems in 4000 Swedish men aged 18 to 64 years (hypertension: OR = 1.5, 95%CI: 0.9-2.4; heart problems: OR = 2.5, 95%CI: 1.4-4.3). Ohayon *et al*[12] reported heart disease made a significant independent contribution to RLS (OR = 1.41, 95%CI: 1.06-1.88). In a cohort study, Elwood *et al*[14] identified RLS is associated with a significant increase in ischaemic heart disease events among 1871 men in South Wales, United Kingdom during the following 10 years (OR = 1.24, 95%CI: 0.89-1.71). In the Wisconsin Sleep Cohort study of 2006, Winkelman *et al*[15] observed a dose-related association between RLS symptoms and CVD (Frequent: OR = 1.61, 95%CI: 0.82-3.13; Daily: OR = 2.58, 95%CI: 1.38-4.84). Moreover, Winkelman *et al*[15] also demonstrated the association of RLS with CVD and CAD in a large cross-sectional observational community-based study of 1559 men and 1874 women (CAD: OR = 2.05, 95%CI = 1.38-3.04; CVD: OR = 2.07, 95%CI: 1.43-3.00) for subjects with RLS compared to those without RLS, and the associations were stronger in those with RLS more frequent or severer symptoms[15]. Li *et al*[18] performed a large-scale prospective study to examine whether RLS was associated with an increased risk of CAD in women of the Nurses' Health Study (HR = 1.46, 95%CI: 0.97-2.18). The fact suggests that CVD could be result from the long-term impact of RLS or RLS-associated conditions. Nevertheless, a study from Walters *et al*[16] showed that there was no statistically difference in the prevalence of CVDs or risk factors between RLS patients and controls, which may be caused by the limited sample size. Another two large prospective cohort studies (Women's Health Study and Physicians' Health Study, United States) also did not support that RLS is a marker of increased risk of vascular disease. The discrepancy between these two results and those of previous studies may be explained by the prospective cohort study, which was designed to assess incident CVD cases[19].

Ninety-nine percent of PLMS are related to greater heart rate response, which result in sympathetic activation as a cause of cardiovascular complications[1,23,24]. In 1996, Hanly *et al*[10] for first time found an association between congestive HF and increased prevalence of PLMS. Furthermore, a cross-sectional study was performed in the five European countries, identifying CVD certainly associated with PLMS (OR = 1.61, 95%CI: 1.09-2.39). A study published in 2011 from Koo *et al*[17] supported PLMS frequency may be a predictive factor of incident CVD. In a recent study by Mirza *et al*[23], periodic limb movement index > 35/h were found to confer a high risk for HF (OR = 1.62; 95%CI: 1.14-2.30).

To clarify the controversial results of previous studies regarding the association of sleep-associated movement disorders with CVD, we performed this meta-analysis. Our analysis suggested that sleep-associated movement might play an important role in the development of heart disease, particular in prevalence of CAD. As different study design of the previous works might contribute to discrepancies between previous reports, thus we conducted subgroup analysis by study types which suggested the association was only to be weaker but still significant in cohort studies. In addition, our results also provided a stronger evidence for the significant relationship between RLS and CVD. However, the exact mechanism of the effect of sleep-associated movement disorders on cardiovascular system remains unclear. The most accepted hypothesis is these disorders may result from sustained adrenergic surges caused by sympathetic nervous system activation, which predispose to persistent elevated blood pressure as well as increased left ventricular afterload and heart rate. Another possible explanation is that sleep-associated movement disorders interrupt sleep which raises heart risk[25].

Some limitations of our meta-analysis should be considered. First, the results of the present meta-analysis remain cautious due to heterogeneity across

studies. Second, the risk estimate of each study included was not adjusted by the same covariable related to risk of CVD. Third, the asymmetry shape of the funnel plot suggested the possibility of publication bias, even the trim and fill sensitivity analysis has been used to test the stability of the results. Fourth, all sample sources are of European or United States descent, which lead to lacking data from other ethnicity backgrounds.

In conclusion, the current meta-analysis suggests that sleep-associated movement disorders are associated with prevalence of CVD, which may be predictive of CVD. This finding may settle the controversy among previous investigations. However, further well-designed and mechanistic work should undertake to confirm this association.

COMMENTS

Background

The burden of cardiovascular disease (CVD) is increasing globally, especially in developing countries such as China. CVD has been the first leading cause of mortality in China. It has been known that unhealthy life style is the most common induced factor of CVD which can also lead to other disease like diabetes, obesity and so on. Therefore, the prevention of CVD, which consumes less, is more important than treatment in developing countries. Sleep-associated movement disorders is a group of symptoms that easily been ignore by the public and some limited studies seem to indicate they may be also the underlying cause of CVD, although this association is not been well established.

Research frontiers

Over the recent 2 decades, many studies attempted to understand the associations between sleep-associated movement disorders and CVD. However, it is difficult to obtain an inconsistent conclusion about the association from the previous studies.

Innovations and breakthroughs

From this meta-analysis, sleep-associated movement disorders may increase the risk of CVD by approximately 51%. Significant associations also showed in subgroup analyses of nine cohort studies. And sleep-associated movement disorders may be predictively used in the prevention of coronary artery disease in the future based the current investigation.

Applications

Sleep-associated movement disorders appear to be either directly or indirectly associated with the risk of CVD. An exploration of the mechanism for this association may help us decrease the prevalence of CVD.

Terminology

Sympathetic nervous system is a web of nerves and neurons spreading excitement to each organ of body. Left ventricular afterload is the encountering resistance when the myocardial of left ventricular contracts.

Peer-review

Well written and concise meta-analysis.

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