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Why meta-analyses are important for complementary and alternative medicine research

Holger Cramer

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Abstract

Complementary and alternative medicine (CAM) is defined as a group of interventions that are not generally considered part of conventional medicine. This definition already implies that CAM interventions are often not systematically studied; and the research evidence from single trials on CAM is often limited by small sample sizes, unclear methodology, and inadequate statistics. As a result, both, significant and insignificant results are often

hard to interpret based on single trials. Summarizing the evidence from single CAM trials, qualitative systematic reviews still have to deal with the same problems as individual trials as they can only rely on the original reports. Thus, effects of CAM interventions are often underestimated or overestimated based on single trials or qualitative systematic reviews. While meta-analyses still are limited by the methodological shortcomings of the included studies, a well-conducted meta-analysis can deal with two common problems of CAM trials: inadequate statistics that rely on within-group comparisons and small underpowered sample sizes. Although large and high quality trials are urgently needed for most CAM interventions, funding often is limited. Until higher quality research is available, meta-analyses provide a useful tool to investigate the actual level of evidence of currently published CAM trials. This editorial presents examples of meta-analyses in the field of CAM and discusses how they contribute to the consolidation of evidence.

Key words: Complementary therapies; Meta-analysis; Review; Randomized controlled trial; Bias

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Core tip: The research evidence from single trials on complementary and alternative medicine (CAM) is often limited by small sample sizes, unclear methodology, and inadequate statistics. Qualitative systematic reviews still have to deal with the same problems as individual trials as they can only rely on the original reports. While meta-analyses still are limited by the methodological shortcomings of the included, they can deal with two common problems of CAM trials: inadequate statistics that rely on within-group comparisons and small underpowered sample sizes.

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TEXT

The National Center for Complementary and Alternative Medicine of the National Institute of Health defines complementary and alternative medicine (CAM) as “a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine”^[1]. A growing number of randomized controlled trials (RCTs) aimed to investigate the effectiveness of CAM therapies in varied medical conditions. However, while these trials are urgently needed to consolidate evidence for interventions that have been - by definition - rarely studied systematically in the past, the research evidence from single trials on CAM is often limited by small sample sizes, unclear methodology, and inadequate statistics. Both, significant and insignificant results are often hard to interpret based on single trials. On the one hand, while randomized trials are generally conducted to compare effects of two or more different treatments on a specific condition, especially CAM trials often solely rely on within-group comparisons that do not take into account unspecific effects. Thereby, the value of having a control group is lost and it is often impossible to estimate the real specific effects of the intervention; overestimating its actual specific efficacy. On the other hand, small trials that often have to deal with marked baseline differences between groups are often underpowered to detect specific effects of the intervention. Based on those problem, it has even been encouraged to abandon RCT designs in CAM research altogether. However, most problems of CAM RCTs can be adequately addressed by proper methodology use. In recent years, a continuously growing number of systematic reviews have been conducted in order to summarize evidence from single CAM trials. While this tendency is definitely useful to consolidate evidence, qualitative reviews still have to deal with the same problems as individual trials as they can only rely on the original - often heavily biased - reports. This is where meta-analyses should come into play. While meta-analyses still are limited by the methodological shortcomings of the included trials and badly conducted meta-analyses can even worsen the situation, a well-conducted meta-analysis can deal with two common problems of CAM trials: inadequate statistics that rely on within-group comparisons and small underpowered sample sizes. By ignoring the original statistical method of the published analyses and by quantitatively pooling the results of several trials, a between-group analysis based on a larger sample can be created that compensates for at least some of the shortcomings of the original trials. Although a trained statistician would surely be able to assess the real effect sizes from the published data without relying on a published meta-analysis, CAM trials are often used to guide clinical decision making; and a clinician often will

not be able to re-evaluate the statistics of a published trial. While it does not reduce the risk of bias of the original studies, a meta-analysis can address the problem of inadequate statistics and improve the power of the analysis. Take, *e.g.*, yoga. Yoga has now become a popular means to improve health and well-being and several studies have investigated yoga's effectiveness in varied medical conditions. In 2011, a systematic review on yoga for low back pain included a total of seven RCTs published until March 2011^[2]. Five of the RCTs found significant effects of the yoga interventions while the other two did not. The systematic review concluded that yoga might be able to alleviate low back pain but that any definitive claims should be treated with caution^[2]. A second systematic review on the same condition included trials that were published until January 2012^[3]. While the first review refrained from meta-analyzing the data due to heterogeneity of the included trials, the second review was able to include a meta-analysis. Based on ten RCTs, this meta-analysis found strong evidence for short-term effectiveness and moderate evidence for long-term effectiveness of yoga for chronic low back pain in the most important patient-centered outcomes^[3]. As a consequence, this review concluded that yoga can be recommended as an additional therapy to chronic low back pain patients. While the obvious divergences in conclusions might also be accounted to the increased number of included RCTs in the second review, they are likely to be at least partly based on the inclusion of a meta-analysis whose findings can go beyond just balancing the results of individual trials against each other. On the other hand, meta-analyses can also help to revise falsely overoptimistic conclusions of single trials. A 2012 systematic review on the effects of yoga for schizophrenia included three RCTs that were published until October 2011^[4]. Despite the low number of eligible trials, the overall positive findings of those led to the conclusion that yoga could be helpful in reducing general psychopathology, positive, and negative symptoms in patients with schizophrenia. However, as these conclusions were based on the results that were reported in the original articles, and one out of three RCTs reported only within-group pre-post comparisons rather than between-group comparisons, these results were not robust against reporting bias. Accordingly, based on the same trials, a recent meta-analysis failed to find any effects of yoga on schizophrenia psychopathology^[5], resulting in the counterintuitive finding that a meta-analysis of three RCTs that all reported positive effects resulted in insignificant group differences.

A problem of meta-analyses - especially for but not limited to CAM research - is heterogeneity between trials; specifically clinical heterogeneity (differences in, *e.g.*, interventions that might be labeled with the same term) which often results in statistical heterogeneity (differences in the interventions' effects). While studies in a meta-analysis will inevitably differ from each other, substantial statistical heterogeneity can reduce the precision of effect estimates. Thus, authors of CAM-related meta-

analyses should be aware of the heterogeneity of CAM interventions and define the focus of their meta-analysis as precisely as possible.

Small underpowered and poorly conducted trials are by no means only a problem of CAM research. However, as external funding for CAM trials is limited to non-existent in most countries, large well-conducted trials are especially difficult to conduct in this research area. While meta-analyses cannot compensate for low-quality original research, they provide a useful tool to investigate the actual level of evidence of currently published CAM trials until higher-quality research evidence is available.

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Prophylactic tracheal intubation for upper GI bleeding: A meta-analysis

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Abstract

AIM: To evaluate usefulness of prophylactically intubating upper gastrointestinal bleeding (UGIB) patients.

METHODS: UGIB results in a significant number of hospital admissions annually with endoscopy being the key intervention. In these patients, risks are associated with the bleeding and the procedure, including pulmonary aspiration. However, very little literature is available assessing the use of prophylactic endotracheal intubation on aspiration in these patients. A comprehensive search was performed in May 2014 in Scopus, CINAHL, Cochrane databases, PubMed/Medline, Embase, and published abstracts from national gastroenterology meetings in the United States (2004-2014). Included studies examined UGIB patients and compared prophylactic intubation to no intubation before endoscopy. Meta-analysis was conducted using RevMan 5.2 by Mantel-Haenszel and DerSimonian and Laird models with results presented as odds ratio for aspiration, pneumonia (within 48 h), and mortality. Funnel plots were utilized for publication bias and I^2 measure of inconsistency for heterogeneity assessments.

RESULTS: Initial search identified 571 articles. Of these articles, 10 relevant peer-reviewed articles in English and two relevant abstracts were selected to review by two independent authors (Almashhrawi AA and Bechtold ML). Of these studies, eight were excluded: Five did not have a control arm, one was a letter to the editor, one was a survey study, and one was focused on prevention of UGIB. Therefore, four studies ($N = 367$) were included. Of the UGIB patients prophylactically intubated before endoscopy, pneumonia (within 48 h) was identified in 20 of 134 (14.9%) patients as compared to 5 of 95 (5.3%) patients that were not intubated prophylactically ($P = 0.02$). Despite observed trends, no significant

differences were found for mortality ($P = 0.18$) or aspiration ($P = 0.11$).

CONCLUSION: Pneumonia within 48 h is more likely in UGIB patients who received prophylactic endotracheal intubation prior to endoscopy.

Key words: Prophylactic endotracheal intubation; Upper gastrointestinal bleeding; Endoscopy; Complication; Pneumonia; Aspiration

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Core tip: Patients with upper gastrointestinal bleeding (UGIB) require endoscopic treatment with variable outcomes of aspiration, pneumonia, non-endoscopic interventions, and mortality. It is suggested that endotracheal intubation prior to endoscopy might reduce aspiration, pneumonia, and mortality. Few studies have evaluated this issue. We performed a meta-analysis of observational studies examining endotracheal intubation *vs* no intubation in UGIB patients. We found that patients intubated had higher incidence of pneumonia within 48 h. There was no significant increase in aspiration and mortality in the intubated group. This meta-analysis demonstrates the need for randomized controlled trials to assess the issue.

Almashhrawi AA, Rahman R, Jersak ST, Asombang AW, Hinds AM, Hammad HT, Nguyen DL, Bechtold ML. Prophylactic tracheal intubation for upper GI bleeding: A meta-analysis. *World J Meta-Anal* 2015; 3(1): 4-10 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/4.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.4>

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is still significant in the United States^[1]. Health-resources utilization in those with UGIB is significantly higher than those without UGIB^[2-5]. Although UGIB hospitalizations have decreased in the last decade, likely because the use of acid suppression therapy^[6,7], mortality has not decreased and UGIB continues to be a significant cause of hospital admissions^[8-13].

Many strategies have been implemented to reduce the morbidity, mortality, and cost associated with UGIB, including scoring systems, appropriate resuscitation, and improvements in endoscopic and non-endoscopic therapies^[14-19]. In an attempt to reduce aspiration and aspiration pneumonia in patients presenting with UGIB, prophylactic tracheal intubation prior to performing endoscopy has been used, but is there any evidence to support such a practice. Tracheal intubation might prevent aspiration in selected cases but outcomes could be related to how experienced medical personnel performing

the intubation is and how sick the patient is, *i.e.*, with altered mental status or massive bleeding^[20-22]. However, controversy does exist, even at our own institution, of the utility of prophylactic intubation in patients with UGIB. The largest reason for this controversy is that limited observational studies have addressed the utilization of tracheal intubation in the setting of UGIB^[23-27]. These studies evaluated outcomes, including aspiration, mortality, aspiration pneumonia, and hospital length of stay. As our knowledge to answer the question of the utility of tracheal intubation in the setting of UGIB is still lacking, we conducted a meta-analysis to further evaluate such limited data.

MATERIALS AND METHODS

Search of literature

A complete search of Scopus, CINAHL, Cochrane databases, PubMed/Medline, and Embase was completed in May 2014. Search terms were used individually or in various combinations and included “endotracheal intubation”, “tracheal intubation”, “upper gastrointestinal bleeding”, “upper gastrointestinal hemorrhage”, “variceal hemorrhage”, “non-variceal hemorrhage”, “esophagogastroduodenoscopy”, “peptic ulceration”, “duodenal ulceration”, and “gastric ulceration”. Peer-reviewed studies on UGIB patients that compared prophylactic to no prophylactic intubation were selected and reviewed. References of relevant papers were searched as well for possible additional articles that were not identified in the original search. Search also included published abstracts in the major digestive disease conferences in the United States in the last 10 years. Three investigators reviewed all studies selected for inclusion criteria. Studies in children or in languages other than English were excluded from this meta-analysis.

Data extraction

All included studies were reviewed with two investigators (AA, MB). At least two of three primary outcomes were evaluated in all included studies. If a study had missing data on these subjects or clarification was needed, attempts were made to contact the authors to obtain the necessary information. Data from the studies chosen were extracted by two investigators individually and were settled by mutual agreement.

Statistical analysis

This meta-analysis followed principles of the MOOSE guidelines^[28]. Meta-analysis was performed comparing the results of UGIB patients by calculating pooled estimates presented as odds ratio (OR) of outcomes with Mantel-Haenszel (if no heterogeneity) or DerSimonian and Laird models (if heterogeneity). Heterogeneity analyzed by calculating I^2 measure of inconsistency (significant if $P < 0.10$ or $I^2 > 50\%$). A sensitivity analysis was done if heterogeneity was statistically significant. RevMan 5.2 (Copenhagen: The Nordic Cochrane Centre, The

Table 1 Details of the studies

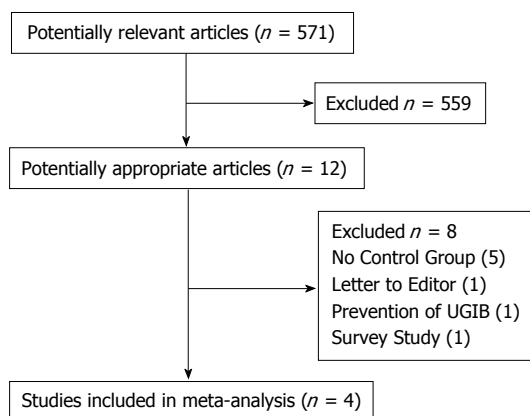
Ref.	Study type	Country	Time	No. of patients	Group	<i>n</i>	Age (mean/median years)	Gender (% male)	Population (inclusion criteria)
Koch <i>et al</i> ^[25]	Retrospective	United States	1995-2002	62	PI	42	49	74	Bleeding varices
					No PI	20	48	65	No radiographic or clinical respiratory issues
Rehman <i>et al</i> ^[24]	Retrospective	United States	2002-2006	98	PI	49	62 ^b	61	Cirrhosis
					No PI	49	68 ^b	82	Hematemesis
^a Perisetti <i>et al</i> ^[26]	Retrospective	United States	2000-2013	138	PI	69	61 ^b	NA	Shock
					No PI	69	66 ^b	NA	Endoscopy with intubation
^a Tang <i>et al</i> ^[27]	Retrospective	United States	2008-2013	69	PI	43	53	69.8	Matched controls
					No PI	26	55	61.5	Endoscopy in suspected variceal bleeding

^aAbstract; ^bMedian. PI: Prophylactic intubation; NA: Data not available.

Table 2 Quality assessment of studies included in meta-analysis

Ref.	Study design	Selection bias	Confounders	Blinding	Data collection methods	Withdrawals and dropouts	Intervention integrity	Analyses	Quality assessment
Koch <i>et al</i> ^[25]	Retrospective	Moderate	Moderate	Weak	Strong	NA	Moderate	Moderate	Moderate
Rehman <i>et al</i> ^[24]	Retrospective	Moderate	Strong	Weak	Strong	NA	Strong	Moderate	Moderate
Perisetti <i>et al</i> ^[26]	Retrospective	Moderate	Weak	Weak	Strong	NA	Moderate	Moderate	Weak
Tang <i>et al</i> ^[27]	Retrospective	Moderate	Strong	Weak	Strong	NA	Moderate	Moderate	Moderate

NA: Data not available.

**Figure 1** Details of article search. UGIB: Upper gastrointestinal bleeding.

Cochrane Collaboration, 2012) used for statistical analysis. Funnel plots were visually inspected for publication bias assessment.

Study quality assessment

The Effective Public Health Practice Project model was used to assess study quality^[29]. This scale is based upon strong, moderate, or weak rankings for analysis, interventional integrity, withdrawal/dropout descriptions, data collection, blinding, confounders, design, and potential selection bias. Study quality is determined by how many weak ratings in each category (no weak ratings

is strong, one weak is moderate, and ≥ 2 weak is weak).

Biostatistics

The corresponding author (Bechtold ML) is a biostatistician and has reviewed and approved all statistical data in the manuscript. Four of the authors (Hinds AM, Hammad HT, Nguyen DL, Bechtold ML) are extensively trained in the statistics used in meta-analysis.

RESULTS

Search of literature

Initially, 571 articles were discovered in the electronic databases (Figure 1). Ten relevant peer-reviewed articles in English and two relevant abstracts were selected for review by two independent authors (Almashhrawi AA and Bechtold ML). Of these studies, eight were excluded: Five did not have a control arm, one was a letter the editor, one was a survey study, and one was focused on prevention of UGIB. Therefore, four studies were identified as meeting inclusion criteria^[24-27]. All the four studies included ($N = 367$) were retrospective cohorts. The studies were conducted throughout the United States and were published 2007 to 2014. All included studies examined the impact of prophylactic endotracheal intubation on UGIB outcomes (Table 1). The study quality was adequate based upon the Effective Public Health Practice Project model (Table 2).

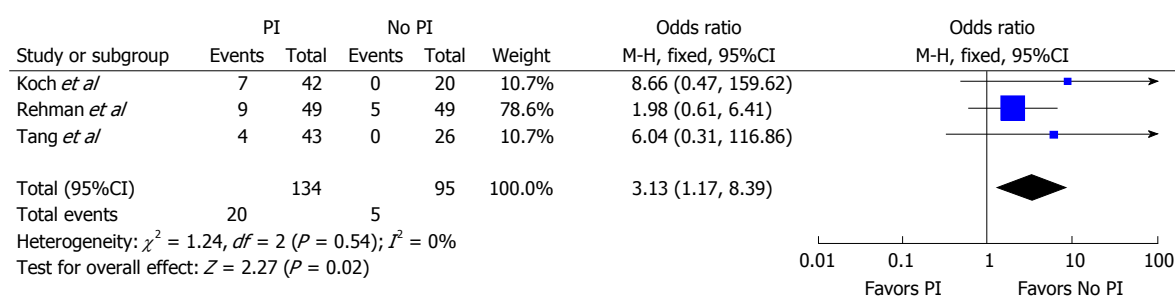


Figure 2 Forest plot demonstrating comparison of prophylactic intubation vs no intubation for patients with upper gastrointestinal bleeding for pneumonia within 48 h. PI: Prophylactic intubation.

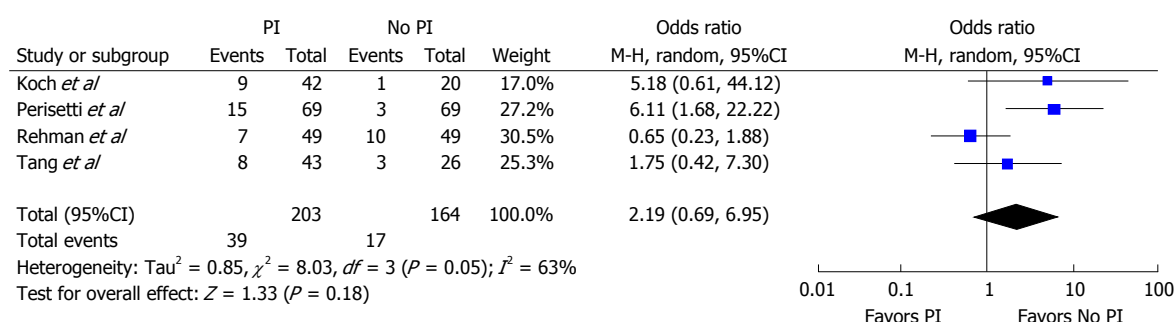


Figure 3 Forest plot demonstrating comparison of prophylactic intubation vs no intubation for patients with upper gastrointestinal bleeding for mortality. PI: Prophylactic intubation.

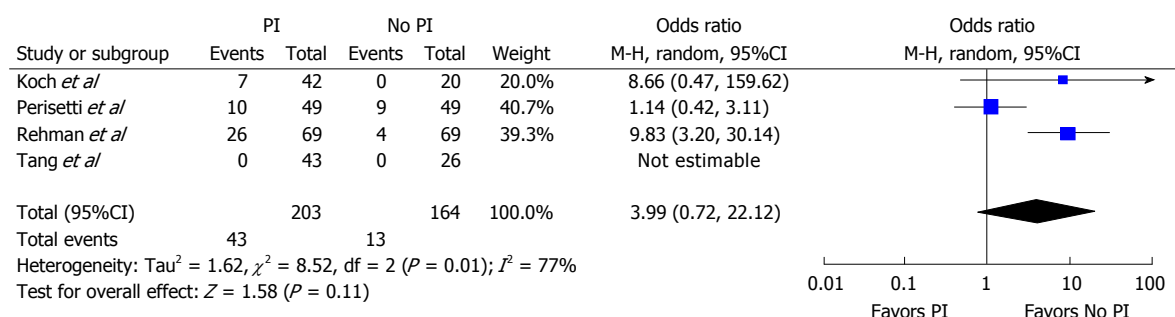


Figure 4 Forest plot demonstrating comparison of prophylactic intubation vs no intubation for patients with upper gastrointestinal bleeding for aspiration. PI: Prophylactic intubation.

Pneumonia within 48 h

Pneumonia within 48 h was examined in three studies ($N = 229$)^[24,25,27]. With prophylactic intubation, 20 of 134 (14.9%) patients with UGIB developed pneumonia. For those not being intubated, 5 of 95 (5.3%) patients with UGIB developed pneumonia within 48 h. Those UGIB patients who underwent prophylactic intubation had higher amount of pneumonia than those not prophylactically intubated with odds ratio of 3.13 (95%CI: 1.17-8.39; $P = 0.02$) with no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.54$) (Figure 2).

Mortality

Mortality was examined in four studies ($N = 367$)^[24-27]. Mortality was noted in 39 of 203 (19.2%) patients with UGIB prophylactically intubated and 17 of 164 (10.4%) patients with UGIB not prophylactically intubated. No statistically significant higher mortality was noted for those patients prophylactically intubated (OR = 2.19;

95%CI: 0.69-6.95; $P = 0.18$) with statistically significant heterogeneity observed ($I^2 = 63\%$, $P = 0.05$) (Figure 3). Given significant heterogeneity, a sensitivity analysis was performed by excluding the Rehman *et al*^[24] study which demonstrated a statistically significant higher mortality for those patients with prophylactically intubated as compared to those not intubated without significant heterogeneity with OR = 3.72 (95%CI: 1.55-8.92; $P < 0.01$).

Aspiration

Aspiration was analyzed in four studies ($N = 367$)^[24-27]. Aspiration was noted in 43 of 203 (21.2%) patients with UGIB prophylactically intubated and 13 of 164 (7.9%) patients with UGIB not intubated. Statistically non-significant higher aspiration was noted in patients with UGIB prophylactically intubated (OR = 3.99; 95%CI: 0.72-22.12; $P = 0.11$) with statistically significant heterogeneity ($I^2 = 77\%$, $P = 0.01$) (Figure 4). Given significant heterogeneity, a sensitivity analysis was per-

formed by excluding the Perisetti *et al*^[26] study which demonstrated a statistically significant more episodes of aspiration for those patients with prophylactically intubated as compared to those not intubated without significant heterogeneity (OR = 9.67; 95%CI: 3.40-27.52; $P < 0.01$; $I^2 = 0\%$, $P = 0.94$).

Publication bias

Publication bias was not observed in any outcomes in this meta-analysis based upon funnel plots.

DISCUSSION

In an effort to provide airway protection and reduce aspiration complications, providers may elect to perform tracheal intubation for patients presenting with UGIB. Unfortunately, there are no published guidelines to direct the use of endotracheal intubation in this group of patients, partly because of the lack of evidence-based recommendations. Emergent tracheal intubation is clearly indicated as a measure to protect airways in specific clinical presentations such as patients with altered mental status or those hemodynamically unstable. On the other hand, complications can arise directly from emergent tracheal intubations and the benefits of tracheal intubation should be weighed against the risks in each case individually. Schwartz *et al*^[30] found that emergency intubation results in esophageal intubation in 8%, new pulmonary infiltrates identified post-intubation in 4%, and 3% died within 30 min of intubations, although those who died were those hemodynamically unstable before intubation. Only few studies evaluated this important subject and all were of retrospective design and varied in results^[24-27].

Koch *et al*^[25] evaluated the outcomes of 62 patients with 69 episodes of variceal bleeding who were either prophylactically intubated or not intubated prior to endoscopy and discovered significantly more aspiration in those who were prophylactically intubated. However, no differences were noted for mortality or length of stay^[25]. Rehman *et al*^[24] utilized 49 matched controls to 49 patients with UGIB and shock, cirrhosis, or hematemesis. Although cardiopulmonary complications are common in this population, no difference was discovered between the prophylactic intubation and no intubation in matched controls for mortality, length of stay, pneumonia, or aspiration^[24]. Similarly, an abstract by Tang *et al*^[27] in 69 patients with suspected variceal hemorrhage showed no significant differences between prophylactic intubation *vs* no prophylactic intubation for mortality, pneumonia, and length of stay. In contrast, an abstract by Perisetti *et al*^[26] demonstrated that prophylactic intubation in patients with UGIB resulted in significantly more aspiration, length of stay, and mortality during hospitalization. Therefore, results has varied among the retrospective studies in regards to important outcomes such as aspiration, pneumonia, and mortality.

Due to this variability, we conducted this meta-analysis to evaluate the available evidence from four

published retrospective studies that compared outcomes in UGIB patients who were prophylactically intubated and those who were not prophylactically intubated.

All studies evaluated mortality and aspiration^[24-27], while only three studies evaluated pneumonia within 48 h as an outcome^[24,25,27]. Our results show that there was a significant higher amount of pneumonia within 48 h in patients with UGIB who received endotracheal intubations prophylactically in comparison with those who were not intubated. In regards to aspiration and mortality, trends were noted toward worse outcomes in those patients who were prophylactically intubated but no statistically significant differences were noted. However, given significant heterogeneity, the sensitivity analyses demonstrated statistically significant worse outcomes for mortality and aspiration in those patients undergoing prophylactic intubation.

Strengths of our study are as follows. First, this is the first meta-analysis that evaluates outcomes difference between prophylactic intubation and no intubation in UGIB patients. Second, a large extensive search for relevant studies was conducted using several electronic search engines and three major gastroenterology and endoscopy conferences proceedings and abstracts for the period from 2004-2014. Third, each study included and evaluated at least two of the three outcomes studied in our meta-analysis. Fourth, the study populations were from different geographic areas in the United States and different time periods over 10 years, making it relevant to a large population. Fifth, no heterogeneity was identified in the pneumonia outcome. Finally, no publication bias was noted by the funnel plot. On the other hand, limitations were also apparent. First, a small number of studies were included. However, these studies are the only studies to-date on the subject. Second, all studies were observational with no randomized controlled trials on this issue which requires attention when forming conclusions from this meta-analysis and taken into consideration. Finally, significant heterogeneity was identified in two of the three outcomes (mortality and aspiration). Therefore, the DerSimonian and Laird model was utilized, limiting heterogeneity impact. Also, sensitivity analyses were performed which demonstrated statistically significant higher mortality and more aspiration in those patients undergoing prophylactic intubation. However, given the limited number of studies, subgroup analysis for sources of heterogeneity (such as location, timing, abstract exclusion) was not performed.

In conclusion, this meta-analysis demonstrates that patients with UGIB who received prophylactic endotracheal intubation have higher odds of having pneumonia within 48 h. Trends showing higher odds of mortality and aspiration in those prophylactically intubated were noted but no statistically significant differences were seen in comparison to those not intubated. Although these results must be interpreted with caution in light of the small number of studies in this meta-analysis leading to one or two studies having significant weight on the results, this

study addresses prophylactic intubation in UGIB patients prior to endoscopy. Based upon these results, prophylactic tracheal intubation is not beneficial in patients with UGIB and should not be recommended.

COMMENTS

Background

Endoscopic treatment is the main treatment for upper gastrointestinal bleeding (UGIB) and preventing complications during endoscopy is important. Endotracheal intubation might be used to protect airways and prevent aspiration, pneumonia, and reduce mortality. This study shows no evidence to support this practice generally and appropriateness of endotracheal intubation should be determined for each case individually.

Research frontiers

The authors performed the first meta-analysis comparing prophylactic endotracheal intubation to no intubation for UGIB to evaluate for pneumonia (within 48 h), aspiration, and mortality.

Innovations and breakthroughs

This is the first meta-analysis comparing prophylactic endotracheal intubation to no intubation for UGIB. The authors found that there is no evidence to support universal use of prophylactic endotracheal intubation prior to endoscopy. On the contrary, significantly more episodes of pneumonia occurred with the intubated group, and trends for worse aspiration and mortality were seen as well in the intubated group although not statistically significant.

Applications

Endotracheal intubation should be determined on an individual case-by-case approach when considered prior to endoscopy for UGIB treatment. Further studies, preferably randomized controlled trials, are likely needed to fully assess the practice of prophylactic intubation in UGIB patients prior to endoscopy.

Terminology

Odds ratio: Statistical term for the odds an event did or did not occur. Mean difference: Statistical term of difference between the means for a given variable. Heterogeneity: Test for uniformity in composition of studies included. Publication bias: Phenomenon where positive studies are more likely to be published than negative studies, leading to possible misrepresentation of data in meta-analysis.

Peer review

This is a very early systematic review and meta-analysis investigating the impact of prophylactic tracheal intubation on iatrogenic pneumonia, all-cause mortality and aspiration arising from complications due to endoscopy for upper GI bleeding.

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Risk of infectious diseases and cutaneous tumours in solid organ recipients: A meta-analysis of literature

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from our cohort were compared with those obtained by a systematic review of the literature of the last 20 years about the same topic.

RESULTS: Infectious diseases were the most frequent dermatological disorders that were diagnosed after transplantation, affecting about the 16.5% of patients. Herpes virus reactivation occurs in about the 35% of patients and is more common within 6 mo from transplantation, whereas when the immunosuppression is reduced, skin infections are mainly represented by Human Papilloma Virus infections and localized mycosis, such as pityriasis versicolor and superficial candidiasis. Bacterial infections were relatively rare and occur mainly in the first months after transplantation. The cumulative risk to develop skin cancer enhance significantly over the time, as consequence of long-term immunosuppressive regimens. Endogenous and exogenous risk factors, as well as the schedule of immunosuppression can play a role and justify the different incidence of skin cancer in the various series.

CONCLUSION: Skin infections and cancer, commonly diagnosed in transplanted patients, impact on survival and life-quality, justifying the realization of follow-up programs for the early diagnosis and treatment.

Key words: Skin infectious disease; Cutaneous tumours; Transplantations; Risk; Solid organ recipients

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Abstract

AIM: To compare the risk of cutaneous infections and tumours in kidney transplant recipients with data recently published about this topic.

METHODS: In the present work, we evaluated the incidence of bacterial, fungal and viral cutaneous infectious diseases and the development of skin cancers in a cohort of 436 patients who underwent a renal transplantation. The median age at transplantation of our patients was 50 years and the median duration of the immunosuppression was of 7.2 years. Data obtained

Core tip: Patients who underwent solid organ transplantation frequently suffer from skin infections and malignancies, due to the effects of long-term immunosuppressive therapy. Here, we compare our data about the risk to develop infectious disease and non-melanoma skin cancer in solid organ transplantation recipients, together with a meta-analysis of data recently reported

by literature about this topic.

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INTRODUCTION

It has been shown that patients receiving solid organ transplants have an increased risk of developing cutaneous infectious disease and skin tumours, as consequence of the long-term immunosuppressive treatment^[1-3]. Infective complications are an important cause of morbidity and mortality, and the introduction of potent immunosuppressive agents like tacrolimus or mycophenolate mophetil may result in an increased risk of bacteric, fungine or viral infections^[4]. The risk to develop skin cancer increase over the time and the various immunosuppressive regimens has different oncogenetic potential: the risk to develop a skin cancer is mainly related with azathioprine and cyclosporine^[5], whereas mammalian target of rapamycin inhibitors have been associated with a lower incidence of *de novo* skin cancer^[6]. However, the risk could also depend by other endogenous and exogenous conditions: history of sunburns and ultraviolet (UV) exposure, life habits, skin phototype, concomitant infections and specific genetic signatures can have a major impact in the onset and progression of these specific tumours^[6-8]. In particular, different oncogenic and non-oncogenic Human papilloma virus (HPV) strains are frequently isolated from both normal skin and cutaneous tumours in transplant recipients, but their carcinogenetic role should be definitively established.

In this study, we report data about infective skin diseases and cutaneous tumours in a group of 436 renal transplant recipients followed-up at our centre. We also provide an overview and meta-analysis of data published in the recent literature about this topic.

MATERIALS AND METHODS

Data about 436 renal transplant recipients with a dermatological follow-up at our centre were recorded. The 61.3% of these were males and the 38.7% females; median age at transplantation was 50 years and the median duration of immunosuppression was 7.2 years. For each patient, we evaluated the presence of any infectious dermatological disease and the development of skin cancers.

Moreover, a review of the English language literature of the last 20 years was performed using the MEDLINE database, using the key words “infectious skin diseases”, “cutaneous tumours” and “solid organ recipients”. We included only peer reviewed series with more than 50

cases; single case reports and series with less than 50 cases were excluded as well as articles published on journals without peer review system. No restrictions on the basis of ethnicity were applied.

Fifty-two papers were considered for the analysis.

Statistical analysis was performed with SPSS software (SPSS, Chicago, IL) and with Kaplan-Mayer curves.

RESULTS

Infective disease

Viral, bacterial and fungal diseases were frequently reported in almost all the solid organ recipients cohort published in literature. In our cases, infectious diseases were the most frequent dermatological disorders that were diagnosed after transplantation, affecting the 16.7% of patients.

Viral infections

Herpes simplex virus (HSV) infections are relatively frequent in organ transplant recipients. Infections with reactivated HSV occur with an incidence of up to 35% primarily in the first three weeks following transplantation^[9]. Marrow transplant patients are most at risk, but also solid organ transplant recipients show an higher incidence of HSV infections than immunocompetent people especially when preventive antiviral treatment was not performed^[10]. There are very different incidence rates of HSV infections in literature depending on the type of immunosuppressive treatment, the geographical area considered and the mean time from transplantation (Table 1). However, there are no remarkable differences when considering the type of organ transplanted. We found a prevalence of HSV recurrent infections (2.4%) similar to those reported by Bakr *et al*^[11] and Belloni-Fortina *et al*^[12].

Human herpesvirus 6 and 7 (HHV-6 and HHV-7), ubiquitous in humans, cause exanthema subitum in childhood and remain in a latent form in the body after primary infection. Two to three weeks following transplantation up to 30% of all transplant recipients have a reactivation of HHV-6 even if most infections remain asymptomatic^[13].

Primary or recurrent varicella zoster virus (VZV) infections can occur in 1%-30% of solid organ transplant recipients with a mean time of onset from transplantation of 9-23 mo and a peak after 6 mo^[14]. As it can be seen in Table 1 some authors report lower incidence rates of VZV infections probably because herpetic eruptions develop more commonly during the first year after transplantation^[15] and the mean time since transplantation was lower than 1 year^[11,12]. Cito megalo virus (CMV), another member of Herpesvirus, is found in 50%-75% of solid organ transplant recipients. CMV rarely causes cutaneous infections but can facilitate other opportunistic skin infections by modulating cell-mediated immunity^[14].

Viral warts and condiloma acuminata are clinical expression of HPV infection. Viral warts are frequent in long-term immunosuppressed patients with prevalence rates

Table 1 Incidence of viral infections in solid organ recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	HSV infections	VZV infections	HPV infections
Greenberg <i>et al</i> ^[53]	68/Kidney	NA	NA	NA	NA	10 (14.7)	NA	NA
Hogewoning <i>et al</i> ^[15]	134/Kidney	32.6 ± 10.3	80/54	NA	NA	9 (6.7)	24 (17.9)	NA
Bakr <i>et al</i> ^[11]	302/Kidney	35.9 ± 11.3	216/86	0.25-23 yr	Miscellaneous	9 (3)	3 (1)	33 (10.9)
Savoia <i>et al</i> ^[65]	286/Kidney	NA	273/163	9.3 (0.1-39.8) yr	66.7% combination therapy (tacrolimus in 90%)	11 (2.5)	NA	45 (10.3)
Belloni-Fortina <i>et al</i> ^[12]	161/Liver	47.4 ± 11	116/45	NA	NA	3 (2)	3 (2)	30 (19)
Lima <i>et al</i> ^[22]	53/Kidney	44	28/25	52.5% of patients over 5 yr	44% prednisone 31% mycophenolate	3 (5.7)	4 (7.5)	14 (26.4)

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by herpes simplex virus (HSV), varicella zoster virus (VZV) and human papilloma virus (HPV) infections. NA: Data non available in the considered study; M: Male; F: Female.

-ranging from 35% and 85% 5 years after transplantation^[15,16]. We found a prevalence of 12.2% similar to those reported in different studies conducted on other kidney and liver transplant patients^[11,12].

Viral warts usually develop on sun-exposed areas, especially in fairer skin-type patients. They are usually multiple and display fewer tendencies for spontaneous regression than in immunocompetent individuals. Their extension may be so widespread to constitute general verrucosis. The types of human HPV found in organ transplant recipients may be different from that seen in the general population. In a study, nine of 10 HPV detected in organ transplant recipients were gamma-PV and one belonged to the genus beta-PV^[17]. Other authors report that the most frequent HPV types are HPV-5 and HPV-8, *i.e.*, the same types that can be easily found in epidermodysplasia verruciforme (EV)^[18].

Bacterial infections

In the first month by transplantation there is an high frequency of generally trivial nosocomial diseases. The frequent wound infections that can be seen in this period are increasingly been caused by antibiotic resistant strains [vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus Aureus* (MRSA)]^[11,19].

In immunosuppressed individuals *Staphylococcus aureus* infections manifest frequently as pyoderma. However, subcutaneous abscesses, erysipelas, and impetigo may develop in the long term^[14].

Interestingly a prospective study on 604 heart transplant patients report an high prevalence of infections in the first year from transplantation with a majority of bacterial infections^[20], probably as a consequence of higher dosage of immunosuppressive treatment in order to avoid acute rejections. However, when considering only skin infections, the prevalence was similar to those reported by Perera *et al*^[21] and Lima *et al*^[22]. When confronted to other reports (Table 2), bacterial infections were relatively rare in our experience and occurred only in 1.4% of the patients.

Necrotizing fasciitis (NF) is a devastating infectious disease with 0.04 cases per 1000 person-years in the

general population. The mortality rate is 25% to 30% and the most common pathogen in type II NF is *Streptococcus pyogenes*^[23]. The characteristics of NF in renal transplant patients are poorly understood due to the rarity of NF in this population. To date, there have only been described 12 cases^[24]. When comparing with NF in immunocompetent individuals, fungal etiology appears more common but, surprisingly, the overall mortality rate is lower (16.7% *vs* 25%-30%). Age and use of mycophenolate are associated with an increased risk of death^[24].

Nocardiosis is a rare opportunistic infection caused by aerobic Actinomycetes *Nocardia* and can be associated with severe complications in kidney transplant recipients. Studies showed, in the last 2 decades, that the incidence of *Nocardia* infection in kidney transplant recipients was approximately 0.4%-1.3%^[25]. To date, more than 70 cases of Nocardiosis in renal transplant recipients have been described. Nocardiosis appears after a mean time of 34.1 mo from transplantation and is more frequent in patients with a prior history of acute rejection and in treatment with cyclosporine. Lung, brain, skin, and subcutaneous tissue were the most frequently involved organs^[26]. The mortality rate varies between 16.67%^[26] and 25%^[27].

Although the incidence of tuberculosis in renal transplant recipients is 5 times higher than in the general population tuberculosis is still rare in organ transplant recipients with reported rates of 0.35%-15% depending on the geographical area considered^[19]. Among infected transplant recipients, 63% have a pulmonary involvement, 25% have systemic dissemination and 12% have an exclusively extrapulmonary involvement^[28].

Skin involvement is generally a sign of disseminated tuberculosis and imposes the research of a visceral involvement. Only 18 cases of cutaneous miliary tuberculosis in patients older than 15 have been described in literature from 1889 and 1991^[29-31].

Atypical mycobacterioses are rarer than *M. tuberculosis* infections and are seen in 0.16%-2.8% of solid organ transplant recipients^[32]. Among them, some sporadic cases of infections by *M. Abscessus* and *M. Marinum* are reported in literature^[33,34].

Table 2 Incidence of bacterial infections in solid organ recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	Bacterial infections
Bakr <i>et al</i> ^[11]	302/Kidney	35.9 ± 11.3	216/86	0.25-23 yr	Miscellaneous	47 (16) Mainly folliculitis and impetigo
Hogewoning <i>et al</i> ^[15]	134/Kidney	32.6 ± 10.3	80/54	NA	NA	28 (20.9) Mainly folliculitis, ectyma and erysipelas (3)
Alangaden <i>et al</i> ^[66]	127/Liver	47 ± 12	79/62	NA	79% prednisone 72% tacrolimus 28% sirolimus	17 (13) Mainly wound infections and skin and soft tissue infections
Perera <i>et al</i> ^[21]	100/Liver	42.5	NA	5.5 (0.75-16) yr	35% cyclosporine, azathioprine and prednisone 48% prednisone and tacrolimus 17% tacrolimus	5 (5) Mainly folliculitis and 1 case of erythrasma
Sánchez-Lázaro <i>et al</i> ^[20]	604/Heart	51	506/98	First year after transplantation	NA	36 (5.9)
Savoia <i>et al</i> ^[65]	286/Kidney	NA	273/163	9.3 (0.1-39.8) yr	66.7% combination therapy comprising tacrolimus in 90%	6 (1.4) All cases of erysipelas
Lima <i>et al</i> ^[22]	53/Kidney	44	28/25	52.5% of patients over 5 yr	44% prednisone 31% mycophenolate	3 (5.7) 2 cases of furuncle and 1 cellulitis

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by bacterial infections; when available, type of bacterial infection has been specified. NA: Data non available in the considered study; M: Male; F: Female.

Table 3 Incidence of fungal infections in solid organ transplant recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	<i>Candida spp</i>	<i>Malassezia furfur</i>	<i>Dermatophytes</i>
Virgili <i>et al</i> ^[36]	73/Kidney	22-68	44/29	0.25-26 yr	50.7% association of prednisone, cyclosporine and azathioprine	4 (5.4)	20 (27.4)	7 (9.6)
Güleç <i>et al</i> ^[37]	102/Kidney	31.9 ± 10.3	68/34	4.5 ± 4.55 yr	38.2% association of prednisone, mycophenolate and cyclosporine	31 (30.4)	37 (36.3)	10 (9.8)
Perera <i>et al</i> ^[21]	100/Liver	42.5	NA	5.5 (0.75-16) yr	48% association of prednisone and tacrolimus	19%	4%	11%
Lima <i>et al</i> ^[22]	53/Kidney	44	28/25	NA	83% prednisone 58.5% mycophenolate 50.9% cyclosporine	14 (22.6)	9 (17)	8 (15)

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by fungal infections. NA: Data non available in the considered study; M: Male; F: Female.

Fungal Infections

Among superficial fungal infection, candidiasis of the mouth and intertriginous skin areas is frequent in the early post-transplant time^[35], probably as a consequence of the higher dosage of immunosuppressant treatment in this period (Tables 3 and 4).

Pityriasis versicolor (PV) is such as frequent as superficial candidiasis. Some authors reported prevalence rates of this infection caused by *Malassezia furfur* higher than 30% in cohorts of renal transplant patients^[36,37]. Whereas, there are very few literature reports about the prevalence of PV in other solid organ transplant recipients. Perera *et al*^[21] report a prevalence ratio of PV of 4% in a group of liver transplant recipient. In our cohort, mycosis, mainly represented by onychomycosis, tinea cruris and genital candidiasis, were observed in the 1.8% of cases.

Deep fungal infections comprise two distinct group of conditions, the subcutaneous and systemic mycoses. Subcutaneous mycoses are caused by fungi that have been introduced directly into the skin through a penetrating injury^[36,38]. Systemic dissemination is rare in the immunocompetent patients but could be more frequent in immunosuppressed subjects. Sporotrichosis, mycetoma and chromoblastomycosis are the most frequent subcutaneous infections observed in this group of patients.

Systemic mycoses are fungal infections whose initial portal entry into the body is usually a deep site (*e.g.*, lung and gastrointestinal tract). Skin is usually affected as consequence of systemic dissemination but it may be the primary site in the immunocompromised patients that usually develop systemic candidiasis, aspergillosis, histoplasmosis and cryptococcosis^[39-42]. Incidence rates of

Table 4 Incidence of fungal infections in solid organ transplant recipients *n* (%)

Ref.	No. of cases/ population	Age (yr)	M/F	Median follow- up time	Therapy	Systemic infections	<i>Candida</i> spp	<i>Aspergillus</i> spp
Collins <i>et al</i> ^[45]	158/Liver	46	84/74	NA	Cyclosporine, azathioprine and prednisone	34 (21.5)	28 (17.7)	5 (3.2)
Briegel <i>et al</i> ^[44]	141/Liver	47 ± 12	79/62	NA	Prednisone, cyclosporine and azathioprine	25 (17.7)	10 (7)	11 (7.8)
Kanj <i>et al</i> ^[46]	73/Heart-Lung	NA	NA	NA	NA	37 (50.6)	19 (26)	18 (24.6)
Abbott <i>et al</i> ^[47]	33479/Kidney	43	20154/13325	NA	72.2% with cyclosporine, 65.2% with mycophenolate	595 (1.7)	445 (1.3)	80 (0.2)
Singh <i>et al</i> ^[39]	130/Liver	NA	NA	NA	tacrolimus	11 (14)	6 (5)	4 (3)
Alangaden <i>et al</i> ^[66]	127/Kidney	47.1 ± 12.5	76/51	NA	72% tacrolimus	5 (3.9)	5 (3.9)	NA
Pugliese <i>et al</i> ^[67]	278/Miscellaneous	NA	NA	5.5 ± 5.9 yr	Various	46 (16.5)	45 (16.2)	1 (0.3)
Tessari <i>et al</i> ^[43]	3293/Miscellaneous	NA	2384/909	NA	NA	22 (0.7)	NA	NA

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age, sex, median follow-up time after solid organ transplantation, type of immunosuppressive treatment and the percentage of patients affected by systemic fungal infections. NA: Data non available in the considered study; M: Male; F: Female.

deep fungal infections in solid organ transplant recipients varies from 0.5% to 30%^[39,40]. These studies, however, do not clearly distinguish between primary deep skin mycoses and systemic infections. In an Italian series of 3293 consecutive organ transplant recipients with a mean follow-up time since transplantation of 2.5 ± 2 years, only 22 cases of deep mycoses were detected with a prevalence ratio of 0.7%. Six patients had subsequent systemic involvement and three died of systemic dissemination^[43]. In a US study conducted on 130 liver transplant patients the authors found 6 cases of systemic candidiasis and 4 of aspergillosis^[19]. Other older series conducted on liver transplant patients and exclusively based on detection of systemic mycosis found higher rates of *Candida* and *Aspergillus* infections^[44,45]. This higher incidence could probably derive by an higher use of cyclosporine and azathioprine as tacrolimus and sirolimus weren't still commonly used until the late 90 s.

When considering lung transplant recipients, invasive fungal infections occur in 15% to 35% of the patients with *Aspergillus* species accounting for nearly half of them^[46-48]. The reported prevalence of *Candida* infections is similar^[46].

On the other, hand kidney transplant patients seem to be less frequently affected by invasive fungal infections as reported in some United States series^[38,47]. This incidence could be affected by a lower dose of immunosuppressive treatment and a higher use of tacrolimus instead of cyclosporine and azathioprine when confronted with lung and liver transplant recipient.

Cutaneous tumours

Data about the risk to develop non-melanoma skin cancer (NMSC) and the clinical characteristics of the various published series are resumed in Table 5.

The percentage of NMSCs diagnosed after a solid organ transplantation varied from 25% to 35% in the larger series published by literature^[3,49,50]. The Basal cell carcinoma (BCC)/Squamous cell carcinoma (SCC) ratio was from 1:1.2 to 1:7^[3,49-51]. Fekets *et al*^[52] report a

significantly lower percentage of solid organ recipients affected by NMSC (9.5%), but in this study there is a bias due to the relatively short follow-up period.

The 23.5% of our patients developed a NMSCs in the post-transplant period, with a BCC/SCC ratio of 2.45:1. This percentage was similar to that reported in our previous work, conducted on smaller series^[53]. Fifty-four per cent of BCCs and 81% of SCCs develop on sun-exposed areas. Patients who developed skin cancers were preferentially males ($P = 0.0017$) and were characterized by a significantly higher age at transplantation ($P < 0.001$) and by a significantly longer duration of immunosuppressive regimen ($P < 0.0001$), according with data reported by others authors^[3,50,54]. Also elderly patients^[51] showed a higher risk to develop cutaneous tumours. In our experience, exogenous risk factors significantly linked to NMSC risk were outdoor job ($P = 0.0413$), as well as demonstrated in others series^[52,53], and incorrect use of sunscreen ($P = 0.0252$). We failed to demonstrate a significant association between lower phototypes and risk of NMSC, as demonstrated by several literature series^[3,50,51,53].

In the majority of published studies, cyclosporine and/or azathioprine-based immunosuppressive regimens showed a significant correlation with the risk of developing skin cancer^[3,49,51,52]. On the contrary, we could not identify a specific immunosuppressive drug as a distinctive factor for the development of NMSC.

DISCUSSION

Organ transplantation ensures a prolonged life expectancy and a better quality of life for patients affected by chronic renal, liver, lung or heart failure. However, long-term immunosuppressive therapy causes important inhibitory effects on immune defence mechanism, leading to frequent skin infections and malignancies that are an important cause of morbidity and mortality for solid organ transplant recipients^[1-3].

The schedule of immunosuppressive drugs influences

Table 5 Risk to develop non-melanoma skin cancer and clinical characteristics of the various published series

Ref.	No. of cases/ population	NMSC	BCC/SCC ratio	Median age at transplantation	Median follow- up time	Risk factors associated with NMSC
España <i>et al</i> ^[54]	92/Heart	15.2%	1:1.5	NA	NA	Immunosuppression UV exposure Skin type
Ong <i>et al</i> ^[68]	455/Heart Australia	31%	3:1	NA	NA	Caucasian origin Age at transplantation Duration of follow up Cyclosporin
Hiesse <i>et al</i> ^[5]	1710/Kidney France	7.5%-8.2%	NA	35.5 yr	9 yr	
Moloney <i>et al</i> ^[8]	1755/Kidney Ireland	27.7%	1:2	40 yr	5.35 yr	Age at transplantation Duration of immunosuppression Age at transplantation Male sex
Mackenzie <i>et al</i> ^[49]	384/Kidney New Zealand	25%	1:1.2	41.5 yr	5.3 yr (0.01-33.4)	Cyclosporine/Azathioprine Duration of immunosuppression
Sandoval <i>et al</i> ^[63]	91/Kidney Chile	16%	1:1-9	NA	7.3 yr (1 mo-29 yr)	
Fekecs <i>et al</i> ^[52]	116/Kidney, pancreas Hungary	9.5%	1:4	49.3 yr	NA	Painful sunburns Occupational UV exposure Cyclosporine

For each literature study has been indicated number of included patients, type of solid organ transplantation, median age at transplantation, median follow-up time after solid organ transplantation, percentage of patients affected by NMSC and BCC/SCC ratio. Risk factors significantly associated to the development of non-melanoma skin cancer in each study are indicated in the right column. NA: Data non available in the considered study; UV: Ultraviolet; NMSC: Non-melanoma skin cancer; BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma.

the type and the timing of skin disease. The main problems in the first months are usually represented by wound infections and HSV reactivations, whereas opportunistic infections and herpes zoster develop mainly within 6 months from transplantation. Thereafter, as immunosuppression is reduced, the most frequently observed skin infections are represented by mycoses and HPV infections^[55]. On the contrary, the risk to develop skin cancer increases over time: the cumulative incidence of skin cancers increases significantly with the duration of graft, increasing from 5% after 1 year to 43% after 10 years, as demonstrated in several European series^[51,52]. In the kidney recipients from our series the median time to onset of skin tumours was 9.9 years from the transplantation.

Moreover, tacrolimus and micophenolate mofetil are mainly related to the risk to develop skin infections, whereas the higher carcinogenic risk has been described for azathioprine and cyclosporine^[3,6,49,51]. The oncogenic power of cyclosporine in solid organ recipients was confirmed by a large retrospective study^[5] that demonstrated a risk of skin cancer significantly higher in the group of CyA-treated patients in comparison with the historical group of patients treated with azathioprine-steroids regimens. Moreover, it has recently been demonstrated that azathioprine induces chronic oxidative stress by forming reactive oxygen species (ROS) causing mutagenic damage of the DNA, that could lead to development of NMSC in organ transplantation recipients.

In literature^[55-57], the frequency of HPV infections in transplant recipient varies from 6% to 92%, depending on the type and the duration of the immunosuppressive protocol. We observed viral warts in 10.3% of patients from our series, a percentage superimposable to that

of 8.2% recently reported in another Italian study^[58], probably due to the similarity in the immunosuppressive treatment schedules. Despite some investigations demonstrated that persistent HPV infections can induce malignant transformation of squamous epithelial cells by inactivation of p53, and clinical and histological analyses show progression of viral warts *via* dysplastic lesions up to invasive squamous cell carcinomas, the pathogenic role of HPV in skin tumorigenesis is still in part unclear^[59]. With the use of PCR methods, a prevalence of HPV in 69%-88% of squamous cell carcinoma in transplant recipients was found, in particular high-risk HPV types like HPV-16 and epidermodysplasia verruciformis associated HPV types. The prevalence in organ transplant recipients is significantly higher in comparison to immunocompetent patients (about 50%)^[60]. On the other side, there were no significant differences of HPV prevalence in basal cell carcinoma between immunocompromised and immunocompetent individuals^[1].

Herpes zoster was diagnosed in 2.1% of our patients; this percentage is relatively lower in comparison with data reported by other authors^[55]. However, no significant differences from other series were found when data were stratified on the basis of different age groups. In fact, Herpes zoster affects essentially patients over 60 years, whereas median age of our population was 50 years. In transplanted patients, HSV and HVZ usually provoke limited infections but can also generate diffuse, hemorrhagic, ulcerated and widespread skin lesions more frequently than in immunocompetent individuals^[61]. Also visceral implication are not rare.

When confronted to other reports, bacterial infections were relatively rare in our experience. This could be

considered a consequence of an higher mean time from transplantation in our cohort, as it has been seen that bacterial infections develop more frequently in the first month from transplantation. Moreover we didn't consider folliculitis because they were all of minor entity and we believed that they were more associated to chronic use of steroid rather than to bacterial infections.

A wide variation (7%-75%) in the frequency of superficial fungal infections is reported in several studies; literature data suggest that cutaneous fungal infections in renal transplant recipients are more common in tropical and sub-tropical countries^[37]. However, different authors report similar prevalences of dermatophytosis in immunosuppressed and immunocompetent people. Probably that could derive by the necessity of the coexistence of an environmental exposure to pathogenic fungi together with the administration of immunosuppressive agents^[37]. Also in our experience, the incidence of superficial fungal infections was low, and only 3 cases of onychomycosis (1.1%) were identified. Systemic fungal infections occur in the 5%-20% of solid organ recipients, mainly caused by *Candida* or *Aspergillus*^[55].

The problem about increased risk of skin cancer in solid organ transplant recipients is well known in literature. In particular, it has been estimated a 10-fold increased risk for BCC and a 50-100-fold for SCC. In our experience, the percentage of patients who developed NMSC was 24.8%. This percentage and the BCC/SCC ratio were similar to those reported in recent studies conducted in Italy^[7,58] and Spain^[50,62] (22% and 25.2%, respectively), probably due to the similarity in skin phenotype, exogenous risk factors exposure and in the immunosuppressive treatment schedule^[49,63]. On the contrary, the prevalence of skin cancers in a group of Australian kidney transplant recipients was significantly higher (35%), supporting the importance of latitude and sun exposure on tumour development^[3]. Moreover, differences in the median age at transplantation in the various series could partially justify the variability in the percentage of patients that develop a NMSC. Higher age at transplantation is in fact a factor strictly related to the risk of skin cancer in the majority of published series^[3,49,50,64]. The length of follow-up could also represent a bias in the different series; the majority of the authors state in fact that the risk to develop cutaneous tumours increase over the time, as the consequence of the longer immunosuppression period^[8].

In conclusion, solid organ transplant recipients today have a prolonged life expectancy and a better quality of life. However, cutaneous infections and NMSCs can heavily impact on the quality of life and prognosis of these patients. For this reason it is necessary to perform periodical accurate dermatological controls in order to promptly identify any suspicious lesions. Individual follow-up programs should be realized on the basis of specific risk factor analysis, to optimize the cost-benefit ratio.

COMMENTS

Background

Cutaneous disorders are frequent in chronic renal failure. The majority of these dermatological disorders disappear after kidney transplantation; however, infectious diseases and cutaneous malignancies occur frequently in organ transplant recipients, mainly as a consequence of the long-term immunosuppressive treatment. Infectious skin diseases were frequently diagnosed after transplantation, affecting about the 16.5% of patients whereas dermatological screening identifies cutaneous tumours in about 35% of KTR patients. The relative risk of developing skin cancer is 20 to 40 fold increased, in comparison with the general population.

Research frontiers

Type and duration of the immunosuppressive treatment are currently considered as the major factors related to the development of infective and malignant skin lesions in patients receiving solid organ transplants. However other endogenous and exogenous risk factors can justify the different prevalence ratios reported in several literature studies.

Innovations and breakthroughs

Comparing data from the English language literature of the last 20 years with the results from our cohort of 436 kidney transplant recipients, the authors highlight the characteristics and risk factors for the different skin diseases occurring in transplant recipients.

Applications

Development of an integrated risk stratification protocol for skin diseases in transplant recipients with the aim of optimizing cost-benefit ratio of their treatment.

Peer review

The authors have performed a good study, the manuscript is interesting.

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Fate of meta-analyses: The case of *Helicobacter pylori*

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Conflict-of-interest: I disclose any financial or personal relationship with other people/organization that could inappropriately influence their work (employment, consultancies, stock ownerships, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding).

Data sharing: I declare that the data the present manuscript is based on meta-analysis published in the literature, there are no personal data concerning the patients or any other person, and the manuscript was not shared with any unauthorized person. There were no persons/participants who would have given informed consent, so there are definitely no harms outweighing the potential benefits.

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from PubMed/Medline. The topics of meta-analyses were determined. Some topics (genetics, extragastric tumors) were analysed separately. Core journals publishing meta-analyses on *Helicobacter pylori* were ranked. The rate of citation of meta-analysis in major guidelines was calculated.

RESULTS: Between 1992 and 2014, some 356 meta-analyses were published on PubMed. These mainly appeared in core journals, but were also found in 128 other journals. Eradicating of the infection was the most addressed topic with 134 articles. Meta-analyses were rarely used in formulating statements and recommendations in the international guidelines. In other topics - genetics, extraintestinal manifestations - meta-analyses were rather overused.

CONCLUSION: The implementation of meta-analysis in current guidelines is rather rare, while other topics benefit from many studies. A more extensive use of meta-analyses in evidence-based medicine is recommended in the future, otherwise their continuous proliferation will lose reason and scientific significance.

Key words: Consensus guidelines; *Helicobacter pylori*; Meta-analysis; Randomised controlled trials; Systematic review

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Core tip: The article provides a subjective overview of the meta-analysis published on the subject of *Helicobacter pylori*, profiling the topic, their distribution in literature, giving examples of over- and underuse, and revealing a discordance between the low implementation of meta-analysis in guidelines and their importance as top-level evidence.

Abstract

AIM: To overview the current diversity of meta-analysis and the implementation of their results in international guidelines.

METHODS: Relevant meta-analysis were identified

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INTRODUCTION

The discovery of *Helicobacter pylori* (*H. pylori*) had a tremendous impact on the clinical practice, public health and basic research, leading to an unsurpassed proliferation of written and electronic literature^[1]. Besides 35472 articles published in peer-reviewed journals (<http://www.pubmed.com>, accessed on September 5 and 30, 2014), dozens of printed and some e-books have been published in the past 30 years. The plethora of literature created confusion, as readers were faced with many contradictory results and statements. The general purpose of this subjective overview is to present the development from a historical viewpoint and the current state of meta-analysis in the field of *H. pylori*; specifically, to analyse the use and implementation of meta-analytical results in current international guidelines for diagnosing and treating of the infection.

Historical background

The history of meta-analysis differs according to the source: according to the anonymous writer of Wikipedia's entry, the first meta-analysis was performed by Chinese philosopher Chu Hsi^[2] (1130-1200) by simply summarising data from literature of his time. Scholars date the roots of meta-analysis back to the 17th century, when Blaise Pascal (1623-1662) approached games of chance mathematically^[3]. The first medical meta-analysis was published in 1904: Karl Pearson^[4] (1857-1936) summarised data on the effect of enteric fever bacteria inoculation in volunteer soldiers across the British Empire and studied the association of infection, mortality and inoculation. Considerable progress was subsequently made by the works of Ronald Fisher (1890-1962) and Frank Yates (1902-1994), although they were active in the agricultural field. William Gemmel Cochran (1909-1980) stressed the need for randomised controlled trials and studied the results of the then in vogue vagotomy for curing peptic ulcer. In the modern era, the first meta-analysis was performed by Gene V Glass^[5], a psychologist at the University of Colorado, in 1976. He also coined the term "meta-analysis", which later gained several entries and definitions in dictionaries (Merriam-Webster's, Dorland's Medical Dictionary, A Dictionary of Epidemiology, *etc.*).

Meta-analysis is a rapidly evolving field of statistics and over the past 3 decades increasingly sophisticated methods have been developed: these are available in books^[6,7], online courses are also accessible and included in statistical packages and software programmes. It became clear that robust meta-analytical data could only be obtained by using (1) a selection of high-quality trials; and (2) a complex statistical workup of the data, including an assessment of heterogeneity, effect sizes, random or fixed effects, subgroup analysis, meta-regression, publication bias, *etc.* Specific statistical methods were introduced from 2002, when Higgins *et al.*^[8] from Cambridge University elaborated methods to identify heterogeneity between studies. The QUORUM and PRISMA statements were proposed in 2006 and 2010 respectively, as a uniform

reporting mode for meta-analysis: unfortunately, only a small number of authors report their results according to these statements^[9]. Weak data leads to uncertain results and doubtful conclusions: mixing of good and bad studies is an early mistake and is increasingly avoided in recent studies; on the other hand, weak data is perhaps better than no data at all. For reasons unknown to the author, there are no mega-trials on *H. pylori* including thousands of patients as in the case of hypertension, diabetes or hyperlipidaemia treatment. Most of the studies on *H. pylori* included a rather small number of cases and under these circumstances, assessing heterogeneity and selecting adequate statistical methods are of pivotal importance. This was not always the case. In the meantime, other more sophisticated methods emerged, like network- and combinatorial meta-analysis: both are only starting to be used in *H. pylori* research.

It must be emphasised that meta-analyses are (1) retrospective; and (2) they include studies on populations with different ethnic and genetic backgrounds, mostly geographically remote from each other, and probably infected with different strains of *H. pylori*, resulting in a "mixed bug". Therefore, meta-analysis do not rule out the need for local, well-designed, prospective and adequately sized controlled trials^[6,9].

Systematic reviews are structured studies of a focused subject-*H. pylori*, in our case-aiming to synthesize the evidence from the literature based on the most relevant publications. They may or may not use statistics to combine the results of the selected studies (both full-length articles or abstracts). The PRISMA statement standardised the requirements the complete reporting requirements for systematic reviews^[9]. In practice, meta-analysis and systematic reviews are often performed and reported together.

The fate of meta-analysis in *H. pylori* research

The first meta-analysis on *H. pylori* was published 10 years after the discovery of the bacterium: Chiba *et al.*^[10] from the McMaster University, Canada calculated the pooled eradication rates of single, double and triple therapies against *H. pylori* from 27 studies. In 1996, Scandinavian authors assessed the efficiency of omeprazole-based and bismuth-based triple therapies in the same way^[11]. Obviously, these studies are no longer valid today because of the simplified methodology, and many other regimens against the infection have been proposed in the meantime^[12].

MATERIALS AND METHODS

Using the MESH terms "*Helicobacter pylori*" AND "meta-analysis" AND "systematic review", 504 articles were found in Medline/PubMed (accessed on September 5 and 30, 2014). After reviewing the abstracts, 148 were found to be irrelevant to our subject and 356 eligible meta-analyses/systematic reviews were identified. This is a fairly low compared to other fields (Table 1) (PubMed, accessed on September 30, 2014), but comparable with

Table 1 Number of meta-analyses published on selected topics (from PubMed, accessed on September 30, 2014)

Topic/field	No. of meta-analyses
Diabetes mellitus	3245
Hypertension	2964
Coronary heart disease	3159
Gastrointestinal cancer	2787
Statins	957
Hepatitis C	550
Liver cirrhosis	435
Proton pump inhibitors	356
<i>Helicobacter pylori</i>	356
Peptic ulcer	395
Gastroesophageal reflux	231

other gastrointestinal diseases. The articles were classified according to their topic and method of study (meta-analysis, systematic review or combined) and total percentages were calculated (Table 2).

The spectrum of journals publishing meta-analyses and systematic reviews on *H. pylori* was also studied and a group of core journals was selected, defined arbitrarily as those publishing > 10 meta-analyses and/or systematic reviews (Table 3).

The reference list of the main consensus meetings between 2007 and 2013 (Table 4) was searched for citations of meta-analysis and a similarity analysis was performed^[13-19].

To assess the average citation rates, five meta-analyses published in core journals between 2006 and 2010 were randomly selected and their citation was searched on the Web of Science (accessed on September 4, 2014)^[19-23]. The reference list of 5 randomly selected expert review articles from special issues on *H. pylori*, published with the 20th anniversary of the *World Journal of Gastroenterology* was also analysed^[24-28].

RESULTS

Our search identified 356 studies. Most of the authors (75%) preferred to use meta-analysis, the rest of the studies were either systematic reviews (11.3%) or a combination of the two methods (13.4%). This preference for meta-analysis was maintained in almost every one of the 14 topics (Table 2).

The topic addressed most often was that of eradication therapy: 134 (37.6%) papers analysed the efficiency of antimicrobial regimens against *H. pylori*, followed by the extraintestinal manifestations of the infection (49 studies, 13.7%) and genetics (32 articles, 8.9%). The association of the infection with tumours other than gastric cancer also elicited high interest with 26 studies (7.3%) (laryngeal cancer: 1, oesophageal: 8, pancreatic: 5, colon: 7, liver and biliary tract: 2, lung: 1). Although peptic ulcer disease is the most important complication of *H. pylori* infection, it merited only 9 studies (2.5%).

Of the 356 studies, 153 (42.97%) were published in 7 core journals (Table 3). The rest of the articles (203,

57.29%) were found in 128 journals, mostly publishing 1-2 meta-analyses on *H. pylori*. Top-ranked journals such as *Gastroenterology*, *Gut* and *Lancet* published a small number of studies on this topic (editorial policy? high rate of rejection?). Impact factors and the number of meta-analysis published were seemingly not related.

The citation rate of meta-analysis in recent reviews on *H. pylori* is also low, achieving a mean of only 7.5%/article. By contrast, the citation of meta-analysis in journals of gastroenterology published between 2006 and 2010 is fairly high (43-172, with a mean of 97 ± 28 citations).

DISCUSSION

Inclusion of meta-analysis in the consensus statements

In biomedical research, meta-analyses are considered the highest level of evidence. The importance of these studies was recently summarised by Gisbert^[12] of Madrid, who performed 36 meta-analyses and systematic reviews with his team between 2003 and 2013, concluding that “meta-analysis provides a means of combining raw statistical data from all eligible primary studies addressing an identical question of interest to arrive at conclusions that are more precise and reliable than those presented in a single study.” By analysing all regimens against the bacterium historically, he stated that “meta-analysis has contributed in a relevant way to our understanding of the management of patients with *H. pylori* infection”.

It could be expected that their results would be included in the recommendations of expert panels. Surprisingly, meta-analysis and systematic reviews represents only 10.6% of the citations in international guidelines (Table 4), and 34% of the cited meta-analyses are identical (*i.e.*, cited in ≥ 3 consensus materials). One can conclude, that meta-analyses are underused in formulating consensus statements. Experts probably prefer to express their opinion based on randomised controlled trials and basic science.

In some areas, meta-analysis seems to be overused (extraintestinal manifestations of *H. pylori* infection, its associations with extragastric cancers, genetics) resulting in little practical use. Their release in the medical press could be explained by publication pressure too. According to most consensus statements, however, eradication of the infection is only recommended in cases of iron deficiency anaemia and idiopathic thrombocytopenic purpura. Although genetics was studied extensively, genetic counselling and tests are neither available nor recommended in diseases associated with *H. pylori* infection.

The association of extragastric cancer with the infection is largely documented, but there is no recommendation to screen and treat the infection in high risk patients, as it is in first-degree relatives of gastric carcinoma patients. In all these cases, however, association does not mean causation, further studies are necessary to see if the associations are casual or causal.

In a random selection of recent expert reviews, meta-analyses are again barely cited^[20-23] (Table 5), excepting the

Table 2 Profile and No. of published meta-analyses and systematic reviews on *Helicobacter pylori*

Topic	Total No. of publications	Meta-analyses	Systematic reviews	Meta-analysis + systematic review
Epidemiology	6	5	1	0
Diagnosis	23	13	4	6
Antibiotic resistance	7	5	2	0
Genetics	32	30	0	2
Eradication regimens	134	98	17	19
Extragastric manifestations	49	35	2	12
Probiotics	11	11	0	0
Peptic ulcer	9	7	1	1
Gastric cancer	16	12	0	4
Pathogenesis	22	21	1	1
Other cancers (oesophagus, colon, pancreas, liver, biliary, lung)	26	24	0	2
Children	8	7	0	1
Methodological issues	12	0	12	0
Traditional Chinese medicine	1	0	0	1
Total	356	268 (75.2%)	40 (11.3%)	48 (13.4%)

Table 3 Core journals publishing meta-analyses and systematic reviews on *Helicobacter pylori*

Title	No. of meta-analyses	Impact factor (2013)
<i>Alim Pharmacol Ther</i>	45	5.478
<i>Helicobacter</i>	27	2.993
<i>World J Gastroenterol</i>	25	2.433
<i>Am J Gastroenterol</i>	21	9.131
<i>Plos ONE</i>	14	3.534
<i>BMJ</i>	11	16.378
<i>Eur J Gastroenterol Hepatol</i>	10	2.152
Total	153	Not applicable

Table 4 Implementation of meta-analyses in international consensus guidelines

Year	Consensus meeting	No. of ref.	No. of meta-analyses/ systematic reviews cited
2007	Maastricht III consensus	99	10 (9.9%)
2007	Cervia II Working Group guideline	72	5 (6.5%)
2007	American College of Gastroenterology guideline	175	23 (13.1%)
2009	Second Asia-Pacific Consensus Guidelines	118	12 (10.1%)
2012	Maastricht-Florence 4 guideline	325	36 (11.0%)
2013	3 rd Brazilian Consensus	216	25 (11.3%)
2013	Revised Korean consensus	208	19 (9.3%)
	Total	1223	130 (10.6%)

Table 5 Citation of meta-analyses in recent expert reviews

Ref.	Year	Journal	No. ref.	No. and % of meta-analyses cited
[20]	2014	<i>World J Gastroenterol</i>	115	5 (4.3)
[21]	2014	<i>World J Gastroenterol</i>	137	8 (5.8)
[22]	2014	<i>World J Gastroenterol</i>	158	14 (8.8)
[23]	2014	<i>World J Gastroenterol</i>	69	1 (1.4)
[24]	2014	<i>World J Gastroenterol</i>	79	14 (17.7)
		Total	558	42 (7.5)

Table 6 Citation of randomly selected meta-analyses on *Helicobacter pylori* (Web of Science, accessed on September 4, 2014)

Ref.	Year	Journal	Total citations	Independent citations
[24]	2006	<i>Aliment Pharmacol Ther</i>	172	172
[25]	2009	<i>Am J Gastroenterol</i>	127	127
[26]	2009	<i>Helicobacter</i>	84	84
[27]	2010	<i>Am J Gastroenterol</i>	62	62
[28]	2010	<i>Am J Gastroenterol</i>	43	43

Spanish team, which is the most active in this field^[29].

In contrast with this, meta-analyses are adequately cited generally speaking. The data suggests, that meta-analyses are as frequently cited as other clinical studies in the literature, but not in consensus materials, where they really should be (Table 6)^[24-28]. The reason for this discordance is not known.

In conclusion, meta-analysis represent the highest level of evidence in medical research and are themselves under continuous mathematical and statistical development. In the field of *H. pylori* research, 356 meta-analyses and systematic reviews or both were published between 1992 and 2014. Although these studies are widely cited in literature, their implementation in the national/international consensus guidelines is rather rare. Other topics, of less practical importance, benefit from many meta-analyses. In the future, a more extensive use of meta-analyses would be welcome, to maintain the scientific significance of the guidelines and statements: otherwise, they will proliferate simply as a result of publication pressure and will progressively loss their scientific significance.

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COMMENTS

Background

Meta-analyses have come strongly to the fore in the past 3 decades and are considered the highest grade of evidence in medical research. Their further use and implementation in the guidelines and consensus statements is unknown.

Research frontiers

The article provides an analysis of the spectrum of meta-analysis published between 1992 and 2014 in the field of *Helicobacter pylori* (*H. pylori*) research, providing the distribution of topics, ranking of core journals publishing meta-analysis, giving examples of under- and overuse of meta-analysis in some areas. The author's main conclusion is that meta-analysis are underused in the formulation of statements from recent international guidelines for diagnosing and treating the infection.

Applications

The article suggests that meta-analysis must be more widely read, used and cited, especially when experts formulate their opinions/recommendations for treating the *H. pylori* infection. On the other side, their overuse in some topics (genetics, extraintestinal manifestations) did not resulted any benefit.

Peer review

The manuscript "Fate of meta-analysis: The case of *Helicobacter pylori*" is very interesting and original in its contents.

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Effect of institutional volume on laparoscopic cholecystectomy outcomes: Systematic review and meta-analysis

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Abstract

AIM: To determine whether institutional laparoscopy cholecystectomy (LC) volume affects rates of mortality, conversion to open surgery, bile leakage and bile duct injury (BDI).

METHODS: Eligible studies were prospective or retrospective cohort studies that provided data on outcomes from consecutive LC procedures in single institutions. Relevant outcomes were mortality, conversion to open surgery, bile leakage and BDI. We performed a Medline search and extracted data. A regression analysis using generalized estimating equations were used to determine the influence of annual institutional LC caseload on outcomes. A sensitivity analysis was performed including only those studies that were published after 1995.

RESULTS: Seventy-three cohorts (127404 LC procedures) were included. Average complication rates were 0.06% for mortality, 3.23% for conversion, 0.44% for bile leakage and 0.28% for bile duct injury. Annual institutional caseload did not influence rates of mortality ($P = 0.142$), bile leakage ($P = 0.111$) or bile duct injury ($P = 0.198$) although increasing caseload was associated with reduced incidence of conversion ($P = 0.019$). Results from the sensitivity analyses were similar.

CONCLUSION: Institutional volume is a determinant of LC complications. It is unclear whether volume is directly linked to complication rates or whether it is an index for protocolised care.

Key words: Abdominal; Cholecystectomy; Quality control; Systematic review; Meta-analysis

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Core tip: We performed a meta-analysis to determine whether institutional laparoscopy cholecystectomy (LC) volume affects rates of mortality, conversion to open surgery, bile leakage and bile duct injury. Annual institutional caseload did not influence rates of mortality ($P = 0.142$), bile leakage ($P = 0.111$) or bile duct injury ($P = 0.198$) although increasing caseload was associated with reduced incidence of conversion ($P = 0.019$). Our results suggest that institutional LC volume may be a determinant of LC complications. It is unclear whether institutional LC volume is directly linked to complication rates or whether its influence is a surrogate for improved quality of care.

Murray M, Healy DA, Ferguson J, Bashar K, McHugh S, Clarke Moloney M, Walsh SR. Effect of institutional volume on laparoscopic cholecystectomy outcomes: Systematic review and meta-analysis. *World J Meta-Anal* 2015; 3(1): 26-35 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/26.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.26>

INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most commonly performed operations—close to 400000 procedures are performed annually in non-federal community hospitals in the United States^[1] and around 50000 procedures are performed annually in the United Kingdom^[2]. LC is preferred over open cholecystectomy as it leads to a shorter hospital stay and a quicker recovery^[3]. However, there are risks of serious complications with LC such as biliary leaks (0.4%-1%)^[2,4], bile duct injury (BDI) (0.2%-0.3%)^[3,5] and mortality (0.1%-0.4%)^[3,5]. Conversion rates vary from about 15%-5%^[5].

An expanding body of evidence suggests that outcomes in a variety of conditions are improved when patients are managed in high-volume centres or by high-volume healthcare providers^[6]. High-volume centres dramatically improve the management of pancreatic cancer (≥ 20 cases per year), oesophageal cancer (≥ 30 cases per year), paediatric cardiac conditions (≥ 300 cases per year), unruptured abdominal aortic aneurysms (AAA) (≥ 36 cases per year) and acquired immune deficiency syndrome (≥ 100 cases per year)^[6]. Similarly, high-volume surgeons or physicians dramatically improve the management of pancreatic cancer (10-42 cases per year), ruptured AAAs (≥ 10 cases per year), paediatric cardiac conditions (≥ 75 cases per year), colorectal cancer (≥ 22 cases per year), carotid endarterectomy (≥ 30 cases per year) and coronary artery bypass grafting (≥ 150 cases per year)^[6]. In contrast, no proven volume-outcome relationships exist for conditions such as diabetes, cystic fibrosis, rheumatoid arthritis, appendicitis and hernias^[7,8].

Recently, data have emerged confirming that high-

volume surgeons improve outcomes following LC^[2,4,5,9-12]. Giger *et al*^[5] found improved results with surgeons who performed > 100 LCs per year, Nuzzo *et al*^[10] found improved results with surgical teams who performed > 450 LCs in three years, Csikesz *et al*^[11] found improved results with surgeons who performed > 15 LCs per year and McMahon *et al*^[12] found improved results for surgeons who had performed more than 200 cases. Andrews *et al*^[2] and Hobbs *et al*^[4] did not specify thresholds although they identified significantly reduced complications with increasing surgeon volume. However, it is unclear whether a volume-outcome relationship exists for LC at institutional level. If such an institutional relationship can be proven and understood, the creation of high-volume LC centres may become a priority. Therefore we performed a systematic review and meta-analysis focusing on institutional volume/outcome relationships for LC. The aim was to determine whether institutional LC volume affects rates of mortality, conversion to open surgery, bile leakage and bile duct injury.

MATERIALS AND METHODS

This systematic review was performed in accordance with the PRISMA guidelines^[13]. These guidelines are an evidence-based set of items that aim to enhance methodological and reporting clarity.

The Medline electronic database was searched from 1st January 1990 to 9th April 2014 using the free text “laparoscopic cholecystectomy”.

Eligible studies were prospective or retrospective cohort studies that provided details on outcomes from consecutive LC procedures in single institutions. The relevant outcomes were the incidences of conversion to open surgery, bile leakage, BDI or mortality. The definitions and timeframes of these outcomes were those specified in retrieved manuscripts. There were no limitations on cohort sizes or on recruitment dates of studies. Studies reporting combined results from multiple centres were eligible provided that data were provided separately for individual centres. Studies were excluded if results did not allow the calculation of institutional complication rates. This led to the exclusion of studies that reported on selected LCs rather than all consecutive LCs and studies that did not specify study start and finish dates. Case reports, narrative reviews and non-English language studies were also excluded.

One author (Murray M) identified eligible studies. Firstly, titles and abstracts were screened. Full-text manuscripts of potentially relevant studies were examined to finalise eligibility. Uncertainties regarding eligibility were discussed with a second author (Healy DA). For each included study, the following data were extracted independently by two authors (Murray M and Healy DA): author, publication date, study design, the institution's name, start and finish dates, duration, number of LCs, number of mortalities, number of conversions to open surgery, number of bile leaks and the number of cases of

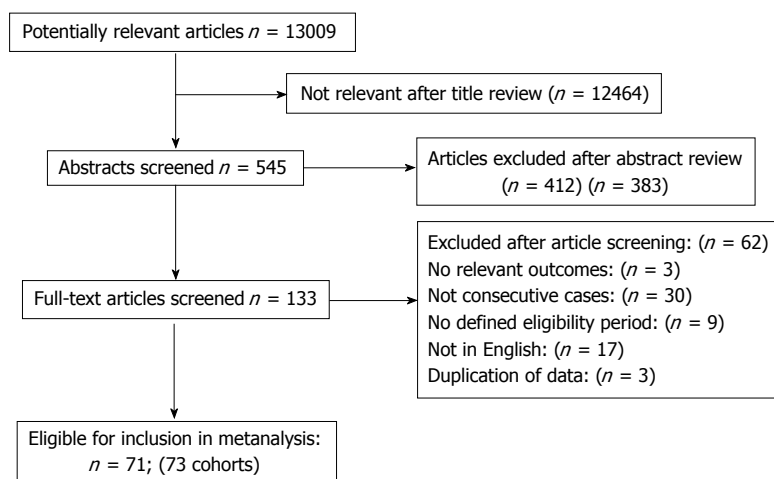


Figure 1 Summary of the results of the search.

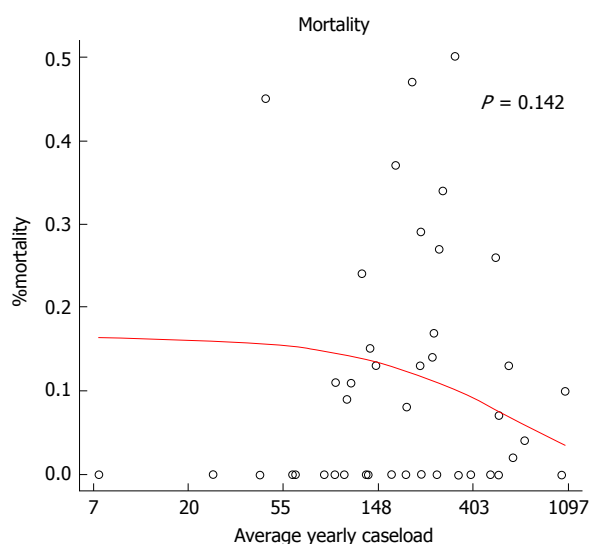


Figure 2 Scatterplot with regression line demonstrating the relationship between percentage mortality rate and average annual institutional volume of laparoscopic cholecystectomy (average caseload is plotted on a logarithmic scale).

BDI. Percentage complication rates were calculated for each outcome. Disagreements regarding data extraction were resolved by discussion with a third author (Walsh SR). Data were entered into a computerised spreadsheet for analysis.

All analyses were designed and performed by a biomedical statistician (JF). Scatterplots were used to summarise the relationships between numbers of LC procedures per year and percentage complication rates. Regression analyses were performed using generalized estimating equations. The generalized estimation equations were fit using a variance structure based on the binomial distribution. The response was the percentage of complications out of all procedures performed. A robust variance was used to account for extra variance around the regression line because of center specific effects. The function “gee” in the statistical language R was used. A sensitivity analysis was performed that was limited to

studies that were published after 1995. This time point was chosen with the aim of eliminating the effects of learning curves and improvements in perioperative care. Significance was set at 5%.

Statistical analysis

The authors state that all statistical analyses were designed and performed by a biomedical statistician. A statement to this effect is included in the methods section.

RESULTS

Figure 1 summarises the results of the search. 13009 citations were identified and 12876 were excluded based on titles and abstracts. 133 full text manuscripts were retrieved and 71 articles (corresponding to 73 cohorts) were finally eligible for inclusion.

Table 1 provides a summary of the 73 eligible cohorts^[14-84]. Most were retrospective and some were prospective cohorts. Study recruitment periods varied from 1990 to 2013. The total number of LC procedures was 127404.

Forty-three studies (71305 patients) provided data on mortality (43 cases of mortality; average mortality was 0.06%). Figure 2 displays the relationship between average annual number of LC procedures and institutional mortality rates as percentages. There was no significant relationship between mortality and annual number of procedures ($P = 0.142$). When only those cohorts published after 1995 were included (32 cohorts, 64273 patients) there was no significant relationship ($P = 0.168$).

Fifty-eight studies (87840 patients) provided data on conversion rates (2835 cases of conversion; average conversion rate was 3.23%). Figure 3 displays the relationship between average annual number of LC procedures and institutional percentage conversion rates. Increasing caseload was associated with lower conversion rates ($P = 0.019$). When only those studies that were published after 1995 were included (43 studies, 79311 patients) the result remained significant ($P = 0.019$).

Table 1 Characteristics and results of included studies

Ref.	Publication year	Study duration in months	Design	Total LC number	Average annual LC number	Mortality incidence	Percentage mortality rate (%)	Conversion to open surgery incidence	Percentage conversion rate (%)	Bile leak incidence	Percentage bile leak rate (%)	Bile duct injury incidence	Percentage bile duct injury rate (%)
Szego <i>et al</i> ^[14]	1991	6	Retrospective	31	62.00	0	0.00	2	6.45	0	0	0	0
Bailey <i>et al</i> ^[15]	1991	16	Prospective	375	281.25	1	0.27	20	5.33	1	0.27	1	0
Peters <i>et al</i> ^[16]	1991	6	Prospective	100	200.00	0	0.00	4	4.00	2	2	1	1
Rees <i>et al</i> ^[17]	1992	12	Retrospective	155	155.00	N/A	N/A	8	5.16	2	1.29	1	1
Huang <i>et al</i> ^[18]	1992	11	Retrospective	200	218.18	N/A	N/A	N/A	N/A	1	0.5	1	1
Davis <i>et al</i> ^[19]	1992	24	Retrospective	622	311.00	N/A	N/A	26	4.18	N/A	N/A	1	0
Fielding <i>et al</i> ^[20]	1992	12	Retrospective	220	220.00	N/A	N/A	8	3.64	2	0.91	N/A	N/A
Soper <i>et al</i> ^[21]	1992	21	Prospective	600	342.80	0	0.00	18	3.00	N/A	N/A	1	0
Périssat <i>et al</i> ^[22]	1992	32	Retrospective	700	262.50	1	0.14	41	5.86	N/A	N/A	3	0
Troidl <i>et al</i> ^[23]	1992	14.5	Prospective	400	331.00	2	0.50	20	5.00	3	0.75	N/A	N/A
Rubio <i>et al</i> ^[24]	1993	31	Retrospective	500	193.55	N/A	N/A	4	0.80	1	0.2	1	0
Huang <i>et al</i> ^[25]	1993	18	Retrospective	350	233.33	0	0.00	6	1.71	4	1.14	1	0
Cox <i>et al</i> ^[26]	1994	24	Prospective	410	205.00	N/A	N/A	N/A	4.00	N/A	N/A	3	1
Williams <i>et al</i> ^[27]	1994	27	Retrospective	600	266.67	1	0.17	24	4.00	N/A	N/A	N/A	N/A
Cappuccino <i>et al</i> ^[28]	1994	14	Retrospective	563	482.57	0	0.00	5	0.89	N/A	N/A	0	0
Bonatos <i>et al</i> ^[29]	1995	41	Retrospective	1788	523.32	0	0.00	45	2.52	19	1.06	0	0
Newman <i>et al</i> ^[30]	1995	36	Retrospective	1525	508.33	4	0.26	34	2.23	0	0	0	0
Chen <i>et al</i> ^[31]	1996	42	Retrospective	2428	693.71	1	0.04	N/A	N/A	1	0.04	4	0
Bond <i>et al</i> ^[32]	1996	36	Retrospective	534	178.00	2	0.37	N/A	N/A	N/A	N/A	N/A	N/A
Sartori <i>et al</i> ^[33]	1996	14	Retrospective	322	276.00	0	0.00	N/A	N/A	N/A	N/A	N/A	N/A
Rather <i>et al</i> ^[34]	1997	24	Retrospective	340	170.00	0	0.00	26	7.65	6	1.76	2	1
Jan <i>et al</i> ^[35]	1997	60	Retrospective	1115	223.00	N/A	N/A	N/A	N/A	4	0.36	3	0
Ahmad <i>et al</i> ^[36]	1997	45	Retrospective	1300	346.67	0	0.00	40	3.08	6	0.46	0	0
Kok <i>et al</i> ^[37]	1998	58	Prospective	220	45.52	1	0.45	9	4.09	N/A	N/A	1	0
Targarona <i>et al</i> ^[38]	1998	61	Retrospective	1630	320.66	N/A	N/A	109	6.69	N/A	N/A	16	1
Kurauchi <i>et al</i> ^[39]	1998	32	Retrospective	1408	528.00	1	0.07	89	6.32	N/A	N/A	9	1
Jones-Monahan <i>et al</i> ^[40]	1998	60	Retrospective	2654	530.80	N/A	N/A	N/A	N/A	1	0.04	6	0
Matthews <i>et al</i> ^[41]	1999	53	Retrospective	1025	232.08	3	0.29	27	2.63	2	0.2	1	0
Calvete <i>et al</i> ^[42]	2000	72	Prospective	784	130.67	0	0.00	4	0.51	4	0.51	7	1
Patel <i>et al</i> ^[43]	2000	38	Prospective	135	42.63	0	0.00	7	5.19	2	1.48	N/A	N/A
Sikora <i>et al</i> ^[44]	2001	72	Retrospective	1200	200.00	N/A	N/A	N/A	N/A	N/A	N/A	16	1
Lichten <i>et al</i> ^[45]	2001	12	Retrospective	300	300.00	N/A	N/A	17	5.67	N/A	N/A	N/A	N/A
Miroshnik <i>et al</i> ^[46]	2002	110	Retrospective	1216	132.65	N/A	N/A	90	7.40	7	0.58	1	0
Hasanah <i>et al</i> ^[47]	2002	84	Retrospective	2750	392.86	0	0.00	127	4.62	11	0.4	3	0
Fathy <i>et al</i> ^[48]	2003	93	Retrospective	2000	258.06	N/A	N/A	147	7.35	11	0.55	7	0
Duca <i>et al</i> ^[49]	2003	108	Retrospective	9542	1060.22	10	0.10	184	1.93	54	0.57	17	0
Mahatharadol <i>et al</i> ^[50]	2004	116	Retrospective	1522	157.45	N/A	N/A	N/A	N/A	N/A	N/A	9	1
Daradkeh <i>et al</i> ^[51]	2005	108	Retrospective	1208	134.22	0	0.00	32	2.65	N/A	N/A	0	0
Diamantis <i>et al</i> ^[52]	2005	132	Retrospective	2079	189.00	N/A	N/A	N/A	N/A	N/A	N/A	13	1
Söderlund <i>et al</i> ^[53]	2005	50	Prospective	1568	376.32	N/A	N/A	N/A	N/A	23	1.47	24	2
Baird ^[54]	2005	16	Prospective	782	586.50	1	0.13	18	2.30	N/A	N/A	0	0
Vagenas <i>et al</i> ^[55]	2006	156	Retrospective	1220	93.85	0	0.00	23	1.89	3	0.25	2	0
Tan <i>et al</i> ^[56]	2006	9	Prospective	202	269.33	N/A	N/A	14	6.93	3	1.49	1	0
Mufti <i>et al</i> ^[57]	2007	12	Retrospective	60	60.00	0	0.00	3	5.00	1	1.67	0	0

Brekalo <i>et al</i> ^[58]	2007	120	Retrospective	952	95.20	1	0.11	32	3.36	N/A	N/A	0	0
Marakis <i>et al</i> ^[59]	2007	144	Retrospective	1225	102.08	N/A	N/A	91	7.43	1	0.08	2	0
Herve <i>et al</i> ^[60]	2007	120	Retrospective	1255	125.50	3	0.24	25	1.99	N/A	N/A	12	1
Brekalo <i>et al</i> ^[58]	2007	120	Retrospective	1066	106.60	1	0.09	N/A	N/A	43	4.03	3	0
Shrestha <i>et al</i> ^[61]	2007	21	Prospective	140	80.00	N/A	N/A	13	9.29	N/A	N/A	N/A	N/A
Tantia <i>et al</i> ^[62]	2008	156	Retrospective	13305	1023.46	0	0.00	8	0.06	10	0.08	52	0
Priego <i>et al</i> ^[63]	2009	204	Retrospective	3933	231.35	5	0.13	331	8.42	17	0.43	13	0
Avgerinos <i>et al</i> ^[64]	2009	72	Prospective	1046	174.33	N/A	N/A	27	2.58	5	0.48	0	0
Clegg-Lamprey <i>et al</i> ^[65]	2010	24	Prospective	52	26.00	0	0.00	1	1.92	1	1.92	0	0
Al-Kubati <i>et al</i> ^[66]	2010	48	Retrospective	336	84.00	0	0.00	43	12.80	3	0.89	2	1
Ying <i>et al</i> ^[67]	2010	144	Retrospective	2400	200.00	2	0.08	11	0.46	7	0.29	3	0
Zha <i>et al</i> ^[68]	2010	156	Prospective	13000	1000.00	N/A	N/A	N/A	N/A	N/A	N/A	11	0
Wichmann <i>et al</i> ^[69]	2010	18	Prospective	140	93.33	N/A	N/A	11	7.86	3	2.14	N/A	N/A
Wichmann <i>et al</i> ^[69]	2010	18	Prospective	219	146.00	N/A	N/A	18	8.22	2	0.91	N/A	N/A
Kanakala <i>et al</i> ^[70]	2011	120	Retrospective	2117	211.70	10	0.47	133	6.28	31	1.46	7	0
Al-Mulhim <i>et al</i> ^[71]	2011	36	Prospective	968	322.67	N/A	N/A	5	0.52	3	0.31	N/A	N/A
Halilovic <i>et al</i> ^[72]	2011	12	Prospective	293	293.00	1	0.34	8	2.73	N/A	N/A	N/A	N/A
Hasbahceci <i>et al</i> ^[73]	2012	129	Retrospective	1557	144.84	2	0.13	39	2.50	10	0.64	4	0
Bekele <i>et al</i> ^[74]	2012	60	Retrospective	681	136.20	1	0.15	20	2.94	N/A	N/A	N/A	N/A
Le <i>et al</i> ^[75]	2012	24	Retrospective	3371	1685.50	N/A	N/A	86	2.55	N/A	N/A	N/A	N/A
Afuwape <i>et al</i> ^[76]	2012	20	Retrospective	13	7.80	0	0.00	1	7.69	N/A	N/A	1	8
Grbas <i>et al</i> ^[77]	2013	202	Retrospective	10317	612.89	2	0.02	220	2.13	52	0.5	25	0
Sultan <i>et al</i> ^[78]	2013	120	Retrospective	4434	443.40	N/A	N/A	234	5.28	N/A	N/A	N/A	N/A
Pulvirenti <i>et al</i> ^[79]	2013	120	Retrospective	882	88.20	N/A	N/A	51	5.78	N/A	N/A	N/A	N/A
Dip <i>et al</i> ^[80]	2014	5	Prospective	43	103.20	0	0.00	N/A	N/A	0	0	0	0
Comajuncosas <i>et al</i> ^[81]	2014	12	Prospective	276	276.00	N/A	N/A	26	9.42	N/A	N/A	N/A	N/A
Paijanen <i>et al</i> ^[82]	2014	204	Retrospective	1895	111.47	2	0.11	126	6.65	14	0.74	2	0
Alvarez <i>et al</i> ^[83]	2014	248	Retrospective	11423	552.73	N/A	N/A	N/A	N/A	5	0.04	20	0.18
Afaneh <i>et al</i> ^[84]	2014	44	Retrospective	1382	376.91	N/A	N/A	44	3.18	N/A	N/A	2	0.14

LC: Laparoscopic cholecystectomy; N/A: Not available.

Forty-four studies (86025 patients) provided data on bile leak rates (381 cases of bile leakage; average bile leak rate was 0.44%). Figure 4 displays the relationship between average annual number of LC procedures and the institutional percentage bile leak rate. There was no significant relationship between bile leak rates and annual number of procedures ($P = 0.11$). When only those studies that were published after 1995 were included (33 cohorts, 80381 patients) the result was similar ($P = 0.123$).

Fifty-six cohorts (113526 patients) provided data on bile duct injury rates (316 cases of bile duct injury; average bile duct injury rate was 0.28%). Figure 5 displays the relationship between average annual number of LC procedures and institutional percentage bile duct injury rate. There was no significant relationship between bile duct injury rates and annual number of procedures ($P = 0.198$). When only those studies that were published after 1995 were included (42 cohorts, 105570 patients) the result was similar ($P = 0.19$).

DISCUSSION

This systematic review examined the effect of institutional LC volume on LC outcomes-it identified 73 single centre cohorts involving 127404 patients. Using regression analyses based upon generalised estimating equations we found that there were no significant relationships between institutional LC volume and mortality ($P = 0.142$), bile leakage ($P = 0.111$) or bile duct injury ($P = 0.198$). However, increasing institutional LC volume was associated with reduced incidence of conversion ($P = 0.019$). These pooled results relate

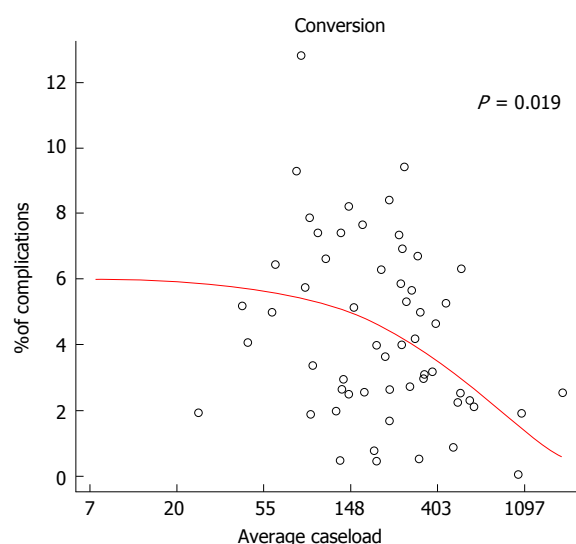


Figure 3 Scatterplot with regression line demonstrating the relationship between percentage conversion rate and average annual institutional volume of laparoscopic cholecystectomy (average caseload is plotted on a logarithmic scale).

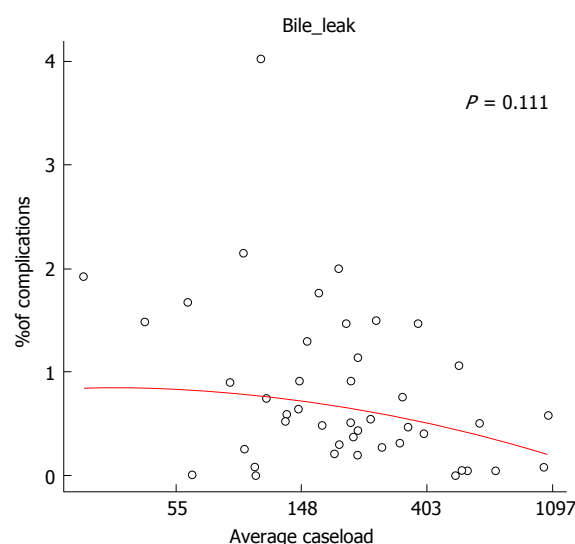


Figure 4 Scatterplot with regression line demonstrating the relationship between percentage bile leak rate and average annual institutional volume of laparoscopic cholecystectomy (average caseload is plotted on a logarithmic scale).

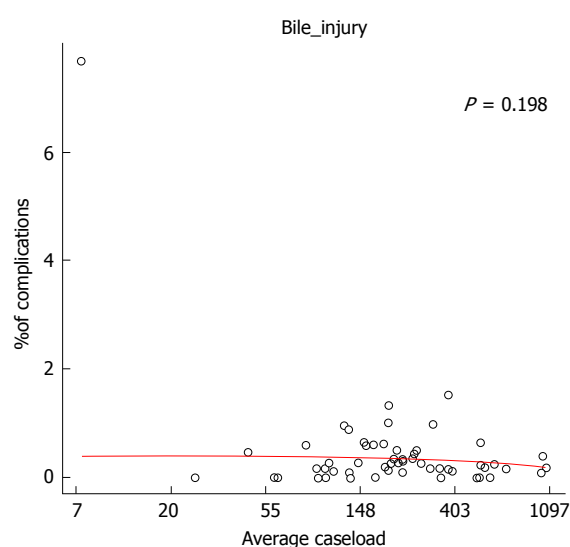


Figure 5 Scatterplot with regression line demonstrating the relationship between percentage bile duct injury rate and average annual institutional volume of laparoscopic cholecystectomy (average caseload is plotted on a logarithmic scale).

to cohorts that involved procedures performed between 1990 and 2013. Our sensitivity analysis was designed to limit the influence of the learning curve by excluding publications from before 1995-this analysis yielded similar results. Our findings are timely as mounting evidence confirms the importance of high-volume LC surgeons. Furthermore, evidence confirms the importance of high-volume centres and high-volume care providers in relation to other conditions^[6]. Therefore the observation that LC complications may be influenced by institutional case load has implications for the future research and future service provision.

Our results are broadly consistent with previous studies that have examined the topic. The largest previous

study was a retrospective population based study involving over one million patients from the United States National Inpatient Sample^[85]. In a univariate analysis the authors of this study found that high-volume centres (≥ 225 LCs annually) had slightly improved major complication rates compared with lower-volume centres (6.4% *vs* 7.0%, $P < 0.0001$)^[85]-significance was likely to have been related to the sample size and not to a clinically important effect. The effect on major complications was lost on multivariate testing. However an effect of hospital volume on conversion rates was present in a multivariable analysis-hospital volume of ≤ 120 cases per year was associated with an odds ratio (OR) for conversion of 1.32 (95%CI: 1.18-2.19) when compared with hospital volume of ≥ 225 per year. Another large population based study from Scotland involving 59918 procedures found higher mortality in lower volume (< 173 cases/year; OR = 1.45; 95%CI: 1.06-2.00; $P = 0.022$) and medium volume (173-244 cases/year; OR = 1.52; 95%CI: 1.11-2.08; $P = 0.01$) centres when high-volume centres (> 244 cases/year) were the reference group^[86]. Although this again represents evidence for a hospital volume-outcome relationship for mortality, absolute effects were negligible for those patients at average risk-this suggests that the finding of significance may have simply been a reflection of the large sample size. In the late 1990s, another United States retrospective cohort study of 8602 procedures found no relationship between hospital volume and mortality^[87] although a study from Norway on 4332 cases found a significant association between hospital volume and severe complications index^[88]. Notably, the latter two studies only involved hospitals that nowadays would be deemed small volume.

From a wider perspective, patient safety is likely to have many underlying components and it is likely that hospital volume probably reflects clustering of these

factors^[86]. In the future it is important that studies explore the possibility that “high volume” may be a surrogate for streamlined management and strict adherence to protocolised care. Equivalent outcomes may be achievable in smaller centres provided that a high quality of care is maintained. High volume LC centres should only be required if institutional volume is shown to have a clinically important effect that is independent of other aspects of quality of care. As mentioned previously, several studies suggest the existence of a surgeon volume-outcome relationship for LC^[2,4,5,9-12]—this seems plausible given the high-volume but low-risk nature of gallbladder surgery. The relatively low overall complication rate of gallbladder surgery makes volume-related research difficult and therefore it is essential that high quality registries including case-mix data are maintained into the future. In the long term, this will be the only way to determine important patient, surgeon and hospital-related components of safety.

The chief strength of the current study relates to the inclusion of a large number of studies, including both small and large cohorts. Furthermore, we used an extensive search strategy and we focused on patient-important outcomes that are simply defined and easily diagnosed and are thus likely to be accurate even in retrospective studies. The external validity of the study is further enhanced by the finding of average complication rates that are quite similar to accepted published rates. The main limitation is the lack of data on case mix. Furthermore, as we included studies that spanned a twenty year period across all areas of the world, undoubtedly temporal and geographical variations in care would have existed. Notably, we declined to evaluate trends in outcomes over time as study inclusion periods were heterogeneous (Table 1) and results were not provided by year but rather for entire study inclusion periods. Finally we were limited to univariate analyses, thereby restricting conclusions on other factors that influence safety. We also wish to highlight that we did not aim to estimate specific optimal volume thresholds but rather we aimed to measure the effect of institutional volume on outcomes using a regression analysis. Overall, we think that the results of our review are striking. We wish to encourage research on volume-outcome relationships in surgery, particularly through the use of large scale registries.

COMMENTS

Background

Laparoscopic cholecystectomy (LC) is one of the most commonly performed operations worldwide. It is preferred over open cholecystectomy as it offers a shorter length of hospital stay and a quicker recovery but it is associated with the chance of needing conversion to open surgery and the risks of bile leakage, bile duct injury and mortality.

Research frontiers

Studies have shown that institutional volume is an important determinant of outcome in a variety of conditions such as cancers, aortic aneurysms and cardiac surgery. Furthermore surgeon experience is an important factor in these conditions also. Although recent evidence suggests that surgeon volume is an important determinant of outcomes following LC, the authors have a

poor understanding of the effect of institutional volume. Knowing the effect of institutional volume is important as it may influence how healthcare systems are organised.

Innovations and breakthroughs

Based on the authors review, they have identified that conversion rate is related to institutional volume. Increasing institutional LC volume leads to reduced incidence of conversion to open surgery. The authors found no evidence to suggest the institutional volume influences mortality, bile leakage or bile duct injury rates.

Applications

Institutional volume is an important determinant of outcomes following LC. However, it is uncertain whether this is a direct effect or a surrogate for optimum standardised and protocolised care. Large scale prospective registries are needed to explore this topic further.

Terminology

Bile duct injury is a serious and potentially life-threatening complication of LC resulting from inadvertent damage to biliary system structures during the operation. Bile leakage refers to a serious complication that results to continued leakage of bile from the biliary system after the operation. Most bile leaks can be managed effectively but they contribute to morbidity and have economic implications.

Peer review

The current meta-analysis presents interesting.

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Antithrombotic treatment in chronic heart failure and sinus rhythm: Systematic review

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Abstract

AIM: To assess the efficacy and safety of anti-thrombotic drugs (antiplatelet or anticoagulant drugs) compared to no antithrombotic treatment or placebo in patients with heart failure (HF) and sinus rhythm.

METHODS: We searched Medline and Cochrane Library for randomized controlled trials evaluating antithrombotic treatment and no antithrombotic treatment in patients with HF and sinus rhythm. Risk ratio (RR) and 95% CIs were estimated performing meta-analysis with random effects method.

RESULTS: Two studies met the inclusion criteria: Heart failure Long-term Antithrombotic Study and Warfarin/Aspirin Study in Heart failure, with 336 patients and mean follow-up 1.8-2.25 years. Stroke risk was not reduced by acetylsalicylic acid (RR = 1.18, 95%CI: 0.17-8.15), oral anticoagulation (RR = 0.30, 95%CI: 0.03-2.65) or overall antithrombotic drugs (RR = 0.52, 95%CI: 0.10-2.74). Acetylsalicylic acid showed a significant increased risk of worsening HF (RR = 1.78, 95%CI: 1.08-2.92), while oral anticoagulation had no impact in this outcome (RR = 1.03, 95%CI: 0.61-1.75). Overall antithrombotic drugs showed a significant risk increase of major bleeding (RR = 6.99, 95%CI: 0.89-54.64).

CONCLUSION: Best available evidence does not support the routine use of antithrombotic drugs in patients with HF and sinus rhythm. These drugs, particularly oral anti-

coagulation has the hazard of increase significantly major bleeding risk.

Key words: Heart failure; Sinus rhythm; Platelet aggregation inhibitors; Anticoagulants

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Core tip: In patients with atrial fibrillation, chronic heart failure (CHF) increases thromboembolic risk and oral anticoagulation is essential to decrease the risk of thromboembolic complications. Evidence suggests a positive association between CHF, impaired hemostasis and thromboembolic events. Whether antithrombotic drugs should be recommended for these patients (in sinus rhythm) is still debated. We looked for the best available evidence and we found 2 studies fulfilling the inclusion criteria. We performed a meta-analysis of antithrombotic drugs *vs* placebo and strengthened that antithrombotic drugs do not decrease the risk of stroke (fatal or non-fatal) and increase the risk of major bleeding.

Caldeira D, Cruz I, Calé R, Martins C, Pereira H, Ferreira JJ, Pinto FJ, Costa J. Antithrombotic treatment in chronic heart failure and sinus rhythm: Systematic review. *World J Meta-Anal* 2015; 3(1): 36-42 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/36.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.36>

INTRODUCTION

Chronic heart failure (CHF) is an increasingly prevalent cardiovascular disease with significant associated morbidity and mortality^[1]. CHF constitutes a significant economic burden^[2,3], which is expected to increase over the next decades due to increasing prevalence of associated diseases and risk factors as well as population aging. Former observational studies suggest a positive association between CHF, impaired hemostasis and thromboembolic events^[4,5]. In patients with atrial fibrillation (AF), CHF increases thromboembolic risk and oral anticoagulation is the cornerstone of AF treatment aiming to decrease the risk of thromboembolic complications^[6]. The results from the WARCEF trial (Warfarin *vs* Aspirin in Reduced Cardiac Ejection Fraction) has highlighted the role of antithrombotic treatment in patients with CHF and sinus rhythm^[7]. There were no differences between warfarin and acetylsalicylic acid in the primary outcome (time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause). However, warfarin was associated with fewer stroke events (2.5% *vs* 4.7%) but also with a higher rate of major bleeding events (5.8% *vs* 2.7%). The clinical interpretation of these findings was that the choice between warfarin and aspirin should be

made on the basis of the individual patient^[8].

Previous systematic reviews with meta-analyses comparing oral anticoagulation (namely warfarin) and acetylsalicylic acid in patients with CHF and sinus rhythm reached conclusions overlapping those from the WARCEF study^[9-13].

Although much effort have been done comparing and discussing the relative effectiveness of oral anticoagulation *vs* acetylsalicylic acid in patients with CHF and sinus rhythm, significantly less is known about the true efficacy of the overall antithrombotic treatment. Therefore, we aimed to perform a systematic review to better estimate the true clinical benefit of antithrombotic treatments (oral anticoagulation or antiplatelet drugs) against placebo, standard care or no treatment, in patients with CHF and sinus rhythm.

MATERIALS AND METHODS

Guidance

This work followed PRISMA guidelines for systematic reviews and meta-analyses promoted by the EQUATOR network^[14].

Eligibility criteria

We have searched for all randomized controlled trials (RCTs) evaluating patients with CHF and sinus rhythm treated with oral antithrombotic therapy or control. We considered for antithrombotic treatments both oral anticoagulants (such as vitamin K antagonists, like warfarin, acenocoumarol or phenprocoumon) and antiplatelet drugs [such as acetylsalicylic acid (ASA), clopidogrel or ticlopidine]. We allowed controls under placebo, standard care or no antithrombotic treatment. Studies had to report clinical and/or echocardiographic features for the enrolled CHF patients, such as impaired left ventricle ejection fraction or shortening fraction.

Database and search method

Medline and Cochrane Library (CENTRAL) databases were searched from inception to November 2013 for eligible studies. The search strategy details are available at the Online Supplementary Material. We considered all studies irrespective of language. References of obtained studies were also comprehensively searched and cross-checked to identify possible missing studies.

Studies and data selection

Citations obtained from electronic search were independently screened by two authors, followed by full-text assessment of potentially eligible studies for inclusion in accordance with previously mentioned criteria.

Primary outcome was stroke (fatal or non-fatal). Secondary outcomes were all-cause mortality, myocardial infarction, worsening heart failure (HF), major bleeding and a composite of major adverse clinical events, defined as the combination of mortality, stroke, myocardial infarction and HF.

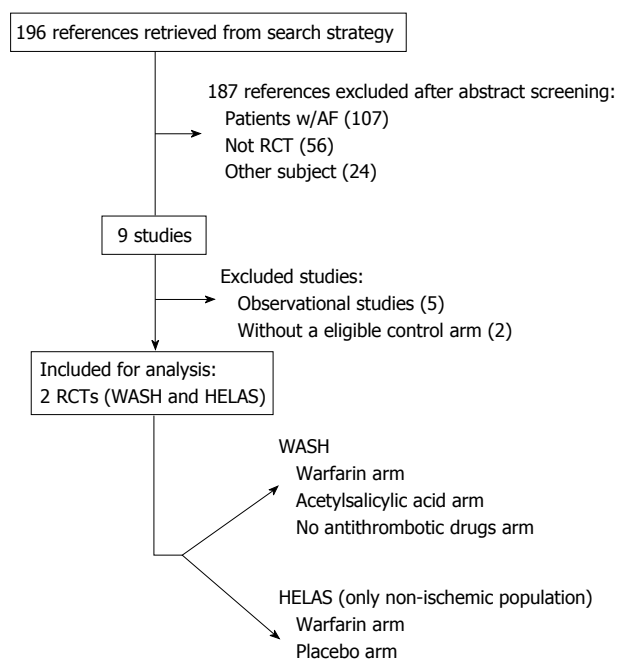


Figure 1 Flowchart of studies' selection. AF: Atrial fibrillation; RCT: Randomized controlled trial; WASH: Warfarin/Aspirin Study in Heart failure; HELAS: Heart failure Long-term Antithrombotic Study.

We extracted detailed data about demographics, comorbidities, interventions, follow-up and outcomes. Data extraction and data entry into software was double-checked. Disagreements were resolved by consensus.

Quality reporting assessment

Quality of reporting was analysed by using a qualitative classification according to risk of bias (high, unclear or low risk), adapted from Cochrane Collaboration's Tool^[15]. Studies were not excluded based on quality of reporting.

Statistical analysis

Outcomes data were summarized as frequencies. Statistical analyses were performed using the RevMan version 5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to derive forest plots with pooled estimates of risk ratios (RR) and their 95%CI. Statistical heterogeneity was assessed with χ^2 test and quantified with Higgins I^2 test^[16]. Pooled results estimates were based on the random or fixed effects model according to the existence ($I^2 \geq 50\%$) or not ($I^2 < 50\%$) of significant heterogeneity^[17]. Publication bias was assessed through visual inspection of funnel plots symmetry and Peters' regression tests^[18,19]. Pooled results were evaluated for the overall antithrombotic treatment, as well separately for antiplatelet and anticoagulation groups.

RESULTS

Search

After title and abstract screening of citations obtained in Medline and Cochrane Library, 196 citations were retrieved. One-hundred and eighty seven studies did not

meet inclusion criteria through initial assessment: 107 included AF patients; 56 studies were not randomized and 24 did not address the pretended topic (either different population and/or other interventions).

The remaining 9 studies were fully-evaluated, of which 7 were further excluded: 5 were observational studies, and 2 RCTs did not include a placebo, standard care or no antithrombotic treatment arm (WARCEF and WATCH trials)^[5,20]. Therefore, 2 RCTs were eligible for the purpose of this systematic review^[21,22]. The search of reference lists of review articles and included studies failed to identify any additional eligible study^[23-27]. Figure 1 shows the flowchart of studies' selection.

Characteristics of obtained studies and quality of reporting

Studies Warfarin/Aspirin Study in Heart failure (WASH) and Heart failure Long-term Antithrombotic Study (HELAS) met the outlined inclusion criteria^[21,22].

WASH study was an open-label RCT with blinded endpoint assessment, published in 2004. WASH enrolled 254 patients (80 warfarin; 80 ASA; 94 no anti-thrombotic treatment) with CHF and sinus rhythm and followed them for a mean period of 2.25 years. About 60% had CHF of ischemic etiology, 75% of the patients were male, mean age was 63 years old, and 30% were in New York Heart Association class III/VI. About 34% of the patients had hypertension, and 20% had diabetes. In terms of echocardiography mean parameters, patients had a fractional shortening of 15% and a left-ventricular end-diastolic diameter of 66 mm. Regarding treatments, the daily dosage of acetylsalicylic acid was 300 mg and international normalized ratio (INR) target for warfarin-treated patients was 2.5 (range 2-3). Primary outcome was the composite of all-cause death, non-fatal myocardial infarction, or non-fatal stroke^[21].

HELAS study was published in 2006 and included two comparisons: warfarin *vs* acetylsalicylic acid in patients with CHF of ischemic etiology (not evaluated in this review due to absence of a placebo/no treatment control arm); and warfarin *vs* placebo in 82 patients (38 *vs* 44) with dilated non-ischemic CHF in sinus rhythm. Study's mean follow was 1.8 years. Most of the patients were male and mean age was 55 years. Hypertension was present in 25% of the patients, and diabetes in 11%. No significant differences were noticed in the main baseline characteristics. Echocardiographic features of these patients were remarkable for a baseline ejection fraction of 28%, left ventricle end-systolic diameter of 58 mm and end-diastolic diameter of 70 mm. Target INR for warfarin treatment was 2-3. Primary outcome was the composite of all-cause mortality, non-fatal stroke, non-fatal myocardial infarction, peripheral or pulmonary embolism, hospitalisation, or HF worsening^[22].

Quality of reporting assessment is available in Figure 2. The main methodological flaws were the open-label design of WASH and the unknown method of allocation concealment in HELAS.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
HELAS	+	?	+	+	+	+
WASH	+	-	-	+	+	+

Figure 2 Studies quality of reporting. WASH: Warfarin/Aspirin Study in Heart failure; HELAS: Heart failure Long-term Antithrombotic Study.

Quantitative evaluation

Meta-analysis was performed for the following comparisons: antiplatelet drugs *vs* control, anticoagulant drugs *vs* control, and antithrombotic drugs (antiplatelet plus anticoagulant drugs) *vs* control.

While anticoagulation *vs* control data was derived from both WASH and HELAS studies^[21,22], WASH study was the only that provided data for antiplatelet (acetylsalicylic acid) *vs* placebo^[21]. For quantitative evaluation of overall antithrombotic treatment in this population, we considered both oral anticoagulation and antiplatelet from WASH study as a single arm and efficacy was directly obtained from WASH study^[21].

Primary outcome

Antithrombotic drugs did not reduce stroke risk against placebo or no treatment, with RR = 1.18 (95%CI: 0.17-8.15) for antiplatelet drugs, RR = 0.30 (95%CI: 0.03-2.65) for anticoagulants, and RR = 0.52 (95%CI: 0.10-2.74) for overall antithrombotic drugs.

Secondary outcomes

Antithrombotic drugs showed an increased risk of CHF worsening (RR = 1.61, 95%CI: 1.04-2.48), mainly due to the single antiplatelet drug studied, acetylsalicylic acid, which had RR = 1.78 (95%CI: 1.08-2.92), while oral anticoagulants were not different from controls (RR = 1.03, 95%CI: 0.61-1.75).

Warfarin showed a significant increased risk of major bleeding (RR = 9.00, 95%CI: 1.14-70.90) and acetylsalicylic acid showed a non-significant trend (RR = 3.26, 95%CI: 0.13-79.04). The RR for overall major bleeding risk with antithrombotic drugs was 6.99 (95%CI: 0.89-54.64).

None of the antithrombotic drugs or overall antithrombotic treatment showed reduction of mortality and

myocardial infarction risk in patients with systolic HF and sinus rhythm.

Antiplatelet drug/acetylsalicylic acid, but not warfarin, showed increased risk of the composite outcome of mortality, stroke, myocardial infarction, and worsening HF, most probably due to the increased risk of CHF worsening. Statistical heterogeneity was present in the evaluation of mortality when comparing antithrombotic drugs with control ($I^2 = 58\%$). Figure 3 shows the pooled results. Publication bias was not evaluated due to the scarcity of studies^[28].

DISCUSSION

Our main findings were the lack of proven efficacy of antithrombotic treatments, in patients with systolic HF and sinus rhythm, in the risk reduction of clinically important outcomes such as stroke, mortality and myocardial infarction; moreover, warfarin is associated to a significant 9-fold increased risk of major bleeding; and acetylsalicylic acid was associated with increased risk of CHF worsening.

The spotlight of this theme looks for Warfarin *vs* Acetylsalicylic acid comparison. By conducting this systematic review, the authors aimed to move back to the original problem and ask the question of whether antithrombotic treatments are, in the first place, effective in the treatment of CHF with sinus rhythm. If we accept that RCTs are the unique type of clinical studies that can prove causality with a reasonable margin of error, our results show that these interventions still have to prove their efficacy in this population, knowing that they owe an important bleeding risk. Furthermore, our attempt to perform a bayesian mixed treatment comparison meta-analysis, with data from clopidogrel arm from WATCH study^[20], and warfarin *vs* acetylsalicylic acid presented in multiple systematic reviews and meta-analyses, failed due to high inconsistency in the statistical analysis of the network (data not shown). Although this inconsistency strongly compromises the results of such exercise, it is worth to report that placebo had a high probability of being the best treatment option. This reinforces the need of further trials to elucidate whether these interventions do/do not interfere with the prognosis, rather than have contradictory signs.

Accordingly, the 2012 consensus document of the HF Association of the European Society of Cardiology (ESC) and the ESC Working Group on Thrombosis corroborates our conclusions^[29]. This consensus document stated that warfarin and acetylsalicylic acid should not be routinely used for thromboprophylaxis in patients with systolic HF and sinus rhythm, in the absence of concomitant comorbidities with clear indications for anticoagulation (*e.g.*, AF) or acetylsalicylic acid (*e.g.*, documented coronary artery disease).

Safety concerns regarding acetylsalicylic acid and HF (in patients with previously optimized background therapy with drugs such as angiotensin-converting enzyme inhibitors) were previously mentioned^[30-32]. However if we

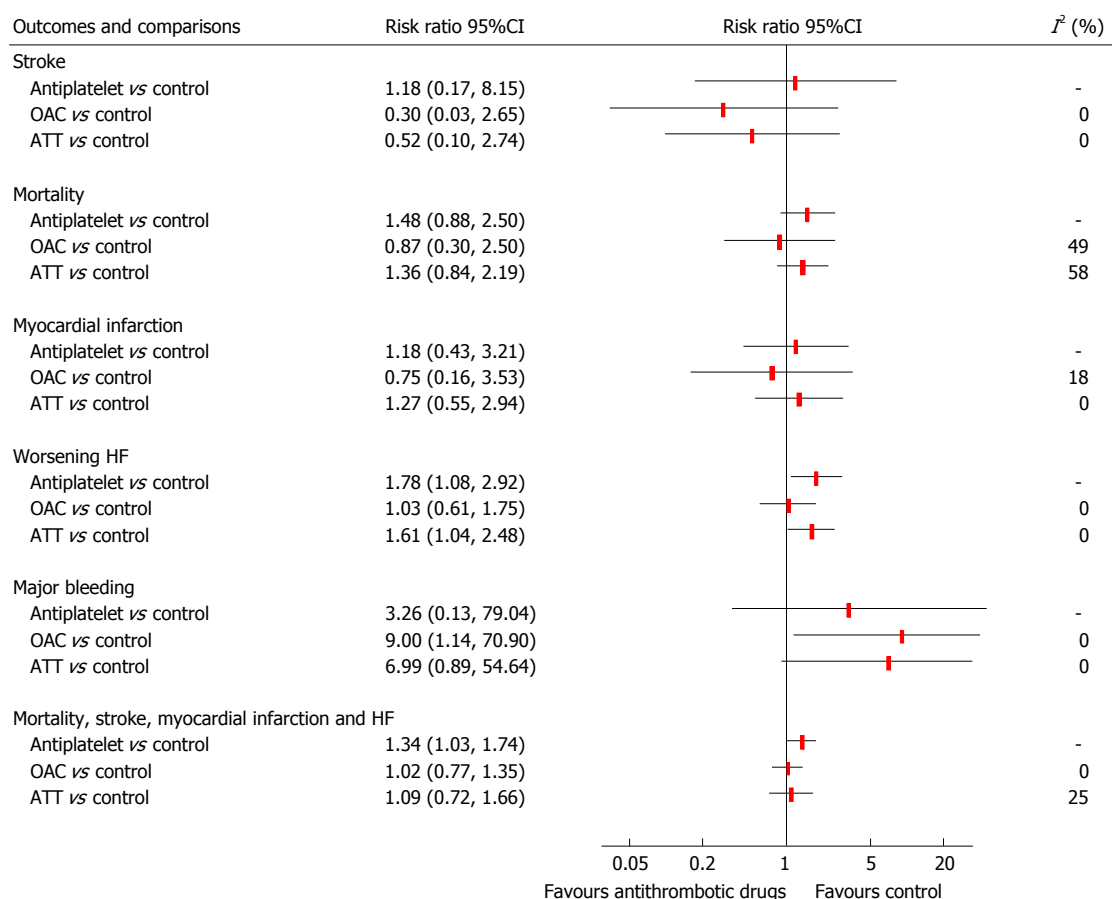


Figure 3 Forest plot evaluating antithrombotic drugs vs control. Data for “Antiplatelet vs control” comparison derived from WASH study. ATT: Antithrombotic treatment; OAC: Oral anticoagulation; HF: Heart failure; WASH: Warfarin/Aspirin Study in Heart failure.

consider warfarin as a “negative control”, the pooled rates of HF worsening (after the WARCEF trial) were similar between acetylsalicylic acid and warfarin^[7].

Along this century, antithrombotic treatment has gone forward in many therapeutic indications, but in patients with systolic HF and sinus rhythm the evidence to determine the prognostic importance of antithrombotic treatment (individually or globally) remained stationary and unsatisfactory for those who have to deal with CHF patients with sinus rhythm.

Limitations

This systematic review with meta-analysis has limitations attributed to included studies and analysis method.

As for included studies, WASH study had an open-label design; the control arm of this study was a no-antithrombotic treatment group (*i.e.*, not a placebo controlled trial), and included 7% of patients with AF that could not be excluded in the analyses. Furthermore the dosage of acetylsalicylic acid used in this trial was considerably higher than recommended^[33].

Both studies had different proportions of HF etiologies. Although it can be important, particularly in ischemic HF cases where acetylsalicylic acid may play recognized prognostic role, here we aimed evaluate the thrombotic and embolic risk of patients with clinically important left ventricle impairment.

Major bleeding definitions were not common along

the included trials. Worsening HF was defined by the investigator in WASH and no definition was provided in HELAS.

Periods of unrecognized paroxysmal AF could have biased of results. However it would bias favouring the antithrombotic drugs, which did not occur.

In conclusions, current evidence does not support the routine use of antithrombotic drugs (anticoagulant or antiplatelet drugs) for thromboprophylaxis in patients with systolic HF and sinus rhythm, as it carries a well known and documented bleeding risk without proven benefits compared to placebo or no antithrombotic treatment.

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COMMENTS

Background

In patients with atrial fibrillation (AF), chronic heart failure (CHF) increases

thromboembolic risk and oral anticoagulation is essential to decrease the risk of thromboembolic complications. Evidence suggests a positive association between CHF, impaired hemostasis and thromboembolic events. Whether antithrombotic drugs have an prognosis impact in patients with CHF in sinus rhythm (*i.e.*, without history of AF) is still very debated.

Research frontiers

Anticoagulation has been established as the gold standard treatment of stroke and embolism prevention in AF. The WARCEF trial did not show differences between warfarin and acetylsalicylic acid concerning major cardiovascular events in patients with CHF and sinus rhythm. Warfarin reduced the risk of ischemic stroke in this trial. However the efficacy of any of these drugs compared should be evaluated before drawing any conclusions and recommendations.

Innovations and breakthroughs

Based on the best available evidence (2 randomized controlled trials Warfarin/Aspirin Study in Heart failure and Heart failure Long-term Antithrombotic Study), this systematic review emphasizes the lack of efficacy of any antithrombotic drugs (individually or pooled together) in patients with CHF and sinus rhythm. In addition should be considered that these drugs increase significantly the risk of major bleeding.

Applications

Warfarin and acetylsalicylic acid should not be routinely used for thromboprophylaxis in patients with systolic HF and sinus rhythm, in the absence of concomitant comorbidities with clear indications for anticoagulation (*e.g.*, AF) or acetylsalicylic acid (*e.g.*, documented coronary artery disease).

Peer review

A systematic review and meta-analysis of two studies addressing antithrombotic drugs in patients with CHF and sinus rhythm. The manuscript is well written and adds new points to the discussion of anticoagulation.

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Effect of supervised exercise on aerobic capacity in cancer survivors: Adherence and workload predict variance in effect

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Abstract

AIM: To examine the efficacy of supervised aerobic exercise training on aerobic capacity in survivors of cancer.

METHODS: We conducted a systematic search identifying randomized controlled trials of supervised aerobic exercise interventions among adult cancer survivors with aerobic capacity ($VO_{2max/peak}$) as the primary outcome. We calculated pooled effect sizes and performed multiple regression moderator analysis.

RESULTS: We identified 18 studies including 1149 survivors of cancer. Studies included mixed cancer groups (4 studies), breast cancer (10 studies), hematological cancers (2 studies), lung cancer (1 study) and liver cancer (1 study). Survivors of cancer who participated in supervised aerobic exercise training improved aerobic capacity (VO_{2peak}) more than controls (18 comparisons, 1093 participants; standardized mean effect: 0.74; 95%CI: 0.52, 0.96; $P < 0.001$). However, there was significant heterogeneity among the included trials (I^2 : 63%; $P < 0.001$). Sixty-six percent of the between-study heterogeneity was explained by differences in exercise adherence and total exercise workload among studies (R^2 : 65.8%; $P < 0.04$).

CONCLUSION: Supervised aerobic exercise training provides a moderate-to-large beneficial effect on aerobic capacity among survivors of cancer. Aerobic capacity was improved to a greater degree in exercise studies with better participant attendance and higher overall exercise workload.

Key words: Exercise; Neoplasms; Physical therapy modalities; Physical fitness; Meta-analysis

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Core tip: The optimal exercise prescription for survivors of cancer is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors who are at different time points in their cancer care. We performed a meta-analysis of data from randomized controlled trials examining the effect of supervised aerobic exercise training on aerobic capacity in cancer survivors. We found that aerobic capacity was improved to a greater extent in exercise studies that prescribed a higher exercise workload and had better participant adherence.

Beaudry R, Kruger C, Liang Y, Parliament M, Haykowsky M, McNeely ML. Effect of supervised exercise on aerobic capacity in cancer survivors: Adherence and workload predict variance in effect. *World J Meta-Anal* 2015; 3(1): 43-53 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/43.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.43>

INTRODUCTION

The burden of cancer continues to increase worldwide due to population growth and aging^[1]. More effective cancer screening and novel treatment therapies have resulted in improved detection, earlier treatment and better disease free and overall survival, with the numbers of cancer survivors growing disproportionately to the number of new cancer cases and deaths^[2]. Many cancer survivors experience symptoms and side effects related to their cancer or cancer treatment. As many of these effects go undetected and/or untreated, the survivor is placed at increased risk for other health issues such as declining functional status and cardiovascular disease^[3,4]. As a result, there is an emerging need for the integration of services and interventions to address the long-term health of survivors^[3].

Exercise training is gaining recognition as an important intervention to address acute, late and long-term effects of cancer, and is becoming more widely acceptable as confidence in safety is now established. Importantly, evidence is accumulating to support the benefit of exercise to improve the physical functioning and quality of life of survivors. Currently, the optimal exercise prescription is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood^[5]. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors at different times through the cancer continuum^[5].

Cardiorespiratory fitness, measured objectively as the highest oxygen consumed during maximal aerobic exercise, provides a means to evaluate associations with disease outcomes. Aerobic capacity is inversely related to

the risk of a cardiovascular event and all-cause mortality in healthy individuals and cancer patients^[6-10]. Aerobic capacity is best increased by habitual aerobic exercise training that is of a moderate-to-vigorous intensity^[11].

Aerobic capacity (VO_{2max}) is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level^[12]. This volume is expressed as an absolute rate in litres per minute (L/min) or as a relative rate in millilitres per kilogram of bodyweight per minute (mL/kg per minute). VO_{2peak} is the term used most commonly in clinical populations when a true maximal value is not attained^[12]. For example, the test is described as VO_{2peak} rather than VO_{2max} when the test is carried out on a cycle ergometer (bike) rather than a treadmill, or when the highest value reached on the test is limited by the participant's symptoms.

A meta-analysis by Jones and colleagues included data from six randomized controlled trials (RCTs) and reported a significant benefit from supervised aerobic exercise training, compared with usual care, on VO_{2peak} (2.90 mL/kg per minute; 95%CI: 1.16, 4.64; $P = 0.01$)^[13]. However, statistical and clinical heterogeneity was found among the exercise trials included in their review, leading them to recommend further research to build on and extend the current knowledge in the field. Since this publication, a number of newer studies have been published. Given this amount of new data, we contend that an updated review is warranted.

The primary purpose of this meta-analysis was to examine the efficacy of supervised aerobic exercise training programs on VO_{2peak} in survivors of cancer. Quality of life was analyzed as a secondary outcome measure. As well we aimed to explore heterogeneity in study findings through subgroup analyses and meta-regression where appropriate.

MATERIALS AND METHODS

The review conforms to the requirements of PRISMA reporting standards. The published protocol for the review can be found at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006215#.U1cOn-le9aw).

Inclusion criteria

Studies were considered eligible for inclusion if they were RCTs comparing supervised aerobic exercise training with a placebo, controlled comparison or standard care. For the purposes of the review, exercise was defined as a form of leisure-time physical activity that was performed on a repeated basis over an extended period of time, with the intention of improving fitness, performance or health^[14]. Studies with an additional treatment arm or combined intervention (*e.g.*, exercise with diet modification) were included only if the effects of exercise could be isolated. A priori, we excluded reports that were available only in abstract form.

Table 1 Example of medline search

(1) Exp neoplasms/
(2) (Cancer* or neoplasm* or (tumor* not tumor necrosis factor) or (tumour* not tumour necrosis factor) or malignan* or carcino* or leukaemia* or leukemi* or lymphoma* or myeloma* or adenocarcinoma*).mp.
(3) (1) or (2)
(4) Exercise therapy/ or motion therapy, continuous passive/ or muscle stretching exercises/ or plyometric exercise/
(5) (Aerobic* or exercise or running or treadmill* or training).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
(6) (4) or (5)
(7) (3) and (6)
(8) (VO ₂ or Aerobic capacity).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
(9) (7) and (8)
(10) Limit (9) to clinical trial, all

Trials were included if they involved adults (17 years and older) diagnosed with cancer who were actively receiving cancer treatment or off treatment. Included studies were required to measure maximal, peak, or estimated maximal oxygen consumption (VO_{2max/peak}) as a study outcome.

Systematic search

A search was performed of the databases including OVID MEDLINE (1948 to October 2013), PubMed (1975 to October 2013), SCOPUS (1950 to October 2013), Web of Science (1950 to October 2013), EMBASE (1988 to October 2013), Cochrane Central Registry of Controlled Trials (1991 to October 2013), and LILACS (1982–October 2013). The search strategy was developed and approved by a librarian with extensive database searching knowledge and experience. We searched terms related to cancer (*e.g.*, neoplasms, tumor), exercise (*e.g.*, exercise, exercise therapy/ or motion therapy, aerobic training), publication type (*e.g.*, random allocation, clinical trial), and aerobic capacity (*e.g.*, VO₂). The search strategy was modified as necessary for each database. Non-English language publications were eligible for inclusion. To locate unpublished research, we reviewed clinical trial registries and websites housing theses and dissertations. Fourteen experts in the field of cancer and exercise were contacted in order to identify any research that was not published or was pending publication. Table 1 includes an example of the MEDLINE search strategy.

Coding and reliability

The titles and abstracts were screened for eligibility by two independent evaluators (C.K. and R.B.), and coded for exclusion or potential inclusion. Potentially eligible manuscripts were obtained and the same evaluators performed a second round of screening to evaluate full eligibility criteria. Any disagreements were resolved by consensus (C.K., R.B., and M.M.). The two evaluators

(C.K. and R.B.) then independently abstracted data on study participants, the intervention and control (usual care) protocols, and study outcomes, and assessed for quality. Studies were evaluated using the quality assessment framework for RCTs developed by the Cochrane Collaboration^[15] to assess risk of bias in the individual studies. Sensitivity analyses were conducted to examine the effect of including studies with high risk of bias.

For the purpose of evaluating exercise prescription variables, exercise intensity was standardized to a single %VO_{2max} value^[16–18]. For studies that used %VO_{2max} as the intensity prescription the average of the range was used; time spent at different intensities was factored in to create the mean value. High intensity intervals were weighted at 50% of the contributing time. Resistance exercise was not included in intensity ratings. Total exercise workload, or intensity-minutes, was calculated by multiplying the exercise intensity by the prescribed exercise volume (program duration, minutes per session and sessions per week).

Study outcomes and effect size calculation

Study results were pooled using random effects models. For continuous outcomes, pooled statistics were calculated using mean differences (MD) when data were on a uniform scale and using standardized MD (SMD) when data were on different scales. All results were calculated with 95%CI. The SMD was interpreted as 0.2, 0.5 and 0.8 representing small, medium and large effects on outcomes respectively^[19]. Statistical heterogeneity was assessed using a χ^2 test that considered a *P*-value of less than 0.10 to indicate significant heterogeneity. *I*² values, ranging from 0% (homogeneity) to 100% (heterogeneity) were also calculated to quantify variability in study effect and values of 25%, 50% and 75% were used to describe low, moderate and high heterogeneity respectively^[20]. Subgroup analyses and multiple regression moderator analyses were performed to explore and explain heterogeneity among studies. A priori subgroup analyses included examining the pooled effect estimate by level of supervision of exercise (group or individual), the timing of the intervention (on or off treatment), and cancer type. Meta-regression was performed to explore exercise variables of frequency, time, intensity, duration and adherence on effect estimate.

Statistical analysis

A biomedical statistician (Y.L.) provided oversight on the statistical methods, and performed the meta-regression analyses. All data were entered into Review Manager 5.2 and analyzed with SPSS v15 software utilizing meta-regression scripts created by Lipsey and Wilson and Stata/SE (version 13.0)^[21]. Figures were created using Comprehensive Meta-Analysis (version 3: <http://www.meta-analysis.com/index.php>).

RESULTS

Methodological characteristics

The search protocol yielded 1269 eligible studies; after

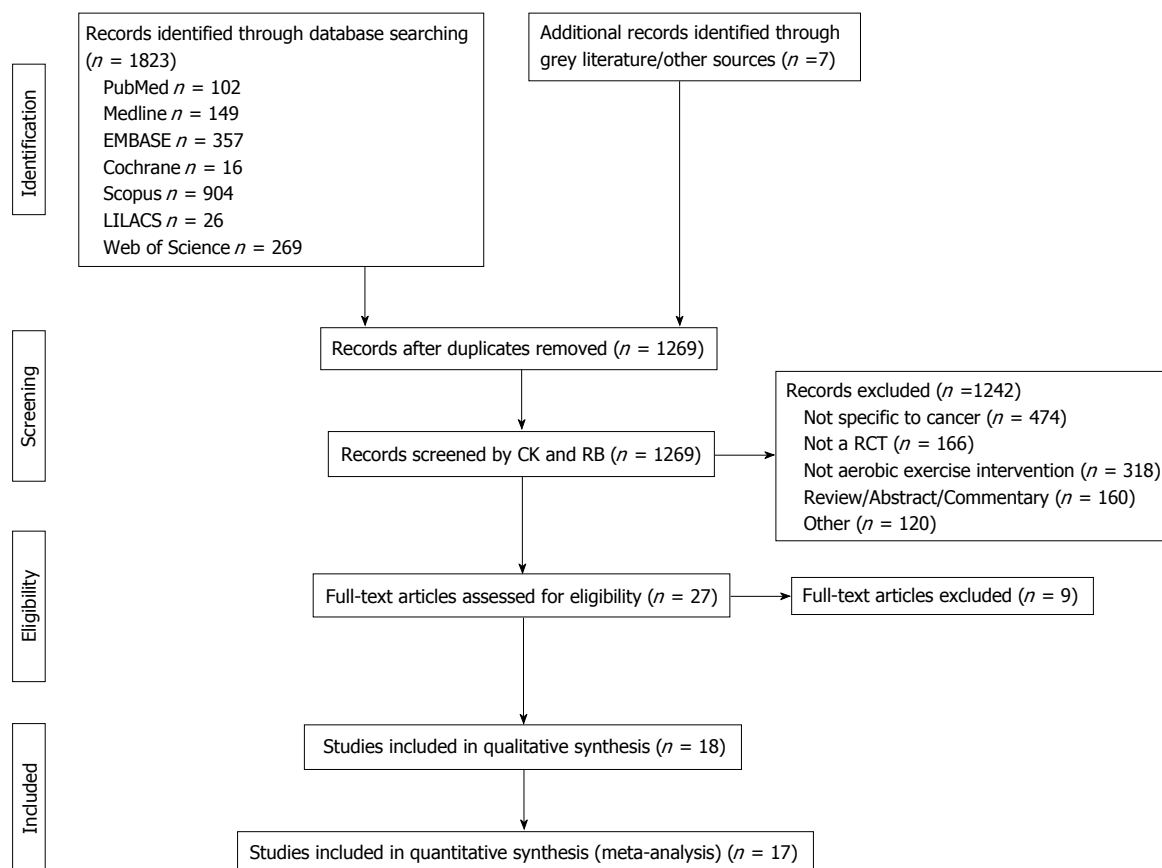


Figure 1 PRISMA flow diagram of study selection process.

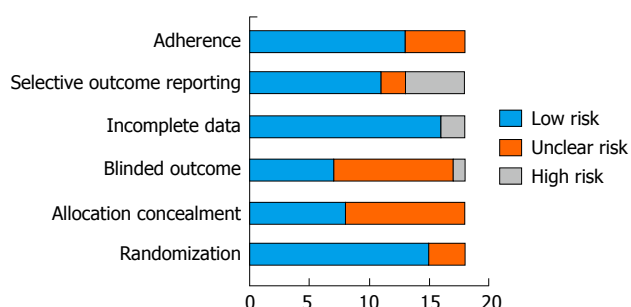


Figure 2 Risk of bias summary.

removal of duplicates and screening of abstracts, 23 studies remained. Reference tracking and contacting of experts accounted for 4 additional studies. Grey literature and trial register searches yielded no further articles. Full text review of the 27 studies excluded a further 9, leaving 18 studies for qualitative and quantitative synthesis^[22-39]. One study was not used for the quantitative analyses due to missing data^[32] and one study was divided into two comparison groups as it involved both on and off treatment subgroups^[27] (unpublished data provided by author). The remaining 17 studies, generating 18 comparisons, were included in the meta-analyses (Figure 1). Kappa statistics for the inclusion of studies was 0.9 ($P < 0.001$). Following discussion there was 100% agreement in scores between evaluators.

Risk of bias

In general there was high or unclear risk of bias for selection (allocation concealment) and detection bias (lack of blinding of outcome assessors) and low risk of bias for attrition (handling of incomplete data) and reporting bias (outcome reporting) among the included studies (Figure 2). Sensitivity analyses were performed after excluding studies with a high or unclear risk of bias for allocation concealment ($n = 10$)^[24,31-39] and for use of blinded outcome assessment ($n = 11$)^[24,26,27,31-36,38,39]. The results showed minimal differences in the pooled effect estimates for aerobic capacity based on risk of bias. For allocation concealment, the pooled effect estimate increased by 0.6 (SMD: 0.80; 95%CI: 0.51, 1.25) whilst for blinding of outcome assessment the estimate decreased by 0.4 (SMD: 0.7; 95%CI: 0.35, 1.05). After excluding studies with a high or unclear risk of bias for any factor ($n = 13$), the pooled effect estimate decreased by 0.8 (SMD: 0.66, 95%CI: 0.22, 1.11).

Cancer survivor characteristics

The 18 included studies involved 1149 participants of which 576 were randomized to receive an aerobic exercise intervention and the remaining 573 received usual care or no exercise. Participants were on average 53 years of age and 76% were female. Survivors of breast cancer were most commonly studied in both breast cancer specific

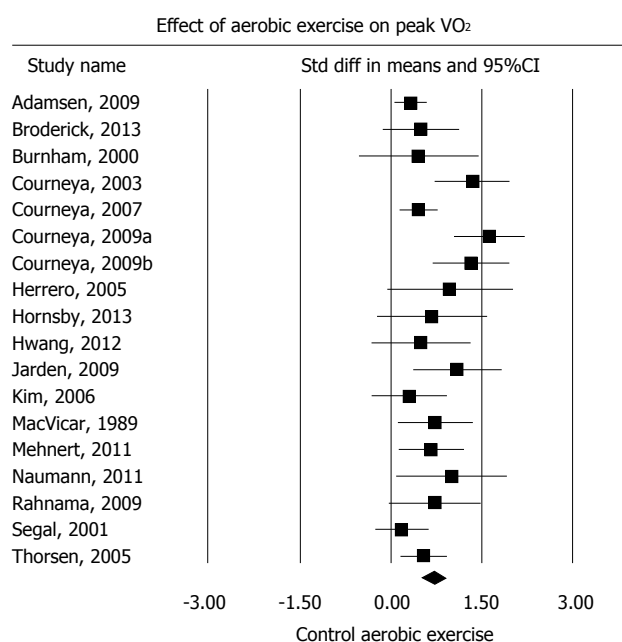


Figure 3 VO₂ effect size.

trials and mixed cancer type trials (14 studies)^[22-26,28,29,33-39] accounting for 686 participants (60%) of the total participants in the review. Further details on the included studies are provided in Table 2.

Exercise intervention characteristics

Ten studies consisted exclusively of aerobic exercise training^[23-27,29,30,33,34,38], six studies included a resistance exercise component with or without flexibility training^[22,28,31,36,37,39], one included physiotherapy exercises and relaxation^[35], and one included flexibility training plus a dietary intervention^[32]. Exercise interventions consisted primarily of cycling^[23-31,34,39] or walking/jogging^[23,24,32,35,37,39]. Five studies^[22,23,28,35,38] offered exercise programs in a class setting (group exercise format) and the remaining 13 studies^[24-27,29-34,36,37,39] were individualized exercise programs, although further detail on the level of supervision was not often provided. Eight studies were carried out during active cancer treatment^[22,26,29-31,33,34,38], nine in the post treatment phase^[23-25,28,32,35-37,39] and one included participants both on and off treatment^[27]. The duration of exercise programs ranged from 4-6 wk to 26 wk with individual exercise sessions ranging from 20-90 min including warm up and cool down. Seventeen studies prescribed aerobic exercise that was of moderate intensity with 4 of these studies^[22,27,29,34] including high intensity intervals. One study combined both low and moderate intensity intervention groups into a single intervention group for their analysis due to the small sample size of the study^[24]. Further information on the exercise prescription variables is provided in Table 3.

The effect of supervised aerobic exercise on aerobic capacity

All eighteen studies reported VO_{2peak}, with 13 studies (14 comparisons) indexing this outcome to body weight

(mL/kg per minute)^[23-30,35-39], 4 studies measuring absolute (L/min)^[22,31,33,34], and 1 study measuring percent change in VO_{2peak} (mL/kg per minute)^[32]. The study measuring percent change in VO_{2peak} was excluded from analysis due to insufficient data on measures of variability.

Pooling of all 18 comparisons showed a moderate-to-large effect estimate (SMD: 0.74; 95%CI: 0.52, 0.96; $P < 0.001$) in favour of supervised aerobic exercise training; however, moderate heterogeneity was found among the included studies ($I^2 = 63\%$; $P < 0.001$) (Figure 3). Pooling of the 13 studies (14 comparisons) reporting VO_{2peak} (mL/kg per minute) showed a statistically significant mean difference in VO_{2peak} of 3.13 mL/kg per minute (95%CI: 2.21, 4.05; $P < 0.001$) in favour of supervised aerobic exercise training; however, again moderate heterogeneity was found among the included studies ($I^2 = 58\%$; $P < 0.001$).

Subgroup analysis

Subgroup analyses were performed for level of supervision, treatment timing and cancer type (Table 4). A significantly smaller effect estimate ($P = 0.003$) was found for group/ class-led exercise studies^[22,23,35,38] (SMD: 0.36; 95%CI: 0.17, 0.56) when compared to studies involving individualized exercise programs^[24-31,33,34,36,37,39] (SMD: 0.87; 95%CI: 0.60, 1.15). Non-significant effects ($P = 0.11$) were observed between on and off treatment studies. Statistically significant differences in pooled effect estimates were observed between cancer types with a significantly larger beneficial effect found among studies including survivors with hematological cancers ($P < 0.001$)^[27,31] when compared to other cancer tumor groups (breast cancer, lung cancer and mixed cancer).

Meta-regression

Meta regression was performed analyzing the effect estimate with exercise parameters of exercise workload and participant adherence as potential moderators. These two variables, workload and adherence, explained 65.8% ($P = 0.04$) of the between-study variance in effect estimate among the included studies (Figure 4).

Quality of life

Nine studies reported data for health-related quality of life as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale^[23,25,29,31], the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: EORTC-QLQ-C30^[22,28,30,39] and Medical Outcomes Survey: Short Form: SF36^[38]. Pooling of all nine studies demonstrated a non-significant effect on quality of life (SMD: 0.3; 95%CI: -0.11, 0.71; $P = 0.16$), with high heterogeneity found among studies ($I^2 = 80\%$; $P < 0.001$). Further details are provided in Table 5.

DISCUSSION

This meta-analysis found that supervised aerobic exercise resulted in a moderate-to-large significant benefit on

Table 2 Description of Included Studies

Ref.	Sample size/ cancer type	Age (SD/range)	Gender (F/M)	Intervention group	Comparison group	Key outcomes	Adverse events
On treatment studies/subgroups							
Adamsen <i>et al</i> ^[22] , 2009 Denmark	<i>n</i> = 117 Mixed Cancer Groups	47.2 (\pm 6.7) yr	F: 78 M: 39	Aerobic Training with High-intensity Intervals + Resistance Exercise + Relaxation + Massage	Usual care: allowed to freely increase physical activity	Estimated VO _{2max}	Seizure (<i>n</i> = 1)
Courneya <i>et al</i> ^[26] , 2007 Canada	<i>n</i> = 133 Breast Cancer	49 yr (26-78)	F: 133	Aerobic Training	Usual care: continue usual activities	VO _{2peak} QoL: FACT- Anemia	Hypotension (<i>n</i> = 1) Dizziness (<i>n</i> = 1)
¹ Courneya <i>et al</i> ^[27] , 2009 ^b Canada	<i>n</i> = 54 NHL, HL	² 53.2 yr (18-80)	² F: 50 M: 72	Aerobic Training with High-intensity Intervals	Usual Care: continue usual activities	VO _{2peak} QoL: FACT-B/ Ac/An	Back (<i>n</i> = 1), hip (<i>n</i> = 1) and knee (<i>n</i> = 1) pain
Hornsby <i>et al</i> ^[29] , 2013 United States	<i>n</i> = 20 Breast Cancer	51 (\pm 6) yr	F: 10	Aerobic Training with High-intensity Intervals	Control: Continue usual exercise levels	VO _{2peak} FACT-B Adverse Events	Leg pain (<i>n</i> = 1)
Hwang <i>et al</i> ^[30] , 2012 Taiwan	<i>n</i> = 24 Lung	61 (\pm 6.3)	F: 12 M: 12	Aerobic Training	Usual Care: general patient education	VO _{2peak} QoL: EORTC	Not reported
Jarden <i>et al</i> ^[31] , 2009 Denmark	<i>n</i> = 42 Mixed Cancer Groups	39.1 (12.2)	F: 16 M: 26	Aerobic Training + Resistance Exercise + Flexibility	Usual Care	Estimated VO _{2max} QoL: EORTC, FACT-An	None
Kim <i>et al</i> ^[33] , 2006 United States	<i>n</i> = 41 Breast Cancer	51.3 (6.7) yr	F: 41	Aerobic Training	Waitlist Control	VO _{2peak}	Not reported
MacVicar <i>et al</i> ^[34] , 1989 United States	<i>n</i> = 34 Breast Cancer	45.4 (10.2) yr	F: 34	Aerobic Training with High-intensity Intervals	Control: Continue normal activities	VO _{2max} L/min	Not reported
Segal <i>et al</i> ^[38] , 2001 Canada	<i>n</i> = 66 Breast Cancer	51 (\pm 8.7) yr	F: 66	Aerobic Training	Control group encouraged to exercise	Estimated VO _{2max} QoL: SF36	Not reported
Off treatment studies/comparisons							
Broderick <i>et al</i> ^[23] , 2013 Ireland	<i>n</i> = 43 Mixed Cancer Groups	52.3 (8.3) yr	F: 37 M: 6	Aerobic training	Usual Care	Estimated VO _{2max} QoL: FACT-G, SF36	Not reported
Burnham <i>et al</i> ^[24] , 2000 United States	<i>n</i> = 18 Mixed Cancer Groups	54.2 (8.1) yr	F: 15 M: 3	Aerobic training	Control	VO _{2peak} QoL: LASA	Not reported
Courneya <i>et al</i> ^[25] , 2003 Canada	<i>n</i> = 50 Breast Cancer	59 (\pm 6) yr	F: 54	Aerobic training	No exercise	VO _{2peak} QoL: FACT- Breast	Lymphedema (<i>n</i> = 3) Gynecological complication (<i>n</i> = 1)
¹ Courneya <i>et al</i> ^[27] , 2009 ^a Canada	<i>n</i> = 68 NHL, HL	² As per Courneya, 2009 ^b	² As per Courneya, 2009 ^b	² As per Courneya, 2009 ^b	² As per Courneya, 2009 ^b	² As per Courneya, 2009 ^b	² As per Courneya, 2009 ^b
Herrero <i>et al</i> ^[28] , 2005 Spain	<i>n</i> = 16 Breast Cancer	51 (10) yr	F: 16	Aerobic plus Resistance Training	No Exercise	VO _{2peak} QoL: EORTC	Not reported
Kaibori <i>et al</i> ^[32] , 2013 Japan	<i>n</i> = 51 Liver Cancer	68 (9.1) yr	F: 15 M: 36	Aerobic Training + Stretching + Diet Intervention	Diet Intervention	VO _{2peak}	Not reported
Mehnert <i>et al</i> ^[35] , 2011 Germany	<i>n</i> = 58 Breast Cancer	53 (7.4) yr	F: 58	Aerobic Training + Physiotherapeutic Exercises + Relaxation	Waitlist Control	VO _{2max} QoL: BIQ	Not reported
Naumann <i>et al</i> ^[36] , 2011 Australia	<i>n</i> = 21 Breast Cancer	49 (10) yr	F: 21	Aerobic Training + Resistance Exercise + Flexibility	Usual Care	Estimated VO _{2max} QoL: FACT-B	Not reported
Rahnama <i>et al</i> ^[37] , 2010 Iran	<i>n</i> = 29 Breast Cancer	58.3 (6.3) yr	F: 29	Aerobic Training + Resistance Exercise	No exercise	Estimated VO _{2max}	Not reported
Thorsen <i>et al</i> ^[39] , 2005 Norway	<i>n</i> = 111 Mixed Cancer Groups	39 (8.4) yr	F: 36 M: 75	Aerobic Training + Resistance Exercise	Usual Care	Estimated VO _{2max} QoL: EORTC	Not reported

¹Courneya 2009 publication: Courneya 2009^b-subgroup of participants on-treatment; Courneya 2009^a-subgroup of participants off-treatment; ²Data as per Courneya 2009^b. QoL: Quality of life; FACT-G: Functional Assessment of Cancer Therapy-General scale; EORTC: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SF36: Medical Outcomes Survey Short Form; VO_{2max}: Maximal oxygen consumption; VO_{2peak}: Peak oxygen consumption.

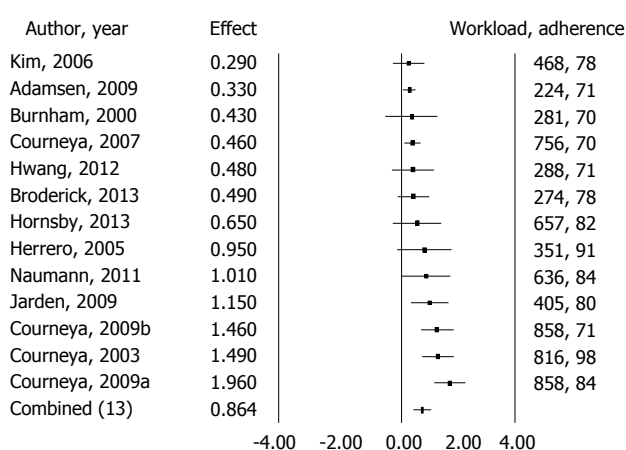
Table 3 Exercise prescription variables

Ref.	Study duration (wk)	Days/week	Mins/session (mean)	Volume	Standardized intensity (mean)	Workload (intensity minutes)	Adherence (attendance)
Adamsen <i>et al</i> ^[22]	6	3	15	270	0.83	224	71%
Broderick <i>et al</i> ^[23]	8	2	30	480	0.57	274	78%
Burnham <i>et al</i> ^[24]	10	3	23	690	0.41	281	70%
Courneya <i>et al</i> ^[25]	15	3	25	1125	0.73	816	98%
Courneya <i>et al</i> ^[26]	12	3	30	1080	0.70	756	70%
Courneya <i>et al</i> ^[27] (1)	12	3	30	1080	0.79	858	84%
Courneya <i>et al</i> ^[27] (2)	12	3	30	1080	0.79	858	71%
Herrero <i>et al</i> ^[28]	8	3	25	600	0.59	351	91%
Hornsby <i>et al</i> ^[29]	12	3	23	828	0.79	657	82%
Hwang <i>et al</i> ^[30]	8	3	20	480	0.60	288	71%
Jarden <i>et al</i> ^[31]	5	5	22.5	563	0.72	405	80%
Kim <i>et al</i> ^[33]	8	3	30	720	0.65	468	78%
MacVicar <i>et al</i> ^[34]	10	3	NR	-	0.73	-	NR
Mehnert <i>et al</i> ^[35]	10	2	30	600	0.60	360	NR
Naumann <i>et al</i> ^[36]	8	3	53	1272	0.50	636	84%
Rahnama <i>et al</i> ^[37]	15	2	35	1050	0.28	289	NR
Segal <i>et al</i> ^[38]	26	3	NR	-	0.55	-	72%
Thorsen <i>et al</i> ^[39]	14	2	30	840	0.62	518	NR

NR: Not reported.

Table 4 Subgroup analyses

Subgroup category	Subgroup	No. studies	Mean Difference in mL/kg per minute (95%CI)	P value between subgroups	No. studies	Standardized mean difference (95%CI)	P value between subgroups
Level of exercise supervision	Group Exercise Class	3	1.77 (0.04, 3.51)	P = 0.07	4	0.36 (0.17, 0.56)	P = 0.003
	Individual Exercise	11	3.53 (2.64, 4.43)		14	0.87 (0.60, 1.15)	
Treatment status	On Treatment	5	2.59 (0.7, 4.48)	P = 0.26	9	0.56 (0.32, 0.81)	P = 0.11
	Off Treatment	9	3.74 (3.06, 4.42)		9	0.92 (0.56, 1.29)	
Cancer tumor group	Breast	8	2.41 (1.5, 3.31)		10	0.64 (0.34, 0.88)	
	Hematologic	3	5.08 (4.01, 6.16)		3	1.55 (1.09, 2.02)	
	Lung	1	2.10 (-1.36, 5.56)	P = 0.002	1	0.48 (-0.34, 1.30)	P = 0.0002
	Mixed Cancers	3	3.17 (1.34, 5.0)		4	0.41 (0.21, 0.61)	


Figure 4 Meta-regression analysis: Workload, adherence.

VO_{2peak} in survivors of cancers. The pooled mean difference showed an improvement in VO_{2peak} of 3.13 mL/kg per minute, which is close to one metabolic equivalent (MET) improvement in fitness and similar to the 2.9 mL/kg per minute increase reported by Jones *et al*^[13]. In the general

population, each one MET increase in fitness has been found to translate to a 12% decrease in mortality in men^[6] and a 17% decrease in women^[40]. In the cancer population, a number of studies have reported an inverse correlation between VO_{2peak} and all-cause mortality, including cardiovascular, lung and breast cancer related deaths^[41-43].

We did not find an overall significant effect of supervised aerobic exercise interventions on quality of life. Studies in our review used a variety of quality of life measures and when data were pooled significantly high heterogeneity was found. This finding suggests that the differences between study populations and/or differences inherent in the quality of life questionnaires may be factors. Supporting this premise, the pooled data from four studies using the FACT-General scale showed both statistical homogeneity and significant benefit on quality of life.

Our results showed that survivors of cancer participating in individually-based exercise experienced greater improvement in VO_{2peak} than those participating in group or class-led exercise. A reported advantage to group or class-led exercise is the social interaction and group

Table 5 Quality of life outcome

Quality of life measure	No. of studies	Mean difference (95%CI)	P value between groups	Standardized mean difference (95%CI)	P value between groups
All combined	9	Not applicable	-	0.3 (-0.12, 0.70)	P = 0.16
EORTC Global	4	1.45 (0.58, 2.32)	P = 0.001	0.13 (-0.06, 0.33)	P = 0.17
FACT-G	4	3.25 (-0.41, 6.92)	P = 0.08	0.47 (0.14, 0.79)	P = 0.005
MOS SF36	1	2.2 (1.34, 3.06)	P < 0.001	1.22 (0.69, 1.74)	P < 0.001

EORTC Global: European Organisation for Research and Treatment of Cancer Global Quality of Life Questionnaire; FACT-G: Functional Assessment of Cancer Therapy-General scale; MOS SF36: Medical Outcomes Survey Short Form.

support that may foster improvements in quality of life among survivors. Similar to our findings, a previous meta-analysis comparing group to individual exercise on quality of life in survivors of breast cancer reported that group exercise showed no benefit over individual exercise^[44]. While the findings of our review appear to support individually based exercise programs for the outcome of aerobic capacity, we found that data were generally lacking on the ratio of the exercise participant to exercise specialist to allow for closer examination of impact of the level of supervision.

In contrast to the meta-analysis by Jones *et al.*^[13] we did not find a significant difference between groups based on the timing of the intervention relative to cancer treatment. Inspection of adherence across studies revealed a bimodal distribution with clusters in the 70-75 and 85-98 percent ranges. This bimodal distribution appeared to reflect on/off treatment status, as better adherence and larger effects were generally seen from exercise intervention studies carried out after completion of cancer treatment. Moreover, the direction of exercise effects compared to usual care may differ in relation to treatment status. For example, Jarden *et al.*^[31] demonstrated that exercise during active cancer treatment prevented a decline in VO_{2peak} when compared to usual care, whereas Kim *et al.*^[33] found that exercise following cancer treatment increased VO_{2peak} over usual care. More research is required to elucidate the influence of the timing of the exercise intervention through the continuum of cancer treatment and survivorship.

While our overall findings support the benefit of supervised aerobic exercise on VO_{2peak} , the relative benefit varied significantly across studies. As the number of research studies in the area has increased we were able to examine the influence of exercise prescription variables on aerobic capacity. Our analyses showed that VO_{2peak} improved to a larger extent in studies examining survivors of haematological cancers over other cancer groups. However, this finding was based on data from only 2 studies (3 comparisons) and thus, while compelling; further research is needed within this particular cancer subgroup. Of note, significant improvements were found within the subgroups of both breast cancer and mixed cancer groups; however, the effect was smaller.

Better participant adherence and overall exercise workload emerged as important predictors of intervention efficacy. Adherence, in this review, represented attendance to exercise sessions. Data on adherence to intensity and

exercise volume were not reported in the majority of trials. Attendance to exercise sessions may reflect the impact of treatment-related side effects, patient motivation, or aspects of the study protocol such as opportunities for making up missed sessions. High adherence to the exercise prescription is critical for ensuring an adequate training stimulus to induce physiological change in cardiorespiratory function. Better reporting of adherence to prescription factors of intensity and duration would allow for more precise examination of the dose response to exercise^[5].

Previous meta-analyses examining exercise interventions have reported benefit from more intense aerobic exercise interventions for both quality of life and depressive symptoms^[45,46]. In the present meta-analysis, however, overall workload rather than intensity alone was found to predict response to exercise. We found that the majority of studies in the review prescribed moderate intensity exercise training, although some included high intensity interval work. Multiplying the exercise volume by the prescribed intensity provided a workload metric (*i.e.*, intensity-minutes) for discriminating between trials finding large effects from those with small effects. While some studies prescribing lower exercise volumes showed benefit, a target workload (intensity-minutes) of around 600 intensity-minutes (*e.g.*, 10 wk program of 90 min per week of supervised exercise at 70% VO_{2peak}) appears to represent the threshold workload required to obtain a clinically significant large improvement (effect size > 1.0) in VO_{2peak} . A recent meta-analysis by Carayol *et al.*^[47] examined the effect of exercise on fatigue and quality of life and found a workload in the range of 90-120 min of moderate intensity exercise was more beneficial in improving fatigue and quality of life than higher volumes of exercise. Our findings suggest that improvements in aerobic capacity can be attained at an exercise workload level that, in theory, should not negatively impact fatigue and quality of life.

Limitations

The major limitations of this meta-analysis were the assumptions revolving around exercise prescription factors. All intensity values represented average values obtained and were standardized to an estimated % VO_{2max} value. Conversions are imperfect as are average values created from studies using intervals and step protocols. Therefore we acknowledge that there is some associated error in our intensity estimates. As well, no data were provided

on actual adherence to intensity among participants in the individual studies to allow more precise estimation of intensity. Thus our crude estimates of targeted intensity functioned merely as a means to determine relative ranking for between study comparisons. Assumptions were also made that resistance exercise provided minimal contributions to $\text{VO}_{2\text{peak}}$. A further limitation of our meta-analysis was the small number of included studies, which permitted the analysis of only two moderator variables. Thus, further research is needed particularly in survivors of cancers other than breast cancer.

Studies included in this review were generally of good methodological quality with low risk of bias. However, further attention to study quality is needed, as many studies did not adequately report methods for allocation concealment and use of blinded assessment, limiting our ability to evaluate the impact of risk of bias across studies. Of note, the estimated effect size was lower when excluding studies at high risk of bias; thus, our findings may represent an overestimate of the effect of supervised exercise on aerobic capacity.

A final limitation is that the mechanism(s) responsible for the improvement in $\text{VO}_{2\text{peak}}$ along the oxygen cascade were not studied in any of the studies included in our review; thus, the favourable finding in $\text{VO}_{2\text{peak}}$ may be due to improved convective and/or diffusive oxygen transport coupled with improved oxygen utilization by the active muscles^[48].

Supervised aerobic exercise training was found to have a moderate-to-large beneficial effect on $\text{VO}_{2\text{peak}}$. Aerobic capacity increased in a dose response fashion with overall workload, with larger effects found in studies prescribing a higher overall workload of aerobic exercise. Larger benefits were also seen in studies with better participant attendance and among survivors of haematological cancers. There is a need for further randomized controlled trials examining supervised aerobic exercise interventions in understudied but common cancers such as prostate, lung and colorectal cancer.

COMMENTS

Background

Evidence is accumulating to support the benefit of exercise to improve the physical functioning and quality of life of survivors. Currently, the optimal exercise prescription is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors at different times through the cancer continuum.

Research frontiers

A previous meta-analysis included data from six randomized controlled trials and reported a significant benefit from supervised aerobic exercise training, compared with usual care, on $\text{VO}_{2\text{peak}}$ (2.90 mL/kg per minute; 95%CI: 1.16, 4.64; $P = 0.01$). However, statistical and clinical heterogeneity was found among the exercise trials included in their review, and therefore further research was indicated to build on and extend the current knowledge in the field.

Innovations and breakthroughs

Pooling of the 13 studies (14 comparisons) reporting $\text{VO}_{2\text{peak}}$ (mL/kg per minute) showed a statistically significant mean difference in $\text{VO}_{2\text{peak}}$ of 3.13 mL/kg per minute (95%CI: 2.21, 4.05; $P < 0.001$) in favour of supervised aerobic exercise training; however, again moderate heterogeneity was found among the included

studies ($I^2 = 58\%$; $P < 0.001$). Meta-regression was performed analyzing the effect estimate with exercise parameters of exercise workload and participant adherence as potential moderators. These two variables, workload and adherence, explained 65.8% ($P = 0.04$) of the between-study variance in effect estimate among the included studies.

Applications

Supervised aerobic exercise training is an effective intervention to improve aerobic capacity in survivors of cancer. Aerobic capacity increased in a dose response fashion with overall workload, with larger effects found in studies prescribing a higher overall workload of aerobic exercise. Larger benefits were also seen in studies with better participant attendance and among survivors of haematological cancers.

Terminology

Aerobic capacity ($\text{VO}_{2\text{max}}$) is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level. Aerobic capacity is best increased by habitual aerobic exercise training that is of a moderate-to-vigorous intensity.

Peer review

An excellent systematic review.

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Hypertension in Zimbabwe: A meta-analysis to quantify its burden and policy implications

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Abstract

AIM: To estimate the pooled prevalence of hypertension in Zimbabwe and describe its trend since independence in 1980 using secondary source data.

METHODS: MEDLINE, EMBASE and Scopus databases from April 1980 to December 2013 were searched for population and community based studies on the prevalence of hypertension among adults (≥ 18 years) in Zimbabwe. The key words used were "prevalence", "epidemiologic studies", "hypertension" or "high blood pressure", based on the cut-off (≥ 140 mmHg systolic blood pressure and/or ≥ 90 mmHg diastolic blood pressure). We conducted a meta-analysis on the published studies, using the random-effects model to estimate the pooled prevalence.

RESULTS: The search retrieved 87 publications, of which four studies met the selection criteria. The four studies had a total of 4829 study participants between 1997 and 2010 across 5 provinces in Zimbabwe. Two studies were in urban areas, while the other two had mixed study settings (urban and rural). The overall pooled prevalence of hypertension was 30% (95%CI: 19%, 42%, $I^2 = 98\%$, $\chi^2 = 164.15$, $P = 0.00$).

CONCLUSION: Our results show a high prevalence of hypertension in Zimbabwe, with urban areas having higher prevalence than rural areas.

Key words: Hypertension; High blood pressure; Prevalence; Meta-analysis; Zimbabwe

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Core tip: A systematic review and meta-analysis of studies on the prevalence of hypertension in Zimbabwe, from April 1980 to December 2013 reveals a high prevalence of 30%. Hypertension prevalence was higher

in studies in urban settings compared with studies in mixed settings (urban and rural), indicating the increase of cardiovascular risk factors associated with urbanization and economic progress. The development of national prevention policies and control strategies for hypertension are critical to reduce the increasing burden of hypertension in Zimbabwe.

Mutowo MP, Mangwiro JC, Lorgelly P, Owen A, Renzaho AMN. Hypertension in Zimbabwe: A meta-analysis to quantify its burden and policy implications. *World J Meta-Anal* 2015; 3(1): 54-60 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/54.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.54>

INTRODUCTION

Hypertension-related conditions are the most common cause of death from non-communicable diseases (NCDs) in sub-Saharan Africa^[1]. Hypertension is recognized as a global public health crisis due to it being asymptomatic and its high mortality rate^[2]. The prevalence of hypertension is estimated at 22.9% in developing countries and 37.3% in developed countries^[3]. Unfortunately, Zimbabwe faces the particular challenge of high morbidity and mortality from communicable diseases and increasing prevalence of NCDs^[4]. NCDs accounted for an estimated 21% of total deaths in 2008 in Zimbabwe^[5] and hypertension was ranked first amongst the NCD outpatient visits recorded in Zimbabwean public hospitals in 2006^[4]. The limited data available suggests that there was a four-fold increase in the prevalence of hypertension from 1990 to 1997^[6], and the age-standardized rate of hypertension in Zimbabwe (33.1%) was reported in one study to be higher than that seen in developed countries such as United States of America (20.3%), Canada (21.4%) and England (29.6%)^[3].

Urbanization has resulted in the westernization of lifestyles in parts of Zimbabwe. In urban areas, diets high in refined, starchy carbohydrates are leading to high obesity rates and increased prevalence of hypertension, diabetes and cardiovascular diseases^[7]. Hypertension awareness is low, resulting in inadequate treatment and management of hypertension in the Zimbabwean population, and hence there is an urgent need for a national policy for the prevention and control of hypertension in Zimbabwe^[8]. This should include a major focus on prevention, as this may be more cost effective for a developing country with limited resources^[9]. This will require development of evidence-based prevention strategies, which must be informed by a clear understanding of the hypertension burden across the country. However in Zimbabwe, as in many other resource-limited settings, the infrastructure available to enable detailed disease surveillance activities is lacking and no national studies on hypertension prevalence in Zimbabwe are available. The purpose of this study was to systematically review the epidemiological results of published studies and estimate the pooled prevalence of

hypertension in Zimbabwe using meta-analysis.

MATERIALS AND METHODS

Search strategy

The systematic review and meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Group^[10]. Published epidemiologic studies on the prevalence of hypertension we searched for between April 1980 and December 2013 in three electronic databases: MEDLINE, EMBASE and Scopus. The medical subject headings (MeSH) terms used in all databases were ("hypertension" OR "high blood pressure") AND ("prevalence" OR "epidemiological studies") AND ("Zimbabwe"). Prior to the national independence of Zimbabwe, on 18 April 1980, the nation had been known by several names including Rhodesia, Southern Rhodesia, and Zimbabwe-Rhodesia. We further searched the grey literature databases and individual Zimbabwean public health institute websites for relevant studies.

Criteria for inclusion and exclusion

Inclusion criteria for studies included studies on the prevalence of hypertension or high blood pressure, conducted among Zimbabwean residents (≥ 18 years old); population or community studies that were cross-sectional or cohort studies and cut off points for hypertension were systolic blood pressure (SBP) (≥ 140 mmHg) and/or diastolic blood pressure (DBP) (≥ 90 mmHg).

Studies had to abide by the hypertension diagnostic criteria of the Seventh Report of the Joint National committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)^[11], and/or the 1999 World Health Organization (WHO)/International Society of Hypertension (WHO/ISH) classification of blood pressure levels^[12], and/or the 2003 WHO/ISH Statement on Management of Hypertension^[13], whose cut-off points are based on 140/90 mmHg. Studies conducted before 1999 had blood pressure cut-off points defined as $\geq 160/95$ mmHg. Subgroup prevalence based on the cut-off point based on 140/90 mmHg was included from these studies. Articles were excluded if the participants were limited to gender (male or female only), pregnant participants, studies conducted on animals, editorial letters, abstracts, and reviews of original studies.

Study selection

Identified studies were screened by two independent reviewers (MM and AR) to confirm whether they satisfied the inclusion criteria. Lack of consensus about study selection was resolved through discussions with a third author (JC). Retrieved articles and their reference lists were searched for additional publications.

Data extraction

All data was independently extracted by the two reviewers

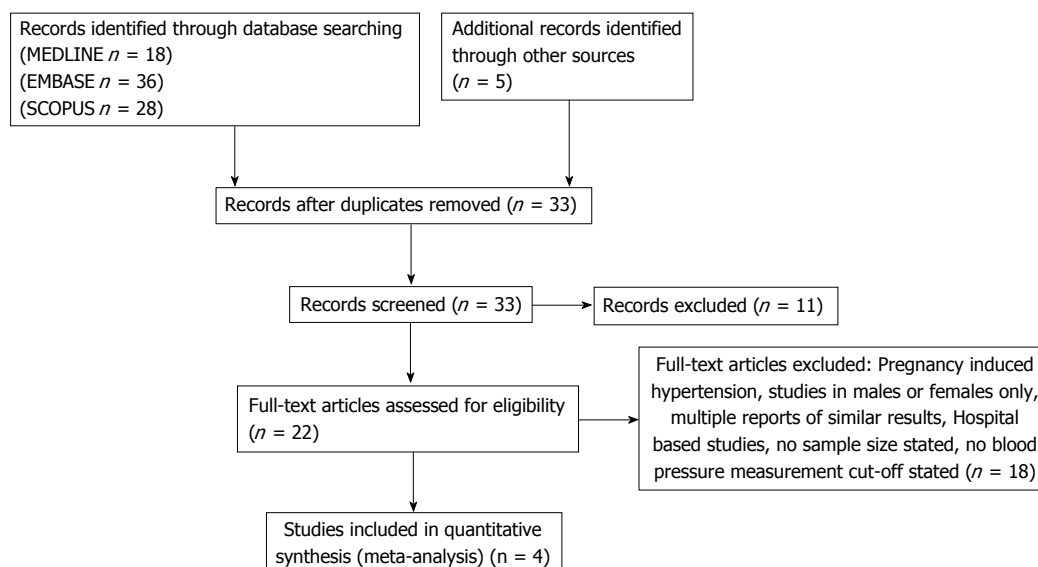


Figure 1 Flow diagram of the study selection process. As shown in Figure 1, our initial search yielded 87 citations: 18 from MEDLINE, 36 from EMBASE, 28 from Scopus, and 5 from grey literature. After screening titles and abstracts, 22 studies were considered potentially eligible and retrieved in full text. Of these, 18 studies were subsequently excluded because they did not satisfy the inclusion criteria. Thus, four fully eligible studies were identified.

(MM and AR), cross-checked and any disagreements were resolved by consensus. The following information was recorded from the included studies: author, year of publication, year of investigation, study period, study setting, sampling frame and method, sample size, age range of study population, reported prevalence, and diagnostic method and criteria used in the study.

Statistical analysis

The Cochran Q test or χ^2 and the I^2 statistic were used to evaluate and quantify statistical heterogeneity^[14,15]. The values for χ^2 and I^2 (low is < 25%, moderate 25%-50%, high > 50%) are mentioned in the forest plot used to visualize the magnitude of heterogeneity among studies. As the differences between studies were very large (I^2 = 98%), we used a random-effects model to estimate the prevalence of hypertension and calculate the 95%CI^[15]. All statistical analysis was done using MetaXL 1.4, Software^[16]. The statistical methods of this study were reviewed by Dr. Baki Billah, Senior Biostatistician Consultant and Senior Lecturer in Biostatistics, from Monash University, Australia.

Dr. Baki Billah, Senior Biostatistician Consultant and Senior Lecturer in Biostatistics at Monash University reviewed and confirmed that the statistical approach reported in the manuscript was adequate and correct.

RESULTS

We initially identified 87 references from our search: 82 from electronic databases and 5 from other sources (Figure 1). After the application of inclusion and exclusion criteria, and removing duplications, as described in Methods, we selected four studies for the meta-analysis.

The four studies^[8,17-19] were conducted across five provinces in Zimbabwe. The studies had a total of

4829 subjects and the enrollment years of the studies ranged from 1997 to 2010. Two studies^[8,17] conducted in predominately urban areas, had a total sample size of 1077, while the other two studies^[18,19], conducted in both urban and rural settings, had a total sample size of 3752. The four studies did not state age-specific data related to gender, and age was limited to above 25 years old in the four studies. Two studies^[17,19] stated the use of JNC7 and WHO/ISH 2003 classifications, while the other two used cut-off points within the inclusion criteria.

Awareness of hypertension was found to be low and treatment and management of hypertension inadequate in one study sample^[8]. One study reported a prevalence which was higher in females than in males and a family history of hypertension which was strongly associated with hypertension in participants in the study^[19]. The commonly reported family members were mothers of participants and on stratified analysis, the association of hypertension and family history of hypertension was stronger in females than males. The study reported a high prevalence of abdominal obesity which is a powerful determinant of subsequent risk of hypertension^[19]. Three studies reported the use of standardized measurement protocols, utilizing nurses or certified personnel for blood pressure measurement, with validity of readings done by a supervising physician^[8,17,19]. Blood pressure was measured two times in a single visit in two studies^[17,18], three times in a single visit in one study and the process for obtaining blood pressure readings was not reported in one study^[8,19]. Two studies used standard mercury sphygmomanometer to measure blood pressure^[8,17], one study used digital blood pressure machines^[19], while no specific instrument was reported for the remaining study^[18].

Based on the reported hypertension prevalence in the included studies, Bulawayo (south Zimbabwe) had the highest prevalence of 38.4% (95%CI: 33%-44%)^[19].

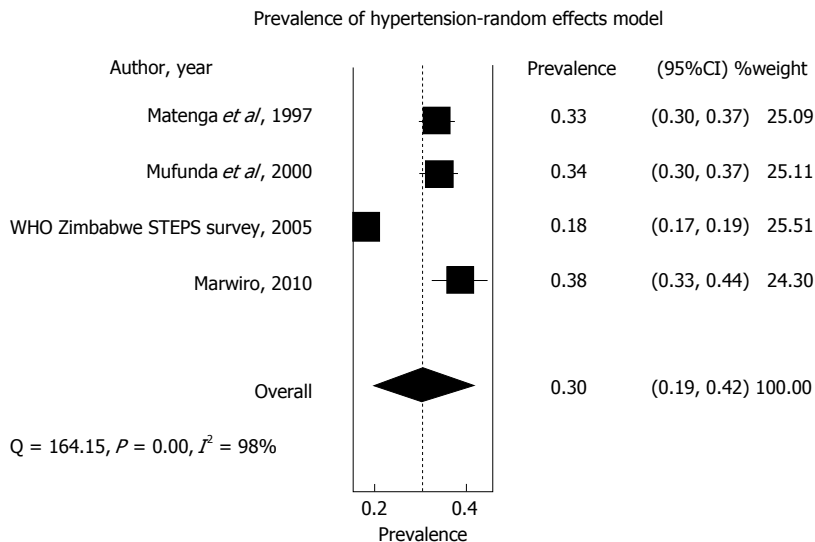


Figure 2 Forest plot of studies conducted from 1997 to 2010 on Hypertension prevalence. The forest plot depicted in Figure 2 (above) represents a meta-analysis of studies that measured the prevalence of hypertension in Zimbabwe from 1997 to 2010. Individual studies with their unadjusted prevalence are represented by a black square and a horizontal line, which corresponds to the point estimate and 95%CI of prevalence. The size of the black square reflects the weight of the study in the meta-analysis. The diamond at the bottom represents the pooled estimate of all studies with its 95% confidence interval. In this case, Figure 2 indicates the pooled estimated prevalence of hypertension is 30% (95%CI: 19-42). The test for overall prevalence also indicates statistical significance ($P < 0.0001$).

The lowest prevalence of 17.9% (95%CI: 17%-19%) was recorded across three provinces in mixed study setting (urban and rural)^[17] (Table 1 summarizes the extracted data from included studies). Using the random-effects model for the meta-analysis, the overall hypertension prevalence is estimated to be 30% (95%CI: 19%-42%, $I^2 = 98\%$, $\chi^2 = 164.15$, $P = 0.00$) (Figure 2).

DISCUSSION

There is a shortage of national data on hypertension prevalence in Zimbabwe. This study summarized the prevalence of hypertension in Zimbabwe over a 14 year period (1997 to 2010). The estimated pooled prevalence for hypertension for the 14 year period was 30%, however as this was not age-standardized and is likely to be an underestimate. The hypertension prevalence for Zimbabwe, estimated by the WHO was higher at 39% for both genders aged at least 25 years, 38.2% (95%CI: 29.9-46.9) in men and 39.9% (95%CI: 30.4-49.4) in women^[20]. However, concerns remain over the different cut-off points used for hypertension measurement in prevalence studies, data sources and modelling methodology and assumptions used, so this creates difficulties in comparing prevalence rates across Africa^[21-23].

Despite this, the observed trend towards increasing hypertension prevalence in our meta-analysis is congruent with the literature. Studies have indicated that the prevalence of hypertension has increased in developing countries over recent decades, with hypertension increasingly prevalent in lower socio-economic groups with limited access to essential treatment^[24,25].

Hypertension was found to be higher in the urban Zimbabwe population^[8,19]. Rapid urbanization and lifestyle changes have been implicated in the development of

hypertension in African urban populations, notably adoption of Western-type diet, physical inactivity and increased psychosocial stress^[6]. Hypertension was found to be prevalent in the lowest income groups, more common in women, linked with overweight and obesity and in heavy alcohol consumers in low income countries^[25]. The Zimbabwe National Health Strategy reports that the prevalence of hypertension in Zimbabwe is increasing mainly because of physical inactivity, tobacco smoking, high salt diet and excessive alcohol consumption^[4]. Therefore preventive measures need to take into account urban planning, whereby effective policies can promote physical activity through re-designing the landscape.

Hypertension is generally asymptomatic until chronic vascular disease develops, with the risk of disease doubling with each blood pressure reading increase of 20/10 mmHg, beginning at lower readings of 115/75 mmHg^[21]. The lack of symptoms contributes not only to the lack of awareness of the condition in those who have it, but also reduces the levels of compliance and persistence with blood pressure lowering interventions, as an improvement in blood pressure control may not result in perceptible benefit to the individual^[25]. The largest cause of years of life lost in low income countries is cardiovascular disease^[25], and with a growing prevalence of hypertension, the burden of cardiovascular diseases in Zimbabwe is likely to increase, which has significant implications for healthcare, individual wellbeing and social stability.

The limited number of population-based studies on hypertension prevalence and risk factors may have contributed to its low priority as a public health problem in Zimbabwe, when compared to higher profile communicable diseases like human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS),

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Study period	Setting	Sampling method	Sample size	Age range (yr)	Prevalence (cases)	Diagnostic criteria	Description of geographic area ¹
Matenga <i>et al</i> ^[8]	October to early December 1996	Community-household	Random	749	> 34	33.4% (250)	Hypertensive described as mean diastolic BP > 94 mmHg untreated or on antihypertensive medication, controlled BP described as mean DBP < 95 mmHg while on drug treatment	Marondera, Mashonaland East (mainly urban and unspecified rural area)
Hakim <i>et al</i> ^[7]	May to July 2005	Subnational-household	Multi-stage	3003	≥ 25	17.9% (538)	Systolic ≥ 140 and/or diastolic ≥ 90 mmHg	Urban and mainly rural communities in Midlands, Mashonaland Central, and Matebeleland South
Mufunda <i>et al</i> ^[18]	July-October 1995	Community-household	Cluster sampling	775	> 25	33.5% (260)	Systolic ≥ 140 mmHg and diastolic ≥ 90 mmHg and/or antihypertensive medication	Marondera, Mashonaland East (urban)
Marwiro ^[19]	June-July, 2010	Community-employee register	Systematic	302	> 25 to > 55	38.4% (116)	The 7 th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Hypertension stage 1: systolic 140-159 mmHg, diastolic 90-99 mmHg, Hypertension stage 2: systolic ≥ 160 mmHg, diastolic ≥ 100 mmHg	Bulawayo (urban)

¹Geographic area refers to the geographic location where study took place in Zimbabwean urban or rural areas. DBP: Diastolic blood pressure.

malaria and tuberculosis. Unlike HIV/AIDS, hypertension is not considered a health priority in Zimbabwe, and no national hypertension program has been established to date. However the HIV/AIDS epidemic in Zimbabwe adds a new dimension to the hypertension burden. The use of highly active antiretroviral therapy to treat HIV is also associated with increased risk of high blood pressure^[20-28].

National programs to diagnose and treat hypertension can lower cerebrovascular disease burden by at least one third^[9]. A focus on primary prevention, through awareness and screening programs, training the health work force to deal with hypertension and its associated risk factors, and access to low-cost anti-hypertensive agents is likely to be more cost-effective for a developing country with limited resources^[29]. Emphasis should be placed on modifiable behavioral factors, such as lifestyle behaviors of family environment, dietary changes, weight reduction and cessation of smoking, all potentially modifiable, and likely to yield greater impact than concentrating on genetic factors for hypertension^[21,30]. Primary prevention of hypertension prevents and reduces the expensive management of hypertension and its ensuing complications^[31].

Limitations

We followed the guidelines for reporting systematic reviews and meta-analysis^[10], however certain drawbacks deserve attention.

Heterogeneity: The sample sizes in the studies used for the meta-analysis totalled a few hundred in three studies to a few thousands in one study. The number of included studies was very small, and various risk factors known to influence heterogeneity were not taken into account. The use of a few studies with large differences in sample size in a meta-analysis, results in pooled estimates with low precision and power, and higher χ^2 and I^2 ^[32]. Due to insufficient data in the included studies, we were unable to perform subgroup analysis to assess the outcome of variations on the pooled prevalence.

Blood pressure measurement: The different methods of measuring blood pressure are documented in literature^[22,23,33]. The World Health Organization recommends risk factor surveys measure blood pressure three times per single visit and use the average result^[33], which was only done in two studies^[8,18], as one measurement per single visit could result in overstated readings^[34]. The number of blood pressure readings recorded has been found to determine whether a patient is classified as hypertensive^[35].

Representativeness: A significant obstacle in developing effective national hypertension prevention programs is the lack of high quality health information systems to inform policy makers^[36]. The burden of NCDs, such as hypertension, is not well documented in Zimbabwe, as its information system has communicable diseases as the main priority. Results from our meta-analysis indicate information on hypertension prevalence in Zimbabwe is limited with no studies providing age-standardized data, thus making direct comparison of results between studies difficult.

In conclusion, our study highlights that estimating the true prevalence of hypertension in Zimbabwe is a challenge due to methodological differences. Therefore, longitudinal national surveys using standardized methodologies are urgently needed in the future to further define the prevalence of hypertension and depict trends.

COMMENTS

Background

World Health Organization estimates the prevalence of hypertension in Sub-Saharan Africa to be 46%, making hypertension a major threat to public health. However the response of many governments and international aid agencies to hypertension has been described as similar to the "reaction to human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) 20 years ago". Zimbabwe (like most sub-Saharan African countries), faces the dual challenge of communicable and non-communicable diseases, however funds donated to fight HIV/AIDS consistently exceed all other national healthcare expenditure. Many countries at a similar stage of development receive more than 50 percent of their total healthcare budgets from donors. Hypertension and its ensuing complications accounted for less than 3% of the global health assistance between 2001 and 2008, despite 80% of deaths from cardiovascular disease occurring in low and middle-income countries. Therefore an estimate of the magnitude of the burden caused by hypertension in Zimbabwe is required to enable the government and international organizations to work together to reduce risk factors for non-communicable diseases such as hypertension.

Research frontiers

There are very few studies on hypertension prevalence in Zimbabwe. This is the first meta-analysis, to the knowledge, to systematically review studies conducted in Zimbabwe, and provide a pooled estimate of hypertension prevalence in Zimbabwe, with the aim of promoting increased awareness of hypertension, and initiate a policy response in Zimbabwe.

Innovations and breakthroughs

By providing a pooled estimate for the prevalence of hypertension in Zimbabwe using studies conducted in Zimbabwe, can assist policy makers in preventive policies and strategies suited for the Zimbabwean urban and rural population.

Applications

The meta-analysis aimed to consolidate data on hypertension prevalence in Zimbabwean urban and rural areas to determine the burden of hypertension in the country.

Terminology

Meta-analysis combines results from independent studies and explores the heterogeneity, as some studies are affected by small sample size and the quality of data. Heterogeneity is the differences in methodology or study populations used in the different studies under examination. Sources of inconsistency include study design, various forms of bias, and how the outcome is measured. The random-effects model is applied when studies have different effects and different characteristics. Forest plots enable the reader to view all the studies at once. One axis of the Forest plot displays the effect estimates (prevalence of hypertension expressed as a percentage for each study in the meta-analysis) and corresponding confidence intervals. The overall pooled prevalence estimate (with 95%CI) is represented as a diamond and placed towards the bottom of the plot.

Peer review

This manuscript is a meta-analysis on the prevalence of hypertension in Zimbabwe. Its' results have provide evidences on policies and interventions hypertension. The results are interesting.

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Operative *vs* nonoperative treatment of displaced intra-articular calcaneal fracture: A meta-analysis of randomized controlled trials

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Conflict-of-interest: The authors have declared that no competing interests exist.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at nanfanghot@126.com. No additional data are available.

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Abstract

AIM: To investigate clinical efficacy of displaced intra-articular calcaneal fracture (DIACF) following operation and nonoperation.

METHODS: Literature search was performed of PubMed and Cochrane Library by two independent authors to identify randomized controlled trials (RCTs) comparing operative *vs* nonoperative treatment of DIACF from inception to December 31st, 2013. RCT quality was evaluated by the modified Jadad scale. Dichotomous variables were pooled using risk ratios by review manager 5.3 software. Fixed-effects or random-effects models were adopted with $P > 0.05$ or $P \leq 0.05$ for heterogeneity tests, respectively.

RESULTS: Eight RCTs comprising 767 cases met inclusion criteria. Results revealed that more surgically treated patients could resume pre-injury job ($P = 0.006$). No statistical differences were found between the two groups in residual pain ($P = 0.33$), shoe fitting problems ($P = 0.07$), limited walking distance ($P = 0.56$) or secondary late arthrodesis ($P = 0.38$). However, operative treatment was associated with a higher complication rate ($P = 0.003$). Subgroup analyses of specific complications revealed that except for a higher risk of superficial wound problems ($P < 0.0001$) in operative group, the two groups had similar complication rate in deep wound infection ($P = 0.34$),

compartment syndrome ($P = 0.46$), thromboembolism ($P = 0.32$), reflex sympathetic dystrophy ($P = 0.51$) or traumatic arthritis secondary to DIACF ($P = 0.43$).

CONCLUSION: Current evidence demonstrates that compared with operative treatment, conservative treatment of DIACF lead to similar clinical outcomes regarding residual pain, shoe fitting, walking distance and secondary subtalar arthrodesis but a significantly lower complication rate.

Key words: Displaced intra-articular calcaneal fracture; Surgery; Conservative treatment; Meta-analysis

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Core tip: This updated meta-analysis regarding the optimal treatment of displaced intra-articular calcaneal fracture suggests that operative and nonoperative treatment have similar clinical outcomes in residual pain, shoe fitting, walking distance and secondary subtalar arthrodesis. However, operative treatment has a higher complication risk than nonoperative treatment.

Jiang N, Song HJ, Xie GP, Wang L, Liang CX, Qin CH, Yu B. Operative vs nonoperative treatment of displaced intra-articular calcaneal fracture: A meta-analysis of randomized controlled trials. *World J Meta-Anal* 2015; 3(1): 61-71 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/61.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.61>

INTRODUCTION

Calcaneal fracture is the most frequent tarsal fracture in the human body^[1,2] and approximately 75% are intra-articular^[3,4]. Since they are mostly caused by high energy trauma^[4,5], the great violence delivered to the foot usually causes displaced intra-articular calcaneal fracture (DIACF).

DIACF can be treated by operation as well as by nonoperation. However, conclusions by randomized controlled trials (RCTs) comparing clinical efficacy of the two methods were conflicting. In the year 1993, Parmar *et al*^[6] showed no significant differences regarding outcomes between operation and nonoperation. However, subsequently in 1996, Thordarson *et al*^[7] revealed a markedly superior functional score following operative treatment. In 2002, Buckley *et al*^[8] found the two methods had equivalent functional outcomes without stratification of the groups but that operation was superior to non-operation only after exclusion of the data from patients who were receiving Workers' Compensation. In 2007, Ibrahim *et al*^[9] reported similar clinical efficacy between the two strategies after 15-year follow-up.

Likewise, conflicting conclusions also existed in published meta-analyses. In a systematic review of three RCTs in 2000, Bridgman *et al*^[10] found slightly better

benefits following operative treatment, in consistent with a meta-analysis^[11] published in the same year. However, both of them recommended further investigation because they believed the evidence was not strong enough to support operative treatment. In 2005, Bajammal *et al*^[3] indicated there was no sufficient evidence to support with certainty that operation was better than nonoperation. This was also concluded by an updated systematic review^[12] in 2009. In our meta-analysis^[13] of RCTs and controlled clinical trials (CCTs) in 2012, we found that the data favored operative treatment of DIACF. However, in Jan, 2013, a systematic review^[14] of four RCTs and quasi-RCTs up to 2011 concluded that operation and nonoperation could achieve similar clinical efficacy while it admitted insufficiency of the evidence.

In fact, although it is still problematic whether operative or nonoperative treatment is better for DIACF, the problem is clinically significant and warrants further study. It is also one of our chief concerns after we published our preliminary finding on this topic.

To our knowledge, there have been two more RCTs^[15,16] comparing operative vs nonoperative treatment of DIACF since the year 2011. In addition, we believe the inclusion of four CCTs^[17-20] in our previous meta-analysis^[13] might have caused a bias which could have made our conclusions less reliable. Therefore, we decided to make a new meta-analysis of only and all retrieved RCTs until the most recently comparing clinical efficacy of operative and nonoperative treatment of DIACF.

MATERIALS AND METHODS

Ethics

No ethics approval was acquired.

Protocol

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement^[21,22].

Search strategy

All RCTs comparing operative vs nonoperative treatment of DIACF were searched in electronic databases of PubMed and Cochrane library by two authors independently. A structured search was performed using the following search string: (displaced intra-articular) AND [(calcaneal fractures) OR (fractures of the calcaneus)] AND (operative OR operation OR surgical OR surgery OR conservative OR conservation). There was no restriction to publication language. The search time was set from inception to 31st December, 2013. We also consulted the references of published systematic reviews^[10-12,14].

Eligibility criteria

Only RCTs and quasi-RCTs that reporting operation vs nonoperation for DIACF were taken for inclusion. CCTs, cohort studies and case reports were excluded. In addition, studies that did not report the primary outcomes were also

Table 1 Detailed assessment items of modified Jadad scale

Item assessed	Response	Score
Was the study described as randomized?	Yes	1
	No	0
Was the method of randomization appropriate?	Yes	1
	No	-1
	Not described	0
Was the study described as blinded? ¹	Yes	1
	No	0
Was the method of blinding appropriate?	Yes	1
	No	-1
	Not described	0
Was there a description of withdrawals and dropouts?	Yes	1
	No	0
Was there a clear description of the inclusion/exclusion criteria?	Yes	1
	No	0
Was the method used to assess adverse effects described?	Yes	1
	No	0
Was the method of statistical analysis described?	Yes	1
	No	0

¹Double-blind RCTs 1 score; single-blind RCTs 0.5 score. RCTs: Randomized controlled trials.

excluded.

Study identification

Two independent authors viewed all titles of searched articles. Further review of article abstract was performed in those whose titles were relevant to the topic. If information from the abstract was inadequate, a full article was referred to. Disagreement on eligibility of included studies was resolved by the third author.

Risk-of-bias evaluation and scores of methodology

Risk-of-bias was assessed using the Cochrane Collaboration guidelines with seven items: generation of random sequence, allocation concealment, participants and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias graded by high, low or unclear bias risk^[23].

In current study, the modified Jadad scale^[24] was used to calculate the methodological scores of eligible studies. The scale includes eight items (Table 1) with scores range from 0 (lowest quality) to 8 (highest quality). The cut-off value between high quality and low quality was score 4. Scores higher than 4 mean high-quality trials while scores lower than 4 indicate low-quality trials. The methodological evaluation was performed by two independent reviewers and discrepancy was solved by discussion.

Data extraction

Two authors participated in data extraction independently. Discrepancies in outcome extraction were resolved by checking relevant studies until consensus was achieved.

Outcome measures

Primary outcomes covered assessment of resuming pre-injury job, residual pain, shoe fitting problems, limited walking distance and secondary late arthrodesis.

Secondary outcomes were complication rate and subgroup analyses for specific complications.

Statistical analysis

Statistical heterogeneity was assessed using I^2 statistics, which can be calculated from the formula $I^2 = 100\% \times (Q - df)/Q$, (Q represents Cochrane's heterogeneity statistic, df represents the degrees of freedom)^[25]. An I^2 value of 0% means no heterogeneity, with cut-off values of 25%, 50%, 75% or more as low, moderate and high risk of heterogeneity, respectively. For outcomes of heterogeneity test when $P > 0.05$, a fixed-effects model was used in the meta-analysis. Otherwise, a random-effects model was adopted for $P \leq 0.05$. Dichotomous variables are revealed as relative risk (RR) with 95% CIs. The data syntheses and publication bias were conducted using Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The level of statistical significance was set at P value ≤ 0.05 .

RESULTS

Study selection and characteristics

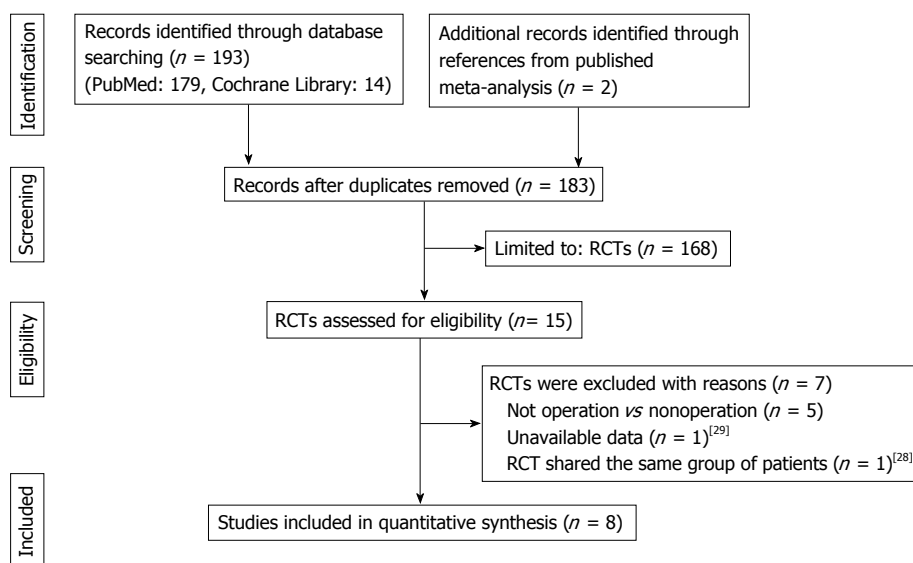
A total of 195 potentially relevant articles were identified (Figure 1). After reference to titles, abstracts and even full texts, eight published RCTs^[6-9,15,16,26,27] comprising 767 patients were included for analysis. General information of eligible studies were listed in Table 2.

During the process of eligibility assessment, we found that the two RCTs by Buckley *et al*^[8] and Howard *et al*^[28] shared the same groups of patients with the same base line characteristics but reported different measures and clinical outcomes. Therefore, the two studies were regarded as one trial for analysis though the data of outcomes were extracted separately. In addition, one study^[29] was excluded because of the unavailability of

Table 2 General information of eligible randomized controlled trials

Ref.	location	Cases (O/N)	Sex ratio (M/F)	Mean age (O/N) (yr)	Follow-up time (O/N) (yr)	Main outcome measures
Parmar <i>et al</i> ^[6]	England	25/31	48/8	48.3/48.8	2.1/1.8	Pain level, site, pattern; walking problems; shoe wear; resuming pre-injury job; deformity; ankle and subtalar movement; foot function; complications
O'Farrell <i>et al</i> ^[27]	Ireland	12/12	20/4	33/38	1.3/1.2	Shoe wear; pain-free walking distance; resuming pre-injury job; restoration of Böhler angle and Gissane angle; motion range of ankle, subtalar and calcaneocuboid
Chrintz <i>et al</i> ^[26]	Denmark	33/35	NR	NR	1.5/1.5	Radiography outcomes
Thordarson <i>et al</i> ^[7]	United States	15/11	21/5	35/36	1.4/1.2	Functional assessment scale; motion range of subtalar and ankle; gait analysis; restoration of Böhler angle; pain; daily activity; shoe wear; walking; exercise; work; complications
Buckley <i>et al</i> ^[8]	Canada	206/218	381/43	41/39	3.0/3.0	Complications; SF-36 scale; VAS; shoe wear; numbness
Ibrahim <i>et al</i> ^[9]	United Kingdom	15/11	21/5	61/58	15.2/14.8	AOFAS score; FFI score; calcaneal fracture score; restoration of Böhler angle and calcaneal height; arthritic grading of the subtalar joint
Nouraei <i>et al</i> ^[16]	Iran	31/30	NR	46/52	3.0/3.0	Motion range of ankle and subtalar; X-ray findings; width of heel; pain in walking; shoe wear; swelling of foot and ankle; reflex systematic dystrophy
Agren <i>et al</i> ^[15]	Sweden	42/40	59/23	49/48	10 (8-12) ¹	VAS; SF-36 scale; AOFAS score; OM scale; complications

¹Mean follow-up time was 10 yr with range of 8-12 yr. NR: Not reported; O/N: Operative group/non-operative group; M/F: Male/female; SF-36: Short-form-36 health survey; VAS: Visual analogue scale; AOFAS: American Orthopaedic Foot and Ankle Society; FFI: Foot function index; OM: Olerud-Molander.

**Figure 1** Flow chart of eligibility selection. RCT: Randomized controlled trial.

effective data.

Risk-of-bias evaluation and scores of methodology

Results of the bias risk was shown in Figure 2, indicating most of the eligible RCTs had low to moderate risk of bias. As revealed in Table 3, six^[7-9,15,16,26] out of eight studies scored 4 or more than 4 by current rating scale, implying that most of the eligible RCTs were high quality studies. However, several problems were still existed in these studies. Firstly, none of the eligible studies provided detailed description regarding the blinding method. Moreover, most of the

RCTs^[6,7,9,15,16,26,27] failed to use method to assess adverse effects. In addition, some trials^[6,9,16,26,27] still had problems in randomization and blinding. These disadvantages might cause biases.

Outcome measure reporting

Primary outcomes: As shown in Figure 3, 40 of 52 patients after operation compared with 28 of 54 patients after conservative treatment successfully resumed pre-injury work after treatment. No statistically significant difference was found between the two groups [RR = 1.53,

Table 3 Methodological assessment of eligible randomized controlled trials using modified Jadad scale

Item assessed	Parmar 1993	O'Farrell 1993	Chrintz 1993	Thordarson 1996	Buckley 2002	Ibrahim 2007	Nouraei 2011	Agren 2013
Was the study described as randomized?	√	×	√	√	√	√	√	√
Was the method of randomization appropriate?	?	?	?	√	√	?	?	√
Was the study described as blinded?	×	×	×	√	√	×	×	√
Was the method of blinding appropriate?	?	?	?	?	?	?	?	?
Was there a description of withdrawals and dropouts?	×	√	√	√	√	√	√	√
Was there a clear description of the inclusion/exclusion criteria?	×	×	√	√	√	√	√	√
Was the method used to assess adverse effects described?	×	×	×	×	√	×	×	×
Was the method of statistical analysis described?	√	√	√	√	√	√	√	√
Total score	2	2	4	5.5	6.5	4	4	5.5

√: Yes; ×: No; ?: Not described.

95%CI: (1.13, 2.07), $P = 0.006$].

Three RCTs^[6,7,16] compared the number of patients who had residual pain during the follow-up period. But no statistical difference was identified [RR = 0.73, 95%CI: (0.40, 1.36), $P = 0.33$] (Figure 4).

With regard to shoe fitting problems after treatment, outcome based on six RCTs^[6-8,15,16,27] indicated similar efficacy [RR = 0.61, 95%CI: (0.37, 1.04), $P = 0.07$] (Figure 5).

Two RCTs^[6,7] reported the number of patients who had limited walking distance during follow-up time. As shown in Figure 6, no significant difference was found between operation and nonoperation groups [RR = 0.88, 95%CI: (0.57, 1.36), $P = 0.56$].

During the follow-up period, 12 of 248 surgically treated patients compared with 41 of 258 nonsurgically treated patients had secondary late arthrodesis. However, no significant group difference was identified [RR = 0.46, 95%CI: (0.08, 2.64), $P = 0.38$] (Figure 7).

Secondary outcomes: A total of 77 of 288 surgically treated patients compared with 51 of 300 nonsurgically treated patients had complications (26.74% *vs* 17.0%). The significant difference indicated a higher complication risk in operative group [RR = 1.60, 95%CI: (1.17, 2.18), $P = 0.003$] (Figure 8).

Subgroup analyses were performed to explore further differences between the two approaches regarding the specific complications. As revealed in Figure 9, except for a higher risk of superficial wound problems [RR = 30.64, 95%CI: (6.38, 147.29), $P < 0.0001$] after operative

treatment, no significant differences were found in deep wound infection [RR = 3.01, 95%CI: (0.32, 28.60), $P = 0.34$], compartment syndrome [RR = 1.71, 95%CI: (0.42, 7.06), $P = 0.46$], thromboembolism [RR = 3.17, 95%CI: (0.33, 30.28), $P = 0.32$], reflex sympathetic dystrophy [RR = 0.68, 95%CI: (0.22, 2.11), $P = 0.51$] or traumatic arthritis secondary to DIACF [RR = 0.88, 95%CI: (0.64, 1.21), $P = 0.43$].

Sensitivity analysis: Sensitivity analysis was performed by excluding studies with Jadad score lower than 4. As shown in Table 3, we excluded two studies^[6,27] of score < 4 and performed another meta-analysis. P values for outcome measures of residual pain, shoe fitting problems, limited walking distance and complications remained unchanged (Table 4). However, after excluding low quality studies^[6,27], outcome regarding the number of patients who resumed pre-injury job showed insignificant difference between operative and nonoperative treatment (Table 4).

Publication bias: Publication bias was performed for incidence of shoe fitting problems and subgroup analyses of complications. Results indicated a potential publication bias of the above two outcome measures (Figures 10 and 11).

DISCUSSION

This updated meta-analysis with all retrieved RCTs suggests that compared with operative treatment, conservative

A

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agren 2013	+	+	+	?	+	+	+
Buckley 2002	+	+	+	?	+	+	+
Chrintz 1993	+	?	?	-	?	?	?
Ibrahim 2007	+	?	?	?	?	+	+
Nouraei 2011	+	?	?	?	?	+	+
O'Farrell 1993	-	-	?	?	+	+	+
Parmar 1993	+	?	?	-	+	?	+
Thordarson 1996	+	+	+	?	+	+	+

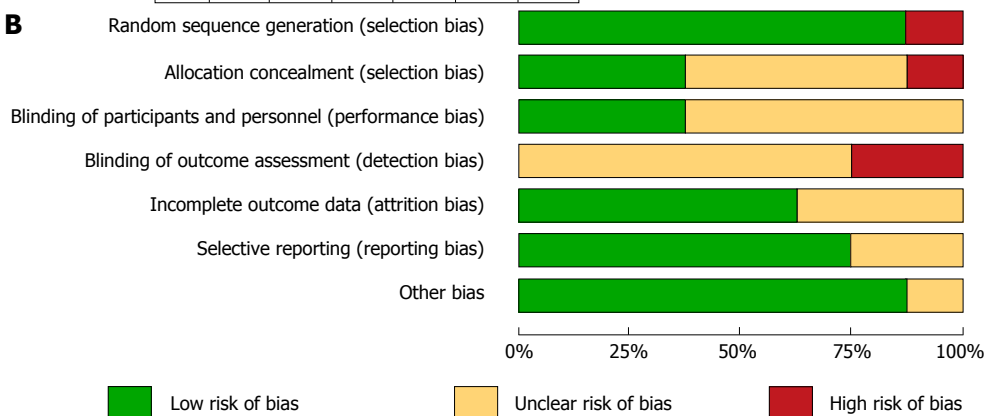
B

Figure 2 Risk of bias summary and graph. A: Risk of bias summary; B: Risk of bias graph.

Table 4 Results of sensitivity analysis

Outcomes	All eligible RCTs included					Only high score RCTs included				
	<i>n</i>	Patients	<i>I</i> ²	RR (95%CI)	<i>P</i> values	<i>n</i>	Patients	<i>I</i> ²	RR (95%CI)	<i>P</i> values
Resume pre-injury job	3	106	55%	1.53 (1.13, 2.07)	0.006	1	26	NA	2.20 (0.97, 5.00)	0.06
Residual pain	3	143	80%	0.73 (0.40, 1.36)	0.33	2	87	93%	0.63 (0.19, 2.11)	0.45
Shoe fitting problems	6	667	63%	0.61 (0.37, 1.04)	0.07	4	587	73%	0.57 (0.27, 1.21)	0.15
Limited walking distance	2	82	71%	0.88 (0.57, 1.36)	0.56	1	26	NA	0.42 (0.16, 1.08)	0.07
Complications	4	588	0%	1.60 (1.17, 2.18)	0.003	3	532	1%	1.59 (1.14, 2.22)	0.006

NA: Not applicable; RCTs: Randomized controlled trials.

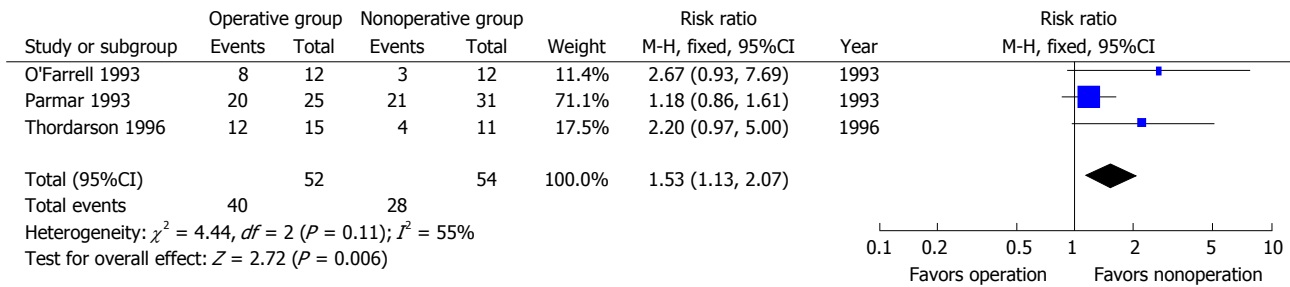


Figure 3 The number of patients who resumed pre-injury job after treatment.

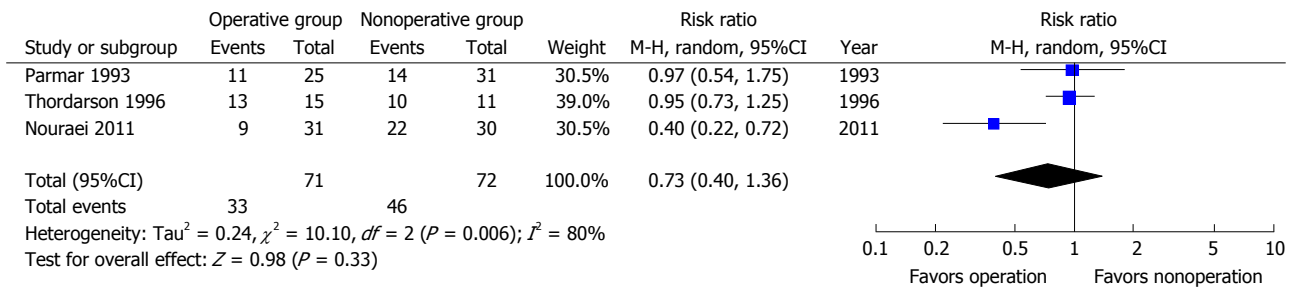


Figure 4 The number of patients who had residual pain after treatment.

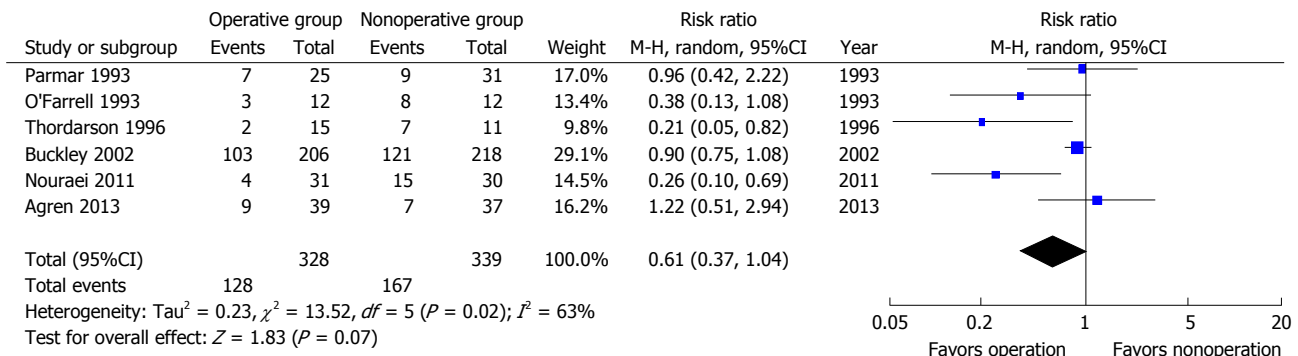


Figure 5 The number of patients who had shoe-fitting problems after treatment.

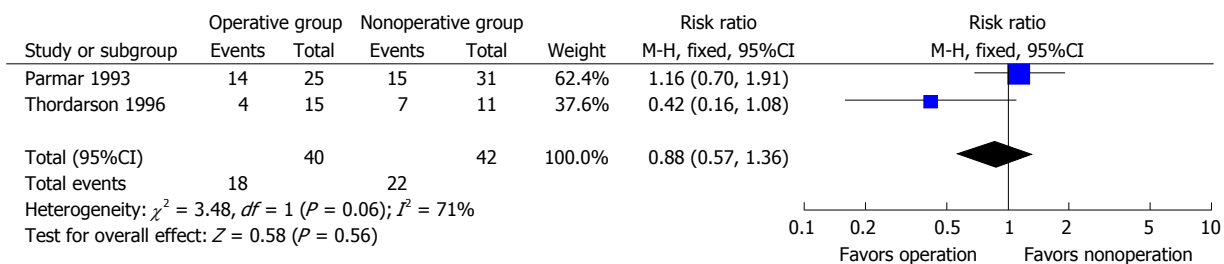


Figure 6 The number of patients who had limited walking distance after treatment.

treatment of DIACF can bring similar clinical outcomes regarding residual pain, shoe fitting, walking distance and secondary late arthrodesis. The only advantage following operative treatment was that more patients could resume pre-injury job after surgery. However, this superiority disappeared after sensitivity analysis by excluding low quality studies. In addition, operative treatment of DIACF elevated the risk of complications. Outcomes of the present study were different from historical meta-analyses,

which was mainly because the inclusion of updated RCTs as well as only inclusion of RCTs for analysis.

The present study based on three RCTs^[6,7,27] showed that more surgically treated patients could resume pre-injury job. However, Bruce *et al*^[14] indicated that no significant differences were identified between operation and nonoperation, neither in returning to the same work nor to any work. Although result of the sensitivity analysis also revealed no statistical difference, cautious

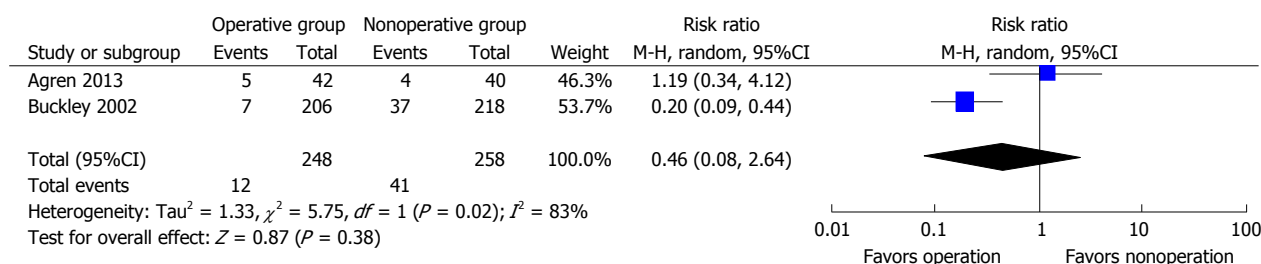


Figure 7 The number of patients who had secondary late arthrodesis.

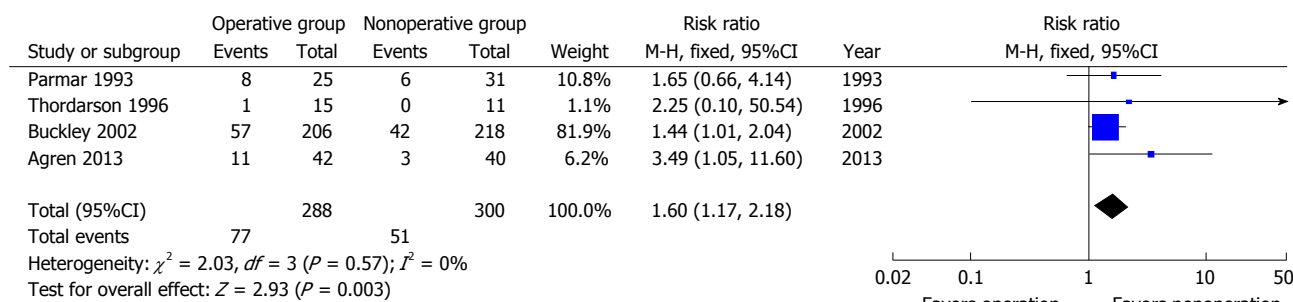


Figure 8 Incidence of complications after operative and nonoperative treatments.

attitude should be taken due to the following two reasons. On one hand, only one RCT was left for the analysis, making the outcome less reliable. On the other hand, different workload may also affect the result. Just as Buckley *et al.*^[8] analyzed, light or moderate workload might lead to better recovery from DIACF, but patients with heavy workload were unlikely to recover well regardless of treatment strategies.

No significant difference was identified regarding the number of patients with residual pain between the two methods. But the heterogeneity among the eligible studies was high ($I^2 = 80\%$, $P = 0.006$), which was probably associated with several factors, such as pain tolerance, fracture type and analgesic strategy. Quite different from our previous study^[13] of fewer shoe-wear problems in the operative group, the present study revealed no statistical difference between the two groups, which was probably because of the inclusion of two additional RCTs^[8,15]. Howard *et al.*^[28] found no significant differences between the two approaches in the number of patients who required shoe-wear modifications at 2 wk, 6 wk, 3 mo, 1 year, 2 years or more than 2 years, respectively. Agren *et al.*^[15] reported the incidence of shoe-wear problems following operation and nonoperation was 23% and 19%. However, the authors of the two studies^[15,28] did not give possible reasons for their findings.

The pooled result regarding the number of patients who had limited walking distance based on two RCTs^[6,7] showed insignificant difference between operation and nonoperation. Parmar *et al.*^[6] only listed the percentage of patients without limited walking distance and did not provide the precise definition of the distance. Thordarson *et al.*^[7] defined the distance as six blocks. Therefore, the lack of consistent definition of limited walking distance might

account for the high heterogeneity of included studies ($I^2 = 71\%$, $P = 0.06$). With respect to the number of patients who had secondary late arthrodesis, outcome based on two studies^[8,15] also revealed no statistical difference. One RCT^[28] reported the incidence of arthrodesis in nonoperative group was significantly higher than operative group [16% *vs* 3%, $RR = 0.20$, 95%CI: (0.09, 0.44), $P < 0.0001$]. This was probably because the calcaneal geometry was comparatively better preserved after operation^[30]. However, Agren *et al.*^[15] reported the arthrodesis rates for operative and nonoperative managements were 12% and 10%, respectively [$RR = 1.19$, 95%CI: (0.34, 4.12), $P = 0.78$]. The authors also did not give explanations for a relatively higher incidence of arthrodesis following operative treatment. We considered it might due to the slightly larger percentage of more severe types of fracture in the operative group.

The present meta-analysis supported that surgically treated patients had a significantly higher risk of complication than those in nonsurgical group. To investigate the detailed differences of complications between the two groups, subgroup analysis was further performed on specific complications. Outcomes of the subgroup analysis implied that superficial wound problems might be the main cause of a higher complication rate after operation. Although no significant differences were identified in the number of patients who had compartment syndrome, thromboembolism or reflex sympathetic dystrophy, they need to be reported so that patients treated for DIACF are fully informed of potential complications regardless of the treatment strategy chosen. It was interesting that the incidence of traumatic arthritis secondary to DIACF was similar between the two groups (operative group of 41.67% *vs* nonoperative group of 44.78%). However,

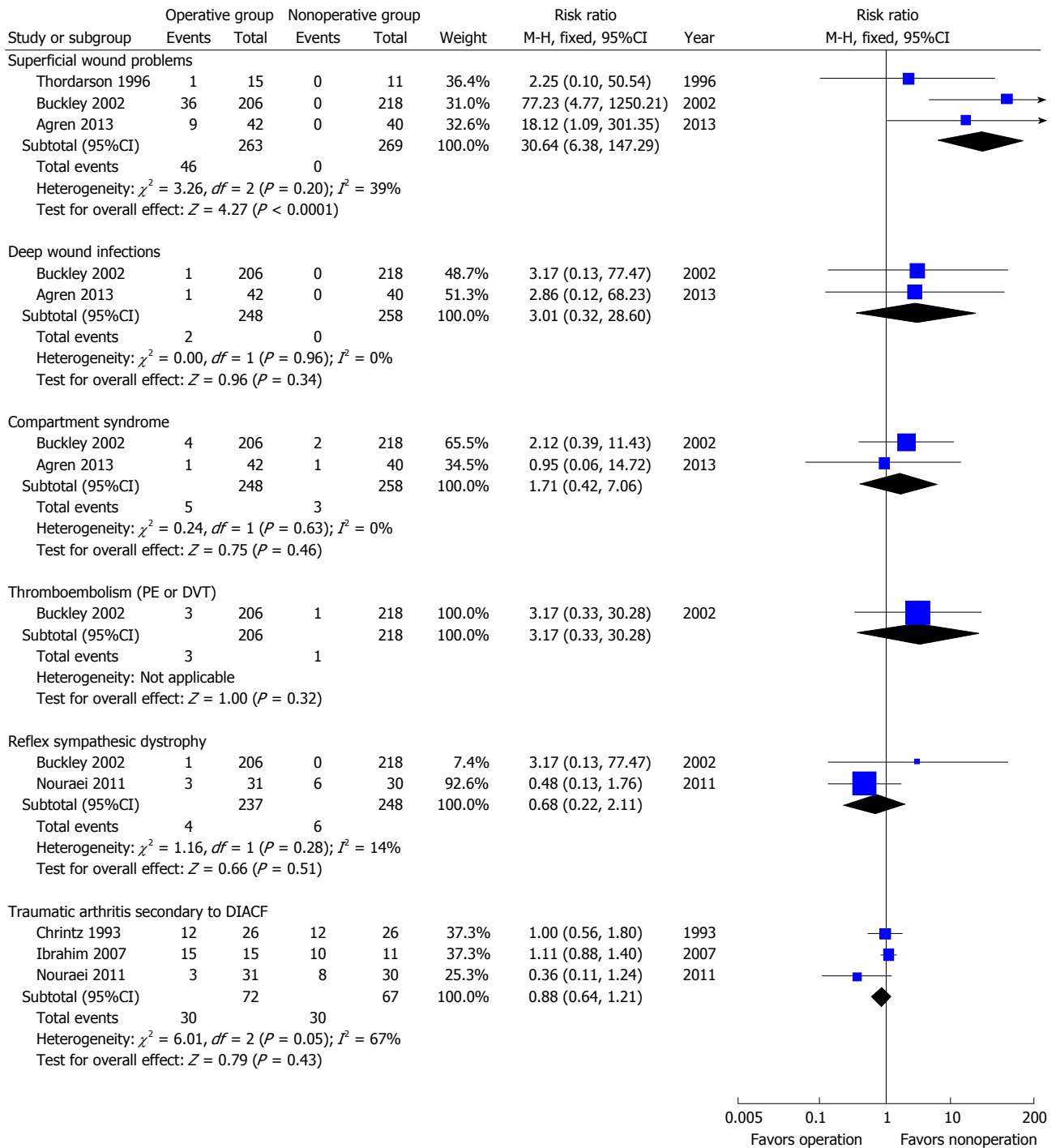


Figure 9 Subgroup analysis on specific complications. DIACF: Displaced intra-articular calcaneal fracture; PE: Pulmonary embolism; DVT: Deep venous thrombosis.

the outcome was based on three RCTs^[9,16,26] with 139 participants, and it also might be affected by different follow-up time. Therefore, whether difference indeed exists requires more studies with adequate follow-up time.

Several scales or scores were adopted to evaluate clinical efficacy of the two methods in eligible RCTs. Ibrahim *et al*^[9] showed that no significant differences were identified in total AOFAS score, total FFI score or calcaneal fracture score at 15 years' follow-up time. After analyzed outcomes of SF-36 and VAS scores, Howard *et al*^[28] concluded that the functional outcomes were partly

associated with treatment strategy and partly related to the complications. Agren *et al*^[15] used several stratified scales to show clinical efficacy at one year follow-up and at eight to twelve years' follow-up, including visual analog scale (VAS) pain and function scoring by patients as well as by surgeon, VAS pain at rest and during weight-bearing, SF-36 physical and SF-36 mental scores, AOFAS and OM scores. However, outcomes from all these scales and scores were similar between the two methods. We did not pool these results for meta-analysis due to the following reasons: (1) not correct report form for

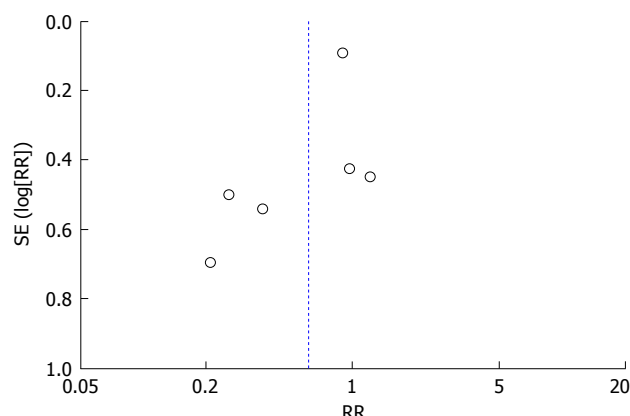


Figure 10 Funnel plot based on studies with data on incidence of shoe-fitting problems.

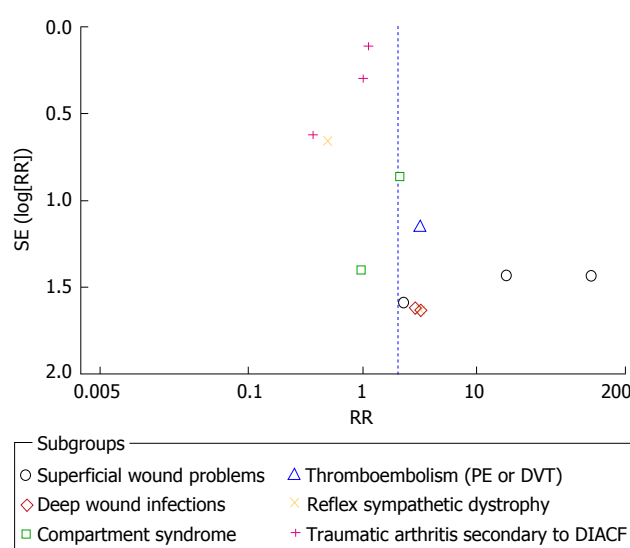


Figure 11 Funnel plot based on studies with data on subgroup analyses of complications. DIACF: Displaced intra-articular calcaneal fracture; SE: Standard error; PE: Pulmonary embolism; DVT: Deep venous thrombosis.

data synthesis in meta-analysis (correct form should be mean \pm standard deviation); (2) a single report; and (3) outcomes were not reported at the same follow-up time.

The main limitation of the current study might be the still limited number of eligible RCTs with limited number of participants. Although a total of eight RCTs with 767 participants was included in our study, more than half of the participants were from one study^[8], which may cause a bias. In addition, the current study was purely based on a methodological standpoint, which lacks practical information regarding treatment strategies on different fracture types, especially severe and challenging injuries. Therefore, conclusions of this analysis should be interpreted with caution and more high quality RCTs are needed in the future.

In summary, the current study indicates that compared with operative treatment, conservative treatment of DIACF lead to similar clinical outcomes regarding residual pain, shoe fitting, walking distance and secondary subtalar

arthrodesis but a significantly lower complication rate.

ACKNOWLEDGMENTS

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COMMENTS

Background

Displaced intra-articular calcaneal fracture (DIACF) can be managed by both operative and nonoperative strategies. However, up till now, controversy still exists regarding the optimal treatment of this fracture, which is mainly due to the conflicting outcomes derived from previous studies.

Research frontiers

It is generally believed that intra-articular fractures should be treated operatively as operative management can provide better fracture reduction, promote early functional rehabilitation and reduce the rate of traumatic arthritis. However, several studies showed that conservative treatment can achieve similar functional recovery as surgery but had a lower complication risk. Therefore, whether surgery is a must for DIACF treatment requires more investigations.

Innovations and breakthroughs

Compared with previous systematic reviews or meta-analyses, the present study included more studies with high quality in methodology and thus made the outcomes more reliable. In addition, the current study once again confirmed similar clinical efficacy following operation and nonoperation.

Applications

The present study provides evidence to support conservative treatment of DIACF. However, cautious attitude should be taken towards the conclusion because of the still limited number of randomized controlled studies (RCTs) and future more high quality surveys are warranted.

Terminology

Clinical RCT is a type of scientific experiment, where the people being studied are randomly allocated one or other of the different treatment methods under study. RCT is a golden standard for a clinical trial. However, the quality of an RCT is important, which will affect the reliability of the outcomes. Meta-analysis is a statistical method of combining different treatment outcomes derived from different studies to generate more conclusive and reliable conclusions.

Peer review

This is a well written meta-analysis which confirms with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

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Association between SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk: A meta-analysis

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2014. To avoid missing any additional studies, we looked through all the references of relevant articles. Case-control studies concerning the (CAG)n variants in the *AR* gene or the (TAAAA)n polymorphism in the *SHBG* gene in PCOS patients were included. Five studies regarding the (TAAAA)n polymorphism in the *SHBG* gene and 14 studies regarding the (CAG)n polymorphism in the *AR* gene met our criteria. Odd ratio (OR) and weighted mean difference (WMD) were selected as the effect size measurements to evaluate the influence of the (TAAAA)n polymorphism and (CAG)n variants on PCOS risk. Begg's test was used for the evaluation of publication bias.

RESULTS: With respect to the relationship between the (TAAAA)n polymorphism and PCOS risk, the statistical results showed that there was no significant difference between PCOS patients and controls in the alleles of TAAAA (S: OR = 0.91, 95%CI: 0.78-1.05; L: OR = 1.10, 95%CI: 0.95-1.27). Subgroup analyses of the combination of alleles indicated similar results (short-short: OR = 0.87, 95%CI: 0.66-1.14; short-long: OR = 1.12, 95%CI: 0.86-1.46; long-long: OR = 1.03, 95%CI: 0.72-1.47). As for the relationship between the (CAG)n polymorphism and PCOS risk, we found no association between CAG repeat variants and PCOS risk (WMD = 0.03, 95%CI: -0.13-0.08). Subgroup analyses by race and diagnosis criteria indicated the same results (Asian: WMD = -0.03, 95%CI: -0.14-0.07; Caucasian: WMD = -0.02, 95%CI: -0.24-0.21; the criteria of Rotterdam: WMD = 0.01, 95%CI: -0.01-0.03).

CONCLUSION: There is no association between (TAAAA)n polymorphism in *SHBG* gene, (CAG)n repeat variants in *AR* gene and PCOS.

Key words: Sex hormone-binding globulin; TAAAA; Androgen receptor; CAG; Polycystic ovarian syndrome

Abstract

AIM: To systematically assess the association between sex hormone-binding globulin (SHBG) (TAAAA)n and androgen receptor (AR) (CAG)n polymorphisms and polycystic ovarian syndrome (PCOS) risk.

METHODS: We searched MEDLINE (PubMed), EMBASE and Web of Science database from inception to May

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Core tip: Our study investigated the association between sex hormone-binding globulin (SHBG) (TAAAA)n and androgen receptor (AR) (CAG)n polymorphisms and polycystic ovarian syndrome (PCOS) risk. Five studies regarding the (TAAAA)n polymorphism in the *SHBG* gene and 14 studies regarding the (CAG)n polymorphism in the *AR* gene were included based on the strict inclusion criteria. The overall meta-analysis, as well as the subgroup analysis, showed that there was no association between PCOS risk and the SHBG (TAAAA)n polymorphism or AR (CAG)n repeat variants.

Jin JW, Chen SL, Deng ZT. Association between SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk: A meta-analysis. *World J Meta-Anal* 2015; 3(1): 72-81 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i1/72.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i1.72>

INTRODUCTION

The morbidity of polycystic ovarian syndrome (PCOS) is estimated to be 7%^[1] in women of reproductive age and it is characterized by hyperandrogenism, chronic anovulation and polycystic ovaries^[2]. There are three main diagnostic guides for PCOS, including the 1990 National Institutes of Health criteria, the 2003 Rotterdam criteria and the 2006 Androgen Excess and PCOS Society criteria^[3-5]. Hyperandrogenism plays an important part in these PCOS diagnostic features and is increasingly considered a main pathogenic factor of PCOS^[6]. Recently, the genetic aspects of PCOS have been clarified to prove the presence of genetic abnormalities in PCOS patients. Although the specific genetic alterations that contribute to the development of PCOS remain unclear, several candidate genes have been proposed, including the sex hormone-binding globulin (*SHBG*) gene and the androgen receptor (*AR*) gene^[6].

The *SHBG* gene (17p13-p12) encodes a 373 amino acid polypeptide that regulates the bioavailability of sex steroids by binding androgens, particularly testosterone and estrogens^[7,8]. The free SHBG levels frequently diminish in patients with hyperandrogenism, especially in those who have PCOS, which may result in an increase in free androgen levels and magnify the biological impact of androgens. SHBG can be influenced by many factors, including gender, age, metabolic, genetic and nutritional factors, with genetic factors being more important^[9,10]. A (TAAAA)n repeat variant in the 5' non-coding region of *SHBG* promoter has been described and its influence on *in vitro* transcriptional activity has been reported^[11]. Compared with normal women, those with PCOS tend to have a significantly greater frequency of longer (TAAAA)n alleles (more than eight repeats)^[10]. However, the genetic association studies between (TAAAA)n repeat polymorphism of *SHBG* and PCOS risk show controversial results, which make it difficult to judge

PCOS by the number of SHBG (TAAAA)n repeats.

The *AR* gene (Xq11-q12)^[12] consists of eight exons and seven introns. The CAG trinucleotide repeats in exon 1 ranged in length from 8 to 35 in healthy individuals and have been reported to influence the transcriptional activity of AR^[13]. Chamberlain *et al*^[13] reported that there was a negative correlation between the number of CAG repeats and the AR activity, which means that a higher number of CAG repeats is associated with a lower AR biological activity. There are several studies focusing on the relationship between CAG repeat number and PCOS risk, but inconsistent results make it hard to assess the importance of CAG repeat number in PCOS.

Currently, there is no consensus regarding the relationship between SHBG (TAAAA)n polymorphism, AR CAG length and PCOS, although this relation may influence the time to diagnosis and drug intervention. For this reason, we conducted this meta-analysis to address such inconsistency.

MATERIALS AND METHODS

Data sources and searches

We underwent a systematic search of MEDLINE (PubMed), EMBASE, and Web of Science database with the assistance of computer from inception to May 2014, attempting to find all publications about the relationship between (TAAAA)n SHBG and (CAG)n AR polymorphisms and PCOS. Key words for the search of MEDLINE were as follows: ("sex hormone-binding globulin" or "SHBG") and "TAAAA" and ("polycystic ovarian syndrome" or "PCOS") for the *SHBG* gene and ("androgen receptor" or "AR") and "CAG" and ("polycystic ovarian syndrome" or "PCOS") for the *AR* gene. We used similar strategies to search EMBASE. The abstracts of additional meetings were mainly from Web of Science. To avoid missing any additional studies, we looked through all the references of relevant articles.

Study selection

We skimmed titles and abstracts of identified papers to exclude studies that clearly not meeting the inclusion criteria and retrieved the full texts of selected studies for further review and evaluation.

The inclusion criteria for studies were as follows: (1) studies concerning the association between the (CAG)n polymorphism in the *AR* gene or (TAAAA)n variants in the *SHBG* gene and PCOS risk; (2) independent case-control study; (3) specific diagnosis criteria for PCOS; (4) hospital-based healthy women were selected as controls; and (5) data were enough for our further analysis. In order to avoid overlapping data, only the latest study or the study having the most sufficient data was enrolled in our analysis if several studies were conducted by the same author.

Data extraction

Two authors (Jin JW and Chen SL) extracted data from

Table 1 Characteristics of studies on (TAAAA)n sex hormone-binding globulin polymorphism and polycystic ovarian syndrome

Ref.	Year	Country	Race	PCOS women	Controls	PCOS alleles (2 n)		Controls alleles (2 n)		PCOS women genotype		Controls genotype		PCOS diagnostic criteria		
						S (< 8 repeats)		L (≥ 8 repeats)		SS		LL				
Xita <i>et al</i> ^[10]	2003	Greece	Caucasian	185	324	230	140	446	202	NR	NR	NR	NR	A		
Zhao <i>et al</i> ^[24]	2005	China	Asian	157	156	180	134	175	137	48	84	25	48	79	29	B
Ferk <i>et al</i> ^[26]	2007	Slovenia	Caucasian	123	110	155	91	151	69	54	48	21	52	47	11	C
Liu <i>et al</i> ^[27]	2008	China	Asian	187	176	216	158	210	142	59	96	32	66	78	32	C
Diaz <i>et al</i> ^[25]	2010	Spain	Caucasian	70	107	102	38	139	75	NR	NR	NR	NR	NR	NR	D

A: The 1990 National Institutes of Health–National Institute of Child Health and Human Development conference on PCOS; B: (1) Amenorrhoea or oligomenorrhoea; (2) LH/FSH ≥ 2.5 or T ≥ 1.56; (3) More than 10 follicles measuring 2–8 mm in diameter at least in one ovary; and (4) Exclusion of congenital adrenal hyperplasia, Cushing’s syndrome, androgen-secreting tumor, hyperprolactinaemia and thyroid dysfunction; C: The criteria of Rotterdam Revised 2003 (two of three) diagnosis; D: (1) Hirsutism; (2) Amenorrhoea or oligomenorrhoea; (3) Increased serum T and/or androstenedione and 17OHL-P hyperresponse to GnRH agonist; and (4) Hyperinsulinaemia during an oral glucose tolerance test. PCOS: Polycystic ovarian syndrome; S: Short alleles; L: Long alleles; SS: Short-short genotype; SL: Short-long genotype; LL: Long-long genotype; NR: Non-reported.

each selected article independently and the specific items were as follows: (1) first author; (2) year of publication; (3) regions of the population investigated; (4) diagnosis criteria for PCOS; (5) size of controls and PCOS patients; (6) the number of cases and controls for SHBG (TAAAA)n alleles and genotype; and (7) the mean and standard deviation of cases and controls for AR (CAG)n repeats. We extracted quantitative data directly from articles or using original information provided in the tables and figures^[14].

Statistical analysis

We used STATA Statistical Software for all the analyses (version 12.0, STATA Corporation, United States). The evaluation indicators were odd ratio (OR) with 95%CI for the SHBG gene and weighted mean difference (WMD) with 95%CI for the AR gene.

Meta-analysis

We used two models to calculate the pooled OR and WMD estimates with 95%CI: a fixed-effects model known as Mantel Haenszel method^[15] or a random-effects model known as Der Simonian-Laird method^[16]. We used the χ^2 test to evaluate the heterogeneity of the studies^[17] and the quantity I^2 was also calculated^[18,19]. I^2 is the percentage of between-study variation in total variation. The value of 25% is regarded as low heterogeneity while the value of 75% represents high heterogeneity. While I^2 was over 50%, the random-effect model was used instead of the fixed-effect model.

Publication bias was evaluated to find whether the results of the studies were homogeneous^[20], and the Egger regression asymmetry test^[21] and the Begg-Mazumdar adjusted rank correlation test^[22] were used. When the *P*-value of the Egger’s test or Begg’s test was < 0.05, we considered significant bias among the studies.

RESULTS

Search results

For the (TAAAA)n polymorphism in the SHBG gene, 22 records were found in electronic databases, including 8 records in MEDLINE, 11 records in Web of Science database and 3 records in EMBASE. According to the selection criteria, we ultimately identified 5 studies for our final statistical analysis (Figure 1). Table 1 summarizes the characteristics of all the included studies. For the (CAG)n repeats in the AR gene, a total of 65 studies were found, including 26 records in MEDLINE, 37 records in Web of Science database and 2 references from reference lists. According to the selection criteria, we identified 14 studies for our meta-analysis (Figure 2) and present their characteristics in Table 2.

Meta-analysis of the SHBG (TAAAA)n polymorphism and PCOS risk

We involved 5 studies, a total of 722 cases and 873 controls, to compare short (S) alleles and long (L) alleles in PCOS patients with those in controls. Because heterogeneity

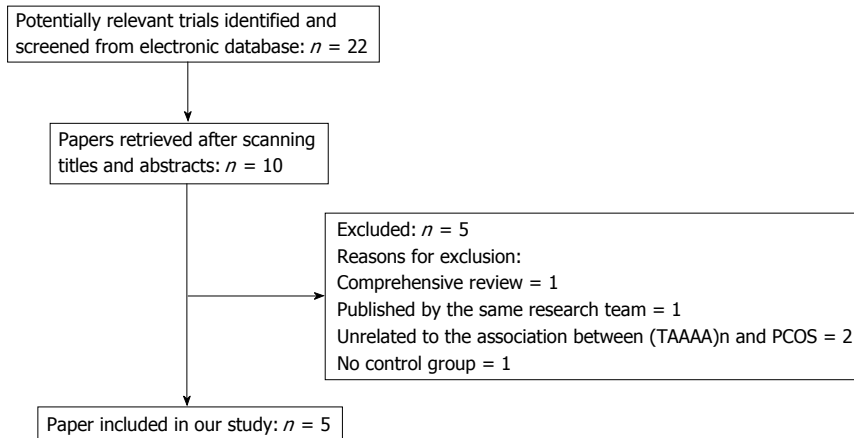


Figure 1 Strategy for searching studies concerning the association between the (TAAAA)n sex hormone-binding globulin polymorphism and polycystic ovarian syndrome risk. PCOS: Polycystic ovarian syndrome.

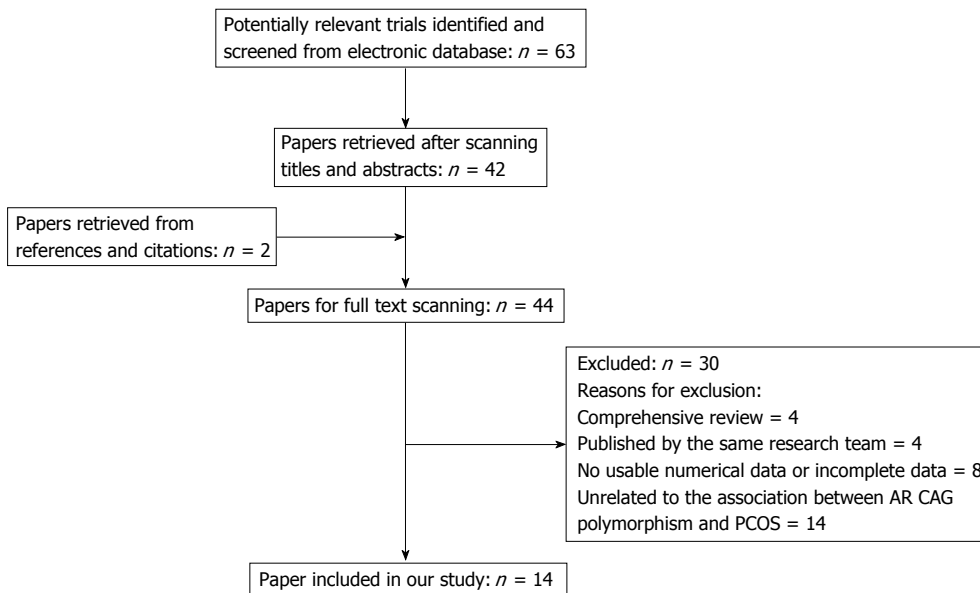


Figure 2 Strategy for searching studies concerning the association between the (CAG)n androgen receptor polymorphisms and polycystic ovarian syndrome risk. AR: Androgen receptor; PCOS: Polycystic ovarian syndrome.

was moderate ($I^2 = 47.8\% < 50\%$), we calculate the pooled OR estimates with 95%CI using the fixed-effects model (S: OR = 0.91, 95%CI: 0.78-1.05; L: OR = 1.10, 95%CI: 0.95-1.27) (Figure 3 and Table 3). We considered there was no significant association between PCOS and (TAAAA)n SHBG allele. No obvious publication bias was found in all the selective studies.

On the other hand, we identified 3 studies to compare short-short (SS) genotype, short-long (SL) genotype and long-long (LL) genotype in PCOS patients with those in controls. Because heterogeneity was low (SS: $I^2 = 0$; SL: $I^2 = 0$; LL: $I^2 = 29.6\%$), we calculated OR using the fixed-effects model (SS: OR = 0.87, 95%CI: 0.66-1.14; SL: OR = 1.12, 95%CI: 0.86-1.46; LL: OR = 1.03, 95%CI: 0.72-1.47) (Figure 4 and Table 3). Similar to the results of alleles, there was no association between PCOS and (TAAAA)n SHBG genotype. No obvious publication

bias was found in all the selective studies.

Meta-analysis of the AR (CAG)n polymorphism and PCOS risk

We involved 14 studies (1882 cases and 1988 controls in total) to compare biallelic mean of CAG length in PCOS patients with controls. Because heterogeneity was moderate ($I^2 = 51.0\% > 50\%$), we calculate the pooled WMD estimates with 95%CI using the random-effects model (WMD = 0.03, 95%CI: -0.13-0.08) (Figure 5 and Table 4). Begg's test ($P = 0.621$) and Egger's test ($P = 0.866$) showed no obvious publication bias. Further, subgroup analyses were done by race and diagnosis criteria. Because the heterogeneity was high in subgroup by race (Asian: $I^2 = 72.9\%$; Caucasian: $I^2 = 41.9\%$) and low by diagnosis criteria (The criteria of Rotterdam: $I^2 = 0$), random and fixed models were used, respectively.

Table 2 Characteristics of studies on (CAG)n androgen receptor polymorphism and polycystic ovarian syndrome

Ref.	Year	Country	Race	PCOS			Controls			PCOS diagnostic criteria
				Size	Mean	Std dev	Size	Mean	Std dev	
Mifsud <i>et al</i> ^[23]	2000	Singapore	Asian	91	22.97	0.24	112	23.09	0.23	A
Hickey <i>et al</i> ^[37]	2002	Australia	Caucasian	122	23	2.025	83	22.34	2.094	B
Jääskeläinen <i>et al</i> ^[43]	2005	Finland	Caucasian	106	21.5	2.2	112	21.5	2.1	C
Kim <i>et al</i> ^[39]	2008	South Korea	Asian	114	23.3	1.8	205	23.1	2	D
Ferk <i>et al</i> ^[38]	2008	Slovene	Caucasian	102	22.4	3.5	110	21.9	3.5	E
Liu <i>et al</i> ^[27]	2008	China	Asian	148	22.88	1.76	104	22.85	1.6	D
Shah <i>et al</i> ^[36]	2008 (1)	America	Caucasian	270	21.8	3.1	165	22.3	3.11	B
Shah <i>et al</i> ^[36]	2008 (2)	America	Black	37	20.1	3.44	84	20.2	3.08	B
Van Nieuwerburgh <i>et al</i> ^[40]	2008	Belgium	Caucasian	97	21.93	2.122	31	21.823	3.112	NC
Dasgupta <i>et al</i> ^[41]	2010	India	Asian	250	18.74	0.13	299	18.73	0.12	D
Laisk <i>et al</i> ^[34]	2010	Estonia	Caucasian	32	21.5	1.6	79	21.6	1.8	D
Robeva <i>et al</i> ^[44]	2010	Bulgaria	Caucasian	52	21.6	2.62	41	21.3	3.71	D
Skrkatic <i>et al</i> ^[42]	2011	Croatia	Caucasian	214	22.1	3.4	209	21.9	3.2	D
Schüring <i>et al</i> ^[35]	2011	Germany	Caucasian	72	21.43	1.87	179	21.99	2.07	D
Rajender <i>et al</i> ^[47]	2013	India	Asian	169	17.39	2.29	175	17.43	2.43	D

A: (1) Proven fertility; (2) No history of subfertility treatment; and (3) Normal menstrual cycles (25-32 d); B: National Institutes of Health criteria; C: (1) Non-hirsute; (2) Proven fertility; (3) Regular menstrual cycles; and (4) Normal ovaries; D: The criteria of Rotterdam Revised 2003 (two of three); E: (1) Oligo-/amenorrhea; (2) Polycystic ovaries; and (3) Hyper-androgenism. PCOS: Polycystic ovarian syndrome; NC: Unclear.

Table 3 Meta-analysis of (TAAAA)n sex hormone-binding globulin polymorphism and polycystic ovarian syndrome

	No. of studies	OR (95%CI)	Heterogeneity			Publication bias	
			χ^2	I^2 (%)	P	Begg's P	Egger's P
S (< 8 repeats)	5	Fixed, 0.91 (0.78-1.05)	7.59	47.8	0.108	0.221	0.221
L (\geq 8 repeats)	5	Fixed, 1.10 (0.95-1.27)	7.30	45.2	0.121	0.221	0.225
SS	3	Fixed, 0.87 (0.66-1.14)	0.60	0.0	0.749	1.000	0.564
SL	3	Fixed, 1.12 (0.86-1.46)	1.64	0.0	0.441	0.296	0.072
LL	3	Fixed, 1.03 (0.72-1.47)	2.84	29.6	0.242	1.000	0.256

OR: Odds ratio; S: Short alleles; L: Long alleles; SS: Short-short genotype; SL: Short-long genotype; LL: Long-long genotype.

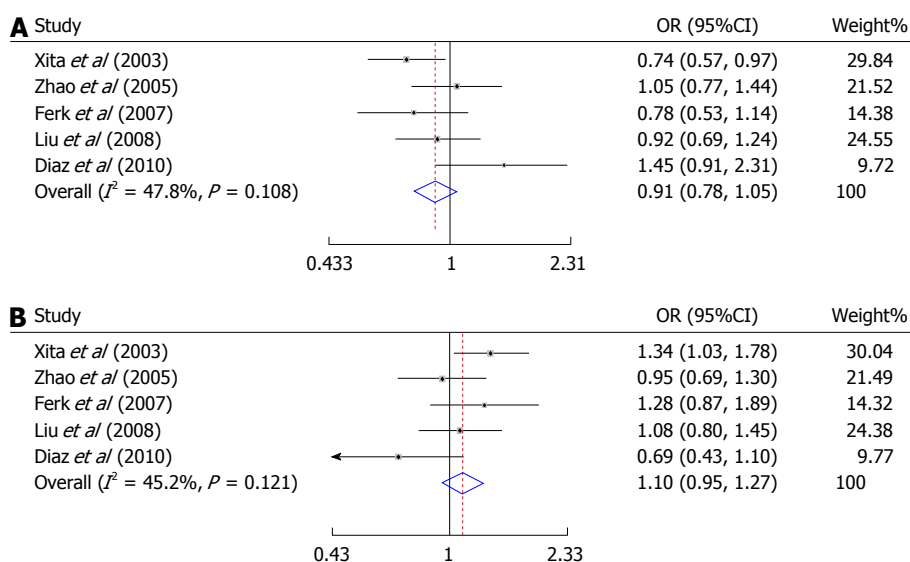


Figure 3 Association between polycystic ovarian syndrome risk and (TAAAA)n sex hormone-binding globulin alleles. A: Comparison of short alleles in the PCOS group with those in the control group; B: Comparison of long alleles in the PCOS group with those in the control group. PCOS: Polycystic ovarian syndrome.

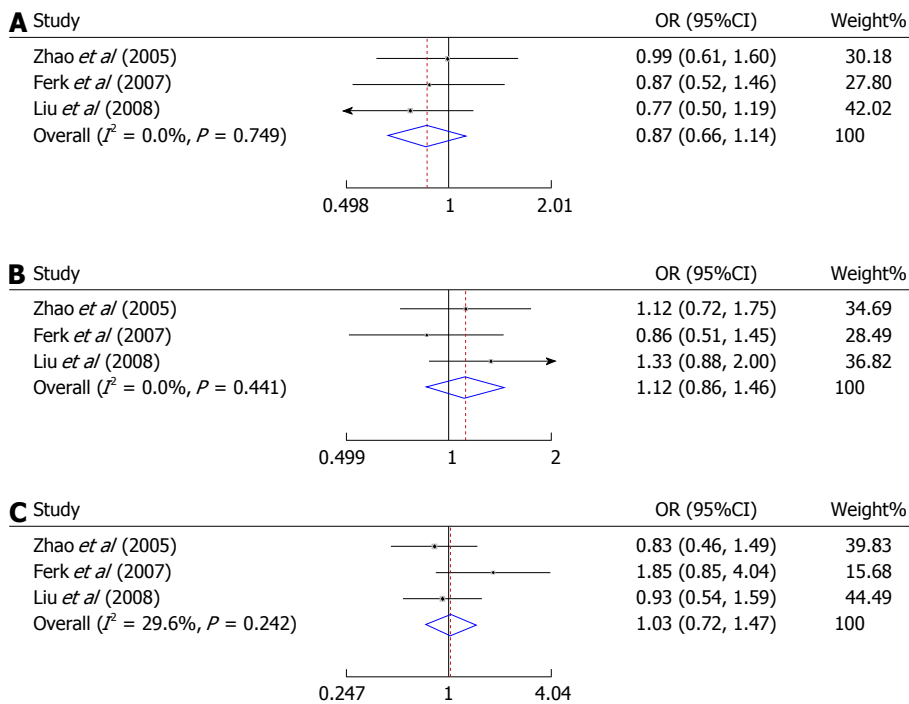
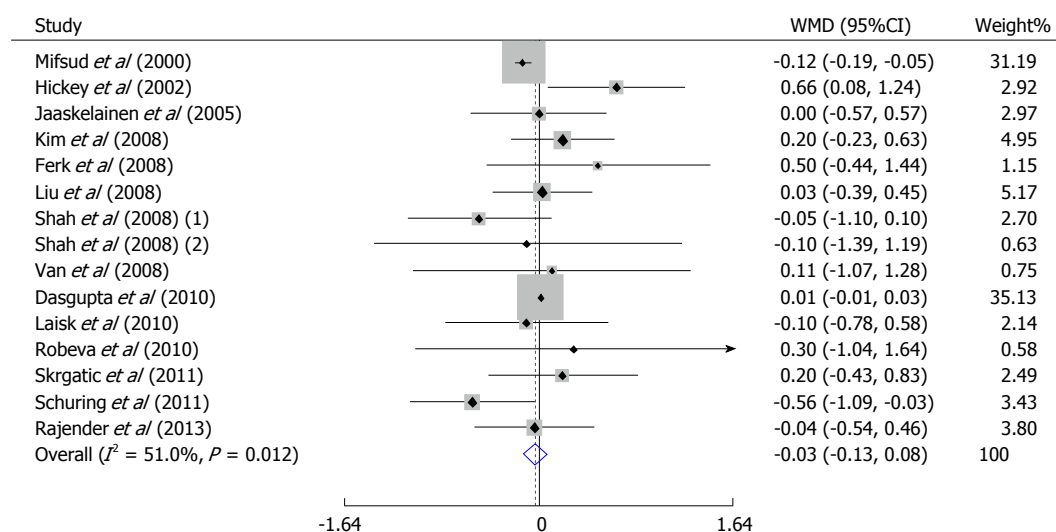
We found that the (CAG)n repeats in race group (Asian: WMD = -0.03, 95%CI: -0.14-0.07; Caucasian: WMD =

-0.02, 95%CI: -0.24-0.21) (Figure 6 and Table 4) and in diagnosis criteria group (the criteria of Rotterdam: WMD

Table 4 Meta-analysis of (CAG)n androgen receptor polymorphism and polycystic ovarian syndrome

			WMD (95%CI)	Heterogeneity			Publication bias	
Number of studies				χ^2	I^2 (%)	P	Begg's P	Egger's P
All		15	Random, -0.03 (-0.13, 0.08)	28.55	51.0	0.012	0.621	0.866
Race	Asian	5	Random, -0.03 (-0.14, 0.07)	14.74	72.9	0.005	0.806	0.875
	Caucasian	9	Fixed, -0.02 (-0.24, 0.21)	13.77	41.9	0.088	0.175	0.596
The criteria of Rotterdam		8	Fixed, 0.01 (-0.01, 0.03)	5.91	0.0	0.550	1.000	0.784

WMD: Weighted mean difference.

**Figure 4** Association between polycystic ovarian syndrome risk and (TAAAA)n sex hormone-binding globulin genotypes. A-C: Comparison of short-short (A), short-long (B), long-long (C) genotype in the PCOS group with those in the control group. PCOS: Polycystic ovarian syndrome.**Figure 5** Association between polycystic ovarian syndrome risk and (CAG)n repeats in androgen receptor in all selected studies. WMD: Weighted mean difference.

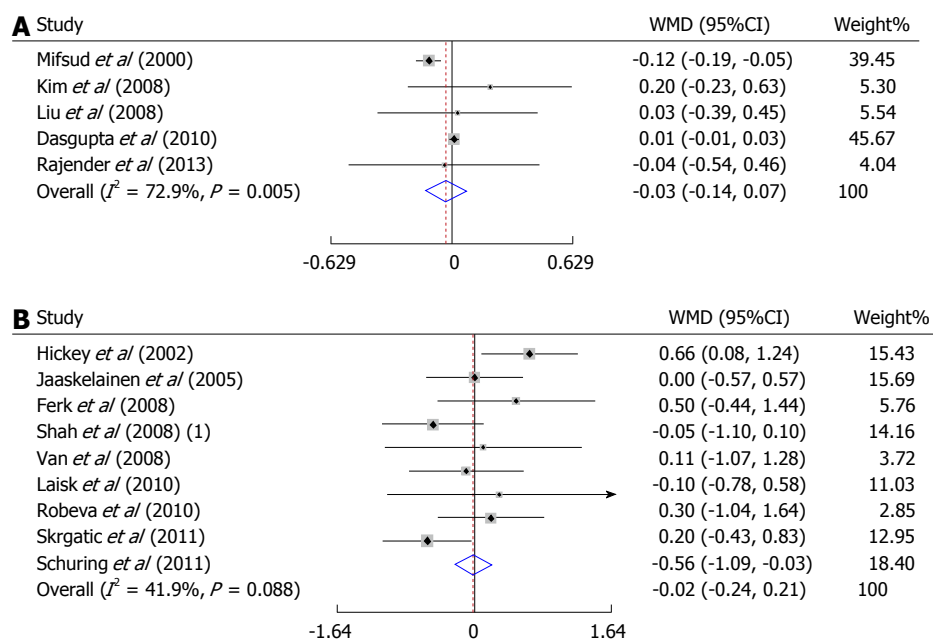


Figure 6 Association between polycystic ovarian syndrome risk and (CAG)n repeats in polycystic ovarian syndrome by race. A: Asian; B: Caucasian. WMD: Weighted mean difference.

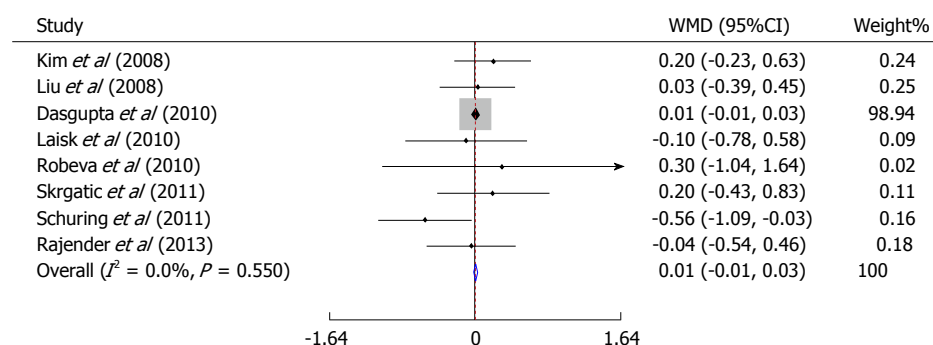


Figure 7 Association between polycystic ovarian syndrome diagnosed according to the criteria of Rotterdam Revised 2003 and (CAG)n repeats in androgen receptor. WMD: Weighted mean difference.

= 0.01, 95%CI: -0.01-0.03) (Figure 7 and Table 4) had no association with PCOS, which was similar to the previous results.

DISCUSSION

PCOS is a multifactorial disorder of unclear etipathogenesis. Hyperandrogenism is gradually being the hallmark of PCOS, and it is an item included in all the three worldwide diagnostic guides. SHBG regulates the bioavailability of sexual hormones to target tissues and is the primary plasma transport protein for those hormones, while AR is the protein to bind androgen and activate the downstream pathway in target cells. Since Xita *et al*^[10] first reported PCOS risk in association with genetic variants in SHBG and Mifsud *et al*^[25] reported the relationship between PCOS risk and AR polymorphic CAG repeat, a series of following studies were performed. If there was a definite conclusion of PCOS risk with SHBG or AR polymorphism, PCOS could be caught earlier and

prognosis would be better.

For the *SHBG* gene, Xita *et al*^[10] discovered that PCOS women had a greater frequency of longer (TAAAA)n (more than 8 repeats) than normal women and proposed that (TAAAA)n repeat variants may be implicated in the development of PCOS. Whereafter, some case-control experiments proved this^[24], but others did not^[25-27]. In our meta-analysis, we selected OR as the effect size measurement to estimate the influence of (TAAAA)n repeat variants on PCOS risk. The summary ORs for TAAAA alleles (including S and L) indicated that there was no association between the TAAAA polymorphism and PCOS risk. Furthermore, the ORs of the combination of TAAAA alleles (SS, SL and LL) showed no differences between PCOS patients and controls either. These results indicate that the (TAAAA)n polymorphism has no influence on the development of PCOS. As Martínez-García *et al*^[28] proposed SHBG as a candidate gene for PCOS, our result may be partly explained by the influence of other single nucleotide polymorphisms in the *SHBG*

gene, such as *rs1799941*^[29], *rs2075230*^[30], *rs6257* (T/C)^[31], *rs727428*^[32] and *rs6259*^[28].

Our analysis on the *SHBG* gene has several strengths: (1) selection of different combinations of alleles; (2) comprehensive search for original case-control studies without limitation of language; and (3) adoption of bias measurements to avoid publication bias in study selection and data abstraction. On the other hand, limitations exist in this meta-analysis: (1) the numbers of studies and subjects included in this meta-analysis were small; (2) the diagnosis criteria for PCOS in selected studies were different and could not guarantee that involved PCOS cases had similar characteristics; and (3) only publications were enrolled in our meta-analysis, resulting in potential publication bias which was inevitable.

For the *AR* gene, there has been a study showing that higher AR activity correlated with shorter CAG and speculating that the CAG repeat variants were a sign in the development of PCOS^[23]. A series of following case-control studies were performed to confirm this result. After scanning titles, abstracts and full texts, fourteen studies were included in our analysis. Among those, four showed that there were more short CAG alleles in PCOS patients compared with controls^[33-36], while eight reported the opposite results^[27,37-42] and the remaining two found no significant difference between the two groups^[43,44]. We selected WMD as the effect size measurement to estimate the association between (CAG)n repeat variants and PCOS risk. The summary WMD for mean of CAG alleles showed that there was no statistical relationship between CAG repeat variants and PCOS risk. Furthermore, the WMD of CAG biallelic mean in subgroups (by race: Asian and Caucasian; by diagnosis criteria: the Rotterdam criteria) displayed no difference between cases and controls. These statistical results indicate that the CAG repeat variants have no influence on the development of PCOS, which was similar to the conclusions of three other meta-analysis^[45-47].

Our meta-analysis on the *AR* gene has several strengths: (1) subgroup analysis was performed by race and diagnosis criteria; (2) comprehensive search for original case-control studies was done without limitation of language; and (3) most studies were proved to be homogeneous. Further, there are some limitations in our study: (1) only biallelic mean of CAG repeat variants was analyzed, without analysis on CAG alleles and genotype; (2) the number of studies focusing on Black was small, making it hard to analyze the association in the Black population; and (3) most results were not adjusted because of the inconsistent characteristics of participants among different studies.

In summary, there is no association between SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk. In order to further understand the relationship between gene polymorphisms and PCOS risk, more studies should be launched to enlarge the sample size and variety of gene polymorphisms with unified diagnostic criteria, which will make the meta-analysis more convincing and useful.

COMMENTS

Background

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and its risk is increasing in the association with genetic variants. The (TAAAA)n polymorphism in the sex hormone-binding globulin (*SHBG*) gene and the (CAG)n polymorphism in the androgen receptor (*AR*) gene are two hotspots, but there are no definite results regarding the association between those two genetic variants and PCOS risk.

Research frontiers

Over the past two decades, many studies have been performed to understand the associations between SHBG (TAAAA)n and AR (CAG)n repeat variants and PCOS risk. Moreover, several systematic reviews were recently performed to investigate these associations. However, the inclusion criteria varied greatly among those reviews and thus could not achieve a comprehensive conclusion.

Innovations and breakthroughs

Based on this meta-analysis, neither the TAAAA polymorphism in the *SHBG* gene nor the CAG polymorphism in the *AR* gene has no influence on the risk of PCOS. Similar results were indicated in subgroup analyses of the combination of alleles by race and diagnosis criteria, which were not presented clearly in previous reviews.

Applications

SHBG (TAAAA)n and AR (CAG)n repeat variants have no association with PCOS risk, which prompts a further investigation of other single nucleotide polymorphisms in those genes, including *rs1799941*, *rs2075230*, *rs6257* (T/C), *rs727428* and *rs6259*.

Terminology

Polymorphism is the regular and simultaneous occurrence in a single interbreeding population of two or more discontinuous genotypes. The concept includes differences in genotypes ranging in size from a single nucleotide site to large nucleotide sequences visible at the chromosomal level.

Peer review

This is a good meta-analysis in which the authors investigated the association among SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk. The result definitely proved the results of previous reviews and informed that other polymorphisms in the *SHBG* and *AR* genes may contribute to PCOS risk. The meta-analysis is innovative and the manuscript is well written.

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