ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2020 February 28; 8(1): 1-40

Published by Baishideng Publishing Group Inc

WJMA

World Journal of Meta-Analysis

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World Journal of Meta-Analysis
Volume 8 Number 1 February 28, 2020

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NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Irregular

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Waiting for recruitment

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https://www.wjgnet.com/2308-3840/editorialboard.htm

EDITORIAL OFFICE
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PUBLICATION DATE
February 28, 2020

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World J Meta-Anal 2020 February 28; 8(1): 1-3

DOI: 10.13105/wjma.v8.i1.1

ISSN 2308-3840 (online)

EDITORIAL

Is there still a role for sucralfate in the treatment of gastritis?

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Author contributions: Bramhall SR, Mourad MM made the concept of manuscript, manuscript review and accuracy check; Bramhall SR wrote the manuscript.

Conflict-of-interest statement: The authors have nothing to disclose.

Manuscript source: Invited manuscript

Received: November 1, 2019
Peer-review started: November 1, 2019
First decision: November 22, 2019
Revised: December 3, 2019
Accepted: December 14, 2019
Article in press: December 14, 2019
Published online: February 28, 2020

P-Reviewer: Annibale B, Lan C, Nakajima N,
S-Editor: Dou Y
L-Editor: A
E-Editor: Qi LL

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Abstract

The endoscopic diagnosis of gastritis is usually made when a patient develops symptoms and undergoes an upper gastrointestinal endoscopy. There are often obvious aetiological causes such as smoking, alcohol *Helicobacter pylori* infection or drug treatment. Lifestyle changes can sometimes improve symptoms but often patients will be treated with a proton pump inhibitor. The stomach mucosa produces a protective mucous to prevent damage cause by gastric acid and exogenous agents can disrupt this layer. Repair of this protective layer can be enhanced by reduction in gastric acid secretion using H2 receptor antagonist or proton pump inhibitors or by cytoprotective drugs such as misoprostol, sucralfate, aluminium ions or bismuth subsalts. Sucralfate is a complex polymer which at a low pH changes its chemical configuration and binds to serum protein to form a protective layer protecting the mucosa against further injury. Cytoprotective drugs were the first line treatment for peptic disease including gastritis for many years but since the launch of cimetidine in 1976 and the subsequent launch of omeprazole in 1988, their use has slowly declined. First line treatment for patients with symptomatic gastritis after removal of potential causative factors is likely to be a proton pump inhibitor in 2019. This is despite the fact that there is some evidence that sucralfate is superior than a H2 receptor antagonist in the endoscopic healing rates in patients with gastritis. The logical treatment choice in patients with resistance symptoms is a combination of a proton pump inhibitor and sucralfate but evidence is lacking. Until such evidence is available In the meantime, we would suggest that there is a role for sucralfate in the treatment of intransigent gastritis and that mucosal protection should be considered even ahead of acid suppression given its favourable safety and toxicity profile.

Key words: Sucralfate; Enoscopy; Gastritis; Treatment; Anti-acid

Core tip: An endoscopic diagnosis of gastritis is commonly made. When patients have

significant symptoms associated with this finding and no other explanation can be found for their symptoms the first line treatment tends to be with a proton pump inhibitor. The combination of a proton pump inhibitor and sucralfate can however, be useful in the treatment of these patients when conventional treatment has failed and symptoms are severe.

Citation: Bramhall SR, Mourad MM. Is there still a role for sucralfate in the treatment of gastritis? *World J Meta-Anal* 2020; 8(1): 1-3
URL: https://www.wjgnet.com/2308-3840/full/v8/i1/1.htm
DOI: https://dx.doi.org/10.13105/wjma.v8.i1.1

Gastritis is a common endoscopic diagnosis and can range from asymptomatic to severely symptomatic and be acute or chronic. Experts have long argued whether the endoscopic diagnosis of gastritis is in fact a gastropathy rather than a gastritis but in the present of an endoscopic diagnosis and symptoms treatment is usually offered. If we accept the endoscopic diagnosis of gastritis or gastropathy can cause symptoms then gastritis (as we will term in from here) is an inflammation, irritation or erosion of the gastric mucosa and can have a number of aetiological factors that include alcohol, smoking, various medications, *helicobacter pylori*, bile reflux or bacterial/viral infections. This condition should be differentiated from non-ulcer dyspepsia which has been extensively studied and is not associated with any endoscopic abnormality[1].

Management of gastritis can sometimes be difficult as it can be unresponsive to conventional therapy. Where there is an obvious aetiology for the gastritis removal of the cause is the first line option such as stopping smoking and reducing alcohol intake. This becomes more difficult when the cause is medication related and the medication in question is important to either quality or quantity of life. Under these circumstances, it usually comes down to a balance of risks. Treatment of *helicobacter pylori* infection where present often improves symptoms and there might be dietary changes that can be made to improve symptoms. Once these options have been, exhausted conventional medical treatment will be directed towards a reduction in acid secretion from the gastric mucosa, mucosal barrier protection or where gastritis is believed to be alkaline, gastric pro-kinetic agents.

The symptoms associated with gastritis are non-specific and it is therefore important to exclude any other cause for the patient's symptoms before assuming that they are related to gastritis. Symptoms include epigastric discomfort, nausea and early satiety. Patients will usually require a minimum of an endoscopy, *helicobacter pylori* test and an ultrasound scan. A careful drug, surgical and lifestyle history is necessary.

The gastric mucosa is protected by a layer of water-insoluble mucus gel that is approximately 180 micron thick[2]. This adherent mucus is the first line in mucosal defence against gastric acid in the lumen. Exogenous agents such as alcohol and certain drugs can disrupt the gel layer. The disruption of this layer is in part responsible for exposing the gastric mucosa to either acid or alkali and this can lead to gastritis. Repair of the gastric mucosal barrier can be facilitated by either anti-secretory agents such as H2 receptor antagonists or proton pump inhibitors or by cytoprotective drugs such as misoprostol, sucralfate, aluminium ions or bismuth subsalts.

Sucralfate is a complex polymer of sucrose with multiple substitutions of sulphate and aluminium salts. At a low pH it changes its chemical configuration, which allows it to bind to serum protein to form a protective layer over ulcerated areas. This protects the mucosa against further injury. Sucralfate also stimulates the synthesis and release of prostaglandins, epidermal growth factor and nitric oxide as well as improving gastric mucosal blood flow, bicarbonate secretion and mucus production[3]. Sucralfate is not absorbed systemically and therefore has a good safety and toxicity profile.

Prior to the introduction of H2 receptor antagonist and the subsequent introduction of proton pump inhibitors mucosal cytoprotective drugs were the first line treatment for peptic disease including gastritis. Since the launch of cimetidine in 1976 and the subsequent launch of omeprazole in 1988, the use of cytoprotective agents in the treatment of dyspepsia has slowly declined. First line treatment for patients with symptomatic gastritis after removal of potential causative factors is likely to be a proton pump inhibitor in 2019. This is despite the fact that there is some evidence that sucralfate is superior than a H2 receptor antagonist in the endoscopic healing rates in

patients with gastritis[4,5]. There is little evidence of superiority of proton pump inhibitors over sucralfate in the treatment of gastritis although the only evidence appears to be in post-cholecystectomy biliary gastritis[6]. There is no evidence of benefit from sucralfate alone or in combination in non-ulcer dyspepsia[1].

The logical treatment strategy in patients with symptomatic gastritis is the combination of acid suppression and mucosal protection. There is little or no literature that addresses this combination in any peptic disorder[7] and specifically the combination of sucralfate and a proton pump inhibitor does not seem to have been assessed in the treatment of resistant gastritis.

In our own practice, we have a selective group of patients, who have been extensively investigated to exclude other causes of their symptoms and who have symptoms resistant to conventional acid suppression. We have found anecdotal evidence of symptom relief with the combination of a proton pump inhibitor and sucralfate or in those with strong evidence of bile reflux and therefore alkaline gastritis from sucralfate alone. Our advice is always to take the proton pump inhibitor before the sucralfate and wait for an hour so that absorption is not affected. Our only concern is a lack of an evidence base to support this regime.

As this type of patient is common in both general practice and secondary care it would seem logical to design and conduct a randomised controlled trial to assess whether this approach is supported by scientific data.

In the meantime, we would suggest that there is a role for sucralfate in the treatment of intransigent gastritis and that mucosal protection should be considered even ahead of acid suppression given its favourable safety and toxicity profile[8].

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World Journal of Meta-Analysis

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World J Meta-Anal 2020 February 28; 8(1): 4-14

DOI: 10.13105/wjma.v8.i1.4

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

L-carnitine supplementation in non-alcoholic fatty liver disease: A systematic review and meta-analysis

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Author contributions: Thiagarajan P designed the study and wrote the manuscript; Grindlay D assisted with systematic literature search; Thiagarajan P and Chalmers J performed data extraction and quality assessment; Ban L performed the meta-analysis; Aithal G is senior author, provided critical feedback and helped to shape the research, analysis and manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) dominates the landscape of modern hepatology. Affecting 25% of the general population, there is critical unmet need to identify broadly available, safe and cost-effective treatments. Cumulative evidence in animal and human models suggests that intrahepatic and skeletal muscle fatty acid oxidation is impaired in NAFLD, such that lipid accretion is not matched by efficient utilisation. L-carnitine is a crucial mediator of fatty acid metabolism *in vivo*, promoting mitochondrial lipid β-oxidation and enhancing tissue metabolic flexibility. These physiological properties have generated research interest in L-carnitine as a potentially effective adjunctive therapy in NAFLD.

AIM

To systematically review randomised trials reporting effects of dietary L-carnitine supplementation on liver biochemistry, liver fat and insulin sensitivity in NAFLD.

METHODS

Search strategies, eligibility criteria and analytic methods were specified *a priori* (PROSPERO reference: CRD42018107063). Ovid MEDLINE, Ovid EMBASE, PubMed, Web of Science and the Cochrane Library were searched from their inception until April 2019. Outcome measures included serum concentrations of alanine and aspartate aminotransferase (ALT and AST), liver fat and insulin

Manuscript source: Unsolicited manuscript

Received: October 22, 2019
Peer-review started: October 22, 2019
First decision: December 5, 2019
Revised: December 17, 2019
Accepted: February 15, 2020
Article in press: February 15, 2020
Published online: February 28, 2020

P-Reviewer: Andreone P, Basaranoglu M, Cheng TH, Enosawa S
S-Editor: Wang J
L-Editor: A
E-Editor: Qi LL

sensitivity assessed by the homeostasis model of insulin resistance (HOMA-IR). A random effects meta-analysis was performed for, ALT, AST and HOMA-IR measures separately. Between-study heterogeneity was measured using I^2 statistics.

RESULTS

Five eligible randomised trials were included in the qualitative and quantitative synthesis (n = 338). All of the 5 included trials assessed the effect of L-carnitine on serum ALT, identified from Italy, South Korea and Iran. Weighted mean difference (WMD) for ALT between L-carnitine and control groups after intervention was -25.34 IU/L [95%CI: -41.74-(-8.94); P = 0.002]. WMD for AST between L-carnitine and control groups was -13.68 IU/L (95%CI: -28.26-0.89; P = 0.066). In three studies (n = 204), HOMA-IR was evaluated. WMD for HOMA-IR between L-carnitine and control groups was -0.74 units [95%CI: -1.02-(-0.46); P < 0.001]. Two studies using validated outcome measures reported a significant reduction in liver fat in L-carnitine *vs* control groups post-intervention (P < 0.001).

CONCLUSION

Pooled results indicate that L-carnitine supplementation attenuates ALT, liver fat and insulin resistance in NAFLD cohorts, confirming a beneficial effect of L-carnitine for a highly prevalent condition with a growing economic burden.

Key words: L-Carnitine; Non-alcoholic fatty liver disease; Nonalcoholic steatohepatitis; Liver function; Insulin resistance; Meta-analysis; Systematic Review

Core Tip: Non-alcoholic fatty liver disease (NAFLD) presents a major public health challenge. As a leading cause of abnormal liver chemistry, rising in prevalence together with obesity and insulin resistance, there is critical unmet need to identify cost-effective, population-based treatment. We synthesised evidence from randomised trials published to date evaluating the effect of dietary L-carnitine supplementation on transaminases, liver fat and insulin resistance in NAFLD. We demonstrate a significant reduction in serum alanine aminotransferase, homeostasis model of insulin resistance and liver fat with dietary L-carnitine supplementation. L-carnitine could therefore present a novel therapeutic tool for NAFLD and its metabolic associations.

Citation: Thiagarajan P, Chalmers J, Ban L, Grindlay D, Aithal GP. L-carnitine supplementation in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *World J Meta-Anal* 2020; 8(1): 4-14
URL: https://www.wjgnet.com/2308-3840/full/v8/i1/4.htm
DOI: https://dx.doi.org/10.13105/wjma.v8.i1.4

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has rapidly emerged as a leading cause of chronic liver disease and liver transplantation worldwide[1]. The global prevalence of NAFLD is estimated to be 25.24%[2], rising to 66% and 90% in those with type 2 diabetes and obesity, respectively[3]. Although progression to non-alcoholic steatohepatitis (NASH) is limited to approximately 30% of individuals with NAFLD, the high population prevalence of NAFLD heralds a looming socioeconomic burden due to the consequences of its progression, including end-stage liver disease[4]. In EU4 countries alone (France, Germany, Italy, United Kingdom), the annual cost associated with NAFLD is estimated to be €35 billion[5]. Diet and lifestyle modification remain current standard of care, and there is no specifically licensed disease-modifying therapy available.

L-Carnitine is a naturally occurring water-soluble quaternary amine which acts as a crucial mediator of fatty acid metabolism *in vivo*. The role of carnitine as a key regulator of intracellular bioenergetics has gained traction in the search for broadly applicable treatments for metabolic disorders, including obesity and type 2 diabetes.

The ability of L-carnitine to regulate muscle mitochondrial fuel selection, through promoting both lipid oxidation and non-oxidative glucose disposal, renders it an attractive target for therapeutic intervention in the context of insulin resistance[6]. Cumulative evidence in both animal and human models suggests that intrahepatic and skeletal muscle fatty acid transport and oxidation is impaired in NAFLD and insulin resistance, such that excessive lipid accretion is not matched by efficient utilisation[7,8]. Thus, the effect of carnitine supplementation in the context of NAFLD specifically has been the focus of recent interest. This review aims to critically and systematically evaluate all human randomised trials investigating the effect of carnitine on liver fat and/or metabolic parameters in NAFLD.

MATERIALS AND METHODS

Search strategies, eligibility criteria and analytic methods were specified *a priori* in the study protocol, which was registered with the PROSPERO database (CRD42018 107063).

Search strategy

We performed a systematic literature search for randomised trials reporting the effects of dietary L-carnitine supplementation on liver biochemistry and liver fat in adult individuals with NAFLD and NASH.

The databases searched were PubMed, Ovid EMBASE, Ovid MEDLINE, Web of Science Core Collection and the Cochrane Library. The full search strategy used in Ovid MEDLINE is provided in Appendix 1. Databases were searched from their inception until April 2019. No language restrictions were used. For each database, a comprehensive list of alternative terms for NAFLD were combined with alternative terms for L-carnitine, using the Boolean operator AND. Reference lists of studies ultimately selected for inclusion were searched to identify any other relevant research.

Diagnostic criteria for NAFLD varied significantly between studies, but eligible studies included adult individuals diagnosed with NAFLD on the basis of validated histological, imaging or biochemical tests, including the following, and where other causes of hepatic steatosis had been excluded: (1) Liver histology; (2) Magnetic Resonance Imaging with proton density fat fraction (MRI-PDFF) or proton magnetic resonance spectroscopy (^{1}H-MRS); (3) Computed Tomography (CT); (4) Ultrasound and (5) Serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in conjunction with impaired glucose tolerance and in the absence of documented alcohol excess.

Primary outcome measures included change in serum concentrations of ALT, AST and liver fat (as assessed either by liver biopsy, cross-sectional imaging or ultrasound). Secondary outcome measures included changes in insulin sensitivity parameters (as assessed by the HOMA-IR) and, where available, markers of inflammation and oxidative stress.

Study selection was performed independently by two separate reviewers (PT and JC) with any disagreements revolved by a third researcher (GPA). Titles and abstracts of returned searches were evaluated against eligibility criteria. Those meeting eligibility criteria based on title and abstract were subsequently read in full. Wherever journal articles were found to contain insufficient information for critical analysis, attempts were made to contact the authors directly for clarification of missing details.

Eligibility criteria

Eligible published studies included human randomised trials evaluating the effect of carnitine supplementation on liver fat, liver enzymes, glucose and markers of inflammation or oxidative stress in adult individuals with NAFLD. Only full reports were considered as eligible for inclusion on the basis that they provided sufficient data to permit critical analysis. Studies were considered eligible for inclusion if they: (1) Were randomised in design; (2) Evaluated L-carnitine versus placebo, L-carnitine plus another intervention versus that intervention alone, or L-carnitine versus no intervention; (3) Included a patient population diagnosed with NAFLD and/or NASH based on validated histological, radiological or biochemical parameters as listed above; and (4) Included only subjects aged 18 years or above. Studies were excluded if they: (1) Were non-randomised in design *e.g.*, case reports, reviews or observational studies; (2) Included patients with another cause of hepatic steatosis *e.g.*, alcohol, genetic or viral liver disease; (3) Were animal studies; and (4) Did not evaluate outcomes of interest as detailed above.

There were no restrictions based on dosage, formulation or frequency of administration. Interventions in the control group included active placebo supplementation, hypocaloric diet and metformin therapy. Trials evaluating L-

carnitine supplementation together with other interventions, in the absence of a control group consisting of the other interventions alone, were excluded. No specific treatment duration was specified for inclusion in this review.

Data extraction and quality assessment

Data extracted from individual studies included (1) participant demographics; (2) intervention type and dose; (3) method of NAFLD diagnosis; (4) outcome measurements of liver fat, liver enzymes, glycometabolic profile and markers of inflammation and oxidative stress; (5) documentation as to whether informed consent was gained; (6) methods of randomisation; (7) allocation concealment; (8) participant and staff blinding; (9) blinding of outcome assessment; (10) presence of incomplete outcome data; and (11) evidence of any selective reporting. The Cochrane risk of bias tool[9] was then used to systematically appraise each included study in terms of methodological quality and validity according to the criteria of the Cochrane guidelines.

Statistical analysis

A random effects meta-analysis was performed for ALT, AST and HOMA-IR measures separately. Weighted mean difference (WMD) with 95%CI were calculated. Between-study heterogeneity was measured using I^2 statistics, with $I^2 > 50\%$ indicating significant heterogeneity. The analysis was performed using Stata software version 11.0 Stata (Version 11.2, StataCorp, College Station, Texas). Resultswere summarised using Forest plots.

RESULTS

Search results

Figure 1 depicts the PRISMA flowchart process of identification and selection of eligible studies for inclusion in the qualitative and quantitative syntheses. Primary database searches yielded 883 citations. After de-duplication, 692 remaining citations were screened for eligibility by reading titles and abstracts. Of these remaining studies, 675 were excluded. Of the remaining 17 citations, full text articles retrieved were read in full to determine eligibility. Twelve studies were subsequently excluded.

Table 1 summarises study characteristics for the five randomised trials ultimately included in the qualitative and quantitative synthesis[10-14]. In total, these trials comprised 338 patients (234 men, 104 women). In 3 trials, non-diabetic patients with NAFLD were recruited and the other 2 trials recruited individuals with type 2 diabetes mellitus and NAFLD.

Quality of included studies

Methodological quality was assessed using criteria set out in the Cochrane Handbook for Systematic Reviews (Figure 2). All trials described randomising participants to L-carnitine and control arms. However, only two of the five trials[10,11] reported the methods used to generate random allocation sequence (*i.e.*, computer generated tool) to a standard sufficient enough to be judged as having a low risk of bias. In the other 3 trials, no information was provided regarding methods of blinding and insufficient information was provided to enable informed decision-making regarding adequacy of randomisation. One trial reported randomising participants by using random numbers allocated to consecutive patients; this was considered to confer a high risk of selection bias[12].

Regarding allocation concealment, only two studies[10,11] reported efforts to conceal allocation sequences from personnel as well as patients. In two of the studies, genuine blinding was considered impossible due to lack of a placebo arm[13,14]. In the remaining two trials, insufficient information was given to determine whether a robust allocation concealment process was undertaken. Three of the five studies accounted for incomplete outcome data and clearly explained any loss to follow up and exclusions[10,11,13]. The other two studies lacked explanations for trial exclusion.

Selective reporting was considered to be present in two out of the five included studies. Alavinejad *et al*[12] (2016) with sonographic grade of liver fat as an outcome measure in their study, noted that "follow up ultrasonography did not show any significant change in comparison with baseline reports". However no baseline or post-intervention values were reported. Somi *et al*[14] (2014) reported changes from baseline in sonographically-determined grade of NAFLD in patients in the L-carnitine arm of the study, with nine of the L-carnitine treated patients having no evidence of NAFLD on post-intervention ultrasound. However it was unclear how many patients had progressed or regressed in steatosis grade.

In three out of the five trials, funding sources and conflicts of interests were

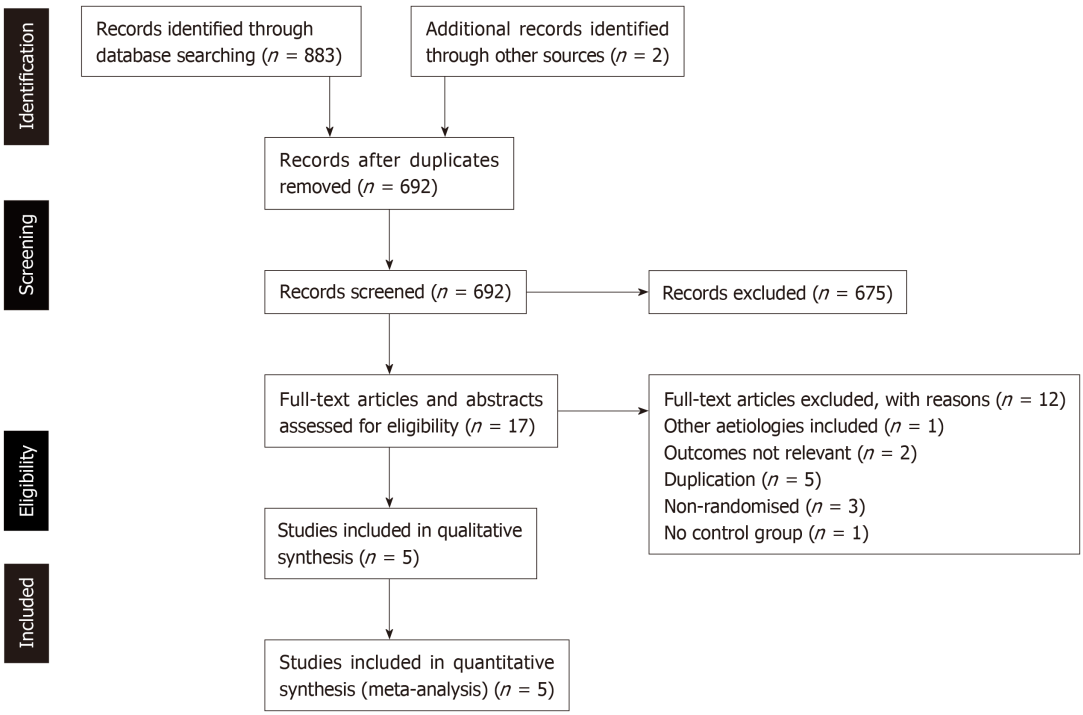

Figure 1 PRISMA flow diagram.

explicitly stated, whereas in the other two trials no mention was made of either[12,14]. Efficacy, safety and compliance measures were reported in 3 studies but no description of methods to evaluate compliance was made in the other two studies and Somi *et al*[12,14] (2014) did not report any safety visits for subjects during 24 wk of supplementation. Statistical analyses were reported in all five trials.

Outcomes

Estimates were made on the effect of L-carnitine on outcomes including liver transaminases, the HOMA-IR and liver fat (where measured).

ALT: All of the five included trials were for meta-analysis of ALT measures after intervention (Figure 3). The WMD for ALT between the L-carnitine groups and the control groups after intervention was -25.34 IU/L [95%CI: -41.74-(-8.94), P = 0.002] (Figure 3). The I^2 was 95.8%, indicating statistically significant heterogeneity between the studies.

AST: All five trials were included for meta-analysis of AST measures after intervention. The WMD for AST between the L-carnitine group and the control group after intervention was -13.68 IU/L (95%CI: -28.26-0.89) (P = 0.066) (Figure 4). The I^2 was 93.4%, indicating high statistical heterogeneity between the studies.

Liver fat: Four of the included studies evaluated hepatic steatosis at baseline and post-intervention. Outcome measures differed between the studies, precluding the possibility of a quantitative synthesis of results. In two studies, ultrasonography was used to grade liver fat at baseline and post-intervention[12,14]. In another study, CT imaging was used[11] and in the fourth study, liver fat was evaluated histologically[10].

Malaguarnera *et al*[10] (2010) assessed liver fat using paired biopsies; the group reported a significant reduction in steatosis in the group randomised to L-carnitine compared to placebo (1.68 ± 0.76 *vs* 0.94 ± 0.88; P < 0.001). However, within-group analysis also demonstrated that steatosis reduction was significant in the placebo group (hypocaloric diet + placebo) compared to baseline values (P < 0.001). In the same study, other histological features of NASH were shown to be significantly attenuated following 24 wk of L-carnitine therapy compared to placebo, including parenchymal inflammation (P < 0.001), hepatocellular injury (P < 0.05) and fibrosis (P < 0.05). However, it is again worth noting that within-group comparisons with baseline values also determined a significant reduction in these parameters following placebo supplementation.

Another study used hepatic CT with liver attenuation index (LAI) to evaluate steatosis before and after the study[11]. Authors reported that the patient group

Table 1 Published studies to date evaluating the effect of L-carnitine supplementation on liver fat and/or biochemistry in non-alocholic fatty liver disease

Ref.	Study population (diagnosis); comorbidities	Sample size (M/F) Control/ Carnitine	Age (yr)	BMI	Duration (wk)	Intervention (dose)	Outcome Measures	Control	Results
Malaguarnera *et al*[10]	Biopsy-proven NASH without diabetes	74 (40/34) 38 (CTRL) 36 (CAR)	47.8 ± 5.8 (CTRL) 47.9 ± 5.4 (CAR)	26.5 ± 3.8 (CTRL) 26.6 ± 3.7 (CAR)	24	L-carnitine (1000 mg BD) plus hypocaloric (1600 cal) diet	Primary: Improvement in histological features of NASH Other: ALT, AST, lipid profile, GLC, HOMA-IR, CRP, TNFα	Placebo plus Hypocaloric (1600 cal) diet	Primary Outcome: ↓ NASH activity score[1] (9.42-3.19), ↓ALT[1] ↓AST[1], ↓GGT[1] ↓TC[1], ↓LDL[1], ↑HDL[1], ↓GLC[1], ↓HOMA-IR[1], ↓CRP[1], ↓TNFα[1]
Bae *et al*[11]	NAFLD with type 2 diabetes	78 (54/24) 39 (CTRL) 39 (CAR)	52 ± 9.4 (CTRL) 50.6 ± 9.3 (CAR)	26.7 ± 3.7 (CTRL) 28.2 ± 2.6 (CAR)	12	Carnitine orotate complex (824 mg TDS)	Primary: Change in ALT Other: Liver attenuation index (CT)	Placebo	Primary outcome: ↓ALT (89.7% *vs* 17.9%)[1] Other: ↓Liver attenuation index[1] (0.74 ± 8.05 *vs* 6.21 ± 8.96)[1], ↓HbA1c, ↓GLC, ↓HOMA-IR[2]
Alavinejad *et al*[12]	NAFLD (ultrasound+ raised ALT) with T2DM	54 (38/16) 26 (CTRL) 28 (CAR)	59 ± 9 (CTRL) 60 ± 5 (CAR)	29.5 ± 3.6 (CTRL) 28.6 ± 4.6 (CAR)	12	L-carnitine (750 mg TDS)	Primary: AST, ALT Other: TG, GLC, HbA1c	Placebo	Primary outcome: ↓ALT[1], ↓AST[1] Other: ↓TG[2], ↓GLC[2], ↓HbA1c[2]
Hong *et al*[13]	NAFLD (plasma ALT 40-250) and impaired glucose tolerance (HbA1C ≥ 6.0%)	52 (36/16) 26 (CTRL) 26 (CAR)	52.0 ± 9.6 (CTRL) 51.5 ± 9.4 (CAR)	27.0 ± 3.1 (CTRL) 27.2 ± 2.6 (CAR)	12	Carnitine-orotate complex (300 mg TDS) + metformin	Primary: change from baseline ALT Other: GLC, HbA1c, m t DNA copy number, urine 8-OHdG	Metformin alone	Primary outcome: ↓ ALT[1] Other: ↓HbA1c[2], ↑ plasma mtDNA copy number[1], ↓GLC[2], ↓urine 8-OHdG
Somi *et al*[14]	NAFLD (ultrasound + plasma ALT ≥ 40)	80 (66/14)	40.7 ± 8	29.4 ± 3.9	24	L-carnitine (250 mg BD)	Primary: ALT, AST Other: Sonographic change in liver fat, BMI	No treatment	Primary outcome: ↓ALT[1], ↓AST[1] Other: ↓ liver fat on USS

NASH: Nonalcoholic steatohepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GLC: Glucose; HOMA-IR: Homeostasis model of insulin resistance; CRP: C-reactive protein; TNFα: Tumour Necrosis Factor alpha; HbA1C: Haemoglobin A1C; T2DM: Type 2 diabetes mellitus; TG: Triglyceride; mt DNA: Mitochondrial DNA; oHdg: 8-hydroxydeoxyguanosine.
[1]Denotes statistically significant results.
[2]Denotes non-statistically significant results.

receiving L-carnitine complex supplementation had a mean increase in LAI values of 6.21 ± 8.96 Hounsfield Units (HU) ($P < 0.001$), indicating significant reduction in liver fat, whereas the placebo group showed no significant change (LAI increased by 0.74 ± 8.05 HU, $P = 0.582$). The changes in LAI were found to correlate inversely with changes in ALT.

Alavinejad *et al*[12] (2016) reported no significant difference between baseline and post-intervention sonographic liver fat in either the L-carnitine or placebo groups in

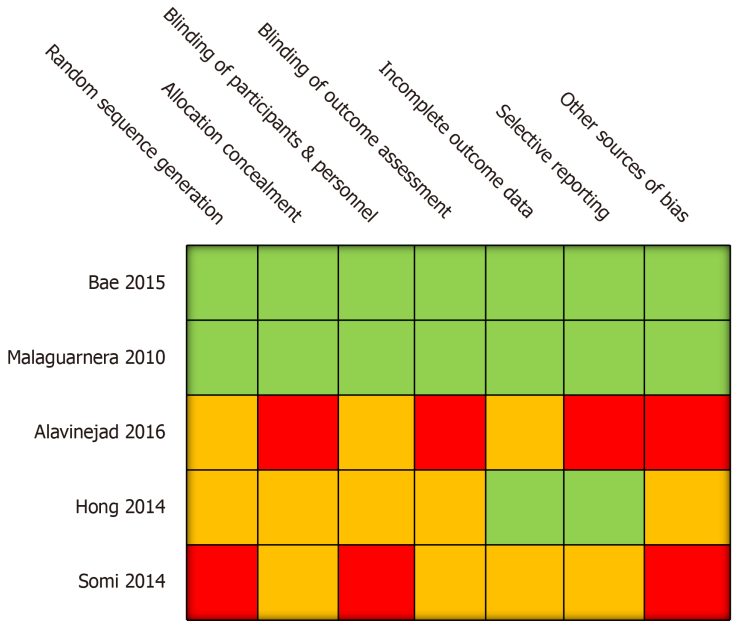

Figure 2 Methodological quality assessment according to the Cochrane risk of bias tool.

their study. However, absolute values were not provided in the published article. Finally, Somi *et al*[14] (2014) reported a significant reduction in patients with sonographic grade 2 liver fat in the placebo but not the L-carnitine groups. In the L-carnitine group, 9 patients with sonographic evidence of fatty liver at baseline had resolution of fatty liver disease on post-intervention ultrasonography, suggesting a beneficial effect of L-carnitine on liver fat; however, this was reported to be non-significant. Thus, two high quality RCTs utilising histology and cross-sectional imaging for quantifying liver fat reported significant outcomes following L-carnitine supplementation, whereas the two trials utilising ultrasonography reported no significant difference in liver fat with L-carnitine.

HOMA-IR and glycometabolic profile: Three papers were included for meta-analysis of HOMA-IR measures after intervention. The WMD for HOMA-IR between the L-carnitine and control groups after intervention was -0.74 units [95%CI: -1.02-(-0.46)] ($P < 0.001$) (Figure 5). The I^2 was 0%, indicating statistical homogeneity between the studies.

Adverse events: Adverse events (AE) were reported in 3 studies included in this review, including mild headache, musculoskeletal pain and gastrointestinal disturbance[10,11,13]. All AE rates were lower in the intervention versus placebo groups and no serious adverse events were reported.

Inflammation and oxidative stress: Malaguarnera *et al*[10] (2010) reported a significant reduction in hepatocellular injury ($P < 0.05$), parenchymal inflammation ($P < 0.001$), plasma C-reactive protein (CRP) and tumour necrosis factor alpha (TNFα) ($P < 0.001$) in L-carnitine treated patients compared to placebo. Hong *et al*[13] (2014) evaluated inflammation and oxidative stress at baseline and post-intervention in using high-sensitivity CRP (hs-CRP) and urine 8-hydroxy-2′-deoxyguanosine (8OHdG), respectively and report significant reduction in 8OHdG in the group treated with L-carnitine ($P = 0.034$).

DISCUSSION

Summary of evidence

To our knowledge, this is the first reported systematic review to evaluate the effect of dietary L-carnitine supplementation on liver fat, markers of liver injury and insulin resistance profiles in NAFLD populations. Pooled results from five randomised trials suggest that L-carnitine supplementation is associated with significant attenuation of liver fat, and reduction in serum ALT levels, the most commonly used surrogate biomarker of hepatocellular injury. A reduction in AST following L-carnitine therapy was also seen, though this did not reach statistical significance. Our results further

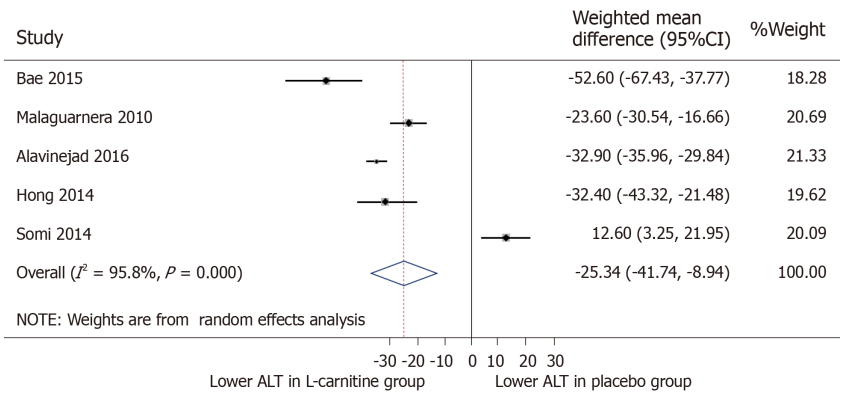

Figure 3 Meta-analysis of alanine aminotransferase measures after intervention.

suggest that L-carnitine can improve insulin sensitivity in NAFLD cohorts, as measured indirectly using the HOMA-IR index. These outcomes are potentially important to clinical practice, as they confirm a beneficial effect of a broadly available nutrient.

Strengths and limitations

This review comprised a robust and comprehensive database search with no language restrictions. The search strategy was implemented by two reviewers separately, and both authors agreed on papers selected for inclusion as well as reasons for exclusion. Included studies were read and assessed for bias independently by each reviewer; any disagreements in the risk of bias tool were referred to a third reviewer for final arbitration. No publication bias was found to be present for selected outcomes entered into the meta-analysis.

There were several limitations associated with this review. Firstly, despite an extensive literature search, only five randomised studies were available evaluating L-carnitine on liver markers in NAFLD. Of these, only four evaluated change in liver fat as an outcome measure. Despite another trial being published, we were unable to obtain the full text after attempts to contact the authors of the paper.

Secondly, poor methodological quality was inherent in three of the included studies. For example, while all studies claimed randomisation, only Malaguarnera *et al*[10] (2010) and Bae *et al*[11] (2015) described robust methods of random sequence generation. Lack of placebo control use in the studies conducted by Somi *et al*[13] (2014) and Hong *et al*[14] (2014) further reduced methodological quality and reliability of reported results. Double-blind trial design is an important tool in minimising bias and maximising reliability of research outcomes. In two of the included studies, there was insufficient evidence to judge that robust blinding of participants and personnel occurred. In the study conducted by Somi *et al*[14] (2014) no mention of blinding was made. This led us to judge these studies as having as high risk of bias and thus further reduced reliability of reported results.

There was heterogeneity of the trials with respect to duration, type of active comparator drug and background therapy, as well as carnitine formulation and dose. Two studies used carnitine in complex with orotic acid (carnitine-orotate); thus establishing a true effect of L-carnitine alone on outcomes measures was not possible. Doses varied widely, from 500 mg daily to 2.25 grams daily, resulting in differential exposure to active L-carnitine among patients in each individual study. The NAFLD patient populations studied were also heterogenous, including patients both with and without diabetes, patients with different stages of NAFLD and geographical differences in populations. However, all 5 studies reported reductions in ALT, suggesting a consistent beneficial effect of L-carnitine on hepatocellular injury across populations.

As a marker of treatment response, ALT appears to be reliable, and has been closely correlated to objectively measured reductions in liver fat using histological and imaging methods in NAFLD post-intervention[15,16]. In phase 2 RCTs, ALT continues to be used as a surrogate marker of disease activity in addition to estimation of fat[17]. The overall significant reduction in ALT following intervention in the included studies suggests a global reduction in hepatocellular injury in patients treated with L-carnitine. Indeed, Malaguarnera *et al*[10] (2010) demonstrated an improvement in all histological parameters in their biopsied NAFLD cohort following L-carnitine therapy, including steatosis, inflammatory activity and fibrosis. Steatosis reduction was confirmed using CT with liver attenuation index by Bae *et al*[11] (2015).

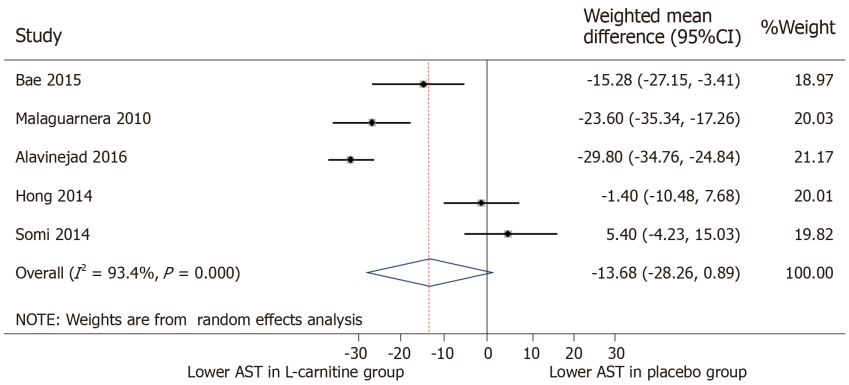

Figure 4 Meta-analysis of aspartate aminotransferase after intervention.

With respect to translation into clinical practice, none of the 5 trials evaluated plasma levels of Trimethylamine-N-Oxide, a metabolite of L-carnitine associated with increased risk of atherosclerosis. In a population already at high risk for cardiovascular outcomes, the safety profile of L-carnitine supplementation would require rigorous assessment in this context. However, the evidence base for a direct adverse link between L-carnitine supplementation and cardiovascular events is to our knowledge limited. On the contrary, a meta-analysis of 13 placebo-controlled trials including 3629 patients evaluated the clinical impact of L-carnitine supplementation in patients with ischaemic heart disease and concluded that carnitine administration was associated with clinical benefit, including reduced mortality and reduction in onset of cardiac arrhythmias and angina[18]. A recently published study further concluded that although 24-wk of L-carnitine supplementation increased plasma Trimethylamine-N-Oxide concentrations, no changes in lipid profile or other serum biomarkers of atherosclerosis were seen[19].

The evidence collated from studies included in this review forms a compelling argument for further robust, randomised trial data evaluating mechanisms of action of L-carnitine on liver and muscle tissue in a NAFLD phenotype, as well as its effect on validated outcome measures such as liver histology, magnetic resonance imaging and spectroscopy. Further, effects of L-carnitine supplementation on metabolic outcomes in NAFLD require specific attention, for example through utilising gold-standard measures of liver-specific and whole-body insulin sensitivity such as the euglycaemic hyperinsulinaemic clamp technique. As a naturally occurring, broadly applicable, safe and cost-effective agent, L-carnitine could overcome traditional barriers to translation to become routinely available for patients in clinical practice as an adjunctive treatment for NAFLD.

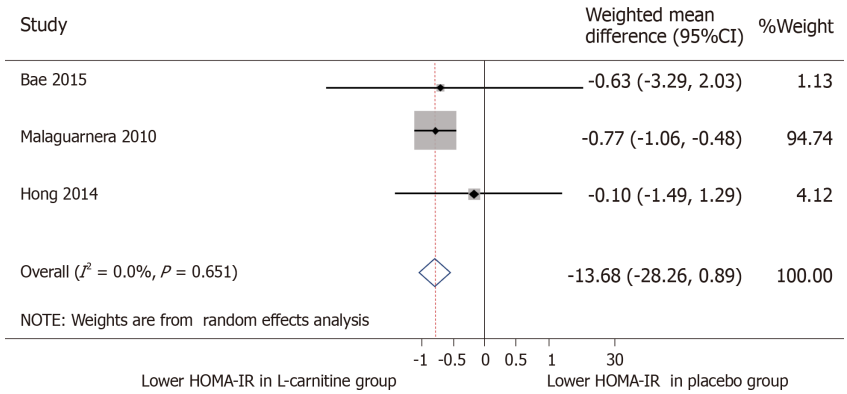

Figure 5 Meta-analysis of homeostasis model of insulin resistance measures after intervention.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver disease worldwide, affecting approximately 25% of the general population. To date, there are no licensed disease-modifying treatments to attenuate global burden of NAFLD. A growing body of evidence suggests that NAFLD is characterised at a cellular level by impaired mitochondrial fat oxidation. L-carnitine, a naturally occurring nutrient, is a key mediator of mitochondrial fuel selection and promotes lipid oxidation. In this article, we synthesise available evidence of a role for L-carnitine supplementation in the treatment of NAFLD.

Research motivation

L-carnitine has gained traction in recent years as a potential tool for the treatment of metabolic disorders including type 2 diabetes and heart disease. At the nexus of glucose and lipid metabolism, L-carnitine promotes mitochondrial lipid oxidation and enhances tissue metabolic flexibility. It may confer protective effects in NAFLD through these mechanisms. There is a critical unmet need for broadly applicable, population based treatment in NAFLD, which inspired this narrative and quantitative synthesis.

Research objectives

In this study, we aimed to systematically review randomised trials reporting effects of dietary L-carnitine supplementation on liver biochemistry, liver fat and insulin sensitivity in NAFLD.

Research methods

Ovid MEDLINE, Ovid Embase, PubMed, Web of Science and the Cochrane Library were searched from their inception until April 2019. Outcome measures included serum concentrations of alanine and aspartate aminotransferase (ALT and AST), liver fat and insulin sensitivity assessed by the homeostasis model of insulin resistance (HOMA-IR). A random effects meta-analysis was performed for, ALT, AST and HOMA-IR measures separately. Between-study heterogeneity was measured using I^2 statistics. A protocol for the systematic review was published a priori in the PROSPERO database (Reference: CRD42018107063).

Research results

Results from the synthesised evidence suggest that L-carnitine is associated with a significant reduction in serum alanine aminotransferase (ALT), the most commonly used biomarker of hepatocellular injury. In two robust, high-quality randomised trials, L-carnitine supplementation reduced liver fat significantly. Further, in subgroup analysis of studies assessing insulin resistance, L-carnitine supplementation was associated with a significant reduction in the HOMA-IR.

Research conclusions

We present an argument for further robust, randomised trial data evaluating mechanisms of action of L-carnitine on liver and muscle tissue in NAFLD populations. Currently availabile evidence suggests that as a naturally occurring, broadly applicable and cost-effective agent, L-carnitine could be an effective tool for patients in clinical practice as an adjunctive treatment for NAFLD. However, we emphasise that further research using robust and validated endpoints is required to consolidate existing evidence of benefit.

Research perspectives

Micronutrient supplementation presents a novel and exciting avenue for the treatment of population-level diseases, including NAFLD. A broader impact of L-carnitine on metabolic health (including improved insulin sensitivity) could have implications beyond NAFLD alone and its effect in other metabolically challenged populations deserves attention. Ultimately, further well-conducted prospective, randomised data will be required to translate a speculative

benefit of L-carnitine in NAFLD into the clinical sphere.

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World J Meta-Anal 2020 February 28; 8(1): 15-26

DOI: 10.13105/wjma.v8.i1.15

ISSN 2308-3840 (online)

META-ANALYSIS

Gender prevalence of cardiovascular diseases in the geriatric population of India: A meta-analysis using R

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Author contributions: Nanda H and Shivgotra VK both designed the study, the literature was reviewed by the first author, then by the second author; data collection, data analysis and writing of the paper was performed by Nanda H under the supervision of Shivgotra VK.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

PRISMA 2009 Checklist statement: The authors prepared the research paper after reading the PRSIMA checklist 2009.

Manuscript source: Unsolicited manuscript

Received: September 3, 2019
Peer-review started: September 3, 2019
First decision: November 12, 2019

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Abstract

BACKGROUND

Population ageing is an important challenge for developed as well as developing countries due to the downward trends in mortality rates. The elderly population is increasing worldwide. Cardiovascular diseases (CVDs) are one of the most common diseases in the geriatric population. These diseases involve the heart or blood vessels and include hypertension, rheumatic heart disease, heart failure, and heart attack. An estimated 17.7 million people in India will die from CVDs representing 31% of all global deaths.

AIM

To perform a systematic review and meta-analysis of the gender prevalence of CVDs in the geriatric population of India.

METHODS

In the present study, we searched databases such as Google Scholar, PubMed and MEDLINE from the year 2003 to 2019 to identify the prevalence of CVDs in the Indian geriatric population. A meta-analysis was conducted using the statistical software R version 3.4.3 and the random effect model was used to determine the pooled estimate of the prevalence of CVDs in the geriatric population of India along with the 95% confidence interval rather than using the fixed effect model. The random effect model takes into consideration the heterogeneity across the various studies.

RESULTS

The prevalence of CVDs in the Indian geriatric population was determined in 6586 male subjects from 32 studies and 8164 female subjects from 32 studies, respectively. The overall prevalence of CVDs in the Indian geriatric population was 36.6% (95%CI: 31.9%-41.3%). In addition, calculation of the various heterogeneity statistics (Cochran's Q = 3836.85, I^2 = 98.6%, P < 0.0001) indicated heterogeneity in the prevalence of CVDs in the elderly Indian population in these studies. The prevalence of CVDs in elderly males was 38.0% (95%CI: 33.0%-43.0%) and the prevalence of CVDs in elderly females was 40.9% (95%CI: 35.5%-

Revised: November 21, 2019
Accepted: January 1, 2020
Article in press: January 1, 2020
Published online: February 28, 2020

P-Reviewer: Erkut B, Dai X, Karatza AA, Kharlamov AN, Rostagno C
S-Editor: Dou Y
L-Editor: Webster JR
E-Editor: Qi LL

46.2%).

CONCLUSION
The results indicate that the prevalence of CVDs in the female geriatric population was relatively higher than that in the male geriatric population. Policy makers must take immediate steps to prevent CVDs and improve geriatric health care services in India.

Key words: Ageing; Cardiovascular diseases; Geriatric; Systematic review; Meta-analysis; Prevalence

Core tip: A systematic review and meta-analysis of the prevalence of cardiovascular diseases in the geriatric population in India from the year 2003 to 2019 revealed that there was a higher prevalence of cardiovascular diseases in the female geriatric population (40.9%) as compared with the male geriatric population (38.0%). In addition, the measures of consistency such as I^2 and Cochran's Q suggested heterogeneity between the studies. These findings indicate that health care professionals should take immediate steps to improve geriatric health care services in India.

Citation: Nanda H, Shivgotra VK. Gender prevalence of cardiovascular diseases in the geriatric population of India: A meta-analysis using R. *World J Meta-Anal* 2020; 8(1): 15-26
URL: https://www.wjgnet.com/2308-3840/full/v8/i1/15.htm
DOI: https://dx.doi.org/10.13105/wjma.v8.i1.15

INTRODUCTION

Ageing is a universal phenomenon associated with deteriorating health status. It is said that nobody grows old merely by living a certain number of years. With the passage of time, certain changes take place in an organism leading to morbidity, disability and even death. Populations around the world are growing old at a high rate with increasing life expectancy. The challenge for health care in the coming years is to ensure quality of life in the geriatric population[1]. The elderly consist of people surpassing the average life span of humans. The contribution of the elderly population to demographic figures is increasing day by day. Increasing problems in health care, psychological, personal and socio-economic factors are associated with the elderly[2]. The growing healthy ageing population is a source of both joy and worry. Joy as people are living longer and healthier lives, and worry about how to respond to a future with a larger older population and their demands and needs[3].

According to the World Health Organization (WHO) Report on Ageing and Health 2018, persons aged 60 years and older are considered elderly. It is suggested that between 2015 and 2050, the proportion of the world's elderly population will nearly double from 12% to 22%, respectively. By 2050, the world's population aged 60 years and older is expected to total 2 billion, up from 900 million in 2015[4]. According to the population census 2011, there are nearly 104 million elderly persons in India which constitutes approximately 8% of the total world population. This share of the population is expected to increase from 8% to nearly 12.6% in 2025 and to 19% in 2050[5].

The geriatric population is vulnerable to long-term diseases such as cardiovascular diseases (CVDs), cancer, diabetes, musculoskeletal disorders, depression, arthritis, kidney problems, *etc*. Due to the increase in life expectancy and modification of lifestyle, CVDs are emerging as one of the major problems in elderly people in India. CVDs generally refer to disorders of the heart and blood vessels and include hypertension, heart attack, cerebrovascular diseases or stroke, peripheral heart disease, rheumatic heart disease, congenital heart disease and cardiomyopathies[6]. The symptoms of heart diseases may vary with respect to disease type. Most CVDs can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, *etc*. CVDs are a major cause of mortality all over the world as well as in India. According to the WHO Report, an estimated 17.9 million people will die every year from CVDs representing

31% of all deaths worldwide and over 23 million people will die from CVDs by 2030[7]. Our study aims to provide a pooled estimate of the gender prevalence of CVDs in the geriatric population of India.

MATERIALS AND METHODS

Literature search

The search strategy, selection of publications and reporting of results for the review were conducted in accordance to the PRISMA guidelines. All published studies related to the prevalence of CVDs in India over the last 15 years (*i.e*., from the year 2003 to year 2018) were obtained from MEDLINE/PubMed, Google Scholar and from non-electronic materials such as journals, theses, *etc*. Internet searches using a combination of keywords such as prevalence, CVDs, hypertension, stroke, elderly, morbidity, *etc*. were used to identify prevalence studies of CVDs in the Indian geriatric population. The limitations included were: English for the language category and geriatric humans for the study category.

Selection of studies

All identified research papers were independently reviewed by the reviewers. Disagreements between the reviewers were resolved by considering the facts mentioned in the PRISMA checklist.

Inclusion criteria

Studies that m*et a*ll the following criteria were included in the present analysis: (1) The studies in the mentioned databases with full text, despite the language of the original text; (2) The studies were conducted in the Indian population and were prevalence studies conducted after the year 2002; (3) The study design was cross-sectional; and (4) The age group included in the study was 60 years and older.

Exclusion criteria

Studies which did not satisfy the above criteria were not included in our analysis. We also excluded studies in which age-specific prevalence was not reported. Some studies in which calculated proportions acted as outliers were also excluded from the study to ensure normal distribution of the data.

Data extraction and methodological assessment

Data extraction was performed by the first reviewer and confirmed by the second reviewer, and the whole process was discussed by both reviewers. The eligible studies were further reviewed and information on the author, year of publication, gender, location, total number of subjects, number of cases, type of study, *etc*. from each included study was extracted and the data were summarized in the form of a table.

Statistical analysis

The meta-analysis was used to combine the results of studies using the statistical software R version 3.4.3. The pooled estimate of prevalence of CVDs in the Indian geriatric population was provided by the random effect model. The random effect model assumes that observed estimates of treatment effect can vary across studies because of real differences in the treatment effect in each study as well as sampling variability (chance). Variation (heterogeneity) across studies must also be considered. The random effect meta-analysis allows for heterogeneity by assuming that underlying effects follow a normal distribution. Cochran's Q and I^2 were used to incorporate heterogeneity in the studies and 95% confidence intervals (CIs) are reported in the analysis. Forest plots and funnel plots were used for graphical representation of the meta-analysis. The squares in the forest plot represent the effect estimates of individual studies with their 95%CI of the prevalence of CVDs with the size of squares proportional to the weights assigned to each study in the meta-analysis. The diamond represents the overall result and 95%CI of the random effect meta-analysis. The funnel plots were used to investigate publication bias in the study. The inverted funnel shows that there is no publication bias, whereas the asymmetric funnel plot may suggest publication bias. The dots in the funnel plot represent the studies involved in the meta-analysis. Generally, the studies with larger power are placed towards the top, whereas the lower power studies are placed at the bottom.

RESULTS

Literature review

Figure 1 summarizes the search strategy carried out. Our search strategy identified approximately 720 articles. Of these, 390 duplicate articles were excluded. We also excluded 245 articles after screening the title and abstract. The full text of the remaining 85 articles was screened and 50 articles were further excluded due to lack of inclusion criteria and 35 articles were finally included in the study.

Study characteristics

We included 35 studies of CVDs in the Indian geriatric population in this meta-analysis. The included articles consisted of 32 studies based on male and female geriatric populations in India. Table 1 shows the characteristics of each study in our analysis after applying the exclusion criteria.

Meta-analysis

Meta-analysis of the prevalence of CVDs in the Indian geriatric population involved 6586 male subjects from 32 studies. The pooled estimate of prevalence of CVDs in the male geriatric population using the random effect model was 38.0% (95%CI: 33.0%-43.0%) (Table 2). Significant heterogeneity (I^2 = 95.0% and Cochran's Q = 621.09, P < 0.0001) among the 32 studies was found (Table 3). The forest plot (Figure 2) and the funnel plot (Figure 3) represent the proportion of subjects affected by CVDs in each study and the pooled estimate of the prevalence of CVDs in the male geriatric population, respectively.

Meta-analysis of the prevalence of CVDs in the female geriatric population included 8164 subjects from 32 studies. The pooled estimate of prevalence of CVDs in the female geriatric population using the random effect model was 40.9% (95%CI: 35.5%-46.2%) (Table 4). Significant heterogeneity (I^2 = 96.4% and Cochran's Q = 873.0, P < 0.0001) among the 32 studies was found (Table 5). The forest plot (Figure 4) and funnel plot (Figure 5) represent the proportion of subjects affected due to CVDs in each study and the pooled estimate of prevalence of CVDs in the female geriatric population, respectively.

DISCUSSION

CVD in the geriatric population is emerging as a major problem in India. In the present analysis, we attempted to provide an estimate of the pooled prevalence of CVDs among the Indian geriatric population along with the 95%CI. The estimated overall prevalence of CVDs in the Indian geriatric population was 36.6% (95%CI: 31.9%-41.3%).

The estimated prevalence of CVDs in the male geriatric population was 38.0% (95%CI: 33.0%-43.0%) which was less than the prevalence (46.9%) reported by Naushad *et al*[8] in Raipur, Chhattisgarh, India. The highest prevalence (64.2%) of CVDs in the male Indian geriatric population was observed by Hazarika *et al*[9]. Similar findings were reported by Lena *et al*[31] and Barman *et al*[3] in their respective studies. Rapid urbanization, lifestyle changes, dietary changes and increased life expectancy were factors attributed to this rising trend. The lowest prevalence (10.2%) of CVDs in the male Indian geriatric population was observed by Bardhan *et al*[10]. Chandrashekhar *et al*[1] also reported similar findings in their study in which the prevalence of CVDs in the geriatric population was 19.3%.

The estimated overall prevalence of CVDs in the female geriatric Indian population was 40.9% (95%CI: 35.5%-46.2%) which is higher than the prevalence (35.7%) reported by Shubha *et al*[11]. The highest prevalence (62.9%) of CVDs in the female Indian geriatric population was observed by Hazarika *et al*[9] Bharati *et al*[16], Joshi *et al*[25], Naushad *et al*[8] and Alam *et al*[12] who reported a similar high prevalence of CVDs in female subjects. The lowest prevalence (9.6%) was observed by Bardhan *et al*[10]. Studies by Banjare *et al*[14] and Shubha *et al*[11] also showed a similar pattern of low prevalence of CVDs in elderly female subjects.

The current statistics for CVDs show that almost 80% of premature heart attacks and strokes are preventable. The government should promote awareness of these diseases through mass media and other means and provide information on diet and physical health.

Conclusion

The present systematic review and meta-analysis demonstrated that the prevalence of CVDs in the male and female geriatric population in India was estimated to be 38.0% and 40.9%, respectively. These considerable prevalence rates require supportive interventions for the prevention and early diagnosis of CVDs in the geriatric population. It is imperative to provide geriatric health services at primary health

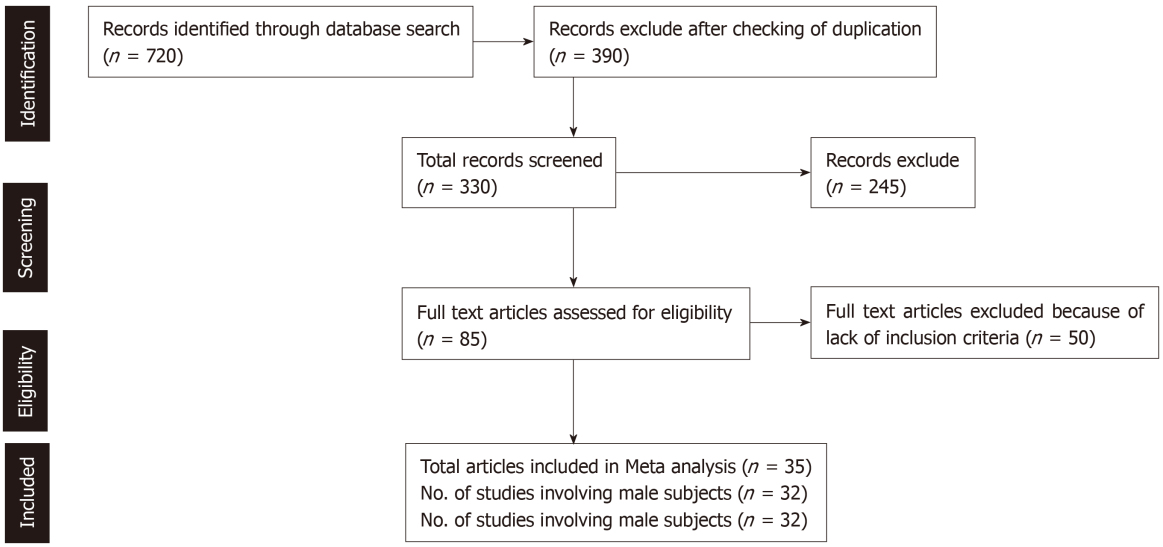

Figure 1 Flowchart showing the selection process of relevant studies.

centers in addition to increasing the awareness among elderly people of health, diseases and health care facilities in order to improve their quality of life.

Limitations

Given the limited amount of data available on the prevalence of CVDs in the geriatric population in India; studies conducted in subjects with different bio-social characteristics have been included in the meta-analysis. Also, the pooled estimate of prevalence of CVDs in the Indian geriatric population does not provide an overview of the problem of CVDs.

Implications for future research

The prevalence of CVDs in the Indian geriatric population presents a formidable challenge to the Indian health system. In future, researchers should identify the location- and age-specific pooled estimate of CVDs in the geriatric population of India. Other areas of research should include determination of the pooled prevalence of other morbidities such as diabetes, arthritis, *etc*. in the geriatric population.

Table 1 The characteristics of each study

Ref.	Study period	Study design	State	Sampling method	Age group	Sample size
Joshi *et al*[25]	2001	Cross-sectional	Haryana	Cluster sampling	≥ 60	200
Hazarika *et al*[9]	2002	Cross-sectional	Assam	Simple random sampling	≥ 60	888
Lena *et al*[31]	2003	Cross-sectional	Karnataka		≥ 60	213
Prakash *et al*[2]	2003	Cross-sectional	Rajasthan		≥ 60	300
Kishore *et al*[29]	2004	Cross-sectional	Uttarakhand		≥ 60	285
Khanam *et al*[28]	2004	Cross-sectional	Bangladesh	Simple random sampling	≥ 60	452
Bhatia *et al*[17]	2006	Cross-sectional	Haryana	Stratified random sampling	≥ 65	361
Chandrashekhar *et al*[1]	2008	Cross-sectional	Karnataka	Systematic random sampling	≥ 60	370
Bharati *et al*[16]	2008	Cross-sectional	Tamil Nadu	Simple random sampling	≥ 60	225
Bhatt *et al*[18]	2008	Cross-sectional	Gujarat	Simple random sampling	≥ 60	218
Jacob *et al*[23]	2010	Cross-sectional	Kerala	Cluster sampling	≥ 60	403
Sharma *et al*[36]	2010	Cross-sectional	Himachal Pradesh	Multistage simple random sampling	≥ 60	400
Ghosh *et al*[20]	2011	Cross-sectional	Bihar		≥ 60	431
Kamble *et al*[26]	2011	Cross-sectional	Maharashtra	Systematic random sampling	≥ 60	494
Qadri *et al*[33]	2011	Cross-sectional	Haryana	Simple random sampling	≥ 60	660
Banjare *et al*[14]	2012	Cross-sectional	Odisha	PPS, Systematic sampling	≥ 60	310
Dutta *et al*[19]	2012	Cross-sectional	Assam	Multistage sampling	≥ 60	370
Banjare *et al*[13]	2012	Cross-sectional	Odisha	Multistage simple random sampling	≥ 60	310
Barman *et al*[3]	2013	Cross-sectional	Bihar		≥ 60	160
Shubha *et al*[11]	2013	Cross-sectional	Karnataka	Simple random sampling	≥ 60	180
Karanth *et al*[27]	2013	Cross-sectional	Karnataka		≥ 60	500
Alam *et al*[12]	2014	Cross-sectional	Chhattisgarh	Multistage simple random sampling	≥ 60	640
Bardhan *et al*[10]	2014	Cross-sectional	Uttar Pradesh	Simple random sampling	≥ 60	980
Bartwal *et al*[15]	2014	Cross-sectional	Uttarakhand	Systematic sampling	≥ 60	440
Gupta *et al*[21]	2014	Cross-sectional	Punjab		≥ 60	534
Kumar *et al*[30]	2014	Cross-sectional	Uttar Pradesh	Stratified random sampling	≥ 60	402
Naushad *et al*[8]	2014	Cross-sectional	Chhattisgarh	Multistage simple random sampling	≥ 60	640
Jain *et al*[24]	2014	Cross-sectional	Maharashtra	PPS	≥ 60	600
Noor *et al*[32]	2014	Cross-sectional	Odisha	Simple random sampling	≥ 60	224
Venkateshkrishna *et al*[37]	2015	Cross-sectional	Karnataka		≥ 60	1452
Sahu *et al*[35]	2017	Cross-sectional	Uttar Pradesh		≥ 60	231
Reddy *et al*[34]	2017	Cross-sectional	Telangana	Systematic random sampling	≥ 60	1265
Gupta *et al*[22]	2018	Cross-sectional	Haryana	Simple random sampling	≥ 60	300

Table 2 Prevalence of cardiovascular diseases in the male Indian geriatric population

Ref.	*n*	Cases	Proportion	95%CI	W (Random) (%)
Joshi *et al*[25]	98	41	0.4184	[0.3195-0.5223]	3.0
Hazarika *et al*[9]	500	321	0.6420	[0.5982-0.6841]	3.3
Prakash *et al*[2]	190	84	0.4421	[0.3703-0.5158]	3.2
Kishore *et al*[29]	177	70	0.3955	[0.3229-0.4716]	3.1
Bhatia *et al*[17]	152	53	0.3487	[0.2733-0.4301]	3.1
Chandrashekhar *et al*[1]	181	35	0.1934	[0.1385-0.2585]	3.2
Lena *et al*[31]	92	53	0.5761	[0.4686-0.6785]	3.0
Bhatt *et al*[18]	74	19	0.2568	[0.1622-0.3716]	3.0
Bharati *et al*[16]	92	34	0.3696	[0.2712-0.4766]	3.0
Khanam *et al*[28]	204	74	0.3627	[0.2968-0.4328]	3.2
Kamble *et al*[26]	232	50	0.2155	[0.1644-0.2741]	3.2
Sharma *et al*[36]	196	64	0.3265	[0.2614-0.3970]	3.2
Qadri *et al*[33]	336	135	0.4018	[0.3489-0.4564]	3.2
Barman *et al*[3]	88	47	0.5341	[0.4246-0.6412]	2.9

Banjare *et al*[13]	153	40	0.2614	[0.1938-0.3385]	3.2
Noor *et al*[32]	132	62	0.4697	[0.3823-0.5585]	3.1
Ghosh *et al*[20]	196	96	0.4898	[0.4179-0.5620]	3.2
Kumar *et al*[30]	190	66	0.3474	[0.2799-0.4197]	3.2
Bardhan *et al*[10]	293	30	0.1024	[0.0702-0.1429]	3.3
Dutta *et al*[19]	162	57	0.3519	[0.2786-0.4307]	3.1
Banjare *et al*[14]	153	40	0.2614	[0.1938-0.3385]	3.2
Shubha *et al*[11]	42	15	0.3571	[0.2155-0.5197]	2.6
Alam *et al*[12]	267	113	0.4232	[0.3632-0.4849]	3.2
Gupta *et al*[21]	244	94	0.3852	[0.3239-0.4495]	3.2
Bartwal *et al*[15]	187	77	0.4118	[0.3405-0.4859]	3.2
Naushad *et al*[8]	241	113	0.4689	[0.4045-0.5340]	3.2
Jain *et al*[24]	262	133	0.5076	[0.4454-0.5697]	3.2
Venkateshkrishna *et al*[37]	530	145	0.2736	[0.2360-0.3137]	3.3
Sahu *et al*[35]	61	15	0.2459	[0.1446-0.3729]	2.9
Jacob *et al*[23]	135	77	0.5704	[0.4824-0.6552]	3.1
Reddy *et al*[34]	594	191	0.3215	[0.2841-0.3608]	3.3
Gupta *et al*[22]	132	59	0.4470	[0.3604-0.5359]	3.1

Table 3 Tests of heterogeneity among studies of the male Indian geriatric population

Test of heterogeneity	Prevalence	LCI 95%	HCI 95%
Pooled Statistics	0.38	0.33	0.43
Heterogeneity	4.48	4.02	4.98
I-squared	95.0	93.8	96.0
Cochran's Q	621.09		
χ^2, *P* value	0.0001		
τ^2	0.0197		

Table 4 Prevalence of cardiovascular diseases in the female Indian geriatric population

Study name	N	Cases	Proportion	95%CI	%W (Random)
Joshi *et al*[25]	102	57	0.5588	[0.4571-0.6571]	3.0
Hazarika *et al*[9]	388	244	0.6289	[0.5787-0.6771]	3.2
Prakash *et al*[2]	110	60	0.5455	[0.4477-0.6407]	3.0
Kishore *et al*[29]	108	48	0.4444	[0.3488-0.5432]	3.0
Bhatia *et al*[17]	209	97	0.4641	[0.3950-0.5342]	3.1
Chandrashekhar *et al*[1]	189	30	0.1587	[0.1097-0.2188]	3.2
Lena *et al*[31]	121	73	0.6033	[0.5104-0.6911]	3.0
Bhatt *et al*[18]	144	56	0.3889	[0.3088-0.4736]	3.1
Bharati *et al*[16]	122	68	0.5574	[0.4647-0.6472]	3.0
Khanam *et al*[28]	248	101	0.4073	[0.3455-0.4712]	3.2
Kamble *et al*[26]	262	69	0.2634	[0.2111-0.3211]	3.2
Sharma *et al*[36]	204	98	0.4804	[0.4101-0.5513]	3.1
Qadri *et al*[33]	324	159	0.4907	[0.4351-0.5466]	3.2
Barman *et al*[3]	72	34	0.4722	[0.3533-0.5935]	2.9

Noor *et al*[32]	92	46	0.5000	[0.3939-0.6061]	2.9
Ghosh *et al*[20]	235	82	0.3489	[0.2881-0.4136]	3.2
Kumar *et al*[30]	212	71	0.3349	[0.2717-0.4028]	3.1
Bardhan *et al*[10]	197	19	0.0964	[0.0591-0.1465]	3.2
Dutta *et al*[19]	208	77	0.3702	[0.3044-0.4397]	3.1
Banjare *et al*[14]	157	20	0.1274	[0.0796-0.1899]	3.2
Shubha *et al*[11]	138	19	0.1377	[0.0850-0.2066]	3.2
Alam *et al*[12]	373	207	0.5550	[0.5029-0.6061]	3.2
Karanth *et al*[27]	500	130	0.2600	[0.2221-0.3008]	3.2
Gupta *et al*[21]	290	158	0.5448	[0.4856-0.6031]	3.2
Bartwal *et al*[15]	253	99	0.3913	[0.3308-0.4544]	3.2
Naushad *et al*[8]	369	207	0.5610	[0.5087-0.6123]	3.2
Jain *et al*[24]	338	144	0.4260	[0.3727-0.4807]	3.2
Venkateshkrishna *et al*[37]	922	402	0.4360	[0.4037-0.4687]	3.2
Sahu *et al*[35]	170	52	0.3059	[0.2376-0.3811]	3.1
Jacob *et al*[23]	268	124	0.4627	[0.4018-0.5244]	3.2
Reddy *et al*[34]	671	193	0.2876	[0.2536-0.3235]	3.2
Gupta *et al*[22]	168	88	0.5238	[0.4455-0.6013]	3.1

Table 5 Tests of heterogeneity among studies of the female Indian geriatric population

Tests of heterogeneity	Prevalence	LCI 95%	HCI 95%
Pooled Statistics	0.409	0.355	0.462
Heterogeneity	5.31	4.82	5.84
I-squared	96.4	95.7	97.1
Cochran's Q	873.0		
χ^2, *P* value	0.0001		
τ^2	0.0229		

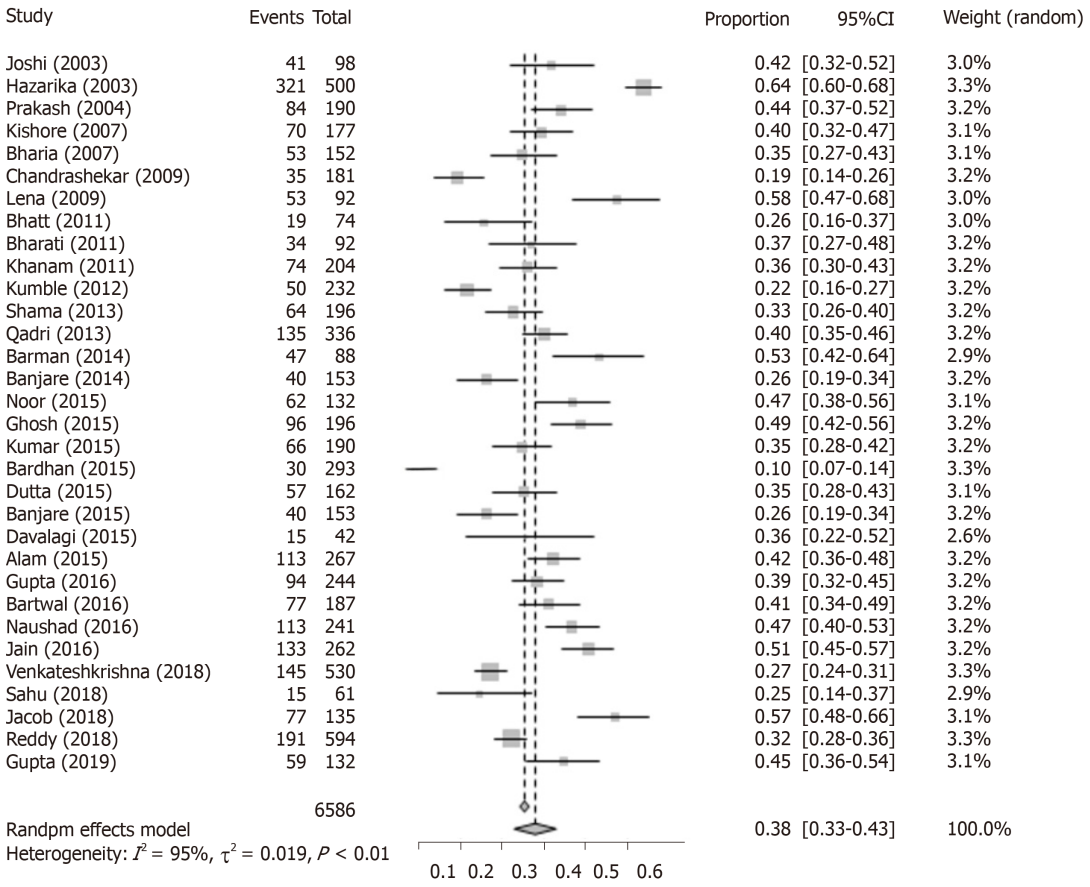

Figure 2 Forest plot of the meta-analysis of cardiovascular disease prevalence in the male Indian geriatric population.

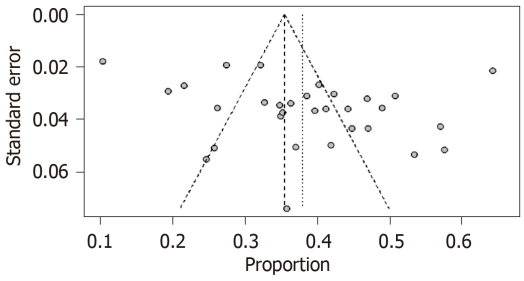

Figure 3 Funnel plot showing publication bias in the meta-analysis of the prevalence of cardiovascular diseases in the male Indian geriatric population.

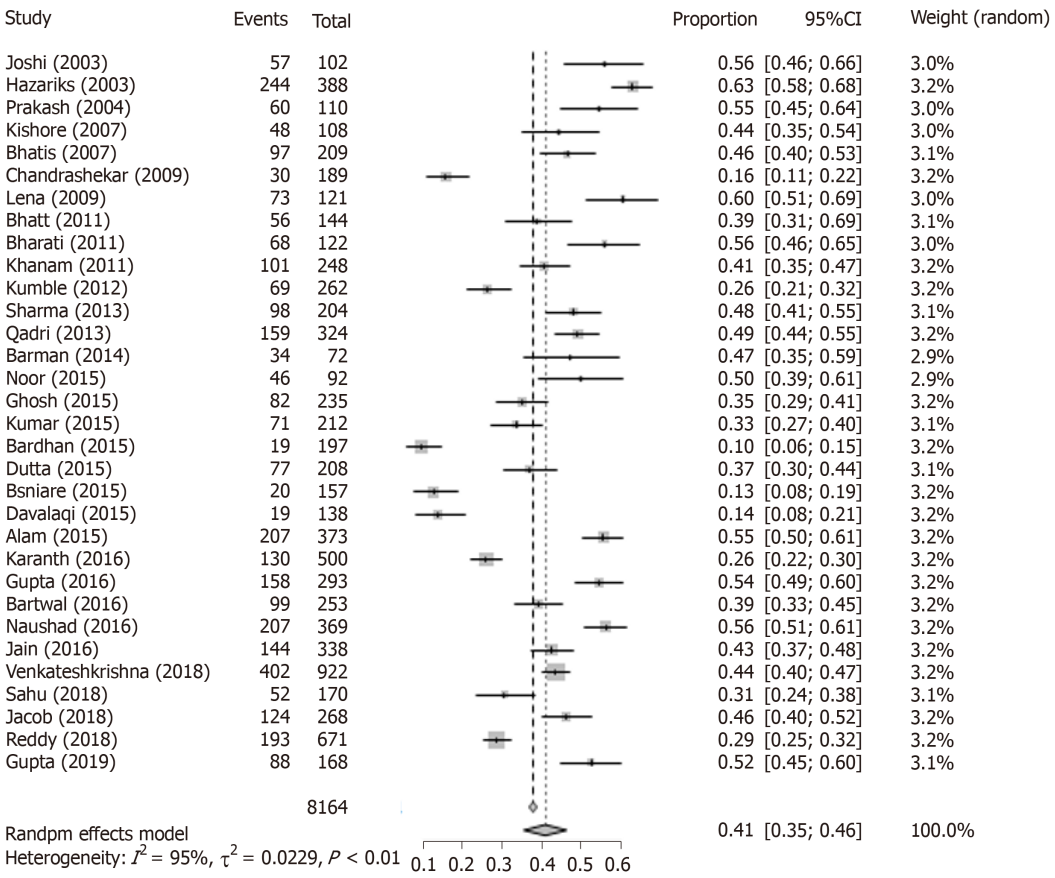

Figure 4 Forest plot of the meta-analysis of cardiovascular disease prevalence in the female Indian geriatric population.

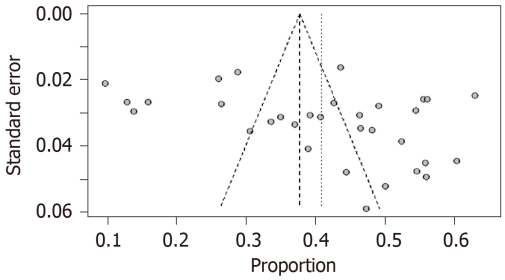

Figure 5 Funnel plot showing publication bias in the meta-analysis of prevalence of cardiovascular diseases in the female Indian geriatric population.

ARTICLE HIGHLIGHTS

Research background

India is in the phase of demographic transition. From the 2011 census, there are 104 million elderly persons in India as compared with 57 million elderly persons in 1991. The elderly are exposed to several morbidities such as cardiovascular diseases (CVDs), diabetes, hypertension, *etc*. CVDs have become the leading cause of mortality in India. An estimated 17.7 million people in India will die from CVDs representing 31% of all global deaths. Therefore, a precise estimate of the prevalence of CVDs in elderly males and females in India is required to assess the magnitude of the problem which needs to be addressed.

Research motivation

Very few studies are available on the prevalence of CVDs in India. The gender pooled estimate of CVDs from various studies conducted in different regions of the country can aid the development of preventive strategies. The difference in the prevalence of CVDs among male and female geriatric subjects was studied to provide an insight into the type of preventive and promotional services required.

Research objectives

The main objective of the study was to provide the gender pooled estimate of the prevalence of CVDs in the geriatric population of India. The large increase in the prevalence of CVDs in the Indian geriatric population has prompted health managers to take immediate steps for the prevention and early detection of these diseases. In addition, researchers are attempting to identify the location- and age-specific pooled estimate of the prevalence of CVDs. The main application of this meta-analysis is to consolidate the available data to determine the burden of CVDs in India.

Research methods

Secondary data related to the prevalence of CVDs in the geriatric population were collected from published research papers and then analyzed using meta-analysis in R software. A meta-analysis integrates the quantitative findings from separate studies and provides a numerical estimate of the overall effect of interest.

Research results

The overall prevalence of CVDs in the Indian geriatric population was estimated to be 36.6% (95%CI: 31.9%-41.3%). The prevalence of CVDs in the male geriatric population was 38.0%, whereas the prevalence of CVDs in the elderly female population was 40.9%.

Research conclusions

The pooled prevalence of CVDs in the female Indian geriatric population was greater than the pooled prevalence of CVDs in the male Indian population. These findings will help policy makers to take immediate steps to provide geriatric health care services in India. It is possible that an insight into the magnitude of the problem of CVDs can help to shape preventive programs for CVDs.

Research perspective

Future studies should be conducted to determine the pooled estimate of CVDs in the geriatric population in both rural and urban areas, and in different age-groups. Subgroup analysis in meta-regression can be used to calculate these values.

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World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2020 February 28; 8(1): 27-40

DOI: 10.13105/wjma.v8.i1.27

ISSN 2308-3840 (online)

META-ANALYSIS

Long-term efficacy of capecitabine plus oxaliplatin chemotherapy on stage III colon cancer: A meta-analysis

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Conflict-of-interest statement: The authors have no conflicts of interest for this manuscript.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Many clinical studies for the long-term survival or efficacy of capecitabine plus oxaliplatin (XELOX) in colon cancer have already been studied, but its clinical benefit is controversial.

AIM

To evaluate the long-term efficacy of XELOX regimen in comparison with other adjuvant chemotherapy protocols in colon cancer.

METHODS

By searching the PubMed, EMBASE and Cochrane databases, a total of 12 randomized controlled trials involving 6698 stage III colon cancer cases (XELOX protocol: n = 3298 cases; other adjuvant chemotherapy protocol: n = 3268 cases) were included. The parameter outcomes included the overall survival and the disease-free survival. The quality control of selected literature was based on the Jadad scale and the GRADE system.

RESULTS

In comparison to other adjuvant chemotherapy regimen, XELOX regimen showed a better overall survival (odds ratio = 1.29, 95% confidence interval: 1.15-1.44, $P < 0.0001$) and a better disease-free survival (odds ratio = 1.32, 95% confidence interval: 1.18-1.46, $P < 0.0001$) for colon cancer patients, suggesting the

Manuscript source: Unsolicited manuscript

Received: June 22, 2019
Peer-review started: June 24, 2019
First decision: August 27, 2019
Revised: September 26, 2019
Accepted: October 20, 2019
Article in press: October 20, 2019
Published online: February 28, 2020

P-Reviewer: Jeong KY, Ogino S
S-Editor: Dou Y
L-Editor: Filipodia
E-Editor: Qi LL

XELOX regimen can be a good option for postoperative treatment of stage III colon cancer.

CONCLUSION

The XELOX regimen can be a preferred option for adjuvant treatment of stage III colon cancer after surgery.

Key words: Capecitabine plus oxaliplatin chemotherapy; Colon cancer; Meta-analysis; Long-term effect

Core tip: Many clinical studies for the long-term survival of patients or the efficacy of capecitabine plus oxaliplatin (XELOX) in colon cancer have already been studied, but its clinical benefit is controversial. The long-term efficacy of the XELOX regimen in comparison with other adjuvant chemotherapy protocols in colon cancer was evaluated. By searching the PubMed, EMBASE and Cochrane databases, a total of 12 randomized controlled trials involving 6698 stage III colon cancer cases were included. Our findings showed that XELOX regimen had a better overall survival and a better disease-free survival. The XELOX regimen can be a preferred option for adjuvant treatment of stage III colon cancer after surgery.

Citation: Fu HT, Xu YY, Tian JJ, Fu JX, Nie SL, Tang YY, Chen P, Zong L. Long-term efficacy of capecitabine plus oxaliplatin chemotherapy on stage III colon cancer: A meta-analysis. *World J Meta-Anal* 2020; 8(1): 27-40
URL: https://www.wjgnet.com/2308-3840/full/v8/i1/27.htm
DOI: https://dx.doi.org/10.13105/wjma.v8.i1.27

INTRODUCTION

Colorectal cancer (CRC) accounts for 9% of all cancers worldwide. It is the second most common cancer in women and the third most frequent cancer in men. More than 70% of the deaths associated with CRC are caused by metastasis to the liver. Although surgery may be potentially curable, less than 25% of cases can be managed with a recurrence rate of up to 70%[1]. The purpose of colon cancer treatment is to cure locally and to prevent metastasis and recurrence. Therefore, in the local excision of colon cancer at the same time, the treatment should be according to individual condition, and chemotherapy is an important method that is based on the patient's condition, surgical situation and clinical stage of appropriate postoperative adjuvant chemotherapy.

Many clinical studies for the long-term survival benefit or efficacy of capecitabine plus oxaliplatin (XELOX) in colon cancer have already been studied[2-4], but its clinical benefit is controversial[5]. Since the 1990s, the introduction of irinotecan or oxaliplatin has extended the spectrum of therapeutic options. The combination of oxaliplatin or irinotecan with 5-fluorouracil (5-FU) plus leucovorin (LV or FA) has been considered the standard regimen for first-line treatment of metastatic CRC. However, this is an inconvenient therapeutic option due to the requirement for continuous vascular infusion of 5-FU. A retrospective study on XELOX plus bevacizumab *vs* LV plus 5-FU plus irinotecan (also known as FOLFIRI) plus bevacizumab treatment for metastatic colon cancer reported that XELOX plus bevacizumab was more effective in response rate and overall survival (OS) compared with LV plus 5-FU plus irinotecan plus bevacizumab[6].

Capecitabine is an orally administered fluoropyrimidine that was rationally designed to generate 5-FU preferentially at the tumor site. Capecitabine demonstrated a safety profile superior to that of 5-FU/LV, with a significantly lower incidence of diarrhea, stomatitis, nausea, alopecia and grade 3/4 neutropenia. Also, oral administration of capecitabine simplifies chemotherapy and provides convenient outpatient therapy. Because capecitabine has been adopted as a substitute for infused 5-FU/LV to overcome the inconvenience of 5-FU, subsequent data have found XELOX (also known as CAPOX) to be a comparable therapeutic regimen to infused 5-FU/LV plus oxaliplatin (known as FOLFOX-4 or FUOX). In the Loree *et al*[7] study,

XELOX and FOLFOX were compared in the treatment of colon cancer. The results showed that XELOX may be associated with improved disease-free survival (DFS) despite greater toxicities and reduced adjuvant chemotherapy duration to 3 mo. In a safety analysis of adjuvant chemotherapy for stage III colon cancer after radical resection of stage III colon cancer, mFOLFOX6/XELOX regimens are acceptable[8].

Randomized phase III trials demonstrated that outcomes using first-line XELOX are comparable with those achieved using continuous infusion of 5-FU and FOLFOX. There are many chemotherapy options for advanced CRC, and the long-term benefit is uncertain. Combining XELOX is advantageous for the reasons as follows: Synergistic effects, no overlapping toxicities, easy to administer and outpatient management[9-12]. XELOX has been studied extensively in rectal cancer where the standard therapy is XELOX plus radiation therapy. To determine the efficacy of XELOX in colon cancer, the long-term efficacy of capecitabine combined with oxaliplatin (XELOX regimen) in comparison with other adjuvant chemotherapy protocols was evaluated.

MATERIALS AND METHODS

This meta-analysis is in terms of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 declaration.

Search strategy

Two researchers independently retrieved randomized controlled trials (RCT) articles involved in oxaliplatin combined with capecitabine in CRC published in PubMed, EMBASE, Cochrane, web of science, clinical trial and China National Knowledge Infrastructure databases from 1991 to August 2017. The retrieval languages were Chinese and English. The retrieval was performed using the following keywords. English search terms for: (PubMed): Search (((Colonic Neoplasms [MeSH Terms]) OR ((((((((((Colonic Neoplasm [Title/Abstract]) OR Colon Neoplasm* [Title/Abstract]) OR Neoplasm*, Colonic) OR Neoplasm*, Colon [Title/Abstract]) OR Cancer of Colon [Title/Abstract]) OR Cancer of the Colon [Title/Abstract]) OR Colonic Cancer* [Title/Abstract]) OR Cancer*, Colonic [Title/Abstract]) OR Colon Cancer* [Title/Abstract]) OR Cancer*, Colon [Title/Abstract])))) AND ((((((((((ECX) [Title/Abstract] OR XELOX) [Title/Abstract] OR Xeloda) [Title/Abstract] OR Capecitabine [Title/Abstract])) ORN (4) - pentyloxycarbonyl – 5′ - deoxy- 5-fluorocytidine [Title/Abstract]) OR Capecitabine)) OR Capecitabine [MeSH Terms]) AND (((oxaliplatin [MeSH Terms]) OR oxaliplatin [Title/Abstract]) OR ((((((((((((((((1, 2 - diamminocyclohexane (trans-1) oxolatoplatinum (II) [Title/Abstract]) OR oxalato-(1,2-cyclohexanediamine) platinum II [Title/Abstract]) OR L-OHPcpd [Title/Abstract]) OR oxaliplatine [Title/Abstract]) OR1,2-diaminocyclohexane platinum oxalate [Title/Abstract]) OR platinum (II)-1,2-cyclohexanediamine oxalate [Title/Abstract]) OR cis-oxalato-(trans-l)-1,2-diaminocyclohexane - platinum (II) [Title/Abstract]) ORoxaliplatin, (SP-4-3-(cis))-isomer [Title/Abstract]) OR oxaliplatin, (SP-4-2-(1R-trans)) - isomer [Title/Abstract]) OR oxaliplatin, (SP - 4 - 2 - (1S-trans)) - isomer [Title/Abstract]) OR ACT-078 [Title/Abstract]) OR ACT-078 [Title/Abstract]) OR Eloxatine [Title/Abstract]) OR Sanofi Synthelabo brand of oxaliplatin [Title/Abstract]) OR Sanofi brand of oxaliplatin [Title/Abstract]) OR Eloxatin [Title/Abstract]))))). Chinese search terms for: Capecitabine, oxaliplatin, XELOX, colon cancer.

Selection criteria

Literature was retrieved and screened in accordance with the PRISMA guidelines. Two reviewers independently screened literature and abstracts based on predefined inclusion and exclusion criteria and screened the full text if necessary. In the literature that met the inclusion criteria, two reviewers used a unified data extraction table to independently extract data. Disagreements were resolved through consultation or by a third researcher.

Inclusion criteria

The inclusion criteria was: (1) Experimental design for RCT; (2) The research object for the pathological diagnosis of patients with CRC; (3) The experimental group intervention for capecitabine combined with oxaliplatin, the control group for other chemotherapeutic drugs; (4) Observation results for patients with long-term efficacy: OS and DFS; (5) If the study included many cases, then only select the required part; and (6) The selected patients were stage III colon cancer patients and had undergone surgery without neoadjuvant chemotherapy.

Exclusion criteria

Studies were excluded if: (1) Non-RCT; (2) Subjects included rectal cancer; (3) DFS or OS was not compared with two chemotherapy regimens in the same trial; (4) No specific data were provided; and/or (5) Repeated publication.

Data extraction

Data for each article was extracted, including the first author and title of the RCT, sample size, follow-up time, publication time, medication regimen, DFS and OS.

Methodological quality and statistical analysis of the RCTs were evaluated with the following criteria. The offset assessment of a single study was evaluated by two independent researchers. Any disagreements were evaluated by a third researcher. Quality evaluation mainly included random sequence generation, randomization concealment, blindness, withdrawal and withdrawal, and the Jadad scale was used to evaluate the score. We defined 1-3 points as low quality and 4-7 points as high quality. At the same time, the meta-analysis software Review Manager Version 5.3 recommended by the Cochrane library was used to test the heterogeneity and calculate the combination of odds ratio (OR) value and 95% confidence interval (CI).

Statistical detection of P values less than 0.05 were considered statistically significant. The heterogeneity of the study was determined by the t test and the I^2 test. The unified random effect model was used for consolidation. $I^2 < 50\%$ were considered as no statistical heterogeneity among the studies, and a random effect model was used to merge effects. Conversely, the random effect model was used to combine the effects. The output combined the OR value and the 95%CI and tests the merging statistic. The Z test was used. The test level was $\alpha = 0.05$.

Sensitivity analysis

Sensitivity analysis included a sensitivity analysis performed in subgroup analyses. If a document was excluded and the impact on the overall outcome was greater, then the literature was reread and the quality was evaluated. Then it was determined whether it was eventually incorporated.

Methodological quality

The literature was included and the GRADE system was used to assess methodological quality. In order to thoroughly reveal the source of heterogeneity, we also conducted meta regression and subgroup analysis. In addition, the funnel plot and application of shear reinforcing method (if the funnel plot was asymmetric or incomplete, then there was publication bias, and shear reinforcing method was applied; symmetry indicates that the publication bias is less likely without using the shear reinforcing method). Begg's funnel plots and Egger's tests were conducted to assess potential publication bias. Data analysis was performed using Stata 12.0 edition.

RESULTS

After searching the database, 360 documents were selected. Eighteen repetitive documents were excluded. After reading the title and abstract, 285 papers were excluded from the study of capecitabine combined with oxaliplatin compared with other drugs that affect colon cancer. After reading the full text, 41 articles were excluded because they did not involve relevant outcome indicators. Two articles were excluded because there were no relevant data, and two articles in the control group did not meet the inclusion criteria. Finally, 12 articles met the requirements[13-24] (Figure 1).

Data and quality evaluation were included in a clinical controlled trial (Table 1).

Statistical analysis

OS: The meta-analysis obtained OS data from 11 articles. Finally, ten papers were included. The combined analysis showed that the XELOX group had longer OS compared with other chemotherapy groups (Figure 2A). The study has statistical significance (OR = 1.29, 95%CI: 1.15-1.44, $P < 0.0001$). There was no heterogeneity among the study sites ($P = 0.46$, $I^2 = 0\%$).

Results of the OS subgroup analysis (subgroup analysis of different follow-up visits) (Figure 3): Annual survival was statistically significant: (OR = 1.70, 95%CI: 1.13-2.56, $P = 0.01$). There was no heterogeneity in the study ($P = 0.66$, $I^2 = 0\%$). The 2-year survival rate was statistically significant: (OR = 3.30, 95%CI: 1.37-7.97, $P = 0.01$). There was no heterogeneity in the study ($P = 0.99$, $I^2 = 0\%$). The 3-year survival rate was not statistically significant: (OR = 0.97, 95%CI: 0.56-1.69, $P = 0.93$). There was no heterogeneity in the study ($P = 0.93$, $I^2 = 0\%$). The 7-year survival rate was statistically

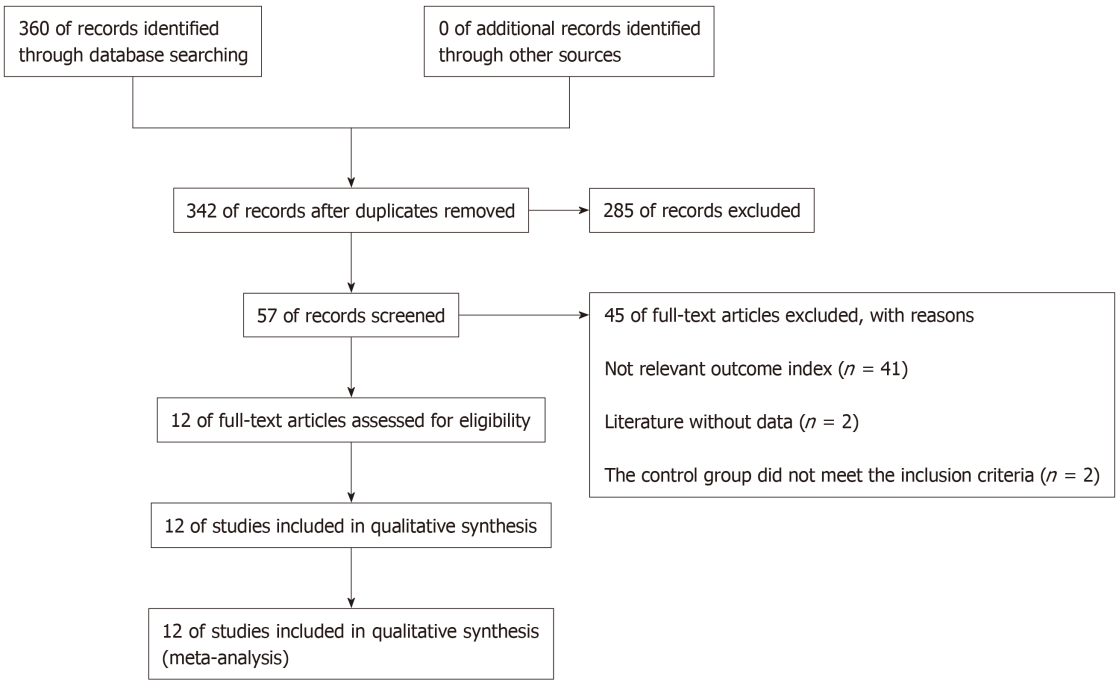


Figure 1 Flow chart of the 12 articles that met the inclusion criteria.

significant (OR = 1.30, 95%CI: 1.13-1.50, P = 0.0003). There was no heterogeneity in the study (P = 0.75, I^2 = 0%).

Results of the OS subgroup analysis (XELOX *vs* other chemotherapy groups) (Figure 4A): XELOX *vs* FU/FA: The study was statistically significant: (OR = 1.24, 95%CI: 1.07-1.44, P = 0.005). There was no heterogeneity in the study (P = 0.73, I^2 = 0%). XELOX *vs* FOLFOX: The study was statistically significant: (OR = 1.29, 95%CI: 1.07-1.55, P = 0.008). There was no heterogeneity in the study (P = 0.32, I^2 = 0%). XELOX *vs* capecitabine: The study was statistically significant: (OR = 1.28, 95%CI: 1.14-1.44, P = 0.008). There was no heterogeneity in the study (P = 0.99, I^2 = 0%).

DFS: In this meta-analysis, DFS data were obtained in five articles, and four articles were finally included. The combined analysis showed that the XELOX group had longer DFS compared with other chemotherapy groups (Figure 2B). The study had significant statistical significance (OR = 1.32, 95%CI: 1.18-1.46, P < 0.0001). There was no heterogeneity in the study (P = 0.68, I^2 = 0%).

Results of the DFS subgroup analysis (XELOX and other chemotherapy drug groups (Figure 4B): XELOX *vs* FU/FA: DFS had significant statistical significance: (OR = 1.34, 95%CI: 1.17-1.53, P < 0.0001). There was no heterogeneity among the study sites (P = 0.94, I^2 = 0%). XELOX *vs* FOLFOX: DFS had statistical significance: (OR = 1.28, 95%CI: 1.08-1.53, P = 0.004). There was low heterogeneity among the studies (P = 0.24, I^2 = 27%).

Process of deflection analysis

Included 11 articles from OS meta-analysis: There was statistical significance (P = 0.004) with moderate heterogeneity in this meta-analysis (P = 0.007, I^2 = 59%) **(**Figure 5A**)**.

Articles were included in the DFS meta-analysis: There was statistical significance (OR = 1.24, 95%CI: 1.04-1.46, P = 0.01) with moderate heterogeneity in this meta-analysis (P = 0.09, I^2 = 51%) **(**Figure 5B**)**. In its subgroup analysis, there was statistical significance (P = 0.02) with high heterogeneity in this meta-analysis (P = 0.02, I^2 = 73%) (Figure 5C).

The sources of heterogeneity

Sensibility analysis 1: There was heterogeneity in the article published by Zhang *et al*[15] (Figure 2A). After evaluating the article, the quality was low and samples were excluded. After exclusion (OR = 1.29, 95%CI: 1.15-1.44, P < 0.0001), there was no heterogeneity among the studies (P = 0.46, I^2 = 0%).

Sensibility analysis 2: The sensitivity analysis (Figure 2B) showed heterogeneity in

Table 1 Data and quality evaluation of clinical controlled trials

Study	Year	T event	T no event	T total	C event	C no event	C total	Outcome	The Jadad score
Haller *et al*[14]	2011	643	295	938	573	353	926	DFS	7
		741	197	938	701	225	926	OS	
Kubicka *et al*[16]	2016	541	320	861	482	379	861	DFS	7
		619	242	861	575	286	861	OS	
Pectasides *et al*[20]	2014	169	44	213	160	41	201	DFS	6
		185	28	213	175	26	201	OS	
Schmoll *et al*[22]	2012	594	350	944	527	415	942	DFS	7
		689	255	944	631	311	942	OS	
Diao *et al*[13]	2008	47	24	71	69	18	87	DFS	2
Xun *et al*[21]	2016	9	21	30	3	25	28	OS	3
Song *et al*[23]	2016	63	10	73	49	6	55	OS	3
Lei *et al*[17]	2016	5	16	21	2	19	21	OS	4
Li *et al*[18]	2012	43	17	60	32	28	60	OS	3
Lian *et al*[19]	2016	2	54	56	2	48	50	OS	4
Zhang *et al*[15]	2011	20	5	25	3	22	25	OS	2
Wang *et al*[24]	2011	8	22	30	3	27	30	OS	3

OS: Overall survival; DFS: Disease-free survival.

the article from Diao *et al*[13]. After evaluating the article, the quality was low and samples were excluded. After exclusion (OR = 1.32, 95%CI: 1.18-1.46, $P < 0.0001$), there was no heterogeneity among the studies ($P = 0.68$, $I^2 = 0\%$). After completely excluding Diao *et al*[13], the study remained statistically significant ($P = 0.004$), and the heterogeneity of the study was greatly reduced ($P = 0.24$, $I^2 = 27\%$) (Figure 4B).

Bias detection of OS: The funnel plot was conducted to evaluate the publication bias. However, we did not observe clear asymmetry suggesting the results from this study are reliable (data not shown).

DISCUSSION

Li *et al*[18] reported that in elderly CRC patients (age above 70-years-old), a reduction in chemotherapy dose did not decrease the DFS with a benefit of less mortality. But, elderly patients receiving 50% of planned cycles had shorter DFS and higher CRC mortality than elderly patients receiving the full planned cycles[25]. Therefore, a reduced dose but full cycles should be considered for elderly CRC patients. Our results are consistent with Kim *et al*[26] who found that OS was better in patients receiving at least 75% of expected cycles, but a dose reduction did not affect OS. These results suggest that a primary dose reduction in elderly patients may reduce the side effects of chemotherapeutics and help them finish the full planned cycles. The choice between mFOLFOX6 and XELOX should be discussed based on the gene subtypes of colon cancer[27-36].

It is well known that the prognosis of CRC patients has significant association with gene mutations. It is generally accepted that dMMR confers favorable prognosis in patients with resected colon cancer[10,11]. Sinicrope *et al*[12,37] found that *KRAS* mutations were associated with adverse prognosis specifically in pMMR tumors, while Blons *et al*[38] showed that *KRAS* mutations conferred shorter DFS in patients with left colon primaries.

Patients with poor compliance may affect the accuracy of the results[39]. Cancer patients are generally expected to have higher adherence to treatment than other patients because they are highly motivated by the gravity of their disease[40,41]. However, studies have shown cancer patients to have similar adherence rates to patients with other diseases[42-45]. Treatment duration plays a role in adherence to the regimen: when medication is continued over a longer period of time, patients become less adherent[46].

For oral cytotoxic agents, which require close monitoring of side effects and regular patient visits. There is no gold-standard measurement, and all methods have limitations[42,47]. Previous studies of oral cytotoxic chemotherapeutic drugs have

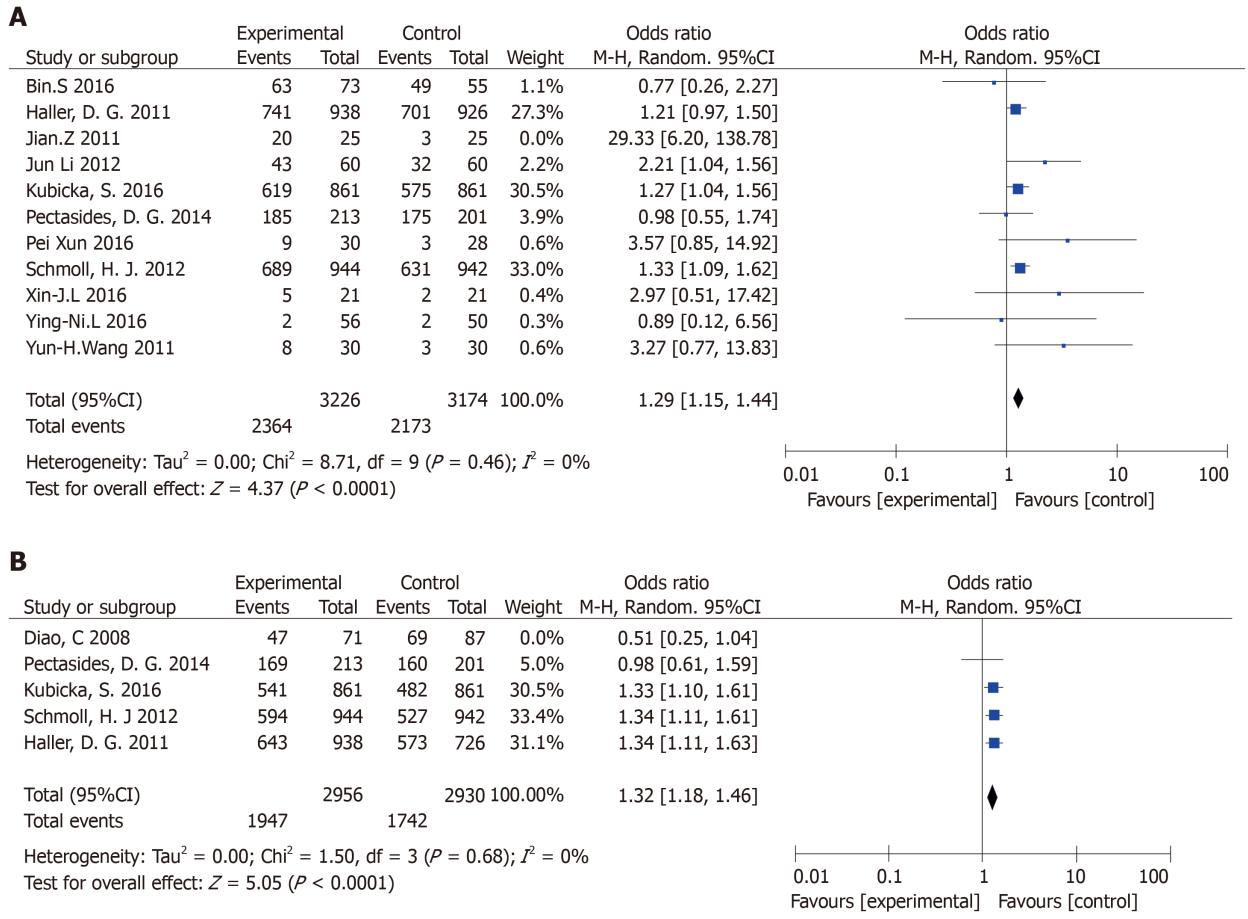


Figure 2 The combined analysis. A: The capecitabine plus oxaliplatin (XELOX) group had longer overall survival compared with other chemotherapy groups; B: The XELOX group had longer disease-free survival compared with other chemotherapy groups.

mainly used self-reported questionnaires[48], which tend to overestimate adherence because patients are inclined to over-report to please their doctors.

The side effects of commonly used adjuvant chemotherapy regimens FOLFOX is more serious[49]. The annoying neurotoxicity side effect of FOLFOX appears at the 8-10th cycle of administration. This time period is the critical time to gain or lose survival benefits. Although treatment series of fewer cycles showed some potential to ameliorate this neurotoxicity[50,51], recent studies failed to show any convincing benefit[52-55], even on a molecular basis[56]. It is still a challenge to be solved. Any "wait and go" policy to reduce side effects needs to be evaluated in a larger cohort of patients[57].

To our knowledge, many studies have indicated that monocyte count is associated with poor survival in patients with many types of cancer, but the potential mechanisms remain unknown[58]. Low monocyte to lymphocyte ratio (MLR) level may help improve the demographic and clinicopathological characteristics[59]. We found that low MLR, low monocyte and high lymphocyte were all associated with better prognosis in advanced gastric cancer patients. Meanwhile, our study indicated that low level MLR and low level neutrophil or high level lymphocyte correlated with better median DFS and OS for all patients. The 5-year DFS and OS rates of patients with low level MLR were higher than those with high level MLR[58,60-67]. We speculate that there may be similar mechanisms in CRC.

Nowadays, tumor molecular pathology assessment serves as a regular part of clinical practice. Treatment effect is unlikely uniform across different molecular subtypes. Molecular pathological epidemiology is an integrative science to determine the molecular pathology in relation to clinical features and outcome in patients and populations. Molecular pathological epidemiology will be a future direction for personal treatment[68,69].

In this study, some of the non-English articles were not included because of the low assessed quality. Secondly, a limited number of RCT trials and small number of included patients may limit the conclusion of this study. Finally, a diversity in genetics, tumor staging and XELOX dose may also influence the results. Therefore,

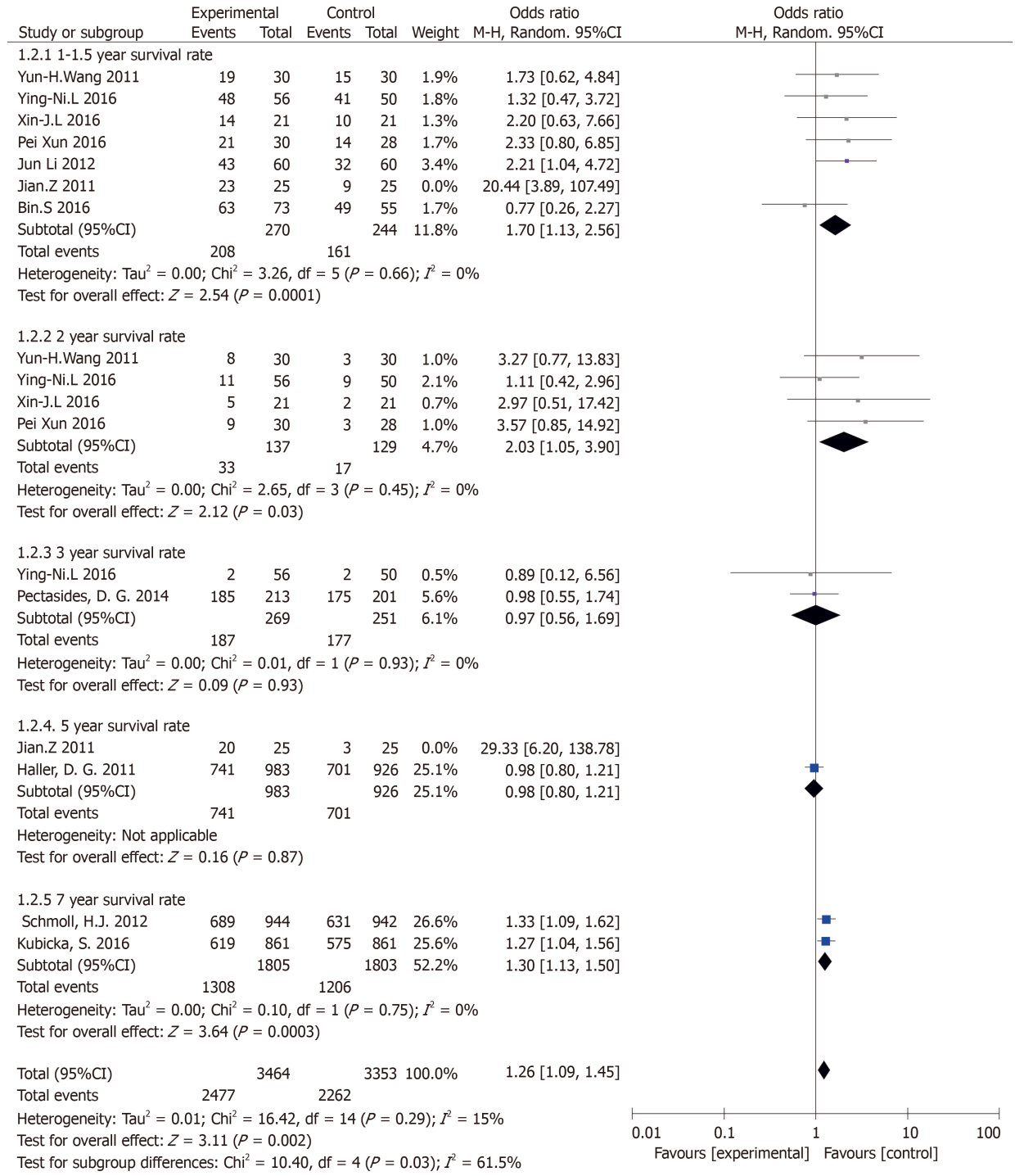


Figure 3 Results of the overall survival subgroup analysis (subgroup analysis of different follow-up visits).

our conclusion needs to be further validated by a large RCT trial in the future.

In conclusion, the XELOX regimen is recommended for stage III colon cancer after surgery.

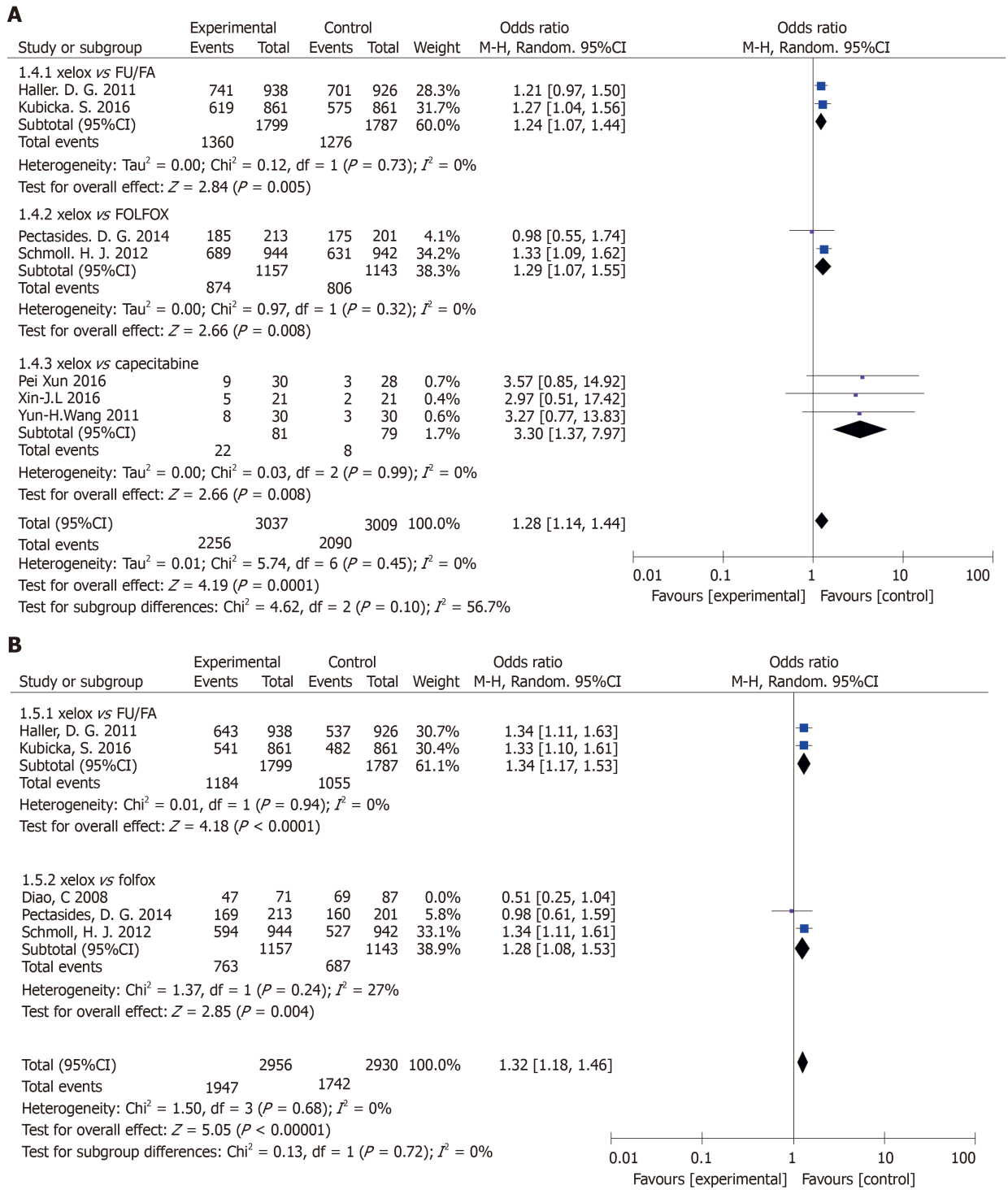
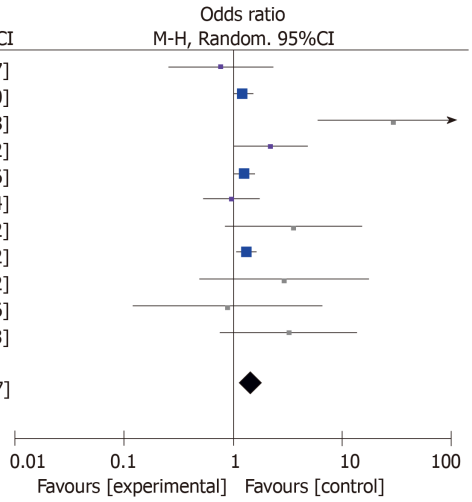


Figure 4 Subgroup analysis of overall survival and disease-free survival [capecitabine plus oxaliplatin (XELOX) *vs* other chemotherapy groups]. A: The capecitabine plus oxaliplatin (XELOX) group had longer overall survival compared with other chemotherapy groups; B: The XELOX group had longer disease-free survival compared with other chemotherapy groups.

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random. 95%CI
Bin.S 2016	63	73	49	55	4.5%	0.77 [0.26, 2.27]
Haller, D. G. 2011	741	938	701	926	21.5%	1.21 [0.97, 1.50]
Jian.Z 2011	20	25	3	25	2.4%	29.33 [6.20, 138.78]
Jun Li 2012	43	60	32	60	7.8%	2.21 [1.04, 4.72]
Kubicka, S. 2016	619	861	575	861	21.8%	1.27 [1.04, 1.56]
Pectasides, D. G. 2014	185	213	175	201	11.1%	0.98 [0.55, 1.74]
Pei Xun 2016	9	30	3	28	2.8%	3.57 [0.85, 14.92]
Schmoll, H. J. 2012	689	944	631	942	22.1%	1.33 [1.09, 1.62]
Xin-J. L. 2016	5	21	2	21	1.9%	2.97 [0.51, 17.42]
Ying-Ni. L 2016	2	56	2	50	1.5%	0.89 [0.12, 6.56]
Yun-H. Wang 2011	8	30	3	50	2.7%	3.27 [0.77, 13.83]
Total (95%CI)		3251		3199	100.0%	1.45 [1.13, 1.87]
Total events	2384		2176			

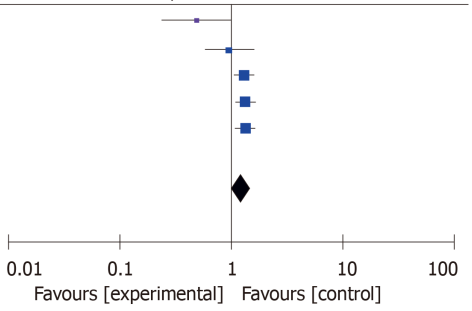
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 24.20$, df = 10 ($P = 0.007$); $I^2 = 59\%$
Test for overall effect: $Z = 2.88$ ($P = 0.004$)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random. 95%CI
Diao, C 2008	47	71	69	87	4.9%	0.51 [0.25, 1.04]
Pectasides D. G. 2014	169	213	160	201	9.7%	0.98 [0.61, 1.59]
Kubicka, S. 2016	541	861	482	861	28.1%	1.33 [1.10, 1.61]
Schmoll, H. J. 2012	594	944	527	942	29.0%	1.34 [1.11, 1.61]
Haller, D. G. 2011	643	938	573	926	28.2%	1.34 [1.11, 1.63]
Total (95%CI)		3027		3017	100.0%	1.24 [1.04, 1.46]
Total events	1994		1811			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.09$, df = 4 ($P = 0.09$); $I^2 = 51\%$
Test for overall effect: $Z = 2.47$ ($P = 0.01$)



C

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random. 95%CI
1.5.1 xelox *vs* FUFA						
Diao, C 2008	47	71	65	98	2.9%	0.99 [0.52, 1.90]
Haller, D. G. 2011	643	938	573	926	28.8%	1.34 [1.11, 1.63]
Kubicka, S. 2016	541	861	482	861	28.5%	1.33 [1.10, 1.61]
Subtotal (95%CI)		1870		1885	60.2%	1.32 [1.16, 1.51]
Total events	1231		1120			

Heterogeneity: $Chi^2 = 0.78$, df = 2 ($P = 0.68$); $I^2 = 0\%$
Test for overall effect: $Z = 4.09$ ($P < 0.0001$)

1.5.1 xelox *vs* FUFA						
Diao, C 2008	47	71	69	87	3.3%	0.51 [0.25, 1.04]
Pectasides D. G. 2014	169	213	160	201	5.4%	0.98 [0.61, 1.59]
Schmoll, H. J. 2012	594	944	527	942	31.1%	1.34 [1.11, 1.61]
Subtotal (95%CI)		1228		1230	39.8%	1.22 [1.03, 1.44]
Total events	810		756			

Heterogeneity: $Chi^2 = 7.42$, df = 2 ($P = 0.02$); $I^2 = 73\%$
Test for overall effect: $Z = 2.33$ ($P = 0.02$)

Total (95%CI)		3098		3115	100.0%	1.28 [1.15, 1.42]
Total events	2041		1876			

Heterogeneity: $Chi^2 = 8.69$, df = 5 ($P = 0.12$); $I^2 = 42\%$
Test for overall effect: $Z = 4.65$ ($P < 0.00001$)
Test for subgroup differences: $Chi^2 = 1.52$, df = 1 ($P = 0.47$); $I^2 = 0\%$

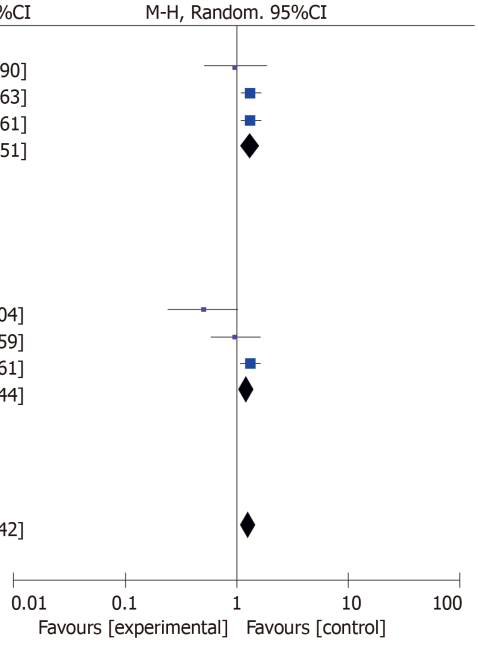


Figure 5 Process of deflection analysis. A: Overall survival (The capecitabine plus oxaliplatin (XELOX) group *vs* other chemotherapy groups); B: Disease-free survival (The XELOX group vs other chemotherapy groups); C: Subgroup analysis of disease-free survival (The XELOX group vs other chemotherapy groups).

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) accounts for 9% of all cancers in the world. In the last decade, it is the third most common malignant tumor in Europe and the United States. There is an urgent need to establish an effective standard treatment for CRC. In addition, more than 70% of CRC-related deaths are associated with the liver metastasis. A recurrence rate and poor overall survival make CRC a serious public health problem.

Research motivation

The aim of treatment for CRC is to cure locally and prevent metastasis and recurrence. Generally, comprehensive treatment is the focus of CRC, and chemotherapy is one of the important treatment methods. Reasonable and effective chemotherapy can prolong the life span and improve the quality of life of patients. Therefore, local resection of colon cancer should be combined with individual treatment. For patients with CRC, the choice of chemotherapy is very important for their prognosis. In patients with CRC, the purpose of adjuvant chemotherapy is to eliminate the occult micrometastasis during surgery, so as to improve the overall survival.

Research objectives

The purpose of this study was to explore the efficacy of capecitabine plus oxaliplatin (XELOX) regimen over other chemotherapy regimens, specifically XELOX *vs* 5-fluorouracil plus leucovorin, XELOX *vs* 5-fluorouracil plus leucovorin plus oxaliplatin, XELOX *vs* capecitabine and XELOX *vs* oxaliplatin plus 5-fluorouracil.

Research methods

By searching the PubMed, EMBASE and Cochrane databases, a total of 12 randomized controlled trials involving 6698 stage III colon cancer cases (XELOX protocol: n = 3298 cases; other adjuvant chemotherapy protocol: n = 3268 cases) were included. The parameter outcomes included the overall survival and the disease-free survival. The quality control of selected literature was based on the Jadad scale and the GRADE system.

Research results

In comparison to other adjuvant chemotherapy regimen, the XELOX regimen showed a better overall survival and a better disease-free survival for colon cancer patients.

Research conclusions

In clinical application, XELOX and 5-fluorouracil plus leucovorin plus oxaliplatin showed similar efficacy, but different types of patients may have different benefits from treatment. According to our data, in comparison to other adjuvant chemotherapy regimen, XELOX regimen showed a better overall survival and a better disease-free survival for colon cancer patients, suggesting the XELOX regimen can be a good option for postoperative treatment of stage III colon cancer.

Research perspectives

The XELOX regimen is recommended for stage III colon cancer after surgery. In addition, our conclusion needs to be further validated by a large RCT trial in future.

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