申请学术型硕士研究生指导教师佐证材料

申请人姓名：缪国斌

一级学科名称：临床医学

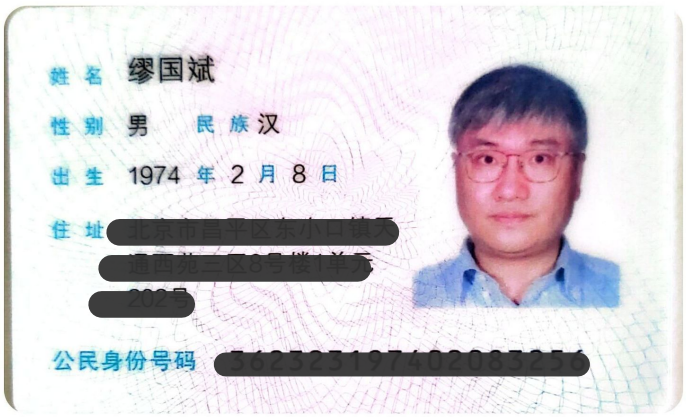
二级学科名称：内科学

工作单位：应急总医院

2025 年 5 月

目　录


中华人民共和国
居民身份证
签发机关 [redacted]
有效期限 2022.02.08-长期


姓名 缪国斌
性别 男 民族 汉
出生 1974 年 2 月 8 日
住址 [redacted]
公民身份号码 [redacted]

普通高等学校

毕业证书

学生 缪国斌 性别 男 现年 21 岁

于一九九0 年九 月至一九九五 年 七 月在

本校 临床医学 专业

五 年制本科学习，修完教学计划规定的

全部课程，成绩合格，准予毕业。

校　　名

校(院)长 王顺德

一九九五 年 七 月 一 日

中华人民共和国国家教育委员会印制

NO: [redacted]

证书编号：[redacted]

博士学位证书

缪国斌，男，1974 年 2 月 8 日生。在 首都医科大学 完成了 临床医学（内科学） 博士专业学位培养计划，成绩合格。根据《中华人民共和国学位条例》的规定，授予 临床医学 博士学位。

首都医科大学

校 长

学位评定委员会主席

证书编号：[redacted]

二〇〇九 年 六 月 廿三 日

（专业学位证书）

电子证照

医师执业证书

姓名：缪国斌

性别：男

出生年月：1974年02月

执业级别：执业医师

执业类别：临床

执业范围：内科专业

任职资格：主任医师

证书编码：[redacted]

执业地点：北京市

主要执业机构：应急管理部应急总医院

签发机关　北京市卫生健康委员会

签发日期　2022年07月15日

中国21世纪议程管理中心文件

国科金议程办字〔2023〕46号

关于国家重点研发计划“重大自然灾害防控与公共安全”重点专项2023年度项目立项的通知

各项目牵头单位：

国家重点研发计划“重大自然灾害防控与公共安全”重点专项2023年度项目立项工作已经完成，具体立项情况详见附件。

请根据《关于改进加强中央财政科研项目和资金管理的若干意见》（国发〔2014〕11号）、《关于深化中央财政科技计划（专项、基金等）管理改革的方案》（国发〔2014〕64号）、《关于进一步完善中央财政科研项目资金管理等政策的若干意见》（中办发〔2016〕50号）、《关于改革完善中央财政科研经费管理的若干意见》（国办发〔2021〕32号）、《国家重点

研发计划管理暂行办法》（国科发资〔2017〕152号）、《国家重点研发计划资金管理办法》（财教〔2021〕178号）、《国家重点研发计划项目综合绩效评价工作规范（试行）》（国科办资〔2018〕107号）及项目实施期间出台的国家重点研发计划管理有关规章制度的要求，认真落实项目（课题）承担单位法人责任，做好项目实施和资金管理使用工作；项目牵头单位和负责人要切实加强课题之间的衔接与协调，确保项目的研究开发目标和任务按期完成；严格按照中央财政科研经费管理的有关规定，资金专款专用，提高资金使用效益。

特此通知。

附件：1.国家重点研发计划“重大自然灾害防控与公共安全”重点专项2023年度项目立项表（略）

2.项目立项批复内容

中国21世纪议程管理中心

2023年12月4日

（此件依申请公开）

抄送：科技资源统筹司、监督评估与诚信建设司。
各项目推荐单位。
各课题承担单位。

中国21世纪议程管理中心　　2023年12月4日印发

附件 2-55:

“重大灾害事故现场应急手术关键技术装备研发及应用示范”项目立项批复内容

一、项目名称（编号）：重大灾害事故现场应急手术关键技术装备研发及应用示范（2023YFC3011900）

二、项目牵头单位：中国人民解放军总医院，项目负责人：孙晓艳

三、项目执行年限：2023 年 11 月-2026 年 10 月

四、项目总经费 3983 万元，其中中央财政经费 1983 万元

五、项目目标和主要考核指标

（一）项目目标

我国是世界上遭受自然灾害最为严重的国家之一，依据损伤控制性手术现场迅速展开的理念，构建具有一线救援适应性、自保障能力并兼顾抢救成功率的现场应急手术保障体系，加速推进关键技术装备研发已迫在眉睫。因此，本项目面向重大灾害事故现场复杂环境、批量伤员紧急救命手术需求，攻克小型移动式高集成多功能成像关键技术、微涡轮自驱动新鲜气体混合流量补偿技术、自清洁膜分离高洁净动态调节技术、混合现实透视术中实时导航技术，研制可现场三维检查、快速检验、生命支持、精准手术、动态监护、远程会诊的一站式应急手术装备体系，并开展应用示范。

（二）主要考核指标

研发具备 CBCT 成像和二维成像两种成像功能、支持手动推行移动、支持车载移动的颌面创伤及创伤性上气道急性梗阻快速诊断的小型可移动低辐射面颈部 CT 装备系统 1 套，占地面积＜1m^2，功率＜2kW，成像视野>23cm×19cm，空间分辨率≥2.0lp/mm，辐射剂量＜20mGycm^2，智能诊断时间<3min，准确率>95%；研制麻醉监护高级生命支持装备 2 套，具备静吸复合麻醉、呼吸支持、监护功能，实现容量控制(VCV)、压力控制(PCV)、同步间歇指令通气(SIMV-VC)、双水平通气(BiLevel)、动态双水平通气(Dyn-BiLevel)、双水平智能通气(BiLevel-ST)等通气模式。新鲜气体流量混合输出压力扬程正压>20kPa，电子空氧混合精度≤5%，整机重量<50kg；研发组配式高净化救援现场手术平台 1 套，其中车载方舱可开展 1 台千级净化手术，过滤精度 0.1～1nm，净化面积≥13m^2，净化时间≤45min。子母式帐篷可开展 3 台万级净化手术，总净化面积≥27m^2，净化时间≤45min。整个组配式现场手术平台展开面积≥60m^2，折展比≥30:1，展开时间≤15min，撤收时间≤15min，重量≤31 吨，满足海陆空多路径运送要求，可同时开展不少于 4 台手术。研发应急手术信息综合支持系统 1 套，平台同时支持≥10 种现场核心医疗设备的接入，颌面创伤、急性上气道梗阻等应急手术场景中的术中导航动态跟踪时延≤50ms，术中 CT、超声等医学影像配准精度≤1mm，支持 4K 高清远程音视频传输。制定灾害事故现场应急手术规范团

体标和应急救援人员的专业技术要求与培训标准。在5家省级医院单位开展一般应用示范不少于5次，使用本项目研发的新型应急手术技术与装备进行应急救援或演练；申请发明专利15项，软件著作权8项。

详细考核指标以项目任务书为准。

六、项目课题安排

序号	课题编号	课题名称	课题负责人	课题承担单位	中央财政经费（万元）
1	2023YFC3011901	可移动低辐射锥形束 CT 装备及智能诊断系统研发	贺洋	北京大学口腔医院	400.00
2	2023YFC3011902	麻醉监护高级生命支持一体机研制	李晓雪	中国人民解放军总医院	460.00
3	2023YFC3011903	组配式高净化救援现场手术平台研制	郝昱文	中国人民解放军总医院	470.00
4	2023YFC3011904	应急手术信息综合支持系统研制	缪国斌	应急总医院	367.00
5	2023YFC3011905	应急手术关键技术装备示范应用	薛峰	北京大学人民医院	286.00

Review Article

Chang Meng#, Zejun Song#, Lingnan Zhang#, Yu Geng, Jing Sun, Guobin Miao*, Peng Liu*

Effects of losartan in patients with NAFLD: A meta-analysis of randomized controlled trial

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Abstract: Losartan has become a hot spot in the treatment of non-alcoholic fatty liver disease (NAFLD) among angiotensin receptor blocker drugs. We sought to conduct a systematic examination and meta-analysis to examine the effects of losartan on patients with NAFLD. We searched for potentially randomized controlled trials in PubMed, Embase, China National Knowledge Infrastructure, Wanfang, and the Cochrane database up to October 09, 2022. We used the Cochrane risk of bias tool to evaluate the study quality. Analysis of subgroups, sensitivity analysis, and publishing bias were explored. The quality of the included studies was moderate to high. Six trials involving 408 patients were included. The meta-analysis demonstrated that aspartate transaminase was significantly affected by losartan therapy (mean difference [MD] = −5.34, 95% confidence interval [CI] [−6.54, −4.13], Z = 8.70, P < 0.01). The meta-analysis subgroup showed that losartan 50 mg once daily could lower the level of alanine aminotransferase (MD = −18.92, 95% CI [−21.18, −16.66], Z = 16.41, P < 0.01). There was no statistically significant difference in serum total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein.

Keywords: losartan, liver function, blood lipids, non-alcoholic fatty liver disease

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a progressive disease characterized by excessive accumulation of fat in the liver, typically characterized by simple steatosis at the onset. These include non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma [1]. Currently, the pathogenesis of this disease is believed to be linked to obesity, insulin resistance, type 2 diabetes mellitus, and hyperlipidemia. In recent years, with the growing incidence of obesity and diabetes, NAFLD has become the most common chronic liver disease, with about 25% of the global population suffering from NAFLD [2]. In addition to lifestyle interventions, such as exercise and diet, there is still a lack of specific drugs to treat NAFLD [3]. The pathophysiology of NAFLD, particularly involving insulin resistance and subclinical inflammation, is closely related not only to these non-communicable diseases but also to the severe course of the infectious disease COVID-19. Damage to glucose and lipid metabolic pathways, driven by the global rise in obesity and type 2 diabetes, is likely to be behind the increase in NAFLD patients [4]. Some studies have also found that the pathophysiological mechanism of NAFLD is closely related to liver and fat metabolism [5]. It is known that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are indicators of the degree of hepatocyte damage. A few studies [11,15,16] have

# These authors contributed equally to this work.

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observed that losartan may play a role in reducing transaminase in NAFLD population.

In some studies, angiotensin receptor blockers (ARBs) have been found to regulate hepatic lipid [4]. In the absence of AT1R, lipid accumulation is reduced and PPAR is significantly induced. Therefore, AT1R blockade may be effective in the treatment of NAFLD or NASH [6]. Although the function of ARBs has been widely used in animal experiments to prevent NAFLD complications, there is a lack of clinical data on patients [7], and the effectiveness of ARBs in the treatment of NAFLD is still controversial. For example, the effects of losartan on biochemical variables, hepatic steatosis, inflammation, and serum biomarkers of fibrosis in patients have also been mixed [8,9].

Thus, reported results have been contradictory. Among all ARBs, losartan has the largest number of randomized controlled clinical studies on NAFLD. In this study, we carried out a meta-analysis to investigate the effects of losartan on liver function and blood lipids in patients with NAFLD.

2 Methods

Our protocol has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database (registration number: INPLASY202211 0006, DOI number: 10.37766/inplasy2022.11.0006).

2.1 Search strategy

Two independent researchers (CM and ZJS) conducted extensive electronic searches for relevant articles published as of October 9, 2022. The database includes PubMed, Embase, China National Knowledge Infrastructure, Wanfang, and the Cochrane database. English retrieval uses the medical subject title (MeSH) in combination with the following terms to search: "nonalcoholic fatty liver disease" and "losartan." Manually select relevant randomized controlled trials (RCTs). The Chinese search uses subject words or synonyms, including "nonalcoholic fatty liver disease," "losartan," and "ARB."

2.2 Literature screening and data extraction

EndNote (X9 version) software is selected for document management; two investigators independently evaluated the eligibility of the identified items. The title and summary are filtered for the first time, and qualified articles are reserved for full-text review. Inclusion criteria for studies meeting the following requirements include (1) adults or children clinically diagnosed as NAFLD; (2) treatment with losartan; and (3) outcomes' indicators, ALT, AST, Tc, Tg, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), including one. The subject may be included in the study. The exclusion criteria are as follows: (1) non-human research; (2) non-randomized controlled trial; (3) there are not enough data to extract, such as the summary of some meetings; literature materials such as review and pharmacological introduction; and (4) animal experiment.

2.3 Bias and quality assessment

The two researchers independently evaluated, preliminarily selected and checked the literature data according to the unified and standardized method, included them in the literature in strict accordance with the admission and exclusion criteria, then collected information, and evaluated the quality of selected articles according to the quality evaluation standard of Cochrane Reviewer Handbook 5.1.0 [10] (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias).

2.4 Statistical analysis

Revman5.3 software is used for meta-analysis. Data that meet homogeneity ($P > 0.10$ and $I^2 \leq 50\%$) through the heterogeneity test are meta-analyzed with the fixed-effect model. If homogeneity ($P \leq 0.10$ or $I^2 > 50\%$) is not met, and heterogeneity cannot be ruled out, random-effect model can be used to combine effects, but it should be noted that sensitivity analysis and subgroup analysis should be considered for the type of analysis data. The mean difference (MD) and 95% confidence interval (CI) were calculated.

3 Results

According to the literature search results, 78 literatures were initially retrieved, 19 duplicates were removed, 47

literatures such as review and irrelevant topics were excluded from reading titles and abstracts, 6 literatures that did not meet the inclusion criteria were excluded from reading the full text, and 6 literatures were finally included, including 4 [11–14] in English and 2 [15,16] in Chinese. The detailed process is shown in Figure 1.

The basic characteristics of literature and the quality evaluation of methodology included 6 articles and 408 researchers in total. The baseline characteristics included in the study are shown in Table 1. There was no statistical difference in the baseline characteristics of all patients, and the quality of the included literature was moderate to high. The quality evaluation of the literature are shown in the supplement.

This study mainly discussed the effect of losartan on liver function and blood lipid in nonalcoholic patients. Six studies [11–16] reported the change of ALT, and there was heterogeneity between literatures. Random effects were used for analysis. Meta grouping results showed that losartan could reduce the ALT level of NAFLD, MD = −15.74, 95% CI [−17.77, −13.71], $Z = 15.23$, $P < 0.01$. Based on statistics and clinical analysis, we further used sensitivity analysis and subgroup study to group the patients according to the dosage of losartan. We found that the subgroups could be analyzed according to the fixed effect ($I^2 = 0\%$, $P > 0.10$). The meta-analysis subgroup results showed that losartan 50 mg once daily [11,15,16] could reduce the ALT level (MD = −18.92,

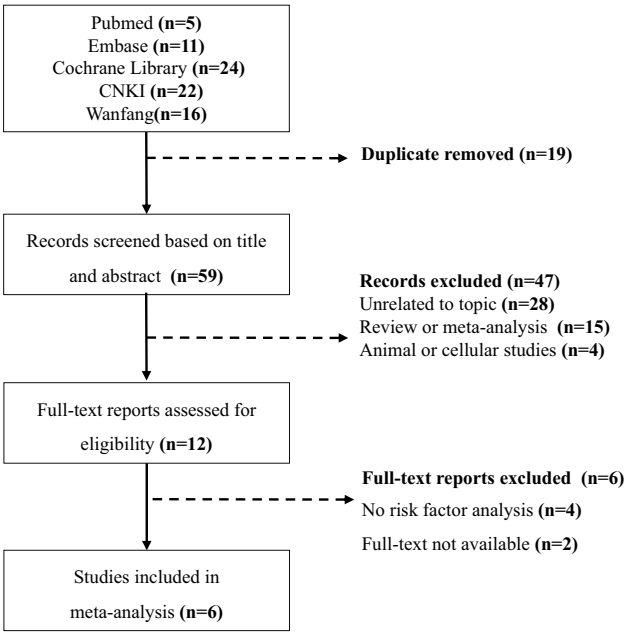

Figure 1: Selection process for studies included in the meta-analysis.

Table 1: Summary of the included studies

Study	Year	Study design	*N*	Included patients	Intervention	Control	Findings	Follow up
McPherson et al. [11]	2017	P,MC	32	Age > 18; NAFLD	Losartan 50 mg qd	Placebo	ALT, AST, TC, TG, LDL, HDL, FS	96 weeks
Vos et al. [12]	2022	P,MC	83	Age 8–17 years; NAFLD	Losartan 100 mg qd	Placebo	ALT, AST	24 weeks
Fogari et al. [13]	2012	P,SC	150	Age > 18; NAFLD	Losartan 100 mg qd	Amlodipine 10 mg/day	ALT, AST, TC, TG, LDL, HDL	12 months
Hirata et al. [14]	2013	P,SC	17	Age > 20; NAFLD	Losartan 100 mg qd	Telmisartan 20 mg once daily	ALT, AST, TC, TG, HDL	12 months
Chen [15]	2020	P,SC	76	Age > 18; NAFLD	Losartan 50 mg qd	Conventional therapy	ALT, AST	6 months
Liu et al. [16]	2019	R,SC	50	Age > 18; NAFLD	Losartan 50 mg qd	Placebo	ALT, AST, TC, TG, FS	96 weeks

P, prospective; R, retrospective; MC, multicenter; SC, single center; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NAS, non-alcoholic fatty liver disease; FS, fibrosis stage; qd, once daily.

95% CI [−21.18, −16.66], $Z = 16.41$, $P < 0.01$). The losartan 100 mg once daily [12–14] group failed to show statistical difference between the experimental group and the control group and only showed a downward trend (MD = −2.75, 95% CI [−7.32, 1.82], $Z = 1.18$, $P = 0.24$). The detailed process is shown in Figure 2a. Six studies [11–16] reported the changes of AST (Figure 2b). There was no heterogeneity between the literatures. Fixed effects were used for analysis. Meta-analysis showed that losartan could reduce the AST level in the experimental group (MD = −5.34, 95% CI [−6.54, −4.13], $Z = 8.70$, $P < 0.01$).

Two studies [11,13] reported the changes in LDL (Figure 3a), and there was heterogeneity between literatures. Randomized effects were used for analysis. Meta-analysis showed that losartan did not show statistical difference between the experimental group and the control group (MD = −0.33, 95% CI [−0.86,0.20], $Z = 1.21$, $P = 0.23$). Three studies [11,13,14] reported the changes in HDL (Figure 3b). There was no heterogeneity between the literatures. Fixed effects were used for analysis. Meta-analysis showed that losartan did not show statistical difference between the experimental group and the control group (MD = −0.01, 95% CI [−0.07,0.04], $Z = 0.50$, $P = 0.62$). Four studies [11,13,14,16] reported the changes in TC (Figure 3c) and TG (Figure 3d). There was no heterogeneity between the literatures. Fixed effects were used for analysis. Meta-analysis showed that losartan in the experimental group did not show statistical difference between the experimental group and the control group (MD = −0.01, 95% CI [−0.06,0.05], $Z = 0.20$, $P = 0.84$) (MD = 0.01,95% CI [−0.11,0.14], $Z = 0.19$, $P = 0.85$).

The funnel chart analysis (publication bias analysis) of the indicators included in the study shows that the inverted funnel chart of each indicator is basically symmetrical, indicating that there is no publication bias. However, the number of relevant studies is relatively small, and there may be some errors in the analysis of the inverted funnel chart.

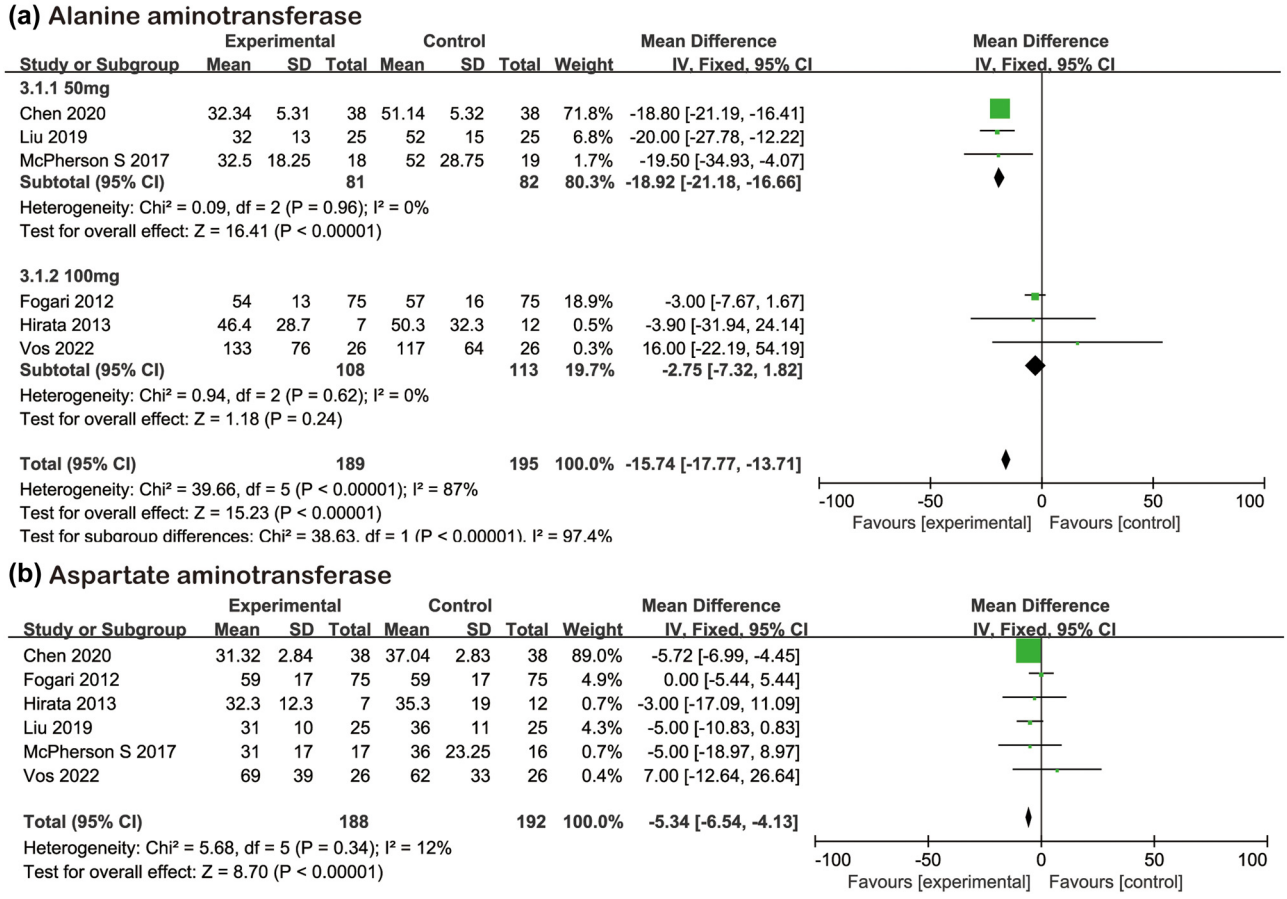

Figure 2: Forest plots of the losartan therapy on liver function. (a) ALT and (b) aspartate aminotransferase.

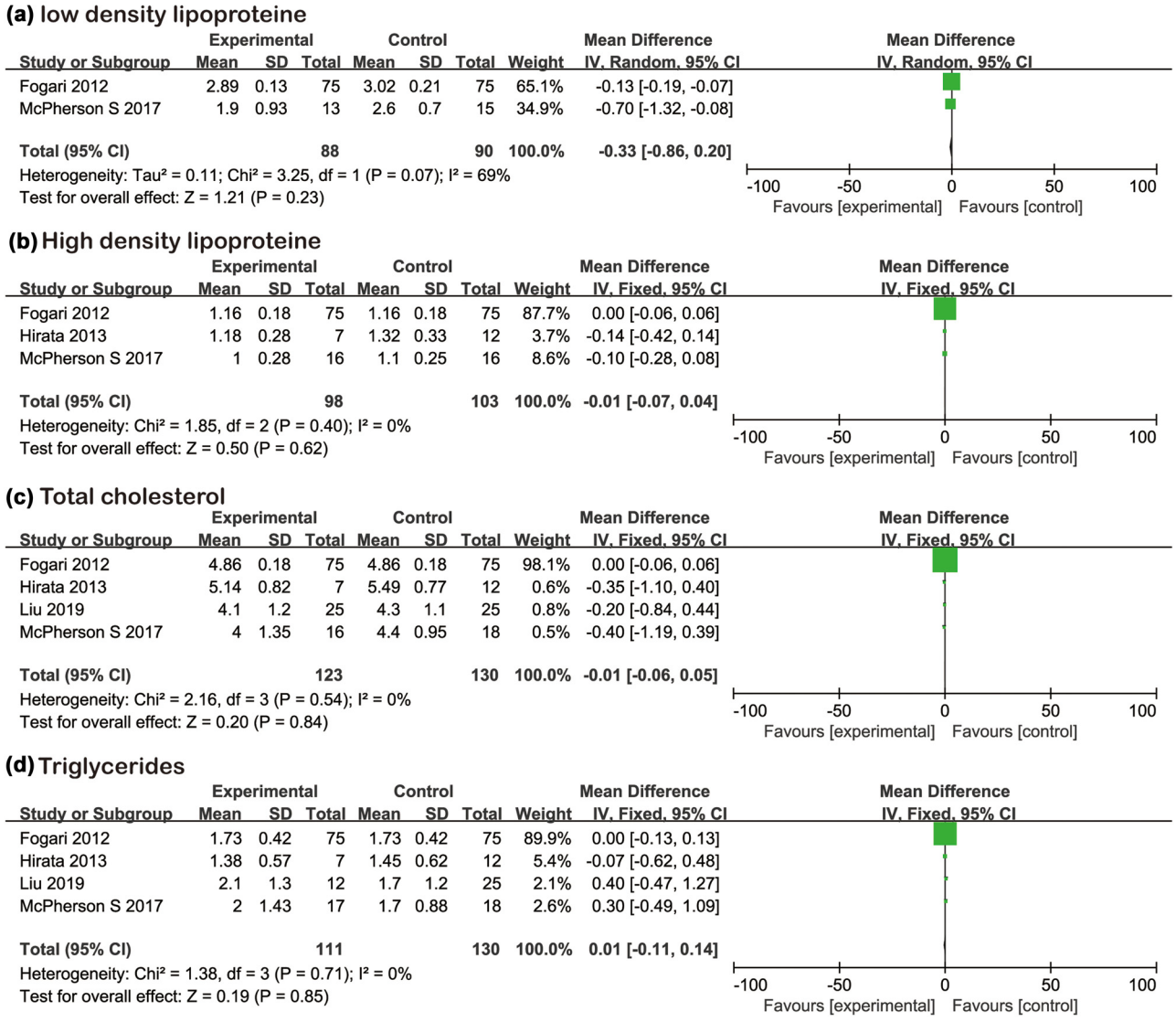

Figure 3: Forest plots of the losartan therapy on blood lipids. (a) LDL; (b) HDL; (c) total cholesterol; and (d) triglyceride.

4 Discussion

At present, NAFLD is the most common but also the most easily ignored disease by patients and clinicians, and its related complications include liver dysfunction, portal hypertension, liver fibrosis, and cirrhosis. However, in clinical practice, NAFLD is still mainly treated by lifestyle interventions, such as diet adjustment and exercise. Currently, the clinical or guidelines are temporarily. There is no drug specifically recommended. Moreira de Macêdo [17] found that the renin–angiotensin system (RAS), as an important regulator, plays an important role in the metabolic process of the body. The potential therapeutic effect of angiotensin-converting enzyme 2 (ACE2) on the regulation of RAS has become a new research direction. Meta-analysis was used in this study to analyze the effect of ACEI/ARB drugs on NAFLD and provide evidence of evidence-based medicine for the clinical application of ACEI/ARB.

The mechanisms of ACEI/ARB in the treatment of NAFLD mainly include the following three aspects: (1) improving insulin resistance (IR). On the one hand, angiotensin II can improve IR by regulating the expression of certain signaling molecules in liver, muscle, and adipose tissue and enhancing insulin negative feedback [18]. Meanwhile, it can reduce systolic blood pressure to a certain extent [19]. (2) ACEI/ARB can improve oxidative stress by upregulating the transcription of ACE2 mRNA; ACEI/ARB can inhibit the c-Jun amino-terminal kinase pathway activated by reactive oxygen species (ROS) by

upregulating the expression of ACE2 gene mRNA. At the same time, it can improve local tissue perfusion and oxygenation by reducing Ang II-mediated vasoconstriction, reduce the increase of ROS caused by fatty acid accumulation, and inhibit nuclear factor kB. The activation of the pathway can further improve the occurrence of metabolic diseases related to inflammation by blocking the activation of related inflammatory factors [20–22]. (3) ARBs can be activated as selective peroxisome proliferators to play a protective role in the liver. At the same time, lipid metabolism can be further improved through the activation and enhancement of adiponectin [23,24]. It can also downregulate the expression of liver sterol regulatory factor-binding protein, inhibit the uptake of lipids by liver cells, reduce hepatocyte steatosis, inhibit the overexpression of cytokine signal transduction inhibitor 3 (SOC-3) in liver tissue, and improve IR and homeostasis of grape [25]. Therefore, ARBs has become a promising new strategy for the prevention and treatment of chronic liver disease, as well as a new therapeutic option for the prevention and treatment of chronic liver disease.

5 Conclusion

Meta-analysis results of this study show that losartan can reduce the level of glutamic oxaloacetic transaminase in patients with NAFLD. In the subgroup analysis, losartan 50 mg once a day can reduce the level of glutamic oxaloacetic transaminase, and the clinical effect is more accurate. This study shows that the effect of losartan on improving lipid (TC, TG, LDL) levels is not ideal. The results of this study not only summarize the population of different countries but also creatively include the NAFLD population of the underage [12]. While further increasing the sample size, the results of all populations are also comprehensively presented. To sum up, losartan 50 mg once daily can significantly improve the liver function of NAFLD patients, and its clinical efficacy is relatively accurate. If there is no contraindication, it should be used as early as possible. We can also find that there are few large sample RCTs about losartan in the treatment of NAFLD, and more high-quality RCTs are needed to supplement and evaluate. Of course, this study also has some limitations. The current number of studies is relatively small, and more RCTs are needed to support it in the future.

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Review Article

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Aspirin versus LMWH for VTE prophylaxis after orthopedic surgery

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Abstract: Low molecular weight heparin (LMWH) is often used to prevent perioperative venous thrombosis after surgery, but aspirin is also recommended by academics. Studies were searched in electronic databases until February 24, 2023. We performed a meta-analysis to evaluate the safety and efficacy of aspirin and LMWH for venous thromboembolism (VTE) prophylaxis in patients after orthopedic surgery. The outcomes were death from any causes, deep vein thrombosis (DVT), pulmonary embolism (PE), etc. This study was registered with INPLASY, number 202320117. Six randomized controlled trials enrolled 13,851 patients with postoperative joint surgery. The risk of DVT was comparable between the two groups when aspirin was combined with mechanical devices (RR 0.61 [95% CI 0.27–1.39], I^2 = 62%, P = 0.24). No significant differences in all cause death, PE, wound infection, and wound complication were found between the aspirin and LMWH groups. In this meta-analysis, the mortality rate was comparable between the aspirin and LMWH groups. However, aspirin alone had a higher risk of DVT than LMWH. Based on the results of this meta-analysis, we suggest aspirin combined with mechanical devices for VTE prophylaxis in patients after orthopedic surgery.

Keywords: aspirin, low-molecular-weight heparin, venous thromboembolism, joint surgery

1 Introduction

Venous thromboembolism (VTE) is a serious consequence in patients with orthopedic trauma [1]. Some clinical guidelines recommend the use of thromboprophylaxis after orthopedic surgery to reduce the risk of VTE after orthopedic surgery and to reduce the associated risk of death and complications [2,3].

Previous studies have analyzed the efficacy and safety of aspirin and low molecular weight heparin (LMWH) in different orthopedic patients [4]. Recent large randomized clinical trials (RCTs) [5] have filled a gap in antithrombotic therapy in patients with surgically treated fractures. The results of most studies indicate that aspirin and low molecular weight have similar outcome markers, but the sample sizes of most studies are relatively small. Some studies have also analyzed the advantages of aspirin combined with mechanical devices to prevent venous thrombosis. After all, aspirin as an oral drug has irreplaceable convenience compared with LMWH, but LMWH as a clotting pathway inhibitor also plays a very important role in thrombosis.

O'Toole et al. [5] included patients who had had surgery for a broken limb or had any pelvic or acetabular fractures at multiple centers, and the results showed that aspirin's thromboprophylaxis was no less effective at preventing death than LMWH. Anderson et al. [6] included total hip arthroplasty patients, and by extending the application time of aspirin to 28 days, compared with the LMWH group, the incidence of deep vein thrombosis (DVT) was similar between the two groups. The author mentioned

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that considering economic factors, aspirin could also be considered for clinical application.

Several subsequent studies [7–10] have looked at similar issues in patients undergoing joint replacement surgery, but with different drug timings and follow-up times. Recent studies [11] have analyzed the effect of other anticoagulant drugs on the prevention of DVT, which is also the direction of future research. Three studies [8–10] combined with mechanical devices, also offer new solutions for future treatment. In this meta-analysis, we summarized previously published RCTs to investigate the efficacy and safety of aspirin and LMWH in antithrombotic therapy for patients after orthopedic surgery.

2 Methods

We carried out the meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [12]. Our protocol has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database (Inplasy protocol: INPLASY202320117), and is available in full on inplasy.com (https://inplasy.com/inplasy-2023-2-0117). Ethics approval was not required for our work.

2.1 Search strategy

Three independent researchers conducted extensive electronic searches for relevant articles published until February 24, 2023. The database includes PubMed, Embase, and the Cochrane database. Manually select relevant randomized controlled trial. The search strategy of the literature is shown in Table A1.

2.2 Inclusion and exclusion

EndNote (X9 version) software is selected for document management; two investigators independently evaluated the eligibility of the identified items. The title and summary are filtered for the first time, and qualified articles are reserved for full-text review. Inclusion criteria for studies meeting the following requirements include: (1) patients after postoperative joint surgery, (2) treat with aspirin or LMWH, and (3) outcome indicators: all cause death, DVT, pulmonary embolism (PE), wound infection, wound complication, including one. We excluded studies enrolling patients <18 years old, and there was not enough data to extract, such as the summary of some meetings, literature materials such as review and pharmacological introduction. We contacted the authors if associated data from their studies were required.

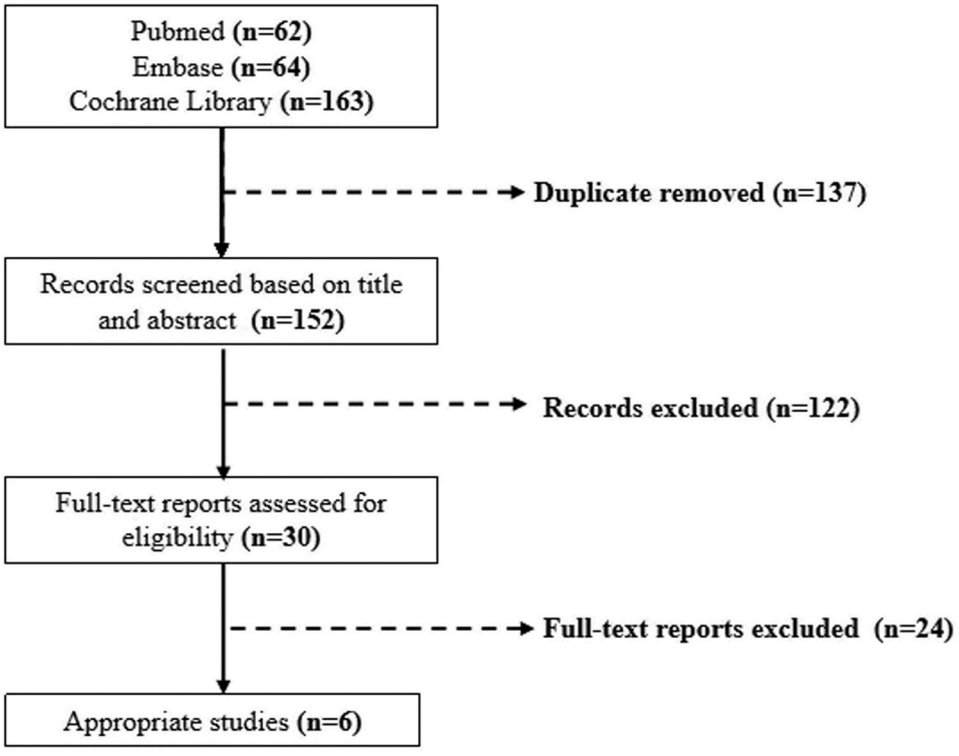

Figure 1: The flow chart of the search and study selection process.

2.3 Bias and quality assessment

The two researchers independently evaluated, preliminarily selected and checked the literature data according to the unified and standardized method, and included them in the literature in strict accordance with the admission and exclusion criteria, and then collected information. Evaluate the quality of selected articles according to the quality evaluation standard of Cochrane Reviewer Handbook 5.1.0 [13].

2.4 Data synthesis and analysis

Revman5.3 was used for meta-analysis. Data which met homogeneity ($P > 0.10$ and $I^2 \leq 50\%$) through heterogeneity test were meta-analyzed using fixed effect model. If homogeneity ($P \leq 0.10$ or $I^2 > 50\%$) was not met, and heterogeneity cannot be ruled out, random effect model can be used to combine effects [14]. While it should be noted that sensitivity analysis and subgroup analysis should be considered for this type of analysis data. For the continuous outcomes, mean differences and 95% CIs were estimated as effective. Some included RCTs reported median as the measure of treatment effect, with interquartile range. A P value <0.05 was considered statistically significant.

3 Results

The flow chart (Figure 1) summarizes the search and study selection process. A total of 289 studies were identified through the electronic searches, of which 137 were excluded due to duplication. Around 122 studies were also excluded after reading the titles and abstracts. The remaining 24 studies were assessed by reading the full texts. Data from six trails of 13,851 patients evaluating the efficacy and safety in postoperative joint surgery treated with aspirin versus LMWH were included.

The main features of the included trials are presented in Table 1. All included studies were randomized controlled trials, and the follow-up time lasted from hospitalization to 6-week or 3-month. Three of the six trials (n = 633) included patients treated with aspirin combined mobile compression device, subgroup analysis of DVT, and wound complications were performed. No differences were observed in terms of the proportion of patients lost to follow up between the aspirin and LMWH groups across trials.

The data of all cause death were available from two trials (Figure 2). There is no significant differences between

Table 1: Design and outcomes of the studies included in the meta-analysis

Num.	Author/Year	Design	Intervention assignments		Participants				Outcomes
			Aspirin	LMWH	Sample size, *n*	Mean age, years (A/L)	Male% (A/L)	Time of medication	
1	Robert/2023	RCTs, MC	81 mg bid	Enoxaparin 30 mg twice daily	12,211	44.5/44.7	62.8/61.7	About 1 month	All cause deaths, PE, DVT, bleeding complication, wound complication, infection (follow 90-day)
2	Zou/2014	RCTs, SC	100 mg qd	AxaIU 4,000 U qd	222	62.7/65.7	25.5/17.9	14 days	DVT, wound complications, limb swelling (follow 4-week)
3	Anderson/2013	RCTs, MC	81 mg qd	Dalteparin 5,000 U qd	785	57.6/57.9	60/53.3	28 days/10 days	All cause deaths, PE, DVT, major bleeding, minor bleeding, wound infection (follow 90-day)
4*	Jiang/2014	RCTs, SC	100 mg qd	5,000 U qd	120	65.1/63.8	8.3/6.7	14 days	All cause deaths, DVT, ematoma, wound complications (follow 6-week)
5*	Colwell/2010	RCTs, MC	81 mg qd	30 mg Bid until discharge and then 40 mg qd	392	63/62	45/46	10 days	DVT; hematoma (follow 12-week)
6*	Gelfer/2006	RCTs, SC	100 mg qd	Enoxaparin 40 mg qd	121	68/67	34/38	In-hospital	All cause deaths, PE, DVT, wound drainage (follow 3-month)

A/L = aspirin group/LMWH group; Bid = twice daily; DVT = deep vein thrombosis; LMWH = low molecular weight heparin; MC = multicenter; PE = pulmonary embolism; PS = prospective study; qd = Once a day; RCTs = randomized clinical trials; SC = single center; *Aspirin combined mobile compression device.

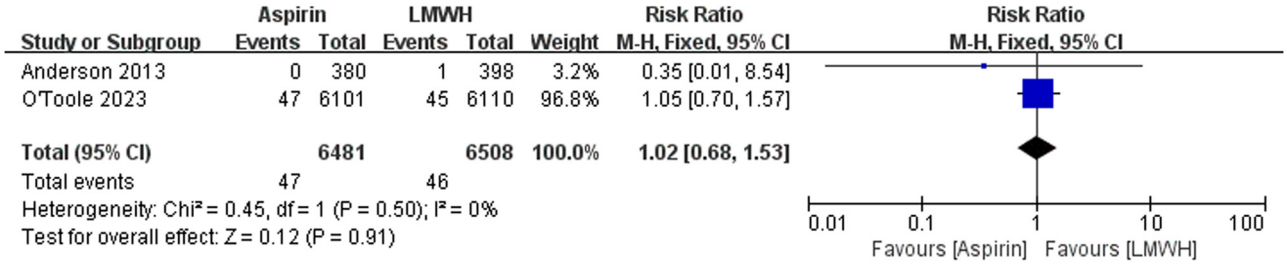

Figure 2: The outcomes of all cause death.

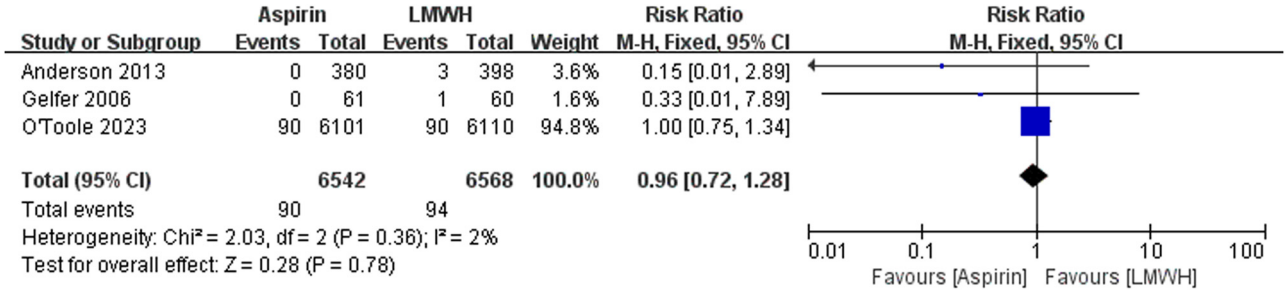

Figure 3: The outcomes of PE.

the aspirin and LMWH groups (RR 1.02 [95% CI 0.68–1.53], I^2 = 0%, P = 0.91). The data of PE were available from three trials (Figure 3). No significant differences were found between the aspirin and LMWH groups (RR 0.96 [95% CI 0.72–1.28], I^2 = 2%, P = 0.78). The data of wound infection were available from two trials (Figure 4). No significant differences were found between the aspirin and LMWH groups (RR 1.07 [95% CI 0.82–1.40], I^2 = 0%, P = 0.60).

The data of DVT were available from six trials (Figure 5). There is no significant differences between the aspirin and LMWH groups (RR 0.92 [95% CI 0.56–1.51], I^2 = 63%, P = 0.73). In the subgroup analysis, we saw that the risk of DVT in the aspirin alone group was higher than that in the low molecular heparin group (RR 1.43 [95% CI 1.14–1.80], I^2 = 0%, P = 0.002), but the risk of DVT was comparable between the two groups when aspirin was combined with mechanical devices (RR 0.61 [95% CI 0.27–1.39], I^2 = 62%, P = 0.24). The data of wound complication were available from five trials (Figure 6). There is no significant differences between the aspirin and LMWH groups (RR 1.13 [95% CI 0.72–1.76], I^2 = 35%, P = 0.60). There was no statistically significant difference between aspirin alone and aspirin combined with mechanical devices (RR 1.14 [95% CI 0.67–1.94], I^2 = 64%, P = 0.63; OR 1.09 [95% CI 0.48–2.47], I^2 = 0%, P = 0.84).

We used Revman to investigate the influence of a single study on the overall pooled estimate of each predefined outcome. We found that the removal of any one study would not affect the following results. The results of the risk of bias assessment with the RoB2 of randomized control trials are summarized in the Table A1.

4 Discussion

Studies have reported that approximately 1.5 million hip and knee arthroplasty procedures are performed each year in the United States [15,16]. The incidence of surgical

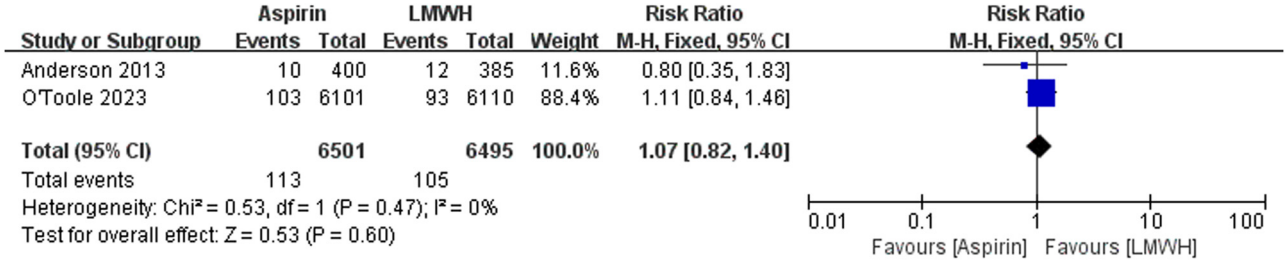

Figure 4: The outcomes of wound infection.

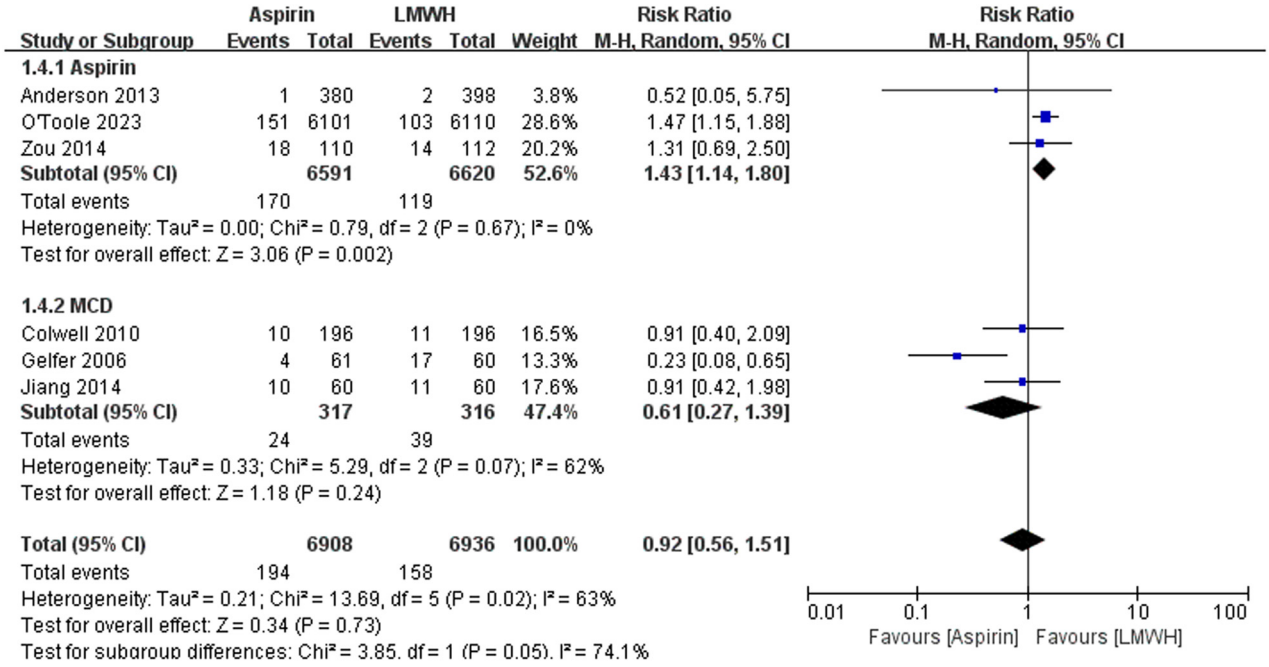

Figure 5: The outcomes of DVT.

symptomatic VTE in patients is about 2%, posing a serious threat to postoperative recovery [11,17]. The prevention of DVT has become the focus of many scholars. LMWH has traditionally been used for anticoagulant therapy. In recent years, the use of aspirin-based thromboprophylaxis has increased [18,19]. This meta-analysis discussed the efficacy and safety of aspirin and LMWH in patients after orthopedic surgery by summarizing several RCTs. Our article had a large sample size and high quality, and the results were very reliable.

However, regarding aspirin in the prevention of DVT in patients after orthopedic surgery, the efficacy of aspirin

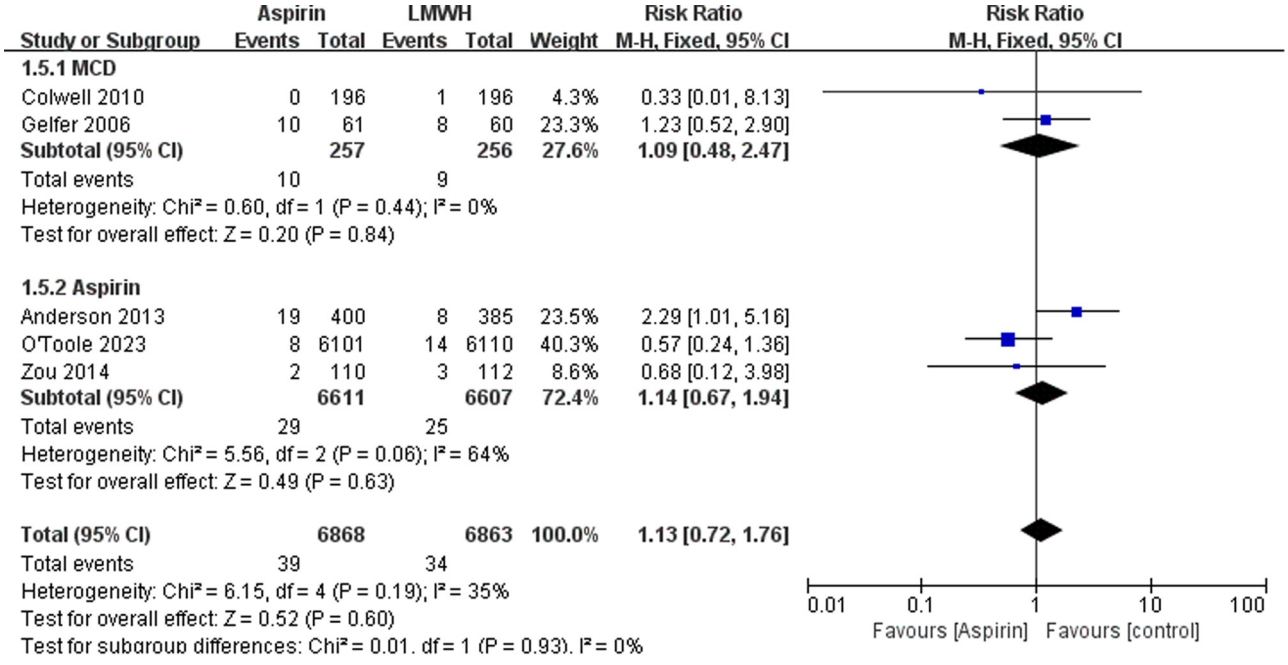

Figure 6: The outcomes of wound complication.

as the only prophylactic drug is also questioned [20], which is consistent with the results of this study. In this meta-analysis, we could see that there was no statistical difference between the aspirin group and the LMWH group in the prevalence of PE and wound complications. In terms of the incidence of DVT, we can see that aspirin alone is worse than LMWH, and aspirin combined with mechanical device changes this outcome. This may seem different from the conclusions of individual studies, but it is probably the most realistic conclusion because our analysis included a large sample size and relied on standardized statistical analysis, after all, aspirin is more commonly used as an antiplatelet agent for the prevention of arterial embolization events. Therefore, we suggest that aspirin combined with mechanical auxiliary devices can be considered in the prevention of DVT after orthopedic surgery. On the one hand, aspirin can reduce the pain of patients, and it is easy to operate and implement. Future research can further explore the advantages and disadvantages of different mechanical devices, and provide a more simple and feasible program for patients after fracture surgery. Recent studies compared the risk of thromboembolic events under different routes of administration, which also provides some inspiration for this study [21]. There are also studies that female patients have a low risk of gynecological surgery embolization events, and gender classification is also one of the future research directions [22]. The metabolic pathways of embolic events have also been studied, which may also be one of the future research directions [23].

There are several limitations to be mentioned. First, we included several RCTs, in which different populations had different oral aspirin doses, medication cycles, and follow-up times, which may have increased the heterogeneity of the findings. Second, the number of patients was relatively small and some follow-up outcomes could not be obtained. For example, the cerebral function in different oxygen supply strategies could not be evaluated for cardiac arrest patients.

5 Conclusion

Death rates were comparable between the aspirin group and the LMWH group. Based on the results of this meta-analysis, we recommend the use of aspirin in combination with mechanical devices for the prevention of VTE in patients after orthopedic surgery.

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Data availability statement: Datasets are available on request from the corresponding author.

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Appendix

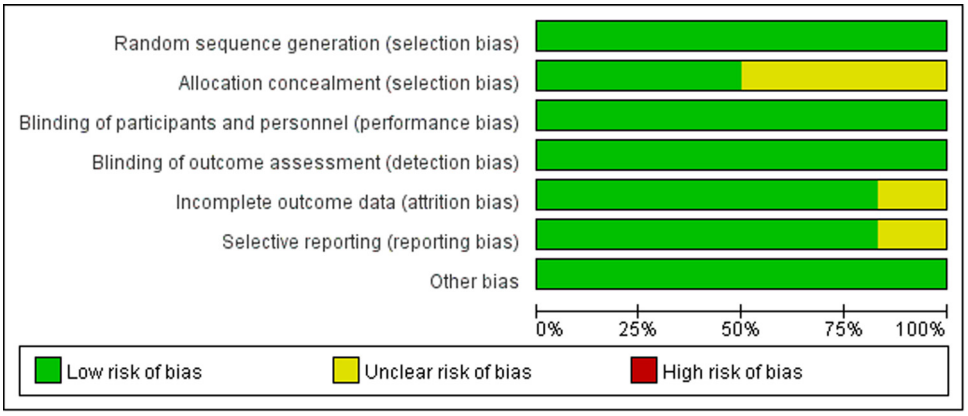

Figure A1: Risk of bias graph.

Table A1: Search strategy

Electronic database	Search strategy
PubMed (NCBI)	(“aspirin”[Title/Abstract] OR “acetylsalicylic acid”[Title/Abstract] AND (“Low molecular weight heparin”[Title/Abstract] OR “lmwh”[Title/Abstract] OR “nadroparin”[Title/Abstract] OR “Lovenox”[Title/Abstract] OR “heparin”[Title/Abstract]) AND (“cataclasis”[Title/Abstract] OR “fracture”[Title/Abstract] OR “joint”[Title/Abstract] OR “articulation”[Title/Abstract] OR “arthroplasty”[Title/Abstract]) AND (“randomized controlled trial” OR “randomized” OR “placebo” OR “randomly” OR “trial”)
Embase	#1 (‘aspirin’:ab,ti OR ‘acetylsalicylic acid’:ab,ti) #2 (‘Low molecular weight heparin’:ab,ti OR ‘lmwh’:ab,ti OR ‘nadroparin’:ab,ti OR ‘Lovenox’:ab,ti OR ‘heparin’:ab,ti) #3 (‘cataclasis’:ab,ti OR ‘fracture’:ab,ti OR ‘joint’:ab,ti OR ‘articulation’:ab,ti OR ‘arthroplasty’:ab,ti) #4 (‘randomized controlled trial’:ab,ti OR ‘randomized’:ab,ti OR ‘placebo’:ab,ti OR ‘randomly’:ab,ti OR ‘trial’:ab,ti) #5 #1 AND #2 AND #3 AND #4
Cochrane	(aspirin OR acetylsalicylic acid) AND (lmwh OR Low molecular weight heparin OR nadroparin OR Lovenox OR heparin) AND (cataclasis OR fracture OR joint OR articulation OR arthroplasty)

European Journal of Medical Research

RESEARCH

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Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19: a systematic review and meta-analysis

Jing Sun[1†], Shufang Wang[2†], Xin Ma[3†], Qingqing Wei[1], Yujuan Peng[1], Ying Bai[1], Guobin Miao[2*], Chang Meng[2*] and Peng Liu[4*]

Abstract

Objectives Several clinical trials have evaluated the efficacy and safety of baricitinib in COVID-19 patients. Recently, there have been reports on critical patients, which are different from previous research results. The meta-analysis was performed to investigate the effects of baricitinib in COVID-19, by pooling data from all clinically randomized controlled trials (RCTs) available to increase power to testify.

Methods Studies were searched in PubMed, Embase, and Cochrane Library databases on January 31, 2023. We performed a meta-analysis to estimate the efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19. This study is registered with INPLASY, number 202310086.

Results A total of 3010 patients were included in our analyses. All included studies were randomized controlled trials or prospective study. There was no difference in 14-day mortality between the two groups [OR 0.23 (95% CI 0.03–1.84), $I^2 = 72\%$, $P = 0.17$]. In subgroup analyses we found that baricitinib did not seem to improve significantly in 24-day mortality critically ill patients [OR 0.60 (95% CI 0.35–1.02), $I^2 = 0\%$, $P = 0.06$]. Fortunately, baricitinib have led to faster recovery and shorter hospital stays for COVID-19 patients. There were no difference in infections and infestations, major adverse cardiovascular events, deep vein thrombosis and pulmonary embolism.

Conclusions Baricitinib did not increase the incidence of adverse reactions. At the same time, we can find that it reduces the mortality of COVID-19 patients, not including the critically ill.

Keywords Baricitinib, COVID-19, Efficacy, Safety

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Introduction

Many COVID-19 remains an important cause of death in recent years, especially among unvaccinated people with comorbidities or the elderly. A large number of literatures have reported that SARS-CoV-2 infection is often accompanied by excessive inflammation, which may lead to multiple organ dysfunction and even death [1–3]. People are constantly seeking for better drugs to improve patient mortality, including Baricitinib [4]. Barisinib is an oral Janus kinase (JAK) 1/2 inhibitor that was previously approved by the European Medicines Agency (EMA) for several chronic autoimmune diseases [5].

Studies have found that barisinib can reduce inflammatory storms, and serological examination showed that the application of the drug reduced cytokines and biomarkers related to the pathophysiology of COVID-19 in patients [6–8]. Later, World Health Organization (WHO) guidelines recommended the use of baricitinib, a Jak 1,2 inhibitor, for hospitalized COVID-19 patients receiving corticosteroid treatment. However, at that time, the relevant clinical evidence was relatively limited, so WHO recommended initiation of treatment "depending on availability," as well as "clinical and contextual factors" [9].

In the past, five clinical studies [4, 6, 10–12] have compared the efficacy and safety endpoint of baricitinib and placebo for COVID-19 patients. We analyzed 14-day mortality, 28-day mortality, recovery and shorter hospital stays as efficacy endpoints of the study. The safety outcomes include infections and infestations, major adverse cardiovascular events, deep vein thrombosis and pulmonary embolism. Although all of these studies included patients with COVID-19, the severity of the groups included in different studies varied, and their conclusions were inconsistent. While the novel coronavirus is still prevalent today, many countries are facing multiple rounds of virus impact. Our study systematically evaluated the mortality, length of stay and related adverse events of hospitalized patients with COVID-19 after the application of basitinib, which will provide certain guidance for clinical practice.

Methods

We carried out the meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [13]. Our protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database (Inplasy protocol: INPLASY202310086), and is available in full on inplasy.com (https://inplasy.com/inplasy-2023-1-0086). Ethics approval was not required for our work.

Search strategy

Three independent researchers (Jing Sun, Shufang Wang and Xin Ma) conducted extensive electronic searches for relevant articles published on Jan 31, 2023. The database includes PubMed, Embase and the Cochrane database. Manually select relevant randomized controlled trial. The search strategy of the literature was shown in the supplement (Additional file 1: Table S1).

Inclusion and exclusion

EndNote (X9 version) software is selected for document management, two investigators independently evaluated the eligibility of the identified items. The title and summary are filtered for the first time, and qualified articles are reserved for full-text review. The included studies were randomized controlled trials. Inclusion criteria for studies meeting the following requirements include: (1) Patients of hospitalized adults with COVID-19. (2) Treatment with baricitinib or placebo or conventional therapy. (3) Outcomes Indicators: Death from any cause/ Duration of hospitalization/ Median time to recovery/ lnfections and infestations/Major adverse cardiovascular events (MACEs)/Pulmonary embolism (PE)/Deep vein thrombosis(DVT), including one. We excluded animal testing, studies enrolling patients < 18 years old, and there was not enough data to extract, such as the summary of some meetings, literature materials such as review and pharmacological introduction. Documents that are not consistent with the content of this study will also be excluded. We contacted the authors if associated data from their studies were required.

Bias & quality assessment

The two researchers independently evaluated, preliminarily selected and checked the literature data according to the unified and standardized method, and included them in the literature in strict accordance with the admission and exclusion criteria, and then collected information. Evaluate the quality of selected articles according to the quality evaluation standard of Cochrane Reviewer Handbook 5.1.0 [14].

Data synthesis and analysis

Revman5.3 were used for meta-analysis. Data which met homogeneity ($P > 0.10$ and $I2 \leq 50\%$) through heterogeneity test were meta-analyzed using fixed effect model. If homogeneity ($P \leq 0.10$ or $I2 > 50\%$) was not met, and heterogeneity cannot be ruled out, random effect model can be used to combine effects [15]. While it should be noted that sensitivity analysis and subgroup analysis should be considered for this type of analysis data. Results were expressed as odds ratio (OR) with a 95% confidence

interval (CI) with discontinuous outcomes. For the continuous outcomes, mean differences (MD) and 95% CIs were estimated as effective. Some included RCTs reported median as the measure of treatment effect, with interquartile range (IQR). We estimated the mean from median and standard deviations (SD) from IQR using the methods described in the previous studies [16]. A p-value < 0.05 was considered statistically significant.

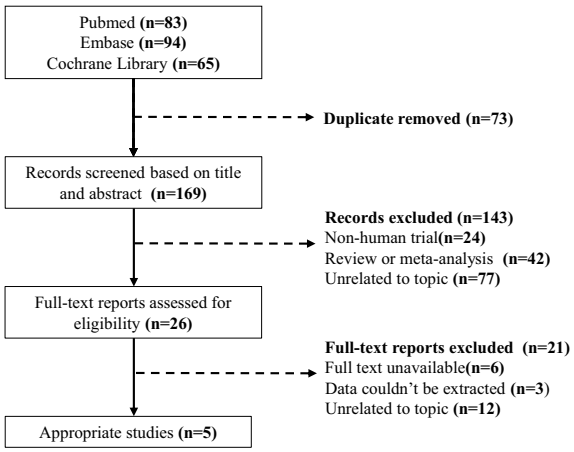

Fig. 1 The flow chart of the search and study selection process

Results

The flowchart (Fig. 1) summarizes the search and study selection process. A total of 242 related literatures were retrieved, of which 73 were excluded due to duplication. 143 studies were also excluded after reading the titles and abstracts. The remaining 26 studies were assessed by reading the full texts. Data from 5 trails evaluating the Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 were included.

The main features of included trials are presented in Table 1. A total of 3010 patients were included in our analyses. All included studies were randomized controlled trials or prospective study. All of the studies were comparing the efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19. The first three of the five studies in Table 1 are for hospitalized patients who have all been diagnosed with COVID-19, and the last two are for critically ill COVID-19 patients who have severe oxygenation disorder or receive mechanical ventilation/extracorporeal membrane oxygenation. No differences were observed in terms of proportion of patients lost to follow up across trials.

The efficacy outcomes are summarized in Fig. 2A, B, C and D in the Additional file 2: Figure S2AB). There was no difference in 14-day mortality (A) between the two groups [OR 0.23 (95% CI 0.03–1.84), $I^2 = 72\%$, $P = 0.17$].

Table 1 Design and outcomes of the studies included in the meta-analysis

Num	Author/ Year	Design	Intervention assignments		Participants				Outcomes
			Baricitinib	Control	Sample size, n	Mean age, years(B/C)	Male:Female, (B/C)	Time of medication	
1	Bronte/2020	PS, MC	4mg bid for 2 days, followed by 4mg qd	conventional therapy	76	68/77.5	7:13/31:25	7 days	All cause deaths; Incidence of ARDS; Duration of hospitalization
2	Kalil/2021	RCTs,MC	4-mg qd	Placebo	1033	55/55.8	319:196/333:185	14 days or until hospital discharge	14-day mortality, 28-day mortality Median time to recovery
3	Marconi/2021	RCTs,MC	4-mg qd	Placebo	1525	57.8/57.5	490:274/473:288	14 days	28-day mortality; Median time to recovery; Duration of hospitalisation
4*	Ely/2022	RCTs,MC	4-mg qd	Placebo	101	58.4/58.8	25:26/ 30:20	14 days	28-day mortality;Treatment-emergent infection; DVT; PE; MACEs
5*	Trøseid/2023	RCTs,MC	4-mg qd	Placebo	275	59/60	112:27/99:37	14 days	28-day mortality; 60-day mortality; Infections and infestations; DVT; PE; MACEs

ARDS Acute respiratory distress syndrome; *B/C* baricitinib group/ control group; *Bid* twice daily; *DVT* deep vein thrombosis; *MACEs* Major adverse cardiovascular events; *MC* Multicenter; *PE* pulmonary embolism; *PS* prospective study; *Qd* Once a day; *RCTs* randomized clinical trials

* Severe or critical COVID-19

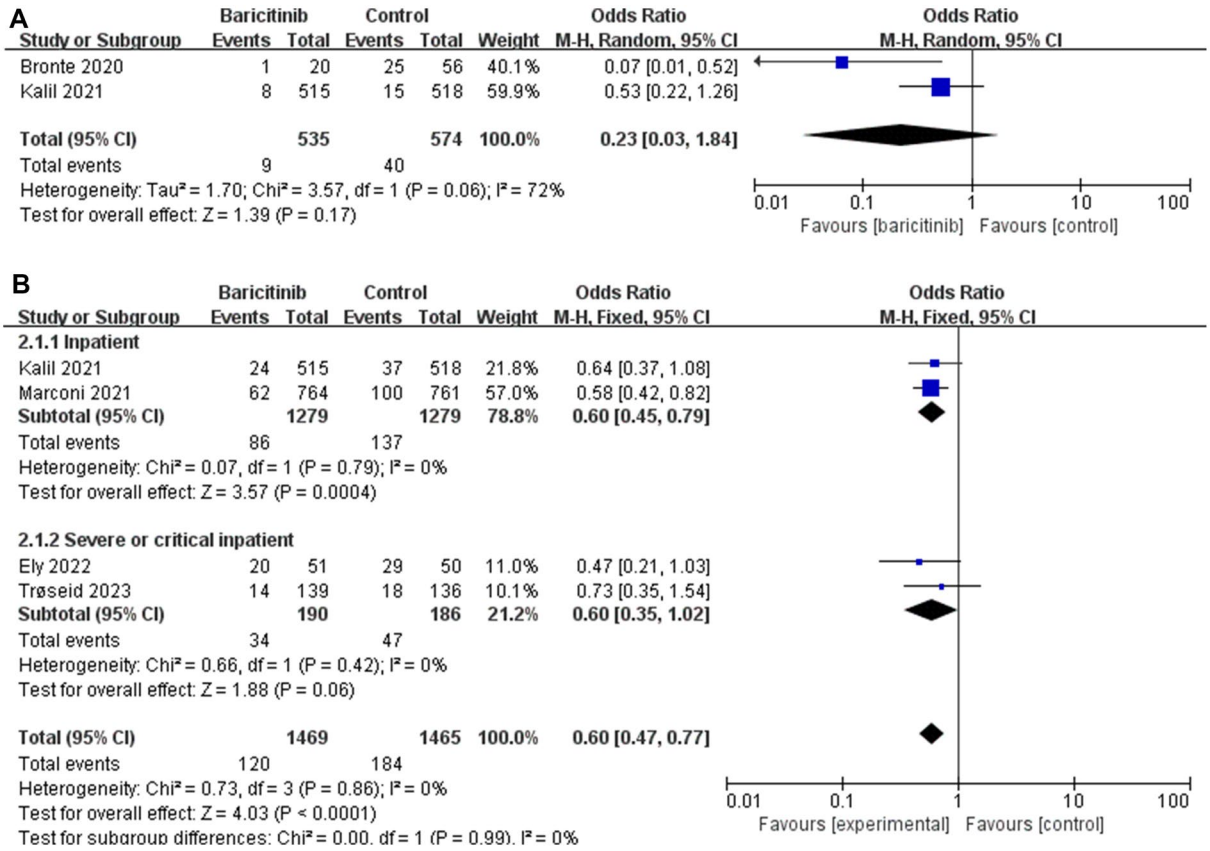

Fig. 2 **a** The efficacy outcomes of 14-day mortality. **b** The efficacy outcomes of 28-day mortality

Four studies reported 28-day mortality (B) outcomes in which baricitinib improved patient outcomes [OR 0.60 (95% CI 0.47–0.77), $I^2=0\%$, $P<0.0001$]. To further analyze the causes, we then performed a subgroup analysis according to disease severity. In subgroup analyses we saw that baricitinib did not seem to improve significantly in critically ill patients [OR 0.60 [95% CI 0.35–1.02], $I^2=0\%$, $P=0.06$]. Fortunately, baricitinib have led to faster recovery (D) and shorter hospital stays(C) for COVID-19 patients [MD = − 1.00 (95% CI − 1.12 to − 0.88), $I^2=0\%$, $P<0.0001$; MD = − 0.80 (95% CI − 0.84 to − 0.76), $I^2=0\%$, $P<0.0001$]. Due to the limited number of reports on the results of the current study, no further analysis is being conducted here. Based on previous experience, it is speculated that this may also be related to the severity of the disease. The safety outcomes are summarized in Fig. 3. There were no difference in infections and infestations (a), major adverse cardiovascular events (b), deep vein thrombosis(c) and pulmonary embolism (d). However, these results are based on the results of two randomized controlled trials conducted in patients with critically ill COVID-19.

We use Revman to investigate the influence of a single study on the overall pooled estimate of each predefined outcome. We found that the removal of any one study would not affect the following results. The results of the risk of bias assessment of these trials are summarized in the Additional file 1: Figure S1. Three studies were considered at low risk for overall risk of bias.

Discussion

This outbreak initially attracted people's attention as an unusual viral pneumonia, and atypical upper respiratory pneumonia has been the main characteristic disease severity of this outbreak so far [17]. Bronchoalveolar lavage fluid was derived from macrophages with high levels of chemokines secreted by severe pneumonia [18]. Postmortem lung tissue analysis of COVID-19 patients with severe pneumonia also found excessive immune cell infiltration [19]. Baricitinib, inhibitors of Janus kinase (JAK)-1 and JAK-2, plays an important role in the regulation of immune response. COVID-19 is still circulating, and different mutated strains are still affecting our lives nowadays. A more detailed mechanism of action may be

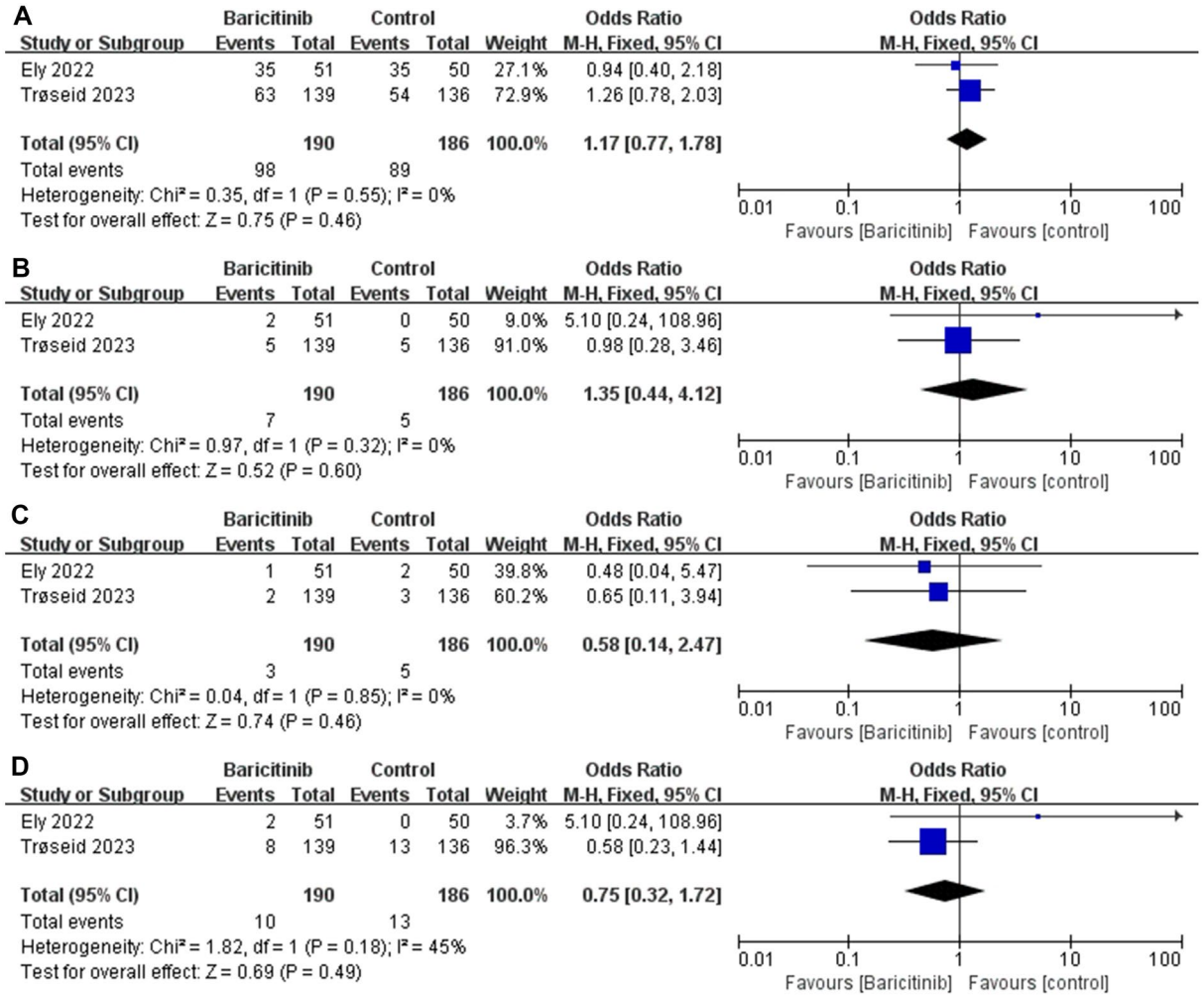

Fig. 3 The safety outcomes of infections and infestations (**a**), major adverse cardiovascular events (**b**), deep vein thrombosis (**c**) and pulmonary embolism (**d**)

the direction of future research, including mixing with other drugs. Our meta-analysis system evaluated the efficacy and safety of baricitinib, which provides a good description for future clinical applications.

This study systematically evaluated the efficacy and safety of basitinib in the treatment of COVID-19 patients by including 5 high-quality studies. It is a meta-analysis with the largest sample size of baricitinib and a high level of evidence. In the analysis of mortality, we adopted 14-day mortality and 28-day mortality. The results showed that baricitinib application improved 28-day mortality in general hospitalized patients, but did not improve 14-day mortality in hospitalized patients or 28-day mortality in critically ill patients. Based on the current evidence, we analyzed that the lack of improvement in 14-day mortality may be related to the small number of studies at present. However, in the description of 28-day mortality, we can see that baricitinib reduces the mortality of hospitalized patients with non-severe COVID-19, which also suggests that the importance of baricitinib in combination with other treatment options for critically ill patients. There have also been studies claiming that the risk/benefit ratio of baricitinib in patients with severe/critical COVID-19 may vary depending on the immune status of SARS-CoV-2, and that potential host factors such as comorbidibility, older age and possible immune response [20] may contribute to this difference, which is worth further analysis and research in the future.

Our study, which pooled existing high-quality studies, has clear advantages, particularly in terms of mortality, and conducted a subgroup analysis of patients who were not at risk, revealing the different effects of the drug in different patients. And the safety of drugs in

critically ill patients was analyzed. It provides a strong guiding value for clinic. Of course, this study also has some limitations. The current number of studies is relatively small, and more RCTs are needed to support it in the future.

Conclusions

Baricitinib shortens the length of hospital stays and reduces the mortality of non-severe COVID-19 patients. It should be noted that the effect of drugs on the mortality of critical ill patients is not significant.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-023-01403-0.

Additional file 1: Table S1. Search strategy. **Figure S1.** Risk of bias graph.

Additional file 2: Figure S2A. The efficacy outcomes of hospital stays. **B** The efficacy outcomes of recovery.

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Author contributions
JS, S-FW and XM searched the scientific literature and drafted the manuscript. Q-QW, Y-JP and YB contributed to data abstract. G-BM, CM and PL contributed to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. The authors read and approved the final manuscript.

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Availability of data and materials
Data sets are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors approved the final manuscript and the submission to this journal.

Competing interests
Authors state no competing interests.

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Publisher's Note

BMC Pharmacology and Toxicology

RESEARCH Open Access

Effects of melatonin on the prevention of delirium in hospitalized older patients: systematic review and meta-analysis

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Abstract

Objectives Melatonin has been demonstrated to exert a preventive effect on delirium. This meta-analysis sought to investigate the preventive effects of melatonin and melatonin receptor agonists (ramelteon) on delirium in hospitalized elderly patients.

Methods This systematic review and meta-analysis delineates the risk of delirium events in older hospitalized patients with melatonin/ramelteon compared with placebo, incorporating randomized controlled trials published up to 8 July 2024. The databases searched were PubMed, Embase and the Cochrane Library. The primary outcome measures were the incidence of delirium, while the secondary outcome measures were the length of hospital stay and mortality. The results are presented as odds ratios (OR) or mean differences (MD) with a 95% confidence interval. The review of publications was conducted in accordance with the guidelines set forth in the Cochrane Handbook and the Preferred Reporting Project for Systematic Review and Meta-Analysis (PRISMA). This study has been registered with INPLASY (number INPLASY202470044).

Results A total of 2086 patients were included in 13 randomized controlled trials. The primary outcome of this meta-analysis demonstrated a statistically difference in the incidence of delirium between the melatonin and placebo groups in hospitalized elderly patients (OR = 0.59, 95% CI: 0.40–0.87, $P < 0.01$, $I^2 = 60\%$), particularly in those who had undergone surgery (OR = 0.60, 95%CI: 0.40–0.89, $P = 0.01$, $I^2 = 53\%$). No statistically differences were observed in terms of length of stay (MD=-0.07, 95%CI:-1.09-0.94, $P = 0.89$, $I^2 = 72\%$) and mortality (OR = 0.79, 95%CI:0.58–1.06, $P = 0.12$, $I^2 = 0\%$).

Conclusions Melatonin has been demonstrated to exert a protective effect on delirium in elderly patients who are hospitalized, particularly in the context of perioperative care.

†Le Liu, Xin Ma and Zejun Song have contributed equally to this work.

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Keywords Melatonin, Delirium, Older patients

Introduction

Delirium is a psychiatric symptom-related syndrome that is estimated to occur in 20–30% of hospitalized elderly patients [1, 2]. However, incomplete knowledge among medical practitioners may result in an incomplete diagnosis of delirium. There is evidence to suggest that delirium exacerbates cognitive decline, prolongs hospitalization and increases mortality rates among elderly patients [3–5].

Patients with delirium may experience hallucinations and delusions, as well as other manifestations. Acute episodes of delirium can affect sleep patterns, and the course of the disease may fluctuate. There is evidence to suggest a potential mechanism relationship between delirium and sleep [6–7]. It is unfortunate that there is currently no effective treatment for delirium. Consequently, doctors often prescribe antipsychotic drugs to delirium patients. Nevertheless, research has demonstrated that antipsychotic aversion does not diminish the likelihood of delirium in patients, and the utilization of antipsychotic aversion is constrained by the occurrence of adverse drug reactions [8–9].

Melatonin is a naturally occurring hormone produced by the body that plays a role in regulating the body's normal circadian rhythm. Given the abnormal secretion of melatonin observed in delirium patients, several studies have evaluated the potential role of melatonin (or melatonin receptor agonists, ramelteon) in preventing delirium in adults. However, the results of these studies have not been entirely consistent [10–22]. Previous meta-analyses have examined the impact of melatonin on delirium in hospitalized patients, yet the findings have been inconclusive. Khaing [23] analysis of 1712 hospitalized patients revealed that melatonin was effective in reducing delirium in surgical and critically ill patients. In contrast, You [24] included 18 randomized controlled trials that demonstrated the beneficial effects of melatonin in reducing delirium in medical patients. The present study aimed to analyze the preventive effect of melatonin (or melatonin receptor agonists, ramelteon) on the occurrence of delirium in a special group of elderly hospitalized patients. Additionally, the length of stay and mortality of elderly hospitalized patients were analyzed, with the objective of providing guidance for clinical practice.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [25]. The preregistration of our meta-analyses could be accessed via the International Platform of Registered Systematic Review and Meta-analysis Protocols database (Number: INPLASY202470044). The full text was available for download from inplasy.com (https://inplasy.com/inplasy-2024-7-0044). It should be noted that ethical approval was not required for this study.

Search strategy

A comprehensive electronic search of the literature was conducted by three researchers (Le Liu, Xin Ma and Zejun Song) for articles published in the field prior to 8 July 2024. A comprehensive search of the PubMed, Embase and Cochrane databases was conducted manually, with the objective of selecting relevant randomized controlled trials. For further details of the specific literature search strategies employed, please refer to the Appendix (Supplement Table S1).

Inclusion and exclusion

The document management process utilized the EndNote (X9) software, with two investigators independently assessing the eligibility of the project. The titles and abstracts were initially screened, and the resulting articles were then subjected to a full-text review. The studies included in the review were randomized controlled trials. The following inclusion criteria were met: (1) elderly patients who were hospitalized; (2) patients who were taking melatonin (or melatonin receptor agonists) or a placebo. The exclusion criteria include studies involving animals, studies conducted on subjects under the age of 60 years old for inclusion through the reading of studies, and studies with insufficient data extraction, including abstracts, reviews, pharmacological reports, and other literature. Should the necessity arise to obtain pertinent research data, the authors will be contacted in a timely manner. The primary outcome measures were the incidence of delirium, while the secondary outcome measures were the length of hospital stay and mortality (either during hospitalization or within 30 days of discharge).

Bias and quality assessment

Two researchers conducted independent evaluations, preliminary selections, and verifications of the literature in accordance with a unified and standardized method. The literature was included or excluded in accordance with the pre-established criteria, after which the data was collected. The quality of the selected articles was evaluated in accordance with the Cochrane Reviewer Handbook 5.1.0 [26]. The RoB tool was used to assess bias risk.

Data synthesis and analysis

The meta-analysis was conducted using RevMan 5.4. Data that met the criteria for homogeneity ($P>0.10$ and $I^2 \leq 50\%$) as determined by the heterogeneity test were subjected to meta-analysis using the fixed-effect model (M-H). In instances where the aforementioned homogeneity criteria were not met ($P \leq 0.10$ or $I^2>50\%$), and the presence of heterogeneity could not be discounted, the random-effect model was employed to consolidate the effects [27]. To compare the effects of melatonin/ramelteon with placebo, the odds ratios (OR) or mean differences (MD) with a 95% confidence interval (CI) were pooled according to the fixed and random effects model. A p-value of less than 0.05 was considered to be statistically significant.

Results

The flow chart (Fig. 1) provided a summary of the search and research selection process. A total of 857 literature sources were searched, 311 of which were excluded due to duplication. Additionally, 494 studies were excluded after a preliminary review of the title and abstract. The remaining 52 studies underwent a comprehensive evaluation based on a thorough reading of the full text. Of these, 13 randomized controlled trials assessed the efficacy of melatonin (or melatonin receptor agonists) in preventing delirium in hospitalized older patients.

The principal characteristics of the included trials were set forth in Table 1. A total of 2,086 patients were included in the analyses. All of the included studies were randomized controlled trials. The estimates are expressed as odds ratios (OR) or mean differences (MD) with a 95% confidence interval (CI). The primary outcome of this meta-analysis demonstrated a statistically difference in the incidence of delirium between the melatonin and placebo groups in hospitalized elderly patients (OR = 0.59, 95% CI: 0.40–0.87, $P<0.01$, $I^2=60\%$). A subsequent subgroup analysis demonstrated that the observed statistical difference was associated with older patients undergoing surgery (Fig. 2) (OR = 0.60, 95%CI: 0.40–0.89, $P=0.01$, I2 = 53%), whereas no statistical difference was observed among patients hospitalised for medical reasons. The analysis of melatonin and melatonin receptor agonists across groups (Fig. 3) revealed a statistically difference in the risk of delirium with melatonin compared to placebo (OR = 0.65, 95%CI: 0.43–0.98, $P=0.04$, $I^2=66\%$), while no statistically difference was observed between melatonin receptor agonists and placebo (OR = 0.36, 95%CI: 0.12–1.09, $P=0.07$, $I^2=49\%$). With regard to secondary outcomes, no statistically differences were identified with respect to length of stay (MD = -0.07, 95% CI: -1.09 to -0.94, $P=0.89$, $I^2=72\%$) (Fig. 4) and mortality (OR = 0.79, 95% CI: 0.58 to 1.06, $P=0.12$, $I^2=0\%$) (Fig. 5).

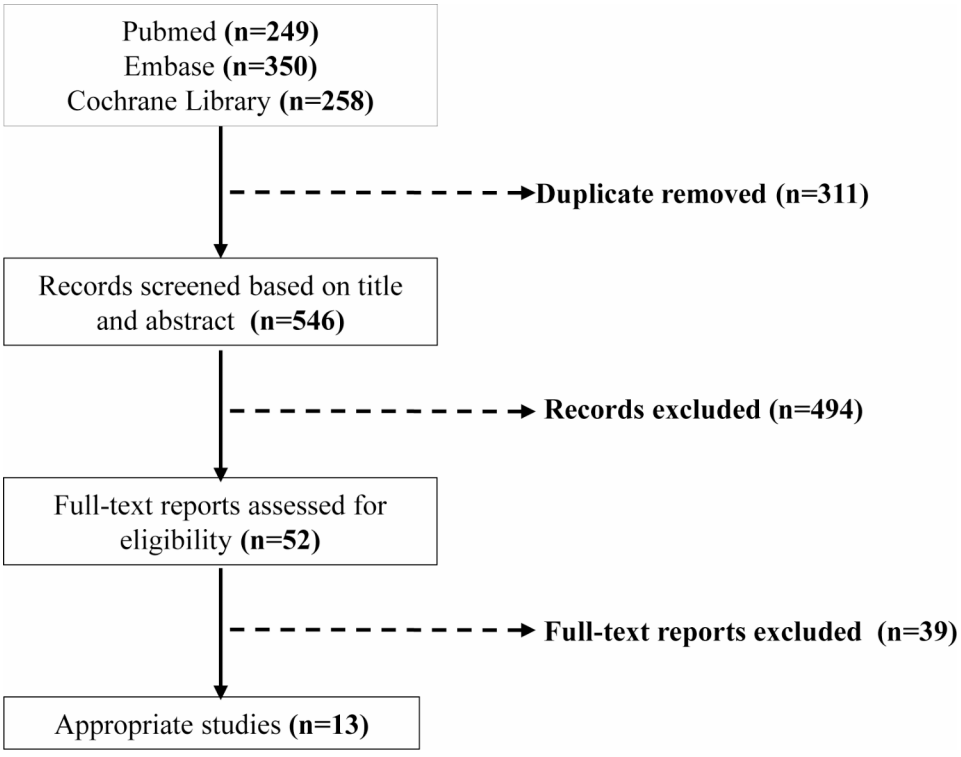

Fig. 1 Selection process for studies included in the meta-analysis

Table 1 Design and outcomes of the studies included in the meta-analysis

Num	Author/Year	Design	Intervention assignments		Participants					Outcome
			Intervention (Time)	Control	Sample, *n*	Mean age, (I/C)	Male%, (I/C)	Patients	Measures	
1	Al-Aama/2010	RCT	M 0.5 mg Qd * 14d	Placebo	122	84/85	46/39	Medical patients	CAM	Incidence of delirium; Death during admission; Length of stay
2	Elbakry/2024	RCT	M 5 mg + 5 mg#	Placebo	100	NR	NR	Colorectal cancer surgeries	CAM	Incidence of delirium
3	Gupta/2019	RCT	R 8 mg + 8 mg#	Placebo	100	69/71	70/66	Various surgery	CAM	Incidence of delirium
4	Hatta/2014	RCT	R 8 mg Qd * 7d	Placebo	67	78/78	48/32	Medical patients	DSM IV	Incidence of delirium
5	Jaiswal/2018	RCT	M 3 mg Qd * 14d	Placebo	87	81/80	42/34	Medical patients	CAM	Incidence of delirium; Length of stay
6	Jonghe/2014	RCT	M 3 mg Qn * 5d	Placebo	378	84/83	53/62	Hip surgery	DSM IV	Incidence of delirium; Length of stay; Death during admission
7	Kinouchi/2023	RCT	R 8 mg Qn * 6d	Placebo	103	78/75	52/53	Elective surgery	CAM-ICU	Incidence of delirium
8	Lange/2024	RCT	M 5 mg Qn * 5d	Placebo	117	87/87	49/48	Medical patients	CAM	Incidence of delirium
9	Oh/2021	RCT	R 8 mg Qn * 3d	Placebo	71	74/75	42/37	Hip or knee replacement	DSM-V	Incidence of delirium
10	Shi/2021	RCT	M 3 mg Qd * 7d	Placebo	297	72/72	62/59	PCI	CAM	Incidence of delirium; 30-day all-cause mortality
11	Sultan/2010	RCT	M 5 mg Qd *4 d	Placebo	102	70/72	45/45	Hip arthroplasty	AMT	Incidence of delirium
12	Yamaguchi/2014	RCT	R 8 mg Qn * 4d	Placebo	45	≥ 70/≥70	NR	Total knee arthroplasty	ICU-Delirium screening checklist	Incidence of delirium
13	Yin/2022	RCT	M 3 mg Qd * 7d	Placebo	497	69/69	61/57	AHF after surgery	CAM-ICU	Incidence of delirium; 30-day all-cause mortality

M Melatonin, *R* Ramelteon, *AMT* Abbreviated Mental Test, *CAM* Confusion Assessment Method, *CAM-ICU* Confusion Assessment Method-Intensive Care Unit, *ICU* intensive care unit, *I/C* Intervention group/ Control group, *NR* not reported, *Qd * nd* Once daily for n days, *Qn* Once a night, *M 5 mg + 5mg#* 5 mg was given 12 h before surgery and another 5 mg was given 2 h before surgery, *R 8 mg + 8mg#* 8 mg was given 12 h before surgery and another 8 mg was given 1 h after surgery

We use Revman to investigate the impact of a single study on the overall pooled estimate of each predefined outcome. The results of the bias risk assessment for these trials are summarized in the Supplementary. From the funnel plot, we can see the symmetric distribution of literature, and we can believe that there is no publication bias. In terms of quality evaluation, with eight of them achieving the maximum score, which serves to fully demonstrate the credibility of the research conclusions presented in this paper.

Discussion

Our meta-analysis clearly described the efficacy of melatonin in preventing delirium in elderly hospitalized patients. First of all, melatonin can reduce the risk of delirium in elderly hospitalized patients, especially postoperative elderly patients, while the incidence of delirium observed in medical patients was not statistically significant, providing certain clinical reference value. Second, the length of hospital stay and mortality of patients did not differ between the melatonin and control groups, suggesting the safety of its use. The distinction between this study and previous research is that our survey targeted older adults and classified them based on whether they had undergone surgical procedures [23–24]. The study population is more precisely defined, which lends credence to the notion that the results will be even more accurate. The findings of our study diverge from those of the aforementioned research [24] in that melatonin has been demonstrated to be a more efficacious intervention in reducing the incidence of delirium in surgical patients than in older patients receiving general medical care.

Patients undergoing surgical procedures are at risk of developing delirium due to the effects of the surgery

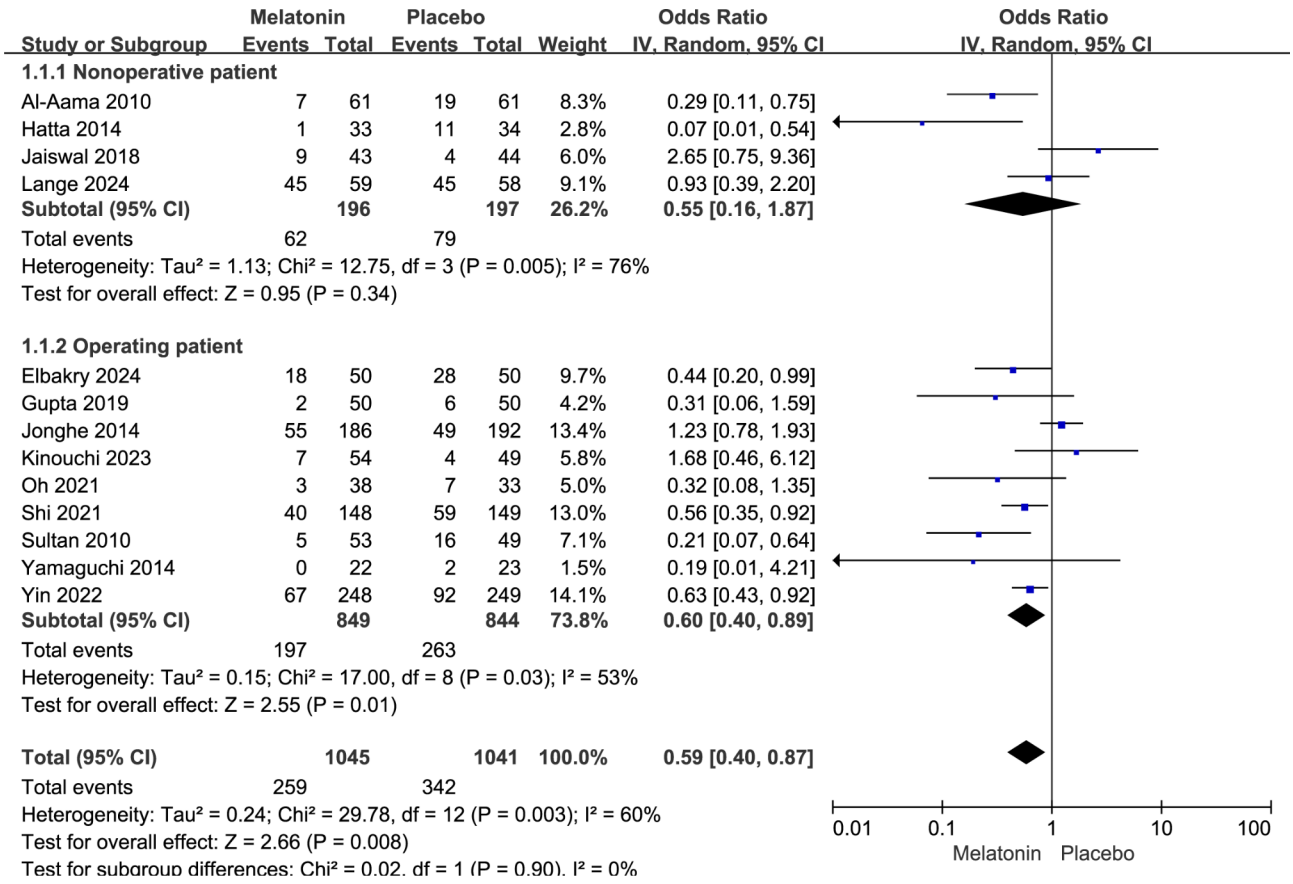

Fig. 2 Incidence of delirium between melatonin and placebo (operation or not)

itself on neurotransmitter levels in the body, which can directly damage the brain. The sedative effects of melatonin may prove beneficial for this group of patients, reducing the risk of delirium [28]. Furthermore, sleep disorders and sleep-wake cycle disorders have been identified as risk factors for postoperative delirium, and the sleep-inducing effects of melatonin have been identified as a potential mechanism of action [23]. Furthermore, delirium and surgical stress may induce the release of inflammatory mediators, and the anti-inflammatory and antioxidant effects of melatonin may also prove beneficial in this regard [29]. These effects may indicate a pivotal role for melatonin in mitigating the risk of delirium in elderly hospitalised patients.

The data indicate that melatonin may reduce the incidence of delirium, particularly in postoperative patients. However, further studies are required to validate these findings in this specific population. Furthermore, melatonin appears to be more effective than ramelteon in the prevention of delirium. However, this finding may be attributed to the limited sample size, and further experimental verification is necessary in the future. The principal advantage of this study is that the elderly were analysed as a group, and 13 randomised controlled trials were included in the meta-analysis, which is currently the largest sample size and may have a positive guiding effect on future clinical treatment.

It is important to note that the study is subject to several limitations. The relatively limited database searched, the language limited to English, and the absence of grey literature may have resulted in a reduction in the sample size of the study. The included randomised controlled trials employed disparate doses of melatonin and varying durations of intervention, in addition to discrepancies in the baseline characteristics of enrolled patients, clinical settings, and methods of measuring outcomes. These factors may have contributed to the heterogeneity of the studies. In the majority of randomized controlled trials, delirium was identified using the CAM or CAM-ICU. However, with a sensitivity of 94% and specificity of 89%, CAM is a screening tool and is not the gold standard for diagnosing delirium [30]. Future studies with larger sample sizes are needed to further confirm the value of melatonin in preventing delirium in elderly patients.

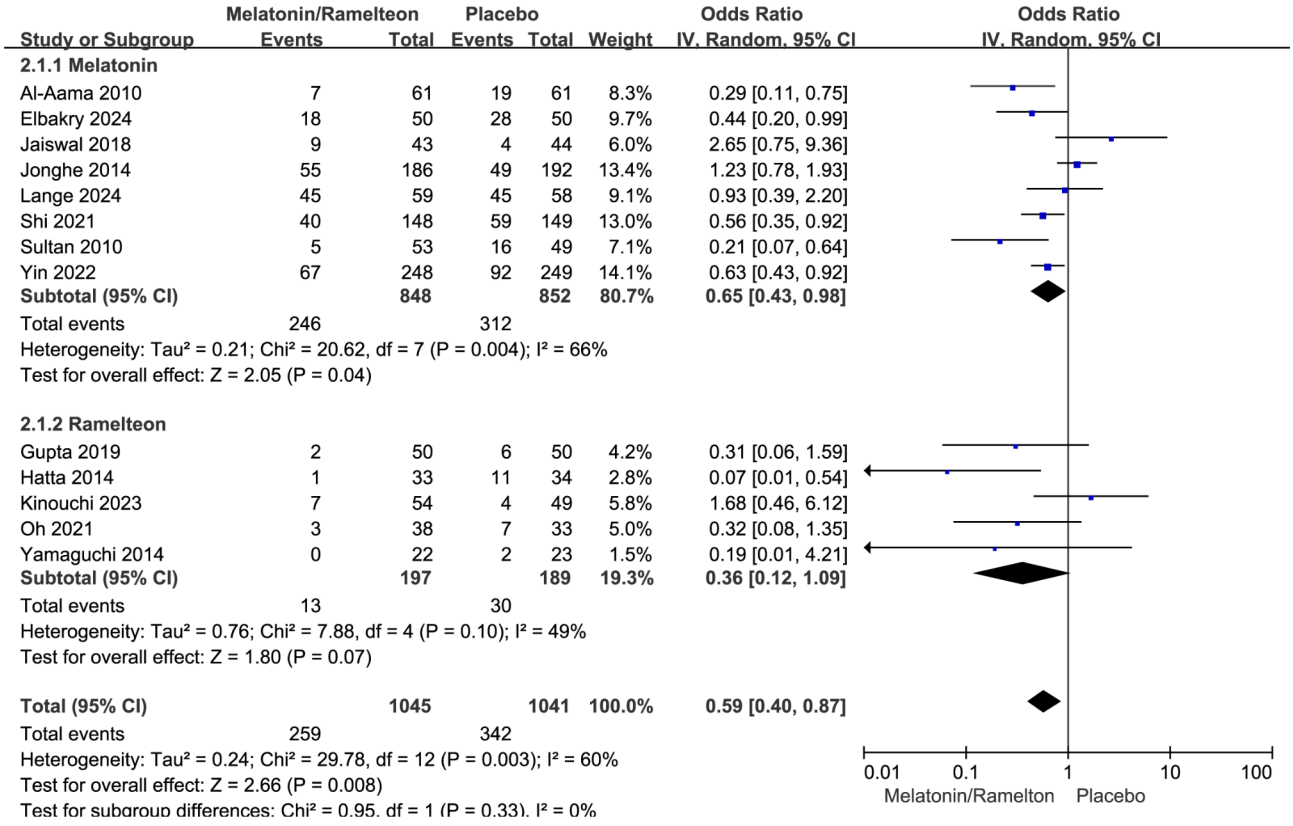

Fig. 3 Incidence of delirium between melatonin and placebo (melatonin or ramelteon)

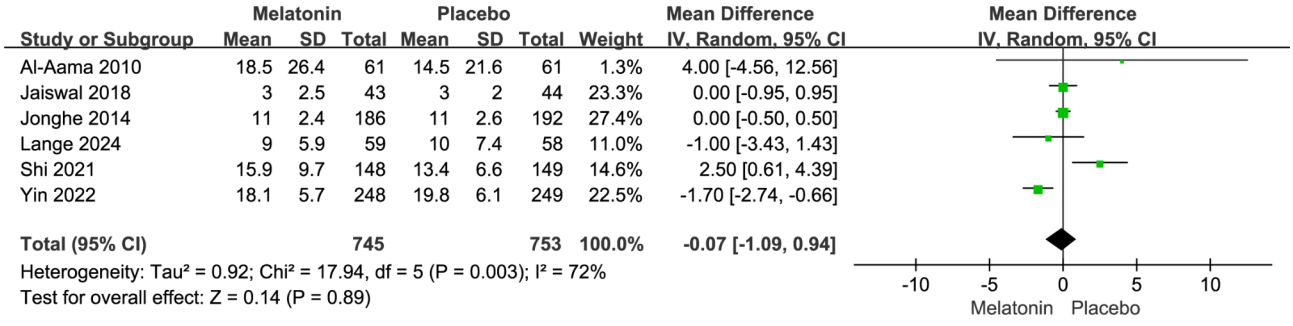

Fig. 4 Comparisons of the 28-day mortality between melatonin and placebo

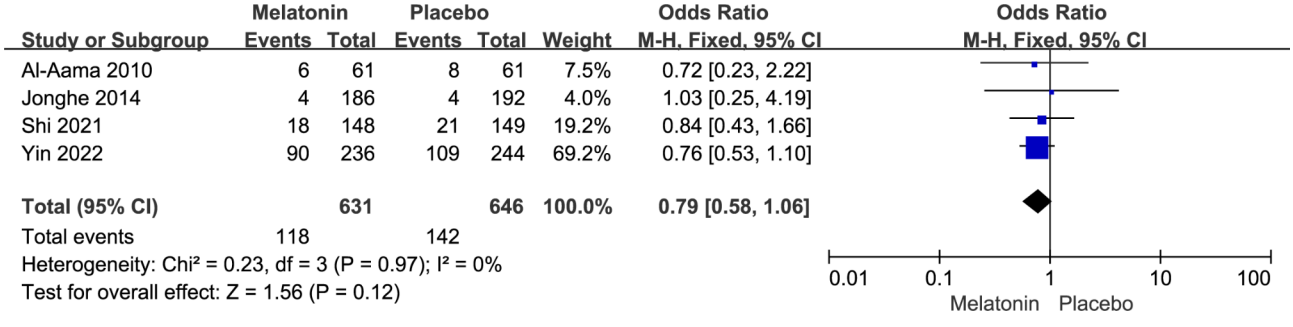

Fig. 5 Length of stay between melatonin and placebo

Conclusions

Melatonin has been demonstrated to have a preventative effect on delirium in elderly patients who are hospitalized. Furthermore, it has been shown not to increase the length of hospital stay or mortality, particularly in elderly patients who are hospitalized following surgery. Therefore, melatonin may be a beneficial intervention for the prevention of delirium.

Abbreviations

AMT	Abbreviated Mental Test
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method-Intensive Care Unit
CI	Confidence Intervals
ICU	Intensive Care Unit
OR	Odds Ratio
RCTs	Randomized controlled trials

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-024-00816-9.

Supplementary Material 1

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None.

Author contributions

LL, XM and Z-J S conducted a comprehensive review of the scientific literature and drafted the manuscript. JL and Y-SZ provided assistance in the compilation of data. S-FW assisted in the processing of the data and the creation of visual representations. CM, G-BM and PL were instrumental in the conceptualization, design, interpretation of data, revision of the manuscript for critical intellectual content, and supervision of the study. The authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the final manuscript and the submission to this journal.

Competing interests

The authors declare no competing interests.

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Publisher's note

BMC Pharmacology and Toxicology

RESEARCH

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Intravenous dexmedetomidine for delirium prevention in elderly patients following orthopedic surgery: a meta-analysis of randomized controlled trials

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Abstract

Objectives We conducted a meta-analysis to investigate the effect of dexmedetomidine on postoperative delirium in elderly orthopedic surgery patients.

Methods A meta-analysis was conducted to identify randomized controlled trials of dexmedetomidine in elderly patients undergoing orthopedic surgery. The data was published on October 25, 2024. PubMed, Embase, and Cochrane Library databases were searched. Outcome measures included incidence of delirium, length of hospital stay, visual analogue scale, and postoperative complications. Estimates are expressed as relative risk (RR) or mean difference (MD) with a 95% confidence interval (CI). The publications were reviewed according to the guidelines of the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results This study was registered with INPLASY (number INPLASY2024110004). A total of 3159 patients were included in 9 randomized controlled trials. The results showed that dexmedetomidine exhibited a preventive effect on delirium compared with the control group in elderly patients after orthopedic surgery (RR: 0.55, 95% CI: 0.45–0.66, $P<0.01$, $I^2=0\%$). Subgroup analysis suggested that dexmedetomidine was significantly different from saline(RR: 0.56; 95% CI: 0.44–0.73, $P<0.01$, $I^2=31\%$) and propofol(RR: 0.52; 95% CI: 0.39–0.70, $P<0.01$, $I^2=0\%$) in reducing postoperative delirium in elderly fracture patients. No statistically significant differences were observed in length of hospital stay, visual analogue scale, and postoperative complications ($P>0.05$). Certainty of evidence for postoperative delirium was moderate.

Conclusions Dexmedetomidine has been shown to have a protective effect on postoperative delirium in elderly patients following orthopedic surgery.

[†]Jing Sun and Duo Wang contributed equally to this work.

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Keywords Dexmedetomidine, Delirium, Orthopedic surgery

Introduction

Postoperative delirium (POD) is a neurological disorder associated with temporary loss of consciousness and cognitive dysfunction. The exact etiology of POD remains uncertain [1]. The occurrence of POD is related to a number of factors, including the patient's age, the type of surgery, the anesthesia and sedation administered during the procedure, and the complications that arise during the surgery. Elderly patients who have undergone fracture surgery have been shown to have a number of characteristic features, including advanced age, prolonged bed rest, blood loss, and the presence of underlying comorbidities. The incidence of POD is 32–53.3% [1], which is significantly higher than in younger patients [2]. POD has been shown to increase the risk of short- and long-term complications in older patients who have sustained a fracture and undergone surgery. Additionally, it has been shown to prolong hospital stay and increase associated costs [3–4]. Therefore, it is of great clinical importance to identify effective preventive measures against delirium in this population.

Dexmedetomidine is a highly selective α-2-adrenergic receptor antagonist that can inhibit sympathetic nerve excitability [5], increase vagus nerve excitability, lower blood pressure, lower heart rate, and reduce myocardial oxygen consumption. In addition, dexmedetomidine has been observed to cause sedation, analgesia, anxiolytic effects, hypnosis, memory loss, and anesthesia-like symptoms. The drug exerts a sedative effect by inhibiting the division of neurons, thereby reducing the perception of pain and anxiety. The pharmacological properties of dexmedetomidine include rapid absorption, rapid distribution, rapid metabolism and rapid excretion. In clinical practice, dexmedetomidine is used for sedation, analgesia and sedation, as well as for intraoperative and postoperative sedation and analgesia [6]. Additionally, dexmedetomidine has been shown to inhibit central nervous system activity, thereby reducing pain in patients [7]. A number of studies have documented the neuroprotective effects of dexmedetomidine [8]. Nevertheless, the results of recent randomized controlled trials suggest that the effectiveness of dexmedetomidine in reducing the incidence and safety of POD in elderly patients undergoing orthopedic surgery is still inconclusive. The aim of this study is to conduct a meta-analysis to evaluate the potential protective effect of dexmedetomidine on the occurrence of POD in elderly patients undergoing orthopedic procedures.

Methods

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [9]. The protocol has been registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols database (Inplasy protocol: INPLASY2024110004) and is fully available on Inplasy.com (https://inplasy.com/inplasy-2024-11-0004/). Ethical approval was not required for this study.

Search strategy

Three researchers (Jing Sun, Duo Wang, and Yue Zhao) conducted a comprehensive electronic literature search for articles published in this area before October 25, 2024. The database includes PubMed, Embase and the Cochrane database. The PubMed basic search strategy as follows: (cataclasis[Title/Abstract] OR fracture[Title/Abstract] OR joint[Title/Abstract] OR articulation[Title/Abstract] OR arthroplasty[Title/Abstract] OR limb[Title/Abstract] OR orthopedic[Title/Abstract]) AND (dexmedetomidine[Title/Abstract]) AND (delirium[Title/Abstract] OR deliriums[Title/Abstract]). Manually select relevant randomized controlled trials. The search strategy of the literature was shown in the supplement (Supplementary file: Table S1). Language is limited to English.

Study selection criteria

This systematic review and meta-analysis focused primarily on elderly patients (60 years or older) undergoing orthopedic surgery. All published full-text randomized controlled trials (RCTs) comparing the effectiveness of dexmedetomidine with other agents (such as placebo or propofol) in preventing postoperative delirium after orthopedic surgery were eligible for inclusion. The outcomes were the incidence of delirium after orthopedic surgery, the length of hospital stay, visual analog scale, and complications 30 days after surgery (defined as new-onset adverse conditions requiring therapeutic intervention according to the Clavien-Dindo classification, which included grade 2 or higher)., including acute renal failure, pulmonary infection, disease control and disease control). Heart failure, myocardial infarction, new cardiac arrhythmias, pulmonary embolism or deep vein thrombosis, and cerebrovascular disease or wound infections. We excluded animal studies, studies involving patients under 18 years of age, and insufficient data to be extracted such as abstracts, reviews, pharmacological presentations, and other literature. Literature that does not agree with the content of this study will also be excluded. If we need relevant research data, we

contact the authors. Chizophrenia, epilepsy, parkinsonism, or coma were excluded from the study population. Non-intravenous administration, inappropriate control group settings, and inaccurate data extraction were also excluded.

Data extraction

Three authors undertook the data extraction independently, using the established standard data collection table. The extracted data are as follows: the first author's name, the year of publication, the basic characteristics of the participants, the type of surgery, the method of assessment of POD, the strategy of dexmedetomidine infusion, outcomes mentioned above, method of anesthesia and exclusion criteria.

Bias & quality assessment

Two researchers independently selected and reviewed the literature data using a uniform and standardized method and included them in the literature in strict compliance with the eligibility and exclusion criteria. They then collected information. The quality of the selected articles was assessed according to the standards of the Cochrane Reviewer Handbook, version 5.1.0 [10], using the RoB 2.0 tool. We used the funnel plot to assess the publication bias of the studies, and to ensure the accuracy of the results, we considered excluding studies with significant publication bias.

Data synthesis and analysis

The meta-analysis was conducted using RevMan 5.4. Data that met the criteria for homogeneity ($P > 0.10$ and $I^2 \leq 50\%$) as determined by the heterogeneity test were subjected to meta-analysis using the fixed-effect model (M-H). In cases where the above homogeneity criteria were not met ($P \leq 0.10$ or $I2 > 50\%$) and the presence of heterogeneity could not be excluded, the random effects model was used to consolidate the effects [11]. A prespecified subgroup analysis was performed according to the control group (saline or propofol) administration strategy. Estimates are expressed as relative risk (RR) or mean difference (MD) with a 95% confidence interval (CI). A p value less than 0.05 was considered statistically significant.

Certainty assessment

This study assessed research certainty according to the criteria of theGRADE (Grading of Recommendations Assessment, Development, and Evaluation) Guidelines Working Group [12]. According to the corresponding evaluation criteria, the evidence level was classified (divided into 4 categories: high, moderate, low and very low) [13].

Results

The flowchart provides a summary of the process for identifying and selecting studies for review (Fig. 1). A total of 219 related literatures were retrieved, of which 91 were excluded due to duplicates. In addition, 109 studies were excluded after a preliminary assessment of titles and abstracts. The remaining 19 studies underwent a more comprehensive assessment through a thorough reading of the full texts. Data from nine studies [14–22] evaluating the efficacy and safety of dexmedetomidine for the prevention of delirium in elderly patients undergoing orthopedic surgery were included in the final analysis.

The trials included in this review were published between 2016 and 2024 and included a total of 3159 patients (1580 in the dexmedetomidine group and 1579 in the control group). The detailed characteristics of the included trials were presented in Table 1.

A total of nine studies with a total of 3159 patients showed that dexmedetomidine significantly reduced the incidence of POD in elderly patients after orthopedic surgery compared to the control group (Fig. 2, RR: 0.55; 95% CI: 0.45–0.66, $P < 0.01$, I^2=0%). Subgroup analysis suggested that dexmedetomidine was significantly different from saline(RR: 0.56; 95% CI: 0.44–0.73, P<0.01, I = 31%) and propofol(RR: 0.52; 95% CI: 0.39–0.70, P<0.01, I^2=0%) in reducing postoperative delirium in elderly fracture patients. Regarding the length of hospital stay (after surgery), we removed studies with significant publication bias that showed no statistically significant difference between dexmedetomidine and control groups (Fig. 3, MD: 0.00; 95% CI: -0.08–0.08, $P = 1.00$, I^2=0%). Furthermore, it had no effect on the visual analogue scale (VAS) (Fig. 4, RR: -1.10; 95% CI: -2.87–0.66, $P = 0.22$, I^2=99%). Three studies reported postoperative complications within 30 days after surgery, which was not a statistically significant difference (Fig. 5, RR: 0.87; 95% CI: 0.61–1.23, $P = 0.23$, I^2=33%).

RevMan software is used to see how an individual study affects the overall outcome for each endpoint. The RoB 2.0 tool was used to assess the quality of the research. The quality of included studies was affected by missing outcome data and selection of the reported result, which caused some concerns. GRADE is used to assess the certainty of evidence affected by the risk of bias, inconsistency and imprecision, as described in the **supplementary file**. Certainty of evidence for postoperative delirium was moderate.

Discussion

Previous research has shown that delirium is a significant health problem [23] that is strongly associated with prolonged hospital stays, mortality, and other complications in patients. Several risk factors have been identified, including a history of cognitive impairment,

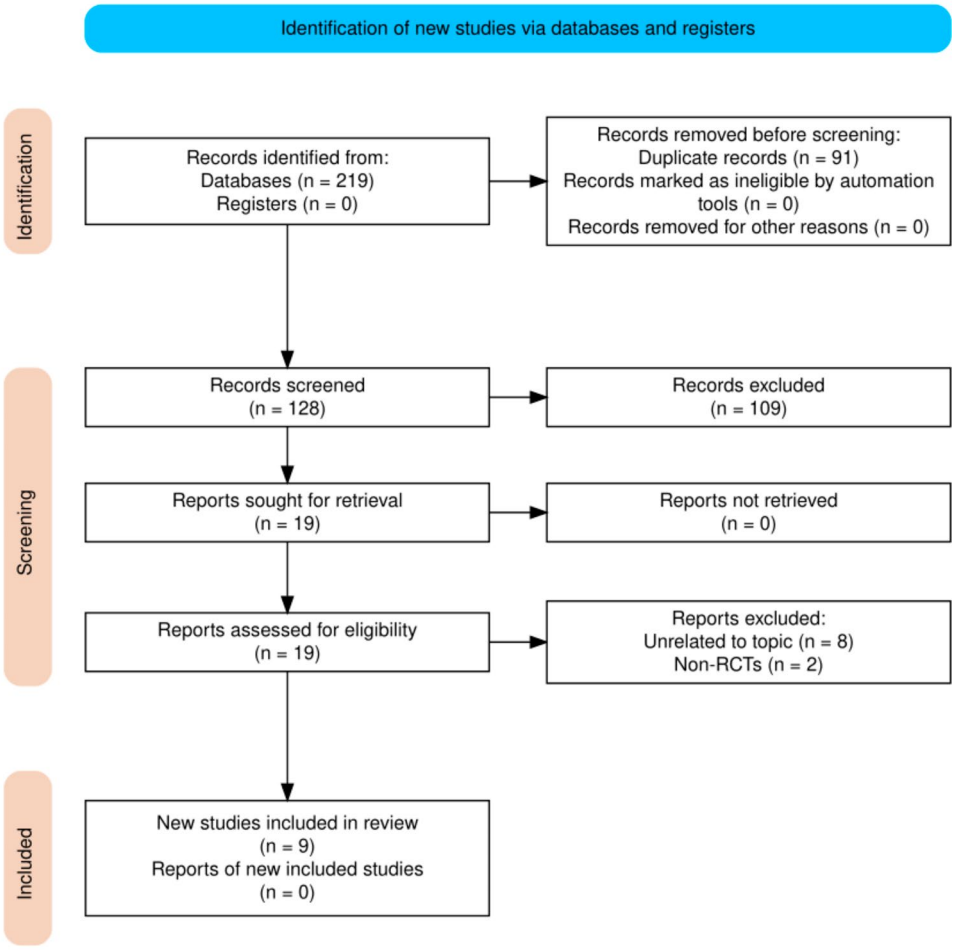

Fig. 1 The flow chart of the search and study selection process

postoperative pain, use of opioids and sedatives, and postoperative inflammation. These factors have been shown to be associated with delirium [24–26]. Consequently, proactive prevention of delirium through non-pharmacological and pharmacological means is a crucial aspect of perioperative management [26].

Dexmedetomidine is a potent α2-adrenergic receptor agonist. Dexmedetomidine inhibits norepinephrine release by activating the α2-adrenergic receptor postsynaptic G proteins, thereby reducing the sympathetic response without significant respiratory depression [6, 7]. Therefore, dexmedetomidine is widely used in orthopedic surgery and postoperative analgesia. The results of this study suggest that perioperative administration of dexmedetomidine may potentially reduce the incidence of POD in elderly patients undergoing orthopedic surgery. The exact etiology of POD remains unclear. The following hypotheses have been proposed: The first hypothesis is the neuroinflammatory process. Surgical trauma promotes the release of cytokines and inflammatory mediators [27], destroys the blood-brain barrier, and increases the inflammatory response of the nervous system, leading to cerebral ischemia and nerve cell apoptosis. Among the studies included in this meta-analysis [14, 18, 20], postoperative serum inflammatory factor levels were measured in included patients, but they could not be combined because the original data could not be extracted. Two studies [14, 20] showed that postoperative serum IL-6 and TNF-a levels were significantly lower in the dexmedetomidine group than in the control group. Secondly, considering the stress response theory [28], patients with bone trauma often suffer from severe pain and long-term abnormal excitation of the sympathetic nerve, resulting in strong stimulation during tracheal intubation and extubation under general anesthesia. This can lead to fluctuations in hemodynamic status and cognitive impairment, with elderly patients being particularly at risk of cognitive impairment due to stress reactions. Third, postoperative sleep arrhythmias [29], postoperative fatigue and metabolic disorders are important risk factors for the occurrence of POD. Studies have shown that sleep deprivation can directly increase astrocyte phagocytosis and promote microglial activation, which has been shown to be a promoting factor for POD

Table 1 Design and outcomes of the studies included in the meta-analysis

Auther/year	Group(*N*)	Age(year)	Gender(M/F)	Grade of ASA	Timing of administering DEX	Type of surgery	Strategy of DEX	Control Group	Delirium assessment	Primary outcome	Mode of anesthesia	Exclusion
Hong/2021	Dex(356)Control(354)	DEX(71 ± 5) Control(71 ± 5)	DEX(116/240) Control(113/241)	I–IV	Post	Joint arthroplasty; Spinal surgery; Hip fracture repair	DEX: 200 μg DEX + 200 μg sufentanil, diluted with 0.9% saline to 160 ml. The patient-controlled pump was programmed to deliver 2-ml boluses with a lockout interval of 8 min and a background infusion of 1 ml.h − 1	Saline	CAM; CAM-ICU	Delirium incidence	NR	Chizophrenia, epilepsy, parkinsonism, or myasthenia gravis; coma, profound dementia
Li/2024	Dex(120)Control(120)	DEX(69.48 ± 6.36) Control(69.38 ± 5.86)	DEX(45/75) Control(37/83)	II-IV	Intra	Total hip arthroplasty; Total knee arthroplasty	DEX: 0.4 mL/kg within 15 min, then 0.3 mL-kg-1·h-1	Saling	CAM	Delirium incidence	General anesthesia combined with nerve block anesthesia	Psychiatric disease; Preoperative cognitive impairment
Liu/2016	Dex(60)Control(58)	DEX(71.23 ± 8.08) Control(72.81 ± 9.22)	DEX(26/34) Control(29/29)	II-III	Intra	Total hip joint or knee joint or shoulder joint replacement surgery	DEX 0.2–0.4 μg/kg/h and stopped 20 min before the end of surgery	Saling	CAM	Delirium incidence	General anesthesia	Neurological diseases that may affect cognitive function
Lv/2022	Dex(152)Control(157)	DEX(67.9 ± 5.9) Control(68.4 ± 6.6)	DEX(73/79) Control(74/83)	NR	Post	Total hip joint replacement	DEX: 0.1 μg/kg/h intravenously within 72 h following surgery	Saling	CAM	Delirium incidence	General anesthetization	Any history of brain injury, neurosurgery, mental illness, epilepsy
Mei/2018	Dex(148)propofol(148)	DEX(76 ± 7 Control(74 ± 6)	DEX(64/84) Control(71/77)	I–IV	Intra	hip arthroplasty	DEX: 0.8–1.0 μg/kg over 15–20 min, then 0.1–0.5 μg·kg-1·h-1	Propofol	CAM; MMSE	Delirium incidence	NR	Patients exhibiting cognitive impairment and/or preoperative delirium
Mei/2019	Dex(183)propofol(183)	DEX(72 ± 9) Control(73 ± 11)	DEX(78/105) Control(69/114)	I–IV	Intra	total knee hip arthroplasty	DEX: 0.8–1.0 μg/kg in 15–20 min and then at 0.1–0.5 μg·kg-1·h-1	Propofol	CAM; MMSE	Delirium incidence	NR	Patients exhibiting cognitive impairment and/or preoperative delirium
Shin/2023	Dex(342)propofol(341)	DEX(68–76) Control(67–75)	DEX(77/289) Control(78/288)	I-II	Intra	Orthopedic Lower Limb Surgery: Hip and femur Knee and tibia/fibula Ankle and foot	DEX: 1 μg/kg for more than 10 min, then 0.1 to 0.5 μg/kg/h	Propofol	CAM	delirium incidence	Spinal anesthesia	Neuropsychiatric diseases
Ye/2024	Dex(110)Control(108)	Dex(78.5 ± 6.4) Control(79.1 ± 6.8)	DEX(34/76) Control(34/74)	NR	Intra	Thoracolumbar compression fractures utilizing percutaneous kyphoplasty (PKP).	DEX: 1 μg/kg/h in 10 min, then adjusted to 0.2 to 0.4 μg/kg/h,	Saline	CAM	Delirium incidence	NR	Psychiatric disorders
Zhu/2023	DEX(109)Propofol(110)	Dex(80/71–84) Control(75/72–82)	DEX(42/66) Control(54/56)	I-III	Intra	Total hip arthroplasty with/without cement, hemiarthroplasty with/without cement and Intramedullary nail	DEX: 0.3 μg/kg for more than 10 min, then 0.2–0.7 μg/kg per hour	Propofol	CAM	Delirium incidence 3days postoperatively	Spinal anesthesia	Severe dementia, intraoperative delirium

ASA = American Society of Anesthesiologists; CAM = Confusion Assessment Method; DEX: dexmedetomidine; ICU Intensive Care Unit; Intra = in operation; MMSE Mini-mental State Examination; NR = no report; Post = post-operation

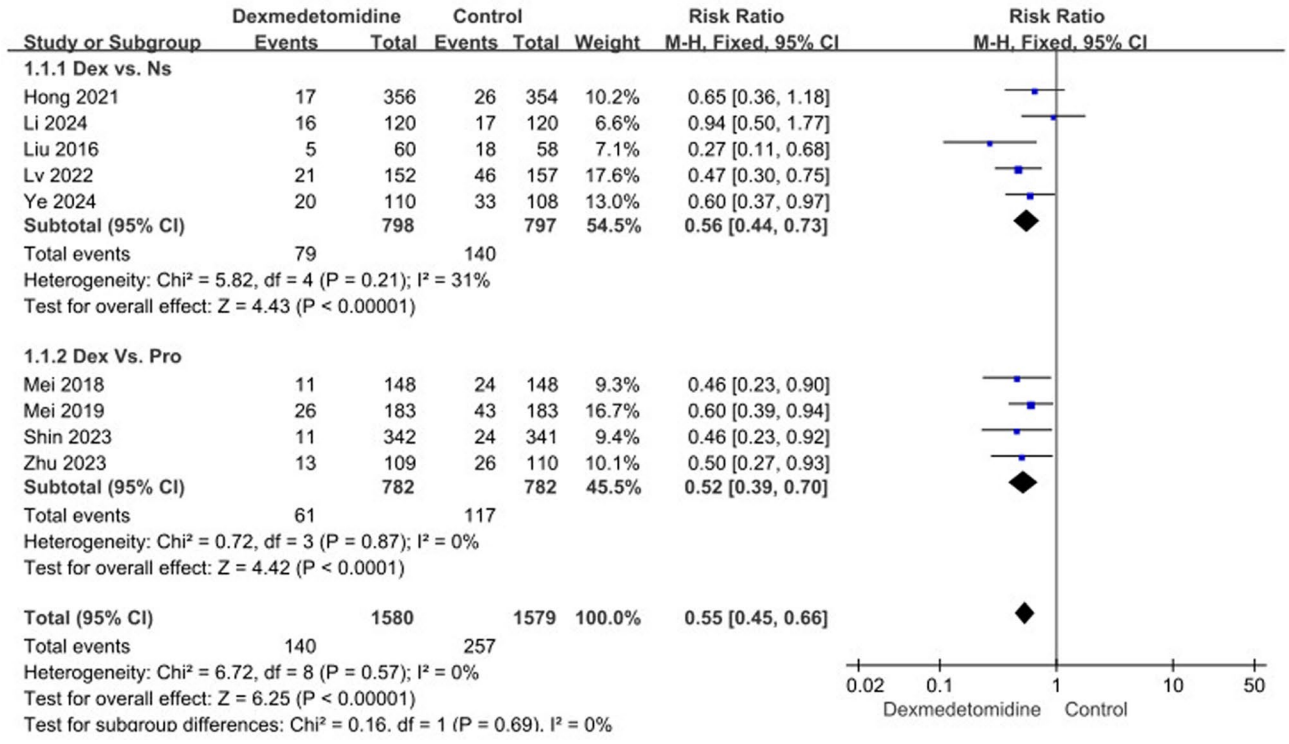

Fig. 2 Forest plot of postoperative delirium (Ns: saline, Pro: propofol)

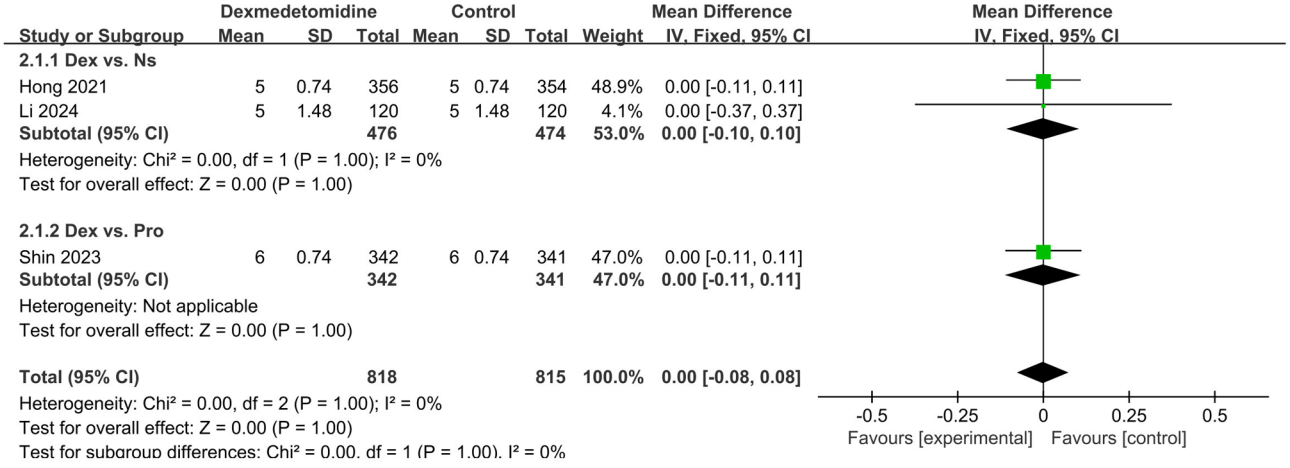

Fig. 3 Forest plot of length of stay (Ns: saline, Pro: propofol)

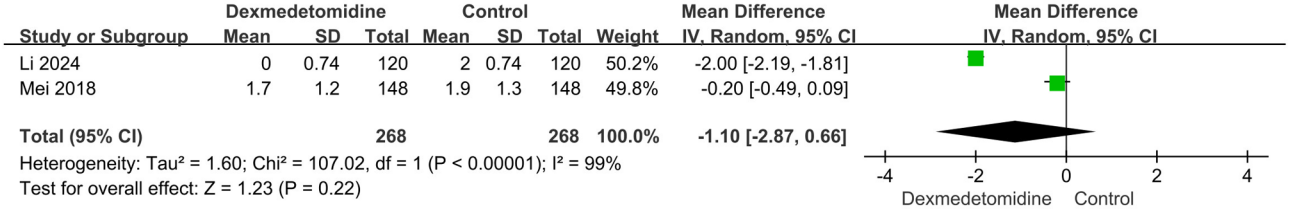

Fig. 4 Forest plot of visual analogue scale

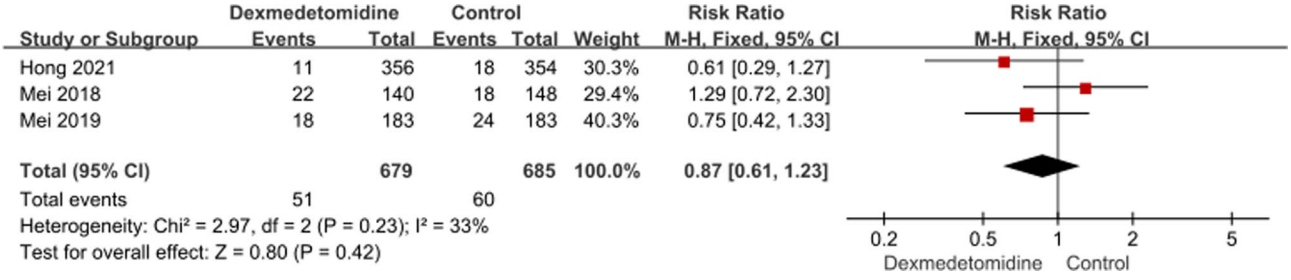

Fig. 5 Forest plot of postoperative complications within 30 days of surgery

development [30]. A study in this meta-analysis showed [14] that intraoperative administration of dexmedetomidine significantly reduced the likelihood of sudden awakening after fast-wave anesthesia compared to controls, a progression comparable to that observed in rapid eye movement sleep, which is often associated with sleep disorders [31]. Finally, opioids are often used for intraoperative analgesia, and the incidence of POD is directly related to the use of opioids, the acute effect of which is to increase the release of serotonin in a wide area ofthe forebrain, which can affect various neurotransmitters [32–33]. The pain assessment in this study was limited to the number and heterogeneity of studies and other factors, and the results showed no statistical differences, which requires further research verification in the future. Regarding the length of stay, this study was also limited by factors such as the number of studies and the small number of participants, and no statistical differences in the results were found, which still need to be verified by further research in the future.

The limitations of this study are as follows. First, in this study, different surgical types, anesthesia methods, and dexmedetomidine application strategies may increase the heterogeneity of outcome measurements. Second, this meta-analysis mainly focuses on studies in China and South Korea, and there are certain differences in the exclusion criteria of different studies, which also increases the calculation of outcome indicators to a certain extent. Third, due to the limited sample size of the study, we did not include 30-day all-cause mortality as an end event, which is a significant limitation, and the sensitivity analysis may also affect the accuracy of the results due to the small number of included studies. In conclusion, multicenter, large-scale, randomized, controlled trials on postoperative delirium in orthopedic patients are still the future research direction. Of course, research into the clinical effects of different strategies for dexmedetomidine administration, including in combination with other medications or care measures, on older orthopedic patients is also a future direction. It is also worth examining the influence of different surgical anesthesia methods on postoperative delirium in orthopedic patients.

Conclusion

This meta-analysis suggests that perioperative administration of dexmedetomidine significantly reduces the incidence of POD in elderly orthopedic postoperative patients.

Abbreviations

ASA	American Society of Anesthesiologists
CAM	Confusion assessment method
CI	Confidence interval
ICU	Intensive care unit
MD	Mean difference
MMSE	Mini-mental State Examination
POD	Postoperative delirium
RCT	Randomized controlled trials
RR	Relative risk

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00841-2.

Supplementary Material 1

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None.

Author contributions

JS, DW and YZ conducted a comprehensive review of the scientific literature and drafted the manuscript. YB provided assistance in the compilation of data. S-FW assisted in the processing of the data and the creation of visual representations. CM, G-BM and PL were instrumental in the conceptualization, design, interpretation of data, revision of the manuscript for critical intellectual content, and supervision of the study. The authors have read and approved the final manuscript.

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Data availability

Data sets are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the final manuscript and the submission to this journal.

Competing interests

The authors declare no competing interests.

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RESEARCH

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Haloperidol for the treatment of delirium in ICU patients: a systematic review and meta-analysis

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Abstract

Objectives Haloperidol is the most frequently prescribed medication for managing delirium in the intensive care unit (ICU). However, there is limited and inconclusive evidence regarding its efficacy. A meta-analysis was conducted by pooling data from recent clinical randomized controlled trials to assess the effectiveness of haloperidol in adult ICU patients with delirium.

Methods Studies were searched in PubMed, Embase and Cochrane Library databases on August 10, 2024. We performed a meta-analysis to estimate the efficacy of haloperidol for the treatment of ICU adult patients with delirium. This study is registered with INPLASY, number 202480104. The estimates are expressed as odds ratio (OR) or mean difference (MD) with a 95% confidence interval (CI).

Results A total of 2863 patients were included in the analyses. All the included studies were randomized controlled trials. The frequency of patients diagnosed with delirium used both confusion assessment method of intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) was 34% ($n=2863$), and used CAM-ICU only was 66% ($n=2863$). There was no difference in short-term (28–30 days) mortality between the two groups [OR = 0.89, 95% CI 0.60–1.32, $P=0.56$] and long-term (90 days to 1 year) mortality [OR = 0.87, 95% CI 0.70–1.07, P = 0.19]. Furthermore, the haloperidol group demonstrated an advantage in reducing the length of ICU stay [MD = -1.13, 95% CI − 1.93–− 0.32, $P<0.05$] compared to the placebo group, with no statistically significant difference in length of hospital stay [MD = − 0.24, 95% CI -1.71–1.24, $P=0.75$].

Conclusions Haloperidol showed a significant trend in reducing the length of ICU stay. However, there was no statistical difference between the two groups in terms of delirium reduction.

Keywords Haloperidol, Delirium, ICU, Efficacy

Introduction

Delirium is a prevalent manifestation of acute brain dysfunction in critically ill patients, representing a clinical syndrome resulting from various underlying causes rather than a singular disease entity. It encompasses cognitive impairment and is not limited to a specific etiology [1]. ICU delirium is a prevalent medical issue among patients in the intensive care unit (ICU) [2]. Patients with delirium are at an elevated risk for adverse outcomes, including increased case fatality and hospitalization costs, as well as the potential for long-term cognitive dysfunction, imposing a substantial burden on both patients and their families. Numerous factors can contribute to the development of delirium, including non-modifiable predisposing factors, triggers, and

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medication-related factors. The incidence of delirium is high among hospitalized patients in general hospitals. However, there is a lack of unified and standardized criteria for diagnosis and treatment.

Delirium is characterized by disturbances in attention and consciousness, which are central to its field of cognitive change. In addition, it includes fundamental symptoms in two other domains: alterations in the sleep–wake cycle and difficulties in comprehension (thought process and language). A comprehensive understanding of these clinical characteristics is crucial for effective diagnosis and management. Recent studies also provided valuable insights into the clinical characterization and phenotype of delirium [3, 4]. Based on the recent research findings, two criteria diagnosis of delirium that should be included in: a specified 24-h diagnostic period and a severity threshold. Changes in activity level or circadian rhythm patterns should be re-evaluated for inclusion as core features in future diagnostic systems [3].

The Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption guidelines (PADIS) do not advocate the routine use of any pharmacological agents for the prevention or treatment of delirium [5]. The evidence regarding the efficacy of haloperidol as a commonly prescribed medication for managing delirium in ICU patients has been limited and conflicting [6]. Despite previous studies evaluating the effectiveness of haloperidol, there is still a lack of existing evidence, and the results are not statistically significant. More trial data are needed to provide higher certainty evidence. In recent years, there are six clinical studies have compared the effects of haloperidol and placebo on mortality and length of stay in patients with ICU delirium [7–12]. These studies are all randomized clinical trials (RCTs). The strength of this study lies in its systematic updating of existing systematic reviews to incorporate additional randomized clinical trials and conduct a comprehensive assessment of the effects of haloperidol versus placebo.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The pre-registration for our meta-analysis can be accessed via the International Platform Database for Registration Systems Evaluation and Meta-Analysis Protocols (reference number: INPLASY202480104). The full text is available for download from inplasy.com (https://inplasy.com/inplasy-2024-8-0104). It should be noted that ethical approval is not required for this study.

Search strategy

A comprehensive electronic search of articles published in the field was conducted by three researchers (Yue Zhao, Qing Wang, Biao Sun) before 10 August 2024. A comprehensive manual search of the PubMed, Embase and Cochrane databases was conducted in order to select relevant randomized controlled trials. For further details regarding the precise literature search strategies employed, please consult the Appendix (Supplementary File).

Inclusion and exclusion

Document management uses EndNote (X9) software, and two investigators independently evaluate the project qualifications to verify the project's eligibility. First, the title and abstract are screened, and then the relevant articles are comprehensively reviewed, and the eligible articles are reserved for comprehensive review. The studies included in this review were all randomized controlled trials. The following inclusion criteria were met: (1) ICU adult patients with delirious. (2) Treatment with haloperidol or placebo or conventional therapy. (3) Outcome indicators: death from any cause/length of ICU stays/length of hospital stays. We excluded animal trials, studies that included patients < 18 years of age, and there was not enough data to extract, such as summaries of some meetings, literature such as reviews, and pharmacological presentations, in addition, literature materials such as review and meeting reports. Unrelated to the study topic, inappropriate intervention and control will also be excluded. We contacted the authors if associated data from their studies were required.

Bias and quality assessment

The two researchers conducted independent evaluations, preliminary selections and verifications of the literature in accordance with a unified and standardized methodology. The literature was included or excluded in accordance with the pre-established criteria, and the data were subsequently collected. The quality of the selected articles was evaluated in accordance with the Cochrane Reviewer Handbook 5.1.0 [14].

Data synthesis and analysis

The meta-analysis was conducted utilizing RevMan 5.4 software. Data that met the pre-established criteria of homogeneity ($P > 0.10$ and $I^2 \leq 50\%$) as determined by the heterogeneity test were analyzed using the fixed effects model (M-H). In the event that the aforementioned homogeneity criteria ($P \leq 0.10$ or $I^2 > 50\%$) are not met and heterogeneity cannot be excluded, a random effects model is employed to consolidate the effect [15].

The estimates are expressed as odds ratio (OR) or mean difference (MD) with a 95% confidence interval (CI). A p value of less than 0.05 was deemed to be statistically significant.

Results

The flow chart (Fig. 1) provides a summary of the search and research selection process. A total of 1333 related literatures were retrieved, of which 412 were excluded due to duplication. 868 studies were also excluded after reading the titles and abstracts. A comprehensive evaluation was conducted on the remaining 53 studies, based on a full reading of the full text. Data from 6 trails evaluating the efficacy of haloperidol for the treatment of delirium in critically ill patients were included.

The principal characteristics of the included trials are set forth in Table 1. A total of 2863 patients were included in the analyses. All the included studies were randomized controlled trials. The estimates are expressed as odds ratios (OR) or mean differences (MD) with a 95% confidence interval (CI). All studies conducted a comparative analysis of the effectiveness of haloperidol for treating delirium in adult ICU patients. The mortality outcomes are summarized in Fig. 2. There was no difference in short-term (28–30 days) mortality (A) between the two groups [OR = 0.89, 95% CI 0.60–1.32, $P = 0.56$]

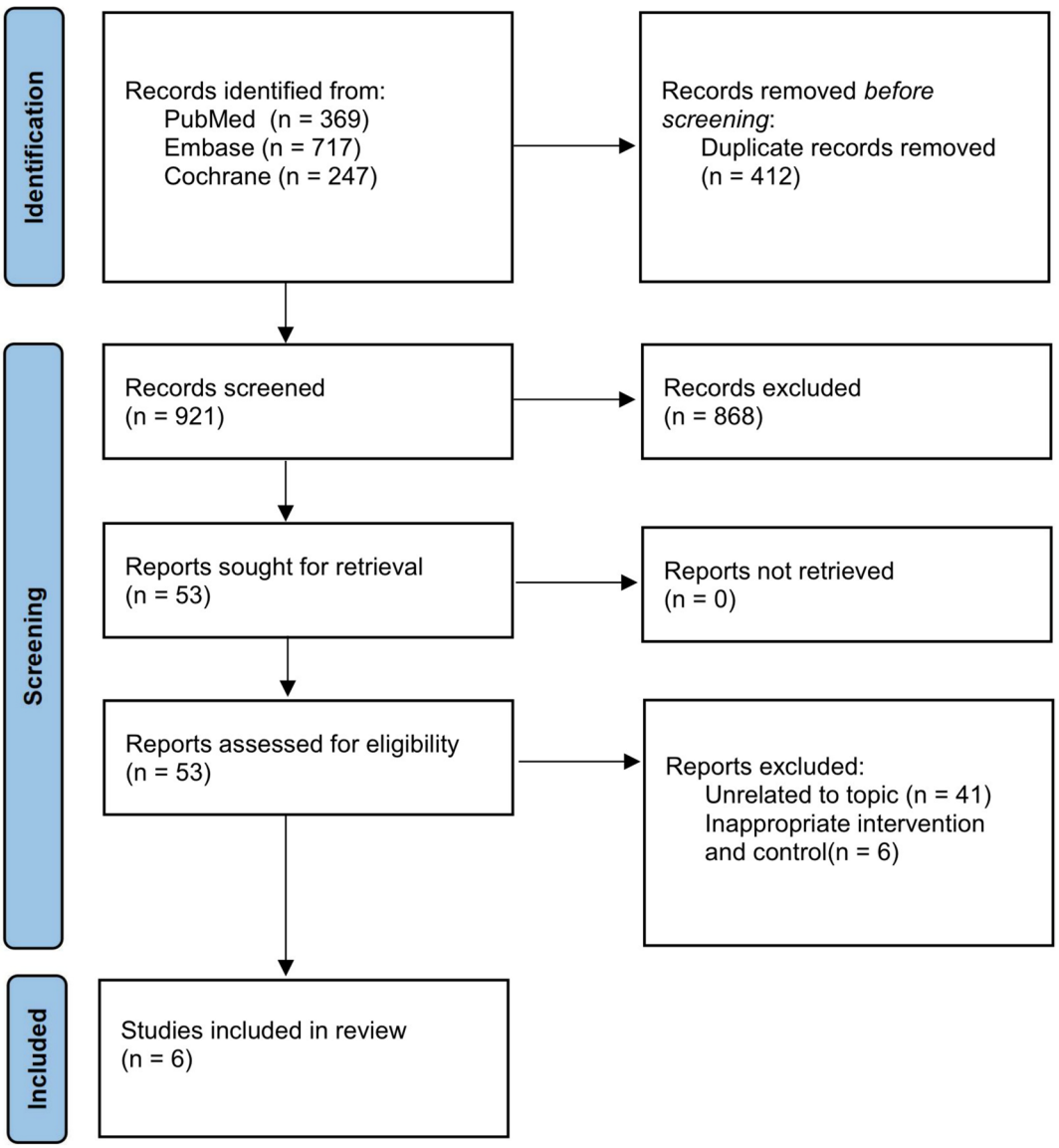

Fig. 1 Selection process for studies included in the meta-analysis

Table 1 Design and outcomes of the studies included in the meta-analysis

No.	Author/year	Design	Intervention assignments		Participants					Outcome		Inclusion and exclusion criteria	
			Haloperidol	Control	Sample, n	Mean age	Male%	Time of research	Measures	Primary outcome	Secondary outcomes	Inclusion criteria	Exclusion criteria
1	Andersen-Ranberg/2022	RCT	2.5 mg tid	Placebo	987	70/71	64.7/66.9	90 days	CAM-ICU ICDSC	Days alive and out of the hospital within 90 days; length of hospital stay	Days alive without delirium or coma; days alive without mechanical ventilation	Adult patients who had been admitted to an ICU	NR
2	Garg/2022	RCT	Maximum dose: 30 mg daily	Placebo	30	57/57	53/53	90 days	CAM-ICU	Days alive without delirium	30-day and 90-day survival; ICU stay; length of hospital stay	Adult patients who had been admitted to an ICU	Severe cognitive impairment
3	Girard/2018	RCT	Maximum dose: 30 mg daily	Placebo	376	61/59	56/58	90 days	CAM-ICU	Days alive without delirium	30-day and 30-day survival; ICU stay; length of hospital stay	Adult patients who had been admitted to an ICU	Severe cognitive impairment; history of neuroleptic malignant syndrome
4	Mart/2024	RCT	Maximum dose: 20 mg daily	Placebo	376	57/59	59/56	1 year	CAM-ICU	3-month mortality	3-month and 12-month participants' cognitive	Adult patients who had been admitted to an ICU	Severe cognitive impairment; history of neuroleptic malignant syndrome
5	Mortensen /2024	RCT	Maximum dose: 20 mg daily	Placebo	962	73/74	63/67	1 year	CAM-ICU ICDSC	1-year all-cause mortality	Health-related quality of life	Adult patients who had been admitted to an ICU	NR
6	Smit/2023	RCT	2.5 mg tid	Placebo	132	66/68	48/42	1 year	CAM-ICU ICDSC	Delirium- and coma-free days	28-day mortality	Adult patients who had been admitted to an ICU	Primary acute neurological condition; neuroleptic malignant syndrome; parkinsonism

NR not reported, *RCT* randomized controlled trial, *CAM-ICU* Confusion Assessment Method of Intensive Care Unit, *ICDSC* Intensive Care Delirium Screening Checklist, *ICU* Intensive Care Unit, *Tid* three times a day

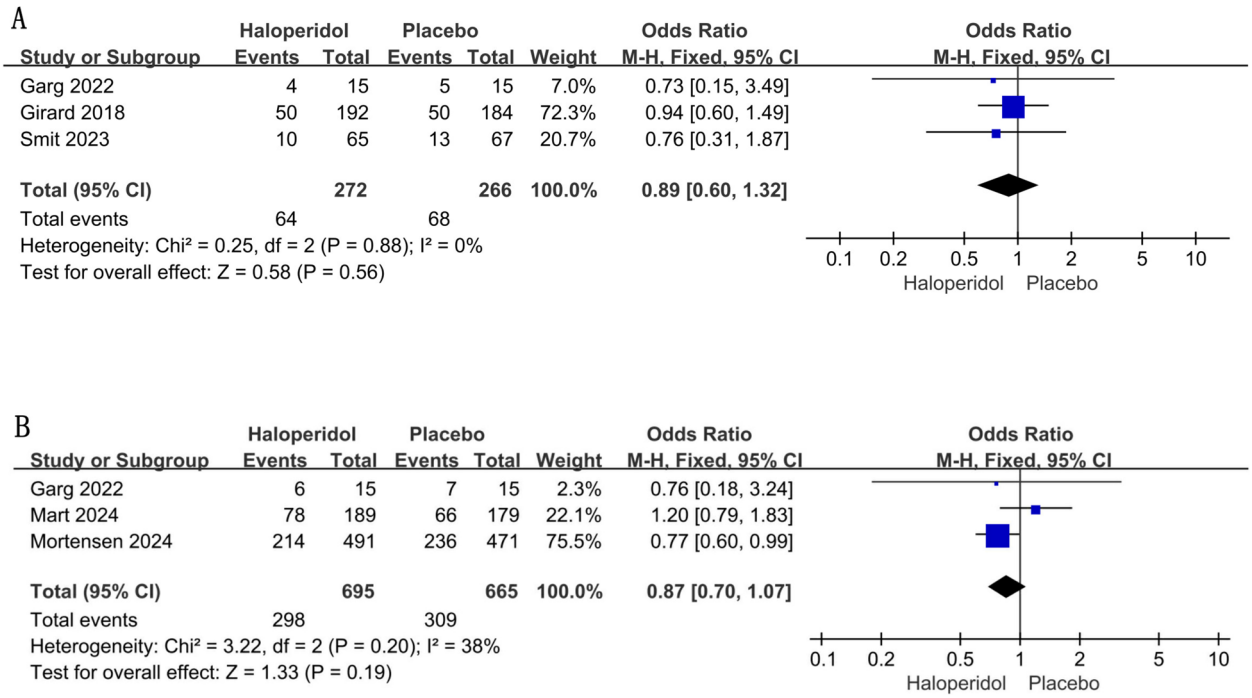

Fig. 2 Comparisons of the short-term (28–30 days) mortality and long-term (90 days–1 year) mortality between haloperidol and placebo

and long-term (90 days to 1 year) mortality (Fig. 2B) [OR = 0.87, 95% CI 0.70–1.07, $P = 0.19$]. Furthermore, the haloperidol group demonstrated an advantage in reducing the length of ICU stay (Fig. 3A) [MD = − 1.13, 95% CI − 1.93–− 0.32, $P = 0.006$] compared to the placebo group, with no statistically significant difference in

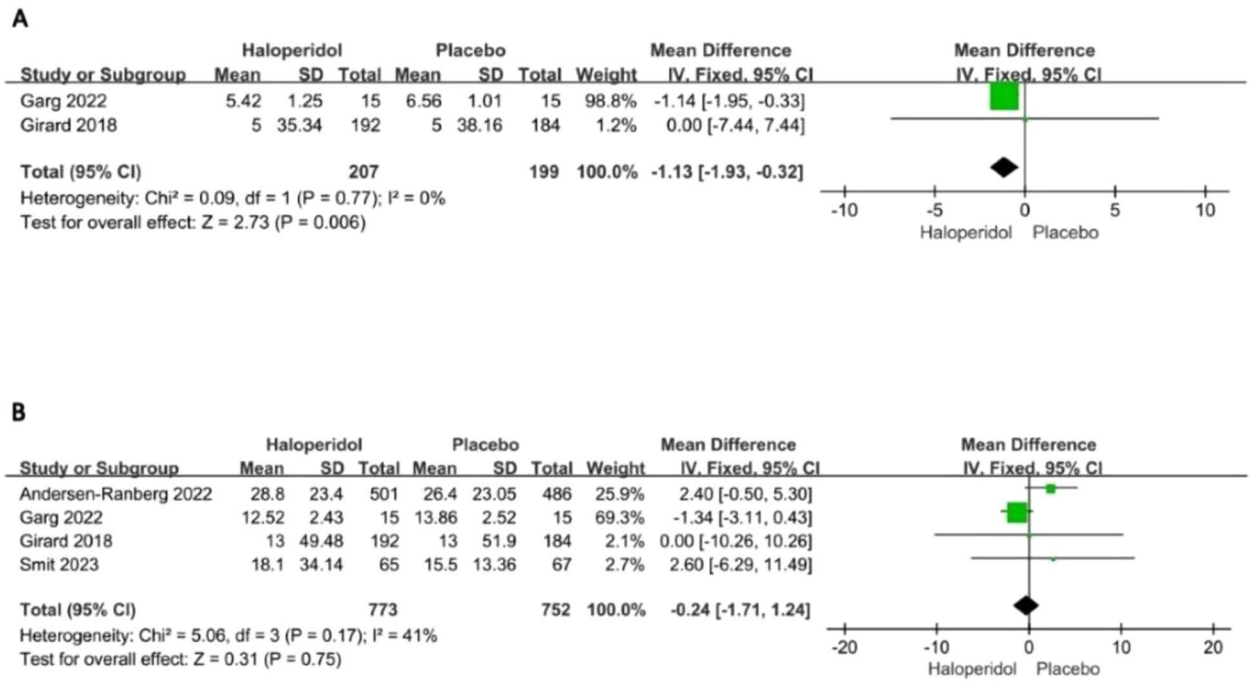

Fig. 3 Comparisons of the length of ICU stay and the length of hospital stay between haloperidol and placebo

length of hospital stay (Fig. 3B) [MD = − 0.24, 95% CI − 1.71–1.24, $P = 0.75$].

This study used RevMan software to assess the influence of an individual study on the overall combined estimate for each predefined outcome. The cost-effective risk evaluation findings from these experiments are presented in Supplement File. The randomized controlled trials (RCTs) included in this study were of high quality and deemed to have a low risk of bias.

Discussion

At present, the pathophysiological mechanism of delirium is not well understood, and it is very important to identify and treat the patients with high risk of delirium and delirium [1]. Delirium may be related to the interaction of multiple factors that cause dysfunction of the brain's neural networks [16]. In addition to its mild antihistamine and antiserotonin effects, haloperidol has potent antiadrenergic properties, as well as some peripheral anticholinergic activity. Therefore, haloperidol can counteract a number of pathways that lead to delirium [17]. Although haloperidol is widely used to treat delirium in the ICU, its efficacy remains uncertain, and many trials have reached inconsistent conclusions about its effectiveness in preventing delirium in ICU patients [18–22].

In this systematic review comparing the efficacy of haloperidol versus placebo in the treatment of critical adult delirium, we analyzed data from six randomized controlled trials published between 2018 and 2024, involving a total of 2,863 patients. Our findings suggest that haloperidol has no tendency to reduce long-term mortality and short-term mortality but significantly shorten ICU stay compared to placebo. A systematic review conducted by Wu published in 2019 concluded that the use of haloperidol did not lead to a reduction in all-cause mortality among ICU patients with delirium [23]. A RCT study by Van Den Boogard published in 2018, similarly confirmed that prophylactic haloperidol use did not improve 28-day survival compared with placebo in critically ill adults at high risk of delirium, and this finding do not support the use of prophylactic haloperidol to reduce mortality in critically ill adults [24]. In our study, for the mortality analysis, we used 28–30 days mortality and 90 days to 1-year mortality. The findings suggest that haloperidol has no tendency to improve long-term mortality (90 days to 1 year) in ICU patients compared to placebo, also has no effect on short-term mortality (28–30 days) in ICU patients compared with placebo. Due to the limited number of RCTs meeting the inclusion criteria, this study did not conduct a meta-analysis comparing the mortality of ICU patients receiving different doses of haloperidol. In a post hoc analysis involving a total of 1,459 delirium-free patients admitted to the ICU, it was confirmed that delirious patients who received haloperidol treatment experienced prolonged stays in the ICU [25]. In our research, we observed that the use of haloperidol led to a significant improvement in ICU stay duration compared to placebo, although it did not affect the overall length of hospital stay for patients. We hypothesized that variations in trial outcomes may be attributed to the severity of ICU-admitted patients, risk factors for delirium, and varying haloperidol dosages.

Many researchers and clinicians rely on screening instruments for the diagnosis of delirium, such as the confusion assessment method of intensive care unit (CAM-ICU), rather than applying the diagnostic criteria of the diagnostic and statistical manual of mental disorders (DSM) or intensive care delirium screening checklist (ICDSC) for assessment. Although CAM-ICU are more convenient compared to DSM, they have been criticized for lacking rigor, which can lead to false-positive diagnoses of delirium [26]. In the RCTs we included, only one RCT research used both the CAM-ICU screening instrument and the ICDSC diagnostic criteria for identifying delirium patients. This approach may result in the inclusion of patients with severe arousal disturbances or multiple neurocognitive changes and neuropsychiatric disorders in clinical trials focused on delirium treatment. This could introduce negative bias in such studies, where some patients may be deemed unresponsive to delirium treatment, even though they do not actually have delirium but rather arousal, neurocognitive, or neuropsychiatric disorders. For these conditions, antipsychotic medications should not be used and/or would be ineffective. Therefore, future clinical trials should employ more appropriate reference standards for diagnosing delirium, such as the diagnostic criteria of DSM or ICD, to avoid the generation of negative bias results.

Limitations of this study need to be noted. First, in this study, different haloperidol application strategies, different severity of patients, and different evaluation systems for delirium may increase the heterogeneity of outcome measures. In addition, although the exclusion criteria of different studies have made certain introductions about the cognitive level of patients, there are differences in the exclusion criteria of different studies, which may also lead to unstable outcomes. Second, due to the limited sample size of the study, the small number of included studies may also affect the accuracy of the results. In summary, multi-center, large-scale randomized controlled trials are still the future research direction. The trial focused only on haloperidol, and the results cannot be extrapolated to other antipsychotics that have been studied. Of course, the exploration of combined use with other drugs,

including the combination of necessary care means, may also be the direction of future research.

Conclusions

Haloperidol showed a significant trend in reducing the length of ICU stay, and there was no significant difference in mortality. Future randomized controlled trials with large samples are needed for further validation.

Abbreviations

CAM-ICU	Confusion Assessment Method of Intensive Care Unit
DSM	The diagnostic and statistical manual of mental disorders
ICU	Intensive care unit
ICDSC	Intensive Care Delirium Screening Checklist
PADIS	The Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption guidelines
RCTs	Randomized controlled trials

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02409-6.

Supplementary Material 1

Author contributions

YZ, BS and QW searched the scientific literature and drafted the manuscript. Y-NL contributed to data abstract. CM and G-BM contributed to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. The authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors approved the final manuscript and the submission to this journal.

Conflict of interest

The authors declare no competing interests.

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