INTRODUCTION

Review question / Objective: 2.1.1 type of research SRs/MAs of RCT (randomized controlled trial) of Xinmailong injection for the treatment of heart failure. 2.1.2 Subject investigated All included patients met internationally recognized diagnostic criteria for heart failure. There are no limitations on age, gender, ethnicity, time of onset, source of cases and language of publication. 2.1.3 Type of Intervention The control group was treated with conventional basic Western medicine recommended by the guidelines related to heart failure[1, 11], including antiplatelet drugs, anticoagulants, vasodilators, beta-blockers, ACEI (angiotensin-converting enzyme inhibitors), lipid-lowering drugs, and diuretic agents. The intervention group was given Xinmailong injection on the basis of the control group.

INPLASY PROTOCOL

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Quality of Evidence Supporting the Effects of Xinmailong injection in Heart Failure: An Overview of Systematic Reviews and Meta-Analyses

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Review question / Objective: 2.1.1 type of research SRs/MAs of RCT (randomized controlled trial) of Xinmailong injection for the treatment of heart failure. 2.1.2 Subject investigated All included patients met internationally recognized diagnostic criteria for heart failure. There are no limitations on age, gender, ethnicity, time of onset, source of cases and language of publication. 2.1.3 Type of Intervention The control group was treated with conventional basic Western medicine recommended by the guidelines related to heart failure[1, 11], including antiplatelet drugs, anticoagulants, vasodilators, beta-blockers, ACEI (angiotensin-converting enzyme inhibitors), lipid-lowering drugs, and diuretic agents. The intervention group was given Xinmailong injection on the basis of the control group.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 October 2022 and was last updated on 04 October 2022 (registration number INPLASY2022100023).
enzyme inhibitors), lipid-lowering drugs, and diuretic agents, and other drug treatment. The intervention group was given Xinmailong injection on the basis of the control group.

Rationale: This overview using AMSTAR-2 (Assessment System for Evaluating Methodological Quality 2), ROBIS (the Risk of Bias in Systematic), PRISMA (the list of Preferred Reporting Items for Systematic Reviews and Meta-Analyses), and GRADE (the Grading of Recommendations Assessment, Development, and Evaluation) to evaluate the quality of the included SRs/ MAs of Xinmailong injection in the treatment of heart failure.

Condition being studied: Heart failure is a group of complex clinical syndromes caused by a variety of reasons resulting in abnormal changes in cardiac structure and/or function, resulting in dysfunction of ventricular systolic and/or diastolic functions. It is the terminal end of various cardiovascular diseases. Major symptoms include dyspnea, fatigue and fluid retention (systemic congestion, pulmonary congestion and peripheral edema). In recent years, as the population ages, there has been a significant increase in the number of patients suffering from heart failure. Once the clinical manifestations of heart failure appear in patients with cardiovascular disease, the prognosis is poor and the risk of death is high, which will bring a heavy burden to the society and family.

As a part of traditional Chinese medicine, insect medicine has great mining value in the treatment of cardiovascular diseases because of its special biological activity. The periplaneta Americana, commonly known as "cockroach", is one of the most powerful, oldest and most successful insect groups in the world. XML (Xinmailong injection) is a small-molecule bioactive peptide preparation extracted and isolated from Periplaneta Americana by Professor Li Shunan of Dali College. XML contains 4 active ingredients: protocatechuic acid, inosine, adenosine, and pyroglutamate dipeptides. A variety of Periplaneta Americana extracts have been made into medicines and marketed, such as Kangfuxin Liquid, Ganlong Capsules, Xiaozheng Yigan Tablets, XML (Xinmailong Injection), etc. Xinmailong injection is a national second-class new drug for the treatment of chronic heart failure independently developed by China and approved for distribution by the State Food and Drug Administration of China in 2006. Mainly contains 4 active ingredients: protocatechuic acid, inosine, adenosine, and pyroglutamate dipeptides. As a traditional Chinese medicine injection, XML has the functions of improving systemic blood circulation, diuresis and dilating coronary arteries.

In recent years, with the in-depth study of the pharmacological effects of XML, it has been found that it has a wide range of effects on the cardiovascular system, which has increasingly attracted the attention of researchers. At present, there have been many articles on SRs / MAs (systematic reviews/Meta-analyses) of XML for the treatment of heart failure at home and abroad. However, due to its short clinical application time, inconsistent intervention measures and outcome indicators, and uneven research quality, it will have a certain impact on the credibility of the conclusions. Therefore, the reliability of the relevant SRs / MAs analysis results remains to be discussed. This overview aims to conduct a summary analysis and evaluation of the existing SRs/MAs and their outcome indicators in the treatment of heart failure with XML, and to provide further evidence-based support for clinical use.

METHODS

Search strategy: This overview systematically searches CNKI (China National Knowledge Infrastructure), Wanfang Database, VIP (China Science Technology Journal Database), Sino-Med Database, and PubMed, EMBASE, Cochrane Library database for SRs/MAs of Xinmailong injection in the treatment of heart failure. In addition, we manually supplemented and searched the references and grey literature of the included studies. The retrieval time is from the
establishment of the database to September 2022. The retrieval adopts the combination of MeSH items and free words, The English search terms include "Xinmailong Injection" "heart failure" "systematic review" "Meta-analysis". The search strategy is shown in Table 1 with Pub Med as an example.

**Participant or population:** SRs/MAs of RCT (randomized controlled trial) of Xinmailong injection for the treatment of heart failure.

**Intervention:** The intervention group was given Xinmailong injection on the basis of the control group.

**Comparator:** The control group was treated with conventional basic Western medicine recommended by the guidelines related to heart failure[1, 11], including antiplatelet drugs, anticoagulants, vasodilators, beta-blockers, ACEI (angiotensin-converting enzyme inhibitors), lipid-lowering drugs, and diuretic agents, and other drug treatment.

**Study designs to be included:** SRs/MAs of RCT (randomized controlled trial) of Xinmailong injection for the treatment of heart failure.

**Eligibility criteria:** Repeated published literature, animal experiments, literature where data cannot be extracted, conference abstracts, network meta-analyses, system ratings that are still in the protocol stage will be excluded.

**Information sources:** This overview systematically searches CNKI (China National Knowledge Infrastructure), Wanfang Database, VIP (China Science Technology Journal Database), Sino-Med Database, and PubMed, EMBASE, Cochrane Library database for SRs/MAs of Xinmailong injection in the treatment of heart failure. In addition, we manually supplemented and searched the references and grey literature of the included studies. The retrieval time is from the establishment of the database to September 2022. The retrieval adopts the combination of MeSH items and free words, The English search terms include "Xinmailong Injection" "heart failure" "systematic review" "Meta-analysis". The search strategy is shown in Table 1 with Pub Med as an example.

**Main outcome(s):** This overview systematically searches CNKI (China National Knowledge Infrastructure), Wanfang Database, VIP (China Science Technology Journal Database), Sino-Med Database, and PubMed, EMBASE, Cochrane Library database for SRs/MAs of Xinmailong injection in the treatment of heart failure. In addition, we manually supplemented and searched the references and grey literature of the included studies. The retrieval time is from the establishment of the database to September 2022. The retrieval adopts the combination of MeSH items and free words, The English search terms include "Xinmailong Injection" "heart failure" "systematic review" "Meta-analysis". The search strategy is shown in Table 1 with Pub Med as an example.

**Additional outcome(s):** None.

**Data management:** The literature was selected independently by two researchers (XQW and JSZ) based on preset inclusion and exclusion criteria. Import the retrieved literature into Note Express 3.6.0.

**Quality assessment / Risk of bias analysis:** ROBIS (Risk of Bias In Systematic Review scale)[13] was used for risk of bias in the production and interpretation of the included SRs/MAs. The process of assessing risk of bias using the ROBIS assessment system consists of three stages: (1) assessing relevance; (2) identifying concerns about bias in the review process; (3) judging risk of bias.

**Strategy of data synthesis:** The two researchers (XQW and JSZ) who completed the data extraction continued to independently evaluate the literature. When the evaluation conclusions were inconsistent, a third researcher (MXF)
participated in the evaluation and formed a consensus through discussion. This overview using AMSTAR-2 (Assessment System for Evaluating Methodological Quality 2), ROBIS (the Risk of Bias in Systematic), PRISMA (the list of Preferred Reporting Items for Systematic Reviews and Meta-Analyses), and GRADE (the Grading of Recommendations Assessment, Development, and Evaluation) to evaluate the quality of the included SRs/MAs of Xinmailong injection in the treatment of heart failure.

**Subgroup analysis:** Unwanted.

**Sensitivity analysis:** Unwanted.

**Language restriction:** none.

**Country(ies) involved:** China.

**Keywords:** Xinmailong injection, Heart Failure, meta-analysis, overview, systematic reviews.

**Contributions of each author:**
Author 1 - Xiaoqi Wu designed the framework of this study and wrote this manuscript.
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