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Evaluation of the Effect of Stem Cell Therapy on Ischemic Heart Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: The present study was conducted to evaluate the effect of stem cell therapy on ischemic heart disease.

Material and methods: All international databases, PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase were examined, searching until April 2023 based on keywords related to the objectives of the study. The current study was conducted based on the PRISMA 2020 checklist, and the Google Scholar search engine was also used to find related articles. The 95% confidence interval mean differences were calculated using the fixed effect model. Stata/MP v.17 software was used to conduct the meta-analysis.

Results: After reviewing the abstracts of 320 articles, 98 articles were selected for full-text review, of which 20 articles were included in the meta-analysis. The left ventricular ejection fraction difference after stem-cell therapy compared to the control group was 8.29% (MD, 8.29 CI; 8.22,8.37; p<0.01). LVEF mean difference values in the ischemia/reperfusion MI model and chronic MI was 5.54% (MD, 5.54 CI; 5.43,5.65; p<0.01) and 10.65% (MD, 10.65 CI; 10.55,10.75; p<0.01).

Conclusions: Based on the present meta-analysis, stem cell therapy on ischemic heart disease improves left ventricular ejection fraction.

1. Introduction

Myocardial infarction (MI) is a growing health problem and a major cause of disability, illness, and mortality worldwide, closely related to lifestyle changes, increased urbanization, and socioeconomic conditions.[1] Global mortality from MI is approximately 1,500,000 per year.[2] Pathologically, MI leads to tissue damage due to myocardial ischemia, followed by biochemical changes caused by reperfusion and pathological changes leading to left ventricular heart failure and cardiac cell death.[3] Myocyte death triggers a cascade of intracellular signals such as inflammation, oxidative stress, necrotic tissue absorption, and hypertrophy. These cellular and molecular changes can manifest clinically as heart size, volume, and function changes.[4] The evidence shows that rehabilitation programs based on physical exercises after cardiovascular accidents have an important effect on reducing the mortality rate and improving the living conditions of these patients.[5] Adverse left ventricular remodeling after myocardial infarction is designed to reduce myocardial scarring, which can improve cardiac function.[6, 7] It is necessary to save dying cells and rebuild blood vessels and heart tissues to treat heart attacks successfully.[8] Despite the recent therapeutic advances in drugs and surgery, these cases only delay the progression of the disease and do not stop the process of heart failure, ultimately leading us to heart transplantation, the last remaining treatment option.[9] According to research, stem cells are considered a promising candidate for treating ischemic heart diseases because these cells are an unlimited source of cardiac cells, endothelial cells, and other types of differentiated cells for use in all stages of repair.[10] Mesenchymal stem cells (MSCs) are considered an ideal source for cell therapy, gene therapy, and a tool for treating congenital diseases.[11] Because they have many advantages: they are easily harvested, can be cultivated and stored, and also can act in different ways, cannot stimulate the immune system, and they do not have ethical restrictions.[12] In the studies conducted on cardiovascular diseases, MSCs are considered a promising cell type in the treatment of ischemic heart disease due to their capacity to differentiate into endothelial cells, participate in the creation of new blood vessels in ischemic tissues, and enhance the activity of resting cardiac cells.[13] The results obtained from the studies are often heterogeneous and contradictory. Therefore, it is very important to review the results of studies to provide stronger evidence. Thus, the present

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study was conducted with the aim of evaluating the effect of stem cell therapy on ischemic heart disease.

2. Material and methods

Search strategy

The present study was conducted using the PRISMA 2020 checklist (14). The search was conducted based on keywords related to the study objectives in the international databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase; All articles were reviewed until May 2023. Keywords and the MeSH terms:

((((((((((((("Stem Cells"[Mesh]) OR ("Mesenchymal Stem Cell Transplantation"[Mesh] OR "Mesenchymal Stem Cells"[Mesh])) OR "Endothelial Progenitor Cells"[Mesh]) OR ("Bone Marrow"[Mesh] OR "Bone Marrow Transplantation"[Mesh] OR "Bone Marrow Cells"[Mesh])) AND "Myocardial Infarction"[Mesh]) OR "Myocardial Infarction/therapy"[Mesh]) OR ("Heart Failure"[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh])) OR "Heart Failure/therapy"[Mesh]) OR "Coronary Artery Disease"[Mesh]) OR "Coronary Artery Disease/therapy"[Mesh]) OR "Cardiac Valve Annuloplasty"[Mesh]) OR ("Ischemic Stroke"[Mesh] OR "Myocardial Ischemia"[Mesh])) AND "Animals"[Mesh]) OR "Swine"[Mesh]) OR "Sheep"[Mesh]) OR "Dogs"[Mesh].

Data collection

First, a checklist including the author's name, publication year, study design, type of animal, type of Infarction, MI, cell type, number of cells, route of delivery, and follow-up was prepared. The mean differences in results were extracted and used for meta-analysis. Two independent, blinded reviewers screened each record, and a third person retrieved each report. The selection of articles was based on inclusion and exclusion criteria.

Inclusion and exclusion criteria

Only articles published in English, randomized controlled trials and non-randomized controlled trials, stem-cell therapy on cardiac function, and animal models. Case studies, case reports, in-vitro studies, and review articles; studies without access to the full text were excluded from the study. The PICO strategy to answer the research questions (Table 1).

Table 1. PICO strategy.

PICO Strategy	Description
P	Population: animal models
I	Intervention: stem-cell therapy
C	Comparison: placebo or sham-operated
O	Outcome: left ventricular ejection fraction

Data analysis

Potential heterogeneity between studies was reported with the I^2 coefficient; values 50%< indicate low heterogeneity, 50% to 75% indicate moderate heterogeneity, and values >75% indicate high heterogeneity. Mean differences (95% confidence interval) were calculated using a fixed effect model with the inverse-variance method. STATA/MP. V17 software was used for meta-analysis.

3. Results

Study selection

First, a search was conducted using keywords in international databases, and 371 articles were found, all of which were entered into End.Note.X8 software; Duplicate papers and records marked as ineligible by automation tools and for other reasons were removed. The abstracts of 320 articles were reviewed, and according to the inclusion and exclusion criteria, 222 studies were excluded, and the full text of 98 studies was reviewed; finally, 20 studies were selected according to the objectives of the present study and included in the meta-analysis (Fig. 1).

Study characteristics

The study included one rat, 12 dogs, and 326 pigs. Infarction type was left anterior descending in 16 articles and left circumflex artery in four studies. Table 2 shows a summary of the data extracted from the selected articles.

Left ventricular ejection fraction difference

Left ventricular ejection fraction difference after stem-cell therapy compared to the control group was 8.29% (MD, 8.29 CI; 8.22,8.37; $p<0.01$) (Fig. 2). Statistically, a significant difference was observed between stem-cell therapy and control group, which indicates that the stem-cell therapy was successful. The heterogeneity between the studies was high (I^2=8.29%; P =0.00), which could be due to the difference in the methodology of the studies.

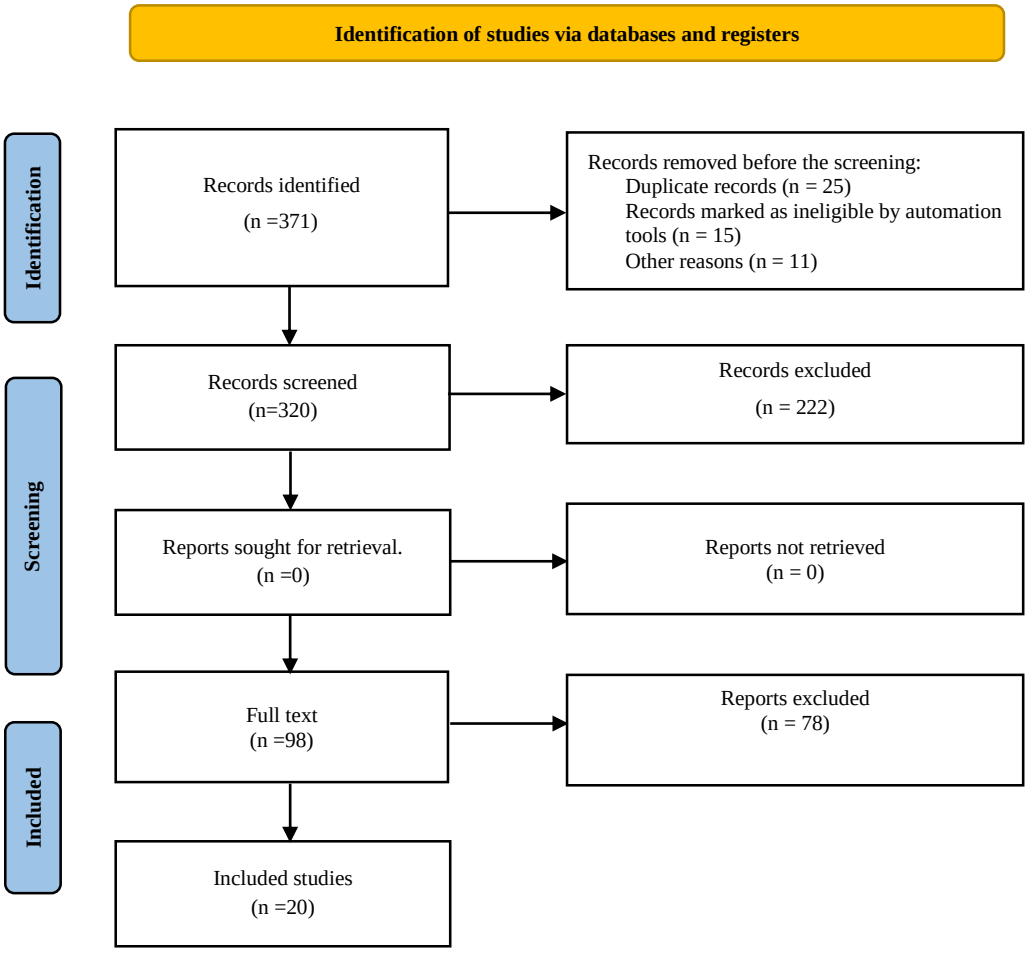

Fig. 1. PRISMA 2020 Checklist.

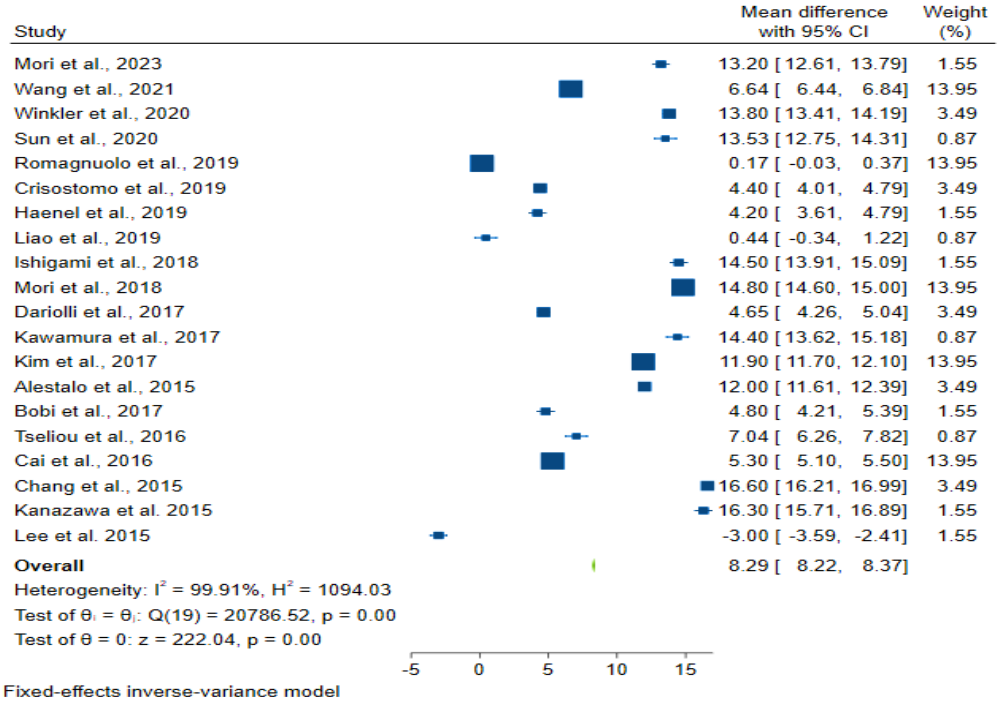

Fig. 2. The forest plot showed a left ventricular ejection fraction difference after stem-cell therapy compared to the control group.

Subgroup meta-analysis

LVEF mean difference values in the ischemia/reperfusion MI model and chronic MI was 5.54% (MD, 5.54 CI; 5.43,5.65; p<0.01) and 10.65% (MD, 10.65 CI; 10.55,10.75; p<0.01), respectively. Test of group differences showed a significant difference between the two groups; Thus, fewer benefits were observed in the ischemia/reperfusion MI model (p<0.01) (Fig. 3). LVEF means difference values with autologous cell treatment and no autologous cell treatment was 7.31% (MD, 7.31 CI; 7.16,7.46; p<0.01) and 8.61% (MD, 8.61 CI; 8.52,8.69; p<0.01), respectively. Test of group differences showed a significant difference between groups; there was an improvement with autologous cell treatment (p<0.01) (Fig. 4). According to the Test of group differences between animal model groups, no significant difference was observed in LVEF (Fig. 5).

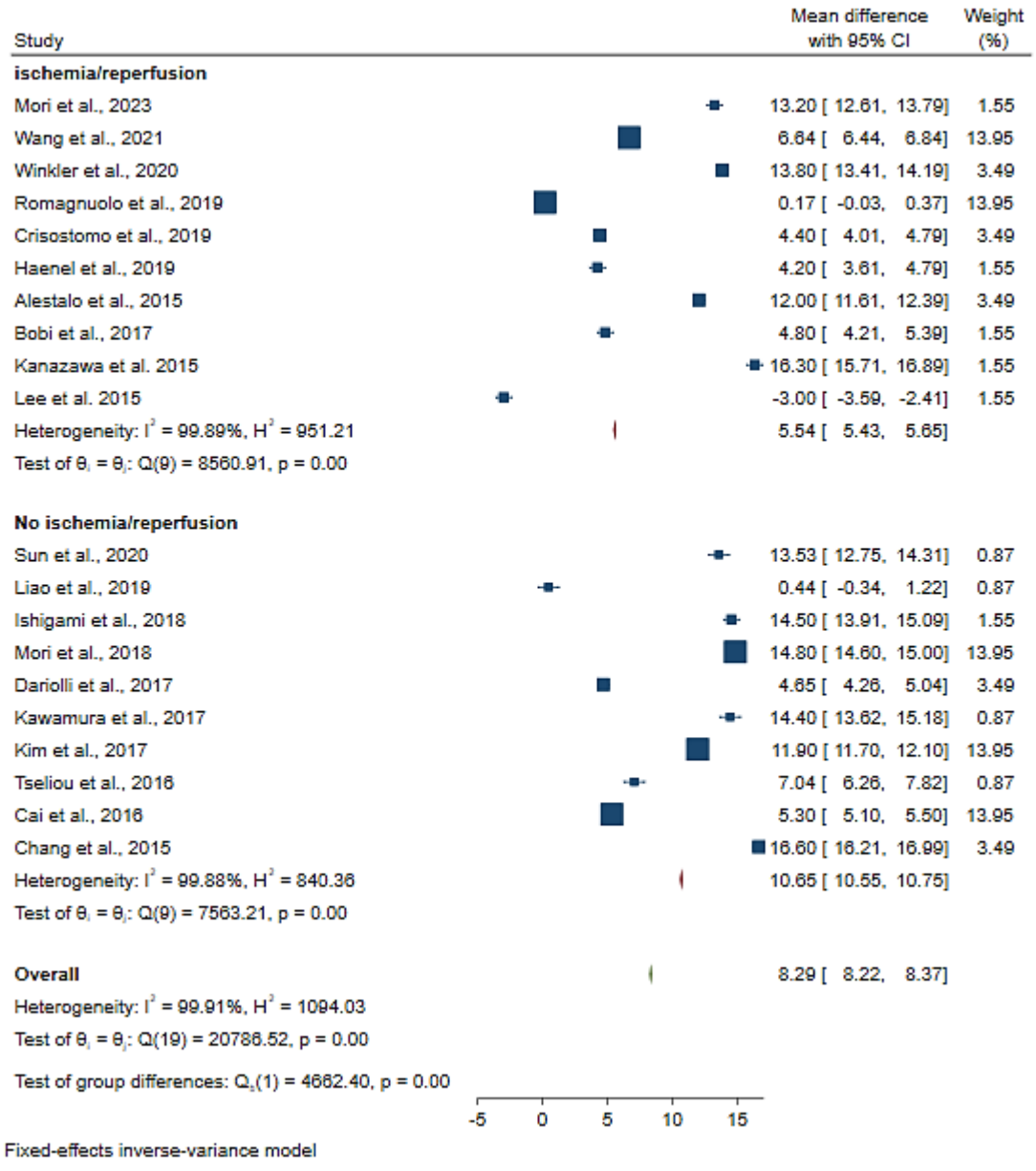

Fig. 3. The forest plot showed LVEF mean difference values in the ischemia/reperfusion and chronic MI models.

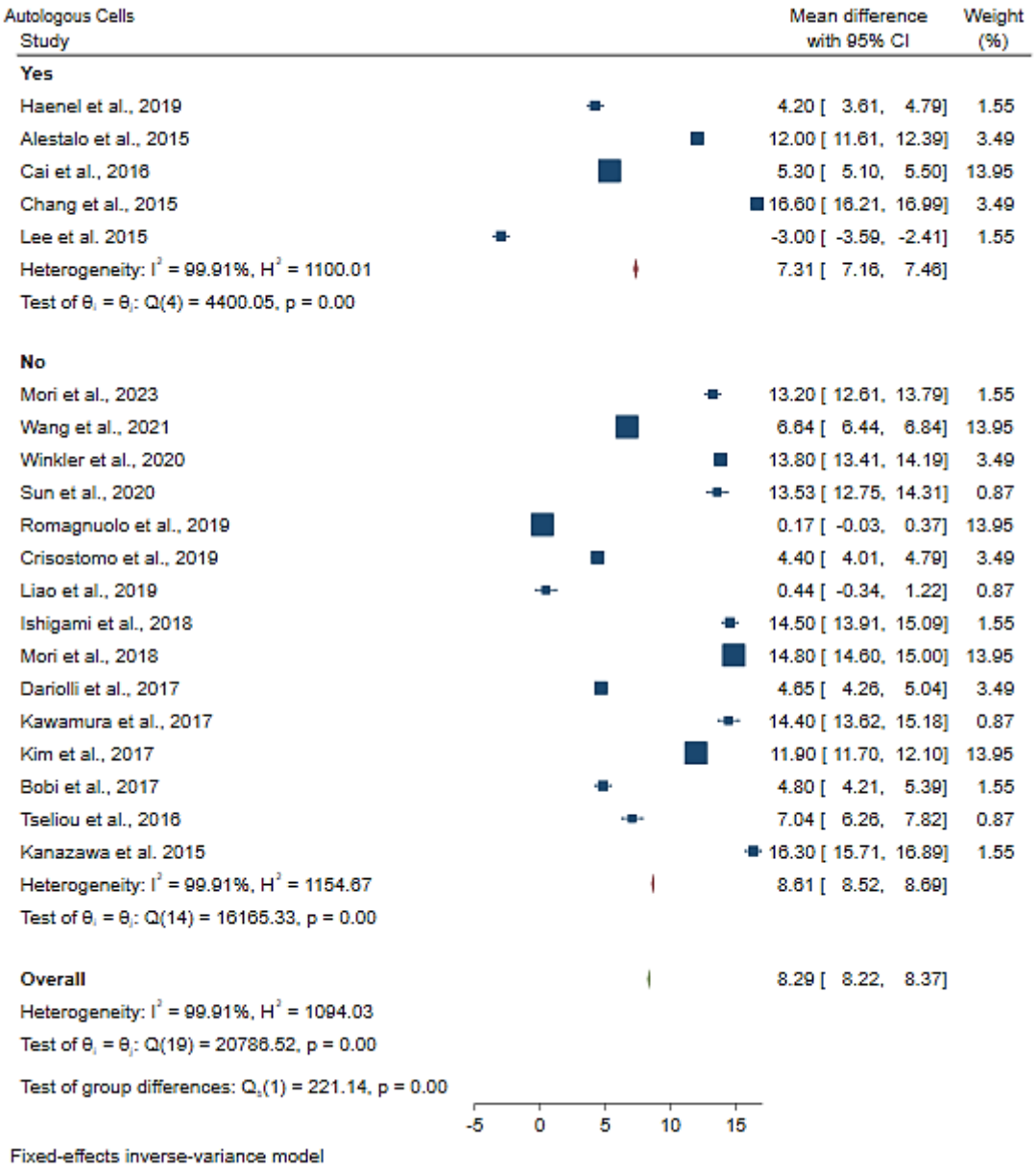

Fig. 4. The Forest plot showed LVEF mean difference values with autologous and no autologous cell treatments.

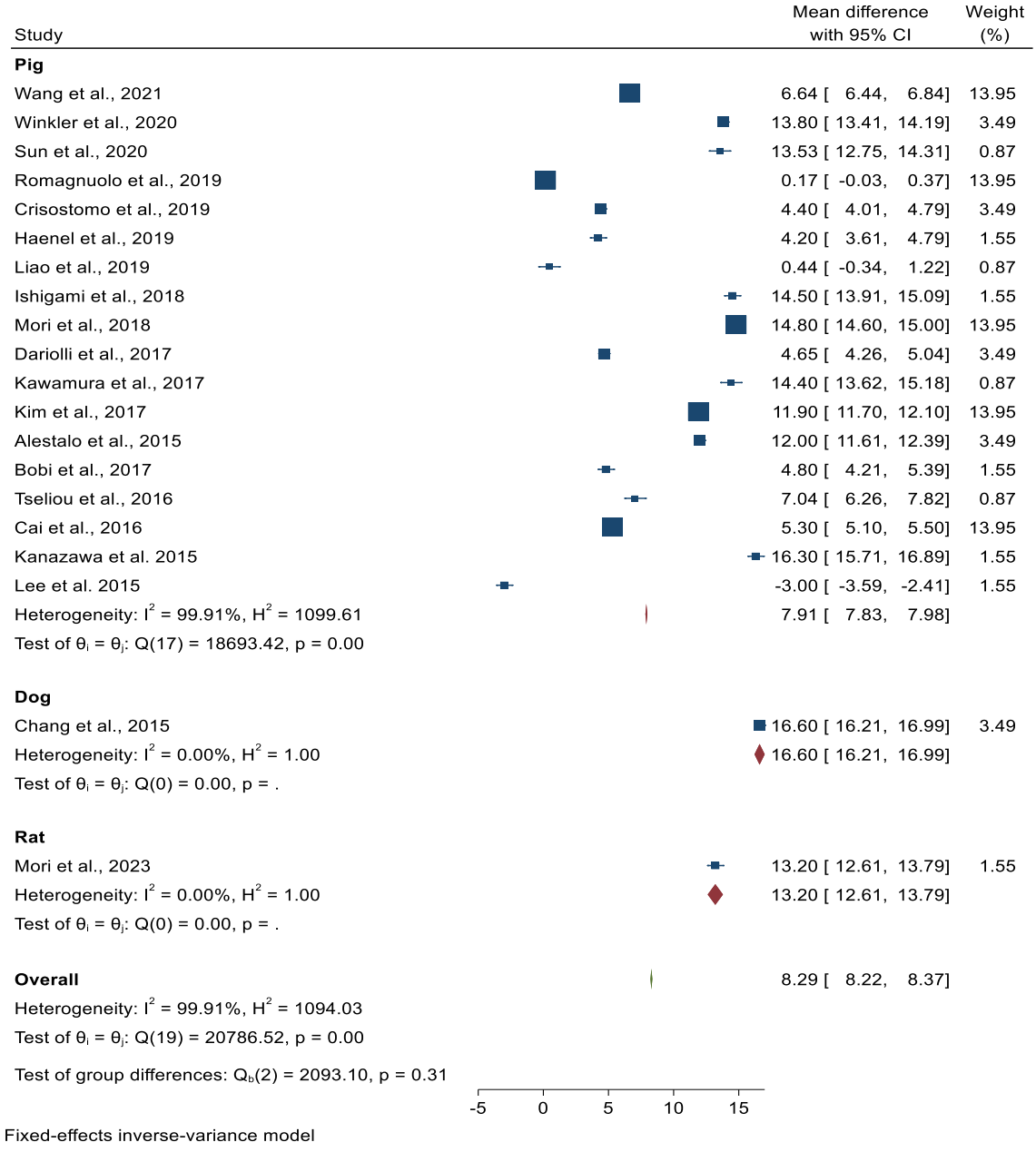

Fig. 5. The Forest plot showed LVEF mean difference values in an animal model.

4. Discussion

In the present study, the effectiveness of stem cell treatment compared to the control group was investigated in animal models. The current meta-analysis showed a significant improvement in LVEF after treatment with stem cells. The previous meta-analysis was consistent with the results of the present study.[35] However, the heterogeneity between the studies was very high, and the results of the present study should be relied on with caution. In the subgroup meta-analysis, improvement of LVEF was observed in the ischemia/reperfusion MI model and autologous cell treatment. In terms of animal models, no difference was observed between the results. However, most of the studies were conducted on the pig animal model,[36] which is widely accepted, and it is better to use the pig animal model in future studies. In the present study, due to the difference in the follow-up period, a subgroup meta-analysis was not performed; According to the results of the studies, the effect of cell therapy between 30 and 60 days leads to better treatment results. According to the results of the present study and previous studies, the use of stem cell therapy in heart diseases can increase cell survival.[37] A meta-analysis that examined human studies reported similar findings to the results of the present study.[38] A meta-analysis study observed that autologous cell therapy improves LVEF[38], and these results are in line with the findings of the present study. The current study had limitations; firstly, the heterogeneity between the above studies is caused by the difference in the cognitive methodology of obedience; Secondly, the follow-up period of the studies was not the same, and it was done in different periods, so it is suggested that future studies should place the follow-up period in the period of 30 to 60 days. Soma, the most significant difference between the studies was the cell type and the number of cells, which can be one of the reasons for the high heterogeneity between the studies.

5. Conclusion

According to the present meta-analysis, stem cell therapy improves left ventricular ejection fraction in ischemic heart disease. Also, the ischemia/reperfusion MI model and autologous cell treatment improve left ventricular ejection fraction. Using the pig animal model can effectively predict the results of clinical trials in the cardiovascular field.

Conflict of Interest

The authors declared that there is no conflict of interest.

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