

Stem cell implants for the treatment of ischemic cardiomyopathy: a systematic review and meta-analysis

Implantes de células-tronco para o tratamento de miocardiopatia isquêmica: uma revisão sistemática e metanálise

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ABSTRACT

Introduction: Cardiovascular diseases are the main causes of global mortality. Adverse cardiac remodeling after AMI often results in heart failure, even with therapeutic advances such as primary angioplasty. In this context, regenerative therapies emerge, such as the use of stem cells and biological grafts, to promote tissue regeneration and prevent ventricular remodeling. **Objectives:** To investigate stem cell implants in the treatment of ischemic cardiomyopathy. **Methods:** This systematic review included controlled clinical trials and experimental studies published between 2013 and September 2023 that evaluated stem cell implants for cardiac regeneration in ischemic cardiomyopathy. Searches were conducted in PubMed, LILACS, and SciELO databases in English, Spanish, and Portuguese. Reviews, case reports, narrative reviews, and studies without a control group were excluded. Risk of bias was assessed using the Joanna Briggs Institute checklist. Study selection followed PRISMA guidelines, and data were analyzed using OpenMetaAnalyst software. **Results:** Initially, 41 studies were identified and after applying the inclusion and exclusion criteria, only 6 remained for the final analysis, which had a sample space of 397 participants. The studies analyzed variables such as mortality, proBNT, LVEF, and infarction rate and demonstrated safety of the intervention and modest improvement in ventricular ejection fraction with the use of stem cells, but without significant impact on long-term clinical outcomes. **Discussion:** This systematic review evaluated the use of bone marrow-derived cells (BMCs) in cardiac regeneration in patients with ischemic heart failure and STEMI. Studies suggest modest improvement in cardiac function, favorable ventricular remodeling, and reduction of heart failure biomarkers after intramyocardial administration of the cells. Some cell phenotypes, such as CD31+ and CD45+CD31+, showed an association with greater reduction in infarct size. However, the results were heterogeneous and not always statistically significant. The main limitations included small sample size, lack of standardization of protocols, and methodological variability. Furthermore, there was no consistent impact on robust clinical outcomes such as mortality and rehospitalization. Despite this, cell therapy shows potential as a complementary strategy in the treatment of advanced heart failure, and larger multicenter studies are needed to confirm its clinical efficacy. **Conclusion:** Bone marrow-derived cell (BMC) therapy is a promising approach for ischemic heart failure and STEMI, showing potential to improve cardiac function, especially with certain cell subtypes. However, the heterogeneity of the results and the lack of consistent impact on primary outcomes limit its clinical application. Progress depends on better standardization of protocols and personalized strategies for each group of interest evaluated, and further studies and with a larger sample size are needed to possibly consolidate this therapy as a routine practice in cardiology.

Keywords: Stem cells; Genetic therapy; Regeneration; Heart; Myocardial ischemia.

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RESUMO

Introdução: As doenças cardiovasculares são as principais causas de mortalidade global. O remodelamento cardíaco adverso após o IAM frequentemente resulta em insuficiência cardíaca, mesmo com avanços terapêuticos como a angioplastia primária. Nesse contexto, surgem terapias regenerativas, como o uso de células-tronco e enxertos biológicos, para promover a regeneração tecidual e prevenir o remodelamento ventricular.

Objetivos: Investigar implantes de células-tronco no tratamento de miocardiopatia isquêmica. **Métodos:** Esta revisão sistemática incluiu ensaios clínicos controlados e estudos experimentais publicados entre 2013 e setembro de 2023 que avaliaram implantes de células-tronco para regeneração cardíaca em cardiomiopatia isquêmica. As buscas foram realizadas nas bases de dados PubMed, LILACS e SciELO em inglês, espanhol e português. Revisões, relatos de caso, revisões narrativas e estudos sem grupo controle foram excluídos. O risco de viés foi avaliado utilizando a lista de verificação do Instituto Joanna Briggs. A seleção dos estudos seguiu as diretrizes PRISMA e os dados foram analisados utilizando o software *OpenMetaAnalyst*. **Resultados:** Inicialmente, foram identificados 41 estudos e, após a aplicação dos critérios de inclusão e exclusão, apenas 6 permaneceram para a análise final, com uma amostra de 397 participantes. Os estudos analisaram variáveis como mortalidade, proBNT, FEVE e taxa de infarto, demonstrando a segurança da intervenção e uma melhora modesta na fração de ejeção ventricular com o uso de células-tronco, porém sem impacto significativo nos desfechos clínicos a longo prazo.

Discussão: Os trabalhos avaliaram potencial na sobrevivência de pacientes submetidos ao tratamento, porém ainda com desafios no que concerne a falta de significância estatística dessa terapêutica. Um fator de destaque é a ausência de um espaço amostral elevado de pacientes em todos os estudos aqui observados que permitisse uma randomização adequada e que poderia reduzir a chance de vieses. **Conclusão:** A terapia com células derivadas da medula óssea (BMCs) é uma abordagem promissora para a insuficiência cardíaca isquêmica e STEMI, mostrando potencial para melhorar a função cardíaca, especialmente com certos subtipos celulares. Contudo, a heterogeneidade dos resultados e a falta de impacto consistente em desfechos primários limitam sua aplicação clínica. O avanço depende da melhor padronização de protocolos e estratégias personalizadas para cada grupo de interesse avaliado, sendo necessário mais estudos e com um número amostral maior, para possivelmente consolidar essa terapia como prática de rotina na cardiologia.

Palavras-chave: Células-tronco; Terapia gênica; Regeneração; Miocárdio; Isquemia miocárdica.

Conflicts of interest:

None.

PROSPERO Registration:

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INTRODUCTION

Cardiovascular diseases are the leading cause of mortality in the world, with acute myocardial infarction (AMI) being one of its most critical clinical forms. Although reperfusion interventions, such as primary angioplasty, have substantially

improved the survival of patients in the acute phase, the abrupt restoration of blood flow in ischemic tissue triggers an inflammatory and scarring process that can progressively compromise the structure and function of the myocardium. Adverse ventricular remodeling, often observed after AMI, is directly associated with systolic dysfunction and progression

to heart failure, contributing to increased morbidity and mortality in the long term.

In this context, regenerative medicine has emerged as an innovative approach with the potential to modify the evolutionary course of ischemic heart disease. Unlike traditional strategies, which focus on preserving residual function, regenerative therapies seek to restore tissue architecture and functional performance of the myocardium through biological repair and regeneration mechanisms. Among these approaches, the use of stem cells with cardiogenic and paracrine properties stands out, as well as the use of autologous biomaterials that act as biological frameworks to support myocardial regeneration.

Such strategies aim not only to limit the extent of ischemic damage, but also to reconstitute the extracellular matrix and the functional integration of the infarcted areas with the remaining viable myocardium. The clinical applicability of these approaches, however, still requires methodological robustness and translational validation, given the heterogeneity of the protocols, cell types used, and cardiac injury models employed in the studies.

In view of this promising scenario, but still under construction, it is essential to critically review the biological and clinical foundations of regenerative interventions in AMI. The present study aims to analyze the main strategies based on cell therapies and autologous biological grafts applied to the context of myocardial infarction, discussing their evidence, limitations and perspectives for integration into clinical practice.

METHODS

PROTOCOL AND REGISTRATION

This systematic review and meta-analysis was conducted in accordance with the *Preferred Reporting Items for Systematic Review and Meta-analysis* (PRISMA) guidelines (located under the topic supplementary materials at the end of the review) and is registered in PROSPERO under the identification number CRD420251016178.

SOURCES OF INFORMATION AND ELIGIBILITY CRITERIA

The PubMed, LILACS, and SciELO databases were analyzed, covering scientific articles that meet the inclusion criteria defined as Controlled Clinical Trials and Experimental Studies published between 2013 and September 2023, in English, Spanish, and Portuguese. The last search date was in September 2023. These studies investigated the use of stem cell implants in cardiac regeneration, meeting the defined methodological specifications. On the other hand, Systematic Reviews, Case Reports, Narrative Reviews and uncontrolled studies were excluded.

RESEARCH STRATEGY

The search strategy was mediated by the construction of the search phrase formed by the Boolean operators with the terms: ("Stem Cells" OR "Stem Cell" OR "Progenitor Cells"

OR "Progenitor Cell" OR "Mother Cells" OR "Mother Cell" OR "Colony-Forming Unit" OR "Colony Forming Unit" OR "Colony-Forming Units" OR "Colony Forming Units") AND (Heart OR Cardiac) AND (Regeneration OR Regenerations OR "Endogenous Regeneration"). In addition, the following filters were applied: free full text, clinical trials, meta-analyses, randomized controlled studies, articles published in the last 10 years and conducted in humans.

STUDY SELECTION PROCESS

The study selection process was carried out in stages. In the first step, a reviewer eliminated the duplicates. In the second stage, two independent reviewers performed the initial screening by reading the titles, followed by the analysis of the abstracts, and, finally, excluding articles whose theme or population did not align with the objective of the study. Disagreements among the reviewers were resolved by consulting a third reviewer.

DATA COLLECTION PROCESS AND ITEM DATA

Data collection was performed by an independent reviewer who used a standardized form made in the Microsoft spreadsheet, Excel, which included information on the identification of the study (author, year of publication, DOI), the type of study design, the level of scientific evidence, the PICO strategy, the characteristics of the sample (number of participants in the control and experimental group, gender, age, mortality rate, morbidity rate, survival rate, and rehospitalization rate), detailed description of the methods, results, discussion, and conclusion of each selected article. The data collected was organized and presented in the excel table of the supplementary material (sTable 1).

RISK OF BIAS

The assessment of risk of bias was performed using the Joanna Briggs Institute checklist, and was conducted by 2 independent reviewers, and the third reviewer evaluated existing disagreements. The instrument used was the Excel spreadsheet to document and demonstrate the results obtained.

MEASURES OF EFFECT

Outcomes evaluated included LVEF, infarct size, NT-proBNP levels, rehospitalization, mortality, and NYHA functional class. For dichotomous outcomes, relative risks (RR) or odds ratios (OR) with 95% confidence intervals (CI) were calculated. For continuous outcomes, mean differences (MD) or standardized mean differences (SMD) were used. Statistical heterogeneity was assessed using the I^2 test, and fixed-effects or random-effects models were applied as appropriate. All analyses were conducted using OpenMetaAnalyst software.

SYNTHESIS METHOD

For each synthesis carried out, studies were selected that, in addition to meeting the inclusion criteria described in item 5 of the PRISMA protocol, presented interventions,

control groups, and outcomes comparable to each other. Reported outcomes such as left ventricular ejection fraction (LVEF), NT-proBNP levels, infarct size, NYHA functional class, rehospitalization, and mortality were also considered. The results of the individual studies were presented in descriptive tables. Quantitative syntheses were represented by forest plots, with confidence intervals (CI) of 95%. Appropriate effect measures were calculated for each type of outcome, such as relative risks (RR), odds ratios (OR), mean differences (MD), and standardized mean differences (SMD). The visual representations were prepared with the help of the Excel program and the OpenMetaAnalyst software, developed by Brown University (Center for Evidence-Based Medicine).

Although heterogeneity was observed in some of the outcomes evaluated, no subgroup analyses or meta-regressions were performed due to the limited number of studies available and insufficient variability in reported clinical characteristics. The decision aimed to avoid conclusions that were not very robust or statistically unreliable.

Sensitivity analyses were not performed, considering the limited number of studies included in some comparisons and the low methodological variation between them. Future updates of the review, with a larger volume of data, may incorporate this type of assessment to increase the robustness of the conclusions.

REPORTING BIAS ASSESSMENT

Due to the limited number of studies included ($n = 6$), it was not possible to perform formal statistical tests to assess publication bias, such as the funnel plot or the Egger test, as recommended by methodological guidelines. Instead, a qualitative evaluation of the completeness of the data reported in the articles was performed. Pre-established outcomes were observed in relation to those actually reported, the presence of possible selective omissions, and possible conflicts of interest. These strategies aim to identify indirect indications of publication bias or non-disclosure bias of results.

ASSESSMENT OF THE DEGREE OF CONFIDENCE

The certainty of the evidence for each main outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Thus, the evidence was classified into four levels: high, moderate, low or very low. The evaluation was conducted independently by two reviewers, with consensus in case of divergence.

RESULTS

Initially, 41 articles were identified in the databases. There was no need for removal due to duplicity. After reading the titles, 24 articles were considered relevant, with 17 excluded because they did not meet the selection criteria. Then, the reading of the abstracts resulted in the

inclusion of 19 articles, with the exclusion of 5 because they did not present information relevant to the proposed theme. Subsequently, 13 studies were included because they met the objectives of the review, and 6 were excluded at this stage. The analysis of the studied population allowed the selection of 6 articles consistent with the research proposal, while 7 were discarded due to incompatibility with the desired population focus. Finally, 6 articles were included for qualitative and quantitative analysis, composing the final database of the systematic review. In addition, the exclusions were duly justified throughout the process. The main reasons included lack of alignment with the inclusion criteria, approach to distinct populations, and irrelevance to the study's guiding question, according to picture 1.

INDIVIDUAL RESULTS AND SUMMARIES BY OUTCOME

The six trials evaluated different outcomes related to the use of bone marrow stem cells (BMC) compared to placebo in patients with ischemic heart disease¹⁻⁶. In total, 11 clinical variables were analyzed, and those with sufficient data for comparable statistical estimates between the groups were highlighted in this study. Among these data, the following are evidenced: mortality, NT-proBNP, infarct size, LVEF.

In addition, as a way to summarize the findings through this systematic review, the following table (table 1) was created in order to summarize the number of initial patients per study and their respective rates according to the outcomes of the studies.

Furthermore, below is a brief description, also by outcome, of the results with a graph that compares the results of the 6 studies (Figure 2) and the forest graph at the end to summarize the results by mean difference (Figure 3).

MORTALITY

In the mortality endpoint, 1 death was observed among 5 patients in the BMC group (20%) and no deaths in the placebo group (0%). Applying continuity correction, the relative risk (RR) was estimated at 2.5 (95% CI: 0.13–48.85), and the odds ratio (OR) was 3.0 (95% CI: 0.095–95.18). Despite the numerical trend unfavorable to the BMC group, the results did not reach statistical significance.

NT-PROBNP

Mean NT-proBNP levels decreased by 996.4 pg/mL in the BMC group and 680.3 pg/mL in the placebo group, with a mean between-group difference of –316.1 pg/mL (95% CI: –1410.4 to 778.2). Despite the greater reduction in the treated group, the confidence interval included zero, which was not statistically significant.

SIZE OF INFARCT

After one year, the mean residual infarct size was 10.1% in the BMC group and 11.4% in the placebo group. The difference between the groups was 1.3% (95% CI: –0.65 to 3.25). These results suggest a possible clinical benefit of the BMC group, but without robust statistical significance in the individual studies.

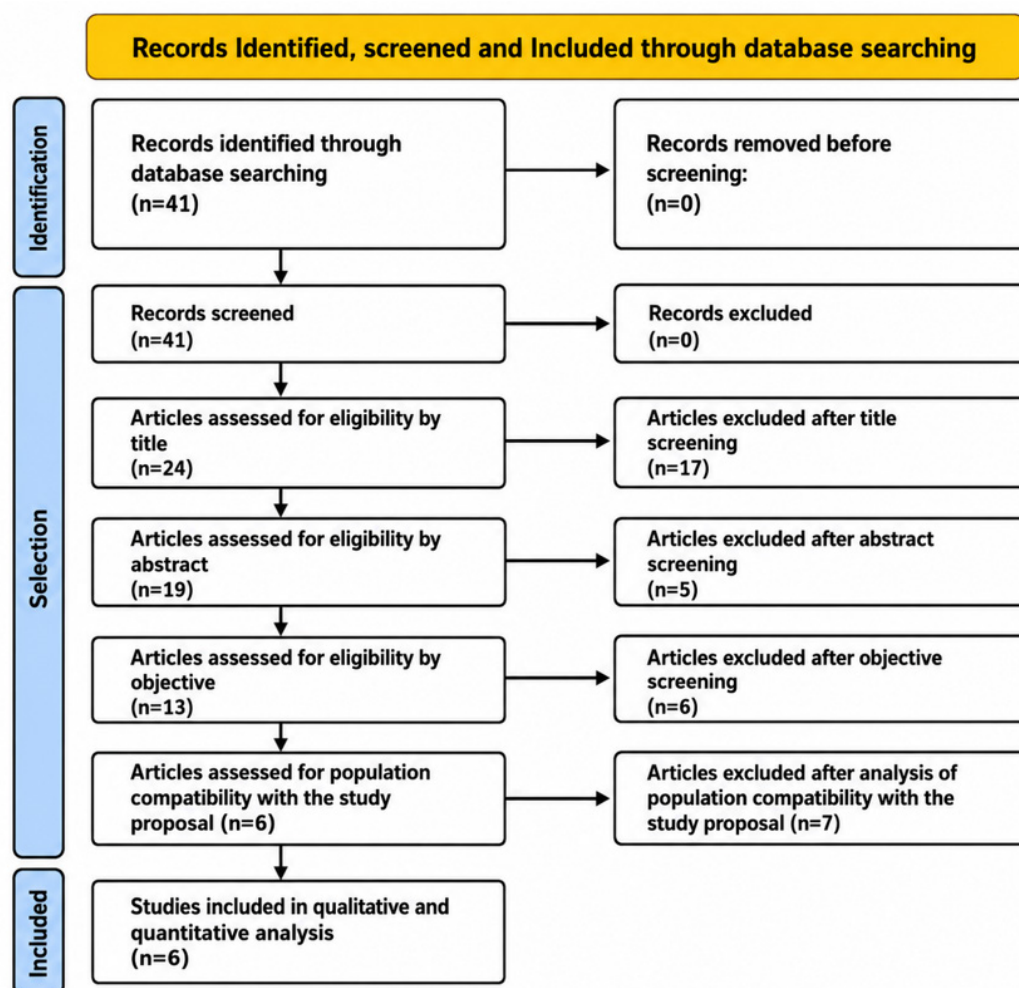


Figure 1. Flowchart of the process of identification, selection, eligibility assessment, and inclusion of studies in the review..

Table 1. Summary of the main outcomes evaluated in the included studies, coveting mortality, NTT-proBNP levels, infarct size, and left ventricular ejection fraction, including a comparison of results between groups, effect measures, and their respective confidence intervals.

Outcome	BMC Group Results	Control/Placebo Results	Comparative Analysis	Effect Measure / CI	Interpretation
Mortality	1 death among 5 patients (20%)	No deaths observed (0%)	Numerically higher mortality in the BMC group	RR = 2.5 (95% CI: 0.13–48.85); OR = 3.0 (95% CI: 0.095–95.18)	No statistically significant difference due to wide confidence intervals and small sample size
NT-proBNP	Mean reduction of 996.4 pg/mL	Mean reduction of 680.3 pg/mL	Greater biomarker reduction in the BMC group	Mean difference = -316.1 pg/mL (95% CI: -1410.4 to 778.2)	Suggests possible improvement in heart failure status, but without statistical significance

Infarct Size	Residual infarct size after 1 year: 10.1%	Residual infarct size after 1 year: 11.4%	Lower infarct size observed with BMC therapy	Mean difference = 1.3% (95% CI: -0.65 to 3.25)	Indicates potential reduction in myocardial injury, though not statistically robust
Left Ventricular Ejection Fraction (LVEF)	Mean increase of 5.1%	Mean increase of 2.8%	Greater improvement in ventricular function in the BMC group	Mean difference = 2.3% (95% CI: -4.0 to 8.6)	Demonstrates a favorable trend toward cardiac function recovery without significant statistical confirmation
Cardiac Remodeling	Favorable ventricular remodeling reported in some studies	Less expressive remodeling changes	Suggestive benefit with intramyocardial stem cell implantation	Heterogeneous across studies	Results varied according to study design and cell phenotype
Safety Outcomes	No major procedure-related adverse effects reported	Similar safety profile	Therapy generally considered safe	—	Stem cell implantation demonstrated acceptable safety in included trials
Functional Status / NYHA Class	Modest improvement in symptoms and functional capacity	Smaller or absent improvement	Better clinical evolution in treated patients	Variable measures among studies	Clinical relevance remains uncertain due to heterogeneity
Overall Clinical Outcomes	Modest qualitative and quantitative benefits	Conventional therapy outcomes maintained	Favorable tendency toward regeneration and cardiac recovery	No consistent impact on hard outcomes	Lack of significant reduction in mortality or rehospitalization limits immediate clinical applicability

LEFT VENTRICULAR EJECTION FRACTION (LVEF)

The mean increase in LVEF was 5.1% in the BMC group versus 2.8% in placebo, resulting in a difference of 2.3% (95% CI: -4.0 to 8.6). As with the other continuous outcomes, the analysis suggests a favorable trend for BMC, but without statistical significance.

RISK OF BIAS

Of the six studies evaluated, four were at low risk of bias, while two were classified as moderate risk. The main uncertainties in low-risk studies were related to the intervention, outcome measurement, and follow-up of participants. Studies with moderate risk presented weaknesses in the allocation of groups, blinding, intervention

and analysis of participants according to randomization. The information was presented in the Tables 2 and 3.

BIASES DENOUNCED

The summary of findings from the evaluated studies highlights the importance of considering uncertainties related to intervention, blinding, and allocation when interpreting the results. The REGENERATE - AMI Study has significant uncertainties that affect the reliability of its findings, while the REGENERATE - IHD demonstrates a low risk of bias, offering more reliable conclusions. The AGTP and PERICOSPE studies, on the other hand, present a moderate risk of bias, potentially compromising the interpretation of the results, especially due to problems with allocation and blinding.

On the other hand, the CCTRN TIME Study reveals a low risk, indicating greater reliability in its conclusions.

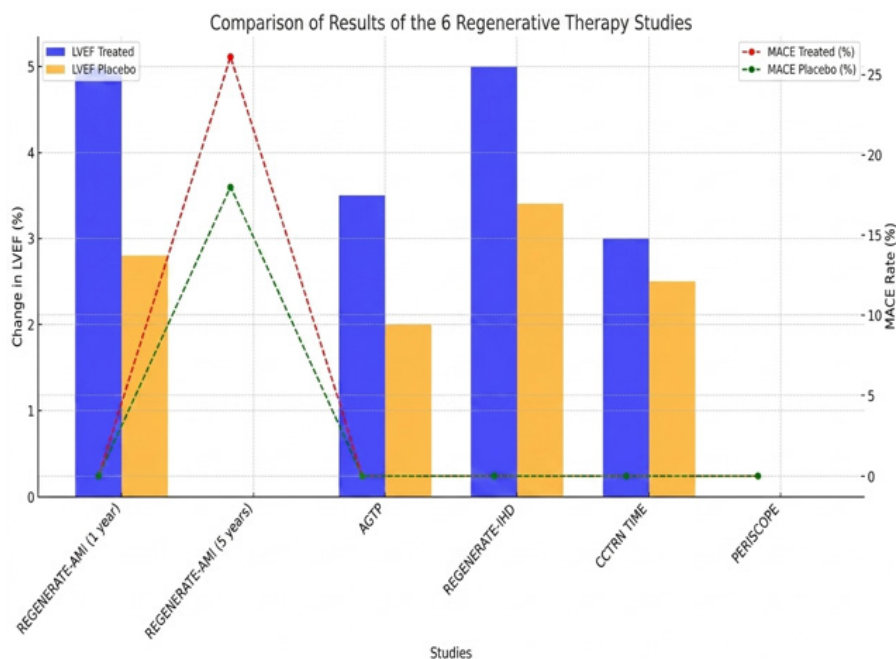


Figure 2. Mixed chart with grouped bars and dotted lines, featuring two vertical axes (LVEF and MACE).

Legend: Comparison of the results of six studies on regenerative therapies in the treatment of ischemic cardiomyopathy. The bars represent the percent change in left ventricular ejection fraction (LVEF) for the treated and placebo groups. The dotted lines show the rate of major adverse cardiac events (MACE) where data are available. The graph shows variations in outcomes between the different therapeutic approaches evaluated.

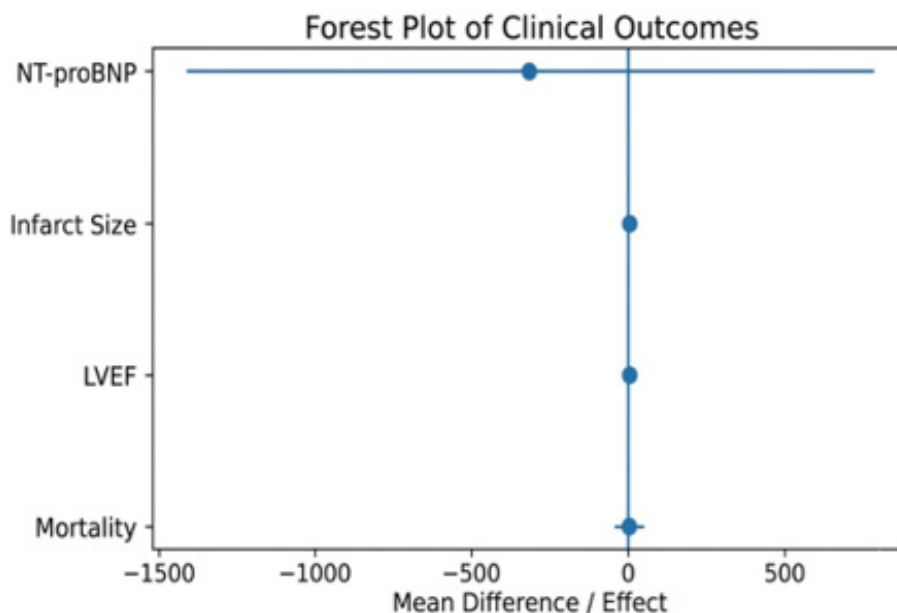


Figure 3. Visual Analysis – Forest Graph.

Legend: Forest graph of the continuous outcomes analyzed. The blue lines indicate the 95% confidence intervals, and the blue dots represent the average difference observed between the BMC and placebo groups. The gray vertical line represents the null value (difference = 0).

Table 2. Risk of Bias Assessment According to the "Joanna Briggs 2023" Critical Evaluation Checklist for Randomized Controlled Trials.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13
Mathur et al. (2022)	Yes	Yes	Yes	Yes	Yes	Confused	Confused	Yes	Confused	Yes	No	Yes	Yes
Bayes-Genis et al. (2016)	Yes	Confused	Yes	Confused	Yes	Confused	Yes	Yes	Confused	Yes	No	Yes	Yes
Choudry et al. (2016)	Yes	Yes	Yes	Yes	Yes	Confused	Yes	Yes	Confused	Yes	Yes	Yes	Yes
Choudhury et al. (2017)	Yes	Yes	Yes	Yes	Yes	Confused	Yes	Yes	Confused	Yes	No	Yes	Yes
Bayes-Genis et al. (2024)	Yes	Confused	Yes	Confused	No	Confused	Yes	Yes	Confused	Yes	Confused	Yes	Yes
Internal validity: a) Bias related to selection and allocation													
1 - Was true randomization used for the assignment of participants to treatment groups?													
2 - Has the allocation to treatment groups been hidden?													
3 - Were the treatment groups similar at baseline?													
b) Bias related to intervention/exposure administration													
4 - Were participants blinded to treatment assignment?													
5 - Were those who administered the treatment blind to the attribution of the treatment?													
6 - Were the treatment groups treated identically beyond the intervention of interest?													
c) Bias related to the assessment, detection, and measurement of the outcome													
7 - Were the outcome assessors blinded to treatment attribution?													
8 - Were the outcomes measured in the same way for the treatment groups?													
9 - Were the results reliably measured?													
d) Bias related to participant retention													
10 - Was the follow-up complete and, if not, were the differences between the groups described?													
Validity of the statistical conclusion													
11 - Were the participants analyzed in the groups to which they were randomized?													
12 - Was appropriate statistical analysis used?													
13 - Was the study design appropriate?													

Table 3. Risk of Bias Assessment According to the "Joanna Briggs 2023" Critical Evaluation Checklist for Cohort Studies.

Study	1	2	3	4	5	6	7	8	9	10	11
Schutt et al. (2015) ⁶	Yes	Yes	Confused	Yes	Yes	Yes	Yes	Yes	Yes	Confused	Yes
<p>1- Were the two groups similar and recruited from the same population?</p> <p>2- Were exposures measured in a similar way to assign people to exposed and unexposed groups?</p> <p>3- Was the exposure measured validly and reliably?</p> <p>4- Were confounding factors identified?</p> <p>5- Have strategies been stated to deal with confounding factors?</p> <p>6- Were the groups/participants free of the outcome at the beginning of the study (or at the time of exposure)?</p> <p>7- Were the results measured validly and reliably?</p> <p>8- Was the follow-up time reported enough to be long enough for results to occur?</p> <p>9- Was the follow-up complete and, if not, were the reasons for the loss described and explored?</p> <p>10- Were strategies used to deal with incomplete follow-up?</p> <p>11- Was appropriate statistical analysis used?</p>											

DISCUSSION

In particular, it is worth noting that some scientific studies have shown that the use of stem cells in situations of myocardial ischemia promotes reconstitution of the injured tissue, through angiogenesis and anti-apoptotic mechanisms, thus allowing the reduction of inflammation and fibrosis, as elucidated by Rebouças et al. (2020)⁷. According to Matsuda et al. (2014)⁸, the benefits of this therapy come from hematopoietic stem cells, skeletal myoblasts and fetal cardiomyocytes, so that, in fact, the beneficial effects of the therapy can be achieved.

Thus, this systematic review findings reinforce and expand upon the evidence previously described by Rebouças et al. (2020)⁷ and Matsuda et al. (2014)⁸, as it highlights the potential impact of bone marrow-derived cell (BMC) therapy on cardiac regeneration, particularly in patients with ischemic heart failure and elevation acute myocardial infarction make the ST segment (STEMI)^{1,2}. The included studies demonstrate that intramyocardial administration of BMCs can improve cardiac function, reduce biomarkers of failure, and contribute to favorable ventricular remodeling^{1,4}. In addition, it was identified that certain cellular phenotypes, such as CD31+, CD45+CD31+, and CD45+CD31low, are associated with a greater reduction in infarct size, suggesting that the efficacy of therapy may depend on the specific characteristics of the injected cells⁶.

The systematic review conducted by Tsilimigras et al. (2017)⁹ on stem cell therapy in congenital heart diseases presents an important convergence with the present study: both studies highlight the therapeutic potential of stem cells in myocardial regeneration and in improving cardiac function. However, as observed in the present review, the study by Tsilimigras et al. (2017)⁹ also shows significant limitations related to the small sample size, methodological heterogeneity, and lack of standardization in therapeutic protocols, factors that compromise the generalization of results and the adoption of the therapy as a consolidated clinical practice.

Overall, the findings suggest that intramyocardial administration of BMCs may have a beneficial effect on the recovery of cardiac function, although the results are heterogeneous and not always statistically significant^{1,2,4}.

Critical evaluation of the evaluated studies indicates that regenerative therapy approaches have potential, but consistent clinical outcomes are still a challenge^{3,5}. It should be noted that the greatest limitation found during the analysis of the studies refers to the samples evaluated, since none of the studies presented a sample that represented a significant number of patients, being limited to a maximum of 100 participants^{1,3}. Thus, there was difficulty in evaluating the effects of this type of workup at the population level. The scientific evidence analyzed seems to suggest an increase in cardiac function in modest results qualitatively and quantitatively^{2,4}. However, the conflicting results between the studies highlight important challenges in the clinical application of cell therapy. The variability in the response

of patients may be related to multiple factors, such as individual characteristics, time of administration after the ischemic event, cell viability, and route of administration⁶. In addition, the absence of a significant impact on robust clinical outcomes, such as mortality or re-hospitalizations, limits the immediate applicability of the therapy in clinical practice^{2,4}.

However, the findings suggest that cell therapy may be a complementary strategy in the treatment of patients with advanced heart failure or STEMI, especially for those whose conventional therapy is not effective^{3,5}. The improvement in left ventricular ejection fraction, quality of life, and NYHA functional class indicates a potential clinical benefit, albeit modest^{2,4}. In addition, the identification of specific cellular biomarkers can assist in the selection of patients who are more responsive to therapy, allowing for a more personalized approach⁶.

Despite the strict adherence to the PRISMA 2020 guidelines and the previous registration in PROSPERO, some methodological limitations must be considered. The search was carried out in three databases, which, although relevant, may have been left out of studies indexed in other sources. In addition, inclusion was restricted to publications in English, Spanish, and Portuguese, which may have introduced language bias, excluding potential relevant evidence in other languages. Although the selection of studies and data extraction were carried out by three reviewers independently, the process is still subject to subjective judgments. The assessment of risk of bias was conducted using the Joanna Briggs Institute tool, recognized for its quality, but which, like any instrument, depends on the interpretation of the evaluators and may have limitations in terms of standardization among reviewers.

The biggest challenge for the clinical implementation of cell therapy in cardiology is the variability of outcomes and the absence of significant impact on robust clinical outcomes, such as mortality and hospitalizations for heart failure^{1,5}. In addition, the need for standardization in obtaining, processing, and applying BMC cells, as well as defining the optimal time for administration, represents a barrier to widespread adoption of the treatment. More comprehensive multicenter studies are needed to confirm the efficacy of the therapy and establish well-defined clinical protocols^{2,4}.

CONCLUSION

Cell therapy with bone marrow-derived cells (BMCs) represents an innovative approach in the management of ischemic heart failure and ST-elevation acute myocardial infarction (STEMI)^{1,2,4,6}. The studies analyzed demonstrate that the intramyocardial administration of BMCs can promote improvement in cardiac function and heart failure symptoms, especially when associated with specific cellular factors, such as the presence of CD31+ and CD45+CD31low cells⁶. However, the heterogeneity of the results highlights the

need for further refinement in the patient selection criteria and in the standardization of therapeutic protocols^{2,4,5}.

Clinical applicability still faces challenges, mainly due to the lack of consistent impact on primary clinical outcomes, such as sustained cardiac remodeling and reduced mortality^{2,3,5}. A greater understanding of the functional properties of cells, combined with personalized therapy strategies, may be the key to maximizing the benefits and overcoming current limitations^{4,6}.

Thus, cell therapy has not yet established itself as a routine alternative in cardiology, but its therapeutic potential is evident in specific cases^{1,3,5}. Future studies should focus on patient stratification and optimization of delivery methods to transform this promising strategy into an effective and affordable treatment for ischemic myocardial regeneration^{2,5,6}.

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Supplementary Materials can be accessed on the article's page on our website and via the following links:

- PRISMA 2020 Abstract Checklist
- PRISMA 2020 Checklist
- sTable 1. Selected articles features

CONTRIBUIÇÃO DOS AUTORES

We describe contributions to the papers using the taxonomy (CRediT) provided below:

Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing. Project administration, Supervision & Writing – original draft. Validation & Software. Resources & Funding acquisition. Data curation & Formal Analysis: All authors contributed equally to these topics.

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