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Lung ultrasound-guided therapy to reduce urgent visits and readmissions in heart failure patients: protocol for a systematic review and meta-analysis of randomized clinical trials

Terapia guiada por ultrassonografia pulmonar para reduzir visitas de urgência e readmissões em pacientes com insuficiência cardíaca: protocolo de revisão sistemática e meta-análise de ensaios clínicos randomizados

William Suzart Coutinho de Araujo[1]; Marina Danielle Senna Souza[1]; Ana Carolina Silva Malta[1]; Dhule Kelly Souza Miranda[1]; Leilla Stefany de Jesus Ferreira[2]; Bruno Souza Soares[3]; Marcelo Farani López[4]; Giulliano Gardenghi[5]; Priscilla Flávia de Melo Fernandes[1]

[1]Departamento de Fisioterapia, Fundação de Ensino e Pesquisa em Ciências da Saúde, Brasília, DF, Brasil
[2]Departamento de Fisioterapia, Universidade Salvador, Salvador, BA, Brasil
[3]Departamento de Fisioterapia, Hospital Universitário Antônio Pedro, Niterói, RJ, Brasil
[4]Departamento de Fisioterapia, Hospital Professor Eladio Lasserre, Salvador, BA, Brasil
[5]Coordenação Científica, Hospital Encore, Aparecida de Goiânia, GO, Brasil

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***Corresponding author:**
William Suzart Coutinho de Araujo.

E-mail: suzartfisio@gmail.com

Abstract

Background: Congestive heart failure is a common condition among hospitalized patients, often linked to high rates of readmission and mortality. Although biomarkers like N-terminal pro-B-type natriuretic peptides (NT-proBNP) are commonly used for monitoring congestive heart failure, their isolated use is not recommended by current guidelines. Lung ultrasound has emerged as a promising non-invasive tool to assess pulmonary congestion and monitor treatment response. **Aim:** To assess the effectiveness of lung ultrasound-guided therapy in reducing urgent visits, readmissions, and mortality in heart failure patients compared to standard care. **Methods:** A systematic review and meta-analysis of published randomized clinical trials will be conducted, including adult hospitalized heart failure patients. Studies will be sourced from databases such as PubMed, EMBASE, and Cochrane without language and date restrictions. Two independent reviewers will screen and select studies based on PICO criteria. Primary outcomes include rates of urgent visits, readmissions, and mortality within 180 days. Methodological quality will be assessed using the Risk-of-Bias 2 tool, and the certainty of evidence will be evaluated using the GRADE system. **Registration:** In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 11 October 2024 (registration number: CRD420250596077).

Keywords: Heart Failure; Hospitalization; Mortality.

Resumo

Introdução: A insuficiência cardíaca congestiva é uma condição comum entre pacientes hospitalizados, frequentemente associada a altas taxas de readmissão e mortalidade. Embora biomarcadores como o peptídeo natriurético tipo B N-terminal (NT-proBNP) sejam amplamente utilizados para monitoramento da insuficiência cardíaca congestiva, seu uso isolado não é recomendado pelas diretrizes atuais. A ultrassonografia pulmonar tem se destacado como uma ferramenta não invasiva promissora para avaliar a congestão pulmonar e monitorar a resposta ao tratamento. **Objetivo:** Avaliar a eficácia da terapia guiada por ultrassonografia pulmonar na redução de visitas de urgência, readmissões e mortalidade em pacientes com insuficiência cardíaca, em comparação ao tratamento convencional. **Métodos:** Será conduzida uma revisão sistemática e meta-análise de ensaios clínicos randomizados publicados, incluindo pacientes adultos hospitalizados por insuficiência cardíaca. Os estudos serão obtidos em bases de dados como PubMed, EMBASE e Cochrane, sem restrições de data e idioma. Dois revisores independentes realizarão a triagem e seleção dos estudos com base nos critérios PICO. Os desfechos primários incluirão as taxas de visitas de urgência, readmissões e mortalidade em até 180 dias. A qualidade metodológica será avaliada utilizando a ferramenta Risk-of-Bias 2 e a certeza da evidência será avaliada pelo sistema GRADE. **Registro:** De acordo com as diretrizes, o protocolo desta revisão sistemática foi registrado no Registro Internacional Prospectivo de Revisões Sistemáticas (PROSPERO) em 11 de outubro de 2024 (número de registro: CRD420250596077).

Palavras-chave: Insuficiência Cardíaca; Hospitalização; Mortalidade.

INTRODUCTION

Congestive heart failure is a common condition among hospitalized patients, with the majority having a preexisting diagnosis, though it is an active problem during hospitalization in only half of these cases. The rates of heart failure with reduced ejection fraction and heart failure with preserved ejection fraction are comparable. In most cases, the trigger for exacerbation cannot be determined, although infection is the most frequently identified cause. Despite basic differences in demographics, clinical characteristics, and therapeutic regimens at discharge between heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, both are associated with an unfavorable prognosis, including high in hospital mortality and elevated rates of short- and long-term readmissions[1].

In clinical practice, N-terminal pro-B-type natriuretic peptides (NT-proBNP) are commonly used to evaluate heart failure severity and prognosis[2]. However, European Society of Cardiology (ESC) and American Heart Association/ American College of Cardiology (AHA/ACC) guidelines did not recommend biomarker-guided therapy in the management of heart failure patients[3]. In recent years, the use of lung ultrasound has increased in emergency departments, intensive care units, and other fields[4]. Although based on a small number of studies, a systematic review suggests that LUS may be a useful, non-invasive method that enables tracking of changes in pulmonary congestion in response to treatment[5].

The assessment of extravascular lung water in heart failure patients using lung ultrasound and B-lines offers an excellent alternative for clinical evaluation[6]. B-lines appear as multiple laser-like signals originating from the hyperechoic pleural line on an antero-lateral chest scan, displaying a to-and-fro motion synchronized with respiration[7]. A notable limitation of cardiology protocols is the consistent exclusion of the posterior chest surface[8].

Recent systematic reviews have evaluated the effectiveness of lung ultrasound-guided therapy in hospitalized heart failure patients concerning urgent visits, readmissions, and mortality[9,10]. However, these reviews did not address the certainty of the evidence. The Cochrane Handbook for Systematic Review of Interventions recommends that authors comment on the certainty of the evidence[11]. Additionally, authors should apply the evidence grading system developed by the GRADE Working Group[12].

This systematic review aims to evaluate the effectiveness and evidence certainty of lung ultrasound-guided therapy compared to conventional care based on clinical practice guidelines in hospitalized heart failure patients, with a focus on urgent visits, readmissions, and mortality related to heart failure within 180 days.

METHODS

The protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol 2015 (PRISMA-P)[13] statement for reporting and was developed based on the PRISMA-P 2015 Elaboration and Explanation[14]. In accordance with the guidelines[15], our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 11 October 2024 (registration number: CRD420250596077).

Eligibility criteria

Study designs

We will include published randomized controlled trials with two or more arms. Cluster RCTs, controlled (non-randomized) clinical trials, cross-over trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports will be excluded.

Participants

We will include studies focusing on patients aged 18 years or older who are hospitalized for heart failure, defined by symptoms of shortness of breath, elevated NT-proBNP levels, and evidence of pulmonary congestion on chest X-ray.

Intervention and comparison

We will include studies in which patients in both groups receive treatment based on relevant clinical practice guidelines, with lung ultrasound-guided therapy available exclusively to the intervention group.

Outcomes

Urgent visits, readmissions, and mortality related to heart failure within 180 days.

Information sources

Literature search strategies were developed using medical subject headings (MeSH), cochrane highly sensitive search strategy for identifying randomized trials[16], and text words related to heart failure and lung ultrasound. A comprehensive search was conducted in MEDLINE (PUBMED interface), EMBASE (EMBASE interface), Cochrane Central Register of Controlled Trials (Wiley interface), CINAHL (EBSCOhost interface), Web of Science (Clarivate Analytics interface), and Biblioteca Virtual em Saúde (BIREME/PAHO/WHO interface).

To ensure a comprehensive literature search, we scan the reference lists of included studies and relevant reviews identified through the search. We also examined the authors' personal files to ensure all relevant material was captured. Finally, we circulate a bibliography of the included articles to the systematic review team and to heart failure and lung ultrasound experts identified by the team.

Search strategy

The search strategies for all databases, including their respective dates, are available at the following link[17]: https://www.crd.york.ac.uk/PROSPEROFILES/596081_STRATEGY_20240930.pdf. No restrictions were applied concerning language or publication date.

Selecting studies

The software Mendeley (Elsevier, London, United Kingdom) will be used for managing records and bibliographic data throughout the systematic review process. All references obtained from electronic databases will be imported into Mendeley, where they will be organized into specific collections for each stage of the process. Automatic and manual checks will be performed to identify and remove duplicate records. Mendeley will also be used to export selected records to other data extraction and analysis tools, when applicable.

Two review authors (WS and AC) will independently screen the titles and abstracts identified through the search against the inclusion criteria. Full reports will be obtained for all titles that meet the inclusion criteria or when there is any uncertainty. Pairs of review authors will then screen the full-text reports and determine whether they meet the inclusion criteria. Additional information will be sought from study authors when necessary to resolve questions about eligibility. Disagreements will be resolved through discussion, with a third reviewer (LS) consulted if consensus cannot be reached. Reasons for trial exclusion will be recorded.

Data extraction

Using Google Sheets, two review authors (WS and DK) will independently extract data from each eligible study. To ensure consistency across reviewers, calibration exercises will be conducted before starting the review. We will extract the trial design, trial size, country, funding sources, conflicts of interest, patient characteristics (average age, gender, ejection fraction), intervention details (lung ultrasound protocol), control group details (clinical practice guideline protocols), occurrence of urgent visits, readmissions, and mortality related to heart failure. Reviewers will resolve disagreements through discussion, with a third reviewer (LS) consulted if consensus cannot be reached.

It is possible that individual studies may consist of multiple treatment groups, such as different types of protocols. To avoid the risk of introducing bias due to multiple statistical comparisons with a single control group, we will combine the groups from multiple-arm studies into a single group. If effect sizes cannot be calculated, we will contact the authors for additional data.

OUTCOMES

Primary outcomes

The primary outcomes will be the rates of urgent visits and readmissions related to heart failure within 180 days.

Secondary outcome

The secondary outcome will be the rate of mortality related to heart failure within 180 days.

Risk-of-bias assessment

To facilitate the assessment of potential risk of bias for each study and outcome, we will collect information using version 2 of the Cochrane Risk-of-Bias tool for randomized trials[18], which covers the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. For each domain, we will describe the procedures undertaken for each study, including verbatim quotes when applicable. A judgment regarding the potential risk of bias in each of the five domains will be made based on the extracted information and rated as "low risk of bias," "some concerns," or "high risk of bias." These judgments will be made independently by two review authors (WS and MD) based on the criteria for assessing risk of bias[19]. Disagreements will be resolved first through discussion and, if unresolved, by consulting a third author (LS) for arbitration. We will generate graphical representations of potential bias within and across studies using the Risk-of-Bias Visualization Tool[20].

Data synthesis and analysis

Measures of treatment effect

Each outcome will be combined and calculated using the statistical software RevMan 5.4.1, following the statistical guidelines referenced in the current version of the *Cochrane Handbook for Systematic Reviews of Interventions*[21]. Since our outcomes will be dichotomous (occurrence of urgent visits, readmissions, and mortality within 180 days), we will synthesize the data by extracting the number of events and the number of participants in each group. The Mantel-Haenszel method will be employed for the meta-analysis to estimate the risk ratio (RR) using a random-effects model.

Unit of analysis issues

For studies reporting repeated outcome measurements at multiple time points, we will extract data from the longest follow-up available, up to a maximum of 180 days. If a study reports data at shorter intervals (e.g., 30, 90, or 120 days) but not at 180 days, the latest available measurement will be used for the primary analysis. Subgroup analyses will be conducted to explore variations across different time points and assess the consistency of results over time.

Dealing with missing data

When data is missing, we will attempt to contact the original study authors to obtain the relevant information. Important numerical data will be carefully evaluated. If the missing data cannot be obtained, an appropriate imputation method will be applied. If necessary, a sensitivity analysis will be conducted to assess the robustness of the results based on the assumptions made during the imputation process.

Assessment of heterogeneity

Statistical heterogeneity will be assessed using the I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity)[21]. If significant heterogeneity ($P < 0.05$) and minimal or no overlap of CIs among the trials exist, the study design and characteristics of the included studies will be analyzed. We will attempt to explain the source of heterogeneity through subgroup analysis or sensitivity analysis.

Subgroup analysis

Subgroup analyses will be conducted to explore sources of heterogeneity based on the following:

- Patient characteristics
- Type of protocol
- Follow-up period
- Setting

Sensitivity analysis will be performed to further investigate the source of heterogeneity, specifically:

- Risk of bias (by omitting studies judged to be at high risk of bias).

Publication bias

We will assess publication bias using funnel plots and Egger's test for asymmetry when at least ten studies are included. Selective reporting bias will be evaluated by comparing reported outcomes with pre-specified outcomes in trial registries.

Assessment of certainty of evidence

The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group methodology[12]. The quality of evidence will be evaluated across the domains of risk of bias, consistency, directness, precision, and publication bias. Quality will be rated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (there is considerable uncertainty about the estimate of effect)[11]. The judgment of the certainty of evidence will be made independently by two review authors (WS and MD). Disagreements will be resolved first through discussion and, if unresolved, by consulting a third author (LS) for arbitration.

Administrative information

This protocol does not represent an update of a previously published systematic review.

Amendments

In the event of protocol amendments, the date of each amendment will be recorded along with a detailed description of the change and its rationale, ensuring full transparency.

FUNDING

This study received no funding.

CONFLICT OF INTEREST

Bruno Souza and Marcelo Farani are mentors and instructors for courses involving lung ultrasound.

RESEARCH DATA AVAILABILITY

Research data is only available upon request.

AUTHOR CONTRIBUTIONS

William Suzart acted as the guarantor of the review, wrote the original manuscript, and was responsible for the development of the search strategy, statistical analysis, and data synthesis. The development of the selection and data extraction criteria involved the collaboration of William Suzart, Marina Danielle, Ana Carolina, and Dhule Kelly. Marina Danielle also participated in the risk of bias assessment and the judgment of the certainty of evidence (GRADE), while Ana Carolina performed the screening of titles and abstracts, and Dhule Kelly handled the data extraction from the studies. Giulliano Gardenghi and Priscilla Mello provided clinical expertise in heart failure, whereas Marcelo Farani and Bruno Souza contributed with the technical review regarding lung ultrasound. Finally, Leilla Stefany acted as the third reviewer for resolving disagreements and arbitration across all stages of the process. All authors reviewed and approved the final version of the protocol.

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