# Biomarker-Guided Versus Clinically Guided Fluid Management in Heart Failure: A Protocol for a Systematic Review and Meta-Analysis

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## *Abstract*

**Background:** Fluid overload in heart failure (HF) remains a critical driver of morbidity and mortality. Current guideline-directed fluid management strategies based on clinical signs and symptoms lack sensitivity for the early detection of congestion. This limitation often leads to delayed interventions or suboptimal fluid removal, contributing to high rates of rehospitalization and poor patient outcomes. Biomarker-guided strategies, particularly using B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), offer a potential solution by providing objective, real-time feedback on hemodynamic stress.

**Objective:** This study aims to conduct a systematic review and meta-analysis to evaluate the efficacy and safety of biomarker-guided fluid management compared to standard, clinically guided strategies in patients with HF. The primary objectives are to determine whether a biomarker-guided approach reduces all-cause mortality and HF-related hospitalizations. Secondary objectives include assessing the impact on renal function, quality of life, and changes in biomarker levels.

**Methods:** We will conduct a systematic search of PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from their inception to May 2025. We will include randomized controlled trials and prospective cohort studies that compare fluid management guided by BNP or NT-proBNP to clinically guided standard care in adult patients with HF. Two investigators will independently perform study selection, data extraction, and risk of bias assessment using the Cochrane Risk of Bias 2.0 (RoB 2) and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tools. The primary outcomes are all-cause mortality and HF-related hospitalizations. Secondary outcomes include worsening renal function, quality of life measured by validated questionnaires, and biomarker trajectory. Statistical analysis will be performed using RevMan 5.4. We will use a random-effects model for meta-analysis and conduct subgroup analyses based on HF phenotype (eg, reduced vs preserved ejection fraction) and biomarker type.

**Results:** This study will synthesize the available evidence on the efficacy and safety of biomarker-guided fluid management in HF. The findings, based on outcomes such as mortality, hospitalization rates, renal function, and quality of life, will be submitted for publication in a peer-reviewed journal.

**Conclusions:** This systematic review will consolidate the current evidence for biomarker-guided fluid management in HF. The findings are expected to inform clinical guidelines and decision-making by providing a comprehensive assessment of the benefits and risks of this approach. Furthermore, this review will identify existing research gaps and suggest directions for future investigations to optimize fluid management strategies in this vulnerable patient population. Clinical Trial: PROSPERO CRD420250652134; https://www.crd.york.ac.uk/PROSPERO/view/CRD420250652134

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# Original Manuscript

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**Trial Registration:** PROSPERO CRD420250652134; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=CRD420250652134

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## KEYWORDS

heart failure; natriuretic peptides; fluid therapy; biomarkers; fluid overload; systematic review; meta-analysis; protocol; clinical outcomes

## Introduction

### Background

Heart failure (HF) is a major global public health challenge, affecting an estimated 64 million people worldwide and imposing a substantial economic burden, with related healthcare costs projected to exceed US $70 billion annually in the United States by 2030 [1,2]. A central pathophysiological feature of HF is fluid overload, which leads to systemic congestion, progressive organ dysfunction, and is a primary driver of recurrent hospitalizations [3]. Despite significant advances in guideline-directed medical therapies (GDMT), such as sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors, suboptimal fluid management remains a key factor in patient outcomes. Up to 50% of patients hospitalized for HF experience acute decompensation within six months of discharge, largely due to unresolved or recurrent congestion [4,5].

Traditional fluid management strategies rely heavily on clinical assessment, including monitoring symptoms like orthopnea, physical signs such as peripheral edema, and daily weight changes. However, these methods lack the sensitivity required for early detection of worsening congestion, often resulting in delayed intervention or, conversely, excessive diuresis that can precipitate renal injury [6]. This therapeutic challenge highlights an urgent need for more objective and reproducible tools to guide fluid removal and maintain euvolemia.

Biomarker-based approaches have emerged as a promising alternative to conventional clinical assessment. B-type natriuretic peptide (BNP) and its inactive N-terminal fragment, NT-proBNP, are released from the ventricles in response to increased myocardial wall stress and volume overload. Their levels correlate strongly with intracardiac pressures and provide a real-time indication of hemodynamic congestion, potentially enabling preemptive adjustments to therapy before clinical signs and symptoms become apparent [10,16].

### Rationale and Objectives

Current clinical practice guidelines emphasize decongestion as a cornerstone of HF management but offer limited specific guidance on achieving and maintaining optimal fluid status for individual patients [7]. Loop diuretics are the first-line therapy, but their administration is complicated by a narrow therapeutic window; overly aggressive diuresis can lead to worsening renal function and electrolyte imbalances, while inadequate decongestion perpetuates neurohormonal activation and adverse cardiac remodeling [8,9].

Several randomized controlled trials (RCTs) have investigated the utility of biomarker-guided therapy. For example, the STRONG-HF trial suggested that a strategy of rapid up-titration of HF therapies, guided by NT-proBNP levels post-discharge, could improve outcomes [11,12]. However, other landmark trials, such as GUIDE-IT, did not demonstrate a significant benefit for NT-proBNP-guided therapy in reducing mortality or cardiovascular events compared to standard care [13]. These conflicting results may be attributable to heterogeneity in study populations (eg, HF with reduced ejection fraction [HFrEF] vs preserved ejection fraction [HFpEF]), variations in biomarker targets and treatment algorithms, and differences in co-interventions [14-18].

Furthermore, existing meta-analyses have often focused on the titration of pharmacotherapy in chronic HF settings, with less attention paid to fluid management strategies in both acute and outpatient contexts [19]. A recent narrative review identified critical knowledge gaps, including the optimal frequency of biomarker monitoring and the influence of patient characteristics like obesity and renal dysfunction on treatment efficacy [20].

This systematic review aims to synthesize the global evidence on biomarker-guided fluid management in HF to address the following key questions:

1. Does BNP/NT-proBNP-guided fluid management reduce all-cause mortality and HF-related hospitalization compared with standard clinical care?
2. What are the implications of biomarker-guided decongestion strategies for renal function and patient-reported quality of life?
3. Do the effects of biomarker-guided therapy differ across HF subtypes (HFrEF vs HFpEF) and clinical settings (inpatient vs outpatient)?

By systematically evaluating the efficacy and safety of biomarker-guided approaches, this review will provide a robust evidence base to inform clinical practice guidelines and identify priorities for future research.

## Methods

### Overview

This protocol will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (see Multimedia Appendix 1). The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420250652134).

### Study Eligibility Criteria

The inclusion and exclusion criteria for this review are detailed in Textbox 1.

**Textbox 1. Inclusion and exclusion criteria.**

**Inclusion criteria**

- **Types of studies:** Randomized controlled trials (RCTs) and prospective cohort studies with multivariate adjustment for key confounders (eg, age, baseline renal function).
- **Types of participants:** Adult patients (≥18 years) with a clinical diagnosis of acute or chronic HF, irrespective of ejection fraction.
- **Types of interventions:** Fluid management strategies guided by serial measurements of BNP or NT-proBNP. The intervention must involve a predefined protocol with specific biomarker thresholds for adjusting therapy (eg, escalating diuretic dosage).
- **Types of comparisons:** Standard fluid management based on clinical assessment (eg, symptoms, physical examination, daily weight) without the use of BNP/NT-proBNP to guide therapy.
- **Types of outcome measures:**
  - **Primary outcomes:** (1) All-cause mortality; (2) HF-related hospitalization.
  - **Secondary outcomes:** (1) Worsening renal function (eg, defined as an increase in serum creatinine ≥0.3 mg/dL or ≥50% from baseline); (2) Quality of life, as measured by validated instruments (eg, Kansas City Cardiomyopathy Questionnaire [KCCQ], Minnesota Living with Heart Failure Questionnaire [MLHFQ]); (3) Change in BNP/NT-proBNP levels from baseline.

**Exclusion criteria**

- Studies without a comparator group (eg, single-arm studies).
- Retrospective studies, cross-sectional studies, case reports, case series, and narrative reviews.
- Studies where biomarkers were used for diagnosis or prognosis only, without guiding a specific fluid management intervention.
- Studies published as abstracts only, if sufficient data for analysis cannot be obtained.

### Electronic Searches

A comprehensive literature search will be conducted in the following electronic databases from their inception to May 31, 2025: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. The search strategy will be developed in collaboration with a medical librarian and will combine Medical Subject Headings (MeSH) and free-text terms related to "heart failure," "natriuretic peptides," "fluid therapy," and "biomarker-guided." No language restrictions will be initially applied. To identify unpublished or ongoing trials, we will also search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). The reference lists of included studies and relevant systematic reviews will be manually screened for additional eligible publications. An example search strategy for PubMed is provided in Multimedia Appendix 2.

## Study Selection and Data Collection

*Two reviewers will independently screen the titles and abstracts of all identified records using Rayyan QCRI software. The full texts of potentially eligible articles will then be retrieved and assessed against the predefined inclusion and exclusion criteria. Any disagreements between the reviewers will be resolved through discussion or, if necessary, by consulting a third senior reviewer. A PRISMA flow diagram will be used to document the entire study selection process, detailing the reasons for exclusion at each stage (Figure 1).*

*A standardized data extraction form will be developed and pilot-tested. Two reviewers will independently extract the following data from each included study:*

1. ***Study characteristics:*** *First author, year of publication, country, study design, follow-up duration, and funding sources.*

2. ***Participant characteristics:*** *Sample size, age, sex, HF etiology, baseline left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) functional class.*

3. ***Intervention and comparator details:*** *Type of biomarker (BNP or NT-proBNP), target thresholds, frequency of measurement, specific fluid management algorithm, and co-interventions (eg, diuretic type and dose, use of ultrafiltration).*

4. ***Outcome data:*** *Definitions of outcomes, measurement time points, and reported effect measures (eg, hazard ratios, risk ratios, mean differences) with corresponding 95% confidence intervals.*

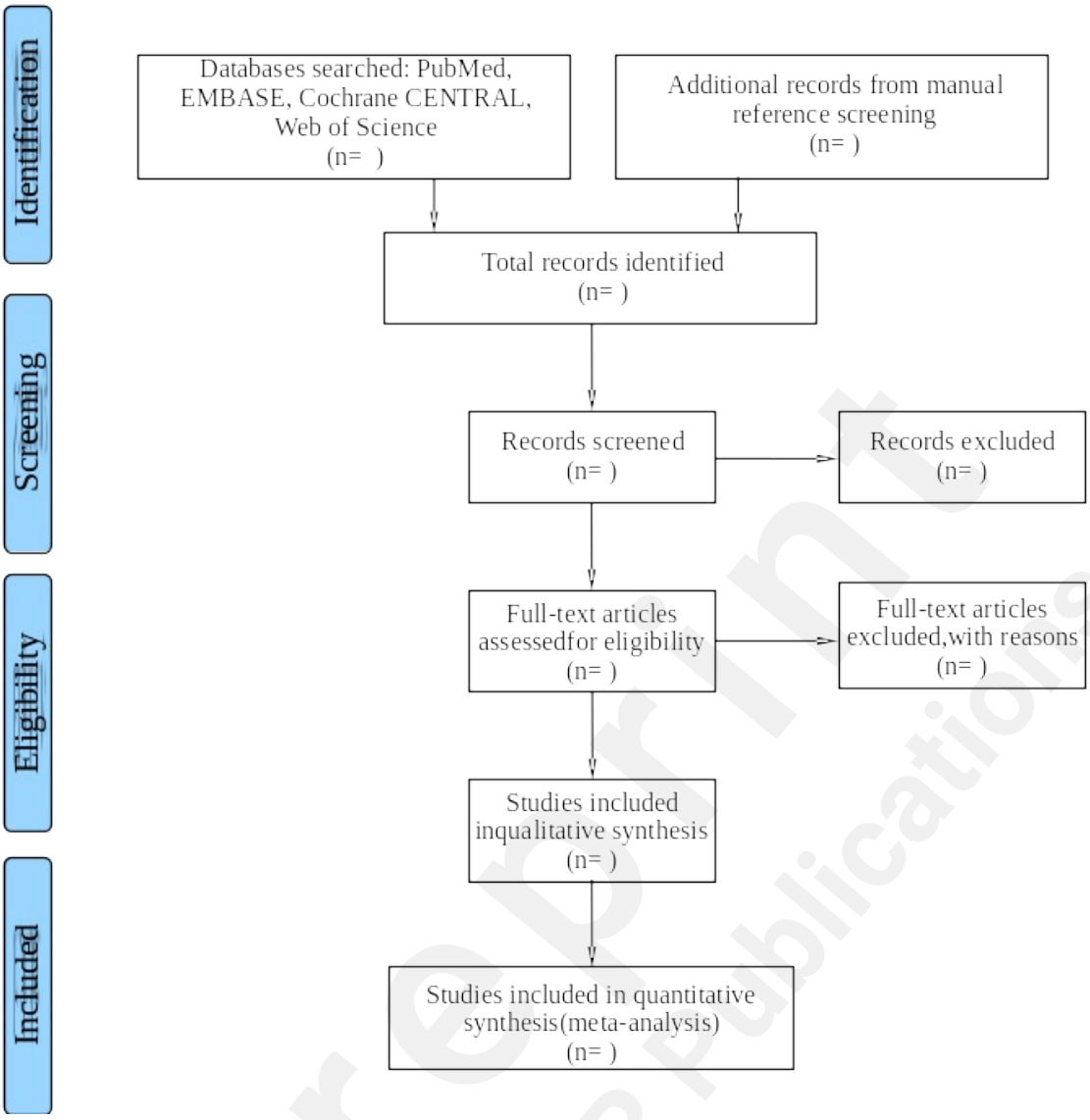


Figure 1 Flow chart of the systematic review.

### Assessing Risk of Bias in Included Studies

The methodological quality of the included studies will be assessed independently by two reviewers. For RCTs, we will use the Cochrane Risk of Bias 2.0 (RoB 2) tool, which evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For non-randomized prospective cohort studies, we will use the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Each study will be categorized as having a "low risk," "some concerns," or "high risk" of bias. Discrepancies will be resolved by consensus with a third reviewer.

### Data Analysis

We will perform statistical analysis using Review Manager (RevMan, version 5.4). For dichotomous outcomes (eg, mortality, hospitalization), we will calculate risk ratios (RRs) with 95% CIs. For continuous outcomes (eg, change in quality of life scores), we will calculate mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs.

We will assess statistical heterogeneity using the Chi-squared test (with a P-value <.10 indicating significant heterogeneity) and the $I^2$ statistic. An $I^2$ value >50% will be considered indicative of substantial heterogeneity. A random-effects model will be used for all meta-analyses to account for anticipated clinical and methodological heterogeneity.

If sufficient data are available, we will conduct the following subgroup analyses to explore potential sources of heterogeneity:

- HF phenotype: HFrEF (LVEF ≤40%) vs HFpEF (LVEF ≥50%).
- Clinical setting: Inpatient vs outpatient.
- Biomarker type: BNP vs NT-proBNP.

Sensitivity analyses will be performed by excluding studies with a high risk of bias to assess the robustness of our findings. If more than 10 studies are included in a meta-analysis, we will use a funnel plot to visually inspect for potential publication bias.

### Grading the Quality of Evidence

The certainty of the evidence for the primary outcomes will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The evidence will be graded as high, moderate, low, or very low based on considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

## Discussion

### Overview

This systematic review aims to provide a comprehensive and rigorous synthesis of the evidence on biomarker-guided fluid management in HF. By addressing key questions unresolved by individual trials and prior reviews, our findings have the potential to significantly impact clinical practice. While previous meta-analyses have often focused on biomarker-guided pharmacotherapy, our review will specifically concentrate on fluid removal strategies, including dynamic diuretic dosing and the role of ultrafiltration, providing a nuanced assessment of the interplay between decongestion, biomarker kinetics, and clinical outcomes.

A key strength of our protocol is the planned subgroup analysis stratified by HF phenotype. Exploring whether treatment effects differ between HFrEF and HFpEF is crucial, as the underlying pathophysiology of congestion may vary between these groups [29]. Such insights could pave the way for more precise, phenotype-specific therapeutic strategies.

### Methodological Considerations

Methodologically, our review will incorporate several robust features. The use of both the RoB 2 and ROBINS-I tools will allow for a thorough quality assessment of both randomized and non-randomized evidence. Furthermore, applying the GRADE framework will provide a transparent and systematic evaluation of the certainty of the evidence, enhancing the translational relevance of our conclusions for clinicians and guideline developers. We also plan to conduct a trial sequential analysis (TSA) for the primary mortality outcome to control for the risk of random errors (type I and

type II errors) due to sparse data and repeated significance testing in cumulative meta-analyses.

### Limitations

We anticipate several potential limitations. First, heterogeneity in the included studies is likely to be a significant challenge. Variations in biomarker assays, target thresholds, and the specific algorithms used to adjust therapy may complicate the synthesis of results. We will attempt to address this through subgroup and sensitivity analyses. Second, the exclusion of non-English literature could introduce a language bias, although we will perform an initial screening of all languages to minimize this risk. Finally, confounding from co-interventions, such as differences in background GDMT or the technical aspects of ultrafiltration, may be difficult to fully account for.

### Conclusion

This systematic review will synthesize the current evidence on the efficacy and safety of biomarker-guided fluid management for patients with HF. The results are expected to provide valuable insights for health care professionals, helping to optimize clinical practice and inform therapeutic decision-making. By identifying gaps in the current literature, this review will also highlight priority areas for future research, ultimately aiming to improve outcomes for this high-risk patient population.

## Abbreviations

BNP: B-type Natriuretic Peptide
CENTRAL: Cochrane Central Register of Controlled Trials
GDMT: Guideline-Directed Medical Therapies
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
HF: Heart Failure
HFpEF: Heart Failure with Preserved Ejection Fraction
HFrEF: Heart Failure with Reduced Ejection Fraction
KCCQ: Kansas City Cardiomyopathy Questionnaire
LVEF: Left Ventricular Ejection Fraction
MLHFQ: Minnesota Living with Heart Failure Questionnaire
NT-proBNP: N-terminal pro-B-type Natriuretic Peptide
NYHA: New York Heart Association
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
QoL: Quality of Life
RCT: Randomized Controlled Trial
RoB 2: Risk of Bias 2.0 Tool
ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions
TSA: Trial Sequential Analysis

## Declarations

Ethics Approval and Consent to Participate
Not applicable, as this is a protocol for a systematic review and meta-analysis of previously published data. No individual patient data will be collected.
Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable. All data used will be from publicly available published articles. Supporting materials, including the full search strategy and data extraction form, will be made available as multimedia appendices.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Key R&D Project of Sichuan Science and Technology Planning Project (Grant No. 2022YFS0356). The funder had no role in the design of this protocol, and will have no role in the study execution, analyses, interpretation of the data, or decision to submit results.

Authors' Contributions

YX and HZ conceived the study. TL and FXL designed the search strategy. KL will contribute to the statistical analysis plan. HZ drafted the manuscript. All authors (HZ, TL, FXL, KL, XW, YX) read, provided critical revisions, and approved the final manuscript.

Acknowledgments

We would like to thank the librarians at the Medical Library of West China Hospital, Sichuan University, for their assistance in developing the literature search strategy.

## Multimedia Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.

## Multimedia Appendix 2

Search strategy in PubMed database.

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# Supplementary Files

Untitled.
URL: http://asset.jmir.pub/assets/a011286188aa86a41363cae0de0fe059.doc

Untitled.
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# Figures

Flow chart of the systematic review.