

Biomarkers and their association with cognitive impairment in patients with chronic heart failure: a systematic review and meta-analysis

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ABSTRACT

Introduction: The aim was to synthesize the evidence on the association between circulating biomarkers and Cognitive Impairment (CI) in patients with Chronic Heart Failure (CHF), and to assess methodological quality and certainty of evidence.

Methods: Systematic review and meta-analysis conducted under PRISMA 2020 (PROSPERO CRD42024626152). Searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and Embase up to April 30, 2025. Observational studies and clinical trials that measured cardiac or extracardiac biomarkers in patients with HF and evaluated CI using validated tools were included. Mean differences (MD) were calculated using random-effects models (DerSimonian–Laird). Methodological quality was assessed with the Newcastle-Ottawa Scale (NOS) and certainty of evidence with the GRADE approach.

Results: Seven studies met the inclusion criteria. Patients with CHF and CI had significantly higher levels of high-sensitivity troponin T (hs-cTnT) compared to those without CI (MD 3.36 ng/L; 95% CI 0.42-6.31; $p = 0.03$; $I^2 = 0\%$). In contrast, NT-proBNP showed a non-significant trend (MD 410.16 pg/mL; 95% CI -276.22-1096.53; $p = 0.24$; $I^2 = 51\%$). Methodological quality was moderate (median NOS 7/9). Extracardiac biomarkers such as GDF-15, S100B, pTau, NfL, BDNF, and sICAM-1/sVCAM-1 were associated with inflammation, endothelial dysfunction, and neurodegeneration. With GRADE, overall certainty was very low for both biomarkers due to observational design, imprecision, and heterogeneity.

Conclusions: hs-cTnT is consistently associated with CI in HF, whereas NT-proBNP does not show a robust relationship. Extracardiac biomarkers may provide complementary information in cognitive stratification, although their clinical application requires validation in multicenter longitudinal cohorts with analytical and neuropsychological standardization.

Keywords: Biomarkers, Cognitive impairment, Heart failure, High-sensitivity troponin, Meta-analysis, Review

Introduction

Heart failure (HF), defined as the inability of the heart to pump sufficient blood to meet the body's metabolic demands, represents a major global public health issue, with an estimated prevalence of between 35 and 64 million people. Approximately 1.2 million hospitalizations related to this

condition are reported annually, with a yearly mortality rate of 13.1 deaths per 100 patients (1,2).

The economic impact associated with HF management is considerable, with hospitalization costs in Europe ranging from 7,000 to 18,000 euros per patient, depending on disease severity and length of stay (3-5). These figures reflect the global healthcare and economic burden, which is further exacerbated by marked disparities between developed and developing countries. In nations with well-established healthcare systems, mortality rates are lower due to timely access to medical care and advanced therapies. In contrast, low- and middle-income countries face limitations in the availability of targeted treatments, leading to a higher mortality of 31.6% within 30 days after hospitalization in low-income countries versus 6.7% in high-income countries (6).

Symptoms resulting from impaired cardiac pump function led to a significant reduction in quality of life among

Received: November 13, 2025

Accepted: August 24, 2026

Published online: October 9, 2026

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patients with HF. Diagnosis is based on medical history, physical examination, and complementary laboratory and imaging studies (7).

The most frequent clinical manifestations include dyspnea, fatigue, peripheral edema, and reduced exercise tolerance. Physical examination may reveal signs such as jugular venous distention, pulmonary crackles, tachycardia, or lower-limb edema (7). Laboratory tests are particularly useful, especially in preclinical stages. B-type natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP) are key biomarkers supporting the diagnosis of heart failure because they reflect myocardial wall stress and increased cardiac filling pressures, regardless of left ventricular ejection fraction. Their concentrations may nevertheless differ according to heart failure phenotype and may also be influenced by age, renal function, obesity, atrial fibrillation, and clinical severity. According to the European Society of Cardiology (ESC, 2021) and the AHA/ACC/HFSA (2022) guidelines, BNP >35 pg/mL or NT-proBNP >125 pg/mL are considered diagnostic thresholds in outpatients, while higher cut-offs apply in acute settings (8).

Transthoracic echocardiography (TTE) is the diagnostic method of choice, as it allows evaluation of left ventricular systolic and diastolic function, ejection fraction (LVEF), chamber size and wall thickness, as well as structural or valvular abnormalities. An LVEF of $\leq 40\%$ confirms heart failure with reduced ejection fraction (HFrEF), values between 41 and 49% correspond to mildly reduced ejection fraction (HFmrEF), and LVEF $\geq 50\%$ indicates preserved ejection fraction (HFpEF). Other tests, such as chest X-ray or cardiac magnetic resonance imaging, may be useful when TTE findings are inconclusive (9).

Cognitive impairment (CI), on the other hand, is defined as a decline in performance in one or more cognitive domains memory, attention, language, executive functions, or orientation that exceeds what is expected for age and educational level. It can be mild, when daily activities remain unaffected, or progress to more severe forms such as dementia, where functional autonomy is compromised (10,11).

According to the World Health Organization (WHO), more than 55 million people worldwide currently live with some form of CI, with nearly 10 million new cases diagnosed each year. Alzheimer's disease accounts for 60-70% of these cases (12).

Diagnosis of CI is based on detailed clinical and neuropsychological assessment, including medical history, identification of risk factors, and use of standardized cognitive tests such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MMSE assesses orientation, memory, attention, calculation, language, and visuospatial abilities; a score below 24 is generally considered indicative of CI. The MoCA is more sensitive for detecting mild impairment, particularly in executive function and attention, with scores below 26 suggesting mild CI (10,13).

It is estimated that between 10% and 20% of individuals over 65 years of age present some degree of CI (14). Among patients with HF, this complication is common: approximately 24% exhibit mild CI (MCI), while 15–30% develop some type of dementia (15-18). Vascular and mixed dementias predominate, followed by Alzheimer's disease. These forms are

associated with hemodynamic alterations and chronic cerebral ischemic injury, which impact both life expectancy and quality of life, and are linked to greater functional decline, higher hospitalization risk, and elevated mortality rates (19-21).

The presence of CI complicates HF management, as it impairs self-care, treatment adherence, and the ability to perform daily activities (21). Even in its mild forms, CI is a strong predictor of mortality and cardiovascular events, including recurrent hospitalizations and cardiac death (22).

Both conditions share a multifactorial etiology. HF may result from ischemic heart disease or hypertension, whereas CI is often associated with reduced cerebral perfusion, systemic inflammation, and endothelial dysfunction (23,24). With aging, progressive deterioration of brain architecture occurs: myelin sheaths degenerate due to chronic ischemic injury, disrupting cerebral perfusion and the integrity of the blood-brain barrier (BBB). This process facilitates infiltration of inflammatory cells, cytokine production, and alterations in neurotransmitters such as serotonin and dopamine, directly influencing cognitive performance (20,25).

In this context, recent research has explored the role of various biomarkers in detecting and predicting CI in patients with HF. Although natriuretic peptides remain standard diagnostic markers (26), other emerging biomarkers have shown significant associations.

Gyanwali et al. demonstrated that elevated levels of NT-proBNP, hs-cTnT, and GDF-15 were associated with CI and brain injury during a three-year follow-up, with significant findings for NT-proBNP ($p = 0.001$), hs-cTnT ($p < 0.001$), and GDF-15 ($p = 0.006$). Additionally, hs-cTnT correlated with global and executive function decline ($p = 0.001$; $p = 0.012$) (27). Tung et al. (2022, Taiwan) found that in patients with decompensated HF and LVEF $< 40\%$, elevated GDF-15 levels (> 1621.1 pg/mL; AUC 0.64; $p = 0.003$) increased the risk of CI and were associated with poorer initial cognitive performance, though some recovery was observed (28). Likewise, Arslan et al. (2024, Turkey) observed that higher GDF-15 concentrations (OR 1.264; 95%CI 1.009-1.583; $p = 0.042$) and NT-proBNP ($p = 0.01$) were linked to greater CI risk in older adults with HF and reduced ejection fraction (29).

Despite these findings, the use of biomarkers for detection still largely relies on subjective clinical evaluations, and their practical use remains limited (30). Most studies, meta-analyses, and systematic reviews focus on general neurodegeneration biomarkers such as tau protein and beta-amyloid. Huszár et al. (2024) reported that individuals with abnormal beta-amyloid levels (A+) have a higher risk of developing dementia (OR 5.18; 95% CI 3.93-6.81; $p < 0.0001$), which increases markedly when phosphorylated tau positivity coexists (A+T+) (OR 11.60; 95% CI 7.96-16.91; $p < 0.001$) (31).

The lack of standardization in cognitive assessment tools (MMSE, MoCA, or comprehensive neuropsychological batteries), together with methodological and population heterogeneity, limits comparison across studies and restricts the clinical applicability of biomarkers in medical practice (30,31). Therefore, the present study aims to identify and analyze

biomarkers associated with CI in patients with chronic heart failure (CHF), integrating the available scientific evidence to establish their potential diagnostic and prognostic value.

Materials and Methods

Study design

A systematic review and meta-analysis were conducted following the reporting standards established by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement. PROSPERO No: CRD42024626152.

Search strategy

A literature search was performed in bibliographic databases. The selected databases were PubMed/MEDLINE, Scopus, Web of Science (WoS), and Embase. The search included studies published up to April 30, 2025. A combination of controlled terms (such as MeSH in PubMed) and free keywords was used. Terms were combined using the Boolean operators AND and OR. Strategies such as the following were employed: ("Heart Failure" OR "Cardiac Insufficiency" OR "Heart Failure, Congestive") AND ("Cognitive Dysfunction" OR "Cognitive Impairment" OR "Cognitive Decline") AND ("Biomarkers" OR "Molecular Biomarkers"). Strategies were adapted for each database according to their specific characteristics. In addition, a manual review of the references of selected articles was conducted to capture relevant studies not identified in the search (ANNEX 1).

Selection criteria

The study population included studies involving patients from the general population diagnosed with CHF, with no restriction on age or sex. The diagnosis of heart failure was based on clinical and objective criteria defined by major international guidelines such as those of the European Society of Cardiology (ESC) and the American Heart Association (AHA).

Inclusion criteria

Randomized clinical trials and observational studies such as cohorts, case-control, and cross-sectional studies that evaluated the association between biomarkers and CI in patients with HF were included. The population of interest comprised patients from the general population diagnosed with CHF, without age or sex restrictions, as long as the diagnosis met the criteria established by international guidelines such as those of the ESC or the AHA.

No restrictions were imposed according to left ventricular ejection fraction or heart failure phenotype. Studies involving heart failure with reduced ejection fraction, mildly reduced ejection fraction, preserved ejection fraction, or mixed heart failure populations were eligible, provided that CHF was diagnosed using recognized clinical and objective criteria. Information on left ventricular ejection fraction and heart failure phenotype was extracted whenever available.

CI had to be assessed using a validated cognitive screening instrument or a standardized neuropsychological battery. Eligibility was not restricted to the Mini-Mental State

Examination or the Montreal Cognitive Assessment. Studies using other validated instruments were also included, whereas studies that assessed cognition using non-validated tools were excluded.

In addition, selected studies had to measure biomarkers. Only research reporting relevant association measures such as odds ratio (OR), hazard ratio (HR), or correlation coefficients and published in English or Spanish was considered.

Exclusion criteria

Studies that did not provide primary data, such as reviews, meta-analyses, editorials, letters to the editor, and case reports, were excluded, as well as those focused on pediatric populations or conditions not directly related to CHF. Research that used non-validated tools to measure cognitive dysfunction, those published in languages other than English or Spanish, studies not available in full text, or whose data could not be extracted, were also excluded.

Study selection process

The study selection process was conducted in several stages. In the first phase, records were identified from the electronic searches in the selected databases, and duplicates were removed using the Rayyan QCRI (Qatar Computing Research Institute) tool. Subsequently, an independent and parallel screening of titles and abstracts was performed by two reviewers trained in systematic reviews, who uniformly applied the predefined inclusion and exclusion criteria. Records that met the criteria progressed to the second selection phase. In the full-text assessment phase, the same reviewers carefully evaluated each study to verify the presence of primary data, the target population, biomarker measurement, and assessment of CI. Discrepancies arising at any stage were discussed until consensus was reached; in cases where disagreement persisted, a senior third reviewer intervened to make the final decision.

Data extraction

Data extraction was carried out in a standardized manner using a pre-designed data collection form in Microsoft Excel, which was pilot-tested in an initial sample of studies to ensure coherence and comprehensiveness of the information. Two independent reviewers performed data extraction in parallel, systematically recording the following variables: first author, year of publication, country of origin, methodological design, population characteristics (sample size, mean age, sex), type of CHF (reduced, preserved, or mid-range ejection fraction), biomarkers evaluated, tools used for cognitive assessment (Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], or other neuropsychological batteries), reported association measures, and main findings of clinical interest.

Discrepancies detected during extraction were jointly discussed; if consensus could not be reached, a third reviewer intervened to make the final decision. Modifications made during the process were transparently documented, ensuring traceability and reproducibility of results.

Statistical analysis

Quantitative analyses were primarily conducted using a random-effects model with the DerSimonian–Laird estimator because clinical and methodological heterogeneity was expected across studies in terms of patient characteristics, heart failure phenotype, biomarker measurement, and cognitive assessment. When statistical heterogeneity was absent or negligible, a common-effect model was additionally calculated as a sensitivity analysis. The random-effects estimate was retained as the primary result. For the hs-cTnT analysis, between-study heterogeneity was absent ($I^2 = 0\%$; $\tau^2 = 0$), and the random-effects and common-effect estimates were therefore identical or materially similar.

For continuous biomarker concentrations reported using the same measurement unit, pooled effects were expressed as mean differences (MDs) with 95% confidence intervals. Standardized mean differences were reserved for outcomes assessing the same construct with different measurement scales. Statistical heterogeneity was evaluated using Cochran's Q test, with $p < 0.10$ indicating statistical heterogeneity, and quantified using the I^2 statistic. I^2 values were interpreted as low ($<25\%$), moderate (25–50%), or high ($>50\%$). For all other statistical tests, $p < 0.05$ was considered statistically significant. Analyses were performed using Review Manager version 5.4.

Because NT-proBNP concentrations usually exhibit a right-skewed distribution, the type of summary measure reported by each study was examined before pooling. Differences in the reporting of means and standard deviations versus medians and interquartile ranges were recorded and considered when evaluating the robustness and certainty of the pooled estimate. No conversions from medians and interquartile ranges were performed; only studies reporting sufficiently comparable means and standard deviations were included in the quantitative synthesis.

Procedures for assessment of scientific study quality

The quality of the selected studies was evaluated using internationally validated tools adapted to the design of each investigation. The Newcastle–Ottawa Scale (NOS) was applied. Results from the quality assessment were summarized in tables that allowed identification of strengths and limitations of each study, and any discrepancy between reviewers was resolved by consensus or through the intervention of a third reviewer.

GRADE assessment of certainty of evidence

The certainty of evidence of included studies was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology. For this purpose, five main domains were considered: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each meta-analysis result was analyzed independently, and the certainty of evidence was classified into four levels: high, moderate, low, or very low, according to the criteria established by the GRADE group.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and international biomedical research regulations; as a systematic review and meta-analysis, informed consent and ethics committee approval were not required. However, the protocol was approved by the Ethics Committee of Universidad Científica del Sur according to institutional guidelines (code PRE-15-2025-00268).

Results

A total of 920 records were identified ($n = 114$ PubMed, $n = 166$ Scopus, $n = 45$ Web of Science, and $n = 595$ Embase). After removal of 470 duplicates and exclusion of 209 records by automation tools, 241 records remained for title and abstract screening. Of these, 227 were excluded, and 14 reports were assessed for full-text eligibility. Seven reports were excluded after full-text assessment, leaving seven studies for inclusion (Fig. 1).

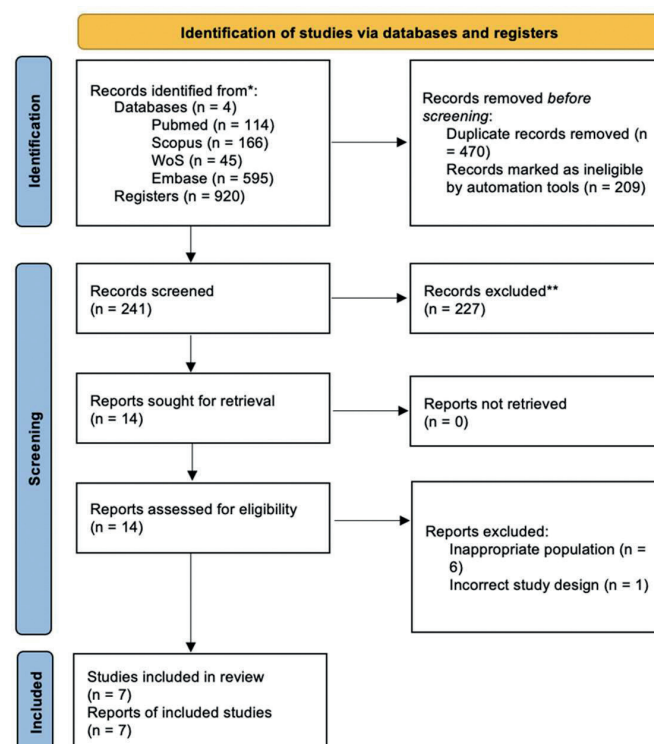


FIGURE 1 - PRISMA flow diagram.

NT-proBNP

The meta-analysis included three studies (Arslan, Dong, and Hilal) (29, 32, 33), with a total of 166 patients with CI and 144 without CI (NO CI) diagnosed with HF. The pooled analysis showed a mean difference (MD) of 410.16 pg/mL in NT-proBNP levels in favor of the CI group, although without statistical significance (95% CI: -276.22 – 1096.53 ; $Z = 1.17$; $p = 0.24$). Heterogeneity among studies was moderate ($I^2 = 51\%$), with a Chi^2 value of 4.05; $df = 2$; $p = 0.13$ and a between-study variance (Tau^2) of 204,771.01. Overall, the findings suggest

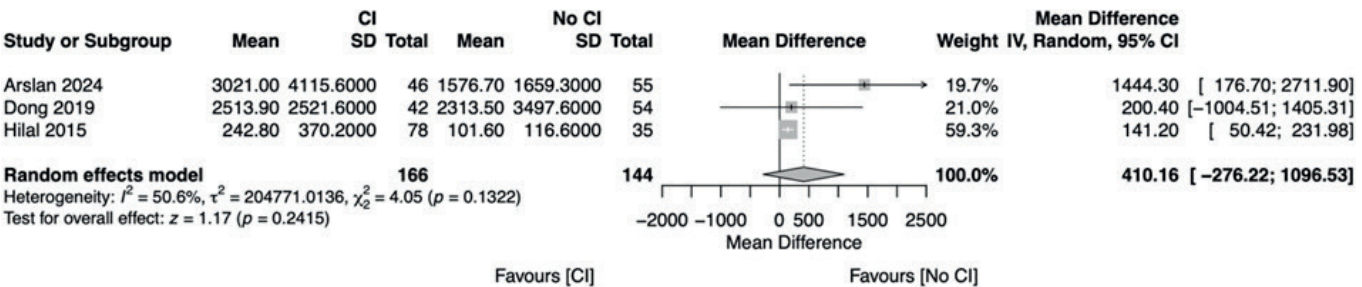


FIGURE 2 - Forest plot of NT-proBNP.

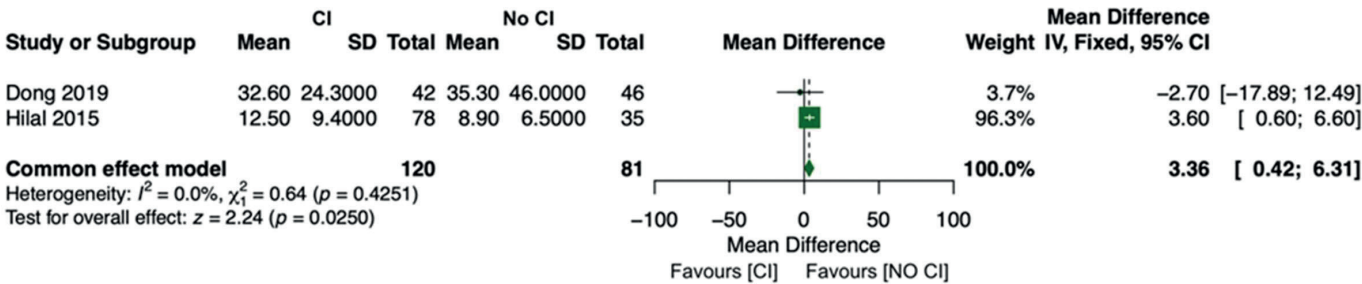


FIGURE 3 - Forest plot of hs-cTnT concentrations using a random-effects model. A common-effect model was additionally performed as a sensitivity analysis; both estimates were materially similar because between-study heterogeneity was absent ($I^2 = 0\%$; $\tau^2 = 0$).

a trend toward higher NT-proBNP levels in patients with CI; however, the lack of statistical significance and the observed heterogeneity limit the strength of the association and warrant cautious interpretation of the results. However, because only three studies contributed to this meta-analysis, the I^2 estimate was considered unstable and highly sensitive to clinical and methodological differences among the included studies, including heart failure severity, cognitive assessment methods, and biomarker reporting. Therefore, the observed I^2 value should not be interpreted as a precise estimate of between-study inconsistency.

hs-cTnT

The meta-analysis included two studies (Dong and Hilal) (32, 33), with a total of 120 patients with CI and 89 without CI (NO CI). The pooled analysis showed that hs-cTnT concentrations were 3.36 ng/L higher in patients with CI than in those without CI, reaching statistical significance (95% CI 0.42-6.31; $Z = 2.23$; $p = 0.03$). Heterogeneity between studies was null ($I^2 = 0\%$; $\chi^2_1 = 0.71$; $p = 0.40$), supporting the consistency of the findings. Regarding relative weight, the study by Hilal 2015 contributed 95.8% to the overall estimate, while Dong 2019 contributed 4.2%, reflecting the predominance of the former in the final synthesis. These results suggest a significant association between elevated hs-cTnT levels and CI in patients with CHF. However, the pooled estimate was largely driven by Hilal et al., which contributed 95.8% of the total weight. A leave-one-out pooled analysis was not informative because removing either study left only one study available for analysis. Therefore, despite the absence of statistical heterogeneity, the robustness and independent reproducibility of this finding remain limited.

Subgroup analyses according to the cognitive assessment instrument were not performed because the small number of studies and the variability in instruments, cut-off values, and definitions of CI did not allow meaningful stratification. The included studies used the MMSE, MoCA, or standardized neuropsychological batteries, either alone or in combination.

Extracardiac biomarkers

The included reports evaluated several extracardiac biomarkers associated with inflammatory, endothelial, glial, and neurodegenerative pathways. Because the biomarkers, measurement methods, cognitive outcomes, and reported association measures differed substantially across studies, quantitative pooling was not considered appropriate, and the findings were synthesized narratively. Arslan et al. reported that higher GDF-15 concentrations were significantly associated with CI in patients with heart failure with reduced ejection fraction ($p = 0.045$). GDF-15 concentrations were also associated with greater clinical severity according to the New York Heart Association functional class ($p < 0.001$) (29). Traub et al. found that higher serum S100B concentrations were negatively correlated with cognitive performance (Spearman's $\rho = -0.17$; $p = 0.039$). After adjustment for NT-proBNP and clinical comorbidities, the association showed a non-significant trend (OR 1.03; 95% CI 1.00-1.06; $p = 0.083$) (36). In another report, higher phosphorylated tau 181 and neurofilament light chain concentrations were inversely correlated with cognitive scores (p -tau181: $p = -0.25$; $p = 0.002$; NfL: $p = -0.21$; $p = 0.013$) (44). Redwine et al. reported that lower brain-derived neurotrophic factor concentrations were associated with poorer MoCA performance ($\beta = -0.468$; $p = 0.008$), accounting for an additional 21.4% of the variance in

the model. Higher circulating sICAM-1 and sVCAM-1 concentrations were also associated with poorer cognitive performance ($p < 0.05$) (35). Bayes-Genis et al. evaluated circulating amyloid- β 40 in patients with heart failure with reduced ejection fraction. Higher amyloid- β 40 concentrations were associated with total mortality (HR 1.22; 95% CI 1.10-1.35; $p < 0.001$) and cardiovascular mortality (HR 1.18; 95% CI 1.03-1.36; $p = 0.02$), although a direct association with CI was not established (34). Overall, these findings suggest that GDF-15, S100B, p-tau181, NfL, BDNF, sICAM-1, and sVCAM-1 may provide complementary information regarding inflammatory, endothelial, and neurodegenerative pathways associated with CI. Nevertheless, methodological heterogeneity and the limited number of studies prevented quantitative synthesis.

Methodological quality assessment (Newcastle–Ottawa Scale)

The methodological quality of the included cross-sectional studies was assessed using the adapted Newcastle–Ottawa Scale (NOS), which considers three main domains: sample selection (maximum 4 points), comparability between groups (maximum 2 points), and outcome assessment (maximum 3 points), with a maximum total score of 9. Overall, the studies showed moderate to high quality, with scores ranging from 6 to 8. The study by Dong (32) obtained the lowest rating (6 points), mainly due to limitations in comparability and sample selection, which could increase the risk of bias in the interpretation of its findings. In contrast, the studies by Bayes-Genis (34), Hilal (33) and Redwine et al. (35) achieved the highest score (8 points), reflecting an adequate selection of the population and an adequate comparability between the groups. The studies by Arslan (29) and Traub (36) obtained 7 points, indicating an acceptable level of quality, although with minor limitations in representativeness and in the reporting of results. Overall, the results showed that the included evidence is supported by studies with reasonable methodological quality, although the presence of bias in some specific domains must be considered when interpreting the overall findings.

Certainty of the Evidence Assessment (GRADE)

The certainty of the evidence was evaluated using the GRADE methodology, considering the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. For the association between hs-cTnT and CI, the certainty of the evidence was rated as very low ($\oplus\oplus\oplus$). Although the results showed a statistically significant mean difference (MD 3.36 ng/L; 95%CI 0.42-6.31; $p = 0.03$; $I^2 = 0\%$), the small sample size and the predominance of a single study (95.8% of the total weight) limited the precision and robustness of the estimate. In the case of NT-proBNP, the certainty was also very low ($\oplus\oplus\oplus$), due to risk of bias, moderate heterogeneity ($I^2 = 51\%$), and the wide confidence interval, which included the absence of effect (MD 410.16 pg/mL; 95% CI -276.22-1096.53; $p = 0.24$). Extracardiac biomarkers (GDF-15, S100B, pTau, NfL, BDNF and sICAM-1/sVCAM-1) were analyzed qualitatively and showed consistent associations with processes of inflammation, endothelial dysfunction,

and neurodegeneration, although with high heterogeneity and limited methodological certainty. Overall, the available evidence suggests a possible relationship between subclinical myocardial injury, reflected by hs-cTnT, and CI in patients with CHF, but the low level of certainty prevents establishing firm conclusions or immediate clinical implications (Table 3).

Discussion

Based on the analysis of the evidence, we found that patients with CHF and CI presented significantly higher hs-cTnT levels compared to those without CI (MD = 3.36 ng/L; 95%CI: 0.42-6.31; $p = 0.03$). On the other hand, NT-proBNP levels did not show a significant association with CI (MD = 410.16 pg/mL; 95%CI: -276.22 to 1096.53; $p = 0.24$), with moderate heterogeneity, but with a tendency that higher levels may be associated with CI, although this association did not reach statistical significance.

hs-cTnT showed a significant association with CI, which suggests a potentially more relevant role of this biomarker in the population with CHF. Previous studies agree with this observation. Qi Niu et al. (2022) reported that elevated troponin T and NT-proBNP levels could be associated with a higher risk of CI, although without being able to establish causality, in addition to reporting a high prevalence of undiagnosed CI (81%) through screening tests (37). A significant association was observed between CI and elevated TNT values ($p = 0.013$), as well as with high NT-proBNP concentrations ($p = 0.015$ and $p = 0.038$) (40). Similarly, Gyanwali et al. found that elevated hs-cTnT levels were related to accelerated deterioration of global cognition, executive function, and visuomotor speed, as well as incidence of cortical infarcts (27). At a pathophysiological level, cardiac troponins, especially hsTnT, reflect not only myocardial damage but also systemic microvascular dysfunction. Evidence suggests that elevated hsTnT levels are associated with lower gray matter volume and alterations in white matter mediated by shared atherosclerotic processes between the heart and the brain. Moreover, hsTnT can be released by vascular smooth muscle cells, linking this biomarker with systemic microangiopathy, myocardial and cerebral hypoperfusion, and ultimately with CI (38,39).

Regarding NT-proBNP, the lack of association could be explained by heterogeneity in the cut-off points used, heterogeneity of CHF patients between the studies explored, and the influence of comorbidities. Wijsman et al. reported that elevated NT-proBNP levels (≥ 450 ng/L) were associated with poorer baseline cognitive performance, particularly in reaction time (mean difference = 3.07 s, 95% CI 0.83-5.32) and processing speed (-1.02 digits, 95%CI -1.65 to -0.39). During follow-up, these participants also showed more accelerated CI, independent of cardiovascular comorbidities, suggesting that NT-proBNP could reflect a vascular phenotype associated with progression of CI (40). At a pathophysiological level, it is proposed that NT-proBNP elevation reflects early cardiac dysfunction and progressive reduction of cardiac output, which could explain why higher levels lead to reduced blood delivery to the central nervous system, resulting in chronic cerebral hypoperfusion. This sustained decrease in

TABLE 1 - Characteristics of the studies included in the review

Author (Year)	Country	Study design	No. of patients	Mean age (years)	Sex (% women)	Degree of cognitive dysfunction assessed	Cognitive impairment diagnostic method	Degree of heart failure (LVEF, %)	Biomarker(s) evaluated	Biomarker measurement method	Associated comorbidities
Hilal et al. (2015)	Singapore	Case-control	193	Controls: 65.9 ± 6.3; CIND: 70.2 ± 9.6; Dementia: 75.6 ± 8.2	F: 98 (50.7%)	CIND (n = 78) and Dementia (n = 80)	MMSE, MoCA, validated neuropsychological battery*	NE	N-Tro-BNP, hs-cTnT	ECLIA	Hypertension, hyperlipidemia, diabetes, smoking
Bayes-Genis et al. (2017)	Spain	Prospective cohort	939	63 ± 13.1 years	F: 257 (27.4%)	MCI (44%)	RAVLT, Trail Making Test A and B, Digit Symbol Substitution Test, Boston Naming Test, MMSE	33.5 ± 13.2%	NT-proBNP, hs-cTnT, GDF-15, ST2, Gal-3	Immunochemiluminiscent assays	Arterial hypertension, type 2 diabetes mellitus, atrial fibrillation, chronic kidney disease, depression, obesity, dyslipidemia, coronary artery disease
Redwine et al. (2018)	United States	Cross-sectional	45	66.3 (SD: 9.9)	F: (6.1%)	MoCA < 24 (48.5%)	MoCA	44.80%	IFN γ , TNF α , sICAM-1, sVCAM-1, BDNF, IL-8, MMP-9, IL-6, CRP, SAA	High-sensitivity ELISA	Major depression, antidepressant use, physical dysfunction
Dong et al. (2019)	Singapore	Prospective cohort	100	58.7 ± 10.5 years	F: 15 (15%)	MoCA (21.3 ± 4.6), MMSE (25.2 ± 3.4)	Validated formal neuropsychological battery. MMSE and MoCA (screening)	35.3 ± 15.9%	NT-proBNP, hs-cTnT	High-sensitivity immunoassays	Type 2 diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, smoking, stroke, chronic kidney disease
Traub et al. (2022)	Germany	Prospective, single-center	146	63.8 ± 10.8	F: 22 (15.1%)	21.3 ± 4.6 (CI group)	Validated formal neuropsychological battery. MoCA, MMSE (screening)	42.5 %	t-Tau, A β 40, A β 42, Ratio A β 42/A β 40, Growth/differentiation factor-15 (GDF-15), Clusterin, Galectin-3	NE	Arterial hypertension, type 2 diabetes mellitus, atrial fibrillation, coronary artery disease, cerebrovascular disease, chronic kidney disease, smoking, depression, dyslipidemia

(Continued)

TABLE 1 - (Continued)

Author (Year)	Country	Study design	No. of patients	Mean age (years)	Sex (% women)	Degree of cognitive dysfunction assessed	Cognitive impairment diagnostic method	Degree of heart failure (LVEF, %) evaluated	Biomarker(s) evaluated	Biomarker measurement method	Associated comorbidities
Traub et al. (2024)	Germany	Prospective, observational, single-center	146	64 years (56–72)	F: 15%	MCI (59%)	Standardized neuropsychological battery, T-score (MCI < 40 in ≥ 1 domain)	44 (38–48) %	S100B, NT-proBNP	Sandwich-type ELISA	Arterial hypertension (80%), dyslipidemia (72%), ischemic heart disease (69%), prior myocardial infarction (55%), chronic kidney disease G2-G4 (54%), smoking (60%), diabetes mellitus (29%), atrial fibrillation (23%)
Arsilan et al. (2024)	Turkey	Prospective cohort	101	71.3 ± 5.1 years	F: 22 (21.8%)	Mild cognitive impairment (MMSE < 24 and/or MoCA < 21) (n = 21)	Mini-Mental State Examination (MMSE) y Montreal Cognitive Assessment (MoCA)	40% (mean: 30.3 ± 7.2%)	GDF-15, NT-proBNP, sST2	Automated ELISA	Type 2 diabetes mellitus (50%), hypertension (52%), dyslipidemia (~23%), chronic kidney disease (~23%), COPD (~11%), anemia (low hemoglobin levels associated with cognitive impairment)

Abbreviations – HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MMSE: Mini-Mental State Examination, brief test for cognitive functions; MoCA: Montreal Cognitive Assessment, screening test for mild cognitive impairment; CIND: Cognitive Impairment No Dementia; MCI: Mild Cognitive Impairment; RAVLT: Rey Auditory Verbal Learning Test; BDNF: Brain-Derived Neurotrophic Factor; CRP: C-reactive protein; SAA: Serum amyloid A protein; MMP-9: Matrix Metalloproteinase-9; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor alpha; IL-6, IL-8: interleukins 6 and 8; t-Tau: total tau protein; Aβ40 and Aβ42: amyloid beta peptides 40 and 42; Aβ42/Aβ40 ratio: diagnostic index of Alzheimer’s disease; Clusterin: protein associated with neurodegeneration and cellular stress; Gal-3: galectin-3; S100B: glial protein associated with neurological damage; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide, standard biomarker in heart failure; hs-cTnT: High-Sensitivity Cardiac Troponin T, biomarker of myocardial injury; sST2: soluble interleukin-33 receptor; GDF-15: Growth Differentiation Factor-15; ELISA: Electrochemiluminescence Immunoassay; ELISA: Enzyme-Linked Immunosorbent Assay.



TABLE 2 - Adapted NOS scale

Study	Selection (4)	Comparability (2)	Outcome (3)	Total (9)
Arslan (2024)	★★★★☆	★★	★★★☆☆	7
Bayes Genis (2017)	★★★☆☆	★★	★★★	8
Dong (2019)	★★★☆☆	★☆☆	★★★★☆	6
Hilal et al. (2015)	★★★★	★★	★★	8
Redwine et al. (2018)	★★★★	★★	★★★	8
Traub et al. (2024)	★★★★☆	★★	★★	7
Traub et al. (2022)	★★★★☆	★★	★★	7

TABLE 3 - Summary of Findings (GRADE)—Association between biomarkers and cognitive impairment in CHF

Outcome	Anticipated absolute effects (95% CI)	Mean difference (95% CI)	Participants (studies)	Certainty of evidence (GRADE)	Comments / Interpretation
hs-cTnT levels (ng/L): cognitive impairment vs. no impairment	Not applicable (continuous variable)	MD 3.36 ng/L (0.42 to 6.31)	209 (2 studies)	⊕○○○ Very low	Patients with cognitive impairment showed higher hs-cTnT concentrations. The evidence is of very low certainty due to the observational design, potential residual confounding, and imprecision (small sample size and predominance of a single study).
NT-proBNP levels (pg/mL): cognitive impairment vs. no impairment	Not applicable (continuous variable)	MD 410.16 pg/mL (-276.22 to 1096.53)	310 (3 studies)	⊕○○○ Very low	The results are uncertain; the confidence interval includes no effect. Moderate heterogeneity was observed ($I^2=51\%$) with no explained cause. The evidence was downgraded due to risk of bias, inconsistency, and imprecision.
Extracardiac biomarkers (GDF-15, S100B, pTau, NfL, BDNF, sICAM-1/ sVCAM-1)	Not pooled (different measurements)	Narrative synthesis	368 (4 studies)	⊕○○○ Very low	Qualitative evidence suggests an association with inflammation, endothelial dysfunction, and neurodegeneration. Certainty downgraded due to indirectness, heterogeneity, and imprecision.

flow favors white matter damage and neurodegeneration, mechanisms linked to the development of CI (41,42).

Whether the association between circulating biomarkers and CI is comparable across heart failure phenotypes remains uncertain. HFrEF and HFpEF differ in ventricular remodeling, hemodynamic abnormalities, congestion, comorbidity burden, and circulating biomarker profiles; consequently, the strength and clinical meaning of biomarker–cognition associations may also differ according to ejection fraction. However, most included studies enrolled mixed populations or did not report biomarker and cognitive outcomes separately for HFrEF, HFmrEF, and HFpEF. Therefore, the present review cannot establish whether these associations vary across heart failure phenotypes (8,9,26).

In the context of acute heart failure (AHF), the behavior of CI appears to be different. Miao et al. reported CI in 19.6% of young and middle-aged patients, a prevalence comparable to that observed in adults ≥ 65 years (20.4%). This CI was associated with a higher 30-day risk of cardiovascular death or rehospitalization (HR 1.52, 95% CI 1.07–2.17, $p = 0.02$) and a marginally higher risk of death or rehospitalization from any

cause (HR 1.34, 95% CI 1.00–1.80, $p = 0.05$), without significant impact at one year (43). Complementarily, Tung et al. observed that patients with CI showed, at admission, MMSE 22.4 vs. 28.5 and Mini-Cog 3.1 vs. 4.5 ($p < 0.001$), along with higher levels of GDF-15 (3129 vs. 2346 pg/mL; $p = 0.008$) and galectin-3 (14.8 vs. 12.5 ng/mL; $p = 0.0498$). However, only GDF-15 showed moderate discriminative capacity (AUC 63.9%, 95% CI 54.8–73%). Unlike chronic insufficiency, cognitive scores improved at 3 months and 1 year, suggesting that CI in the acute phase could be partially reversible after hemodynamic stabilization (28).

Qualitative analysis of the evidence

Several recent studies have explored alternative biomarkers to BNP and cardiac troponins to understand the molecular mechanisms linking HF with CI. In this context, biomarkers have been identified along three main pathways of involvement: neurodegenerative (pTau, NfL, A β 40), endothelial (sICAM-1, sVCAM-1), and inflammatory/metabolic (GDF-15, galectin-3, clusterin). These markers provide a broader view

of processes that extend beyond traditional myocardial damage, including glial activation, blood–brain barrier permeability, and systemic endothelial dysfunction, which could contribute to chronic brain injury observed in this population.

Arslan et al. identified that elevated GDF-15 concentrations were significantly associated with cognitive dysfunction in HFrEF ($p = 0.045$), and that this association remained parallel to clinical severity measured by NYHA ($p < 0.001$) (29). Consistently, Ying-Chang also reported that elevated GDF-15 values were associated with CI in acute HF ($p = 0.003$), in addition to a higher risk of adverse events (mortality or rehospitalization) (28). In that same study, galectin-3 and clusterin showed a positive trend toward worse cognitive performance without achieving statistical significance, supporting the role of inflammatory and apoptotic pathways in the heart–brain axis.

Brain-derived biomarkers with important clinical relevance were also found. Traub et al. (2024) found that the glial marker S100B was negatively correlated with cognitive performance ($\rho = -0.17$; $p = 0.039$) and showed an independent trend after adjusting for NT-proBNP and comorbidities (OR: 1.03; 95% CI: 1.00–1.06; $p = 0.083$) (36). In another analysis from the same group, Traub et al. demonstrated that elevated phosphorylated tau (pTau) and neurofilament light chain (NfL) levels were inversely correlated with cognitive scores (pTau: $\rho = -0.25$; $p = 0.002$; NfL: $\rho = -0.21$; $p = 0.013$), indicating axonal and synaptic damage even in early HF stages (44). This finding suggests that S100B reflects increased blood–brain barrier permeability and glial activation, which favors entry of inflammatory mediators into brain tissue and contributes to chronic hypoperfusion and neurovascular dysfunction.

Redwine et al. found that reduced BDNF concentrations were associated with lower performance on the MoCA scale ($\beta = -0.468$; $p = 0.008$), explaining 21.4% of the additional variability of the model ($\Delta R^2 = 0.214$). In parallel, elevated sICAM-1 and sVCAM-1 levels, circulating markers of endothelial activation and cell adhesion, were associated with poorer cognitive performance ($P < 0.05$), supporting the role of endothelial dysfunction and systemic inflammation as intermediate pathways between HF and brain damage (35).

Bayes-Genis et al. analyzed amyloid- β 40 peptide (A β 40) in 939 patients with HFrEF, finding a significant association between its serum levels and higher risk of total mortality (HR: 1.22; 95% CI: 1.10–1.35; $p < 0.001$) and cardiovascular mortality (HR: 1.18; 95% CI: 1.03–1.36; $p = 0.02$) (34). Although it did not directly evaluate CI, the biological role of A β 40 in amyloidogenic processes suggests a link between abnormal amyloid metabolism, endothelial dysfunction, and progressive brain injury.

Limitations

First, the number of available studies was small and had small sample sizes, which limits statistical power and generalizability of the findings. Most of the included studies were observational, which prevents establishing causal relationships between biomarkers and CI. In addition, considerable methodological heterogeneity was observed, derived from differences in diagnostic criteria for heart failure, methods

of cognitive evaluation, and biomarker measurement techniques, which makes comparison between studies difficult. Lack of standardization in cut-off points and measurement units, along with the absence of uniform adjustments for confounding variables such as age, comorbidities, or renal function, could also have influenced the variability of results. The limited number of studies prevented a formal assessment of publication bias. Furthermore, NT-proBNP typically exhibits a right-skewed distribution. Although no conversions from medians and interquartile ranges were performed in the present analysis, log-transformed or median-based analyses could not be conducted because the required summary data were not consistently available. Because only three studies contributed to the NT-proBNP meta-analysis, the I^2 estimate was also unstable and should be interpreted cautiously. Although the hs-cTnT meta-analysis showed no statistical heterogeneity, 95.8% of the total weight was contributed by a single study. A leave-one-out pooled analysis was not informative because removing either study left only one study available for analysis. Therefore, the statistically significant pooled association should not be interpreted as equally replicated across independent samples. Stratified analyses according to heart failure phenotype were not performed because most studies included mixed populations or did not report biomarker and cognitive outcomes separately for HFrEF, HFmrEF, and HFpEF. Similarly, subgroup analyses according to cognitive assessment method were not feasible. The included studies used different cognitive instruments, cut-off values, and definitions of CI. Because the MMSE, MoCA, and comprehensive neuropsychological batteries differ in sensitivity and in the cognitive domains assessed, this variability may have influenced the observed associations and limited direct comparison across studies.

Conclusions

In patients with CHF, hs-cTnT is significantly associated with CI, while NT-proBNP showed only a non-significant trend. Qualitative synthesis reinforces a consistent signal of extracardiac biomarkers linked to inflammatory and neurodegenerative pathways: GDF-15 was associated with CI and with clinical events; S100B, pTau and NfL were inversely correlated with cognitive performance; and low BDNF levels along with higher sICAM-1/sVCAM-1 suggest endothelial dysfunction and neurovascular damage, while A β 40 was associated with mortality rather than cognition.

Disclosures

Conflicts of interest: The authors declare no conflicts of interest regarding the content of this manuscript.

Financial support: The authors declare that they did not receive specific financial support for the completion of this work.

Data confidentiality: The authors declare that they have followed their institution's protocols regarding the publication of patient data, ensuring the confidentiality and anonymity of the information.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request. No publicly archived datasets were generated or analyzed during this review.

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