

The Prognostic Value of Troponin Levels Adjusted for Renal Function in Heart Failure – A Systematic Review

ANCA BREHA^{1,2*}, CATERINA DELCEA^{1,2*}, ANDREEA CRISTINA IVANESCU^{1,2}, GHEORGHE ANDREI DAN^{1,3}

¹“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

²Cardiology Department, Colentina Clinical Hospital, Bucharest, Romania

³Romanian Academy of Scientists

* Authors with equal contribution

Abstract

Introduction: Heart failure (HF) is a significant global health issue associated with high morbidity and mortality. Accurate biomarkers are crucial for predicting adverse outcomes and informing management. High-sensitivity cardiac troponins T (hs-cTnT) and I (hs-cTnI) are important prognostic indicators in HF, though their predictive value can be affected by comorbidities, particularly renal dysfunction.

Objectives: This review evaluates the prognostic significance of troponin adjusted for renal function in patients with HF.

Methods: A comprehensive literature search was performed in PubMed, including studies from 2011 to September 2024, using specific MeSH terms related to HF, troponin, and prognosis.

Results: Thirty-two studies met the inclusion criteria, all indicating an association between troponin levels adjusted for renal function and cardiovascular mortality in HF patients (HR 1.67–3.22). High-sensitivity cardiac troponins T (hs-cTnT) and I (hs-cTnI) are independent predictors of cardiovascular mortality in acute heart failure (AHF). Increasing hs-cTnI levels, with a baseline threshold of 0.03 ng/mL, significantly correlate with mortality risk ($P = .0011$). Patients with hs-cTnT > 14 ng/L, > 21.5 ng/L, and > 26.5 ng/L exhibit increased all-cause mortality after adjusting for renal function. Despite these associations, the role of troponin in predicting heart failure readmissions remains inconsistent, indicating that elevated troponin levels do not reliably predict rehospitalization risk, particularly in those with advanced renal impairment.

Conclusions: High-sensitivity troponins (hs-cTnT and hs-cTnI) are independent predictors of mortality in heart failure, even after accounting for renal function, while their role in predicting hospitalizations is weaker.

Keywords: troponin, outcome, CKD, renal dysfunction, heart failure, hospitalizations, kidney function, kidney disease, mortality.

INTRODUCTION

The heart failure (HF) epidemic is a relentlessly evolving global health burden [1]. It is recognized as one of the leading causes of mortality worldwide, with constant progress in diagnosis and management, yet with remaining challenges and unmet needs [2]. At the crossroads of multiple comorbidities, kidney disease is a prognostic factor of utmost importance in HF, doubling the risk of all-cause mortality. In this setting, specific cardiac biomarkers play an essential role in evaluating patients' prognosis. Of these, cardiac troponin (cTn) is both a marker of severity and prognosis in HF, as well as a predictor of HF or death in chronic kidney disease [3].

Especially with the use of high-sensitivity assays, troponin levels are elevated in many patients with renal failure, even in the absence of overt myocardial damage, and in most patients with heart failure with reduced ejection fraction (HFrEF). Although the mechanisms underlying this finding remain controversial, a key takeaway is the demonstrated predictive value of troponin for outcomes in these patients [4,5].

Elevated cTnT in patients with renal dysfunction may be caused by uremic cardiotoxins and reduced renal clearance, although the link does not seem to be solely due to these factors. Serum troponin T is increased more frequently than troponin I in patients with renal failure [6].

It is still unknown how much of the elevated concentration of cTn in patients with renal illness is due to impaired renal clearance [7]. Additional mechanisms have been considered, including oxidative injury [8], supply/demand mismatch [9], increased inflammation [10], and dialysis-related physiologic changes such as hemodynamic shifts and anemia [11].

In patients with HFrEF, even in those with mild to moderate CKD, elevated levels of hs-TnT were strongly associated with incident HF [12].

In patients with advanced CKD and preserved LVEF, troponin levels are associated with diastolic dysfunction and an increased risk of mortality [13,14].

A meta-analysis [15] showed that hs-TnT levels independently predict long-term all-cause and cardiovascular mortality, as well as cardiovascular hospitalization. The outcome was unaffected by HF etiology or renal function.

Some studies found an association between long-term all-cause mortality and higher troponin levels in chronic disease (CKD). However, this association lost significance once adjusted for the severity of CKD, leaving uncertainty regarding the role of renal filtration in modulating cardiac troponin levels in CKD [16,17].

Interestingly, it is still unclear why significantly most patients have an increased cTnT versus cTnI in ESRD [16].

Applying general population biomarker thresholds to CKD patients compromises diagnostic accuracy, as many asymptomatic individuals with advanced CKD exhibit positive results, thus obscuring the prognosis of cardiovascular events.

Optimizing troponin cut-off values for prognostication in heart failure (HF) is challenging; a meta-analysis of 10 studies identified 18 ng/L hs-cTnT as ideal, but this value varied by sex and increased with worsening renal function, impacting predictive accuracy, particularly at later stages of CKD [3,15].

A retrospective cohort analysis [18] showed that using the GFR-specific cutoffs, hs-cTnT was strongly associated with cardiovascular events. They determined the optimal cut-off value for hs-cTnT at 22.7 ng/L for an eGFR of 30–44 mL/min, a value of 26.8 ng/L for an eGFR of 20–29 mL/min, and a value of 35.5 ng/L for an eGFR below 20 mL/min. Moreover, these GFR-specific cutoffs showed superior prognostic value compared with standard cutoffs, supporting the concept of GFR-specific cutoffs for cardiovascular risk stratification in patients with advanced CKD.

MATERIAL AND METHODS

The methodology for this systematic review was in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement guidelines [19].

SEARCH STRATEGY

We searched the PubMed (MEDLINE) database from the year 2011 until September 1, 2024, using the main keywords "heart failure", "troponin", "prognosis". A second search was conducted on October 21, 2024, using the same strategy, and the results were considered final. The strategy is detailed in Supplementary Material – Table 1.

Two authors independently reviewed the titles and abstracts of the articles. Each author independently selected articles for inclusion in the analysis. In case of disagreement, a third author determined whether the articles should be included.

Inclusion criteria

Types of participants

We included all study designs that evaluated the prognostic value of troponin in heart failure, provided they also conducted a multivariable analysis that considered renal function.

Evaluation of renal function was considered any type of assessment: eGFR (either qualitative or quantitative assessment), creatinine, urea, cystatin C, BUN levels, diagnosis of CKD, and stratification of CKD.

We did not impose any restrictions on sample size, study duration, or the interventions given to patients.

Only English-written articles were included in the analysis.

Exclusion criteria

Reviews, meta-analyses, systematic reviews, case reports, and animal studies were excluded.

Studies on cohorts including HF among other diagnoses, without separate analysis of the HF subgroups were also excluded.

Studies that reported only composite outcomes were excluded to ensure clarity in assessing individual effects and to avoid potential biases introduced by heterogeneous components.

RESULTS

Our initial search retrieved 1324 publications, of which 992 were considered for inclusion. 65 publications were analysed in the full-text

selection. After applying the inclusion and exclusion criteria 29 full-text records were selected for this review, with a total of 36134 patients evaluated. The selection process is detailed in Figure 1.

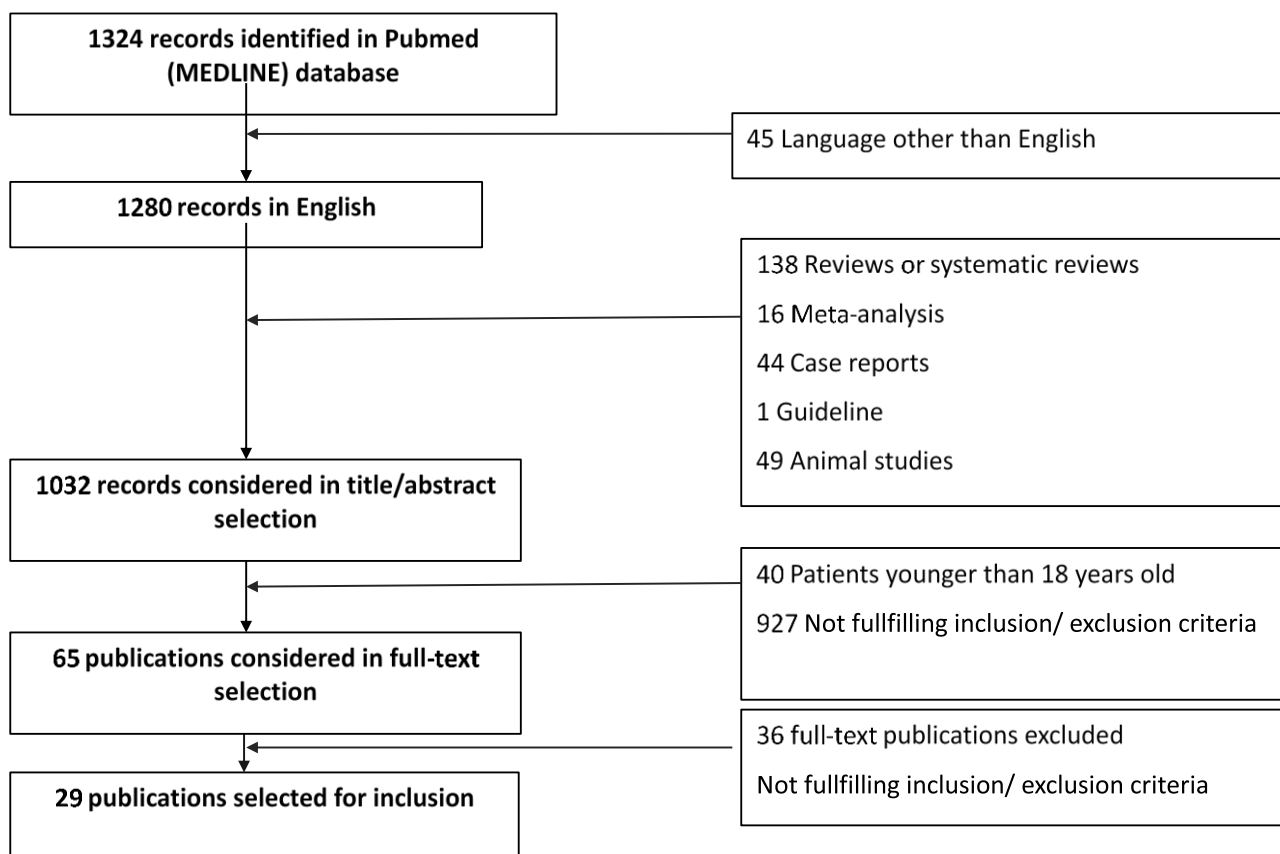


Figure 1. Flowchart for the process of article selection.

CARDIOVASCULAR MORTALITY

Four articles [20–23] evaluated cardiovascular mortality as the primary endpoint. Two studies [22,23] focused on patients with acute heart failure, excluding acute coronary syndromes, while the other two [20,21] focused on patients with non-ischemic chronic heart failure. Among them, two studies analysed hs-cTnI, and the other two examined hs-cTnT.

These studies included a total of 6,670 patients. The largest cohort, comprising 5,284 CHF patients with all types of LVEF, was analysed retrospectively using data from two clinical trials, VAL-HeF [24] and GISSI-HF [25] as reported by Masson *et al.* (2012). The smallest study [21] investigated 95 stable outpatients with nonischemic CHF with dilated cardiomyopathy (DCM) as the underlying etiology in 70 patients.

Data from this studies suggests that high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI) are independent predictors of cardiovascular mortality and cardiac death in patients with acute heart failure (AHF) [23], even after adjusting for various confounding factors including other biomarkers and renal function [22]. Kawahara *et al.* demonstrates an association between increasing troponin levels and mortality risk, hs-cTnI at baseline (0.03 ng/mL) ($P = .0011$), change in hs-cTnI after 6 months (hs-cTnI 0 ng/mL) ($P = .022$) ($P = .0008$) was significant independent predictor of cardiac death [21]. While the inclusion of other clinical risk factors in the models reduced the overall risk estimates, the association between elevated hs-cTnT and mortality risk remained, with hazard ratios ranging from 1.40 to 2.99 across various trials and outcomes [20].

Table 1

General characteristics of the included studies

Author, year	Study Type	Population (N)	Baseline Pathology	Duration of Follow-up	Type of troponin	Main Outcome(s)
Yilmaz Oztekin, 2023 ⁴⁸	Retrospective cohort study	249	Nonischemic CHF LVEF 30 [25 – 35] %	30 months	hs-cTnT	All-cause mortality
Bosselmann, 2013 ⁴⁹	Prospective cohort study	424	CHF LVEF < 45%	4.5 years (IQR: 2-7.7)	hs-cTnT	All-cause mortality
Aulin, 2022 ²⁶	Substudy of a RCT (ARISTOTLE)	4568	CHF All LVEF	1.9 years (median)	hs-cTnT	HF hospitalization All-cause mortality
Berge, 2022 ²⁷	Retrospective analysis of a prospective cohort study (ACE 2 study)	143	AHF All LVEF	823 days (median)	hs-cTnT	All-cause mortality
Berge, 2021 ³¹	Retrospective analysis of a prospective cohort study (ACE 2 study)	143	AHF All LVEF	464(median)	Hs-TnT	All-cause mortality
Aimo, 2019 ²⁸	Retrospective analysis of data from 3 cohorts	1449	AHF All LVEF	11 months (median)	hs-cTnT	In-hospital mortality All-cause mortality Cardiovascular mortality
Ledwoch, 2021 ³⁰	Retrospective cohort study	971	AHF All LVEF	30 days	hs-cTnT	All-cause mortality
Ledwoch, 2022 ²⁹	Retrospective registry	847	AHF All LVEF	30 days	hs-cTnT	All-cause mortality
Jungbauer, 2014 ³²	Prospective cohort study	149	CHF All LVEF	757 days (mean) (IQR 711-809)	hs-cTnT	All-cause mortality Composite endpoint of all-cause mortality or CHF-related rehospitalization
Guisado-Espartero, 2014 ³³	Prospective cohort study RICA registry	406	AHF All LVEF	1 year	cTnT	All-cause mortality Readmission for worsening HF Composite of mortality or readmission
Zymliński, 2017 ²²	Prospective cohort study	130	AHF LVEF 30 [24 – 38] %	1 year	hs-cTnI	Cardiovascular mortality
O'Connor, 2011 ⁵¹	Substudy of an RCT (PROTECT study)	288	AHF with renal insufficiency	60 days (primary) and 7 days (secondary)	cTnT	Composite endpoint including worsening HF despite treatment or worsening renal function
Barlera, 2013 ³⁴	Prospective RCT (GISSI-HF)	6975	CHF All LVEF	3.9 years	hs-cTnT	All-cause mortality
Masson, 2012 ³⁵	Substudy of two RCTs (Val-HeFT & GISSI-HF)	5284	CHF Reduced LVEF	Val-HeFT: 24 months (median); GISSI-HF: 47 months (median)	hs-cTnT	All-cause mortality HF mortality Cardiovascular hospitalization
Lupon, 2013 ³⁶	Prospective cohort study	876	CHF All LVEF	41.4 months	hs-cTnT	All-cause mortality
Ather, 2013 ³⁷	Retrospective cohort study	196	AHF LVEF 26 ± 13 %	5 years	cTnI	All-cause mortality
Lok, 2013 ³⁸	Substudy of an RCT DEAL-HF	209	CHF	Median 8.7 years (8.7 ± 1 year)	hs-cTnT	All-cause mortality

Table 1 (continued)

Author, year	Study Type	Population (N)	Baseline Pathology	Duration of Follow-up	Type of troponin	Main Outcome(s)
Egstrup, 2012 ³⁹	Prospective cohort study	416	CHF LVEF $\leq 45\%$	Median 4.4 years (IQR: 1.9-7.5)	hs-cTnT	All-cause mortality Composite outcome of all-cause mortality and cardiovascular hospitalization
Zhang, 2015 ⁴⁰	Retrospective analysis of a prospective cohort study	1189	CHF Reduced LVEF	1 year	cTnT, cTnI	All-cause mortality
Kawahara, 2011 ²⁰	Prospective cohort study	95	Nonischemic CHF LVEF $< 45\%$	4.25 years	hs-cTnI	Cardiovascular mortality
Fabbri, 2015 ⁴¹	Retrospective analysis of SAFE-SIMEU database	1234	AHF Median LVEF 45%	1 year		All-cause mortality
Lee, 2022 ⁴²	Retrospective analysis of a prospective registry (Kor-AHF)	4396	AHF All LVEF	784 days (IQR 446–1116)	hs-cTnI	All-cause mortality
Bayes-Genis, 2013 ⁴³	Prospective cohort study	879	CHF LVEF 34 [26-43] %	3.46 years (mean)	hs-cTnT	All-cause mortality
Felker, 2012 ⁴⁴	Biomarker substudy within an RCT ASCEND-HF	808	AHF Median LVEF 25%	180 days	cTnI	All-cause mortality Composite of 30-day mortality and rehospitalization Dyspnea improvement at 6 and 24 h Worsening HF or death to day 7 Length of stay
Mcdowell, 2023 ⁴⁵	Biomarker substudy within an RCT (PARADIGM-HF trial)	1559	CHF LVEF $\leq 40\%$	30.7 months (mean)	hs-cTnT	Composite endpoint (cardiovascular death or HF hospitalization) Cardiovascular death All-cause mortality
Demissei, 2021 ²³	Post-hoc analysis of an RCT (RELAX-AHF)	1161	AHF All LVEF	180 days	hs-cTnT	Cardiovascular mortality
Tentzeris, 2011 ⁴⁶	Prospective cohort study	172	CHF LVEF $< 45\%$	1301 days	hs-cTnT	All-cause mortality or HF hospitalization
Bjorman, 2012 ⁴⁷	Prospective cohort study	131	AHF LVEF $43.1 \pm 13.8\%$	3 years	cTnT	All-cause mortality
Horiuchi, 2021 ⁵⁰	Retrospective analysis of a prospective cohort (AKINESIS study)	787	AHF	1 year	hs-cTnI	All-cause mortality HF hospitalization WRF (defined as ≥ 0.3 mg/dL or 50% increase in creatinine within 5 days)

AHF, acute heart failure; CHF = chronic heart failure; CKD, chronic kidney disease; cTnI, cardiac troponin I; cTnT = cardiac troponin T; HF, heart failure; HFREF, heart failure with reduced ejection fraction; hs-cTnI, high sensitivity cardiac troponin I; hs-cTnT, high sensitivity cardiac troponin T; IQR, interquartile range; LVEF, left ventricular ejection fraction; RCT, randomized clinical trial, WRF, worsening renal failure

Table 2
Details of studies evaluating cardiovascular mortality

Author/Year	Type of biomarker	Troponin cut off	HR/OR (95% CI)	HR/OR (95% CI)	Parameters included in the adjusted/multivariable analysis
			Unadjusted (univariable) analysis	Adjusted (multivariable) analysis	
Zymliński 2017 ²²	hs-cTnI	>= URL	1.44	-	systolic blood pressure, natural logarithm of N-terminal pro-B type natriuretic peptide, diabetes mellitus and chronic kidney disease.
		Increase vs stable/decrease	2.22	1.90(0.84-4.29)	
		1Ln/pgml	1.97(1.88-7.87)	1.67(1.01-2.76)	
		Increase vs decrease	3.84(1.88-7.87)	3.22(1.52-6.82)	
Kawahara 2011 ²¹	hs-cTnI	hs-cTnI at baseline (ng/mL) ($\geq 0.03 = 1$, $0.03 = 0$)	15.895	10.679 5.7(1.2-7.9)	age, sex, NYHA class, body weight, creatinine
Demissei 2017 ²³	hs-cTnT		1.63(1.46-1.81)	1.64(1.44-1.88)	Adjusted for a pre-defined baseline model encompassing clinical variables (geographic region, systolic blood pressure, orthopnoea, angina, hyperthyroidism, mitral regurgitation, and atrial fibrillation/flutter at screening), laboratory parameters (white blood cell count, lymphocyte %, blood urea nitrogen, sodium, potassium, calcium, and total protein), and study treatment. The covariate orthopnoea on the ordinal scale (0,1,2,3) was dichotomized into binary as: orthopnoea: 2/3 vs. 0/1. Rationale: there were 0 subjects who died due to cardiovascular causes for orthopnoea level 'none'
Masson 2012 ⁵	hs-cTnT	upper limit of 13.5 ng/L	Mortality for worsening heart failure Val-HeFT 2.32(1.90-2.82)	2.26(1.78-2.86)	age, BMI, LVEF, NYHA class, ischemic etiology of HF, systolic and diastolic blood pressures, prescription of diuretics, beta-blockers or spironolactone, serum creatinine, log baseline hs-cTnT.
			Mortality for worsening heart failure GISSI-HF 2.99(2.30-3.89)	2.9(2.08-4.03)	

BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; HF, heart failure; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; hs-cTnT, High-sensitivity cardiac troponin T;

ALL-CAUSE MORTALITY

Twenty five studies reported the predictive utility of troponin for all-cause mortality in heart failure, adjusted by the renal function [26,27,36–45,28,46–50,29–35]. The total number of patients was 25203, with five studies [27,30,34,43,49] focusing on cohorts partially or fully included in previous analyses [29,31,35,36,39].

The majority of studies reported the prognostic performance of hs-cTnT [27,28,43,45,46,49,50,29–32,35,36,38,39]. Three studies reported cTnT [26,33,47], three studies cTnI [37,42,44], one study

included patients with either cTnT or cTnI measurements [41], one had a separate analysis for cTnT and cTnI [40].

Thirteen studies involved a prospective analysis [27,31,46,47,49,32–34,36,39,40,42,43], and the remaining twelve, a retrospective analysis [26,28,48,50,29,30,35,37,38,41,44,45].

The majority of studies included patients across the entire spectrum of LVEF [26,27,36,41–43,47,28–35], nine investigated patients with LVEF <50% [37,39,40,43–46,48,49], and one did not mention the cohort's LVEF [50].

Table 3

Details of studies evaluating all-cause mortality

3A. ALL-CAUSE MORTALITY IN CHRONIC HEART FAILURE						
Author, year	Type of biomarker	Troponin cut-off	Outcome	HR/OR (95%CI) Unadjusted (univariable) analysis	HR/OR (95%CI) Adjusted (multivariable) analysis	Parameters included in the adjusted/ multivariable analysis
Barlera 2012 ³⁴	hs-cTnT	Continuous variable Log-transformed, natural logarithm	Median 3.9 years	Total cohort HR 2.71 (2.25 – 3.26), p<0.001	HR 1.50 (1.24 – 1.81)	NT-proBNP, NYHA class, age, COPD, SBP, DM, eGFR, sex, uricemia, LVEF, Hb, BMI, aortic stenosis
Bayes-Genis 2013 ⁴³	hs-cTnT	Continuous variable, logarithmic form	Median follow-up 3.46 (1.85 - 5.05) years	Total cohort HR 2.71 (2.25 – 3.26), p<0.001 Renal insufficiency HR 2.62 (2.04 – 3.37), p<0.001	Total cohort HR 1.58 (1.27 – 1.97), p<0.001 Renal insufficiency subgroup HR 1.65 (1.24 – 2.2), p<0.001	age, sex, ischemic etiology of HF, LVEF, NYHA class, DM, Hb (g/dL), serum Na (mmol/L), BB treatment, ACEI/ARB treatment, eGFR (in mL/min/1.73 m2), NT-proBNP, cystatin C, sST2
McDowell 2023 ⁴⁵	hs-cTnT	Continuous variable, log transformed	median 37 months		HR 1.63 (1.31 – 2.03), p<0.001	PREDICT-HF score: Age, sex, race, BMI, region, time since HF diagnosis, NYHA class, prior HF hospitalization, treatment with sacubitril-valsartan/beta-blocker, DM, PAD, prior MI, valvular heart disease, bundle branch block, prior PCI, LVEF, SBP, serum K, Cl, BUN, uric acid, albumin, bilirubin, total cholesterol, LDL, triglycerides, AST, Hb, absolute lymphocyte count, absolute neutrophil count, absolute monocyte count, NT-proBNP or BNP
Lupon 2013 ³⁶	hs-cTnT	Continuous variable quadratic term, logarithmic function of hs-cTnT	Median 41.4 (IQR 22.1 – 60.5) m	HR 11.68 (5.51 – 24.75)	HR 3.9 (1.81 – 8.41)	age, sex, LVEF, eGFR, BMI, NYHA functional class, DM, COPD, AF, ischemic etiology, Hb, serum Na, BB treatment, and ACEI or ARB
Masson 2012 ⁵	hs-cTnT	3 categories: 1. ↓ hs-cTnT over time (changes < - 15%) 2. Stable levels (changes between - 15% and +15%), or 3. ↑ levels (relative changes > +15%).	Median FU ValHEFT 24 (1-3; 18-24) months GISSI 47 (38 - 55) months	Val-HEFT 1.69 (1.49 – 1.92) GISSI-HF 2.23 (1.86 – 2.69)	Val-HEFT 1.60 (1.41 – 1.82) GISSI-HF 1.97 (1.58 – 2.46)	Val-HeFT: age, sex, BMI, LVEF (%), NYHA class (III or IV), ischemic etiology of HF, SBP, DBP, Hr, DM, AF, COPD, prescription of diuretics, beta-blockers or spironolactone, serum bilirubin, serum creatinine, log baseline hs-cTnT. GISSI-HF: age, BMI, LVEF, NYHA class, ischemic etiology of HF, SBP, DBP, HR, DM, AF, COPD, prescription of diuretics or beta-blockers, serum bilirubin, serum creatinine, log baseline hs-cTnT.

Table 3 (continued)

Author, year	Type of biomarker	Troponin cut-off	Outcome	HR/OR (95%CI) Unadjusted (univariable) analysis	HR/OR (95%CI) Adjusted (multivariable) analysis	Parameters included in the adjusted/ multivariable analysis
Lok 2013 ³⁸	hs-cTnT	hs-cTnT > 26.5 ng/ml	Median 8.4 years	HR 1.53 (1.32 – 1.78)	Val-HEFT 1.59 (1.39 – 1.82) GISSI-HF 1.88 (1.50 – 2.35)	Val-HEFT: previous parameters + baseline NT-proBNP and hs-CRP GISSI-HF: previous parameters + baseline NT-proBNP and hs-CRP
Yilmaz Oztekin 2023 ⁴⁸	hs-cTnT	Hs-cTnT ≥ 21.5 ng/L	median follow-up of 30 months	HR 1.012 (1.007-1.017), p<0.001	Model 1: HR 1.45 (1.24 – 1.71)	Model 1 = Age, gender
Tentzeris 2011 ⁴⁶	hs-cTnT	hs-cTnT > 14 pg/mL	median follow-up 1301 [707 – 1636] days	HR 4.54; 95% CI, 1.92–10.73, p<0.001	Model 2: HR 1.36 (1.14 – 1.62) Model 3: HR 1.27 (1.06 – 1.53)	Model 2 = Model 1 + renal function (eGFR), HF etiology, NT-proBNP Model 3 = Model 2 + GDF-15, hs-CRP, galectin 3
Jungbauer 2014 ³²	hs-cTnT	hs-cTnT > 14 ng/L	3-year follow-up	OR 4.80 (1.58 – 14.59) p = 0.0057	HR 1.2 (1.03 – 1.50) p = 0.025	eGFR, hemoglobin, NT-proBNP, BMI, and left atrial diameter
Bosselmann 2013 ⁴⁹	hs-cTnT	Quartile groups	median follow-up of 4.5 (interquartile range: 2-7.7) years	HR 3.07 (1.90 – 4.96) p<0.001	age, sex, LVEF, NYHA class, DM, IHD, eGFR	
Egstrup 2012 ³⁹	hs-cTnT	Quartile groups	Median 4.4 (IQR 1.9 – 7.5) years	Q2, HR 1.8 (1.1 - 2.9), p = 0.014; Q3, HR 2.7 (1.7 - 4.2), p = 0.001; Q4, HR 4.6 (3.0 - 7.0), p = 0.001; Q1 reference	Q2, HR 1.4, 95% CI 0.9 to 2.4, p = 0.15; Q3, HR 1.9, 95% CI 1.3 to 3.1, p = 0.008; Q4, HR 3.1, 95% CI 1.9 to 5.1, p = 0.001)	age, gender, LVEF, NYHA class, DM, CAD, Hb, eGFR, interval of inclusion
		The gender-specific 99th percentile concentration limit as established in a healthy population: men > 18 ng/L women > 8 ng/L			HR 1.4 (95% confidence interval 0.9 to 2.4, p 0.16) for quartile 2, 1.7 (0.9 to 2.5, p 0.12) for quartile 3, and 2.6 (1.6 to 4.4, p <0.001) for quartile 4 Troponin T 99th percentile 1.7 (1.2-2.5) 0.003	age, gender, LVEF, NYHA class, DM, CAD, Hb, eGFR, interval of inclusion, NT-proBNP

Table 3 (continued)

Author, year	Type of biomarker	Troponin cut-off	Outcome	HR/OR (95%CI) (univariable) analysis $\chi^2 = 220$	HR/OR (95%CI) Adjusted (multivariable) analysis $\chi^2 = 127$	Parameters included in the adjusted/ multivariable analysis
Aulin 2022 ²⁶	cTnT	Continuous variable Log-transformed, natural logarithm	Long-term all- cause mortality Median follow- up 1.9 years			Step 1: randomized treatment, age, sex, HTN, DM, CAD, history of stroke/ TIA, BMI, HR, SR, renal function (CrCl)
Zhang 2015 ⁴⁰	Separate analysis for cTnT and cTnI	90 th percentile cTnT > 0.105 ng/ml	1-year all-cause mortality		$\chi^2 = 56$ OR 3.9 (1.96 – 7.76)	Step 2: Step 1 + N-terminal B-type natriuretic peptide (NT-proBNP) age ≥ 75 years, NYHA class III/IV, AF, eGFR < 30 mL/min/1.73 m ² , DM, use of diuretics
		90 th percentile cTnI	1-year all-cause mortality		OR 1.59 (0.65 – 3.88)	age ≥ 75 years, NNYHA class III/IV, AF, eGFR < 30 mL/min/1.73 m ² , diabetes, use of diuretics
3B. ALL-CAUSE MORTALITY IN ACUTE HEART FAILURE						
Berge 2021 ³¹	hs-TnT	Continuous variable Log-transformed using natural logarithm)	Long-term all- cause mortality	HR 1.37 (95%CI 1.10 – 1.71)	HR 1.20 (95%CI 0.93 – 1.55)	Age, male sex, BMI, NYHA class IV, COPD, DM, NT-proBNP, CRP, eGFR
Berge 2022 ²⁷	hs-TnT	Continuous variable Log-transformed using natural logarithm		HR 1.37, 95% CI 1.10 – 1.61	Not statistically significant	NEWS2 score, age, male sex, BMI, smoking, NYHA class IV, HF, AF, COPD, CAD, hypertension, diabetes, NT-proBNP, CRP, eGFR
Ledwoch 2022 ³⁰	hs-TcnT	Continuous variable Log-transformed natural logarithm	30-day all-cause mortality	HFrfEF OR 2.58 (95%CI 1.57 – 4.23) HFmrEF OR 4.53 (95%CI 1.85 – 11.1) HFpEF OR 1.48 (95%CI 0.89 – 2.46)		age, sex, NYHA class, DM, HTN, MI, AF, eGFR
Aimo 2019 ²⁸	hs-cTnT	hs-cTnT ≥ 43 ng/L	In-hospital mortality	In-hospital mortality RR 2.7 (95%CI 1.7 – 4.5)	In-hospital mortality Not statistically significant	Patient cohort, age, sex, new-onset vs. worsening HF, history of CAD, admission LVEF, NYHA class, SBP, Hr, eGFR, Hb, Na, white blood cell count, history of AF, HTN, DM, COPD
				6-month ACM HR 1.73 (95%CI 1.17 – 2.54)		
				12-month ACM HR 1.60 (95%CI 1.11 – 2.33)		
				24-month ACM HR 1.89 (95%CI 1.27 – 2.82)		

Table 3 (continued)

Author, year	Type of biomarker	Troponin cut-off	Outcome	HR/OR (95%CI) (univariable) analysis	Adjusted (multivariable) analysis	Parameters included in the adjusted/ multivariable analysis
Ledwoch, 2021-2022 ³⁰	hs-cTnT	Continuous variable Log2-transformed	30-day all-cause mortality	In-hospital mortality HR 1.45 (95%CI 1.31 – 1.59)	In-hospital mortality HR 1.30 (95%CI 1.07 – 1.60)	N/A
				eGFR $\geq$ 90ml/min AUC 0.75 (0.64 – 0.86)		
				eGFR 60 – 89 ml/min AUC 0.74 (0.62 – 0.85)		
				eGFR 45 – 59 ml/min AUC 0.77 (0.64 – 0.91)		
				eGFR 30 – 44 ml/min AUC 0.63 (0.50 – 0.75)		
Horiuchi 2021 ⁵⁰	hs-cTnI	Continuous variable log-2 transformed	1-year all-cause mortality	eGFR < 30 ml/min AUC 0.62 (0.49 – 0.74)		age, Black race, history COPD, oedema, SBP, Hr, Na, Hb, and BUN, BNP, sNGAL, uNGAL, and Gal3.
				Tertile 1 HR 0.88 (0.37 – 2.11)	HR 1.12 (1.03 – 1.22), p=0.012	
				Tertile 2 HR 1.10 (0.55 – 2.18)		
				Tertile 3		
				HR 1.20 (0.69 – 2.07)		
Guisado Espartero 2014 ³³	cTnT	cTnT > 0.02 ng/mL	1-year all-cause mortality	2.52 (1.58 – 4.01)	1.91 (1.09 – 3.32)	age, female sex, BMI > 25 kg/m2, IHD, previous HF, anemia, LVEF < 45%, NYHA III–IV, eGFR < 60 mL/min/1.73m2, NT-proBNP > 3264 pg/mL
Björman 2013 ⁴⁷	cTnT	cTnT > 10ng/L	All-cause long-term mortality at 3 years	Separate analysis of patients with eGFR < 60: patients with eGFR < 60 mL/min/1.73 and intermediate-high TnT had more deaths than those with eGFR > 60 mL/min/1.73		
				HR 2.94 (1.06 – 8.15), p=0.038	HR 147 (11.2 – 1929.8), p<0.001	Age, ALP, urea, creatinine, orosomucoid, NT-proBNP, TnT, CK-MB, CysC

Table 3 (continued)

Author, year	Type of biomarker	Troponin cut-off	Outcome	HR/OR (95%CI)	Adjusted (multivariable) analysis	Parameters included in the adjusted/multivariable analysis
Ather 2013 ³⁷	cTnI with 3 measurements during 3 different admissions	The median value of minimum cTnI was 0.03 ng/ml (IQR: 0.03 to 0.06 ng/ml) The median overall cTnI was 0.06 ng/ml (IQR: 0.04 to 0.1 ng/ml) The median value of maximum cTnI was 0.15 ng/ml (IQR: 0.08 to 0.42 ng/ml) delta cTnI equal to 0.01 ng/ml (IQR: -0.05 to 0.09 ng/ml)	All-cause long-term mortality (632 person-years)	Minimum cTnI: HR=5.8, 95% CI 1.7 to 19.7 Median cTnI: HR=2.3, 95% CI: 1.3 to 4.1 Delta cTnI: HR=1.1, 95% CI 1.04 to 1.23 Maximum cTnI was not associated with mortality	minimum TnI was the only TnI pattern significantly associated with mortality, with a 2 value of 13.7, pb0.001 and HR of 13.7 (95% CI: 3.7 to 50.8) minimum TnI > 0.04 ng/ml HR=1.6, 95% CI: 1.1 to 2.3, Maximum cTnI was not associated with mortality	age, gender, race, ischemic etiology of HF, EF, NYHA class, number of vessels having more than 50% stenosis on angiography, baseline admission TnI, baseline peak TnI, CV admission, HF admission and total number of admissions during the run-in period; history of smoking, HTN, PAD, AF, DM, COPD, CKD, LVF, CAD
Felker 2012 ⁴⁴	cTnI	Continuous variable, log transformed in using log base 2	Death at 30 days	Doubling of cTnI: OR 1.23 (1.01 – 1.50), p=0.035 20% increase of cTnI OR 3.39 (1.26 – 9.15), p=0.0158 Absolute change in troponin OR 0.76 (0.57 – 1.02), p=0.063	Doubling of cTnI: OR 1.11 (0.89 – 1.38), p=0.37	Age, log(BUN), serum sodium, hypotension (baseline), dyspnoea at rest
Lee 2022 ⁴²	cTnI	cTnI ≥ 0.05 ng/mL (elevated); < 0.05 ng/mL (normal)	Death at 180 days Overall all-cause mortality	Doubling of cTnI: HR 1.25 (1.13 – 1.38), p<0.001 Compared to patients with non-IHF and normal troponin, subgroup categories: Non-IHF and ↑ troponin HR 1.77 (1.52 – 2.07), p<0.001 IHF and normal troponin HR 1.61 (1.26 – 2.06), p<0.001 IHF and ↑ troponin HR 2.29 (1.97 – 2.66), p<0.001	Doubling of cTnI: HR 1.11 (0.99 – 1.25), p=0.086 Compared to patients with non-IHF and normal troponin, subgroup categories: Non-IHF and ↑ troponin HR 1.60 (1.36 – 1.88), p<0.001 IHF and normal troponin HR 1.44 (1.12 – 1.85), p=0.005 IHF and ↑ troponin HR 1.88 (1.60 – 1.55), p<0.001	Age, log(BUN), serum sodium, hypotension (baseline), dyspnoea at rest (baseline). Age, sex, previous history of admission due to HF, HTN, DM, CKD, COPD, CVA, prior history of CAD, MI, malignancy, initial SBP, initial LVEF, initial Na, initial Cr, AF at admission, medication at discharge, including ACEI/ARB, BB, or AA

Table 3 (continued)

Author, year	Type of biomarker	Troponin cut-off	Outcome	HR/OR (95%CI) (univariable) analysis	Adjusted (multivariable) analysis	Parameters included in the adjusted/ multivariable analysis
	cTnI ≥ 0.05 ng/mL		90-day all-cause mortality	Non-IHF HR 3.08 (2.27 – 4.17), p < 0.001	Non-IHF HR 2.47 (1.81 – 3.37), p < 0.001	
				IHF HR 3.47 (2.02 – 5.93), p < 0.001	IHF HR 2.91 (1.65–5.12), p < 0.001	
				Non-IHF HR 1.41 (1.18 – 1.68), p < 0.001	Non-IHF HR 1.36 (1.13 – 1.63), p < 0.001	
				IHF HR 1.03 (0.81 – 1.32), p = 0.79	IHF N/A	
Fabbri 2015 ⁴¹	cTnT or cTnI	cTnT ≥ 50 ug/L cTnI ≥ 0.5 ng/L	1-year all-cause mortality	HR 1.21 (1.05 – 1.39)		age, sex, new-onset dysrhythmias, cardiac valvular diseases, CAD, presence PM or ICD, history of AHF, CKD, COPD, DM, CVD, cognitive defects, poor nutritional status, compliance with pharmacology prescriptions (ACEI, ARB, BB, loop diuretics, MRA, anticoagulants, antithrombotic agents), plasma Na < 135 mEq/L, NT-proBNP > 5000 ng/L, eGFR < 30 mL/min/1.73m ²

AA, aldosterone antagonist; ACEI, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; AF, atrial fibrillation; ARB, /angiotensin II receptor blocker; AST, aspartate transferase; BB, beta blocker; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; CI, confidence interval; Cl, chloride; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; CVA, cerebrovascular accident; CysC, cystatin C; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EF, ejection fraction; Gal3, galectin 3; Hb, hemoglobin; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; Hr, heart rate; hs-CRP, high sensitivity C reactive protein; hs-cTnI, high sensitivity cardiac troponin I; hs-cTnT, high sensitivity cardiac troponin T; HTN, arterial hypertension; IHD, ischemic heart disease; IHF, ischemic heart failure; IQR, interquartile range; K, potassium; LDL, low density lipoprotein; Log, logarithmic transformation; LVH, left ventricular hypertrophy; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; N/A, non applicable; Na, sodium; NYHA, New York Heart Association; OR, odds ratio; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Q, quartile; SBP, systolic blood pressure; sNGAL, serum Neutrophil gelatinase-associated lipocalin; sST2, soluble ST 2; SR, sinus rhythm; TIA, transient ischemic attack; uNGAL, urine Neutrophil gelatinase-associated lipocalin; ↓, decrease; ↑, increase;

All-cause mortality in chronic heart failure (CHF)

Thirteen studies enrolled 14682 patients with CHF [26,32,46,48,49,34–36,38–40,43,45], the majority reporting hs-cTnT [32,34,49,35,36,38,39,43,45,46,48], one using cTnT [26] and one including a separate analysis for cTnT and cTnI [40]. Troponin was expressed as absolute values, percentual variations, logarithmic transformation, dichotomic variable using different cut-offs (Table 3A).

hs-cTnT evaluated as a continuous variable after logarithmic transformation was associated with all-cause mortality independent of renal function assessed by eGFR [34,36,43] or BUN [45] in four studies undertaken on three cohorts of patients with reduced LVEF [45], reduced and mildly reduced EF [36,43] or all types of LVEF [34]. Moreover, in a subgroup analysis of patients with eGFR < 60 mL/min/1.73m², after multiparametric adjustment, hs-cTnT remained an independent predictor of all-cause mortality [43] (Table 3A).

Three distinct cut-off values of hs-cTnT, respectively hs-cTnT > 14 ng/L [32,46], hs-cTnT > 21.5 ng/L [48] and hs-cTnT > 26.5 ng/L [38] were proven to be independently associated with all-cause mortality after adjusting for eGFR as a continuous parameter [32,38,48] or as a dichotomic variable using the eGFR < 60 mL/min/1.73m² cut-off [46]. One study used gender-specific cut-off values, respectively > 18 ng/L for men and > 8 ng/L for women in the multivariable analysis for all-cause long-term mortality and confirmed the predictive power independent of renal function estimated by the eGFR [39] (Table 3A).

Two analyses of the same cohort demonstrated the incremental prognostic value of higher hs-cTnT quartiles for long-term all-cause mortality, independent of eGFR, LVEF, NYHA class and other comorbidities [39,49] (Table 3A).

The rise of hs-cTnT levels > 15% from baseline during follow-up was also associated with all-cause mortality, independent of creatinine levels [35] in a large cohort of patients from two clinical trials, Val-HeFT [24] and GISSI-HF [25] (Table 3A).

cTnT evaluated as a log-transformed continuous variable was also independently associated with all-cause mortality in a sub study of the ARISTOTLE trial, after adjustment for creatinine levels [26]. cTnT and cTnI values in the 90th percentile, analysed separately, were predictive of 1-year all-cause mortality in HF patients with reduced LVEF and ICD implantation in primary prevention, after adjusting for eGFR < 30 mL/min/1.73m² among other parameters [40] (Table 3A).

All-cause mortality in acute heart failure (AHF)

Twelve studies included 10521 AHF patients [27,28,47,50,29–31,33,37,41,42,44], analyzing the entire range of troponin: hs-cTnT [27–31], hs-cTnI [50], cTnT [33,47], cTnI [37,42,44], either cTnT or cTnI [41]. All-cause mortality was documented in-hospital [28], at 30-days [29,30,44], over the first months post-discharge [28,42,44] or after long-term follow-up [27,28,31,33,37,41,42,47,50]. The majority of studies included patients with all types of LVEF [27–31,33,41,42,47] and two included patients with reduced LVEF [37,44] (Table 3B).

hs-cTnT evaluated as a continuous variable was associated with 30-day all-cause mortality after adjustment for eGFR among other parameters, irrespective of the type of LVEF [30]. For in-hospital mortality discordant results were reported [28]. In multivariable analysis including eGFR, log2-transformed hs-cTnT was independently correlated with in-hospital all-cause mortality, while the dichotomic value of hs-cTnT > 43 ng/L was not [28]. The quantitative value of hs-TnT was also evaluated for predicting long-term all-cause mortality with conflictive results from the same cohort after multiparametric adjustment, the negative results arising after including the NEWS2 score in the regression analysis [27,31]. Three different cut-off values of hs-cTnT were independently associated with all-cause long-term mortality in AHF, respectively hs-cTnT > 43 ng/L adjusted for eGFR [28], hs-cTnT > 40 ng/L in patients with eGFR ≥ 45 mL/min and hs-cTnT > 55 ng/L in patients with eGFR < 45 mL/min [29] (Table 3B).

hs-cTnI assessed as a continuous variable log2-transformed was also independently correlated with 1-year all-cause mortality after multivariable adjustment including BUN as a marker of renal function [50] (Table 3B).

The prognostic value of cTnT was evaluated as a dichotomic variable using two cut-off values. cTnT > 20 ng/L was correlated with 1-year all-cause mortality independent of eGFR < 60 mL/min/1.73m² [33]. cTnT > 10 ng/L was predictive of 3-year all-cause mortality after adjustment for creatinine levels [47] (Table 3B).

Discordant results were obtained for cTnI across three different cohorts. cTnI as a continuous variable was not associated with all-cause death at 30 or 180 days in patients with reduced LVEF [44]. In patients with reduced LVEF with multiple admissions for AHF and three cTnI measurements during different hospitalizations, those with the minimum TnI > 40 ng/L had a higher risk of

all-cause long-term mortality, after adjusting for chronic kidney disease among other multiple clinical and biological parameters [37]. When evaluating patients stratified by the HF etiology, cTnI > 50 ng/L was an independent predictor of all-cause 90-day mortality in both patients with ischemic and non-ischemic HF, while the same cut-off was only correlated with post-90-day mortality in non-ischemic HF, and not in ischemic patients [42] (Table 3B).

Using the cut-off values of cTnT $\geq$ 50 ug/L and cTnI $\geq$ 0.5 ng/L, Fabbri *et al.* confirmed that a positive troponin, regardless of the type, was independently associated with 1-year all-cause mortality in AHF patients, after multiple adjustments for clinical, laboratory and treatment parameters, including not only CKD, but also eGFR < 30 ml/min/1.73m² [41] (Table 3B).

HEART FAILURE HOSPITALIZATIONS

Heart failure hospitalizations have been a frequent outcome followed by the articles included in this review, either alone (4 studies) or as part of a composite outcome (10 studies).

Noteworthy, some studies [51,33] found that a baseline troponin T was associated with a higher risk for heart failure hospitalization, compared with patients with negative troponin T at baseline. however, the association did not reach statistical

significance (HR 1.61; P=0.07, respectively p=0.37). Still, for the letter study, comparing the subgroups according to renal function did not reveal differences in heart failure readmission.

A model including hs-cTnT along with other biomarkers identifies eRFG as an independent predictor for mortality but not for CV hospitalizations (HR 0.97; 95%CI 0.87-1.09; p=0.59) [52]. Additionally, hs-cTnT cut-off values that predict endpoints increased with declining renal function. When troponin was analyzed independently, a correlation was observed between its predictive value for rehospitalization as renal function declines. However, this correlation was only evident down to an eGFR of 30 ml/min/1.73m², below which it was no longer present (Table 4).

Other studies, however, found a potential prognostic value for predicting an increased risk of heart failure hospitalization in pts with increased troponin at baseline. In a substudy of the ARISTOTLE trial [26] there were strong indications of non-linear associations between log biomarker levels and the log rate of hospitalization for HF (unadjusted χ^2 =5.54; p=0.062; adjusted χ^2 =6.29; p=0.0454). The model was adjusted into two steps; the first step included renal function. Higher levels of troponin were independently associated with a higher probability of hospitalization for HF, regardless of HF status at baseline.

Table 4

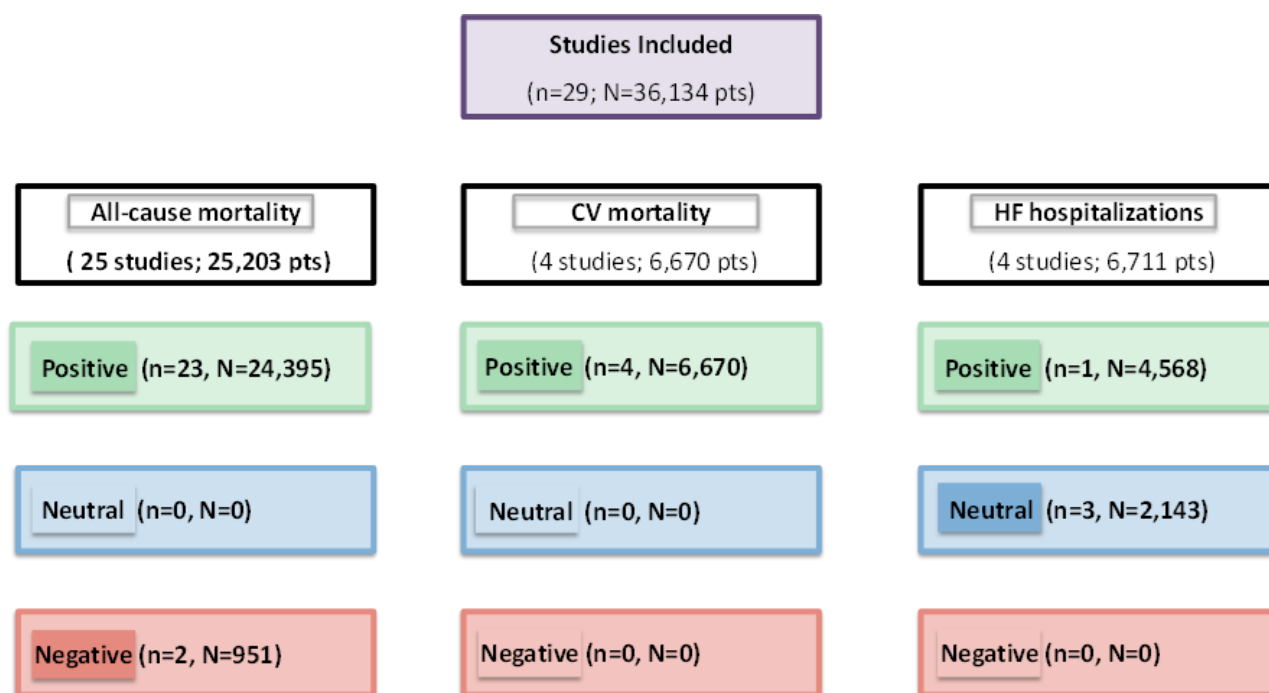
Details of studies evaluating heart failure hospitalizations

Author, year	Type of biomarker	Troponin cut-off	HR/OR (95%CI)		Parameters included in the adjusted/ multivariable analysis
			Unadjusted (univariable) analysis	Adjusted (multivariable) analysis	
O' Connor, 2011 ⁵¹	cTnT	0.01 ng/mL	1.64 ;p=0.08		Age, Sex, BMI, Ischemic heart disease, Previous HF, Anemia, LVEF, NYHA III-IV, eGFR $\geq$ 60 mL/min/1.73 m ² , Troponin T, NT-proBNP
		0.03 ng/mL	1.61 ;p =0.07		
Espartero, 2014 ³³	cTnT	0.02 ng/mL	1.25 (0.83-1.89); p=0.29	1.13 (0.72-1.77); p=0.59	
Aulin, 2022 ²⁶	hs-cTnT	Continuous variable (Log-transformed using natural logarithm)	χ^2 =5.54; p=0.062	χ^2 =6.29; p=0.0454	Step 1: randomized treatment, age, sex, hypertension, diabetes mellitus, coronary artery disease, history of stroke/ (TIA), (BMI), heart rate, sinus rhythm and renal function ([CrCl]) Step 2: Step 1 + NT-proBNP

Table 4 (continued)

Author, year	Type of biomarker	Troponin cut-off	HR/OR (95% CI)		Parameters included in the adjusted/multivariable analysis
			Unadjusted (univariable) analysis	Adjusted (multivariable) analysis	
Aimo, 2019 ²⁸	hs-cTnT	limit of detection 5 ng/L, upper reference value 14 ng/L		HR 0.97; 95%CI 0.87-1.09; p=0.59	NT-proBNP, hs-TnT, hs-CRP were log2-transformed. The prognostic model includes the three biomarkers.
	hs-cTnT			1.41 (1.35-1.47); p<0.001	
	eGFR ≥90 mL/min/1.73 m ²			1.37 (1.06-1.76) p=0.014	
	eGFR 60-89 mL/min/1.73 m ²			1.40 (1.31-1.50); <0.001	
	eGFR 30-59 mL/min/1.73 m ²			1.45 (1.36-1.54); p<0.001	
	eGFR <30 mL/min/1.73 m ²			1.17 (0.96-1.42); p=0.121	

BMI, body mass index; CrCl, creatinine clearance; eGFR estimated Glomerular Filtration; HR, hazard ratio; HF, heart failure; hs-CRP, High-sensitivity C-reactive protein; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type Natriuretic Peptide; TIA, transient ischemic attack;



Legend: n - number of studies; N - total number of patients included.

Positive studies which showed a positive independent correlation between Troponin adjusted for renal function and the specific outcome.

Neutral studies which showed an uncertain or contradictory relationship between Troponin adjusted for renal function and the specific outcome.

Negative studies which showed no independent correlation between Troponin adjusted for renal function and the specific outcome.

Figure 2. Studies divided according to their results.

CONCLUSIONS AND DISCUSSIONS

Troponin levels serve as strong independent predictors of cardiovascular and all-cause mortality in heart failure patients after adjusting for renal function. Notably, renal dysfunction modifies the prognostic value of troponin, with the highest risk observed in patients displaying both elevated troponin levels and worsening renal function. In chronic heart failure (CHF) patients, elevated high-sensitivity troponin T (hs-cTnT) levels are particularly relevant as independent markers for all-cause mortality, regardless of renal function indices [32,34,53,35,36,38,39,45,48,49,52].

In acute heart failure (AHF), various troponin assays (hs-cTnT, hs-cTnI, conventional cTnT, and cTnI) demonstrate independent predictive capabilities for all-cause mortality across different follow-up periods. However, inconsistent findings emerge regarding their ability to predict in-hospital and long-term mortality when adjusted for scores like the NEWS2, as well as post-90-day mortality in ischemic heart failure [27,31].

Most studies indicate a lack of positive correlation between troponin levels and the risk of heart failure rehospitalization when stratified by renal function. While troponin reliably predicts mortality, its association with heart failure hospitalization remains weaker and inconsistent. This association improves when combined with markers of renal dysfunction, such as neutrophil gelatinase-associated lipocalin (NGAL), yet it may diminish in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) [32].

Overall, the relationship between troponin levels and heart failure hospitalizations stratified by renal function remains complex and variable. Some studies suggest a potential correlation between elevated troponin T levels and increased rehospitalization risk, but these findings often lack statistical significance. Interestingly, troponin may have more pronounced predictive value in patients with declining renal function, as certain models suggest higher troponin levels could predict hospitalizations, although only up to a specific threshold of renal function [26,33,51,52]. Despite these potential associations, the evidence remains inconsistent, and troponin levels adjusted for renal

function are not consistently reliable indicators of heart failure readmission risk.

A significant finding of this review is the robust association between elevated hs-cTnT levels and all-cause mortality; Jungbauer *et al.* noted that patients in the highest quartile had a hazard ratio (HR) of 2.6 for mortality after adjusting for renal function, illustrating the importance of troponin as a prognostic marker in heart failure management [32].

Furthermore, understanding the relationship between cardiac and renal functions is essential, as elevated troponin levels often indicate myocardial injury while also reflecting worsening renal function. For example, Tentzeris *et al.* demonstrated that higher hs-cTnT levels correlate with renal failure, underscoring the necessity of a comprehensive evaluation of both heart and kidney health [52].

Lastly, adjusting for renal function is crucial, as demonstrated by studies like those of Horiuchi *et al.* that confirm troponin levels maintain their significance as predictors of adverse outcomes even with renal impairment [50]. This emphasizes the importance of monitoring troponin in heart failure patients, particularly those with renal dysfunction, to provide insights into their overall risk.

Given its strong predictive value for mortality, troponin should be integrated into risk stratification models for patients with concurrent renal dysfunction. Future research should focus on exploring troponin-guided management strategies, refining treatment approaches, and ultimately improving clinical outcomes.

LIMITATIONS

The sample sizes across studies varied significantly, potentially limiting the statistical power and reliability of findings in those with smaller populations. Additionally, the follow-up durations ranged widely, with shorter periods possibly missing long-term prognostic implications and longer studies risking bias from loss to follow-up. Furthermore, the heterogeneity of troponin assays – such as hs-cTnT, hs-cTnI, cTnI, and cTnT – and the use of different cut-off values further complicate comparisons and impact the overall consistency of the results.

Introducere: Insuficiența cardiacă (IC) este o problemă de sănătate globală semnificativă asociată cu morbiditate și mortalitate ridicate. Biomarkerii precisi sunt esențiali pentru precizarea prognosticului sever și pentru management. Troponinele

cardiace de înaltă sensibilitate T (hs-cTnT) și I (hs-cTnI) sunt indicatori de prognostic importanți în IC, deși valoarea lor predictivă poate fi afectată de comorbidități, în special de disfuncția renală.

Obiective: Această sinteză sistematică evaluează semnificația prognostică a troponinei ajustate pentru funcția renală la pacienții cu IC.

Metode: A fost efectuată o căutare cuprinzătoare a literaturii în PubMed, inclusiv studii din 2011 până în septembrie 2024, folosind termeni MeSH specifici legați de HF, troponină și prognostic.

Rezultate: Treizeci și două de studii au îndeplinit criteriile de includere, toate indicând o asociere între nivelurile de troponine ajustate pentru funcția renală și mortalitatea cardiovasculară la pacienții cu IC (HR 1,67–3,22). Troponinele cardiace de înaltă sensibilitate T (hs-cTnT) și I (hs-cTnI) sunt predictori independenți ai mortalității cardiovasculare în insuficiența cardiacă acută (AHF). Creșterea nivelurilor hs-cTnI, cu un prag inițial de 0,03 ng/mL, se corelează semnificativ cu riscul de mortalitate ($P = 0,0011$). Pacienții cu hs-cTnT > 14 ng/L, > 21,5 ng/L și > 26,5 ng/L prezintă o mortalitate crescută de toate cauzele după ajustarea funcției renale. În ciuda acestor asocieri, rolul troponinei în prezicerea reinternărilor cu insuficiență cardiacă rămâne inconsecvent, indicând faptul că nivelurile crescute de troponină nu prezic în mod fiabil riscul de respitalizare, în special la cei cu insuficiență renală avansată.

Concluzii: Troponinele cu sensibilitate ridicată (hs-cTnT și hs-cTnI) sunt predictori independenți ai mortalității în insuficiență cardiacă, chiar și după luarea în considerare a funcției renale, în timp ce rolul lor în predicția spitalizării este mai slab.

Correspondence to: Andreea Cristina Ivănescu, M.D, Ph.D, Cardiology Department, Colentina Clinical Hospital, Bucharest, Romania, Stefan cel Mare No. 19–21 Street, Sector 2, Bucharest, Romania, zip code 020125
e-mail: andreea.cardio@gmail.com

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