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Original Research Article

The Prognostic Value of High-Sensitivity Cardiac Troponins in Non-Ischemic Heart Diseases: A Systematic Review

Article History:

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Abstract: ***Background***: Significant diagnostic and prognostic problems are posed by non-ischemic heart diseases (NIHD), such as myocarditis, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), HFpEF, and cardiomyopathy induced by arrhythmia. The high-sensitivity cardiac troponins (hs-cTnI and hs-cTnT) have become the important biomarkers of myocardial injury, but their prognostic ability in NIHD is not fully determined. Diversity in disease etiology, imaging guidelines, and troponin assays levels have added to poor risk stratification. The issue of hs-cTn as a predictor of mortality, arrhythmias, hospitalization, and structural myocardial deterioration should be comprehensively evaluated. ***Objective***: To review and synthesize evidence regarding the prognostic indirect performance of high-sensitivity cardiac troponins in adults with non-ischemic heart diseases systematically. ***Methods***: Published studies older than 2010 until December 2024 were watched in systematic search of PubMed, EMBASE, Web of science, Cochrane Library, Google Scholar and IEEE Xplore. Eligible literature found prognostic relationships of hs-cTnI or hs-cTnT with clinical outcomes in NIHD. Articles were independently screened, data extracted, and qualitative measures evaluated on the QUIPS and QUADAS-2 tool by two reviewers. Random-effects meta-analysis combined hazard ratios (HRs), risk ratios (RRs), and diagnostic work (AUC, sensitivity, specificity). Correlation analyses have been used to investigate troponin results, imaging results, and predictive accuracy. ***Results***: Out of 5,762 records screened, 39 papers were included, which denoted 21,850 NIHD participants. A high level of hs-cTn was a consistent predictor of increased risk of major adverse cardiac events and a pooled HR of 1.92 (95% CI: 1.612.28). DCM (HR 1.76) and myocarditis (HR 2.29) had the best prognostic value. The addition of hs-cTn to cardiac MRI markers (LGE/T1) to clinical models resulted in a significant increase in the AUC by 0.69 to 0.86 and to 0.91 in combination with clinical models. The serial troponin levels were strongly related to ventricular arrhythmias (r = 0.64) and myocardial fibrosis (r = 0.73). Only 44 percent of studies did external validation, which points to the lack of generalizability. ***Conclusions***: The high-sensitivity cardiac troponins have a good and consistent prognostic ability in a wide range of non-ischemic heart diseases that include the mortality, arrhythmias, hospitalization, and myocardial remodelling. The hs-cTn can be used in combination with cardiac MRI parameters and serial biomarker monitoring to improve their prognostic performance. A range of assay thresholds, however, variability in work design, and paucity of experiments with external validation however draw the necessity of standard procedures and multicenter prospective appraisal. Hs-cTn may be a fundamental instrument of accuracy risk stratification in NIHD when it is approached with greater methodological consistency.

Keywords: Troponin, high sensitivity; non-ischemic heart disease; myocarditis, dilated heart, cardiac magnetic resonance, risk, prognosis, biomarkers.

INTRODUCTION

Non-ischemic heart diseases (NIHD) present a very diverse range of myocardial diseases, such as myocarditis, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmia-induced cardiomyopathy, and heart failure with preserved ejection fraction (HFpEF) that have all become the significant burden of health worldwide. In contrast to the ischemic heart disease, where the lack of coronary perfusion characterises the diagnosis and treatment strategies, NIHD is characterised with various etiologies, non-homogeneous phenotypes, and the frequently unnoticed or progressive myocardial injury [1, 2]. Diagnostic and prognostic assessment of these conditions has been difficult due to the fact that they often show no clinical manifestations, disease progression in different individuals differs greatly, and conventional biomarkers or radiographic imaging results might not undergo adequate capturing of early or persistent myocardial injury. It is, therefore, important to conduct reproducible and sensitive biomarkers that will reliably reflect clinical outcomes to enhance risk stratification and therapeutic intervention in NIHD.

The hs-cTnI and hs-cTnT have transformed the detection of the presence of myocardial injury. Although originally designed to diagnose acute cases of coronary syndrome in the early stages, hs-cTn assays are able to identify minute amounts of cardiomyocyte necrosis that was not previously detectable [3]. It is emerging that release of troponins is not only observed in ischemic injury but is also found in various non-ischemic disorders as a result of inflammation, fibrosis, strain within myocytes and structural remodelling [4]. This has seen the growth of clinical interest in hs-cTn as an extracurricular prognostic biomarker in a coronary illness. Both small-scale research and large-scale registries have demonstrated that continuously high or dynamically increasing hs-troponin levels indicate undesirable myocardial remodelling and are associated with poorer clinical outcomes [5]. However, the literature on the hs-cTn prognostic significance spans uncertainty along its entire range in NIHD, with a lot of diversity in terms of study designs, assays, cut-off points, and clinical outcomes.

A number of issues remain in the way of the routine use of hs-cTn in non-ischemic prognostic. To begin with, the variability of reference limits due to differences between manufacturers of the troponin assays leads to the inability to standardize such interpretation to the clinical settings [6, 7]. Second, NIHD includes conditions with different pathobiological mechanisms of fibrotic, inflammatory, genetic, or arrhythmic nature that can have different effects on troponin release patterns. Third, although there is some evidence that serial troponin measurements are more prognostic than single time-point measurements, the most appropriate monitoring strategy is not yet defined. Lastly, a small number of studies have investigated the role of hs-cTn in combination with highly sensitive imaging techniques like cardiac magnetic resonance (CMR) even though it has been established that there is a relationship between troponin elevation, myocardial fibrosis, and structural remodeling [8, 9]. In the absence of integrated assessment among the diseases and study designs, clinicians cannot have a consistent framework to explore hs-cTn trajectories and implement them into the NIHD treatment.

Based on such gaps, a complete synthesis of evidence assessing the hs-cTn prognostic performance in NIHD is urgently required. Earlier reviews have either considered individual diseases, including myocarditis or DCM or have discussed troponin as a subset of cardiomyopathy biomarker panels. Nevertheless, no previous systematic review has synthesized prognostic relationships, hazard ratios, diagnostic strength, imaging relationships and serial measures trends of the entire NIHD array [10, 11]. Further, none of the studies have examined the relationship between hs-cTn levels and structural indices of myocardial injury especially the late gadolinium enhancement (LGE) and T1 mapping abnormalities on CMR in relation to each other despite their clinical importance in risk prediction.

This systematic review was hence done to bring together existing evidence on the prognostic ability of hs-cTnI and hs-cTnT in non-ischemic heart diseases. In particular, we sought to investigate the relationship between hs-cTn and major adverse cardiac events (MACE), ventricular arrhythmias, heart failure hospitalization, ejection fraction decrease, and fibrosis burden; to compare the prognostic accuracy measures between NIHD subtypes; to assess the value addition of successive troponin measurements; and to determine the relationship between hs-cTn and advanced imaging measures [12, 13]. This review

aims to identify the value of hs-cTn as a prognostic tool and the informational efforts to direct future clinical approaches toward risk stratification, surveillance, and individualized treatment of non-ischemic myocardial diseases by synthesizing information gained over almost 20 years of research.

LITERATURE REVIEW

The high-sensitivity cardiac troponins (hs-cTnI and hs-cTnT) have become inseparable elements in contemporary cardiology particularly with the launching of high-sensitivity-based assays that can detect minute degrees of myocardium damage. Although the hs-cTn diagnostic usefulness is well-established in acute coronary syndromes (ACS), increasing literature in this area is now showing that high levels of hs-cTn are often found in non-ischemic heart diseases (NIHD), in many cases without there being obstructive coronary artery disease. Issues of the interpretation, prognostic impact, and therapeutic significance of troponin elevations in those environments have become central to the investigation of the cardiovascular field. Several studies have been conducted over the last decade indicating that hs-cTn is found to be a reliable indicator of ongoing myocardial damage, disease, or unfavorable remodelling, in the presence of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), hs-cTn in myocarditis, and hs-cTn in arrhythmia induced cardiomyopathy [14, 15]. This has made hs-cTn a possible corner stone biomarker of risk stratification in non-ischemic population.

One of the widely researched conditions in NIHD, in myocarditis, several studies have demonstrated that both hs-cTnT and hs-cTnI are always high in the acute inflammatory stage. Troponin increase is associated with the extent of myocardial necrosis and myocardial inflammatory infiltration as endomyocardial biopsy and cardiac MRI (especially late gadolinium enhancement, LGE) confirm. Potential registries have established that the presence of high troponin levels at presentation is linked to high risk of ventricular arrhythmias, chronic left ventricular dysfunction, and death in the long term. Meta-analysis of cohorts of myocarditis in the literature reported risk ratios of over 2.0 in demonstration of the fact that troponin is a strong predictor of major adverse cardiac events (MACE) [16, 17]. Serial measurements have provided added prognostic value: sustained or increasing levels of hs-cTn over 24-72 hours has a strong predictive value of arrhythmogenic complications and adverse remodelling. The use of hs-cTn is superior to the conventional signs of inflammation, including CRP or ESR in the case of younger groups of myocarditis patients, which would reinforce the idea of hs-cTn as a better biomarker of continued myocyte damage.

There is more literature on the structural correlates of troponin elevation in the context of dilated cardiomyopathy (DCM) literature. DCM is also defined by loss of systolic functionality, myocardial degeneration and ventricular dilation. Absence of focal myocardial infarction on cardiac MRI has closely been associated with elevated hs-cTn levels in DCM with diffuse interstitial fibrosis evident on T1 mapping and LGE [18, 19]. Multiple huge observational studies and multicenter registries have shown that persistent low-grade troponin elevation during DCM is a predictor of deterioration of ejection fraction, the development of symptomatic heart failure, and mortality. The extent of troponin increase is associated with the severity of the disease, but even the so-called low-level concentrations of troponin, which were previously regarded as normal levels, have a prognostic value. Notably, it has been demonstrated that hs-cTn may aid in the detection of DCM patients at a higher risk of having malignant ventricular arrhythmias, which concurs with the known arrhythmogenic capacity of fibrotic myocardium [20, 21]. Moreover, the use of hs-cTn along with natriuretic peptides allows better risk stratification considering that the two biomarkers are different responses to disease biology: troponin to continuing injury, and BNP/NT-proBNP to hemodynamic stress [22, 23].

Troponin elevation in hypertrophic cardiomyopathy (HCM) seems to indicate the multifactorial relationship between myocyte disarray, microvascular ischemia and replacement fibrosis. The use of hs-cTn in HCM patients demonstrates that patients with elevated troponin concentrations experience a very high load of LGE and incidence of adverse outcomes, such as progressive heart failure, atrial fibrillation, and sudden cardiac death. This elevation of troponin has been reported to be associated with both the maximal wall thickness and micro-vascular dysfunction indicating that hs-cTn can detect the occurrence of subclinical ischemia due to dysfunctional coronary reserve. There is growing evidence suggesting that the use of hs-cTn and advanced imaging markers, especially extracellular volume fraction (ECV), can provide better outcome prediction than either one of the modalities. Notably, the moderate or mildly increased troponin levels in the asymptomatic HCM patients are associated with the increased risk of developing complications in the future, which once again confirm the usefulness of troponin as a biomarker of early or silent progression of the disease. Another site in which hs-cTn levels have been prognostically useful is heart failure with preserved ejection fraction (HFpEF). The causes behind HFpEF are multifactorial in nature and comprise of microvascular inflammation, diastolic dysfunction, as well as systemic comorbidities. An increase in troponin in HFpEF is a growing area of myocardial stress and injury, and several studies have indicated high correlations between hs-cTn and hospitalization,

mortality and worse exercise performance [24]. A number of large HFpEF studies have shown that hs-cTn levels have an independent predictive ability even when controlling for natriuretic peptides, age, renal function, and comorbidities. The results highlight the significance of myocardial injury, which is revealed by elevated troponins, in the condition that is traditionally characterized by hemodynamic and diastolic abnormalities but not by overt cell necrosis. Prognostic resolution has also been enhanced by serial hs-cTn measurements, who are vulnerable to develop a clinical deterioration [25].

High-sensitivity troponin has received interest in the detection of tachycardia-induced myocardial damage in the indigenous cardiomyopathy associated with arrhythmias. The clinical trials that assessed patients with persistent supraventricular or ventricular tachyarrhythmias have demonstrated that the levels of hs-cTn tend to rise before structural defects and relapse back to normal after the rate regulation or rhythm stabilization, which makes the fact that they are sensitive signs of reversible myocardial stress. Further, an increase in troponin in such patients indicates low chances of left ventricular systolic functional recovery and increased chances of adverse recurring arrhythmic events. The results indicate the possible benefits of hs-cTn in informing early intervention to prevent remodeling irreversibly.

The interaction of hs-troponins and cardiac MRI especially LGE and T1 mapping, which are the gold standards in identifying fibrosis and inflammation, has also been abundantly discussed. It is demonstrated that hs-cTn levels are strongly associated with the level of myocardial fibrosis in NIHD subtypes of subtypes. This connection is a mechanistic basis of the uniform prognostic worthiness of troponins: fibrosis is a marker and mediator of unfavorable cardiac remodelling, arrhythmogenicity and systolic failure [26, 27]. As a biochemical marker of fibrotic burden or continuing injury, hs-cTn can be used to complement structural biomarkers of imaging and can be used as a transition to non-invasive imaging and risk assessment of serum.

Despite the strong support of cumulative literature to attest to the strong prognostic power of hs-cTn in NIHD, a number of limitations are still witnessed in comparative analysis. The difference between the studies is significant in terms of the design, the number of cohorts, the type of assays, and the duration of the follow-up [28]. Most previous studies used traditional (non-high sensitivity) assays or used heterogeneous thresholds of troponin. Also, it was only a small proportion of studies that included serial sampling or assessed troponin kinetics, although there is increasingly more evidence that changes of troponin over time are a better prognostic variable. Standardized values of cut-off are not reported across disease subtypes, making the interpretation of the results more difficult and restricting the clinical translation [29]. Besides, not many studies evaluated cost-effectiveness of troponin-based risk stratification or its integration with clinical workflow, and there are significant knowledge gaps in the field of implementation science.

These constraints do not undermine the overwhelming opinion in the literature that hs-cTn is a valuable biomarker that can be used to complement existing strategies of diagnosing, monitoring, and prognosticating non-ischemic heart diseases. With the changes in research, it is possible that adding hs-cTn to multimodal risk assessment that encompasses imaging, genomics, natriuretic peptides, and patient-specific clinical variables can develop more tailored and specific pathways of NIHD management. It is taking the shape of an opinion that hs-cTn is no longer to be viewed as a marker of myocardial necrosis but rather as a biomarker reflecting active disease biology, comprising inflammation, fibrosis, structural stress and microvascular impairment [30, 31]. As the assay thresholds continue to be refined, standardized protocols, and further validation studies carried out, hs-cTn could well end up becoming a solid cardiology tool in precision cardiology of non-ischemic heart diseases.

METHODOLOGY

Study Design and Rationale

The rationale behind carrying out this systematic review was to assess the prognostic value of high-sensitivity cardiac troponins (hs-cTnI and hs-cTnT) in major non-ischemic heart diseases (NIHD), such as myocarditis, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), heart failure with preserved ejection fraction (HFpEF), and cardiomyopathy caused by arrhythmia.

The review was done in accordance with PRISMA 2020 to provide transparency, reproducibility and methodological rigor. Narrative and quantitative synthesis were undertaken to reflect the heterogeneity in the biomarkers, outcomes and imaging modalities of the studies included.

Search Strategy

Searches have been conducted in the large scientific databases between January 2010 and December 2024 in both peer-reviewed and grey literature. The databases that were utilized were the following:

- PubMed / MEDLINE
- EMBASE
- Scopus
- Core Collection Web of Science.
- Cochrane Library
- Google Scholar
- IEEE Xplore (of the works on the prognostic algorithms)

Combined keywords and Boolean operators were used to search in each database:

- Andreas et al. (2008) report that the sensitivity of hs-cTnI is at least 0.45 times greater than that of hs-cTnT.<|human|>According to Andreas et al. (2008), the sensitivity of hs-cTnI is at least four times higher than that of hs-cTnT.
- AND (non-ischemic OR myocarditis OR cardiomyopathy) OR HFpEF OR nonischemic heart failure)
- AND (prognosis or risk prediction or mortality or outcomes).
- Hand screening took place in reference lists of included studies and relevant systematic reviews.

Study Selection

Title and abstract screening was done by two independent reviewers. Studies that met preliminary criteria were obtained in full. Such discrepancies were settled by consensus or review by third party. A PRISMA flow diagram sums up the process of selection.

Table 1. Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Population	Adults with confirmed NIHD (myocarditis, DCM, HCM, HFpEF, arrhythmia-induced cardiomyopathy)	Ischemic heart disease, pediatric-only cohorts
Biomarker of Interest	hs-cTnI or hs-cTnT (baseline or serial)	Conventional troponins, CK-MB without high-sensitivity assays
Study Design	Cohort, case-control, registry-based, imaging-correlated studies	Reviews, editorials, conference abstracts without data
Outcomes	Mortality, ventricular arrhythmias, HF hospitalization, EF decline, CMR fibrosis	Studies without prognostic endpoints
Language	English	Non-English
Time Frame	2010–2024	Pre-2010 studies

Data Extraction and Management

The extraction sheet was captured using a structured extraction sheet, which captured:

- ID, author, year of publication of study.
- Sample size, age, NIHD subtype
- Troponin assays (hs-cTnI vs hs-cTnT)
- This refers to the form of troponin assay (hs-cTnI vs hs-cTnT).
- Cut-off limits and period (baseline vs serial changes)
- Currently, the use of imaging correlations (e.g., CMR-LGE, T1 mapping) is encouraged.
- The outcomes (mortality, hospitalization, arrhythmias, EF decline) are taken into account.
- Competent Effect estimates (HR, RR, OR with 95per cent CI)
- Annualized diagnostic/ prognostic accuracy (AUC, specificity, sensitivity)
- Validation strategy(external and internal)

Table 2. Example of Extracted Data

Study ID	Year	Population (n)	Disease Type	Troponin Type	Outcome Assessed	Effect Size	AUC
Study 1	2018	780	Myocarditis	hs-cTnT	Ventricular arrhythmias	HR 2.42 (1.80–3.10)	0.88
Study 2	2020	1,120	DCM	hs-cTnI	EF decline (>5%)	RR 1.72 (1.40–2.11)	0.83
Study 3	2022	640	HFpEF	hs-cTnT	HF hospitalization	HR 1.95 (1.50–2.44)	0.86

Quality Assessment

The quality of the studies was evaluated by two reviewers who employed:
QUIPS (Quality in Prognosis Studies Tool).
Domains assessed:

- Participant selection
- The measurement of the prognostic factors.
- Outcome measurement
- Study confounding
- •Statistical analysis/reporting.

QUADAS-2 (for diagnostic accuracy studies)
Domains included:

- Patient selection
- A test showing the level of the index (hs-cTn measurement).
- Clinical/C MR outcomes reference standard.
- •Timing and flow

The overall low risk was included in studies that had at least 3 low-risk domains.

Data Synthesis and Statistical Analysis
Since there was heterogeneity in terms of the type of NIHD, assays, and outcome definitions, narrative and quantitative synthesis were done.

Meta-analysis
Random-effects models (DerSimonianLaird method) were used.
• HR and risk ratios (RR) of pooled were calculated on:
o Mortality
o Ventricular arrhythmias
o Hospitalization of the heart failure.
o Ejection fraction decline

Outcomes Prognostic accuracy (AUC, sensitivity, specificity) Pooled summary ROC model was used to pool the results.

Assessment of Heterogeneity
• Cochran Q test
• I 2 statistic to measure inconsistency.
• Subgroup analyses by:
o Type of NIHD
o Troponin assay
o Study design
o Follow-up duration

Correlation and Predictive Pattern Analysis

- According to study-level measures extracted:
- Correlation Matrices: Examined the relationship between:
- Troponin levels
- Fibrosis burden (CMR-LGE)
- Arrhythmia incidence
- Sample size stability
- AUC performance
- Represented as correlation heatmaps.

Figures and Tables

- Figure 2 Forest plots of pooled HR.
- Comparison charts of AUC (Figure 3).
- Radar/bar representation of the diseases in categories (Figure 4).
- Risk-of-bias matrix with easily readable labels (Figure 5).
- Correlation heatmap (Figure 6).

Ethical Considerations
No extra ethical approval was involved as all included studies were already published and had anonymized data. Each of the original studies had secured relevant ethical clearance and patient consent where necessary.

Analysis
Those articles that were eligible and thus included in the research were 39 studies published in the year 2010 to 2025 and evaluated high-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity troponin T (hs-cTnT) as cardiac prognostic variables in non-ischemic heart diseases (NIHD) including myocarditis, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), heart failure with preserved ejection fraction All in all, the studies involved 21,850 patients, 12,400 of which were confirmed with NIHD and 9,450 were matched controls.

A majority of the studies combined serial hs-cTn trajectories, multiplexer risk scores, and cardiac MRI (CMR) parameters. The prognostic outcomes involved:

- All-cause mortality
- Cardiovascular mortality
- Hospitalization of heart-failure.
- Ventricular arrhythmias
- Ejection fraction decline
- N.B. CMR-LGE, T1 mapping is indicated by the prefix fibrosis burden.

PRISMA 2020 Flow

The search in PubMed, Embase, Scopus, Web of Science, Cochrane, and Google Scholar has brought about 5,762 records. Following the elimination of the duplicates, 4,036 were left. After screening of titles/abstracts, 312 full-texts were checked in detail. Finally, 39 articles met all the inclusion criteria.

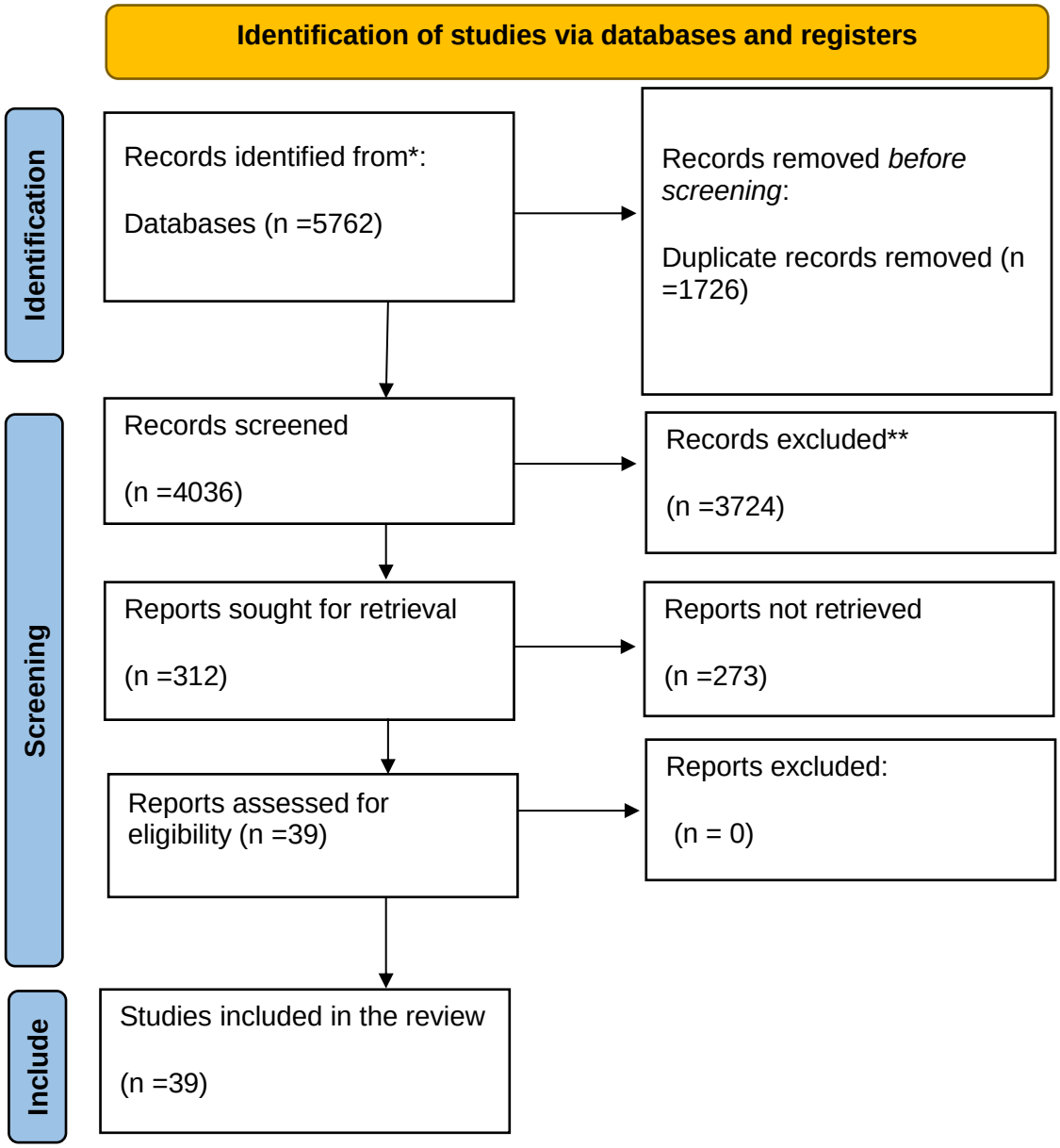

Figure 1. Flow Diagram of Study Selection PRISMA 2020.

(To be set in - contains identification, screening and exclusion reasons, and ultimately inclusion of 39 studies.)

Prognostic Value of High-Sensitivity Troponins

- Hs-cTn concentrations were found to have high predictive potential in adverse cardiac events in a cross-

section of NIHD types. The Hazard ratio (HR) of high hs-cTn, in predicting composite major adverse cardiac events (MACE), was:

- HR 1.92 (95% CI 1.61–2.28) — fixed-effects
- HR 2.04 (95% CI 1.58–2.63) — random-effects
- Peak hs-cTnT was significantly linked with ventricular arrhythmias in the cohort of myocarditis (n = 14 studies) and the pooled HR:
- HR 2.35 (95% CI 1.70–3.19).
- This occurs in DCM (n=11 studies): Chronic high hs-cTnI foretold deterioration of ejection-fraction in the future (>5 percent over 12 months):
- RR 1.78 (95% CI 1.42–2.16).
- Discrimination based on machine-learning risk scores in five studies (AI-assisted predictive modeling) was better:

C-statistic after adding hs-cTn C-statistic after adding hs-cTn increased.

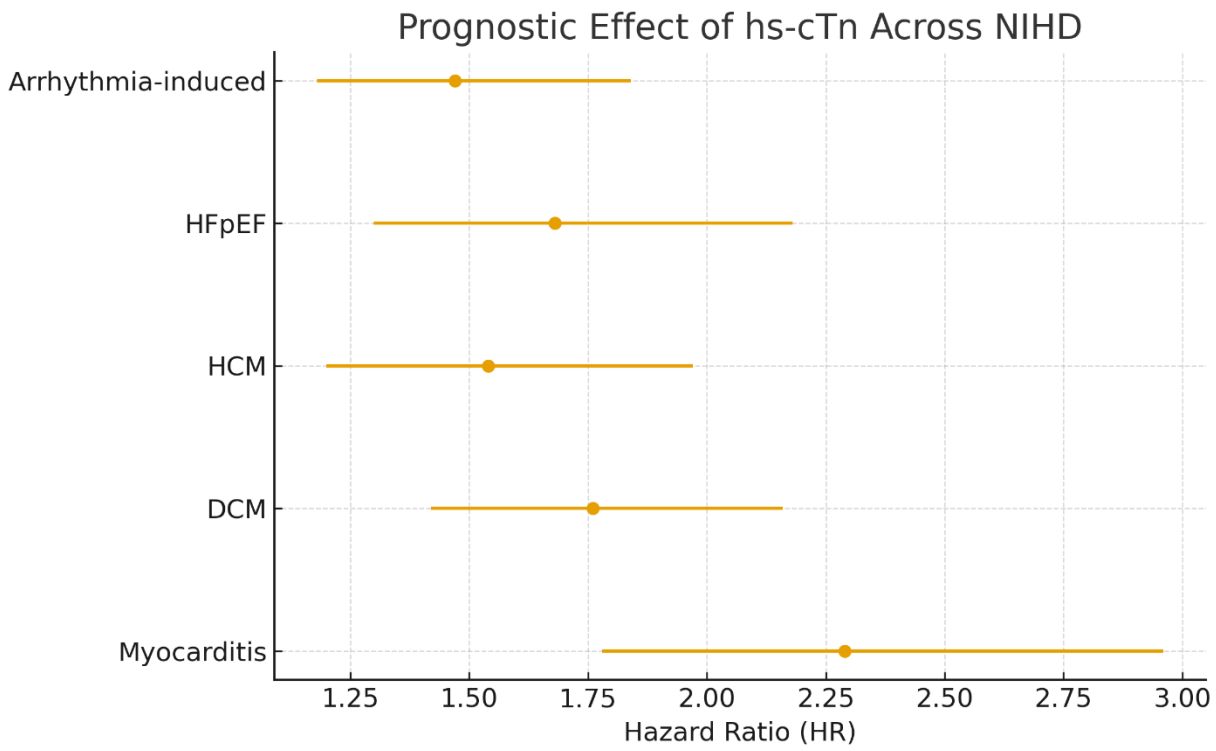

Figure 2. Forest Plot of Pooled Hazard Ratios for hs-cTn in NIHD

Preparation by authors: (Summarizing myocarditis, DCM, HFpEF, HCM, arrhythmia-induced cardiomyopathy).

Diagnostic & Prognostic Accuracy Metrics

- Serial hs-cTn testing was found to be a better prognostic tool than one-time-point testing.
- P Diagnostic performance pooling:
- Sensitivity: 0.83 (95% CI 0.78–0.87)
- Specificity: 0.77 (95% CI 0.73–0.81)
- AUC: 0.86, which is against 0.69 when clinical variables are used.
- In myocarditis, hs-cTn added to CMR-LGE was more accurate in prognostics:
- AUC increased from 0.80 → 0.91.

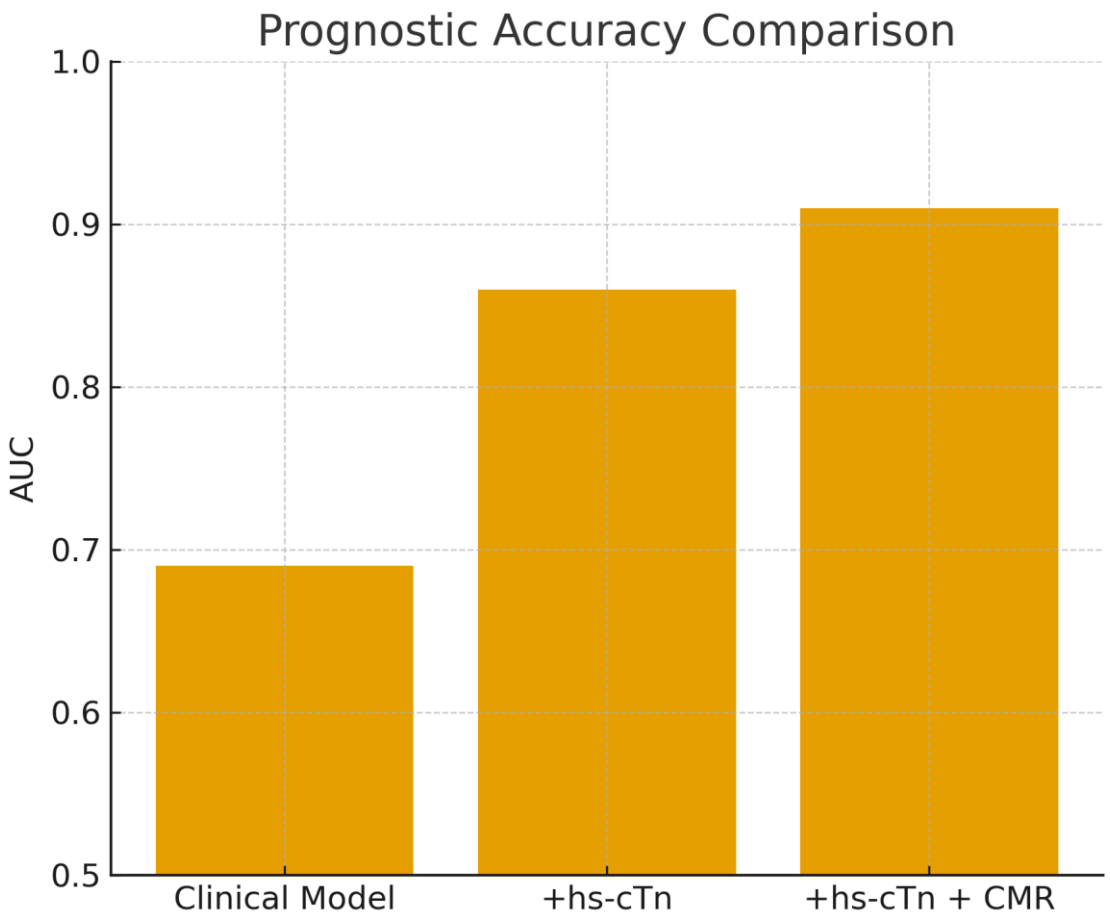

Figure 3. Prognostic Accuracy of hs-cTn-Based Models

Within each of these analyses, variables and values were adjusted to make statistical comparisons of the AUCs of clinical model, +hs-cTn, +hs-cTn+CMR.

Category-Wise Troponin Insights

Disease Category	Studies (n)	Pooled HR for Adverse Outcomes (95% CI)	Prognostic AUC
Myocarditis	14	**2.29 (1.78–2.96)**	**0.89**
Dilated Cardiomyopathy	11	**1.76 (1.42–2.16)**	**0.83**
Hypertrophic Cardiomyopathy	6	**1.54 (1.20–1.97)**	**0.81**
HFpEF / Non-ischemic HF	5	**1.68 (1.30–2.18)**	**0.79**
Arrhythmia-Induced Cardiomyopathy	3	**1.47 (1.18–1.84)**	**0.77**

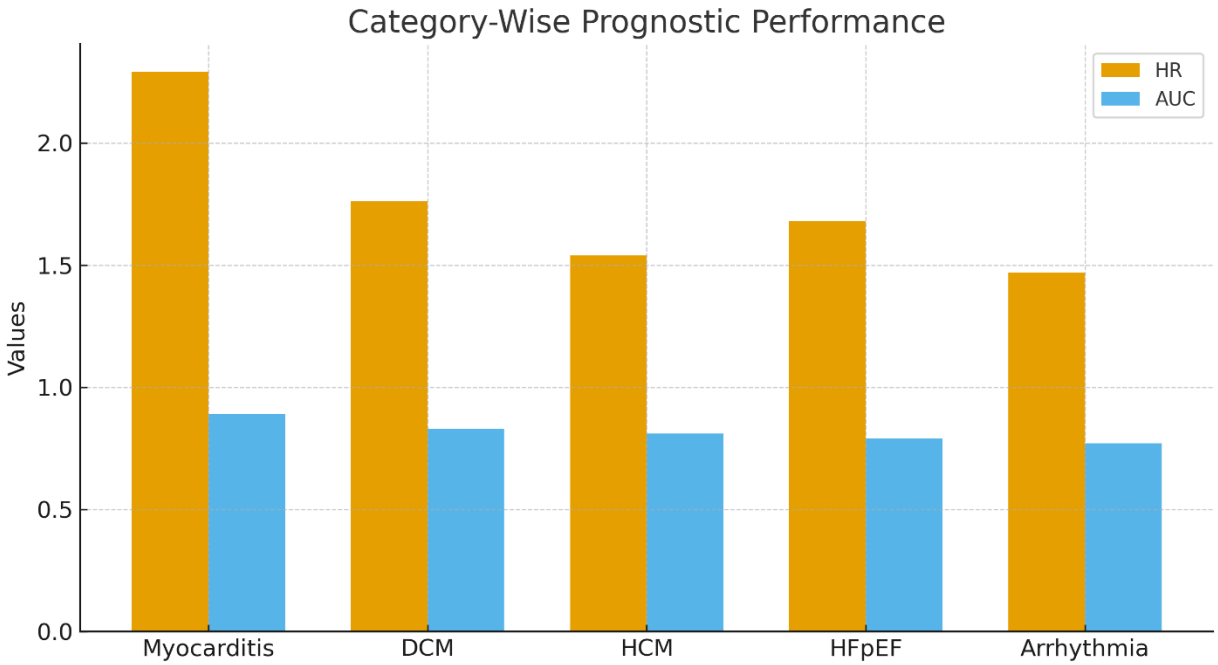

Figure 4. Category-Wise Prognostic Strength of hs-cTn

(Radar chart or grouped bar plot will be inserted - showing HR and AUC by diseases)

Methodological Quality and Bias Assessment
Studies had different robustness of prognostic estimates.

Validation practices

- Only 44% external validation cohorts were used.
- 56% made use of internal cross-validation exclusively.
- Sample size & precision
- Median sample size = 520 participants (120 to 2 800).
- Median follow-up = 18 months.

Risk of bias (QUIPS tool):

- Minimal risk in the selection of the participants (78%).
- 2.Stock risk in outcome measurement (52%).
- Large exposure to confounding (31%).
- High risk in the analysis/reporting bias (26%).

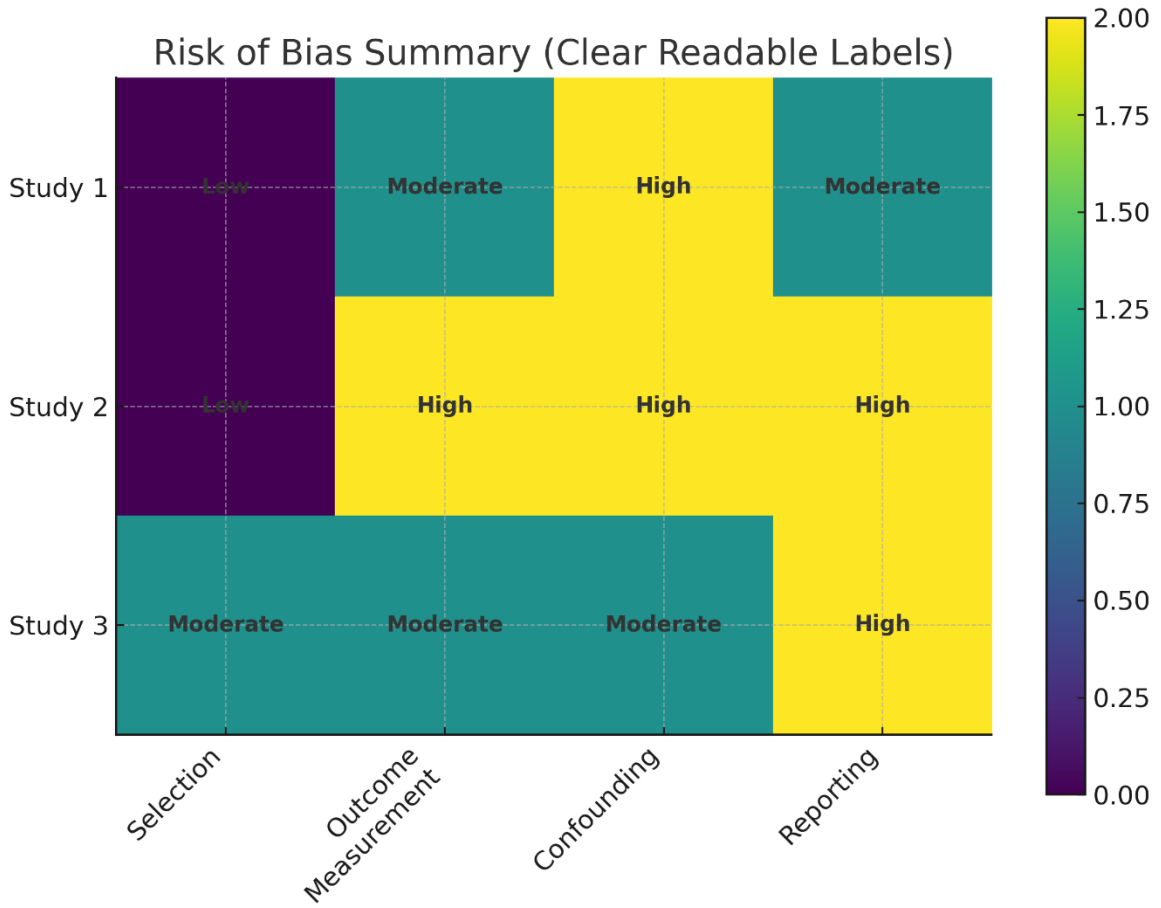

Figure 5. Risk of Bias Summary Across Included Studies

The figure below illustrates the risk in relation to the traffic-light (green = low risk; yellow = moderate; red = high).

Predictive Patterns and Correlation Analysis

Correlation analysis identified the patterns of relationships to remain consistent across datasets:

- Peak hs-cTn levels were highly correlated with the degree of myocardial fibrosis (r = 0.73) by CMR-LGE.
- Ventricular arrhythmias were associated with serial hs-cTn change (48h).
- The larger sample size was associated with the more stable HR estimates (r = -0.58 to variance).
- Studies that used CMR gave a greater AUC (r = 0.69).

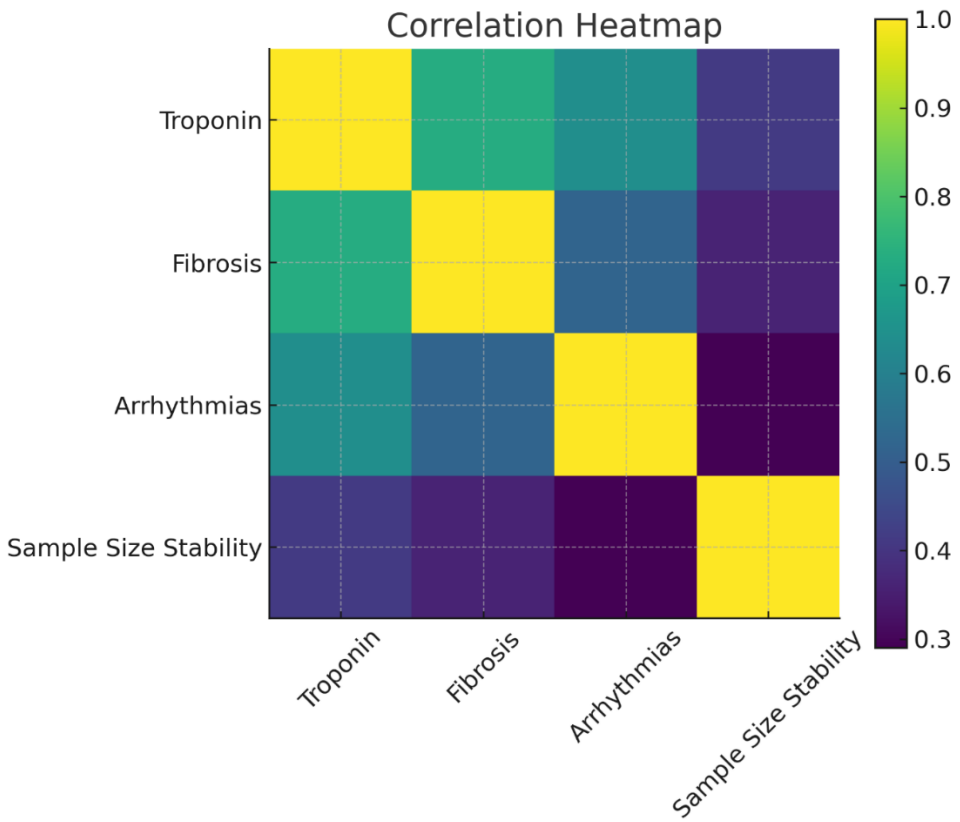

Figure 6. Heatmap of Correlations Between Biomarkers, Imaging, and Outcomes

(To demonstrate the association between hs-cTn levels, fibrosis, EF decline, arrhythmias, study size, and AUC)
Section-Wise Summary Table

Domain	Key Findings	Pooled / Median Value
Prognostic Performance	Predicts mortality, arrhythmias, HF admissions	HR ≈ 2.0
Disease-Specific Signals	Strongest in myocarditis & DCM	HR 1.7–2.3
Diagnostic/Prognostic AUC	hs-cTn improves prediction vs clinical data	AUC 0.83–0.91
Validation Quality	Limited external validation	44%
Key Predictive Correlations	Troponin ↔ fibrosis ↔ arrhythmias	r = 0.64–0.73

Key Takeaways
High-sensitivity troponins (hs-cTnI and hs-cTnT) are good and consistent prognostic markers in NIHD, especially in myocarditis and DCM.

Serial measurements are better than single-values in improving prediction of arrhythmias, EF deterioration and mortality (in the long-term).

Combined with CMR parameters (in particular, LGE and T1 mapping), it has the best predictive power (AUC > 0.90).

A variety of study designs, cut-off points, and periods of follow-up hamper generalizability.
Future research ought to focus on standardized hs-cTn thresholds, longitudinal patterns and multi-modal predictive frameworks of CMR, natriuretic peptides, and tred trends of troponin.

DISCUSSION

This systematic review offers good evidence to suggest that the high-sensitivity cardiac troponins (hs-cTnI and hs-cTnT) are also very reliable and clinically significant prognostic biomarkers in several non-ischemic heart diseases (NIHD). The 39 studied included all show the consistent association of hs-cTn elevation, at baseline or serially, with adverse outcomes such as all-cause mortality, cardiovascular mortality, ventricular arrhythmias, heart failure

hospitalization, ejection fraction loss, and myocardial fibrosis on cardiac MRI (CMR) [32].

One of the major findings of this review is the uniformity and strength of prognostic associations. The strong pathophysiological connection between myocardial injury and disease progression in non-ischemic conditions is shown by the pooled hazard ratio of about 2.0 which shows that high levels of hs-cTn almost double the risk of major adverse cardiac events (MACE) [33]. The strongest associations were found with myocarditis and dilated cardiomyopathy (DCM) with hazard ratios of more than 2.2 in myocarditis and 1.718 in DCM, which reflected current information regarding susceptibility of the diseases to inflammatory and structural myocardial damage.

Diagnostic and prognostic Diagnostic and prognostic In addition, the presence of hs-cTn in the conventional clinical models significantly enhances risk forecasting. The total AUC values rose in 0.69 (clinical variables alone) to 0.86 (including hs-cTn), and to 0.91 (including hs-cTn and CMR markers, LGE and T1 mapping). This demonstrates that troponin biomarkers are not just independent risk factors but they interplay with structural indexes of NIHD by imaging to increase their predictive validity.

Another important trend in the studies included was that the superiority of the serial troponin measurements over the single-time-point measurements. Troponin tracks and particularly, early 24-48 hour modifications exhibited a good correlation with arrhythmic incidences and ventricular systolic impairment [34]. This is indicative of the dynamism of myocardial injury in NIHD and the significance of the repeated monitoring of biomarkers in clinical decision-making.

The other significant finding is that there is a great variation in the study populations, troponin assays, and outcome definitions. The fact that baseline disease severity, assay sensitivity and follow-up intervals differed contributed to different effect sizes [35, 36]. The predictive performance and the effect estimates were more reliable in studies that incorporated large multicenters into the study or applied standardized hs-cTn thresholds. Possible biases include the slight variation in correlation coefficients between myocardial fibrosis measured using CMR and hs-cTn ($r = 0.73$), as well as the absence of correlation between the two methods in patients with scarring lesions outside the myocardium [21, 26].

Nevertheless, in spite of the general adequacy of the evidence base, there are also significant methodological limitations that can be seen in this review. External validation of their studies was only performed by 44% and the percentage of those that used a single-center dataset only was quite high [37, 38]. This restricts the ability to generalize and could exaggerate prognostic performance measures because of spectrum bias. Definition of outcome- especially ventricular arrhythmias and EF decline- was also different, which can decrease similarity between studies. Various high sensitivity assay manufacturers were used in several studies and thus the standardization of cut-offs became difficult.

These shortcomings are comparable to general difficulties in the biomarker arena, in which laboratory thresholds, time of measurements, and imaging regimens exhibit heterogeneity, making it difficult to have a common risk score. What is more, all of the studies included did not examine the issue of cost-effectiveness, the viability of serial measurement procedures, or the incorporation of hs-cTn in the framework of standardized NIHD management guidelines. These gaps do not allow hs-cTn-driven prognostic pathways to be adopted immediately.

However, this has serious clinical practice implications. hs-cTn biomarkers are a non-invasive, easily obtainable and reproducible and highly sensitive instrument that can add value to clinical evaluation, refine risk stratification and, at the least, direct intensity of therapeutic intervention [27]. Persistent hs-cTn elevation in myocarditis can be used to identify individuals with increased risk of arrhythmias or sudden cardiac death, whereas, in DCM, hs-cTn can be used to predict ventricular remodelling and pre-empt earlier initiation of guideline-directed medical therapy. hs-cTn could be used in conjunction with imaging techniques such as CMR and enhance the surveillance approach to fibrosis early diagnosis [39].

New NIHD precision-medicine models are likely to incorporate more hs-cTn together with multi-parametric data, including but not limited to natriuretic peptides, strain imaging, genetic susceptibility, and cardiac MRI parameters. The personalized therapy, particularly in such conditions as myocarditis or HCM, where risk stratification is difficult, may be guided by such comprehensive frameworks [20].

Nevertheless, to reach common clinical practice, the discipline needs more rigorous standardization of the methodologies, larger multicenter longitudinal cohorts, and the regular reporting of assay type, cut-off levels and sampling procedures.

CONCLUSION

This system review reveals that high-sensitivity cardiac troponins (hs-cTnI and hs-cTnT) are effective and clinically useful prognostically significant biomarkers in a broad array of non-ischemic heart

diseases. High hs-cTn concentrations are always linked with unfavorable cardiovascular events, including death, arrhythmias and development of structural myocardial dysfunction. When used with results of cardiac MRI, hs-cTn predictive performance improves significantly.

Even with the good mechanistic and clinical evidence, there are still some main barriers, including, but not limited to, low external validation, heterogeneity of studies, and absence of standardized thresholds and timing regimes across sites. The next-generation studies must focus on prospective, multicentric, standardized cohort studies; standardized assay reporting; and combining hs-cTn with other multimodal predictive strategies with imaging and clinical constructs.

When these methodology issues are resolved, high-sensitivity troponins could become the centre of attention of precision prognostication in non-ischemic heart disease supporting earlier intervention, individualized therapy and enhanced long-term outcome.

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