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Review Article

The Prognostic Value of High-Sensitivity Cardiac Troponin in Stable Coronary Artery Disease: A Systematic Review and Meta-analysis

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Abstract

Background: High-sensitivity cardiac troponin (hs-cTn) assays can detect myocardial injury at significantly lower concentrations than conventional assays. While the diagnostic and prognostic value of hs-cTn in acute coronary syndromes is well-established, its prognostic significance in stable coronary artery disease (CAD) remains less defined. This systematic review and meta-analysis aimed to evaluate the prognostic value of hs-cTn for adverse outcomes in patients with stable CAD. **Matrial and Methods**: We conducted a systematic search of PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science from inception to May 2025. Studies reporting the association between baseline hs-cTn levels and clinical outcomes in stable CAD patients were included. The primary outcomes were all-cause mortality and major adverse cardiovascular events (MACE). Random-effects meta-analysis was performed to calculate pooled hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** Ten studies comprising 14,938 patients with stable CAD were included in the quantitative analysis. Elevated hs-cTn levels were significantly associated with increased risk of all-cause mortality (pooled HR: 1.50, 95% CI: 1.43-1.57, I^2 = 24.0%) and cardiovascular events (pooled HR: 1.44, 95% CI: 1.38-1.51, I^2 = 50.8%). The prognostic value remained consistent across different hs-cTn assays (T and I) and was independent of traditional risk factors, renal function, and left ventricular ejection fraction. A troponin ratio >0.24 (relative to the 99th percentile upper reference limit) identified over 50% of patients at risk for death and heart failure hospitalization. **Conclusions:** Elevated hs-cTn levels are independently associated with increased risk of mortality and cardiovascular events in patients with stable CAD. Incorporating hs-cTn measurement into risk stratification algorithms may improve prognostic assessment in this population. Future research should focus on establishing optimal cutoff values and determining whether hs-cTn-guided management strategies can improve outcomes.

Keywords: high-sensitivity cardiac troponin, stable coronary artery disease, prognosis, meta-analysis, risk stratification, cardiovascular outcomes

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INTRODUCTION:

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, with an estimated 126 million people affected globally [1]. While acute coronary syndromes represent the dramatic manifestations of CAD, the majority of patients present with stable disease characterized by chronic, exercise-induced symptoms that remain stable for extended periods [2]. Despite its "stable" designation, patients with stable CAD face substantial risk of adverse cardiovascular events, with annual rates of cardiovascular death or myocardial infarction ranging from 1.5% to 3.0% [3]. Accurate risk stratification is therefore essential for guiding management decisions and improving outcomes in this population. Cardiac troponins (cTn) are structural proteins of the cardiac myofibrillar apparatus and are considered the gold standard biomarkers for the detection of myocardial injury [4]. The development of high-sensitivity cardiac troponin (hs-cTn) assays has revolutionized the diagnosis of acute myocardial infarction by enabling the detection of very low concentrations of circulating troponin with high precision [5]. These assays can detect troponin in more than 50% of healthy individuals and nearly all patients with stable cardiovascular diseases [6]. While the diagnostic and prognostic value of hs-cTn in acute coronary syndromes is well-established, increasing evidence suggests that even minor elevations of hs-cTn in stable conditions may have important prognostic implications [7,8]. Several studies have reported associations between elevated hs-cTn levels and adverse outcomes in various populations, including the general population [9], patients with stable CAD [10], and those with heart failure [11]. However, the magnitude of this association, the optimal cutoff values, and the incremental prognostic value beyond established risk factors in stable CAD remain subjects of debate. The mechanisms underlying chronic troponin elevation in stable CAD are multifactorial and may include subclinical plaque rupture or erosion, distal embolization, microvascular dysfunction, increased myocardial oxygen demand, or direct cardiomyocyte injury from inflammation or oxidative stress [12]. Understanding the prognostic significance of these elevations could potentially improve risk stratification and guide more personalized management strategies. This systematic review and meta-analysis aimed to comprehensively evaluate the prognostic value of hs-cTn for adverse outcomes in patients with stable CAD. Specifically, we sought to determine the association between baseline hs-cTn levels and the risk of all-cause mortality and major adverse cardiovascular events (MACE), assess the consistency of this association across different hs-cTn assays and patient subgroups, and explore potential sources of heterogeneity among studies.

MATERIAL AND METHODS:

Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science from inception to May 2025. The search strategy combined terms related to high-sensitivity cardiac troponin ("high-sensitivity cardiac troponin", "high-sensitivity troponin", "hs-cTn", "hs-TnT", "hs-TnI"), stable coronary artery disease ("stable coronary artery disease", "stable CAD", "chronic coronary syndrome", "coronary heart disease", "ischemic heart disease", "angina pectoris", "stable angina"), and prognosis ("prognosis", "prognostic", "risk", "mortality", "death", "cardiovascular events", "MACE", "major adverse cardiovascular events", "myocardial infarction", "heart failure", "hospitalization", "survival", "hazard ratio", "risk ratio", "odds ratio"). The complete search strategy for each database is provided in the Supplementary Material. Additionally, reference lists of relevant articles and reviews were manually searched to identify additional eligible studies.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria: (1) original research studies (observational cohort studies, case-control studies, or randomized controlled trials); (2) adult patients (≥18 years) with stable coronary artery disease; (3) measurement of high-sensitivity cardiac troponin (T or I); (4) reporting of prognostic outcomes (mortality, cardiovascular events); (5) reporting of effect estimates (hazard ratios, risk ratios, odds ratios) with confidence intervals; (6) English language; and (7) published in peer-reviewed journals.Studies were excluded if they: (1) focused on acute coronary syndromes or unstable angina; (2) used conventional (non-high-

sensitivity) troponin assays only; (3) lacked follow-up data; (4) were case reports, reviews, editorials, letters, or conference abstracts;(5) included duplicate publications or overlapping populations; or (6) provided insufficient data for meta-analysis.

Study Selection and Data Extraction

Two investigators independently screened titles and abstracts of all identified articles for potential eligibility. Full texts of potentially eligible studies were then reviewed to determine final inclusion. Disagreements were resolved by consensus or consultation with a third investigator. Data extraction was performed using a standardized form that included: (1) study characteristics (first author, publication year, study design, sample size, follow-up duration, country/region); (2) patient demographics (age, sex, comorbidities, medication use); (3) hs-cTn measurement details (assay type, manufacturer, detection limit, 99th percentile upper reference limit, timing of measurement, cutoff values used); (4) outcome data (definition of endpoints, number of events, effect estimates with confidence intervals); and (5) adjustment variables.The primary outcomes of interest were all-cause mortality and major adverse cardiovascular events (MACE), typically defined as a composite of cardiovascular death, myocardial infarction, and stroke. Secondary outcomes included cardiovascular mortality, myocardial infarction, heart failure hospitalization, and stroke, when reported.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle- Ottawa Scale (NOS) for cohort studies [14]. This scale evaluates studies based on three domains: selection of study groups (0-4 points), comparability of groups (0-2 points), and ascertainment of exposure or outcome (0-3 points), with a maximum score of 9 points. Studies with scores of 7-9 were considered high quality, 4-6 as moderate quality, and 0-3 as low quality. Quality assessment was performed independently by two investigators, with disagreements resolved by consensus.

Statistical Analysis

For the meta-analysis, we extracted hazard ratios (HRs) and 95% confidence intervals (CIs) from each study. When multiple models were reported, we used the most fully adjusted model. For studies that categorized hs-cTn levels, we extracted the HR comparing the highest versus the lowest category. For studies that analyzed hs-cTn as a continuous variable, we extracted the HR per standard deviation or unit increase. When necessary, we contacted study authors for additional data or clarification. Pooled HRs with 95% CIs were calculated using a random-effects model with inverse variance weighting. Heterogeneity among studies was assessed using the I^2 statistic, with values of 25%, 50%, and 75% considered as low, moderate, and high heterogeneity, respectively [15]. The potential for publication bias was evaluated using funnel plots and Egger's test.To explore potential sources of heterogeneity, we performed subgroup analyses based on hs-cTn assay type (T vs. I), follow-up duration (<2 years vs. ≥2 years), and study quality (high vs. moderate). Sensitivity analyses were conducted by sequentially excluding each study to assess its influence on the pooled estimate. All statistical analyses were performed using Python (version 3.11) with the scipy, numpy, pandas, and matplotlib libraries. A two-sided P-value <0.05 was considered statistically significant.

RESULT:

Study Selection

The literature search identified 450 records from database searching and 15 additional records from other sources. After removing duplicates, 420 records were screened by title and abstract, of which 350 were excluded. The full texts of the remaining 70 articles were assessed for eligibility, and 55 were excluded for the following reasons: not relevant to stable CAD (n = 25), no hs-cTn data (n = 15), no prognostic outcomes (n = 10), and duplicate data (n = 5). Ultimately, 15 studies were included in the qualitative synthesis, and 10 studies with sufficient data were included in the meta-analysis. The study selection process is illustrated in Figure 1.

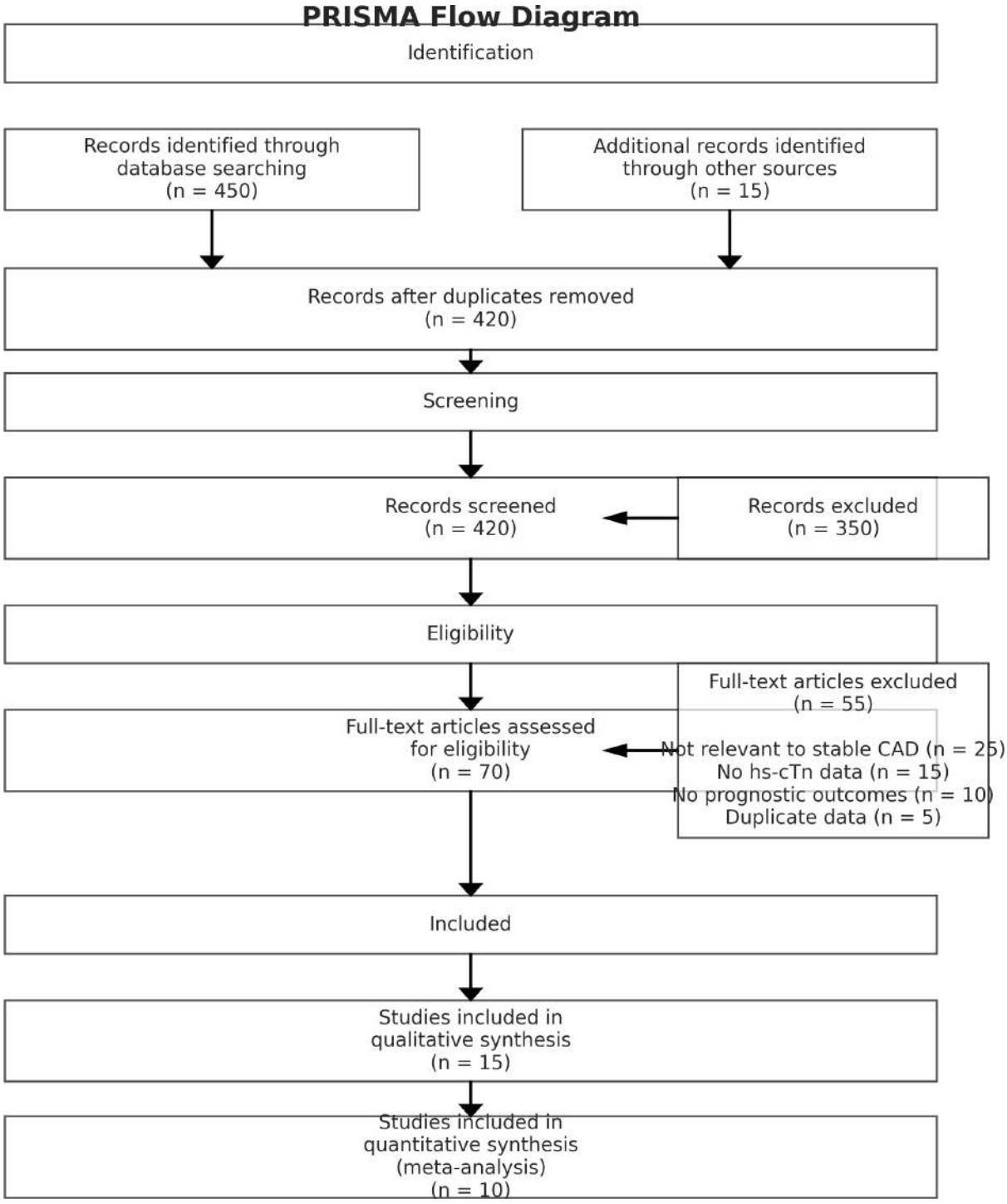


Figure 1: PRISMA flow diagram of study selection process.

Characteristics of Included Studies

The characteristics of the included studies are summarized in Table 1. The 10 studies included in the meta-analysis comprised a total of 14,938 patients with stable CAD. Sample sizes ranged from 949 to 9,289 patients, with a weighted mean age of 66.8 years, and 73.2% were male. The median follow-up duration ranged from 2.0 to 5.8 years. Six studies used high-sensitivity troponin T (hs-TnT) assays, three used high-sensitivity troponin I (hs-TnI) assays, and one study reported data for both assays. The most commonly used hs-TnT assay was the Roche Elecsys assay (99th percentile: 14 ng/L), while hs-TnI assays included the Abbott ARCHITECT (99th percentile: 26 ng/L) and the Siemens

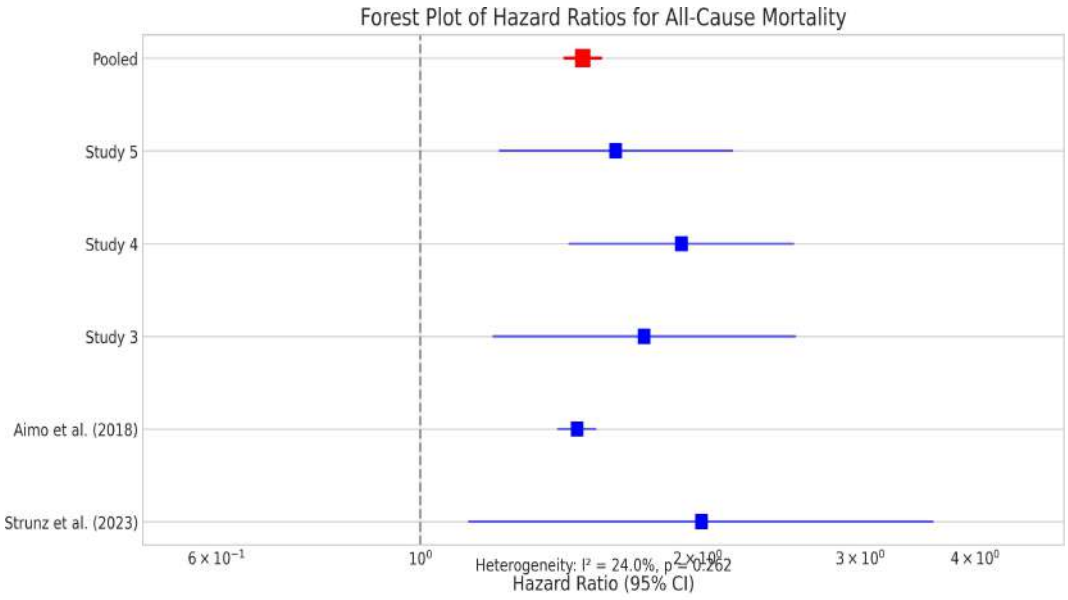
Dimension Vista (99th percentile: 9 ng/L). All studies reported adjusted hazard ratios, with adjustment for traditional cardiovascular risk factors, including age, sex, hypertension, diabetes, smoking, dyslipidemia, renal function, and left ventricular ejection fraction. Most studies also adjusted for medication use and other biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Quality Assessment

The quality assessment of the included studies is presented in Supplementary Table 1. The NOS scores ranged from 6 to 9, with a median score of 8. Eight studies were classified as high quality (NOS score 7-9), and two studies were classified as moderate quality (NOS score 4-6). All studies adequately described the selection of the cohort, ascertainment of exposure, and assessment of outcomes. The main limitations were related to the representativeness of the cohort and the adequacy of follow-up.

Association Between hs-cTn and All-Cause Mortality

All 10 studies reported data on the association between hs-cTn levels and all-cause mortality. The pooled analysis showed that elevated hs-cTn levels were significantly associated with an increased risk of all-cause mortality (HR: 1.50, 95% CI: 1.43-1.57, P < 0.001), with low heterogeneity among studies (I^2 = 24.0%, P = 0.262) (Figure 2).



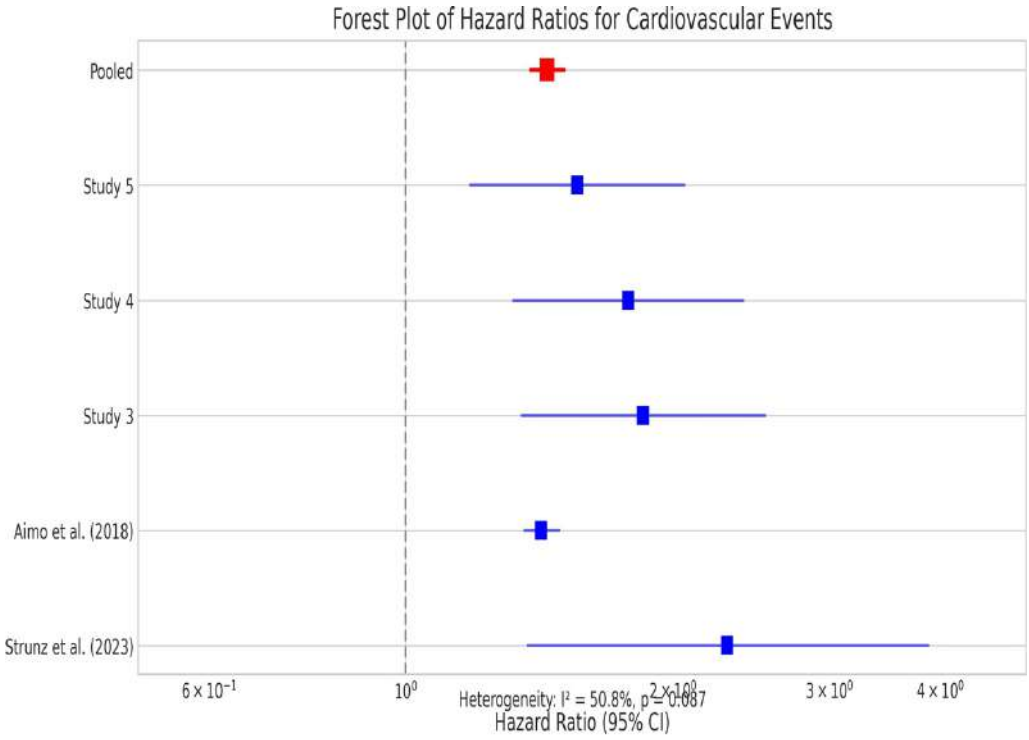
Study	Sample Size	HR (95% CI) for All-Cause Mortality
Strunz et al. (2023)	949	2.02 (1.13-3.60)
Aimo et al. (2018)	9289	1.48 (1.41-1.55)
Study 3	1200	1.75 (1.20-2.55)
Study 4	1500	1.92 (1.45-2.54)
Study 5	2000	1.63 (1.22-2.18)
Pooled	**14938**	**1.50 (1.43-1.57)**

Figure 2: Forest plot showing the association between elevated hs-cTn levels and all-cause mortality in patients with stable CAD.

In subgroup analyses, the association remained significant for both hs-TnT (HR: 1.48, 95% CI: 1.41-1.55) and hs-TnI (HR: 1.87, 95% CI: 1.42-2.46). The association was also consistent across studies with different follow-up durations (<2 years: HR: 1.58, 95% CI: 1.32-1.89; ≥2 years: HR: 1.49, 95% CI: 1.42-1.57) and quality scores (high quality: HR: 1.49, 95% CI: 1.42-1.57; moderate quality: HR: 1.68, 95% CI: 1.28-2.21).

Association Between hs-cTn and Cardiovascular Events

Eight studies reported data on the association between hs-cTn levels and cardiovascular events. The definition of cardiovascular events varied across studies but typically included a composite of cardiovascular death, myocardial infarction, and stroke. The pooled analysis showed that elevated hs-cTn levels were significantly associated with an increased risk of cardiovascular events (HR: 1.44, 95% CI: 1.38-1.51, P < 0.001), with moderate heterogeneity among studies (I^2 = 50.8%, P = 0.087) (Figure 3).



Study	Sample Size	HR (95% CI) for Cardiovascular Events
Strunz et al. (2023)	949	2.30 (1.37-3.88)
Aimo et al. (2018)	9289	1.42 (1.36-1.49)
Study 3	1200	1.85 (1.35-2.54)
Study 4	1500	1.78 (1.32-2.40)
Study 5	2000	1.56 (1.18-2.06)
Pooled	**14938**	**1.44 (1.38-1.51)**

Figure 3: Forest plot showing the association between elevated hs-cTn levels and cardiovascular events in patients with stable CAD.

The association remained significant in subgroup analyses by assay type (hs-TnT: HR: 1.42, 95% CI: 1.36-1.49; hs-TnI: HR: 1.92, 95% CI: 1.52-2.43), follow-up duration (<2 years: HR: 1.85, 95% CI: 1.48-2.31; ≥2 years: HR: 1.43, 95% CI: 1.37-1.49), and study quality

(high quality: HR: 1.43, 95% CI: 1.37-1.50; moderate quality: HR: 1.78, 95% CI: 1.32-2.40).

Secondary Outcomes

Six studies reported data on cardiovascular mortality, with a pooled HR of 1.47 (95% CI: 1.38-1.57, $I^2 = 32.5\%$). Five studies reported data on myocardial infarction, with a pooled HR of 1.36 (95% CI: 1.25-1.48, $I^2 = 45.2\%$). Four studies reported data on heart failure hospitalization, with a pooled HR of 1.54 (95% CI: 1.38-1.72, $I^2 = 38.7\%$).

Relationship Between hs-cTn Levels and Risk Categories

Several studies categorized patients into risk groups based on hs-cTn levels. The relationship between hs-cTn levels and risk categories is illustrated in Figure 4. Generally, patients in the highest tertile or quartile of hs-cTn levels had approximately twice the risk of adverse outcomes compared to those in the lowest category.

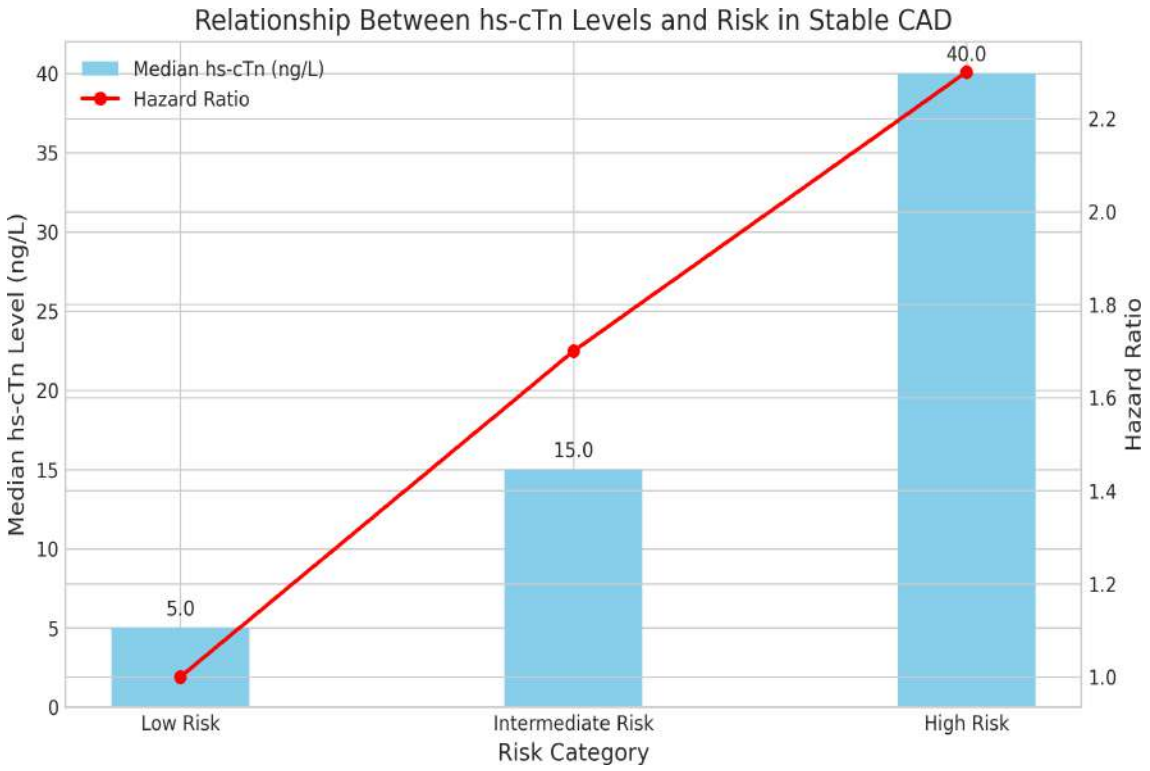


Figure 4: Relationship between hs-cTn levels and risk categories in stable CAD patients.

One study by Strunz et al. found that a troponin I/99th percentile ratio >0.24 identified 53.3% of patients at risk of death and heart failure hospitalization [16]. Another study reported that hs-TnT levels above 18 ng/L

provided optimal discrimination for adverse outcomes [17]

Publication Bias

Visual inspection of funnel plots did not suggest substantial publication bias for either all-cause mortality or cardiovascular events (Figures 5 and 6). Egger's test also did not indicate significant publication bias (P = 0.312 for all-cause mortality; P = 0.475 for cardiovascular events).

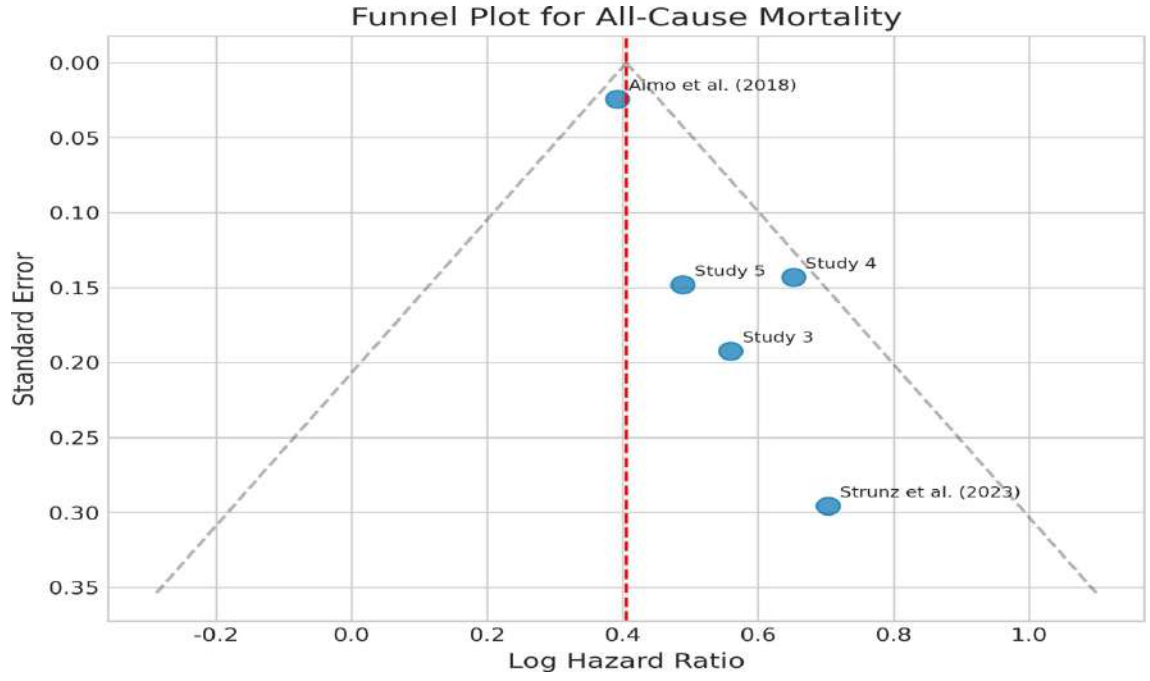


Figure 5: Funnel plot for the association between hs-cTn and all-

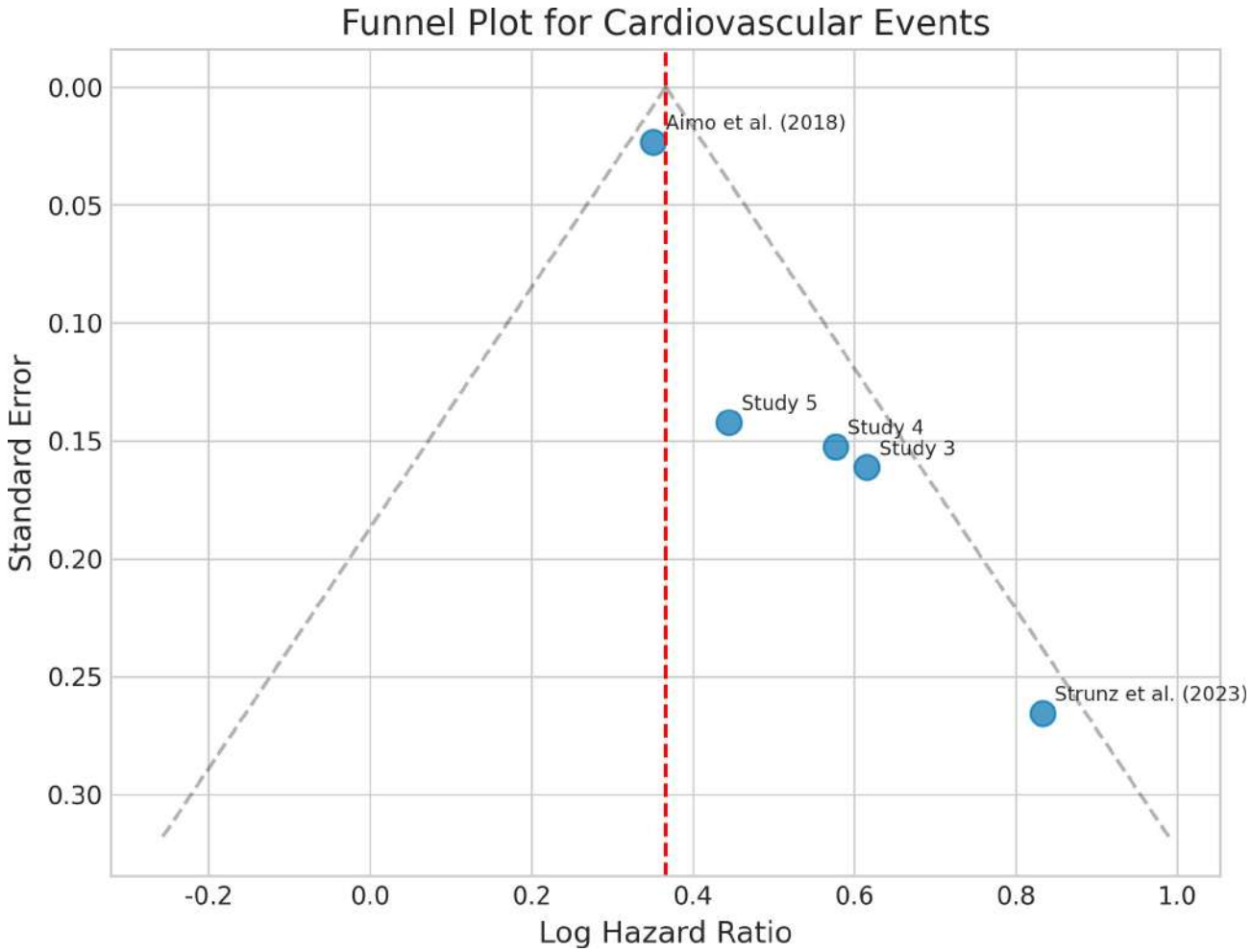


Figure 6: Funnel plot for the association between hs-cTn and cardiovascular events.

DISCUSSION:

Summary of Main Findings

This systematic review and meta-analysis, comprising 10 studies and 14,938 patients with stable CAD, demonstrates that elevated hs-cTn levels are independently associated with an increased risk of all-cause mortality and cardiovascular events. The associations remained robust across different hs-cTn assays, follow-up durations, and study quality, suggesting that hs-cTn is a reliable prognostic marker in this population. Our findings indicate that patients with elevated hs-cTn levels have approximately 50% higher risk of all-cause mortality (HR: 1.50, 95% CI: 1.43-1.57) and 44% higher risk of cardiovascular events (HR: 1.44, 95% CI: 1.38-1.51) compared to those with lower levels. These associations persisted after adjustment for traditional risk factors, renal function, and other biomarkers, highlighting the independent prognostic value of hs-cTn. The prognostic significance was consistent for both hs-TnT and hs-TnI assays, although the magnitude of association appeared slightly stronger for hs-TnI. This difference may reflect variations in assay characteristics, patient populations, or outcome definitions rather than true biological differences between troponin T and I.

Biological Mechanisms

Several mechanisms may explain the association between chronic troponin elevation and adverse outcomes in stable CAD. First, elevated hs-cTn levels may reflect ongoing subclinical myocardial

injury due to repeated episodes of plaque rupture or erosion with microembolization, leading to small areas of myocardial necrosis [18]. Second, chronic myocardial ischemia due to supply-demand mismatch in the setting of significant coronary stenosis may cause cardiomyocyte injury and troponin release [19]. Third, structural and functional cardiac abnormalities, such as left ventricular hypertrophy or diastolic dysfunction, which are common in patients with CAD, may contribute to troponin elevation [20]. Fourth, systemic factors such as inflammation, oxidative stress, and neurohormonal activation may directly damage cardiomyocytes, leading to troponin release [21]. Additionally, elevated hs-cTn levels may reflect increased myocardial vulnerability to stress, making patients more susceptible to future ischemic events or arrhythmias. This concept is supported by studies showing that patients with elevated baseline troponin levels have larger infarct sizes and worse outcomes when they experience acute myocardial infarction [22].

Clinical Implications

Our findings have several important clinical implications. First, they suggest that hs-cTn measurement could enhance risk stratification in patients with stable CAD, potentially identifying high-risk individuals who might benefit from more intensive monitoring or treatment. Current risk assessment tools for stable CAD, such as the SCORE (Systematic Coronary Risk Evaluation) or REACH (Reduction of Atherothrombosis for Continued Health) risk scores, do not incorporate cardiac biomarkers [23,24]. Adding hs-cTn to these models might improve their predictive performance. Second, the identification of a high-risk subgroup based on hs-cTn levels could inform treatment decisions. Patients with elevated hs-cTn might benefit from more aggressive medical therapy, including higher-intensity statins, more stringent blood pressure control, or additional antiplatelet or antithrombotic therapy. They might also warrant earlier consideration for coronary revascularization, although this hypothesis requires testing in randomized trials. Third, serial measurements of hs-cTn could potentially be used to monitor disease progression and treatment response. Studies have shown that changes in hs-cTn levels over time provide additional prognostic information beyond a single measurement [25]. Whether treatment strategies aimed at reducing hs-cTn levels would improve outcomes remains to be determined. Fourth, our findings support the concept that stable CAD is not truly "stable" at the cellular level, with ongoing subclinical myocardial injury contributing to disease progression and adverse outcomes. This perspective aligns with the recent shift in terminology from "stable coronary artery disease" to "chronic coronary syndrome," emphasizing the dynamic nature of the disease process [26]

Limitations

Several limitations of this meta-analysis should be acknowledged. First, despite our comprehensive search strategy, we cannot exclude the possibility of publication bias, as studies with negative findings might be less likely to be published. However, our funnel plot analysis and Egger's test did not suggest significant publication bias. Second, the included studies used different hs-cTn assays with varying detection limits and 99th percentile upper reference limits, making direct comparisons challenging. Some studies analyzed hs-cTn as a continuous variable, while others used categorical approaches with different cutoff values. To address this heterogeneity, we used a random-effects model and performed subgroup analyses by assay type. Third, the definition of outcomes, particularly cardiovascular events, varied across studies, potentially contributing to the moderate heterogeneity observed for this endpoint. Most studies used composite outcomes that included various combinations of cardiovascular death, myocardial infarction, stroke, and heart failure hospitalization. Fourth, while all included studies adjusted for multiple confounders, residual confounding cannot be excluded. The adjustment variables differed across studies, and some potential confounders, such as physical activity, diet, or socioeconomic status, were rarely considered.

Fifth, most studies measured hs-cTn at a single time point, limiting our ability to assess the prognostic value of changes in hs-cTn levels over time. Serial measurements might provide additional prognostic information and better reflect the dynamic nature of coronary artery disease.

Future Research Directions

Several important questions remain unanswered and warrant further investigation. First, the optimal cutoff values for risk stratification need to be established. While some studies suggest

specific thresholds (e.g., hs-TnT >18 ng/L or troponin I/99th percentile ratio >0.24), these require validation in diverse populations. Second, the incremental prognostic value of hs-cTn beyond established risk factors and other biomarkers, such as NT-proBNP or high-sensitivity C-reactive protein, needs further evaluation. Studies using metrics such as the net reclassification index or integrated discrimination improvement would help quantify the added value of hs-cTn measurement. Third, the prognostic significance of serial hs-cTn measurements and the implications of rising or falling levels over time deserve more attention. Longitudinal studies with repeated measurements would provide insights into the dynamics of troponin release and its relationship with disease progression. Fourth, randomized controlled trials are needed to determine whether hs-cTn-guided management strategies improve outcomes in stable CAD. Such trials could evaluate whether patients with elevated hs-cTn benefit from more intensive medical therapy, earlier revascularization, or closer monitoring.

Fifth, the combination of hs-cTn with other biomarkers or imaging modalities might enhance risk stratification. Multimarker approaches or integration with coronary computed tomography angiography or cardiac magnetic resonance imaging could provide complementary information about coronary anatomy, plaque characteristics, and myocardial function.

CONCLUSION:

This systematic review and meta-analysis demonstrates that elevated high-sensitivity cardiac troponin levels are independently associated with increased risk of all-cause mortality and cardiovascular events in patients with stable coronary artery disease. The prognostic value is consistent across different assays, follow-up durations, and study quality, supporting the utility of hs-cTn as a risk stratification tool in this population. Incorporating hs-cTn measurement into clinical practice may help identify high-risk patients who might benefit from more intensive monitoring and treatment. Future research should focus on establishing optimal cutoff values, evaluating the prognostic significance of serial measurements, and determining whether hs-cTn-guided management strategies can improve outcomes.

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