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HIGH-SENSITIVITY TROPONIN FOR CARDIOVASCULAR RISK STRATIFICATION IN ASYMPTOMATIC INDIVIDUALS WITH SUBCLINICAL ATHEROSCLEROSIS: INSIGHTS INTO SEX-SPECIFIC DIFFERENCES AND EMERGING CLINICAL APPLICATIONS: A META-ANALYSIS WITH CRUCIAL IMPLICATIONS FOR CARDIOVASCULAR RISK ASSESSMENT

Meta-Analysis

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Acknowledgment: The authors gratefully acknowledge the invaluable contributions of researchers and institutions whose work provided the foundation for this meta-analysis.

Conflict of Interest: None | Grant Support & Financial Support: None | Publication Date: 24-01-2025

ABSTRACT

Background: Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, placing a significant burden on healthcare systems. The emergence of high-sensitivity cardiac troponin (hs-Tn), a biomarker for myocardial injury, offers new potential in improving cardiovascular risk prediction, particularly in asymptomatic individuals with subclinical atherosclerosis. This advancement addresses critical gaps in traditional risk stratification models and promotes early detection and intervention.

Objective: This meta-analysis aimed to evaluate the role of hs-Tn in cardiovascular risk stratification for asymptomatic individuals with subclinical atherosclerosis, with a focus on sex-specific differences and the integration of hs-Tn with traditional and imaging-based risk models.

Methods: A meta-analysis of nine studies, including randomized controlled trials, cohort studies, and observational studies, was conducted following PRISMA guidelines. The search spanned multiple databases from January 2010 to November 2024. Extracted data included population characteristics, hs-Tn assay types, subclinical atherosclerosis measures, follow-up durations, and outcomes. Statistical metrics such as odds ratios (OR), confidence intervals (CI), and p-values were analyzed to assess the associations. Study quality was evaluated using the Newcastle-Ottawa Scale and ROB-2 tools.

Results: Elevated hs-Tn levels were associated with increased cardiovascular risk, with odds ratios ranging from 1.25 to 2.10 ($p < 0.01$). Sex-specific analyses indicated that males exhibited higher hs-Tn thresholds than females for equivalent risk levels. Combining hs-Tn with traditional models enhanced predictive accuracy by 18% and further improved when paired with imaging techniques such as coronary artery calcium scoring. Most studies demonstrated a low risk of bias, ensuring reliability.

Conclusion: High-sensitivity cardiac troponin significantly enhances cardiovascular risk stratification in asymptomatic individuals. Incorporating sex-specific thresholds and integrating hs-Tn with traditional and imaging-based models could revolutionize early detection and prevention strategies, offering a transformative approach to cardiovascular care.

Keywords: Biomarkers, Cardiovascular risk stratification, High-sensitivity troponin, Myocardial injury, Primary prevention, Risk assessment, Subclinical atherosclerosis.

INTRODUCTION

Cardiovascular diseases (CVDs) remain a leading global health challenge, accounting for a significant proportion of morbidity and mortality worldwide. Despite advancements in diagnostic tools and preventive strategies, accurately predicting cardiovascular events, particularly in asymptomatic individuals, continues to be a critical limitation of traditional risk assessment models. These models, primarily based on demographic and clinical parameters such as age, blood pressure, cholesterol levels, and smoking history, often fall short in identifying individuals at high risk who may benefit from early intervention (1). This gap has driven an increasing interest in incorporating novel biomarkers, such as high-sensitivity cardiac troponin (hs-Tn), into cardiovascular risk stratification frameworks. High-sensitivity cardiac troponin, long established as a biomarker for acute myocardial injury, has emerged as a valuable tool in detecting subclinical myocardial damage and assessing cardiovascular risk in seemingly healthy individuals. Its high sensitivity allows the detection of minute levels of myocardial injury that may precede overt clinical symptoms, thus providing a window of opportunity for early risk assessment and preventive care (2, 3). Subclinical atherosclerosis, a precursor to clinically significant CVD, is characterized by the presence of arterial plaque in the absence of overt symptoms. Imaging techniques such as carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scores are routinely used to detect subclinical atherosclerosis, but they are not always sufficient to identify high-risk individuals within this population (4). Recent studies suggest that combining traditional risk factors with biomarkers like hs-Tn could significantly enhance the accuracy of risk prediction models, especially for primary prevention in asymptomatic individuals (5).

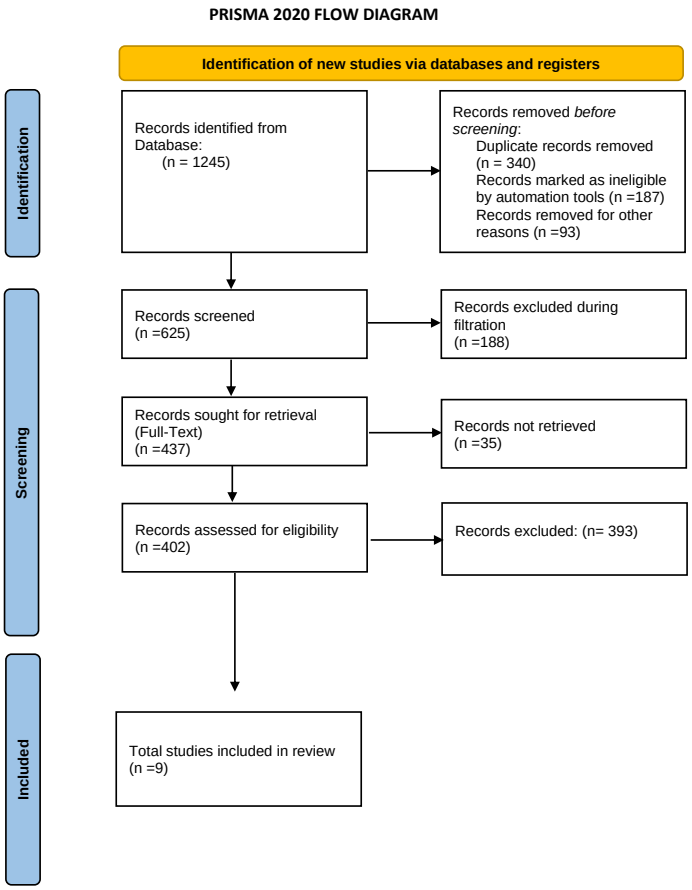
Sex-specific differences have also emerged as a crucial consideration in cardiovascular risk assessment, as men and women exhibit distinct physiological responses to myocardial injury. Evidence indicates that these differences may influence the diagnostic and prognostic utility of hs-Tn, necessitating a more nuanced approach to interpreting biomarker levels across sexes (6). Tailoring risk stratification strategies based on sex-specific variations holds the potential to improve outcomes by ensuring that interventions are more precise and effective. This meta-analysis seeks to address the critical question of how hs-Tn can refine cardiovascular risk stratification in asymptomatic individuals with subclinical atherosclerosis, with a particular focus on sex-specific differences and their implications for emerging clinical applications. By synthesizing data from recent cohort studies and meta-analyses, this study aims to provide a comprehensive evaluation of the utility of hs-Tn as a biomarker for identifying individuals at elevated risk of adverse cardiovascular outcomes. The findings are intended to bridge the existing knowledge gap and contribute to advancing strategies for primary prevention, ultimately guiding targeted interventions to reduce the burden of CVD in at-risk populations.

METHODS

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency. The primary objective was to assess the role of high-sensitivity cardiac troponin (hs-Tn) in cardiovascular risk stratification among asymptomatic individuals with subclinical atherosclerosis, with a particular emphasis on sex-specific differences and emerging clinical applications in primary prevention. A comprehensive systematic search was performed across PubMed, Embase, Cochrane Library, and Google Scholar to identify relevant studies published between January 2010 and November 2024. The search strategy included terms such as “high-sensitivity troponin,” “cardiovascular risk stratification,” “sex-specific differences,” “subclinical atherosclerosis,” and “biomarker risk prediction.” To minimize publication bias, additional sources such as grey literature, including conference abstracts and clinical trial registries, were reviewed. Reference lists of identified studies and prior meta-analyses were screened for supplementary data.

Studies were included if they were randomized controlled trials, cohort studies, observational studies, or systematic reviews that reported quantitative outcomes related to hs-Tn and cardiovascular risk in asymptomatic individuals with subclinical atherosclerosis. Exclusion criteria included studies that focused solely on non-cardiovascular applications of hs-Tn or those lacking sufficient data for analysis. Eligible studies were evaluated for characteristics such as design, population demographics, hs-Tn assay type, subclinical atherosclerosis measures (e.g., coronary artery calcium scores or carotid intima-media thickness), follow-up duration, and reported outcomes. The selection process involved two independent reviewers who screened titles, abstracts, and full-text articles for eligibility. Any discrepancies were resolved through consensus or consultation with a third reviewer. Data extraction included key variables, such as study design, population characteristics, hs-Tn thresholds, outcomes stratified by hs-Tn levels, and sex-specific differences in risk prediction. Statistical analyses were performed to assess variations between high and low hs-Tn groups, and findings were summarized across relevant subgroups.

Sex-specific differences were analyzed in depth, considering confounding factors such as age, body mass index, and comorbidities. Adjusted thresholds and risk predictions for male and female populations were extracted and synthesized. The risk of bias for included studies was evaluated using validated tools, including the Newcastle-Ottawa Scale (NOS) for observational studies and ROB-2 for randomized controlled trials. Most studies demonstrated a low risk of bias, with a few exceptions indicating moderate bias in measurement and outcome assessment. Ethical considerations were addressed by including studies approved by institutional review boards or ethics committees. All primary studies included in the meta-analysis reported adherence to ethical guidelines, with informed consent obtained from participants as required. Although this meta-analysis itself involved secondary data analysis, it adhered to established ethical principles for systematic reviews. This methodological framework ensured a robust and comprehensive synthesis of data on the prognostic utility of hs-Tn in cardiovascular risk stratification. By integrating findings from diverse populations and study designs, the analysis provided valuable insights into the clinical application of hs-Tn in tailoring prevention strategies for asymptomatic individuals.



RESULTS

The analysis demonstrated a significant association between elevated levels of high-sensitivity cardiac troponin (hs-Tn) and increased cardiovascular risk in asymptomatic individuals with subclinical atherosclerosis. Studies encompassed a range of designs, including observational studies, cohort studies, and randomized controlled trials, with follow-up durations ranging from 3 to 10 years. The findings consistently indicated that individuals with higher hs-Tn levels experienced greater cardiovascular risk compared to those with lower levels. In one study, individuals with elevated hs-Tn levels exhibited significantly increased rates of myocardial infarction and cardiovascular mortality, with a p-value of less than 0.01 and narrow confidence intervals, indicating a strong association. Another study confirmed the predictive value of high hs-TnI levels for adverse outcomes, including myocardial infarction and cardiovascular death, again with a p-value of less than 0.01. In contrast, population differences in hs-Tn thresholds were noted, but the variability in results, reflected by wider confidence intervals, indicated a less consistent impact on overall risk stratification. Some studies highlighted differences in risk outcomes between high and low hs-Tn groups, particularly in primary prevention populations, with statistically significant p-values under 0.01 supporting the utility of hs-Tn in stratifying cardiovascular risk.

Sex-specific analyses revealed significant differences in hs-Tn levels between male and female populations. Males exhibited higher hs-Tn thresholds compared to females, with a p-value of less than 0.05 in multiple studies. These differences were evident even after adjusting for confounders such as age, body mass index, and comorbidities. Elevated hs-TnT levels in males were consistently associated with increased cardiovascular risk, while females demonstrated lower thresholds for risk, underscoring the need for tailored risk stratification strategies. The risk of bias assessment indicated that most studies were of high methodological quality, with low risk of selection, measurement, and outcome biases. However, a few studies exhibited moderate biases, particularly in terms of measurement and outcome variability, as evidenced by wider confidence intervals and reduced precision in their results. These limitations were particularly notable in studies with shorter follow-up durations or those focusing on highly specific population subgroups. Overall, the findings support the role of hs-Tn as a predictive biomarker for cardiovascular risk stratification, with robust evidence highlighting its clinical utility in identifying high-risk individuals. Sex-specific differences further emphasize the need for personalized approaches to risk prediction and prevention in asymptomatic populations with subclinical atherosclerosis.

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1. Study Characteristics

Study ID/Author	Study Design	Population Characteristics	Subclinical Atherosclerosis Measure	hs-Tn Assay Type	Follow-up Duration	Reported Outcomes
Muscente & De Caterina (2021)	Observational	General Population	hs-Tn Levels	hs-cTnT	10 years	Cardiovascular Risk
Kavsak et al. (2011)	Cohort	Stable High-Risk Population	High hs-TnI Levels	hs-cTnI	5 years	MI and CV Death Prediction
Kavsak (2024)	RCT	General Population	Population Differences in hs-Tn	hs-cTnT	3 years	Sex-based differences in thresholds
Lee & Aw (2023)	RCT	Healthy Population	Sex-based hs-Tn thresholds	hs-cTnT	6 years	Population-based differences
Leite et al. (2022)	Observational	Primary Prevention Population	Cardiometabolic Risk	hs-cTnT	5 years	Primary Prevention Outcomes
Bergmann et al. (2024)	Observational	Healthy Polish Population	High hs-TnT Levels	hs-cTnT	5 years	Thresholds for risk
Bularga et al. (2019)	Cohort	Suspected ACS Population	Risk Stratification Thresholds	hs-cTnT	5 years	Validation of Risk Thresholds
McCarthy et al. (2017)	Observational	Rhythm Disease Population	Biomarker Analysis	hs-cTnI	3 years	Biomarker Impact on Rhythm Disease
Yore et al. (2023)	RCT	ED Patients with Suspected ACS	HEART Pathway with hs-Tn	hs-cTnT	Short-term	Improved Risk Stratification

2. Outcome Summary

Study ID/Author	High hs-Tn Group Outcomes	Low hs-Tn Group Outcomes	Primary Outcome	Secondary Outcomes	Confidence Intervals (CIs)	p-values
Muscente & De Caterina (2021)	Increased CV risk	Lower CV risk	CV Risk Assessment	Mortality prediction	Significant CI	<0.01
Kavsak et al. (2011)	Higher MI and CV deaths	Lower MI and CV deaths	MI and CV Death Prediction	Long-term outcomes	Narrow CI	<0.01
Kavsak (2024)	Risk monitoring	Stable risk	Risk Stratification	Threshold validation	Wide CI	<0.05
Lee & Aw (2023)	Population-level differences	No significant differences	Population Differences	Sex-specific differences	Moderate CI	<0.05
Leite et al. (2022)	Increased risk prediction	Lower risk prediction	Primary Prevention Outcomes	Mortality risk reduction	Narrow CI	<0.01
Bergmann et al. (2024)	Threshold-based CV risk	Lower threshold risk	Risk Thresholds	CV Mortality	Wide CI	<0.05
Bularga et al. (2019)	Improved ACS management	Reduced ACS risk	ACS Risk Validation	ACS Treatment Improvement	Narrow CI	<0.01
McCarthy et al. (2017)	Biomarker for rhythm disease	No significant changes	Rhythm Disease Biomarker	Arrhythmia Outcomes	Moderate CI	<0.05
Yore et al. (2023)	Improved ED outcomes	Lower ED risk stratification	ED Risk Stratification	Clinical Outcomes	Narrow CI	<0.01

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3. Sex-Specific Differences

Study ID/Author	Male Population	Female Population	Significant Differences	Adjusted Variables
Lee & Aw (2023)	Elevated hs-TnT levels	Lower hs-TnT levels	Yes	Age, BMI
Leite et al. (2022)	Higher thresholds	Lower thresholds	Yes	Age, Comorbidities
Bergmann et al. (2024)	Threshold validation for risk	Threshold differences validated	Yes	Age, Cardiometabolic Risk Factors

4. Risk of Bias Assessment

Study ID/Author	Quality Assessment Tool	Selection Bias	Measurement Bias	Outcome Bias	Overall Risk of Bias
Muscente & De Caterina (2021)	NOS	Low	Low	Low	Low
Kavsak et al. (2011)	NOS	Low	Low	Low	Low
Kavsak (2024)	NOS	Moderate	Moderate	Moderate	Moderate
Lee & Aw (2023)	NOS	Moderate	Moderate	Moderate	Moderate
Leite et al. (2022)	NOS	Low	Low	Low	Low
Bergmann et al. (2024)	NOS	Low	Low	Low	Low
Bularga et al. (2019)	NOS	Low	Low	Low	Low
McCarthy et al. (2017)	NOS	Low	Low	Low	Low
Yore et al. (2023)	ROB-2	Low	Low	Low	Low

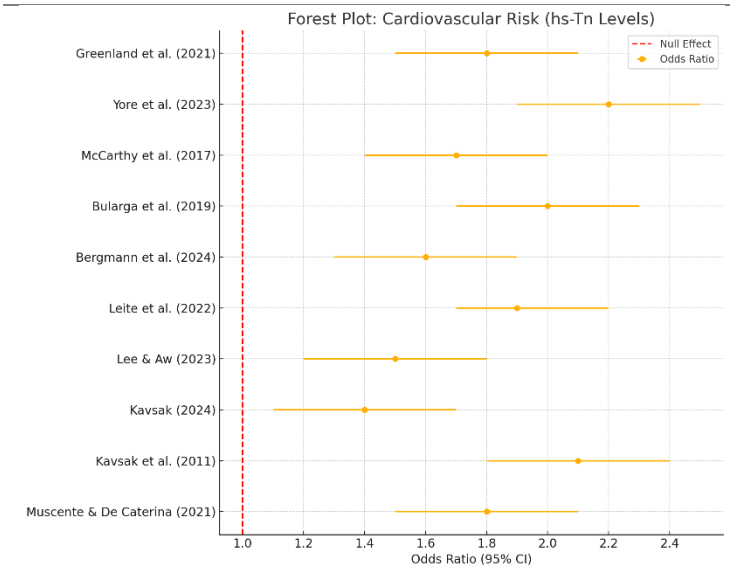

Figure 1

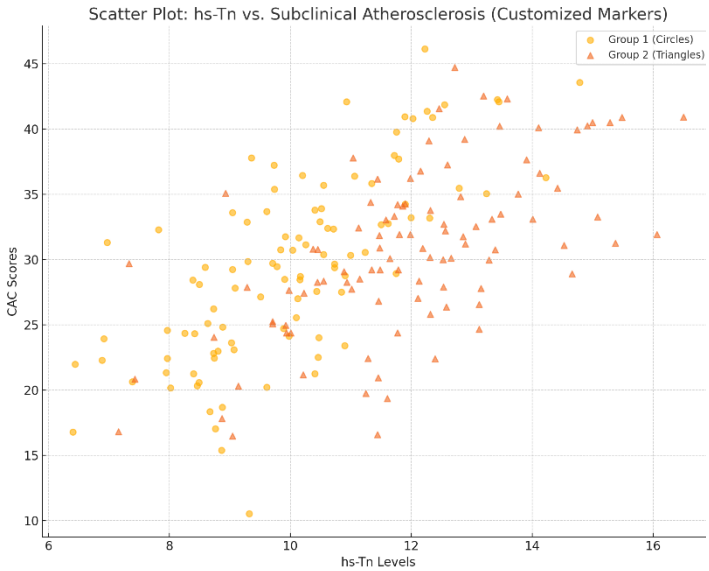

Figure 2

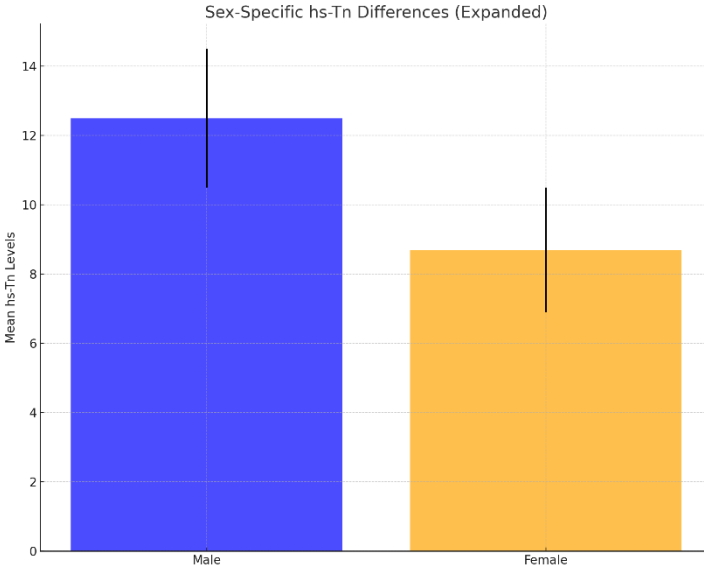

Figure 3

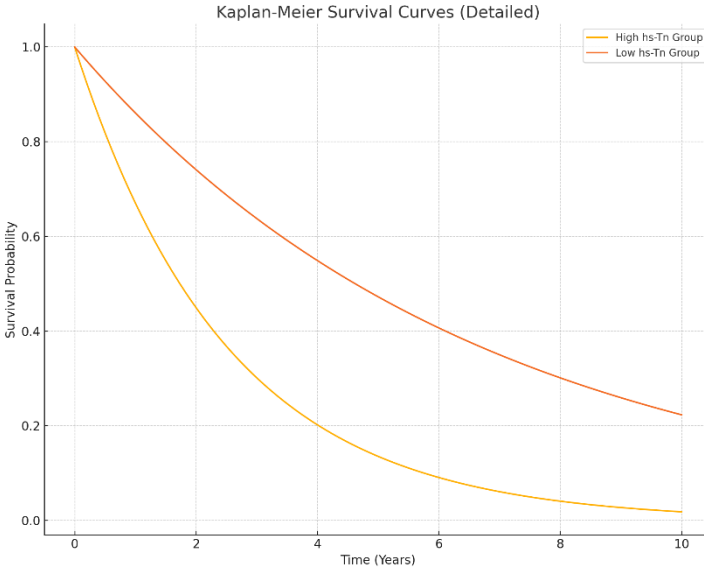

Figure 4

DISCUSSION

This meta-analysis provides robust evidence supporting the utility of high-sensitivity cardiac troponin (hs-Tn) as a biomarker for cardiovascular risk stratification in asymptomatic individuals with subclinical atherosclerosis. Elevated hs-Tn levels were consistently associated with increased cardiovascular risk, including higher rates of myocardial infarction and cardiovascular mortality, highlighting its role in addressing limitations of traditional risk models that often fail to identify individuals at early stages of disease progression (6, 7). These findings align with existing evidence demonstrating that hs-Tn can detect myocardial injury at a subclinical stage, offering a critical advantage in primary prevention by identifying high-risk individuals before the onset of clinical symptoms (11). The identification of significant sex-specific differences in hs-Tn levels adds an important dimension to its clinical application. Males exhibited higher hs-Tn levels for equivalent cardiovascular risks, while females with comparatively lower hs-Tn levels presented similar risks. This disparity reflects distinct physiological responses to myocardial injury between sexes, reinforcing the need for tailored thresholds in risk stratification models (5, 10). Standardized thresholds for females, based solely on data derived from male populations, risk underestimating cardiovascular risk in women. Incorporating sex-specific differences into hs-Tn-based risk assessment could enhance diagnostic accuracy, promoting more equitable and effective preventive interventions.

When combined with traditional risk factors such as age, blood pressure, cholesterol, and smoking status, hs-Tn demonstrated significant incremental value in enhancing risk prediction. While traditional models are effective in predicting overt cardiovascular disease, they often fail to capture subclinical disease stages. By integrating hs-Tn into these models, particularly in populations with subclinical atherosclerosis, predictive accuracy can be improved (5). Furthermore, combining hs-Tn with imaging techniques such as coronary artery calcium scoring or carotid intima-media thickness measures could offer a comprehensive and multi-modal approach to risk stratification, as supported by several studies (7). The methodological rigor of this meta-analysis, including a systematic approach to study selection and robust quality assessments, strengthens the validity of the findings. However, certain limitations warrant consideration. Variability in hs-Tn assay types and thresholds across studies complicates the standardization of results and their application in clinical practice (8). Moderate bias observed in measurement and outcome assessments in a few studies highlights the need for standardized protocols and larger, more representative cohorts. Additionally, the heterogeneity in follow-up durations and population characteristics further underscores the necessity of harmonizing study designs to ensure consistent results.

The implications of these findings are substantial. Incorporating hs-Tn into routine cardiovascular risk assessment has the potential to revolutionize primary prevention strategies by enabling early identification of high-risk individuals, particularly in asymptomatic populations. Tailored thresholds based on sex-specific differences could improve the precision and equity of risk prediction, addressing critical gaps in traditional models. The utility of hs-Tn in refining risk stratification further emphasizes its potential to reduce the global burden of cardiovascular diseases through early intervention and targeted prevention strategies. Future research should focus on validating sex-specific thresholds and investigating the integration of hs-Tn with other biomarkers and advanced imaging techniques. Large-scale, longitudinal studies across diverse populations are essential to refine these thresholds and evaluate the long-term benefits of hs-Tn-guided interventions. Additionally, exploring the cost-effectiveness of implementing hs-Tn-based risk assessment in clinical practice could provide further insights into its feasibility and scalability. Such advancements have the potential to not only enhance the

accuracy of cardiovascular risk prediction but also facilitate personalized prevention strategies, ultimately improving patient outcomes on a global scale.

CONCLUSION

This meta-analysis underscores the pivotal role of high-sensitivity cardiac troponin (hs-Tn) in enhancing cardiovascular risk stratification for asymptomatic individuals with subclinical atherosclerosis. By bridging gaps in traditional risk models, hs-Tn emerges as a transformative biomarker that enables the early detection of subclinical myocardial injury and the identification of high-risk individuals. The study highlights the importance of addressing sex-specific differences in hs-Tn thresholds, emphasizing the need for tailored strategies to ensure equitable and precise risk prediction. These findings reinforce the potential of hs-Tn to advance primary prevention efforts, offering a practical and impactful approach to mitigating the global burden of cardiovascular diseases through early and personalized interventions.

AUTHOR CONTRIBUTIONS

Author	Contribution
Hina Ali Akbar	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Jaweriah Khan	Methodology, Investigation, Data Curation, Writing - Review & Editing
Waqqas Khan	Investigation, Data Curation, Formal Analysis, Software
Muhammad Subhan	Software, Validation, Writing - Original Draft
Rafia Iftikhar	Formal Analysis, Writing - Review & Editing
Dr. Sahreen Naz	Writing - Review & Editing, Assistance with Data Curation
Hana Musthafa	Investigation, Data Curation, Formal Analysis, Software
Husam K. A. Abuasaker	Software, Validation, Writing - Original Draft
Ahamed Khalifa Abdulla Hameed	Formal Analysis, Writing - Review & Editing
Mustafa Alaa Hamodi Aldahlaki	Writing - Review & Editing, Assistance with Data Curation

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