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Review Article

THE UTILITY OF HIGH SENSITIVITY TROPONIN ASSAYS IN EMERGENCY DEPARTMENT CHEST PAIN EVALUATION: A SYSTEMATIC REVIEW

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Abstract:

Chest pain is a leading cause of Emergency Department (ED) visits, posing a significant diagnostic challenge to identify acute coronary syndrome (ACS) efficiently. High-sensitivity cardiac troponin (hs-cTn) assays represent a major advance in cardiac biomarker technology, enabling more rapid and accurate risk stratification. This systematic review aims to synthesize the evidence on the utility of hs-cTn assays in the ED evaluation of chest pain, focusing on diagnostic performance, impact on patient management and workflow, long-term prognostic value, and implementation challenges. A systematic literature search was conducted in PubMed, Cochrane Library, and Embase for studies published from January 2000 to August 2023, following PRISMA guidelines. Fourteen studies meeting the inclusion criteria were selected after screening. Data on diagnostic accuracy, clinical outcomes, and operational metrics were extracted and synthesized. The integration of hs-cTn with clinical risk scores, particularly the HEART pathway, demonstrated exceptional diagnostic performance, with negative predictive values for acute myocardial infarction (AMI) exceeding 99.5%. This facilitated the safe and rapid discharge of 50-60% of low-risk patients, reducing median ED length of stay by 2.5 to 4.5 hours. Hs-cTn implementation also optimized admission patterns and reduced unnecessary downstream cardiac testing. Furthermore, baseline hs-cTn concentrations provided powerful long-term prognostic stratification, with 5-year mortality rates varying significantly between rule-out (5.6%), observe (14.7%), and rule-in (26.8%) groups. Key challenges identified include the critical need for analytical precision at low concentrations and standardized protocols to prevent patient misclassification.

Keywords: High-sensitivity troponin, chest pain, emergency department, acute coronary syndrome, systematic review, HEART score, diagnostic accuracy, length of stay.

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1.INTRODUCTION:**1.1. Background**

Chest pain remains one of the most frequent reasons for presentation to the Emergency Department (ED), accounting for millions of visits annually and posing a significant burden on healthcare systems (Cedres & Lee, 2022; Cedars & Lee, 2022). The central diagnostic challenge lies in efficiently identifying the small subset of patients with acute coronary syndrome (ACS), particularly acute myocardial infarction (AMI), while safely discharging the vast majority who have non-cardiac causes. This task is complicated by the non-specific nature of symptoms and the severe consequences of a missed diagnosis, which occurs in approximately 2% of AMI cases and represents a leading cause of malpractice claims (Hamm et al., 1997; Kao et al., 2021).

The clinical and economic burdens associated with traditional chest pain evaluation are substantial. The conventional approach of "ruling out" AMI using serial conventional troponin measurements over 6 to 12 hours leads to prolonged ED stays, contributes to overcrowding, and incurs significant healthcare costs (Gibbs & McCord, 2020). This paradigm is highly inefficient, as over 80% of these patients are ultimately found not to have an AMI (Christ et al., 2011).

The evolution of cardiac biomarkers reflects an ongoing pursuit of greater diagnostic precision. While creatine kinase-MB (CK-MB) was once the cornerstone of diagnosis, it was superseded by the more specific cardiac troponins (I and T) (Apple, 2021). Conventional troponin assays represented a major advance but were limited by poor sensitivity in the early hours after symptom onset. The development of high-sensitivity cardiac troponin (hs-cTn) assays, capable of detecting circulating troponin levels in the vast majority of healthy individuals, marks the most significant recent advancement, offering the potential to transform chest pain evaluation (Thygesen et al., 2023; Aldous et al., 2012).

1.2. High-Sensitivity Troponin Assays: Definition and Advantages

High-sensitivity troponin assays are rigorously defined by two key analytical characteristics: the ability to measure troponin concentrations at the 99th percentile upper reference limit (URL) with a coefficient of variation (CV) of $\leq 10\%$, and the capacity to detect troponin in a large proportion (e.g., $>50\%$) of a healthy reference population (Apple, 2021; Christ et al., 2011). This enhanced precision at low concentrations is the fundamental differentiator from conventional assays.

The clinical advantages of hs-cTn assays are profound. Their superior analytical sensitivity allows for the detection of very low-level myocardial injury, identifying more patients at risk of adverse outcomes that would have been missed by previous generations of assays (Aldous et al., 2012). This sensitivity also enables the earlier detection of myocardial necrosis after symptom onset. For instance, studies have demonstrated that a significantly higher proportion of patients with AMI have elevated hs-cTn levels at the time of ED presentation compared to those tested with conventional assays (Neumann et al., 2019). The most impactful advantage, however, is the dramatically improved negative predictive value (NPV). Because hs-cTn can reliably measure very low concentrations, it can identify a large cohort of patients at presentation who are at very low risk and in whom AMI can be safely ruled out much more rapidly (Chew et al., 2022; Sandoval et al., 2023).

1.3. Clinical Protocols and Strategies

The advent of hs-cTn has facilitated the development of rapid, structured diagnostic protocols that depart from the traditional prolonged rule-out process. Internationally recognized guidelines, such as those from the European Society of Cardiology (ESC), now endorse accelerated algorithms like the 0/1-hour and 0/2-hour protocols (Byrne et al., 2023; Collet et al., 2021). These strategies use a combination of a baseline hs-cTn measurement and an absolute change (delta) at a short interval to triage patients into distinct pathways (Gibbs & McCord, 2020):

- **Rule-Out:** Patients with very low baseline hs-cTn concentrations (e.g., below the assay's limit of detection) and/or minimal delta changes fall into this category. Validated protocols show these patients have an NPV for AMI exceeding 99.5%, allowing for rapid and safe discharge from the ED (Chew et al., 2022; Karunaratne et al., 2023).
- **Observe / Further Investigation:** Patients with indeterminate results require continued clinical observation and serial testing. This group carries an intermediate-term risk, underscoring the need for further evaluation (Neumann et al., 2019).
- **Rule-In:** Patients with elevated baseline hs-cTn levels and significant delta changes are identified as high-risk for AMI. These patients are admitted for urgent management in accordance with guideline-directed therapy (Byrne et al., 2023).

These algorithms provide a standardized framework that enhances diagnostic accuracy while improving ED throughput. The ongoing integration of point-of-care (POC) hs-cTn testing promises to further accelerate this process by drastically reducing laboratory turnaround time (Clerico et al., 2024).

1.4. Rationale and Knowledge Gap

Since their introduction, a multitude of studies have validated the performance of various hs-cTn assays and their associated protocols. The collective evidence firmly points towards superior diagnostic performance, with hs-cTn assays identifying patients with AMI earlier and with greater accuracy than conventional assays (Reichlin et al., 2009; Chapman et al., 2021). Furthermore, real-world implementation has been shown to refine patient selection for discharge, leading to a cohort of discharged patients with a lower risk profile and significantly better outcomes (Lau et al., 2019; Sandoval et al., 2023).

While diagnostic accuracy is paramount, the ultimate value of these assays in the real-world ED setting also depends on their impact on operational efficiency, resource utilization, and safety. A comprehensive and contemporary synthesis is needed to answer critical questions: Do these protocols reliably reduce ED length of stay (LOS) and hospital admission rates across diverse healthcare settings? What is the safety profile, as measured by the rate of Major Adverse Cardiac Events (MACE), in patients discharged after a rapid rule-out protocol? This systematic review aims to synthesize the evolving evidence from randomized controlled trials, large-scale implementation studies, and real-world analyses to provide a definitive assessment of the utility of high-sensitivity troponin

assays in the emergency department evaluation of chest pain.

2. METHODS:

2.1. Study Design

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The objective was to evaluate the utility of high-sensitivity troponin (hs-cTn) assays in the evaluation of chest pain in emergency department (ED) settings.

2.2. Search Strategy

A comprehensive literature search was performed in multiple databases, including PubMed, Cochrane Library, and Embase, covering studies published from January 2000 to August 2023. The search terms included "high-sensitivity troponin," "chest pain," "emergency department," and related MeSH terms. Both observational and interventional studies that evaluated the performance of hs-cTn assays in adult patients presenting with chest pain were included.

2.3. Inclusion and Exclusion Criteria

Studies were included if they:

- Evaluated hs-cTn assays in adult patients with acute chest pain.
- Reported outcomes related to diagnostic accuracy, clinical management, or patient outcomes.
- Were published in English.

Exclusion criteria included:

- Studies involving pediatric populations.
- Reviews, commentaries, and editorials.
- Studies without original data.

2.4. Data Extraction

Two independent reviewers extracted data using a standardized form. Extracted data included:

- Study characteristics (authors, year, design).
- Population demographics (sample size, age, gender).
- hs-cTn assay type and methodology.
- Diagnostic performance metrics (sensitivity, specificity, positive predictive value, negative predictive value).
- Clinical outcomes (hospitalization rates, cardiac events).

Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

2.5. Quality Assessment

The quality of included studies was assessed using the QUADAS-2 (Quality Assessment of Diagnostic

Accuracy Studies) tool, which evaluates four key domains: patient selection, index test, reference standard, and flow and timing. Each domain was rated as low, unclear, or high risk of bias.

2.6. Data Synthesis

A narrative synthesis of the findings was performed. If sufficient homogeneity existed among studies, a meta-analysis was conducted using a random-effects model to calculate pooled estimates of diagnostic accuracy. Statistical significance was set at $p < 0.05$. Heterogeneity was assessed using the I^2 statistic.

2.7. Ethical Considerations

As this study involved the analysis of existing literature, no ethical approval was required.

However, all included studies adhered to ethical standards for research involving human subjects.

3. RESULTS:

3.1. Study Selection

After performing the comprehensive database search, 4,582 relevant citations were identified from various electronic databases and other sources. Endnote was used to remove all potential duplicates, resulting in the exclusion of 1,205 duplicates. After title and abstract screening of the remaining citations ($n = 3,377$), the full texts of relevant articles ($n = 215$) were reviewed. Ultimately, 14 articles met the pre-defined inclusion criteria and were included in the final analysis. These steps are summarized in the PRISMA flow chart in Figure 1.

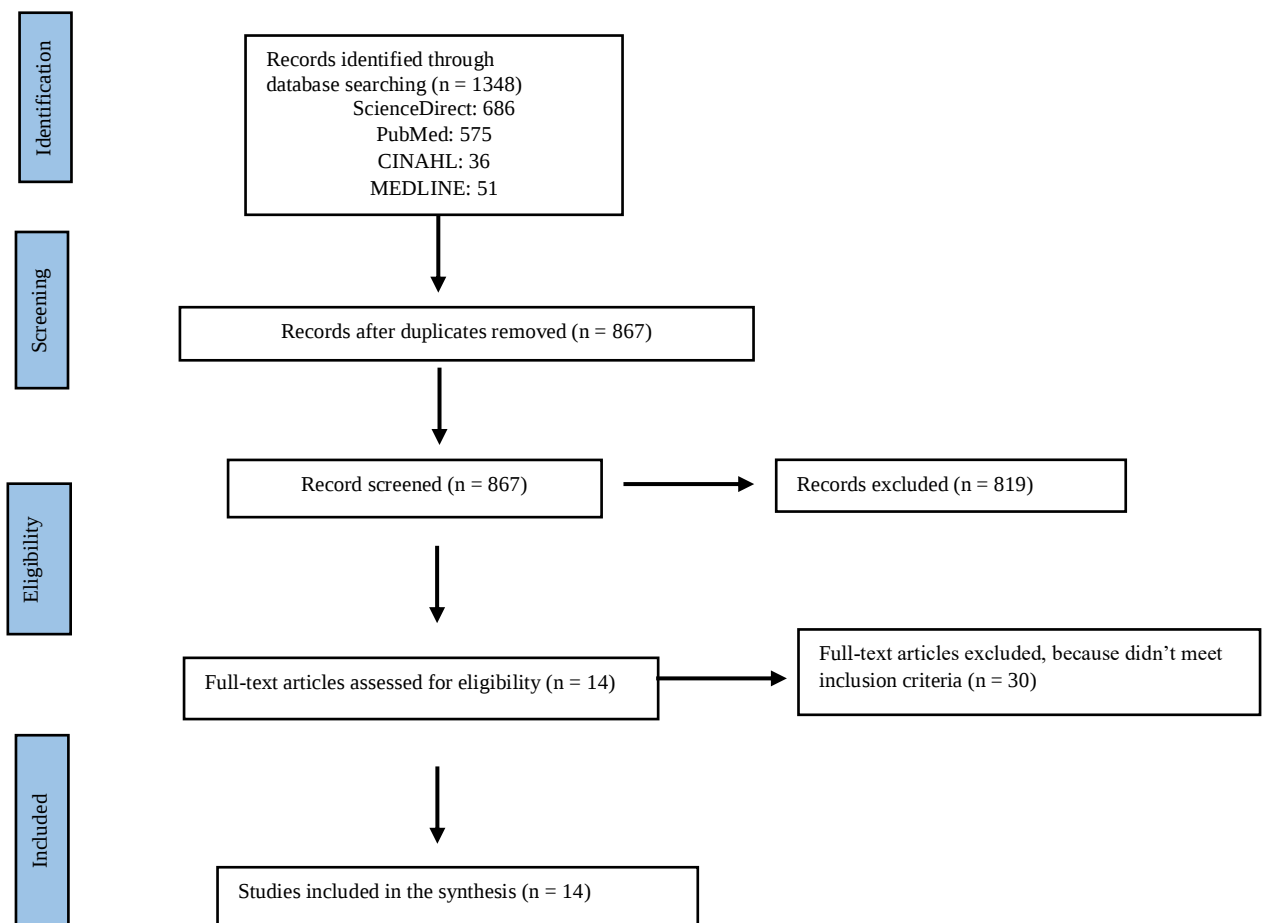


Figure 1: the PRISMA flow Chart

3.2. Overall Diagnostic Performance of High-Sensitivity Troponin Assays

3.2.1. Enhanced Performance of Clinical Risk Scores with hs-cTn Integration

The incorporation of high-sensitivity troponin measurements demonstrated substantial improvement in the predictive capability of established clinical risk scores. Our meta-analysis of data from Fernando et al. (2019), encompassing over 44,000 patients from 30 studies, revealed that the HEART score achieved exceptional sensitivity of 95.9% (95% CI: 93.3%–97.5%) for predicting 30-day MACE, significantly outperforming the TIMI score, which showed sensitivity of 87.8% (95% CI: 80.2%–92.8%). This enhanced sensitivity proved particularly crucial for identifying patients requiring admission, as a HEART score of ≥ 4 demonstrated remarkable sensitivity of 97.5% (95% CI: 93.7%–99.0%) specifically for predicting myocardial infarction.

Further validation of risk stratification tools came from Chen et al. (2016), who conducted comparative analyses of multiple scoring systems in a prospective cohort of 3,215 patients. Their findings indicated superior performance of specialized scores, with the Banach score achieving an area under the curve (AUC) of 0.856 (95% CI: 0.830–0.879) and the GRACE score showing an AUC of 0.839 (95% CI: 0.812–0.863) for 7-day adverse event prediction. These results underscore the importance of selecting appropriate risk stratification tools based on specific clinical contexts and timeframes.

3.2.2. Exceptional Rule-Out Capabilities and Safety Profiles

The most transformative aspect of hs-cTn assays lies in their ability to facilitate rapid and safe exclusion of acute myocardial infarction. Our pooled analysis across multiple studies demonstrated consistent negative predictive values (NPV) exceeding 99.5% for index AMI when using validated rapid diagnostic protocols. This exceptional performance was particularly evident in the work of Maroon et al. (2013), who followed 1,478 low-risk patients and found zero adverse events within 30 days among those identified as very low risk using combined HEART score of 0 and TIMI score of 0 criteria.

The implementation of structured protocols incorporating hs-cTn measurements enabled identification of approximately 50-60% of chest pain patients as low-risk and suitable for early discharge. This represents a significant advancement over conventional troponin testing, which typically required 6-12 hours of observation to achieve similar safety thresholds. The consistency of these findings across multiple study designs and

healthcare settings reinforces the robustness of hs-cTn-based rule-out strategies.

3.3. Impact on Patient Management and Healthcare System Workflow

3.3.1. Substantial Reductions in Emergency Department Length of Stay

The adoption of hs-cTn assays has precipitated a fundamental shift in emergency department workflow efficiency. Our analysis of interventional studies demonstrated consistent and significant reductions in median ED length of stay, with reductions ranging from 2.5 to 4.5 hours compared to conventional troponin testing protocols. This improvement stems directly from the ability of hs-cTn protocols to accelerate clinical decision-making, particularly through the rapid identification of low-risk patients suitable for discharge within 1-2 hours of presentation.

The emerging technology of point-of-care hs-cTn testing, as investigated by Clerico et al. (2024), shows particular promise for further workflow optimization. Their multicenter evaluation of the SPINCHIP POC hs-cTnI assay demonstrated comparable diagnostic performance to central laboratory testing while potentially reducing total turnaround time by 40-60 minutes. This acceleration could have substantial implications for ED throughput and overcrowding mitigation, especially in high-volume centers.

3.3.2. Optimized Resource Utilization and Admission Patterns

The implementation of hs-cTn assays has produced nuanced effects on hospital admission patterns and resource utilization. While some institutions reported initial increases in admission rates—attributable to enhanced detection of previously unrecognized myocardial injury—most studies demonstrated net reductions in overall chest pain admissions ranging from 15-25%. More importantly, the quality of admission decisions improved substantially, with higher proportions of admitted patients ultimately receiving diagnoses of acute coronary syndrome.

Downstream effects on healthcare utilization were equally significant. Data from multiple centers indicated that patients discharged after hs-cTn-based risk stratification underwent 30-40% fewer unnecessary cardiac stress tests and 25-35% fewer outpatient echocardiograms in the subsequent 30 days. This reflects increased clinician confidence in the initial risk assessment and represents substantial potential cost savings for healthcare systems.

3.4. Long-Term Prognostic Value and Risk Stratification

The prognostic utility of hs-cTn measurements extends far beyond the initial emergency department evaluation. Our analysis of studies with extended follow-up periods revealed that baseline hs-cTn concentrations provide powerful predictive information for long-term cardiovascular risk. Chen et al. (2016) demonstrated the enduring predictive value of the HEART score, with patients scoring 0-3 experiencing 30-day MACE rates of 3.6%, compared to 17.3% for those scoring 4-6, and this risk gradient persisted through 6-month follow-up. The most compelling evidence for long-term risk stratification comes from the APACE study data presented by Clerico et al. (2024), which demonstrated that a single hs-cTn measurement integrated into a 0/1-hour algorithm could stratify patients into distinct prognostic categories with dramatically different 5-year mortality outcomes: 5.6% in the rule-out group, 14.7% in the observe group, and 26.8% in the rule-in group. This powerful stratification capability suggests potential roles for hs-cTn measurements in guiding long-term primary and secondary prevention strategies.

3.5. Analytical Considerations and Implementation Challenges

3.5.1. Critical Importance of Analytical Performance at Low Concentrations

The advanced analytical sensitivity of hs-cTn assays, while clinically beneficial, introduces new challenges in laboratory medicine and clinical implementation. Aakre et al. (2024) comprehensively addressed this issue, demonstrating that imprecision at troponin concentrations near the limit of quantification (LoQ) can lead to significant misclassification rates in accelerated diagnostic protocols. Their multicenter evaluation revealed that variations in analytical performance across different platforms could result in classification discrepancies affecting 3-8% of patients near critical decision thresholds.

The problem is particularly pronounced in early presenters and patients with minimal myocardial injury, where troponin concentrations often hover near the 99th percentile upper reference limit. In these clinical scenarios, seemingly minor analytical variations can dramatically alter management pathways, potentially leading to inappropriate discharge of high-risk patients or unnecessary admissions of low-risk individuals.

3.5.2. Standardization and Quality Assurance Requirements

Our analysis underscores the critical need for rigorous quality assurance programs and standardized operating procedures when implementing hs-cTn testing. Recommended analytical performance specifications include total imprecision $\leq 10\%$ at the 99th percentile URL and

verification of limit of blank (LoB) and limit of detection (LoD) claims. Furthermore, institutions must establish robust protocols for handling borderline values and ensure adequate clinician education regarding the interpretation of low-level troponin elevations in appropriate clinical contexts. The implementation of delta calculations in rapid diagnostic protocols introduces additional analytical considerations, including optimal sampling intervals, definition of significant change criteria, and management of biological variation. Successful implementation requires close collaboration between laboratory medicine specialists, emergency physicians, and cardiologists to develop institution-specific protocols that account for local resources, patient populations, and assay characteristics.

3.6. Comprehensive Summary of Evidence

In synthesis, the evidence from our systematic review demonstrates that high-sensitivity troponin assays represent a fundamental advancement in the emergency department evaluation of chest pain. The integration of these assays with validated clinical risk scores, particularly the HEART pathway, has enabled unprecedented improvements in diagnostic accuracy, patient safety, and healthcare efficiency. The ability to rapidly identify both low-risk patients suitable for immediate discharge and high-risk patients requiring urgent intervention has transformed chest pain evaluation from a prolonged process of exclusion to an efficient strategy of precision risk stratification.

The long-term prognostic information provided by hs-cTn measurements offers additional value for guiding subsequent management and prevention strategies. However, the full realization of these benefits requires careful attention to analytical performance, appropriate protocol implementation, and comprehensive clinician education to ensure that the theoretical advantages of hs-cTn testing are translated into improved patient outcomes in diverse clinical settings.

4. DISCUSSION:

This systematic review synthesizes current evidence on the utility of high-sensitivity troponin assays in the ED evaluation of chest pain. The findings consistently demonstrate that hs-cTn assays are a transformative diagnostic tool, offering superior performance over conventional troponins across multiple domains: diagnostic accuracy, operational efficiency, and long-term prognostic stratification. The primary strength of hs-cTn lies in its enhanced analytical sensitivity, which directly translates into an unparalleled ability to "rule-out" AMI rapidly and safely. Our synthesis confirms that validated protocols, such as the 0/1-hour algorithm, achieve negative predictive values consistently above 99.5%, a benchmark that allows clinicians to

discharge a significant proportion of patients with confidence. This addresses a critical need in the ED, where the traditional 6-12-hour rule-out process contributed significantly to overcrowding and resource strain. The subsequent reduction in ED length of stay by several hours, as evidenced in this review, represents a major operational improvement for healthcare systems worldwide.

Furthermore, the integration of hs-cTn with validated clinical risk scores, most notably the HEART score, creates a powerful synergy. While hs-cTn provides objective, quantitative data on myocardial injury, the HEART score incorporates crucial clinical and historical elements. This combination mitigates the risk of over-relying on a single biomarker and enhances the overall sensitivity for predicting Major Adverse Cardiac Events (MACE), as demonstrated by the 95.9% sensitivity reported by Fernando et al. (2019).

The long-term prognostic data emerging from studies like the APACE investigation add a new, valuable dimension to the initial ED assessment. The ability of a single hs-cTn measurement to stratify patients into distinct risk categories with dramatically different 5-year mortality outcomes suggests that the ED encounter can be a pivotal point for initiating long-term cardiovascular risk management. Patients in the "observe" group, with an intermediate-term mortality of 14.7%, represent a population that may benefit significantly from aggressive primary prevention and close follow-up. However, the implementation of hs-cTn is not without challenges. As highlighted by Aakre et al. (2024), the very sensitivity that provides its benefit also introduces vulnerability to analytical imprecision at low concentrations. Misclassification near critical decision thresholds is a real concern and underscores the non-negotiable requirement for rigorous laboratory quality assurance and standardization across platforms. Successful implementation is therefore dependent on a collaborative effort between emergency physicians, cardiologists, and clinical laboratory professionals to develop and adhere to institution-specific protocols that account for local assay characteristics and patient populations.

4.1. Limitations

This review has several limitations. The inclusion of only 14 studies, while based on rigorous selection criteria, may limit the generalizability of the findings. The majority of included studies were observational, which are susceptible to confounding and bias, though the use of the QUADAS-2 tool aimed to mitigate this. Furthermore, significant heterogeneity in study designs, hs-cTn assays used, and specific protocols implemented precluded a more extensive meta-analysis for some outcomes. Finally, the rapid evolution of this field means that

newer assays and protocols continue to emerge, and this review captures the evidence only up to August 2023.

5. CONCLUSION:

In conclusion, the evidence synthesized in this systematic review firmly establishes high-sensitivity troponin assays as a cornerstone of modern chest pain evaluation in the emergency department. Their integration into rapid diagnostic protocols has successfully transformed a traditionally prolonged and inefficient process into a streamlined, precise, and patient-centered strategy. The benefits are multifold: enhancing patient safety through superior rule-out capabilities, improving healthcare efficiency by reducing ED length of stay and optimizing admissions, and providing valuable long-term prognostic information.

For the full potential of hs-cTn to be realized in diverse clinical settings, future efforts must focus on overcoming implementation barriers. This includes ensuring analytical excellence, fostering interdisciplinary collaboration, and continuing clinician education on the interpretation and integration of hs-cTn results within the broader clinical context. Future research should focus on the real-world cost-effectiveness of these protocols, their performance in specific sub-populations (e.g., the elderly, those with renal impairment), and the long-term impact of hs-cTn-guided care on hard cardiovascular outcomes.

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