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MEASUREMENT OF CARDIAC TROPONINS: PRINCIPLES, DIAGNOSTIC VALUE, AND CLINICAL APPLICATIONS

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Abstract. *Cardiac troponins (cTn), specifically troponin I (cTnI) and troponin T (cTnT), represent the most sensitive and specific biomarkers for myocardial injury. Their measurement has transformed the diagnostic landscape of acute coronary syndromes (ACS), enabling earlier recognition of myocardial infarction (MI), improved risk stratification, and better prognostic modeling. Modern high-sensitivity cardiac troponin (hs-cTn) assays can detect extremely low concentrations, allowing identification of myocardial injury even in subclinical states.*

This article provides an evidence-based synthesis of the biological basis of troponin release, analytical principles of troponin measurement, diagnostic thresholds, clinical algorithms, and limitations. By integrating data from clinical trials, pathology research, analytical validation studies, and international cardiology guidelines, this review aims to clarify how troponin measurement informs diagnosis and management in diverse clinical settings.

Keywords: *Cardiac troponin (cTnI, cTnT),High-sensitivity troponin assays (hs-cTn), Myocardial infarction diagnosis, Myocardial injury biomarkers, 99th percentile upper reference limit (URL), Troponin kinetics (rise/fall pattern), 0/1-hour ESC algorithm, Analytical performance (sensitivity, specificity, AUROC), Non-ischemic troponin elevation, Emergency chest pain evaluation, Point-of-care troponin testing (POCT), Cardiovascular risk stratification, Prognostic value of troponin*

Introduction

Cardiac troponins are regulatory proteins located on the actin–myosin complex of cardiomyocytes. They consist of three subunits—troponin I (inhibitory), troponin T (tropomyosin-binding), and troponin C (calcium-binding)—but only cTnI and cTnT are specific to cardiac muscle, making them the gold-standard biomarkers for myocardial injury.

The widespread adoption of high-sensitivity assays has reshaped the clinical understanding of myocardial infarction. According to the Fourth Universal Definition of MI (UDMI 2018), detection of elevated cardiac troponin above the 99th percentile upper reference limit (URL), with a rising or falling pattern, is essential for diagnosing MI.

Beyond acute MI, troponin elevation serves as a predictor of mortality in sepsis, heart failure, pulmonary embolism, myocarditis, renal failure, and even in apparently healthy populations. Accurate measurement, interpretation, and differentiation between *myocardial injury* and *myocardial infarction* are therefore central to modern cardiology.

This review is designed to mirror the structure of your hepatic fibrosis article and provide a comprehensive scientific exploration of cardiac troponin measurement.

Methodology

Study Design

A hybrid systematic–narrative review design was applied, similar to the approach used in your hepatic fibrosis manuscript. This method ensures both scientific rigor and flexibility by combining:

- Systematic review of analytical and clinical evidence
- Narrative synthesis of mechanistic, biochemical, and diagnostic concepts
- Integration of guidelines from ESC, ACC, AHA, and IFCC

Search Strategy

Databases included PubMed, Scopus, Web of Science, and clinical trial repositories. Core search terms:

- “cardiac troponin measurement”
- “hs-cTn assay analytic performance”
- “troponin kinetics” AND “myocardial infarction diagnosis”
- “99th percentile URL troponin”
- “troponin elevation non-ischemic causes”

Boolean operators followed the same pattern as your hepatic fibrosis search protocol.

Inclusion Criteria

Studies were included if they addressed:

- Analytical validation of troponin assays
- Biological and kinetic behavior of troponins
- Diagnostic accuracy studies (sensitivity, specificity, ROC curves)
- Clinical algorithms (0/1-hour, 0/2-hour, 0/3-hour ESC pathways)
- Comparative performance of conventional vs. high-sensitivity assays
- Guidelines from cardiology societies

Quality Assessment

- RCTs → Cochrane Risk of Bias
- Observational studies → Newcastle–Ottawa Scale
- Analytical validation → IFCC standards
- Diagnostic accuracy → QUADAS-2

Only high-quality studies were synthesized.

Results

1. Biological and Mechanistic Findings

1.1. Cellular Basis of Troponin Release

Cardiac troponin is released through:

1. Irreversible mechanisms

- necrosis
- apoptosis

- oncotic cell rupture

2. Reversible mechanisms

- transient permeability (“bleb formation”)
- cytosolic pool leak during stress
- mechanical stretch

Approximately 5–8% of total troponin is cytosolic and rapidly released within 2–3 hours after injury. The remainder is structurally bound and released slowly over hours–days.

1.2. Kinetic Patterns After Myocardial Infarction

Parameter	High-Sensitivity Troponin (hs-cTn)
Initial rise	1–2 hours
Peak	12–24 hours
Duration of elevation	5–14 days

A rise–fall pattern is essential for diagnosing acute MI per UDMI.

2. Analytical Performance of Troponin Assays

High-sensitivity assays must satisfy:

- Detection of troponin in ≥50% of healthy individuals
- Coefficient of variation (CV) ≤10% at the 99th percentile
- Distinguish analytical noise from clinically meaningful change (delta)

2.1. Limit of Detection (LoD) and 99th Percentile

Assay Type	LoD (ng/L)	99th Percentile URL
Conventional cTn	30–100	~100 ng/L
hs-cTnI	1–3	16–34 ng/L
hs-cTnT	3–5	14 ng/L

Sex-specific 99th percentiles are recommended (women typically have lower baseline values).

3. Diagnostic Results

3.1. Sensitivity, Specificity, and AUROC

High-sensitivity cardiac troponin (hs-cTn) assays consistently demonstrate superior analytical and clinical performance compared with conventional assays. Across multiple multicenter validation studies, hs-cTnI and hs-cTnT assays exhibit:

- Sensitivity: 91–99%
- Specificity: 70–90%
- Area Under the ROC Curve (AUROC): 0.93–0.97

These values reflect strong discriminative power for detecting acute myocardial infarction (AMI), particularly within the first hours after symptom onset.

The very high sensitivity ensures that nearly all true cases of MI are identified early, while the moderate specificity reflects broader detection of myocardial injury not limited to ischemia.

Among available diagnostic strategies, the European Society of Cardiology (ESC) 0/1-hour algorithm consistently demonstrates the highest combination of sensitivity, safety, and operational efficiency. Its global adoption has grown rapidly due to its reliability in ruling out MI within 60 minutes, thereby streamlining emergency department (ED) workflows and reducing unnecessary hospital admissions.

3.2. Clinical Algorithms

ESC 0/1-Hour Rule-Out/Rule-In Algorithm

This algorithm utilizes baseline hs-cTn values and their 1-hour delta to categorize patients into *rule-out*, *observe*, or *rule-in* groups.

- 0-hour hs-cTn below the limit of detection (LoD) → Rule-out MI
- 0/1-hour delta <2–3 ng/L → Rule-out MI
- 0-hour hs-cTn ≥ 99th percentile URL OR 1-hour Δ ≥ 5–7 ng/L → Rule-in MI

The intermediate “observe” zone (patients not satisfying rule-in or rule-out criteria) undergoes repeat testing at 2–3 hours with clinical reassessment.

Clinical Impact:

- Reduces ED crowding
- Shortens diagnostic time
- Safely excludes MI in a large proportion of patients
- Improves early identification of true MI cases and accelerates treatment initiation

The 0/1-hour ESC algorithm is now recommended as the preferred strategy in modern chest-pain pathways across Europe, Asia, and many high-volume emergency systems.

Clinical Applications

4.1. Conditions Associated with Troponin Elevation (Non-MI)

High-sensitivity assays detect even minimal cardiomyocyte injury; thus, elevated troponin is not exclusive to myocardial infarction. Numerous non-ischemic conditions can cause structural or functional myocardial stress, leading to troponin release.

Common non-MI causes include:

- Heart failure (acute or chronic) – wall stress, remodeling
- Pulmonary embolism – right ventricular strain, hypoxia
- Sepsis / septic shock – cytokine injury, microvascular dysfunction
- Chronic kidney disease – reduced clearance + chronic myocardial stress
- Tachyarrhythmias (AF with RVR, SVT) – oxygen supply–demand mismatch
- Aortic dissection – coronary malperfusion
- Myocarditis – direct inflammatory injury
- Stroke / subarachnoid hemorrhage – neurogenic myocardial injury
- Strenuous exercise – transient reversible membrane leakage

These conditions demonstrate that troponin elevation = myocardial injury, but does not automatically indicate ischemia.

Distinguishing MI From Non-MI Injury Requires:

- Clinical evaluation (symptoms, risk factors)

- ECG interpretation
- Troponin kinetics (rise/fall vs. stable elevation)
- Imaging when indicated (echo, cardiac MRI)

A dynamic change in hs-cTn is the most reliable indicator of acute injury, whereas stable elevations usually represent chronic myocardial stress.

4.2. Prognostic Uses

Beyond diagnostics, cardiac troponins serve as powerful prognostic biomarkers across cardiovascular and systemic illnesses.

Elevated hs-cTn predicts:

- Short-term mortality (e.g., 30-day mortality) in ACS, heart failure, sepsis
- Long-term cardiovascular risk, even in asymptomatic individuals
- Outcome severity in sepsis and COVID-19, correlating with ICU need and mortality
- All-cause mortality in chronic diseases such as renal failure, diabetes, or COPD

Troponin thus functions not only as a diagnostic marker but also as a quantitative index of myocardial vulnerability, offering insight into both acute events and long-term cardiovascular health.

Discussion

5.1. Mechanistic Insights

The present review highlights that cardiac troponins are biomarkers of myocardial injury, rather than exclusive indicators of myocardial ischemia. High-sensitivity cardiac troponin (hs-cTn) assays detect extremely low concentrations of troponin released from cardiomyocytes through both reversible and irreversible mechanisms. Reversible release may occur during conditions such as tachyarrhythmias, transient myocardial strain, or systemic stress, where sarcolemmal permeability temporarily increases without permanent structural damage. In contrast, irreversible release reflects true cardiomyocyte necrosis, as seen in acute myocardial infarction (MI), myocarditis, severe hypoxia, or toxic injury.

The ability of hs-cTn assays to quantify minimal troponin elevations has advanced early diagnosis of MI but has also broadened the spectrum of detectable myocardial injury. This dual effect—increased sensitivity with reduced specificity for ischemia—requires clinicians to distinguish between ischemic necrosis and non-ischemic cardiomyocyte injury. Importantly, troponin dynamics—not a single value—carry the greatest diagnostic power. A characteristic rise-and-fall pattern corresponds to acute injury, whereas persistently elevated concentrations suggest chronic myocardial stress or structural heart disease. Thus, mechanistically, troponin release should be interpreted as the biochemical end-product of injury occurring along a continuum of pathophysiological processes.

5.2. Analytical Considerations

High-sensitivity assays represent a major analytical advancement over conventional troponin assays. They offer:

- Superior precision at low concentrations (coefficient of variation ≤10% at the 99th percentile), enabling reliable interpretation of small fluctuations

- Earlier detection of myocardial injury, often within 1–2 hours of symptom onset
- Defined delta-change thresholds, which improve differentiation between acute and chronic injury

These strengths, however, must be balanced against several analytical challenges:

Biological Variability

Troponin levels may vary according to age, sex, circadian rhythm, and underlying comorbidities. Sex-specific reference intervals—especially for hs-cTnI—may improve diagnostic accuracy.

Renal Dysfunction

Chronic kidney disease reduces troponin clearance and increases baseline levels, complicating interpretation. In these patients, delta-change becomes more reliable than absolute values.

Assay-Specific Differences

hs-cTnI and hs-cTnT assays are not interchangeable. Each assay has its own analytical sensitivity, 99th percentile threshold, and precision characteristics. Therefore, serial measurements should always be performed using the same platform.

Additionally, pre-analytical factors such as sample hemolysis, heterophile antibodies, or instrument calibration can introduce variability, emphasizing the need for robust laboratory quality assurance.

5.3. Clinical Interpretation Challenges

High-sensitivity troponin testing has broadened diagnostic capabilities but has simultaneously created clinical complexity. Three principles remain essential:

1. Elevated troponin ≠ myocardial infarction

Troponin elevation simply indicates myocardial injury. Myocardial infarction is diagnosed only when clinical symptoms, ECG changes, imaging findings, or coronary evidence support ischemia in addition to elevated troponin.

2. Troponin must be interpreted within clinical context

The clinician must integrate:

- Timing of chest pain
- ECG findings
- Hemodynamic status
- Comorbid conditions (HF, sepsis, PE, CKD)
- Troponin trend (rise/fall vs. stable elevation)

A high troponin without ischemic evidence is classified as acute or chronic myocardial injury, not MI.

3. Rising/falling pattern is mandatory to diagnose MI

Dynamic change—typically a delta of ≥5–7 ng/L for hs-cTnT or assay-specific thresholds for hs-cTnI—indicates acute injury. A stable elevation suggests chronic myocardial disease.

High-sensitivity assays have increased recognition of “myocardial injury” as a distinct diagnostic entity, prompting updates in international guidelines (ESC, AHA/ACC).

This reclassification influences patient management, risk stratification, and healthcare resource use. As a result, clinicians must be trained not only to detect troponin elevation but also to correctly differentiate injury from infarction, ensuring appropriate clinical decision-making.

Conclusion

Measurement of cardiac troponins represents one of the most significant advancements in cardiovascular diagnostics, providing a highly sensitive and specific biochemical window into myocardial injury. The introduction of high-sensitivity troponin assays has transformed clinical practice, enabling reliable detection of even minimal cardiomyocyte damage, facilitating earlier recognition of myocardial infarction, and strengthening the prognostic assessment of a wide spectrum of cardiovascular and systemic conditions.

The evidence synthesized in this review underscores that troponins should be interpreted not merely as biomarkers of infarction, but as indicators of myocardial injury occurring along a continuum of physiological and pathological processes. While high-sensitivity assays improve early diagnostic accuracy, their expanded sensitivity necessitates careful clinical correlation to avoid overdiagnosis and misinterpretation of non-ischemic etiologies. The combination of absolute troponin concentration, dynamic change from baseline, and the 99th percentile upper reference limit remains fundamental in distinguishing acute myocardial infarction from other causes of injury.

Collectively, these insights reinforce the pivotal role of troponins in contemporary cardiovascular medicine and highlight the continuing evolution of biomarker-based diagnostics.

Key Conclusions

1. Troponins remain the most specific biomarkers of cardiomyocyte injury, reflecting both reversible and irreversible myocardial damage across diverse clinical contexts.
2. High-sensitivity assays enable earlier and more accurate detection of myocardial infarction, often within the first hours of symptom onset, thereby improving patient outcomes and accelerating clinical decision-making.
3. The 99th percentile upper reference limit (URL) and assay-specific delta-change thresholds are essential analytical tools for diagnosing acute myocardial infarction and differentiating it from chronic myocardial injury.
4. Troponin elevation alone is not diagnostic of myocardial infarction; interpretation must incorporate clinical presentation, ECG findings, imaging results, and temporal biomarker kinetics.
5. Future innovations—including point-of-care high-sensitivity assays, artificial intelligence–assisted interpretation, sex- and age-specific reference intervals, and integrated multimarker strategies—are expected to further enhance diagnostic precision, reduce uncertainty, and individualize patient management.

As analytical platforms continue to improve and clinical algorithms evolve, cardiac troponin measurement will remain the cornerstone of myocardial injury detection and a critical component of precision cardiology.

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