



Recent clinical research on the value of high-sensitivity cardiac troponin levels in prognostic evaluation after coronary artery bypass graft surgery: a narrative review

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Background and Objective: Coronary artery bypass grafting (CABG) is an effective treatment for coronary artery disease, high risk of complications, making it particularly important to assess patient prognosis. High-sensitivity cardiac troponin (hs-cTn), as a key biomarker of myocardial injury, plays an important role in evaluating the prognosis of patients after CABG. However, the optimal threshold values for hs-cTn in the current guidelines are all artificially set, lacking a unified standard. This narrative review aims to fill the knowledge gap and provide new directions for future research. This is of significant importance for optimizing the management of patients after CABG, improving prognosis, and for developing more precise and personalized treatment strategies.

Methods: We conducted a structured search on PubMed, Web of Science MEDLINE and Cochrane Library using terms like “High-Sensitivity Cardiac Troponin”, “Coronary Artery Bypass Grafting”, “Prognosis”, “Mortality”, and “Postoperative Outcomes” to identify English-language studies from inception to 25 July 2024. This article systematically reviews recent studies on hs-cTn levels and prognostic risk factors after CABG, aiming to comprehensively sort out and analyze existing research findings.

Key Content and Findings: Studies show that the release of hs-cTnT and hs-cTnI is related to postoperative myocardial injury/infarction and short-term mortality, but there is still controversy in the conclusions regarding long-term mortality. In addition, different studies have drawn different conclusions about the application of hs-cTnI in postoperative myocardial infarction, restenosis, and hypoxemia, as well as its association with mortality. However, a common view is that the hs-cTn cutoff values used in current clinical practice are too conservative, which may limit the accuracy of its prognosis assessment.

Conclusions: Hs-cTn has significant value in the prognosis assessment of patients after CABG, but its clinical decision level often exceeds the critical values specified in the guidelines. In the future, more rigorous prospective multicenter trials need to be conducted in different populations to further determine the optimal diagnostic thresholds for hs-cTn, thereby improving the accuracy of prognosis assessment in patients after CABG.

Keywords: Coronary artery bypass graft surgery (CABG surgery); high-sensitivity cardiac troponin (hs-cTn); prognostic assessment; risk factors

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Introduction

Coronary artery bypass graft (CABG) surgery is considered a mainstay approach for managing coronary heart disease (1). The primary objective of this surgery is to restore adequate blood flow to the myocardium by reconstructing the coronary arteries, thereby alleviating angina symptoms and improving patients' overall quality of life (2). Nevertheless, CABG surgery is complex and has inherent risks and potential complications, such as myocardial ischemia and reperfusion injury (3). These factors may result in damage to cardiac cells and subsequently increase the incidence of adverse events following surgery. Consequently, accurate assessment of post-CABG patient prognosis is of paramount importance to devise effective therapeutic strategies while minimizing complication rates.

In patients undergoing CABG, elevated levels of creatine kinase isoenzyme (CK-MB) or troponin within 24 hours after surgery are associated with increased medium- and long-term mortality rates. The current recommended threshold for postoperative high-sensitivity cardiac troponin I (hs-cTnI) testing in patients undergoing CABG is based on non-high sensitivity troponin assays, aimed at determining the optimal threshold and timing for hs-cTnI testing to facilitate postoperative clinical decision-making. hs-cTn, as a key biomarker of myocardial injury, plays an important role in evaluating the prognosis of patients after CABG. Biomarkers are the cornerstone of the diagnosis of primary myocardial infarction (MI), but their clinical significance after CABG is still unclear. Previous literature has summarized that CABG inherently induces the release of cardiac biomarkers and their potential release mechanisms, and evaluated the clinical application of cTn in perioperative treatment after CABG surgery (4). However, the optimal threshold values for hs-cTn in the current guidelines are all artificially set, lacking a unified standard. The purpose of this review is to summarize current research and clarify the value of hs-cTn levels in evaluating the prognosis of CABG surgery. We present this article in accordance with the Narrative Review reporting checklist (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-24-461/rc>).

Methods

We conducted a structured search on PubMed, Web of Science, MEDLINE and Cochrane Library using terms like “High-Sensitivity Cardiac Troponin”, “Coronary

Artery Bypass Grafting”, “Prognosis”, “Mortality”, and “Postoperative Outcomes” to identify English-language studies from inception to 25 July 2024. Our search was designed for comprehensiveness and specificity to ensure inclusion of relevant, high-quality studies. The types of studies included prospective and retrospective cohort studies, meta-analyses, involving patients who have undergone CABG, measuring either hs-cTnT or hs-cTnI, and providing data on the correlation between hs-cTn levels and patient outcomes like mortality and MI. Studies were excluded if they were irrelevant, lacking key data, based on non-human models, or not published in English. Please refer to *Table 1* for a summary of the search strategy.

Cardiac troponin (cTn)

Overview and classification of cTn

cTn, an important biomarker for myocardial injury, comprises a complex formed by three subunits: cardiac troponin T (cTnT); cardiac troponin I (cTnI); and cardiac troponin C (cTnC). CTn plays a crucial role in the prognostic assessment of patients after CABG surgery. Its high-sensitivity and specificity enable early and accurate detection of myocardial injury, providing reliable evidence for clinical diagnosis and evaluation of postoperative recovery (5).

Historical development of cTn measurements to assess myocardial damage

The specific detection of cTn to assess myocardial cell damage was first proposed by Cummins *et al.* in 1987 (6). In 1989, Katus *et al.* used an enzyme-linked immunosorbent assay to detect cTnT (7). In 1999, the National Academy of Clinical Biochemistry (NACB) published consensus guidelines on the clinical use of cTns to standardize their application (8). In 2007, the “Universal Definition of Myocardial Infarction” used cTns instead of CK-MB as diagnostic criteria for MI (9). However, the predictive effect and threshold values of this assessment tool remain controversial. In 2009, a meta-analysis incorporating 17 studies analyzed the association between elevated cTns after cardiac surgery and mortality rates in adult patients. Due to differences in population characteristics, timing of Tn measurement, Tn subunits used, and Tn assays employed across studies, the meta-analysis resulted in no definitive conclusions regarding effect size or threshold values (10).

Table 1 The search strategy summary

Items	Specification
Date of search	25 July 2024
Databases and other sources searched	PubMed, Web of Science, MEDLINE and Cochrane Library
Search terms used	Using terms like “High-Sensitivity Cardiac Troponin”, “Coronary Artery Bypass Grafting”, “Prognosis”, “Mortality”, and “Postoperative Outcomes”
Timeframe	From inception to 25 July 2024
Inclusion and exclusion criteria	The types of studies included prospective and retrospective cohort studies, meta-analyses, involving patients who have undergone CABG, measuring either hs-cTnT or hs-cTnI, and providing data on the correlation between hs-cTn levels and patient outcomes like mortality and myocardial infarction. Studies were excluded if they were irrelevant, lacking key data, based on non-human models, or not published in English
Selection process	The authors determined the research topic, collected literature materials, screened literature materials, organized literature materials, and through discussion, communication, feedback, and modification. We worked independently and collaboratively to reach a consensus

CABG, coronary artery bypass grafting; hs-cTnT, high-sensitivity cardiac troponin T; hs-cTnI, high-sensitivity cardiac troponin I.

Mechanisms of cTn release during myocardial cell injury

There are several hypotheses regarding the mechanisms of cTn release. Early studies suggested that most cTn is bound to myofibrils, with smaller amounts present as unbound molecules in the cytoplasm. This theory explains the release curve of cTn, with an initial rapid release from the cytoplasm when cells are damaged and slower release after cell necrosis or structural changes (11).

However, this hypothesis has been questioned by recent studies. Starnberg *et al.* discovered significant differences in cTn extraction rates with different serum extraction volumes, unlike other cytoplasmic myocardial biomarkers such as myoglobin and CK-MB. The authors proposed that the sustained elevation of circulating cTn after MI is a result of the reversible binding between cTn and myofibrillar tropomyosin being washed out (12).

Moreover, cTn release is not solely associated with myocardial cell death. In 2011, White proposed an association between cTn and multiple interacting pathophysiologic mechanisms, including necrosis, apoptosis, physiologic cardiomyocyte renewal, protein hydrolysis, increased cell membrane permeability, and vesicle formation/release (4).

cTn measurements after CABG surgery

During CABG surgery, cell damage and cTn release is inevitable due to factors such as surgical manipulation, cardiopulmonary bypass (CPB), and cardiac arrest. However,

in cases where surgery goes smoothly, postoperative levels of cTn will decrease rapidly (4). Patients with prolonged cTn release time often have complications, such as graft occlusion or stenosis in target vessels, ischemia-reperfusion injury, or hemodynamic instability during the perioperative period. These complications lead to more extensive myocardial damage causing continuous release of cTn (13).

In clinical practice, serum cTn detection is usually carried out using immunoassay methods, including radioimmunoassay, immunoradiometric assay, enzyme-linked immunosorbent assay, and various chemiluminescence methods. Radioimmunoassay is susceptible to interference from various factors, such as sample processing and hook effects caused by high concentrations of cTn; the advantages of high sensitivity, wide detection range, and ease of operation of chemiluminescence method have gradually become the mainstream method for detecting serum cTn. Due to significant differences in detection methods and research subjects, the relevant guidelines do not specify the reference range for baseline or post stimulus serum cTn. Each testing institution can develop their own reference range based on large sample comparative studies (14,15). Type 5 MI, as defined by the Fourth Universal Definition of Myocardial Infarction, is one of the common complications after CABG surgery (16). According to this definition, patients with normal baseline cTn levels who experience a postoperative increase in cTn concentration exceeding 10 times the upper-reference limit (URL), which corresponds to the 99th percentile of a reference population, with new-

onset pathological Q waves, angiographic evidence of coronary artery disease, or regional wall motion abnormalities are diagnosed with type 5 MI. For patients with elevated cTn values before the procedure, a diagnosis of Type 5 MI requires a post-procedure increase of more than 20% and absolute values meeting the above criteria for Type 5 MI, plus evidence of myocardial ischaemia (17). It should be noted that this diagnostic criterion is arbitrarily established, and its clinical significance remains controversial.

In addition to the European Society of Cardiology (ESC) Joint Working Group, other authoritative organizations such as The American Society of Cardiovascular Angiography and Interventions (SCAI) proposes criteria for MI as troponin levels exceeding 70 times the upper limit of normal (ULN) or 35 times the ULN with new-onset pathological Q waves or left bundle branch block (18). Meanwhile, the Academic Research Consortium-2 (ARC-2) defines MI as troponin levels exceeding 35 times the URL with new-onset pathological Q waves, angiographic evidence, or wall motion abnormalities (19). These algorithms are based on the best available evidence and thoroughly explore the relationship between cTn levels, mortality rates, and myocardial ischemia. By cleverly combining different cTn cutoff values with other criteria in defining type 5 MI, these algorithms provide robust support for clinical decision-making. In short, these algorithms indicate that further investigation is recommended if cTn levels rise to ≥ 70 times URL or increase from 10 times URL to ≥ 35 times URL within 48 hours after surgery, when accompanied by at least one of the following abnormalities: (I) new pathological Q waves on electrocardiogram; (II) complications related to restricted blood flow during angiography; or (III) new loss of viable myocardium on imaging studies (17). In most cases, invasive coronary angiography is suggested.

The emergence of hs-cTn as a biomarker of myocardial injury after CABG surgery

Traditional methods for detecting cTns have low sensitivity and may only detect elevated blood levels of cTn several hours to days after myocardial cell necrosis. After myocardial injury, it takes a certain amount of time for cTn levels in the blood to rise. Therefore, continuous monitoring for 6 to 12 hours and multiple blood samples are required to confirm the diagnosis. This not only increases the risk of complications associated with acute MI but also reduces treatment efficiency in emergency situations and

wastes medical resources (20).

In 2006, Wu *et al.* first reported the use of single-molecule flow cytometry fluorescence analysis for cTn detection, known as hs-cTn detection technology (21). This technique has higher sensitivity and a lower limit of detection (LoD) than traditional methods. In terms of performance requirements, hs-cTn technology requires stable and reliable detection of cTn in no less than 50% (traditional methods range from 20% to 50%) of healthy male and female populations at concentrations equal to or above LoD. Total coefficient variation (CV) at gender-specific URL (99th URL) concentration should be $\leq 10\%$ (traditional methods require total CV $\leq 20\%$, which is clinically acceptable). In recent years, hs-cTn measurement has been widely promoted worldwide and is increasingly being used as a major biomarker for identifying MI. However, its usage rates still vary between continents (22).

Considering that the commonly adopted threshold value of 10 times URL is arbitrarily set by humans, there are controversies regarding its diagnostic threshold and value in prognostic evaluation (23).

Clinical assessment of hs-cTnT

Extensive domestic and international clinical studies have investigated the value of hs-cTnT levels in prognostic risk assessment after CABG surgery only (24-29). A study published in the Journal of the American College of Cardiology found that perioperative release of hs-cTnT reflects postoperative myocardial injury/infarction (PMI) and is associated with 30-day mortality rate. Moreover, the risk of death after CABG surgery rises with an increase in logarithmic peak hs-cTnT values [hazard ratio (HR): 4.79; 95% confidence interval (CI): 2.898-10.21]. The prognostic threshold concentration for assessing post-CABG myocardial injury using hs-cTnT was found to be 2,385 ng/L (170 \times URL). However, it was not related to the 5-year mortality rate (28).

Another retrospective single-center cohort study indicated that elevated hs-cTnT concentrations are significantly associated with increased risk of early postoperative hypoxemia and prolonged hospital stay following off-pump CABG surgery. In contrast, hs-cTnT levels were not related to body mass index, smoking status, serum creatinine, severity of coronary artery disease, or cardiac function (24).

In a retrospective analysis based on the ERICCA trial data, involving 1,206 patients undergoing cardiac surgery,

the study assessed the association between hs-cTnT levels and 1-year all-cause mortality. The study found that an increase in hs-cTnT to ≥ 50 times the URL at 24 hours post-surgery was the optimal threshold for predicting one-year all-cause mortality risk, with a sensitivity of 73% and a specificity of 75%, regardless of whether the baseline hs-cTnT levels were normal or elevated (30).

A meta-analysis including fifteen original studies concluded that the release curve of cTn after CABG surgery is similar to that during primary spontaneous MI, with an early rapid release followed by a stable period. Blood hs-cTn levels peak within 6–8 hours after surgery at approximately 628 ng/L (95% CI: 400–856 ng/L; $45 \times$ URL) (29).

In summary, the prognostic value of hs-cTn has been widely recognized for patients undergoing CABG surgery; however, its clinical decision level still exceeds the critical value specified in guidelines.

Clinical assessment of hs-cTnI

Compared with hs-cTnT, clinical studies hs-cTnI are still in the early stages. A study involving 13,862 patients found that a cTnI threshold of 5,670 ng/L ($218 \times$ URL) measured within one day after isolated CABG surgery was positively correlated with mortality within 30 days (26). Another study involving 4,684 patients found that peak hs-cTnI levels of 13,000 ng/L ($500 \times$ URL) were significantly associated with the need for repeat revascularization within 48 hours after surgery in patients with post-bypass graft vascular restenosis or occlusion. The same threshold value could also predict major adverse cardiovascular events within 30 days and all-cause mortality during a follow-up period of 3.1 years. However, early elevation of hs-cTnI after surgery had a low impact on clinical decision-making; only late elevation (12–16 hours after surgery) was significantly associated with repeat revascularization (13).

In terms of MI, a study of 374 patients showed that in patients with normal preoperative hs-cTnI levels, the average level at six hours post-surgery was 9,193 ng/L ($270 \times$ URL). Among these patients, eleven (7.3%) experienced postoperative MI and had an average hs-cTnI level at six hours post-surgery of 50,218 ng/L ($1,477 \times$ URL). In patients who had elevated preoperative hs-cTnI levels, the average level at six hours post-surgery was 9,449 ng/L ($292 \times$ URL). Eleven (4.9%) of these patients experienced postoperative MI with an average hs-cTnI level of 26,823 ng/L ($789 \times$ URL) at six hours post-surgery (25).

However, a study involving 300 patients presented a

different perspective. Although the majority of patients who underwent CABG surgery were found to have hs-cTnI levels exceeding the threshold recommended by the latest guidelines for diagnosing type 5 MI ($10 \times$ URL), there was no association between hs-cTnI levels and postoperative myocardial injury. Instead, a significant correlation was observed only with a decrease in left ventricular ejection fraction of $\geq 10\%$. The critical value for hs-cTnI at 9–12 hours postoperatively was determined to be 5,556 ng/L, which is 281 times the URL for males and 479 times that for females. Furthermore, no significant association was found between absolute hs-cTnI values and mortality rates, although the average value of hs-cTnI increased by more than double in patients who died during hospitalization (27).

These contrasting conclusions may be attributed to the high sensitivity of hs-cTnI testing weakening its specificity and positive predictive value in the clinical setting of CABG patients. Additionally, statistical results may also be subject to chance when sample size is small and adverse event numbers are low.

Discussion

The strengths of our study lie in its innovative nature, effectively bridging a gap in this research field. However, there are also some limitations. The current research is relatively sparse and predominantly consists of single-center retrospective studies, with inconsistent inclusion and exclusion criteria for participants across the included literature. Furthermore, some studies focus on off-pump coronary artery bypass grafting (OPCABG) while others concentrate on CABG, leading to a lack of uniformity. Additionally, few studies have conducted stratified analyses based on different ethnicities, ages, genders, and circadian rhythms, which hinders in-depth risk assessment for specific populations. In fact, the hs-cTnI threshold is not fixed and can be influenced by various factors including but not limited to the choice of detection method, specific timing of detection, scale and scope of research, as well as differences in patient ethnicity (31–33), age (34,35), gender (33,36,37), and circadian rhythm (38). Therefore, it may still be necessary to conduct larger-scale and more in-depth prospective studies in the future to determine more accurate and practical critical values.

Regarding high-sensitivity troponin detection kits, four studies mentioned them, with two studies using Abbott Laboratories (25,26) and one using Beckman Coulter for hs-cTnI detection (27); for hs-cTnT, only one study specified

the use of Roche Diagnostics (28). Several authoritative guidelines have clearly indicated that high-sensitivity troponin assay kits produced by different manufacturers may impact the test results (9,39,40). Therefore, these guidelines recommend using only a single brand of assay kit within the same testing center to ensure the consistency and comparability of results. However, in our literature review, only a few studies explicitly reported the manufacturer of the assay kits used, which may have an impact on the determination of thresholds and the interpretation of results. This lack of information may complicate the comparison between different studies and the integration of results, thereby affecting a comprehensive assessment of the accuracy and reliability of high-sensitivity troponin assays. Therefore, future research should place greater emphasis on reporting the specific assay kit information used to more accurately assess and compare the results of different studies.

Hs-cTn is also utilized in algorithms for assessing for rule-out/rule-in of MI in the emergency department, demonstrating exceptionally high rule-out performance (41,42). However, it is noteworthy that only 8% of the subjects in existing studies have undergone CABG. And a 2,022 study on an American population indicated lower diagnostic accuracy of hs-cTnI and effectiveness of the ESC 0/1 h hs-cTnI algorithm among previous CABG patients, although sensitivity and specificity remained high (43). Therefore, there is a need for larger and more in-depth studies to promote and apply this algorithm in the specific population of CABG patients.

It is worth noting that the recommended time window for measuring hs-cTnI in most current studies is within 9–24 hours after coronary artery bypass transplantation. This recommendation is based on clinical evidence showing that test results performed during this time period are more effective in predicting postoperative adverse events. In contrast, earlier assay results after surgery are weakly associated with patient prognosis, which may mean that early measurement does not provide an accurate enough prediction of adverse event risk (4). Therefore, performing the assay at the optimal time after surgery can not only improve the accuracy of prediction, but also help to avoid unnecessary early assays, thereby saving medical resources, improving the efficiency of medical services, and reducing the burden on patients. It is important to emphasize that the diagnosis of ischemia and infarction immediately after CABG should primarily rely on clinical assessment, including hemodynamic or electrical instability, echocardiography, and electrocardiography (ECG) changes,

as outlined in previously mentioned guidelines (9,18,19).

In summary, hs-cTnI has predictive value for several major adverse events that may occur after CABG surgery. Different studies have varying conclusions regarding the use of hs-cTnI in patients with postoperative MI, restenosis, and postoperative hypoxemia, and regarding the association of hs-cTnI with mortality rates. However, it is widely recognized that the recommended cutoff values currently used in the medical field are overly conservative and limit its clinical application to some extent.

Conclusions

Hs-cTn has significant value in the prognosis assessment of patients after CABG, but its clinical decision level often exceeds the critical values specified in the guidelines. In the future, more rigorous prospective multicenter trials need to be conducted in different populations to further determine the optimal diagnostic thresholds for hs-cTn, thereby improving the accuracy of prognosis assessment in patients after CABG.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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