The Impact of Elevated Troponin Levels on Clinical Outcomes in Patients with Acute Ischemic Stroke: A Systematic Review

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Abstract

The association between high cardiac troponin (cTn) levels and stroke characteristics and outcomes remains unclear. This systematic review aimed to determine the prevalence and clinical implications of elevated cTn levels in patients with acute ischemic stroke (AIS). We conducted a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines. A comprehensive search of PubMed, Google Scholar, Science Direct, and Research Gate databases was conducted to identify relevant studies published in English up to May 2023. This study included all reports on serum cTn levels and AIS. Two independent reviewers assessed study quality and bias using study-specific tools before inclusion. The systematic review included a total of 14 articles with 16906 participants, including one systematic review, one randomized controlled trial (RCT), and 12 observational studies. The results of this systematic review indicate that the prevalence of high cTn levels is averaged at 17.9%, or 1 in 5 individuals, who have an AIS. The review emphasizes the detrimental effects of increased cTn levels on outcomes for in-hospital and all-cause mortality as well as cardiovascular outcomes in patients with AIS. These results demonstrate that serum cTn has the potential to be a useful tool for risk classification and prognostic assessment in individuals with AIS. AIS patients with elevated serum cTn at baseline have an increased risk of mortality. Early and routine evaluation of serum cTn may contribute to the timely detection of co-morbid cardiovascular injury and prevent unfavorable outcomes in patients with AIS.

Keywords: Acute ischemic stroke, brain ischemia, cardiac cTn, cerebrovascular accident, cTn, stroke

Introduction

Our knowledge of the complex interplay between the heart and the brain has advanced beyond the conventional paradigm, which holds that cardiac mechanisms lead to brain injury, to now include a bidirectional interaction, where an acute dysfunction of one organ system negatively affects the other[1] Acute brain injury, such as an ischemic or hemorrhagic stroke, is a trigger for myocardial injury, also known as neuro-cardiogenic syndromes. These syndromes can range from asymptomatic cardiac troponin (cTn) elevations to symptomatic myocardial ischemic injury and even heart failure like Takotsubo cardiomyopathy.[2]

Acute ischemic stroke (AIS) is triggered by persistent brain damage as a result of blood flow disruption. Stroke remains the second-leading cause of death and the third-leading cause of death and disability (as expressed by Disability Adjusted Life Years Lost DALYs) worldwide. More than 11 million ischemic strokes occur worldwide each year, out of which ischemic strokes account for about 68% of all strokes.[3] Current guidelines on the early management of stroke include evaluating cTn in all patients with suspected stroke. These guidelines were developed to increase the early identification of a cardioembolic source of stroke and to recognize people who are at high risk for adverse outcomes and heart disease. Myocardial injury, as identified by cTn, may occur as a direct result of stroke, a condition known as "Stroke-Heart syndrome".[4] cTn elevation has been linked to ischemic stroke with a cardioembolic etiology, poor functional outcome, and increased short- and long-term mortality. About 20%–60% of individuals with AIS show elevated cTn levels.[5] Multiple studies have identified increased levels of myocardial damage markers in a subset of individuals with acute stroke,[6,7] and these levels are related to mortality.[8,9] In individuals with ischemic stroke, hs-cTn elevation has been found without concurrent acute Myocardial Infarction (MI)[10] and may have contributed to an increased risk of death or cardiovascular events.[4,11] The most recent American Heart Association advisory recommends routine cTn assessment for the early care of patients with AIS, regardless of the inconsistent independent evidence correlating cTn to poor outcomes.[12]

Although a prior stroke is a substantial risk factor for recurrent stroke, it is vital to determine whether myocardial damage

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independently raises this risk after an incident stroke, even though no such association was identified.[1] However, whether the mechanism of cTn increase during the acute stage of ischemic stroke is attributable to concomitant cardiac issues,[13] noncardiac comorbidities,[14] or neurally mediated myocytic injury is yet unknown.[8] The prevalence of acute myocardial infarction in AIS is generally low, and there is a significant lack of data on the diagnostic yield of screening cardiac cTn for Acute MI.[15] The correlation between elevated cardiac cTn levels and stroke outcome has not been elucidated thoroughly yet.[16] The clinical relevance of an increased cTn level as well as its etiology are both unknown. Some studies have demonstrated an independent link between case fatality[7,8,17] and the combined worse outcome of mortality or disability.[13,18] Other investigators, however, have discovered no independent relationship.[19,20,38]

Therefore, we conducted a thorough systematic review of cTn measurement studies in acute stroke to assess the overall prevalence of increased cTn as well as the potential relationship between elevated cTn and functional outcomes such as death, disability, and clinical improvement. The rationale for this systematic review is to address the existing knowledge gap regarding the association between high cTn levels and stroke characteristics and outcomes.

Review questions

This systematic study attempts to address numerous important issues regarding increased cTn levels in patients with AIS. First, it investigates the occurrence of increased cTn and considers its clinical consequences. The review offers insights into the significance and potential diagnostic utility of elevated cTn by examining its frequency in this patient population. Second, it is looked into whether there is a connection between increased cTn levels and clinical outcomes like death, disability, or improvement. The review intends to assess the potential prognostic value of high cTn levels by assessing relevant studies to assess the potential prognostic value of elevated cTn levels. In the end, this study will shed light on the possibility of increased cTn as a biomarker for predicting outcomes in AIS and determine the prognostic importance of this observation.

Methods

We carried out a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) guidelines. The review is carried out at the California Institute of Behavioral Neurosciences and Psychology, Fairfield, California, USA.

Eligibility criteria for considering studies under this review

Inclusion criteria

The studies were chosen for inclusion based on the following participant, intervention, and outcome characteristics. Population: Patients with AIS, Intervention/Exposure: Elevated cTn levels, Comparison: Comparison with patients having normal cTn levels, and Outcome: Clinical outcomes such as mortality, functional impairment, and stroke severity.

The studies with the following criteria were included in the review: Studies published in the English language, focusing on the adult population only (>19 years), involving only human participants, available for free full text, within 20 years of publication date (2003–2023), focusing on AIS including elevated cTn levels or clinical outcomes or both and all studies reporting the association between cTn on admission and mortality in AIS patients.

Exclusion criteria

We restricted our choice of studies to exclude the following: Animal participants, studies published before 2003, patients aged less than 19 years, other language studies, paid articles, gray literature, patients diagnosed with confirmed hemorrhagic stroke by standard methods, and an unfavorable diagnosis such as silent infarcts.

Search strategy for identification of records in this review

The following databases are used: PubMed, Google Scholar, ScienceDirect, and Research Gate. All possibly pertinent articles describing the potential link between increased cTn in patients with AIS and the outcomes are found by searching for relevant keywords and Medical Subject Heading (MeSH) phrases. AIS, cerebrovascular accident, elevated cTn levels, cTn, High cTn levels, Increased cTn levels, Clinical outcomes, AIS, Mortality, Morbidity, Functional outcome, Disability evaluation, Quality of life, Activities of daily living, Hospitalization, and Length of stay were used in the search. To search through numerous databases, the Boolean approach is utilized to combine the keywords and MeSH terms. For duplicate removal, all references are grouped and alphabetized in EndNote. The records are initially examined based on the titles and abstracts, with irrelevant studies being excluded. The full-text papers are subsequently assessed for further exclusion. We utilized artificial intelligence, specifically ChatGPT, for formulating sentences within the manuscript. The details of the search design used for this systematic review are shown in Table 1.

Selection of studies for inclusion in the review

Two reviewers scanned titles and abstracts independently and resolved conflicts through consensus. In the event of a continuing disagreement, a third reviewer intervened. All potentially relevant records are evaluated by the same reviewers. We kept track of the reasons why studies are excluded from this review.

Assessment of the methodological quality and risk of bias

The remaining 19 studies were individually evaluated for quality by two independent authors using study-specific techniques. Each assessment tool has its scoring system, and studies with a score of more than 70% were accepted for inclusion in this study. Out of 19 papers, the quality assessment of the studies, as well as the tools utilized, are summarized in Table 2.

Table 1: Details of the search strategy used in this systematic review

Search strategy	Database used	Filters applied	Number of research papers identified
((“Stroke, Ischemic” OR “Cerebral Infarction” OR “Brain Ischemia” OR “Cerebrovascular Accident” OR “Stroke”) AND ((((“Mortality” OR “Morbidity” OR “Functional Outcome” OR “Disability Evaluation” OR “Disability” OR “Quality of Life” OR “Activities of Daily Living” OR “Hospitalization” OR “Length of Stay”) AND ((“Elevated cTn” OR “High cTn” OR “Increased cTn” OR “cTn Elevation” OR “cTn Release”) OR ((“cTn” OR “Cardiac cTn” OR “cTn T” OR “cTn I”)	PubMed	Human subjects, Adults: 19+years, young adults: 19–24 years, Adults: 19–44 years, Middle Aged+Aged: 45+years, Middle Aged: 45–64 years, Aged: 65+years, 80 and over 80+years, Date of Publication: 2003–2023	110
“elevated cTn levels” OR “high cTn levels” OR “increased cTn levels” AND “clinical outcomes” OR “treatment outcome” OR “mortality” OR “morbidity” OR “functional outcome” OR “disability evaluation” OR “quality of life” AND “acute ischemic stroke” OR “Cerebrovascular accident”	Google Scholar	English papers, Humans	115
levels of cTn in acute ischemic stroke, mortality in stroke, improvement in stroke, cTn, acute ischemic stroke, quality of life, clinical outcomes, stroke mortality, humans, 19+years	Science Direct	2003–2023	42
Acute ischemic stroke, elevated cTn	Wiley online library	2003–2023	27
((((“cTn”[Majr]) OR “cTn C”[Majr]) OR “cTn T”[Majr]) OR “cTn I”[Majr]) AND (((((“Stroke”[Majr]) OR “Ischemic Stroke”[Majr]) OR “Brain Ischemia”[Majr]) OR “Stroke”[Mesh]) OR “Cerebral Infarction”[Majr])	PubMed	English, Humans, Date of Publication: 2003–2023, Adults: 19+years, young adults: 19–24 years, Adult: 19–44 years, Middle Aged+Aged: 45+years, Middle Aged: 45–64 years, Aged: 65+years, 80 and over 80+years	141
Acute ischemic stroke and cTn	Research gate		36

1. ((“Stroke, Ischemic” OR “Cerebral Infarction” OR “Brain Ischemia” OR “Cerebrovascular Accident” OR “Stroke”). 2. ((“Mortality” OR “Morbidity” OR “Functional Outcome” OR “Disability Evaluation” OR “Disability” OR “Quality of Life” OR “Activities of Daily Living” OR “Hospitalization” OR “Length of Stay”). 3. ((“Elevated cTn” OR “High cTn” OR “Increased cTn” OR “cTn Elevation” OR “cTn Release”) OR ((“cTn” OR “Cardiac cTn” OR “cTn T” OR “cTn I”). Combined (#1), (#2), (#3} using Boolean terms

Table 2: Details of quality assessment tools used to assess the studies in this systematic review[42-44]

Quality assessment tool	Type of Study	Total score	Accepted Score (>70%)	Number of accepted studies
Assessment of Multiple Systematic Reviews (AMSTAR) 2[42]	Systematic reviews	16	12	Gillian Kerr (2009)[32]
Cochrane Collaboration Risk of Bias tool (CCBRT)[43]	Randomized controlled trials (RCT)	7	5	Jan F. Schietz (2011)[30]
New Castle Ottawa tool[44]	Observational, cohort	8	6	Hrvoje Budincevic (2016),[16] E Di Angelantonio (2004),[7] Lanying He (2018),[31] Yu-Chin Su (2016),[36] Peter Wrigley, MD (2017),[34] Bum Sung Kim (2022),[10] Pradeep Thapa (2020),[37] Hadi Gharebaghian Azar (2023),[25] Azza A. Ghali (2021),[24] Mathieu Kruska (2022),[33] Yu-Xia Cui (2017),[27] Siamak Abdi (2015).[26]

Abbreviations: AMSTAR 2: Assessment of Multiple Systematic Reviews 2[42], RCT: randomized control trial[43], CCBRT: Cochrane Collaboration Risk of Bias tool[44]

Results

A total of 480 records were identified from four databases, namely PubMed, Science Direct, Google Scholar, and Research Gate. After removing 69 duplicate records, 401 records were screened based on their titles and abstracts. Out of these, 253 records were excluded as irrelevant, leaving 148 studies for full-text screening. Of these, 129 studies were excluded, and 19 studies were assessed for quality using specific tools for each type of study. We excluded five studies, two were excluded because they included patients with hemorrhagic stroke, two were excluded for low scores in the quality assessment tool and one was a review article.

Ultimately, a systematic review included 12 studies with a total of 16,906 participants. These studies scored above 70% in the quality assessment, as evaluated by two reviewers. The selected studies include one systematic review, one randomized controlled trial (RCT), and 12 observational studies. The data collection process for the review concluded on May 8,

2023. Figure 1 presents the PRISMA flow chart detailing the identification and screening process used to select the final studies for inclusion in the review.

Data extraction and management

Table 3 includes a summary of the included studies. The data was extracted in a Microsoft Excel spreadsheet to include authors, year of publication, eligibility criteria, number of participants and type of study, sampling time, cTn cut-offs, study outcomes, and conclusions.

Discussion

This systematic review, which took into account the neurological condition separately, confirmed the overall impact of the comorbidity burden on cTn increase in AIS. In this study, the overall incidence of cTn elevation was not comparable but the study compared the effects of elevated cTn on clinical outcomes after AIS. Repeated cTn readings are advised by traditional AIS care guidelines in a few cases where there is a chance that silent ischemia would develop.[4] A highly sensitive cTn assay for the purposeful detection of dynamic change can help to clarify the role of dynamic changes in cTn levels in determining the cause of cardiomyocyte damage and differentiating acute increases from persistent elevations linked with a range of chronic diseases.[4] In this regard, our study demonstrates that repeated measurements of cTn utilizing a highly sensitive cTn assay can improve the identification and monitoring of cTn elevation, including newly identified as well as minimally-elevated cTn.

Multiple distinct cTn tests and thresholds were utilized in the studies. Additionally, some studies included patients without documented cardiac disease or renal impairment, while others did. The researcher's interpretation of cTn positivity was employed, and studies involving hemorrhagic stroke and review articles were excluded from our analysis. A total of 16,906 participants, encompassing systematic review, observational studies, and clinical trials, were evaluated for elevated cTn levels in cases of AIS. The primary outcomes and conclusions consistently demonstrated significant adverse consequences in patients with heightened levels of cTn in their serum, either upon admission, within 48–72 hours, or seven days of symptom onset or hospital admission. The sample collection for the same generally occurs at the first point of medical contact before initiation of any therapy. The primary and secondary outcomes of the study were assessed based on clinical measures such as deaths, readmission rates, and cardiovascular diseases. Overall, all the reviewed studies reported higher mortality rates and poorer functional outcomes in AIS patients with abnormal cTn levels across a majority of outcome measures.

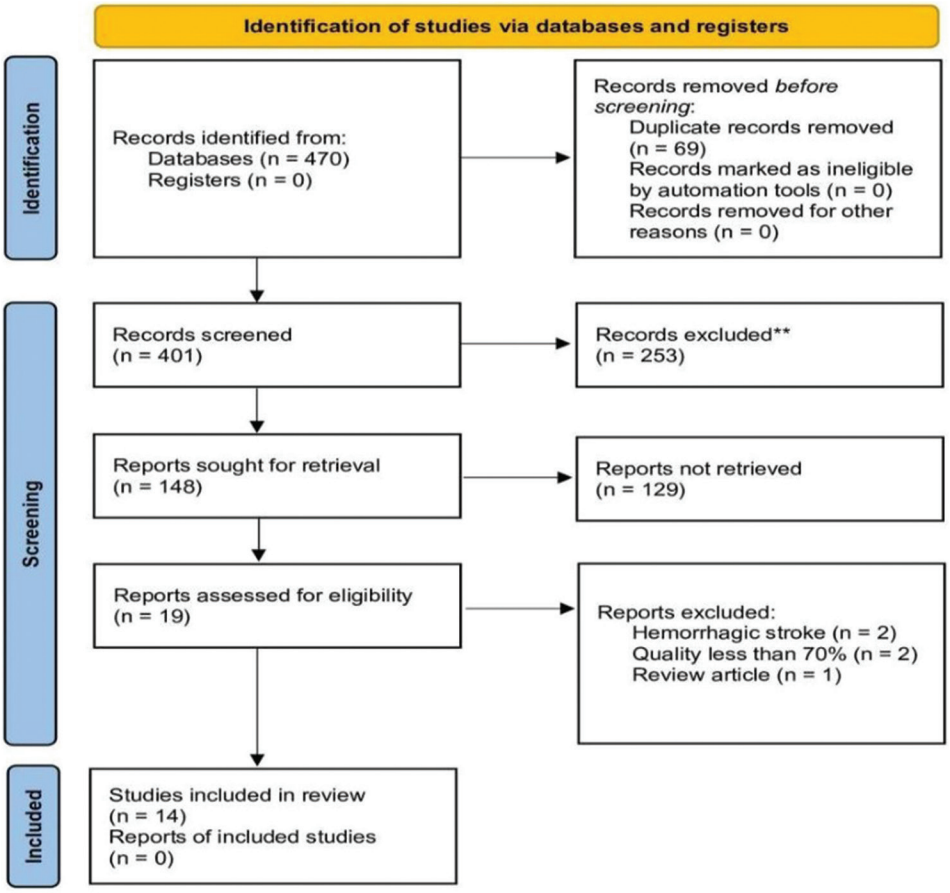

Figure 1: PRISMA Flowchart demonstrating the selection process of the included articles

Table 3: Studies evaluating cTn elevation and clinical outcomes in patients with acute ischemic stroke

Authors and publication year	Eligibility criteria	Number of participants	Study type	Sampling time	cTn types, cut-off values, and abnormal cTn%	Outcomes	Conclusion
Hrvoje Budincevic *et al.*, (2016)[16]	Exclusion criteria: concomitant acute coronary syndrome, severe congestive heart failure, pulmonary embolism, renal failure, rhabdomyolysis, and septic conditions (sepsis, endocarditis, myocarditis)	196	Retrospective study	Up To 72 hours after the onset of stroke symptoms	cTn I (TnI); 0.5 µg/L; 5.05%	The statistically significant difference in the proportion of deaths during Hospitalization. Prior ischemic strokes were more common in the group with elevated TnI levels.	Patients with elevated initial TnI levels are associated with unfavorable outcomes or death.
Jan F. Scheitz *et al.*, (2011)[30]	Inclusion criteria: Acute ischemic stroke (AIS) confirmed by cerebral imaging within 72 hours of symptom onset, High sensitivity cTn T (HsTnT) >=0.05 µg/L Exclusion criteria: Impaired renal function, pregnancy, contraindications to coronary angiography, ST elevation MI (STEMI), patients less than 18 years of age, Limited life expectancy.	58	Prospective matched pair clinical trial	On admission and again on the following day	Cardiac cTnT (cTnT); >0.05 µg/L; 16.67%	Elevated cTn levels occurred in 1/6 patients and are associated with severity and unfavorable short and long-term clinical outcomes.	Patients with acute ischemic stroke frequently experience cTn increase, which is associated with unfavorable outcomes.
Gillain Kerr *et al.*, (2009)[32]	Recruitment had to include consecutive admissions with routine measurement of cTn T (TnT) or TnI. No language restrictions.	2901	Systematic review and meta-analysis	Within seven days after symptom onset	different cTn assays and cut-offs were used; 18.1%	Unfavorable cardiovascular outcomes.	Elevated cTn level after acute stroke is common occurring in 1 in 5 patients and is associated with an increased risk of death.
Azza A. Ghali *et al.*, (2011)[24]	Inclusion criteria: clinical diagnosis of stroke Exclusion criteria: Patients with subarachnoid or hemorrhagic stroke patients with transient focal neurologic deficits; Any recent ischemic heart disease, defined as MI; Symptoms suggestive of Acute myocardial infarction (AMI) or unstable angina before admission; Newly developed pathologic Q waves on admission ECG; Previous coronary angioplasty or coronary bypass surgery; and Other heart diseases and debilitating diseases with the possibility of serum cTnT elevation, such as valvular heart disease, congestive heart failure, and end-stage renal disease.	72	Observational study	12–72 hours after admission	cTnT; 0.5 ng/l; 36.1%	Increased clinical outcomes manifesting as Electrocardiogram (ECG) changes and elevated cTnT levels in acute ischemic stroke.	Elevated cardiac cTn, ECG changes, and ECG changes in acute stroke and poor outcome in ischemic strokes especially with insular involvement.
Di Angelantonio *et al.*, (2005)[7]	All the patients in the emergency department from Feb 2001 to Jan 2002.	330	Prospective cohort study	Within 24 hours of symptom onset	cTn; 0.01 ng/l; 16.3%	Increased rate of death, non-fatal AMI, a major non-fatal cardiopulmonary event during the hospital stay, more common in patients with high abnormal cTnI.	cTnI positivity on admission is an independent prognostic predictor in acute ischemic stroke.

Contd...

Table 3: Contd...

Authors and publication year	Eligibility criteria	Number of participants	Study type	Sampling time	cTn types, cut-off values, and abnormal cTn%	Outcomes	Conclusion
Lanying He *et al.*, (2018)[31]	Eligible patients were all patients admitted to the stroke unit during the study period between May 2012 and December 2017. Inclusion criteria: Admission for first-ever acute ischemic stroke; Evidence of a single acute hemispheric lesion consistent with clinical manifestations. Exclusion criteria: Cardiac diseases (include acute myocardial infarction, congestive heart failure, a history of tachyarrhythmia/bradyarrhythmia or atrial fibrillation), pulmonary disease and impaired renal function (estimated maladministration rate <60 mL/min per 1.73 m^2) were excluded; Any pharmacological treatment, including β-blockers, possibly affecting the autonomic function were excluded; Cerebral hemorrhage, fever, hypoxia also were excluded.	516	Prospective study	On admission	HsTnT; 14 ng/l; 22.87%	The incidence of insular stroke is more likely in patients with hs-cTnT elevation. There was an association between serum hs cTnT elevation and death, major disability, and composite outcome.	Higher serum hs-cTnT levels were independently related to an increased risk of mortality or significant impairment after stroke onset, implying that serum HsTnT may have predictive significance in poor ischemic stroke outcomes.
Hadi Gharebaghian Azar *et al.*, (2023)[25]	All patients diagnosed with acute ischemic stroke who were admitted to Hospital in Kermanshah, Iran, from March 21, 2018 to March 20, 2019. Exclusion criteria: pregnant and breast-feeding patients; patients with renal impairment with Glomerular filtration rate (GFR <30); severe dehydration, pulmonary edema symptom; an acute or chronic pulmonary disease requiring intermittent or permanent oxygen supplementation; Intracranial hemorrhage (ICH) after an ischemic stroke detected by brain CT scan	159	Case-control study	48 hours within the admission	cTnI; 0.015–0.045 ng/l; 1.3%	Increased prevalence of positive cTn among ischemic stroke patients for a year among Iranian Kurdish people.	It is advised that all individuals with AIS have their cTn levels routinely assessed. cTn increase could be associated with a cardioembolic cause of stroke. Because all acute stroke patients undergo routine ECGs, it is debatable whether routine cTn testing is necessary for all patients or can be limited to those with ECG anomalies.
Matheiu Kruska *et al.*, (2016)[33]	Neuroimaging-confirmed AIS or Transient Ischemic attack (TIA) between March 2010 to May 2020	8322	Retrospective observational monocentric study	Within 48 hours after admission	cTnI; 0.01 μg/L; 22.5%	Only 40% of AIS and TIA patients with clinically suspected type I MI presented obstructive CAD.	In patients who have previously experienced a stroke, TIA, increased cTn levels, and are suspected of having concurrent type I MI, the risk of obstructive Coronary Artery Disease (CAD) is relatively low.

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Authors and publication year	Eligibility criteria	Number of participants	Study type	Sampling time	cTn types, cut-off values, and abnormal cTn%	Outcomes	Conclusion
							The subset of AIS patients who have big artery atherosclerosis and high cTn may be particularly sensitive and at risk for developing obstructive CAD.
Yu-Chin Su *et al*., (2017)[36]	Inclusion criteria: Diagnosis of acute ischemic stroke by clinical presentation and neuroimaging. Availability of Serum TnI study in the Emergency Department	871	Retrospective study	Within 48 hours of symptom onset	cTnT and cTnI assays; 0.01 µg/L; 16.8%	Compared to patients with normal cTn, patients with elevated cTn were associated with poor clinical outcomes and in-hospital mortality	For patients with aberrant cTn levels, comprehensive evaluation of cardiac problems is warranted since the elevation of TnI after acute stroke is a strong independent predictor of both poor prognosis and in-hospital death.
Peter Wrigley *et al*., (2017)[34]	Inclusion criteria: Only residents of the 5 study counties were eligible for this study; adult patients (aged≥20 years) with AIS who presented to an emergency department.	1999	Retrospective cohort study	-	cTnT and cTnI assays; 0.01 µg/L; 20.7%	The relationship between cardiac testing abnormalities and long-term mortality with elevated cTn levels within a large biracial population of stroke patients has been described as 21% of AIS patients have hypercTnemia and 10% have ECG findings of interest.	In the context of AIS without concurrent MI, hypercTnemia was related to structural cardiac events and long-term mortality.
Bum Sung Kim *et al*., (2022)[10]	Inclusion criteria: primary diagnosis of cerebral infarction with rapid-onset focal neurologic symptoms lasting at least 24 h within seven days of onset; 18 years of age or older; patients evaluated for high-sensitivity cardiac cTnI (HsTnI) level at the time of admission for ischemic stroke. Exclusion criteria: Patients undergoing Percutaneous intervention (PCI) or urgent Coronary artery bypass graft (CABG) surgery during index admission with ischemic stroke; patients with no follow-up visit after ischemic stroke; patients with insufficient clinical or laboratory data on initial evaluation and follow-up visit.	1019	Retrospective single-center study	Within seven days of onset of symptoms	Hs-TnI; 1.9 ng/l; 30.5%	The patients with elevated hs-TnI have a major adverse cardiac and cerebrovascular event (MACCE) during follow-up and readmission caused by coronary revascularization, heart failure, and stroke.	In patients with ischemic stroke, elevated HsTnI has been independently associated with increased mortality as well as cardiac and cerebrovascular complications, and it may be an effective prognostic indicator in post-ischemic stroke management.

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Table 3: Contd...

Authors and publication year	Eligibility criteria	Number of participants	Study type	Sampling time	cTn types, cut-off values, and abnormal cTn%	Outcomes	Conclusion
Pradeep Thapa *et al*., (2020)[37]	Inclusion criteria: diagnosis of acute ischemic stroke that was confirmed by clinical presentation and proof of an ischemic lesion and/or absence of a corresponding intracranial lesion other than infarction by brain computed tomography or magnetic resonance imaging. Exclusion criteria: Patients with a history of MI in the past four weeks; Patients with a history of renal impairment.	101	Prospective observational study	At the time of admission and within 48 hours of admission regardless of onset of symptoms.	TnI; 0.012 ng/l; 7.9%	Patients of acute ischemic stroke with abnormal TnI had poorer outcomes than normal TnI level patients and significantly higher deaths. Elevated levels of cardiac cTn have been reported in 10%–34% of patients with acute stroke.	cTn I am a stronger source of data for predicting stroke outcomes than age and other laboratory variables. Acute stroke-related elevation of cTn I is a powerful predictor of both unfavorable outcomes and in-hospital death.
Yu-Xia CUI *et al*., (2017)[27]	Inclusion criteria: Acute ischemic stroke confirmed by head CT and diagnosed based on the 2014 diagnostic criteria, specified in the guidelines issued by the Chinese Medical Association, Neurology Branch for the diagnosis and treatment criteria of acute ischemic stroke in China. Exclusion criteria: patients with disease onset time >1 week; patients who did not undergo cTnI testing or those with incomplete clinical data; and where elevated cTnI was caused by some other diseases, including chronic heart failure, severe liver and kidney dysfunction, muscle diseases, tumors, infections, and immune diseases.	248	Retrospective study	-	cTnI; 0.034 ng/l; 18.5%	Patients with acute ischemic stroke with elevated cTnI comprised 18.5% of subjects. Patients with elevated cTnI were older and more likely to have a history of hypertension. In addition, these patients had higher levels of inflammatory markers, reduced renal functions, increased D-dimer levels, higher National Institute of Health Stroke Scale (NIHSS) scores, and lower left ventricular ejection fractions. The duration of hospital stay and incidence of major cardiovascular outcomes were greater in patients with acute ischemic stroke, with or without elevated cTnI.	Elevated cTnI levels in patients with acute ischemic stroke predicted a poor short-term prognosis during hospitalization.
Siamak Abdi *et al*., (2015)[26]	Patients with AIS confirmed by clinical features and neuroimaging presenting to Shariati Hospital Tehran, Iran from January 2013 to August 2013 were enrolled.	114	Observational study	On admission	cTnT; 1 ng/l; 17.6%	TnT was elevated in 20 (17.6%) of 114 patients. Patients with elevated cTn were more likely to have higher age, higher serum creatinine, and ischemic ECG changes. cTn levels were higher in patients with more severe strokes measured by the NIHSS scale. There was no significant association between levels of cTn and the location of stroke and atrial fibrillation.	The severity of the stroke rather than its site was associated with higher cTn levels. Abnormal cTn levels are more frequently associated with cardiac and renal disorders than cerebral ones however, this is not always the case.

cTn: Cardiac cTn, cTnT: Cardiac cTn T, TnI: cTn I, cTnI: Cardiac cTn I STEMI: ST Elevation Myocardial infarction, AIS: Acute Ischemic Stroke, AMI: Acute Myocardial Infarction, TnT: cTn T, ECG: Electrocardiogram, ICH: Intracranial Hemorrhage, CT: Computed Tomography, GFR: Glomerular Filtration Rate, TIA: Transient Ischemic Attack, CAD: Coronary Artery Disease, HsTnT: High Sensitivity cTn T, HsTnI: High Sensitivity cTn I, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Graft, MACCE: Major Adverse Cardiac and Cerebrovascular Accident, NIHSS: National Institute of Health Stroke Scale

Causes of acute elevation of cTn in AIS

As depicted in Figure 2, the possible cause of increased levels of cTn in patients with ischemic stroke can be divided into two main categories: ischemic myocardial injury resulting from coronary ischemia, and non-ischemic myocardial injury not associated with coronary issues. It is important to note that these mechanisms are not necessarily exclusive, as both ischemic and non-ischemic factors can reveal underlying coronary artery disease (CAD).[4] However, numerous non-CAD conditions should be considered as possible causes of cTn elevation.

The timing of blood collection for cTn level is crucial in determining its correlation with the outcome in patients presenting with chest pain. In addition to acute coronary syndrome (ACS), several non-ACS conditions should be considered when interpreting elevated cTn levels.

Acute aortic dissection (AAD) is one such condition where cTn levels can be elevated in up to 18% of patients.[4] This emphasizes the importance of ruling out AAD in patients with chest pain and elevated cTn levels. Pulmonary embolism (PE) is another common non-ACS cause of chest pain with variable cTn elevation, occurring in 10%–50% of cases. Identifying elevated cTn levels in patients with PE helps in risk stratification and management decisions.[23]

Other cardiac conditions that can present with chest pain and elevated cTn levels include post-revascularization myocardial injury, myocarditis, acute pericarditis, and blunt-force trauma to the heart. In myocarditis, cTn elevations are not only common but also prognostically significant. Therefore, considering these alternative diagnoses is crucial to avoid misdiagnosis and provide appropriate management.[4] Elevated cTn levels can also be seen in non-cardiac conditions such as severe hypertension or hypotension, severe upper gastrointestinal bleeding, and systemic inflammatory response syndrome, often associated with myocardial dysfunction and a worse prognosis.[4] Furthermore, acute stroke or head trauma can cause elevated cTn values due to severe central nervous system injury.[1] Recognition of these non-ACS causes of cTn elevation is important to guide further diagnostic investigations and optimize patient care.

Neurogenic heart syndrome

Acute lesions in the central autonomic network disrupt normal sympathetic and parasympathetic neural control of the heart, leading to excessive catecholamine release and subsequent pathological changes in cardiac tissue. This includes hypercontraction of sarcomeres, reduced muscle relaxation, and metabolic disturbances known as coagulative myocytolysis.[4]

A catecholamine surge and microvascular coronary endothelial dysfunction, among other mechanisms, are believed to be involved in transient cTn elevation, a manifestation of neurocardiogenic injury that can happen in up to half of all stroke patients.[1,21] This condition ultimately

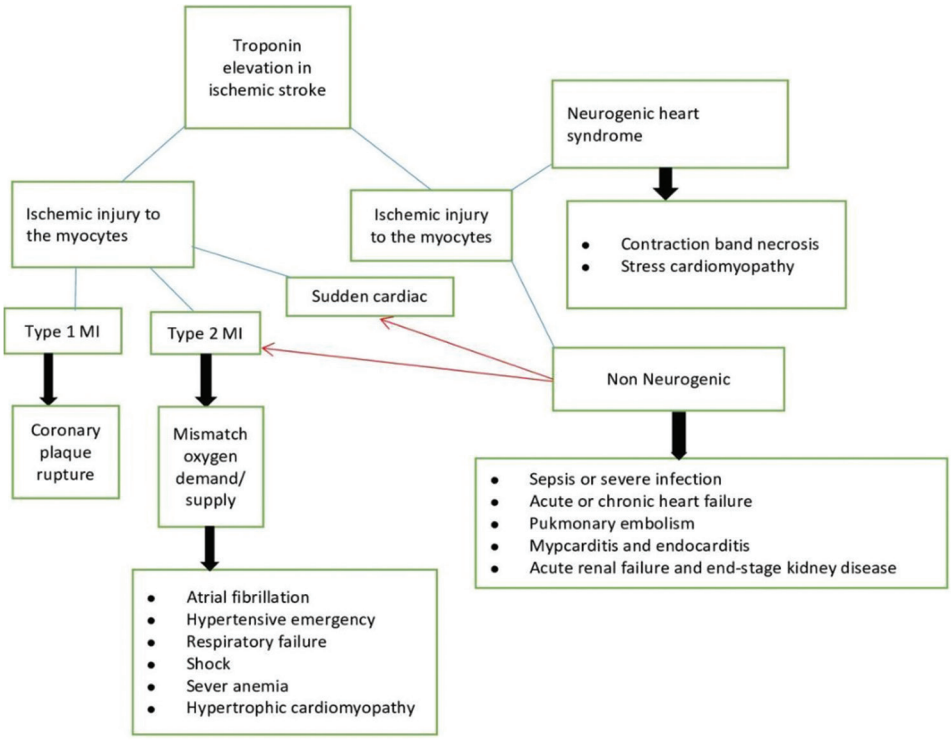

Figure 2: Potential causes of immediate cTn increase in ischemic stroke patients. Both ischemic and nonischemic myocardial infarction (MI) may cause an acute cTn increase (with a rise/fall pattern over time). It is important to understand that the mechanisms are not antagonistic. The arrows show that neurocardiogenic pathways may favor demanding ischemia or unexpected cardiac death[4]

results in myocardial remodeling weeks to months after the initial injury. However, in some cases, myocardial injury may be the result of an underlying cardiac embolic source and may offer insights into the stroke mechanisms, especially in the absence of occult causes. For example, early cTn positivity was associated with a cardioembolic cause and did not correlate with the severity of the stroke in a prospective cohort study involving 1234 patients with ischemic stroke.[22] Because approximately one-third of strokes have no identified etiology, a category known as cryptogenic stroke or embolic stroke of unknown origin (ESUS), a better knowledge of myocardial injury could help in the interpretation of cardiac biomarker derangements in the clinical situation.[23] With an emphasis on silent myocardial infarction and atrial cardiopathy, clinicians are starting to recognize the significance of non-traditional cardiac sources of emboli in the ESUS concept.[23]

Prevalence of cTn elevation in AIS patients

According to the findings of our systematic review, on average 17.9% or 1 in 5 patients who experience an AIS have high cTn levels. Previous research has indicated that the incidence of elevated cTn levels, as measured by standard assays, in patients with acute stroke ranges from 8.7% to 21.4%.[11,24] We accepted the definition of cTn positive provided by the researchers in independent studies, but we also recognize the complexity of the various cTn kinds, assays, and cutoffs. The purpose of this systematic study does not extend to examining the impact of various cTn types and cut-offs. Across the majority of the various cTn assay types and threshold choices, the prevalence of elevated cTn remained largely consistent. There was still some heterogeneity between some studies, though. More specifically, when compared to studies with larger cutoffs, the five[7,24-27] studies that utilized cTn at a low cutoff of 0.1 ng/l had a reduced prevalence of positivity. This unexpected finding might be because patients with heart conditions who were already present in these studies were excluded. Figure 3 illustrates the fluctuation observed in abnormal cTn levels among patients with AIS in the selected studies.

When we compared the study results, Hrvoje Budincevic *et al*.,[16] showed that there were no statistically significant differences between the two groups in terms of age, gender, stroke risk factors, or subtypes. However, there was a statistically significant difference between the two groups in terms of the proportion of prior ischemic strokes, which was higher in the group with elevated cTn levels. Although, Siamak Abdi *et al*., discovered no correlation between the location of the stroke and cTn levels.[26] More research is needed to understand these variations in stroke sites and their relationships. It's certainly possible that a combination of etiologies and pathophysiology can affect the location of stroke. The findings reported by Siamal Abdi *et al*., are consistent with the results found in Barbar and Morton's study.[26,28] Elevated cTn levels occurred in 1/6 patients and are

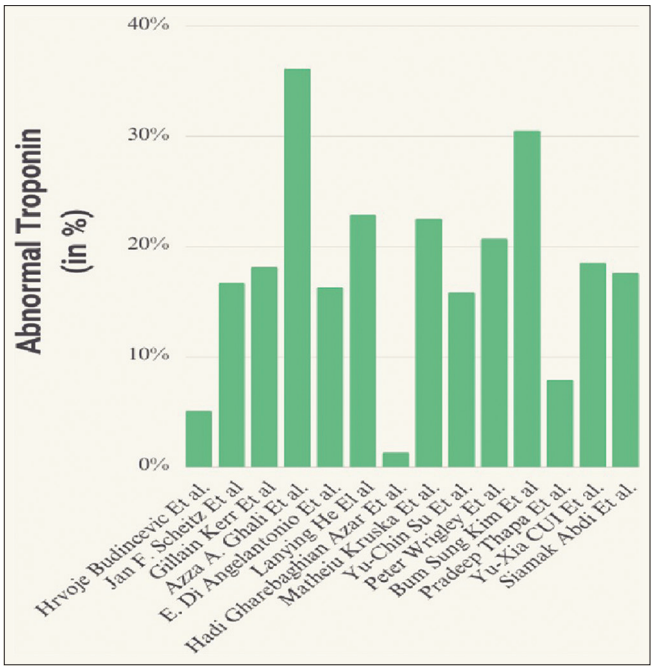

Figure 3: The fluctuation observed in abnormal cTn levels among patients with acute ischemic stroke in the selected studies

associated with severity and unfavorable short and long-term clinical outcomes as per Scheitz *et al*.[29,30]

Elevated cTn levels as a predictor of poor cardiovascular outcomes in AIS patients

The systematic review highlights the noteworthy findings from the studies conducted by Lanying He *et al.,* and Azza A. Ghali *et al.*, emphasizing the substantial correlations observed between levels of cTn and insular stroke.[24,31] In the context of a systematic review, the collective evidence from various studies suggests that elevated cTn levels in AIS are associated with a range of neurogenic cardiac clinical outcomes. Kerr *et al.*,[32] a systematic review reported that 43% of patients exhibited features of Myocardial ischemia. ECG changes were observed in two observational studies by Azza A Ghali *et al.*,[24] and Hadi Gharebaghian Azar *et al.*,[25] while Mathieu Kruska *et al.*,[33] a monocentric observational study found that AIS with large vessel occlusion and elevated cTn was associated with increased vulnerability to obstructive CAD. Peter Wrigley *et al.*, in the cTn elevation in acute ischemic stroke (TRELAS), the trial demonstrated a significant relationship between elevated cTn in AIS and echo changes, indicating a potential cardiac involvement.[34] Additionally, Yu-Xia CUI *et al.*, in a retrospective study demonstrated a relationship between elevated cTn and adverse cardiovascular outcomes.[27] The review encompasses a majority of studies examining the clinical outcomes of elevated cTn in AIS. The findings indicate an increased risk of major cardiac events and higher rates of re-admission for coronary revascularization procedures, as demonstrated by several studies, thus emphasizing the importance of monitoring cTn levels in this patient population.

cTn elevation as a predictor of in-hospital and all-cause mortality in AIS patients

In the context of elevated cTn levels in AIS patients, several studies have investigated the association with all-cause and in-hospital mortality. It is common to observe elevated cTn levels in AIS, which is associated with an increased risk of mortality and poorer overall outcomes.[4,35] E.D. Angelantonio *et al.*, a prospective cohort study of 330 patients reported findings demonstrating a significant association between elevated cTn levels and in-hospital death in AIS patients.[7] This study provides evidence of the impact of cTn elevation on short-term mortality outcomes. However, Lanying He *et al.*, in a prospective study of 530 patients focused on the relationship between elevated cTn levels and death as well as disability in AIS patients. Their findings suggest that cTn elevation not only contributes to mortality but also influences the functional outcomes and disability burden experienced by patients.[31] The observational studies of Pradeep Thapa *et al.*, and Yu-Chin Su *et al.*, also emphasized in-hospital mortality as a primary outcome.[36,37] These studies further support the notion that elevated cTn levels in AIS patients are associated with a higher risk of mortality during the hospital stay. Furthermore, Bum Kim Su *et al*'s. research revealed an increased risk of all-cause mortality in patients with elevated cTn levels. This suggests that cTn elevation in AIS may have broader implications for long-term mortality beyond the immediate hospitalization period.[10]

Elevated cTn levels as a marker for severity assessment and poor clinical outcomes in AIS patients

When examining the role of elevated cTn levels as a marker for severity assessment in AIS patients, several studies provide valuable insights into the relationship between cTn elevation and unfavorable outcomes. Hrvoje Budincevic *et al.*,[16] and Pradeep Thapa *et al.*,[37] conducted studies that demonstrated an association between elevated cTn levels and unfavorable outcomes in AIS patients. These findings suggest that cTn elevation may serve as an indicator of increased stroke severity and a predictor of poor prognosis. Jan F Scheitz *et al.*, and Siamak Abdi *et al.*, focused on the relationship between cTn elevation and stroke severity.[26,30] Their research revealed that elevated cTn levels are associated with increased stroke severity, indicating a potentially more severe ischemic insult in these patients. Furthermore, these studies highlighted the link between cTn elevation and unfavorable long-term and short-term outcomes. Azza A Ghali *et al.*, examined the relationship between cTn elevation and stroke severity, further supporting the notion that elevated cTn levels may be indicative of more severe strokes.[24] In addition, Yu-Chin Su *et al.*, demonstrated that elevated cTn levels are associated with clinical deterioration in AIS patients, suggesting a potential link between cTn elevation and worsened patient outcomes.[36]

Is cTn elevation in AIS prognostically relevant?

The use of cTn as a predictive marker for prognostic significance in AIS patients has been a subject of investigation, with varying findings and perspectives. Several studies have contributed to our understanding of cTn's potential as a prognostic indicator in this patient population. Kerr *et al.*, and Hadi Gharebaghian Azar *et al.*, raise concerns regarding the utility of cTn in AIS, citing the regular use of electrocardiography (ECG) for these patients.[25,22] According to their viewpoint, since ECG is routinely employed in stroke admissions, the additional use of cTn may be questionable. However, it is important to note that cTn and ECG provide complementary information, as cTn reflects cardiac damage and ECG captures electrical abnormalities. Scheitz *et al.*, discussed the unfavorable short-term outcomes of progressively increasing cTn levels in a randomized controlled trial.[30]

However, E. De Angelantonio *et al.*, demonstrated that cTn is an independent prognostic factor in AIS patients. Their findings suggest that elevated cTn levels provide valuable prognostic information beyond the use of ECG alone.[7] This highlights the potential of cTn as a predictive marker for adverse outcomes in this patient population. Furthermore, studies by Lanying He *et al.*, Bum Sing Kim *et al.*, and Pradeep Thapa *et al.*, have provided evidence supporting the high predictive value of cTn in AIS patients. These studies indicate that elevated cTn levels are associated with worse outcomes and increased mortality risk, emphasizing the potential of cTn as a prognostic indicator.[10,31,37] In a different line of investigation, Peter Wrigley *et al.*, hypothesized that hypercTnemia, a biochemical marker of cardiac ischemia, is independently associated with interesting echocardiogram findings after AIS.[34] Their study suggests a potential link between cTn elevation and cardiac abnormalities observed on echocardiography, further highlighting the prognostic value of cTn in identifying cardiac complications in AIS patients.

Regardless of the underlying mechanism, there is evidence that cTn in stroke patients provides predictive data on survival and short- and long-term functional outcomes.[4] In a recent retrospective study, it was discovered that, after adjusting for age, baseline stroke severity, and comorbidities, patients in the highest quartile of cTn measured with a high-sensitivity assay on hospital admission had a 1.6-fold higher risk of all-cause mortality over the course of a 1.5-year follow-up period.[9] The rate of poor functional outcome at discharge (modified Rankin Scale >1) increased significantly with greater peak cTn levels in a prospective trial of 1016 consecutive patients with ischemic stroke who were evaluated serially with a high-sensitivity cTn assay.[29] To establish a clinically accurate predictive threshold of cTn in the setting of stroke for the prediction of a poor functional outcome or mortality, additional data are urgently required. Current acute stroke guidelines in the UK, provided by the National Institute of Clinical Excellence[39] and the Scottish Intercollegiate Guidelines Network,[40] do not advise routine cardiac enzyme testing. Conversely, the American Stroke Association[41] does recommend it, citing the common occurrence of concomitant cardiac ailments, including acute coronary syndromes, as the rationale.

Strengths

The review offers a thorough analysis of the evidence that is currently available and has 16906 participants, increasing the reliability and generalization of the results. The review gives more accurate estimates of the effect of high cTn levels on clinical outcomes, increasing the reliability of the results by synthesizing data from multiple studies. The statistical power of this review is higher than that of individual research since it has accessibility to a bigger pool of data. This makes it possible to draw inferences about the relationship between high cTn levels and successful clinical outcomes in individuals with AIS that are more accurate. The review addressed important clinical questions related to the impact of elevated cTn levels on clinical outcomes in patients with AIS. By examining mortality, functional impairment, and stroke severity, the review contributes to the understanding of prognosis and risk assessment in this patient population. The review acknowledges the existing knowledge gaps and by identifying areas that require additional investigation, the review provides a foundation for future studies and advancements in the understanding of elevated cTn levels in AIS.

Limitations

Studies involving different patient populations, methods, and study designs were included in the review, which might have caused data heterogeneity. The capacity to pool data for meta-analysis may be impacted by this heterogeneity, or subgroup analysis may be necessary to investigate sources of variation and potential bias. This also includes different research settings, multiple exclusion criteria for patients with prior cardiac or renal illness, and various cTn assays and cut-offs. Additionally, we are unable to determine the etiology behind high cTn levels in AIS. As studies with substantial or positive findings are more likely to be published than those with null or negative results, the systematic review may be prone to publication bias. The overall assessment of the effect of higher cTn levels on clinical outcomes could be impacted by this potential bias in the literature currently in practice. The review is limited by the fact that it only includes research that was written in English and published within the last 20 years. Studies published before 2003 or in languages other than English may be biased due to their language of publishing or their publication date, which could result in the loss of data and information. Confounding variables that can have an impact on the connection between high cTn levels and clinical outcomes may not have been fully taken into account in the included research. The original studies may not have consistently controlled for factors including age, co-morbidities, the severity of the stroke, and the therapies received, which could have an impact on how the results should be interpreted. The data analysis in this systematic review is typically based on aggregated data presented in the included research. The inability to undertake thorough subgroup analyses or account for potential confounders at the individual level is caused by the lack of access to individual patient data. The review's exclusive emphasis on patients with AIS may limit the applicability of its findings to other patient groups or stroke subtypes.

Conclusion

Elevated cTn levels have been observed to have a significant prevalence in various clinical settings, including AIS. The majority of patients with AIS demonstrate detectable circulating cTn using very sensitive cTn assays, and almost half of the patients exhibit cTn levels increased above the upper reference limit. The association between elevated cTn and clinical outcomes such as death, disability, or improvement has been extensively studied. This research suggests that an elevated cTn is linked to an increased risk of adverse outcomes, including higher mortality rates and greater disability. Furthermore, elevated cTn has proven to be a valuable prognostic marker for predicting the severity and prognosis of AIS. The findings contribute to the existing knowledge and can shape future research, clinical guidelines, and healthcare policies, ultimately leading to better outcomes and enhanced stroke care practices. Future studies could explore potential interventions to mitigate the negative impact of elevated cTn levels and improve patient outcomes. Further research is required to see whether cTn can be used to predict the recurrence of a stroke or cognitive deterioration. Clinicians could identify high-risk patients and design targeted therapies by having a better grasp of the effects of elevated cTn levels on clinical outcomes in patients with AIS. The outcomes of this evaluation bring up a question regarding whether it is necessary to regularly assess cTn levels in patients who have experienced an acute stroke. However, more research is needed to ascertain the practical value of conducting routine cTn testing following an acute stroke.

Abbreviations

DALYs:	Disability-adjusted life years lost
MeSH:	Medical Subject Headings
AMSTAR 2:	Assessment of Multiple Systematic Reviews 2
RCT:	Randomized controlled Trials
CCRBT:	Cochrane Collaboration Risk of Bias Tool.
AIS:	Acute ischemic stroke
CAD:	Coronary Artery Disease
STEMI:	ST Elevation Myocardial Infarction
AMI:	Acute Myocardial Infarction
MI:	Myocardial infarction
ECG:	Electrocardiogram
GFR:	Glomerular filtration rate
ICH:	Intracerebral hemorrhage
CT:	Computed tomography
TIA:	Transient ischaemic attack
MACCE:	Major adverse cardiac and cerebrovascular events
PCI:	Percutaneous coronary intervention
CABG:	Coronary artery bypass graft
NIHSS:	National Institute of Health Stroke Scale
TRELAS:	Troponin elevation in acute ischemic stroke

cTn: Cardiac Troponin (includes both cTnT and cTnI)
hs-cTnT: High-sensitive cardiac Troponin T.

Statement of ethics

This systematic review is based on published data from databases and therefore does not involve active patient participation in the design, conduct, report, or dissemination plans of the research. Therefore, it does not need ethical approval or consent for participation.

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Conflicts of interest

There are no conflicts of interest.

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