Received: 11 August 2023 | Revised: 1 May 2024 | Accepted: 6 June 2024

DOI: 10.1002/emp2.13228

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
WILEY

ORIGINAL RESEARCH

Cardiology

Delta troponin does not distinguish acute coronary syndrome in emergency department patients with renal impairment and an initial positive troponin

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Meetings: ACEP 2021, Boston, MA.

Abstract

Background: In emergency department (ED) patients with renal impairment, troponin concentrations can be positive without myocardial ischemia. When there is clinical concern for acute coronary syndrome (ACS), guidelines recommend obtaining a delta troponin measurement to identify acute myocardial injury. However, evidence supporting the use of delta troponin to rule in or out ACS in patients with renal impairment and initial elevated troponin levels is limited.

Methods: This retrospective, observational study assessed the diagnostic value of a 20% delta troponin cutoff in the prediction of ACS events in ED patients (estimated glomerular filtration rate [eGFR] <60 mL/min/1.72 m^2) with renal impairment, clinical concern for ACS, and an initial positive troponin concentration using either conventional troponin (cTnT) or high-sensitivity troponin (hsTnT). Clinical concern for ACS was based on initial ED physician-reported diagnoses. Patients with an initial diagnosis of ST-elevation myocardial infarction were not included. A positive initial troponin was identified at a threshold of ≥0.06 ng/mL for cTnT and ≥52 ng/L for hsTnT, and delta troponin measurements were obtained within 24 h of the initial troponin. The primary composite outcome, termed ACS event, included (1) cardiac-related mortality, (2) coronary revascularization (or its recommendation), or a (3) clinically diagnosed type-1 myocardial infarction within 6 weeks of the ED presentation. Sensitivities, specificities, negative predictive values, positive predictive values, and negative and positive likelihood ratios were calculated for these 6-week ACS events.

Results: A total of 608 ED patients with renal impairment, an initial positive troponin, and clinical concern for ACS were included in the study. Of these patients, 234 had an initial positive cTnT (median eGFR 18 mL/min/1.72 m^2) and 374 had an initial positive hsTnT (median eGFR 25 mL/min/1.72 m^2). The overall ACS event rate was 38% in the cTnT group and 33% in the hsTnT group. In those with a negative delta, the 6-week

Supervising Editor: Bory Kea, MD, MCR

ACS event rate was 32% when using cTnT, compared to 24% using hsTnT. Conversely, a positive delta was associated with an ACS event rate of 47% when cTnT was utilized versus 61% when hsTnT was utilized.

Conclusion: In this study, approximately one-third of ED patients with renal impairment who had an initial positive troponin and clinical concern for ACS developed ACS events at 6 weeks. A delta troponin did not appear to provide clinically meaningful assistance in the prediction or exclusion of 6-week ACS events in this cohort.

1 | INTRODUCTION

1.1 | Background

Troponin is a biomarker for myocardial injury, but in patients with renal impairment, serum concentrations are frequently elevated without acute myocardial injury or acute coronary syndrome (ACS).[1,2] When these patients present to the emergency department (ED) with a history concerning for myocardial ischemia, interpreting the significance of a positive troponin value can be challenging. Foremost is the clinical context, established by a combination of identified risk factors, associated symptoms, the patient's story, their physical exam, and the electrocardiogram (ECG). However, in cases where presentations are more ambiguous, clinicians may rely heavily on diagnostic testing and the exclusion of alternative diagnoses. When initial troponin measurements are positive (elevated above the 99th percentile upper reference limit [URL]) in patients with renal impairment and concern for myocardial ischemia, guidelines under the Fourth Universal Definition of Myocardial Infarction recommend obtaining a serial measurement, termed a delta troponin, to calculate a net change in concentration.[3] These guidelines further state that a delta troponin greater than 20% suggests acute cardiac injury and can help diagnose ACS, while a delta troponin less than 20% suggests the absence of acute cardiac injury. To date, data supporting this recommendation is limited, and guidance on the use of delta troponin in this cohort is largely based on expert consensus.[4–7]

The presence of a positive troponin in the setting of renal impairment independently confers an increased risk of cardiovascular morbidity and mortality.[8–10] The cause of baseline elevations can be multifactorial and includes increased left ventricular mass, myocardial inflammation, myocardial fibrosis, and decreased renal clearance.[11–15] Therefore, having a positive troponin in patients with renal impairment requires further clinical assessment.[16] Previously, studies of patients with renal impairment have established the ability of serial troponin measurements to rule out ACS events when initial concentrations are below the 99th percentile URL. However, in patients with renal impairment, where levels are frequently elevated in the absence of ACS, there is currently little evidence to guide management using delta troponins.[10,17,18] Further, more than 65% of hospitals are yet to transition to the use of high-sensitivity troponin (hsTnT) assays, and the benefits of these assays over conventional troponin (cTnT) assays remains in question.[17]

1.2 | Goals of investigation

There is currently limited evidence supporting the use of delta troponin measurements in ED patients with concern for ACS who have renal impairment and initial positive troponin concentrations. This study investigates the association of delta troponin measurements with 6-week ACS events in patients with clinical concern for ACS based on initial ED physician diagnoses.

2 | METHODS

2.1 | Study design and setting

This retrospective, observational, before-and-after study analyzes the use of delta troponin in ED patients with renal impairment, initial positive troponin concentrations, and physician concern for ACS at two tertiary-care, academic hospitals. Each hospital has annual patient volumes of over 85,000 visits and percutaneous coronary intervention (PCI) capabilities. Patient encounters were reviewed over two equal halves of an 11-month period (January 1, 2018, to November 27, 2018). In the middle of this time period, on June 13, 2018, both centers transitioned from the Roche fourth-generation cTnT assay (Roche Diagnostics International AG) to the Roche fifth-generation hsTnT assay (Roche Diagnostics International AG).[3] This time period was selected to assess the value of both cTnT and hs-cTnT in the prediction of 6-week ACS events. All research methods were approved by the health system's Institutional Review Board, and the requirement for informed consent was waived given the lack of direct patient contact and the retrospective nature of the study. Medical data were abstracted by the health system's research informatics department and included demographic data, medical history, lab results, provider and consultant notes, and procedure reports.

2.2 | Selection of participants

Emergency department patients were selected for inclusion if one of the patient's top three billed International Classifications of Diseases 10 (ICD-10) codes were in the R07, I20, and I21 categories at the conclusion of their initial ED evaluation. These codes include diagnoses representing all variants of "chest pain," "angina," and "acute

The Bottom Line

In renally-impaired patients, troponins are often elevated. However, they often have cardiovascular risk factors that increase their risk of acute coronary syndrome (ACS). This study sought to determine whether delta troponins (conventional and high sensitivity) in renally-impaired patients have an association with 6 week ACS events. They found a delta troponin, positive or negative, did not meaningfully predict or exclude 6-week ACS events, thus clinicians must exercise caution on risk stratifying patients based on delta troponins.

myocardial infarction," respectively. These ICD-10 codes were selected purposefully to differentiate patients where the ED clinician had clinical concern for ACS during their initial evaluation, while attempting to avoid those patients where an alternative diagnosis for chest pain was likely (e.g. pulmonary embolism, pneumonia, and cholecystitis). The search was expanded to the top three billed diagnoses because ED physicians may not list chest pain primarily, but rather list elevated troponin, dyspnea, or various other potential diagnoses first. By isolating this cohort of patients, the value of delta troponin to the ED clinician could then be characterized through the confirmation of the presence or absence of an ACS event in the following 6-week period. Importantly, patients with an initial diagnosis of ST-elevation myocardial infarction (STEMI) were not included given that the management of these patients is well established in the literature and not dependent on delta troponin measurements.

Following the selection of ED patients with the described ICD-10 diagnoses, those with both impaired renal function (defined as an estimated glomerular filtration rate [eGFR] <60 mL/min/1.72 m^2) and an initial troponin concentration above the 99th percentile URL were identified for inclusion in the study. To evaluate the use of delta troponin measurements, patients with less than two serum troponin measurements obtained within 24 h of the initial presentation were excluded from the study (see Figure 1). Troponin levels from previous or subsequent visits were not included. Patients with intact renal function, missing renal function, or an initial troponin value less than the 99th percentile URL were also excluded.

2.3 | Lab measurements

2.3.1 Positive troponin and delta troponin

Diagnostic thresholds for a positive troponin concentration were defined as ≥0.06 ng/mL for the Roche fourth-generation cTnT and ≥52 ng/L for the Roche fifth-generation hs-cTnT.[18,19] A delta troponin was then calculated using the subsequent troponin measurement, provided this subsequent troponin measurement was obtained within 24 h of the first. Net interval troponin differences greater ≥20% were deemed a positive delta troponin.[3]

2.3.2 GFR

The eGFR was calculated using the Chronic Kideny Disease Epidemiology Collaboration (CKD-EPI) equation, per hospital protocol, where a patient's eGFR is estimated using the equation: $142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female].[20,21] Renal impairment was defined as eGFR <60 mL/min/1.72 m^2. Subgroups were assigned according to the staging criteria for chronic kidney disease provided by the National Kidney Foundation, where stages 3a, 3b, 4, and 5 correspond to an eGFR of 45–59, 30–44, 15–29, and <15 mL/min/1.72 m^2, respectively.[22] Subgroup analyses stratified by eGFR were used to assess the ability of delta troponin measurements to predict ACS events with varying degrees of renal impairment.

2.4 | Outcomes

2.4.1 Acute coronary syndrome events

In this study, the primary outcome was an acute myocardial injury due to ACS or a type-1 myocardial infarction within 6 weeks of the initial ED presentation. ACS events were defined by one of three primary outcomes: (1) coronary revascularization (or its recommendation), (2) cardiac-related mortality, or (3) clinically diagnosed type-1 myocardial infarction as determined by chart review. Patients with 6-week diagnoses suggestive of type-2 myocardial infarction, or "demand ischemia," were deemed negative for an ACS event.

Four emergency physicians performed chart reviews on all study participants by chronological order to identify 6-week outcomes following training in data abstraction. Chart reviewers were blinded to delta troponin calculations. Chart reviews included evaluations of the index ED visit, inpatient cardiologist notes, cardiac catheterization reports, discharge summaries, and any additional health elements available in the following 6 weeks in the health system's electronic medical record (EMR) and the Regional Health Information Organization (RHIO). The RHIO contains regional medical information from EMS reports, and records from outpatient and inpatient visits from 18 participating regional hospitals, as well as the Statewide Health Information Network for New York, which includes data from various health entities (ambulatory practices, hospitals, prehospital agencies, and home care agencies). Nonparticipating health system data outside of these sources would be unavailable for use in the determination of 6-week outcomes and therefore this study's analysis. A subset of charts ($n = 100$; 16%) was selected for inter-rater reliability. The kappa coefficient was 0.91 (95% confidence interval [CI] 0.83–0.99) for the occurrence of ACS events.

2.4.2 ACS event subgroups

Coronary revascularization was determined first by reviewing all left heart cardiac catheterization reports in chronological order. Then, ACS was deemed present only when balloon angioplasty or coronary artery

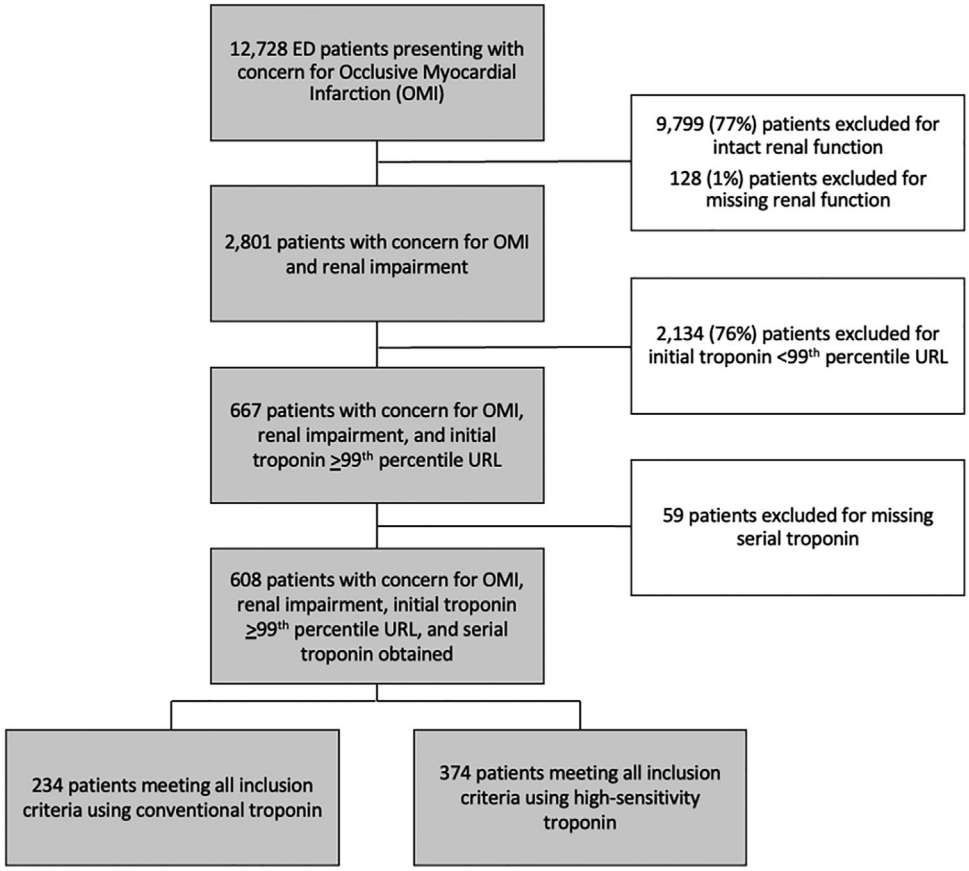

FIGURE 1 CONSORT diagram of study patients.

stenting was reported, or a recommendation for coronary revascularization was made in the cardiac catheterization report, which included consultations for coronary artery bypass grafting or documented plans for a future percutaneous intervention. Notably, chronic total occlusions were considered negative for ACS events. Patients who declined interventions for palliative, religious, or other reasons, but where the cardiologist identified the patient as having ACS, were deemed positive for an ACS event.

Mortality was determined through a review of the EMR and RHIO for patient deaths within 6 weeks of the initial ED presentation. Cardiac-related mortality was established though the identification of provider notes, suggesting death secondary to ACS in the presence of supporting data and clinical variables. Noncardiac-related mortality was established through patient chart reviews and a preceding clinical picture consistent with a cause of death other than ACS, including supporting data and clinical variables suggesting an alternative cause (e.g., sepsis, trauma, and pulmonary embolism).

A clinically diagnosed type-1 myocardial infarction was determined through a review of remaining patient charts for final hospital discharge diagnoses including unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and STEMI. Charts with these diagnoses were physician reviewed to confirm the occurrence of an ACS event using the criteria reported in the Fourth Universal Definition of Myocardial Infarction, with documented clinical signs and symptoms of cardiac ischemia, and supportive data and clinical variables. Importantly, patients with an NSTEMI diagnosis based solely on an elevated troponin value were not deemed positive if there was no further cardiologist or primary team assessment, or supporting clinical variables, to suggest a type-1 myocardial infarction. In cases where there was disagreement regarding a final diagnosis, two reviewers conferred to establish whether any of the above ACS event criteria were met. If an ACS event was not identified at the completion of the chart reviews, the patient was deemed negative for a 6-week ACS event.

2.5 | Statistical analysis

REDCap was used for the storage of patient data, and Microsoft Excel (Microsoft, Inc.) and SAS (SAS Institute) were used for statistical analyses.[23,24] Baseline characteristics are summarized using descriptive statistics, which include proportions for categorical variables and medians for continuous variables. The statistical analyses used to assess the ability of delta troponin measurements to predict or exclude ACS events included sensitivities, specificities, positive predictive values, negative predictive values, positive likelihood ratios, and negative likelihood ratios. These same assessments were applied to subgroups stratified by renal impairment severity.

TABLE 1 Baseline characteristics, comorbidities, and estimated glomerular filtration rate (eGFR) in conventional and high-sensitivity troponin cohorts.

	Conventional troponin, *n* = 234	HIGH-sensitivity troponin, *n* = 374	Median difference or risk difference (95% CI)
Age, years			
Median (95% CI)	71 (68.6–73.4)	71 (68.9–73.1)	0.00 (−2.993 to 2.993)
Sex			
Male, *n* (%)	142 (60.7%)	221 (59.1%)	0.02 (−0.06 to 0.10)
Female, *n* (%)	92 (39.3%)	153 (40.9%)	−0.06 (−0.10 to 0.06)
History of hypertension			
Yes, *n* (%)	216 (92.3%)	345 (92.3%)	0.00 (−0.04 to 0.04)
No, *n* (%)	18 (7.7%)	29 (7.8%)	0.00 (−0.04 to 0.04)
History of diabetes			
Yes, *n* (%)	151 (64.5%)	227 (60.7%)	0.04 (−0.04 to 0.12)
No, *n* (%)	83 (35.5%)	147 (39.3%)	−0.04 (−0.12 to 0.04)
eGFR			
Median (95% CI)	18.0 (13.7–22.3)	25.0 (21.6–28.4)	−6.00 (−11.84 to −0.16)
45–59, *n* (%)	46 (19.7%)	80 (21.4%)	0 (−2.30 to 2.30)
30–44, *n* (%)	40 (17.1%)	86 (23.0%)	0 (−2.77 to 2.77)
15- 29, *n* (%)	44 (18.8%)	81 (21.7%)	0 (−2.27 to 2.27)
0–14, *n* (%)	104 (44.4%)	127 (34.0%)	1.00 (−0.23 to 2.23)

Abbreviation: CI, confidence interval; eGFR, estimated glomerular filtration rate.

3 | RESULTS

3.1 | Characteristics of study subjects

A total of 12,728 patients were first captured for inclusion in the study based on the described initial ED ICD-10 code diagnoses. Of these patients, 9799 (77%) patients were excluded from the study due to intact renal function and 128 were excluded due to missing renal function. A total of 2801 ED patients with renal impairment and clinical concern for ACS remained, and of these, 2134 (76%) had initial nonpositive troponin measurements (below the 99th percentile URL) and were subsequently excluded. Note that 667 patients had a positive troponin, and 59 were excluded for the lack of a serial troponin measurement; 608 renal-impaired patients with positive troponins and serial testing were ultimately identified for inclusion in the study, with 234 patients evaluated using cTnT and 374 using hs-TnT (see Figure 1).

Demographic comparisons of the two groups were performed. The mean age for both the cTnT and hsTnT groups was 71 years (Interquartile range [IQR]aB cTnT 69–73, hsTnT 69–73). Note that 61% of patients in the cTnT group were male, compared with 59% in the hsTnT group. Additional demographic data regarding co-morbidities and the degree of renal impairment are highlighted in Table 1.

3.2 | Main results

Among the 234 patients with renal impairment, ED provider concern for ACS, and an initial positive cTnT, the overall ACS event rate was 38%. Note that 144 (61.5%) patients in this cohort had a negative delta cTnT, and 46 (32%) experienced an ACS event within 6 weeks. In the 90 (38.5%) remaining patients who had a positive delta cTnT, 42 (38.5%) experienced ACS events within 6 weeks.

In the 374 patients with renal impairment, ED provider concern for ACS, and an initial positive hsTnT, ACS events occurred in 33% of patients. Note that 287 (77%) patients in this cohort had a negative delta hsTnT, and 69 (24%) experienced ACS events within 6 weeks. In the 87 (23%) remaining patients who had a positive delta hsTnT, 53 (61%) experienced ACS events within 6 weeks (Table 2).

In patients with a negative delta cTnT, the median initial troponin measurement was 0.15 ng/mL (IQR, 0.09–0.15). The corresponding median absolute change in the serum troponin level was 0.01 ng/L (IQR 0.0–0.01). A negative delta cTnT was determined to have a specificity of 67% (95% CI, 0.77–0.75), NPV of 68% (95% CI, 0.60–0.76), and −LR of 0.78 (95% CI, 0.55–1.01). In those with a positive delta cTnT, the median initial troponin measurement was 0.19 ng/L (IQR, 0.10–0.44). The corresponding median absolute change in the serum troponin level was 0.10 ng/L (IQR, 0.03–0.33). Overall, a positive delta cTnT had a sensitivity of 48% (95% CI, 0.37–0.58), PPV of 47% (95% CI, 0.36–0.57), and +LR of 1.45 (95% CI, 1.13–1.77) (see Table 3).

In those patients with a negative delta hsTnT, the median initial troponin measurement was 103 pg/L (IQR, 69–197). The corresponding median absolute change in the serum troponin level in this group was 7 pg/L (IQR, 3–13). A negative delta troponin using hs-cTnT resulted in a specificity of 87% (95% CI, 0.82–0.91), NPV of 76% (95% CI, 0.71–0.81), and −LR of 0.65 (95% CI, 0.49–0.82). In those with a positive delta hsTnT, the median initial troponin measurement was 134

TABLE 2 Outcomes stratified by troponin assay, positive and negative delta troponin measurements, and presence or absence of acute coronary syndrome (ACS) events within 6 weeks.

		Conventional troponin		High-sensitivity troponin	
		Delta < 20%	Delta > 20%	Delta < 20%	Delta > 20%
		n = 144	*n* = 90	*n* = 287	*n* = 87
ACS events		46 (32%)	42 (47%)	69 (24%)	53 (61%)
	Positive cath	22(48%)	32 (76%)	43 (62%)	37 (70%)
	Mortality	8 (17%)	7 (17%)	9 (13%)	9 (17%)
	Clinical type-1 MI	16 (35%)	3 (7%)	17 (25%)	7 (13%)
Median initial troponin (IQR)		0.15	0.19	103	134
		(0.09, 0.15)	(0.10, 0.44)	(69, 197)	(77, 296)
Median delta troponin (IQR)		0.01	0.10	7	110
		(0.0, 0.01)	(0.03, 0.33)	(3, 13)	(30, 455)
Mean eGFR (SD)		19	32	26	33
		(16.0)	(17.8)	(17.3)	(15.8)
Mean age (SD)		70	73	75	71
		(13.8)	(12.4)	(15.2)	(13.3)

Abbreviation: eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

TABLE 3 Statistical analyses of positive and negative delta troponin measurements using conventional troponin in the prediction of 6-week acute coronary syndrome (ACS) events.

	Total patients	ACS events	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
All patients	234	88 (38%)	0.48	0.67	0.47	0.68	1.45	0.78
			95% CI, 0.37–0.58	95% CI, 0.59–0.75	95% CI, 0.36–0.57	95% CI, 0.60–0.76	95% CI, 1.13–1.77	95% CI, 0.55–1.01
3a (eGFR 45–59)	46	25 (54%)	0.68	0.43	0.59	0.53	1.19	0.75
			95% CI, 0.50–0.86	95% CI, 0.22–0.64	95% CI, 0.41–0.77	95% CI, 0.29–0.77	95% CI, 0.73–1.65	95% CI, 0.01–1.50
3b (eGFR 30–44)	40	17 (45%)	0.67	0.50	0.52	0.65	1.33	0.67
			95% CI, 0.45–0.88	95% CI, 0.29–0.71	95% CI, 0.32–0.73	95% CI, 0.42–0.87	95% CI, 0.80–1.86	95% CI, 0.11–1.44
4 (eGFR 15–29)	44	19 (43%)	0.37	0.56	0.39	0.54	0.84	1.13
			95% CI, 0.15–0.59	95% CI, 0.37–0.75	95% CI, 0.16–0.61	95% CI, 0.35–0.73	95% CI, 0.10–1.57	95% CI, 0.64–1.62
5 (eGFR 0–14)	104	20 (25%)	0.23	0.82	0.30	0.76	1.29	0.94
			95% CI, 0.07–0.39	95% CI, 0.73–0.91	95% CI, 0.10–0.50	95% CI, 0.67–0.85	95% CI, 0.44–2.13	95% CI, 0.70–1.17

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

pg/L (IQR, 77–296). The corresponding median absolute change in the serum troponin level was 110 pg/L (IQR, 30–455). Overall, a positive delta hs-cTnT had a sensitivity of 43% (95% CI, 0.35–0.52), PPV of 61% (95% CI, 0.51–0.71), and +LR of 3.22 (95% CI, 2.85–3.59) (see Table 4).

In subgroup analyses stratified by eGFR, hsTnT demonstrated a +LR 6.97 (95% CI 5.86–8.07) in patients with severe renal dysfunction (Class 5; eGFR < 15). In the remainder of the subgroups analyzed, no clinically meaningful differences were identified regarding the ability of delta troponin measurements to predict ACS events based on CKD stages using both the cTnT and hsTnT.

4 | DISCUSSION

This retrospective, observational study assessed the diagnostic value of a 20% delta troponin cutoff for predicting ACS events in ED patients

TABLE 4 Statistical analyses of positive and negative delta troponin measurements using high-sensitivity troponin in the prediction of 6-week acute coronary syndrome (ACS) events.

	Total patients	ACS events	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
All patients	374	122 (33%)	0.43	0.87	0.61	0.76	3.22	0.65
			95% CI,0.35-0.52	95% CI, 0.83 - 0.91	95% CI, 0.51 - 0.71	95% CI, 0.71 - 0.81	95% CI, 2.85 - 3.59	95% CI, 0.49 - 0.82
3a (eGFR 45–59)	80	28 (35%)	0.54	0.79	0.58	0.76	2.53	0.59
			95% CI, 0.35–0.72	95% CI, 0.68–0.90	95% CI, 0.39–0.77	95% CI, 0.65–0.87	95% CI, 1.90–3.16	95% CI, 0.17–1.01
3b (eGFR 30–44)	86	38 (44%)	0.50	0.85	0.73	0.68	3.43	0.59
			95% CI, 0.34–0.66	95% CI, 0.75–0.95	95% CI, 0.56–0.90	95% CI, 0.57–0.80	95% CI, 2.67–4.18	95% CI, 0.25–0.92
4 (eGFR 15–29)	81	25 (31%)	0.40	0.79	0.45	0.75	1.87	0.76
			95% CI, 0.21–0.59	95% CI, 0.68–0.89	95% CI, 0.25–0.66	95% CI, 0.63–0.86	95% CI, 1.17–2.56	95% CI, 0.42–1.11
5 (eGFR 0–14)	127	31 (24%)	0.29	0.96	0.69	0.81	6.97	0.74
			95% CI, 0.13–0.45	95% CI, 0.92–1.00	95% CI, 0.44–0.94	95% CI, 0.73–0.88	95% CI, 5.86–8.07	95% CI, 0.51–0.97

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

with renal impairment, clinical concern for ACS by the ED physician, and an initial positive cTnT or hsTnT. The study population demonstrated an overall 6-week ACS event rate of 34%, which is comparable to that found in prior studies of renal-impaired patients ranging from 24% to 42%.[19,25–27] When risk stratifying patients based on a 20% delta troponin, there did not appear to be a clinically meaningfully difference in the occurrence of 6-week ACS events, regardless of whether the delta was negative (cTnT group: −LR 0.78, 95% CI 0.55–1.01; hsTnT group: −LR 0.65, 95% CI 0.49–0.82) or positive (cTnT group: +LR 1.45, 95% CI 1.3–1.7; hsTnT group: +LR 3.22, 95% CI 2.8–3.6). This analysis suggests that a delta troponin may have limited utility in the risk stratification of patients with renal impairment and ED physician concern for ACS when initial troponin measurements are positive.

In previous studies of patients with both intact renal function and renal impairment, the ability of delta troponin to rule out ACS has been validated if initial troponin concentrations are below the 99th percentile URL.[28,10] A study by Twerenbold et al. demonstrated that a 0/1-h delta troponin algorithm could be used to rule-out ACS with greater than 98% sensitivity in patients with renal impairment when initial measurements were below the 99th percentile URL.[28] This is important to note when considering that 76% of patients with renal impairment initially captured in our study had initial troponin measurements below the 99th percentile URL. This statistic provides a strong reminder that many patients with renal impairment do not produce initial positive troponins, and these patients can likely have ACS safely excluded using established rule-out algorthims with a delta troponin.[28,10] Conversely, when the initial troponin measurement is positive and above the 99th percentile URL in patients with renal impairment, there is concern that this finding could be related to confounding factors rather than ACS.[2] A recent randomized control trial of patients with renal impairment highlighted this problem, identifying a diagnosis other than type-1 myocardial infarction in two-thirds of patients with renal impairment when serum troponin concentrations were elevated.[27] The results of the current study also support this notion, while additionally bringing attention to high rates of ACS events in this cohort based on initial positive troponin measurements alone.

In subgroup analyses, the current study further investigated the use of delta troponin measurements when stratifying patients by renal impairment severity, and several trends were identified. Notably, the correlation between initial positive troponin values and the development of ACS events appeared to diminish with worsening renal function. The most renal-impaired patients with initial positive troponins had the lowest ACS event rates (cTnT 25%; hsTnT 44%), suggesting an increasing number of false positive results as renal function declines. Several studies have noted similar findings with increasing false positive rates as renal function worsens, calling attention to the challenges faced when interpreting initial troponin values in patients with renal impairment.[19,25,26,29] Comparatively, there did appear to be an improved ability to predict ACS events using a delta hsTnT in patients with severe renal impairment (Class 5, eGFR < 15: +LR 6.97, 95% CI 5.86–8.07); however, further research is be needed to elucidate the importance of this finding. Outside of this subgroup, trends of this significance were not identified using a positive or negative delta troponin. Importantly, almost all negative likelihood ratios approached 1.0 in their 95% confidence intervals regardless of renal impairment severity, suggesting a poor ability to rule-out ACS events.

Comparing the ability of a delta cTnT versus hsTnT to predict 6-week ACS events, there appeared to be a trend in favor of hsTnT over cTnT with improved specificity and positive likelihood ratios. This difference became more pronounced as renal function declined to Class 5 (eGFR < 15), where a delta hsTnT demonstrated a stronger association with 6-weeks ACS events than a delta cTnT (cTnT+LR 1.29, 95% CI 0.44–2.13 versus hsTnT+LR 6.97, 95% CI 5.86–8.07). Conversely, there appeared to be little difference in sensitivities and negative predictive values between a negative delta cTnT and hsTnT. These findings build upon a recent study by Gallacher et al., demonstrating a lack of benefit using hsTnT over cTnT to exclude ACS in patients with renal impairment.[26] This statistic likely reflects the high ACS event rate occurring in this cohort with renal impairment, initial positive troponin measurements, and concern for ACS, regardless of the delta.

As the use of hsTnT increases, clinicians may benefit from further prospective research identifying whether higher initial hsTnT or delta hsTnT thresholds can assist in the diagnosis of ACS events in renal-impaired patients. Additionally, there may be benefits to comparing hsTnT concentrations to those obtained in prior evaluations; however, this has not been studied. Prior studies have investigated the long-term prognostic value of delta troponin measurements in patients with renal impairment, but further research is needed to determine if this information would be beneficial in acute evaluations for ACS.[30,31] Until further evidence is available, this study suggests that clinicians should remain skeptical when interpreting the significance of a delta troponin in patients with renal impairment and initial positive troponins. Although current guidelines recommend delta troponin measurements to differentiate between chronic and acute myocardial injury in these cases, utilizing a delta troponin to rule in or rule out ACS may be faulty, and physicians should continue to place significant weight on their clinical impression.

4.1 | Limitations

We note several limitations regarding our study that must be considered in the interpretation of these results. First and most importantly, we recognize that the population assessed in our study is limited to patients meeting inclusion criteria based on the ED physician's initial impression and the corresponding ICD-10 codes, and not the chief complaint. This study's inclusion criteria were selected with the intent to capture patients with concern for ACS by the ED physician, rather than those patients with clear alternative diagnoses (e.g., PE, pneumonia, aortic dissection, and cholecystitis). Still, it should be recognized that ED physician made diagnoses are likely biased by initial troponin levels and other results during a patient's ED stay, which most likely increased the probability of 6-week ACS events in our cohort. This study may also exclude a subset of patients with atypical presentations for ACS where initial ICD-10 code diagnoses were not captured based on our criteria. Second, although the study institutions' guidelines recommended 3-h serial troponin testing, the exact timing of these measurements was not captured and investigated in this study (all were less than 24 h from initial), and therefore the influence of the timing of serial measurements on the results cannot be fully assessed. Third, patients with intact renal function or initial negative troponin measurements were not included in this study, and therefore the value of delta troponin in our cohort cannot be analyzed with reference to the outcomes in these patient populations. Fourth, calculated eGFR values possess inherent biases and represent renal function at a single point in time and are unable to differentiate patients with acute kidney injury, chronic kidney disease, and end stage renal disease. In this context, this study cannot assess the influence of hydration status or dialysis on the initial and serial laboratory measurements. Finally, given limitations in obtaining medical information for patients evaluated outside of the health system's EMR and RHIO, there may be missing 6-week outcomes and clinical details for a subset of studied patients, and this may have influenced the study results.

AUTHOR CONTRIBUTIONS

Praveen Mital conceived and designed the study. Praveen Mital and Samuel Abecassis supervised data collection. Praveen Mital, Samuel Abecassis, and John Forrester managed the data and oversaw quality control. All authors provided statistical advice on study design and analyzed the data. Praveen Mital and John Forrester drafted the manuscript, and all authors contributed substantially to editing. Praveen Mital takes responsibility for the paper as a whole.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Mital P, Forrester J, Abecassis S, et al. Delta troponin does not distinguish acute coronary syndrome in emergency department patients with renal impairment and an initial positive troponin. *JACEP Open*. 2024;5:e13228. https://doi.org/10.1002/emp2.13228

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