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## The Significance of Historical Troponin Elevation in Acute Heart Failure: Not as Reassuring as Previously Assumed

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### Abstract

**Background:** Historical cardiac troponin (cTn) elevation is commonly interpreted as lessening the significance of current cTn elevations at presentation for acute heart failure (AHF). Evidence for this practice is lacking. Our objective was to determine the incremental prognostic significance of historical cTn elevation compared to cTn elevation and ischemic heart disease (IHD) history at presentation for AHF.

**Methods:** 341 AHF patients were prospectively enrolled at 5 sites. The composite primary outcome was death/cardiopulmonary resuscitation, mechanical cardiac support, intubation, new/emergent dialysis, and/or acute myocardial infarction (AMI)/PCI/CABG at 90 days. Secondary outcomes were 30-day AMI/PCI/CABG and in-hospital AMI. Logistic regression compared outcomes versus initial emergency department (ED) cTn, the most recent electronic medical record cTn, eGFR, age, LVEF, and IHD history (positive, negative by prior coronary workup, or unknown / no prior workup).

**Results—**Elevated cTn occurred in 163 (49%) patients, 80 (23%) experienced the primary outcome, and 29 had AMI (9%). cTn elevation at ED presentation, adjusted for historical cTn and other covariates, was associated with the primary outcome (aOR 2.39; 95% CI:1.30–4.38), 30-day AMI/PCI/CABG, and in-hospital AMI. Historical cTn elevation was associated with greater

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odds of the primary outcome when IHD history was unknown at ED presentation (aOR 5.27, 95% CI:1.24–21.40), and did not alter odds of the outcome with known positive (0.74; 0.33–1.70) or negative IHD history (0.79; 0.26–2.40). Nevertheless, patients with elevated ED cTn were more likely to be discharged if historical cTn was also elevated (78% vs. 32%,  $p=0.025$ ).

**Conclusion**—Historical cTn elevation in AHF patients is a harbinger of worse outcomes for patients who have not had a prior IHD work-up, and should prompt evaluation for underlying ischemia rather than reassurance for discharge. With known IHD history, historical cTn elevation was neither reassuring nor detrimental, failing to add incremental prognostic value to current cTn elevation alone.

### Keywords

Acute Decompensated Heart Failure; ischemic heart disease; troponin; risk prediction; electronic medical record; incremental prognostic value; emergency medicine

## Introduction

Among one million emergency department (ED) visits per year for acute heart failure (AHF)<sup>1</sup>, 80–90% result in hospital admission, despite half being low risk.<sup>2–4</sup> “Transitioning a larger proportion of patients to the outpatient setting” from the ED, by improving risk-stratification at ED disposition, has been identified as a key “unmet need” in AHF research by the Society for Academic Emergency Medicine and Heart Failure Society of America (HFSA)<sup>5</sup>.

Cardiac troponin (cTn) elevation in AHF represents a longstanding and high-stakes problem for ED-risk stratification, being present in roughly half of patients<sup>6</sup>. Around 10% of AHF presentations involve concomitant AMI<sup>2,7,8</sup>, a majority of which present without electrocardiogram ST elevation<sup>2</sup>. The other 40% of AHF patients with cTn elevations have non-ischemic myocardial injury, which has also been associated with adverse events across multiple studies<sup>6</sup>.

SAEM and HFSA recently singled out the question of whether “all AHF patients with a troponin elevation absent suspected acute coronary syndrome require admission to the hospital?” as one of the four highest priority topics for AHF research in the ED setting<sup>9</sup>. cTn elevation, regardless of being due to ischemia or injury, is included as a risk factor suggesting hospital admission in clinical decision rules<sup>10</sup> for ED disposition decisions in AHF. Thus, a common practice is to risk-stratify AHF patients by comparing current cTn to historical values in the electronic medical record (EMR)<sup>11</sup>. The rationale behind this practice aligns with the goal of differentiating when an elevated cTn in AHF should prompt hospital admission vs. ED discharge: 1) it is likely that not all cTn elevations are equally-significant for risk-prediction, 2) it may be possible to identify subgroups with elevated cTn who would vs. would not benefit from hospital admission, and 3) identifying these patients may facilitate fewer unnecessary hospitalizations. The practice assumes that cTn elevations are less serious (i.e., safer) in patients with historical (i.e. “chronic”) elevation, yet literature examining the validity of this assumption is lacking, despite its ubiquitous application.

We hypothesized that elevated cTn in the ED would be associated with adverse events in AHF patients, regardless of prior historical values. Our primary objective was to assess the incremental prognostic value of historical cTn elevation after accounting for ED cTn and other predictors of adverse events. A secondary objective was to determine if prior evaluation for ischemic heart disease (IHD) moderated prognostic significance, such as by delineating subgroups wherein the value of hospital admission for ischemic testing was greater.

## Methods

### Study Design and Setting

We performed a preplanned secondary analysis of two prospective observational patient cohorts<sup>2,3</sup> from five urban academic hospitals during 2017 through 2021 in two U.S. states. Hospitals included three level-1 and two level-2 trauma centers, with ED yearly visits between 60,000–100,000. Study design for both cohorts, REED-AHF<sup>3,12</sup> and CLEAR-AHF<sup>2</sup>, have been published previously. These prior reports and the current manuscript were prepared in accordance with the STROBE guidelines. Research was IRB approved at Wayne State University and Indiana University.

### Participants and Data Sources

Detailed inclusion and exclusion criteria, data collection practices, and data sources in REED-AHF<sup>3,12</sup> and CLEAR-AHF<sup>2</sup> have been published previously. Participants presenting to the ED, including on weekends and outside the hours of 8am-5pm, were enrolled after informed consent if the treating clinician suspected possible AHF (as reported by the physician to the screening research assistant). Diagnosis was adjudicated by two blinded experts (with a third to break ties) to arrive at the final cohorts. Patients with STEMI and cardiogenic shock at ED presentation were excluded from both studies. To meet the requirement for independence of observations in our statistical analysis, duplicate patients were excluded.

### Follow-up and Outcome Adjudication

Patients were followed for 90 days or longer by telephone and EMR follow-up of serious adverse events (SAEs)<sup>2,3,12</sup>. SAEs were checked against statewide health information exchange data to capture events occurring at facilities outside the participating health systems. AMI, as defined by the 4<sup>th</sup> Universal Definition of MI<sup>13</sup>, and AHF-related readmission were adjudicated by two reviewers blinded to one-another, with a third expert to break ties. Adjudication of AMI and diagnosis were performed by two separate groups of investigators, to prevent bias that could arise from the same person adjudicating diagnosis and outcomes. ECG findings in the ED, if commented on by the ED clinician (e.g. “no ST-depression”, “T-wave inversions present but unchanged from prior ECG”, “Smith-Modified Sgarbossa Criteria not present”) were coded as interpreted at that time. If the physician documentation did not explicitly describe one or more ECG findings or their chronicity (i.e. new vs. present on prior ECG), two investigators reviewed the ECG and any prior ECGs independently, with disputes resolved by discussion or a third adjudicator. Source documents for other datapoints were reviewed by 2 blinded adjudicators.

## Outcomes

The primary outcome of this analysis was a composite at 90-day follow-up (“COMP90”) of death/CPR, mechanical cardiac support (MCS), intubation, new or emergent hemodialysis, and/or AMI/PCI/CABG. This specific composite was chosen based on its use in the STRATIFY decision instrument<sup>14,15</sup>, one of 3 structured risk scores endorsed by the American College of Emergency Physicians (ACEP) for aiding ED disposition decisions in AHF<sup>10</sup>, and other recent AHF literature on ED patients<sup>2,3</sup>. Secondary outcomes included the same composite at 30-day follow-up (“COMP30”), 30-day AMI/PCI/CABG, and adjudicated AMI at the index encounter.

## Primary Predictor: Troponin elevation

cTn values were collected from the index ED visit and the most recent historical cTn value available in the EMR (up to two years prior). Elevation was defined as a value exceeding the manufacturer reference range. Since 2007, all cTn assays worldwide have been standardized to an upper reference limit (URL) defined by the 99<sup>th</sup> percentile value of that assay tested in a healthy reference population. While some inter-assay differences remain due to assay precision, scaling of both conventional sensitivity and high-sensitivity troponin assays to the standard of each assay’s 99<sup>th</sup> percentile URL is recognized as the preferred approach for achieving uniformity in clinical diagnosis and trial endpoints by the International Federation of Clinical Chemistry (IFCC), the European Society of Cardiology, American Heart Association, the 4<sup>th</sup> Universal Definition of MI, and others<sup>16</sup>. The 99<sup>th</sup> percentile URL standard has been employed in virtually all analyses of cTn’s significance for AHF over the past 20 years<sup>6,16</sup>.

## Secondary predictors and covariates for adjusted analysis

eGFR, LVEF, age, and history of a prior workup for IHD were considered as potential confounders based on their association with cTn levels and/or AHF SAEs<sup>2,6,13,16</sup>. Each variable was therefore included in the multivariable-adjusted analysis. IHD history was also considered as a potential moderator. An interaction term between IHD and troponin was included in the multivariable models to test the hypothesis that historical troponin elevation has different prognostic implications depending on whether a patient had a positive, negative, or unknown IHD history at the time of the index encounter.

A “positive” IHD history was defined as documentation prior to the index ED visit of known coronary artery disease (CAD), AMI, PCI, CABG, and/or cardiologist diagnosis of ischemic cardiomyopathy. Patients without history of CAD/AMI/PCI/CABG were further subdivided into “negative” (a documented negative CAD workup via cardiac catheterization and/or cardiologist diagnosis of non-ischemic cardiomyopathy) or “unknown” (no prior CAD workup and the patient has not been diagnosed previously as having or not having IHD).

Other variables felt to be informative for the ischemic secondary outcomes were included in the descriptive, but not multivariable, analyses. These included first (earliest) cTn vs. highest/peak value in the ED, “delta” value (percent change) if multiple ED troponins were

ordered, symptoms (chest pain, shortness of breath) at presentation, various ECG findings, and utilization rates of cardiac catheterization.

### **Statistical Analysis – Description of the Cohort**

All statistical analyses were conducted in R (R Studio 2021.09.1). Variables were described as median/interquartile range (IQR) or percent (n). Descriptive comparisons utilized the Wilcoxon Rank Sum or Chi-square tests. For this descriptive analysis, cohort characteristics were stratified by 1) the primary outcome (Table 1); 2) the secondary outcomes (Table 2); and 3) elevated vs. normal initial cTn in the ED (Supplemental Table 1). An alpha of 0.05 was assumed for hypothesis testing.

### **Statistical Analysis – Multivariable Analysis to Assess the Incremental Prognostic Significance of Historical Troponin and IHD History**

Logistic regression was used to evaluate the outcomes vs. historical cTn (elevated vs. not elevated) adjusted for ED cTn, age, LVEF, eGFR, and IHD history. An interaction term between IHD history and historical cTn was included to test whether history of IHD (and history of IHD workup) altered prognostic value. Model results were reported with covariate adjusted odds ratios (aOR) with 95% confidence (95% CI).

### **Statistical Analysis – Ischemic vs. Non-ischemic Adverse Events**

Next, we assessed whether the association between elevated cTn and the primary outcome was driven by ischemic adverse-events, non-ischemic adverse events, or both (Figure 2). Patients experiencing COMP90 were stratified by elevated vs. normal ED cTn and ischemic vs. non-ischemic outcomes. “Non-ischemic outcome” was defined as a patient who experienced any outcome(s) within the COMP90 composite except AMI/PCI/CABG within 90-days (i.e. only death, MCS, new/emergent dialysis, and/or intubation). An “ischemic outcome” was defined as a patient experiencing AMI/PCI/CABG within 90-days, with or without experiencing other components of COMP90.

### **Statistical Analysis – Historical Troponin Association with Emergency Department Clinician Decision Making**

Lastly, we sought to evaluate the validity of a key assumption underlying our primary hypothesis: that ED clinician disposition decisions are associated with historical troponin values. The status quo for many ED physicians is to interpret an elevated ED cTn in AHF as less prognostically significant if a historical troponin is also elevated. Put differently, a common belief underlying ED physician standard practice is that cTn during an encounter for AHF has limited incremental prognostic value if a historical troponin is elevated. In a recent survey of ED attending physicians on their disposition decisions in AHF, physicians rated comparison of the ED cTn to a historical cTn as the third most important factor determining whether they would discharge a patient or admit them to the hospital<sup>11</sup>.

We sought to evaluate the validity of this assumption in the current sample, in case physicians in the current cohort behaved in a way systematically different from what would be expected under ED usual care. If historical cTn had the effects on ED physician decision-making described above, we hypothesized that 2 observations would be true in the current

sample: 1) Patients with elevated cTn in the ED would be more likely to be discharged if historical cTn was also elevated, and 2) the multivariable-adjusted odds of discharge from the ED would increase as historical cTn increased relative to the ED cTn. To test the former, patients discharged from the ED with an elevated cTn were stratified by elevated vs. normal historical cTn and compared by descriptive statistics. To test the latter, a logistic regression model for ED discharge vs. admission (dependent variable) was fit for ED cTn, historical cTn, IHD history, and the Get With the Guidelines Heart Failure Risk Score. The latter is a risk-prediction score based on admission characteristics (blood pressure, age, BUN, sodium, heart rate, COPD history) which is endorsed by the ACC and AHA for risk-stratification in AHF<sup>17</sup>. It has previously been validated to predict both in-hospital mortality<sup>18</sup> and death or cardiovascular events at long term follow-up (median 3-years after admission)<sup>19</sup>.

### Sensitivity analyses

cTn, both the ED and historical values, were also evaluated as continuous variables in a sensitivity analysis to assess whether magnitude of cTn elevation affected the results. The ratio of ED to historical troponin (as a single variable substituted for both terms in multivariable modeling) was tested for a similar reason. Over the study period, multiple conventional sensitivity (cs-cTn) assays and high-sensitivity (hs-cTn) assays came in and out of use at the study institutions. To partially adjust for changing assays within and between institutions over time, all cTn values were converted to a percentage of the assay 99<sup>th</sup>ile URL. We felt this method best reflected clinical reality, particularly for the common clinical practice of comparing current cTn value to prior EMR values, since institutions including our own change cTn assays as frequently as every 2–3 years.

While the 99<sup>th</sup>ile of a healthy reference population should theoretically be equivalent between hs-cTn and cs-cTn sensitivity assays<sup>16</sup>, changing standards for a “healthy reference population” have led to observations that some hs-cTn assays may detect a greater proportion of patients above the 99<sup>th</sup>ile URL than with cs-cTn<sup>16</sup>. Therefore, we performed sensitivity analyses to see if the primary results changed with hs-cTn vs. cs-cTn. Additionally, we compared ED cTn positivity (elevated vs. not) and continuous value (as multiple or URL) in the sample by cs-cTn vs. hs-cTn, after regression adjustment for patient sex and prior history of cTn elevation on a cs-cTn assay to account for selection bias (e.g. differential gender and cTn historical positivity by cs- vs. hs-cTn). In a 2023 analysis of 550 U.S. hospitals in the American College of Cardiology’s NCDR Registry, less than one-third had implemented hs-cTn as of the most recently available data<sup>21</sup>. However, this percentage is expected to increase in the coming years as implementation of hs-cTn in the US increases. Therefore, we felt the results including both cs-cTn and hs-cTn would be timely and informative, particularly in evaluating whether the results of our current research question changed based on assay sensitivity (i.e. this sensitivity analysis).

**Sample Size Determination and Missing Data:** Sample size was determined to target 10 events per variable in logistic regression for the primary outcome and Cohen’s  $\omega$  of 0.3 (99.9% power) to 0.154 (80.3% power). Missing historical cTn was evaluated as “not elevated”, and a sensitivity analysis was performed with and without patients missing historical cTn to evaluate validity of this assumption. Patients with missing ED cTn were

excluded (n=6); other model covariates had 0% missingness. For further details please refer to the Supplementary Materials.

## Results

### Inclusion and Description of the Cohort by ED Troponin Elevation

Of 341 diagnostically-adjudicated patients, 6 did not have cTn drawn in the ED, leaving 335 for the primary analysis. Median (IQR) patient age was 61 years (52–68), initial cTn 0.99 multiples of URL (0.99–2.00), current vs. historical cTn ratio 1.00 (0.82–2.13), eGFR 61 mL/min (37–82), and LVEF 35% (22–55). Historical cTn was elevated in 114 (34%) patients and elevated in the ED for 169 (49%) patients. Rate of elevated ED cTn and the cTn value as a multiple of URL were similar for cs-cTn vs. hs-cTn ( $p=0.749$  and  $p=0.935$ , respectively). The composite primary outcome occurred in 83 patients (24%) at 90 days, and 57 (16%) within 30 days. Adjudicated AMI was present for 29 patients at index visit (9%), and 33 (10%) experienced AMI/PCI/CABG by 30 days.

Elevated ED cTn was associated with ( $p<0.05$ ) historical cTn elevation, ECG criteria suggestive of ischemia, lower eGFR and LVEF, greater proportional change in delta cTn, greater current/prior cTn ratio, and greater rates of the primary outcome (Supplemental Table 1).

### Patient Characteristics by Primary and Secondary Outcomes

Table 1 presents characteristics stratified by the primary outcome, and Table 2 by the secondary outcomes. Greater initial ED cTn value (as multiple of URL), elevated ED cTn, greater change on serial/delta troponins, and higher rates of new ECG abnormalities in the ED were associated with the primary outcome (Table 1) and every secondary outcome (Table 2). The primary outcome was also associated with older age, lower eGFR, higher BUN, lower sodium, and higher Get With the Guidelines HF risk score (Table 1). The composite at 30-days (COMP 30), but not the primary outcome, was associated with historical cTn elevation (Tables 1 & 2).

AMI at the index visit accounted for 29/33 (88%) patients with AMI/PCI/CABG by 30 days, while 4/33 events occurred after discharge from the index encounter. The initial ED cTn was elevated for 23/29 index AMIs, while 5 (21%) experienced their first cTn elevation on a serial lab draw during the ED or inpatient course (Table 2). Patients with 30 day AMI/PCI/CABG or index AMI were older and had lower eGFR (Table 2). Among those experiencing either outcome, only 45% reported chest pain in the ED, compared to 37% without an ischemia-related event ( $p=0.3$ , Table 2).

A minority (17%) of patients with an adjudicated AMI at ED presentation received coronary catheterization during the index hospitalization compared to post-hospital at 30 day (34%) and 90 day (38%) follow-up (Table 2). Over half of all catheterizations were diagnostically negative for AMI and did not result in PCI/CABG (Table 2). Catheterization within 90 days was similarly common in those with vs. without a known IHD workup before the index encounter, as well as those with a positive vs. negative prior work-up (all  $p>0.05$ ).

## Multivariable Analysis to Assess the Incremental Prognostic Significance of Historical Troponin and IHD History

Prognostic value of historical cTn elevation for predicting the 90-day primary outcome, after adjusting for ED cTn elevation, age, eGFR, LVEF, and IHD history, depended on whether patients had a history of workup for IHD at the time of the index ED visit ( $p$  interaction=0.04, Figure 1). In those with a prior IHD workup, regardless of the prior workup being positive or negative, historical cTn did not add significant predictive value ( $p>0.05$ ) to the risk factors at presentation (Figure 1). In patients without a prior workup for IHD, an elevated historical cTn predicted 5-fold greater odds of the 90 day outcome (aOR 5.27; 1.23 – 22.4). Similar relationships, after multivariable adjustment, were present for historical cTn elevation versus each secondary outcome (Figure 1).

Adjusted for IHD history (ischemic, non-ischemic, or unknown), eGFR, LVEF, age, and historical troponin elevation, an elevated ED troponin was associated with greater odds of the 90-day composite (aOR 2.39; 1.30–4.38), 30-day composite (aOR 3.10; 1.49–6.44), 30-day AMI/PCI/CABG (aOR 5.62; 2.05 –15.39), and AMI at the index visit (aOR 7.10; 2.28 – 22.13). ED cTn as a continuous multiple of the URL was also significantly associated with greater odds of each outcome (Figure 1). The ratio of the ED and historical troponins had virtually identical predictive value as the ED cTn alone (for primary outcome; ratio aOR 1.45 {1.13–1.87}, ED cTn alone aOR 1.39 {1.12–1.73}).

None of the observed relationships between cTn (i.e. whether historical vs. ED, binary vs. continuous) and outcomes differed significantly when comparing results by hs-cTn vs. cs-cTn (all  $p>0.05$ ), or when excluding missing historical cTn, in a sensitivity analysis.

### Ischemic vs. Non-ischemic Adverse Events

Figure 2 presents the primary outcome composite stratified by ischemia-related adverse events (AMI, PCI, CABG), versus non-ischemic events, at 90 days. Significantly more patients experienced ischemic adverse events when ED cTn was elevated vs. normal (absolute risk difference {RD} +12.6%, 95% CI:5.2–19.9%,  $p=0.001$ ). Among 40 total patients with at least one ischemic adverse event, 11 (27.5%) also experienced a non-ischemic adverse event. A similar number ( $n=43$ ) experienced a non-ischemic adverse event without any ischemic events. The proportion of patients with strictly non-ischemic outcomes was numerically greater for those with elevated vs. normal ED cTn (Figure 2), but not statistically significant (RD = +3.1%, +10.8% to –4.6%,  $p=0.497$ ).

### Historical Troponin Association with Emergency Department Clinician Decision Making

ED clinicians were significantly more likely to discharge a patient with an elevated ED cTn if there was a history of prior troponin elevation (78% vs. 32%,  $p=0.025$ ). After multivariable adjustment for ED cTn, historical cTn, IHD history (ischemic, non-ischemic, or unknown) and Get With the Guidelines Risk Score, a greater ED cTn was associated with greater odds of admission vs. discharge (aOR 1.51 per multiple URL; 1.05–2.19). However, compared to patients with high ED cTn and normal historical cTn, there was greater multivariable adjusted odds of discharge if both ED and historical cTn were high (aOR 0.970 per multiple URL; 0.94 – 0.99,  $p$  interaction<0.05, figure 3). This effect was

present regardless of IHD status, which was not associated with ED discharge vs. admission decision after multivariable adjustment.

Among those discharged (n=32, 11%), AMI/PCI/CABG occurred in 3 discharged patients (8.3%), including 2 patients (5.6%) adjudicated to have AMI at the index encounter. Figure 4 presents the composite outcome at 30-days stratified by ED disposition and ischemic vs. non-ischemic adverse events. Compared to patients admitted to the hospital or observation, patients discharged from the emergency department had a nearly 3-fold lower rate (7.5% vs. 2.7%) of non-ischemic adverse events at 30-days. Conversely, the rates of ischemic adverse events were similar between ED discharge vs. observation/inpatient disposition (8.3% vs. 9.8%).

## Discussion

In this pre-planned secondary analysis, we evaluated the incremental prognostic value of historical troponin values when risk-stratifying AHF in the ED (Figure 5). Our study has 2 primary findings. First, a prior history of cTn elevation predicted greater adverse event risk in patients without a prior IHD workup (Figure 1), and did not reduce the risk associated with elevated ED cTn when IHD history was known. This runs directly counter to common practice patterns<sup>11</sup>, including what we observed in the current study: patients with an elevated ED cTn had greater multivariable-adjusted odds of discharge if they had a history of prior cTn elevation, while IHD history was not associated with ED disposition. Second, the adverse event risk associated with elevated cTn in the ED was primarily driven by patients with ischemic adverse events (AMI/PCI/CABG, Figure 2), suggesting that accurate identification of ischemic vs. non-ischemic cTn elevations may aid in risk-stratification where comparison to historical values does not. Patients experiencing AMI/PCI/CABG within 30 days, 88% of whom experienced their ischemic event during the index presentation, were just as likely to be discharged from the ED as admitted to inpatient or observation (8.3% vs. 9.8%, Figure 2). Together these results suggest hospital admission for urgent coronary evaluation in AHF patients is valuable among patients with recurrent elevated troponin and no prior ischemic workup. Likewise, with a known IHD history the clinical diagnosis of ischemic vs. non-ischemic cTn elevation should not be overly predicated on comparison to historical cTn, which appears to add little incremental value once IHD history is known. Current ED disposition patterns do not appear to reflect this approach, calling into question current ED risk-stratification paradigms regarding cTn in AHF.

Prior data support our findings that historical cTn elevation is generally not reassuring in heart failure, and may indicate a need for an IHD work-up<sup>6</sup>. In a study of 196 chronic heart failure patients, recurrent low-level cTnI elevation was found to be a worse prognostic indicator than intermittent spikes in troponin<sup>23</sup>. The patients' minimum troponin level across 3 all-cause hospitalizations, but not maximum values or trends between visits, predicted nearly 13-fold higher mortality<sup>23</sup>. Our results here in an ED setting also corroborate prior literature suggesting that persistent elevation of cTn after hospital admission predicts worse AHF outcomes<sup>24</sup>, while persistent cTn elevation after inpatient discharge correlates with adverse cardiac remodeling and underlying heart failure<sup>25</sup>.

While there are likely several possible explanations for why historical cTn elevation did not ameliorate ED troponin risk, the most likely is perhaps that patients with chronic troponin elevations are simply sicker. Lack of a prior workup for IHD appeared to moderate the relationship between historical troponin and adverse events (Figure 1). Patients without a prior IHD workup who have a documented prior troponin elevation likely represent individuals at high risk for underlying IHD who nevertheless have “slipped through the cracks”. To that end, the 5-fold greater odds of adverse events observed in this group suggests that an unknown IHD history together with ED cTn elevation should prompt hospital admission and evaluation for underlying IHD. Among those with a known IHD history, a lack of incremental value (i.e. either positive or negative) for the historical cTn was observed even when considering the magnitude of difference from the historical troponin. Most tellingly, a ratio of ED and historical troponin had virtually the same predictive value as the ED troponin alone.

In contrast, historical cTn elevation was associated with greater odds of ED discharge after adjustment for covariates (IHD history, cTn at the index visit, and GWTG-HF risk score). We suspect that this finding reflects physician beliefs that historical cTn elevation is a reassuring prognostic factor, similar to what doctors have said in surveys<sup>11</sup>, yet contrary to what our data suggests about the relationship between adverse events and historical cTn elevation. Meanwhile, when compared to the association between historical cTn and disposition decisions, other factors associated with ischemic adverse events were underutilized (e.g. multiple ECG patterns, serial (“delta”) troponin, IHD history, Table 2). In a majority of patients discharged from the ED, for example, the clinician did not obtain a delta troponin. Moreover, unknown IHD history was not associated with ED discharge vs. admission after multivariable adjustment (aOR = 0.92; 95% CI: 0.36–2.31), suggesting it did not factor highly into disposition decisions despite being associated with adverse events.

This underlines a key opportunity for improvement: current ED practices operate under an assumption that pre-existing or “chronic” troponin elevations are “safer” than when troponin is newly elevated, and less heavily consider the relationship between IHD history and cTn elevation. In a recent survey of ED physicians’ AHF disposition decision-making practices, attending physicians rated “Higher troponin value in relation to past values” as more important to determining disposition than “troponin value, regardless of prior value”, and as the third most important factor influencing disposition overall<sup>11</sup>. Only “low blood pressure” and “new oxygen requirement” were rated as more important by physicians to their disposition decision making.

Despite how common this assumption may be, this is, to our knowledge, the first report to evaluate it in ED patients with AHF. The ED disposition patterns we observed here and the disposition attitudes reported previously<sup>11</sup> directly conflict with what our results suggest: that admission is likely valuable with elevated historical and ED cTn specifically when IHD history is unknown.

The association of ED cTn elevation and adverse outcomes was predominantly driven by a 12.6% greater incidence of ischemic adverse events (Figure 1, Tables 2). A more modest 3.1% risk difference occurred for adverse events in the absence of any ischemic

outcomes (AMI/PCI/CABG), which failed to reach statistical significance. Given this contrast, accurate identification of ischemic vs. non-ischemic presentations appears to be a critical step towards the broader goal of identifying when and how cTn elevation in AHF informs the value of hospitalization vs. ED discharge. Namely, while both ischemic and non-ischemic cTn elevation are associated with adverse events<sup>6</sup>, the former is a much larger contributor to adverse event risk. It is possible that after excluding ischemia, patients with elevated cTn in the ED and a prior workup for IHD may be appropriate for ED discharge assuming no other indications for admission. This would seem to be corroborated by recent data from Ferman et al. of AHF patients discharged from the ED, in whom AMI had been clinically excluded, which found no association between cTn and adverse events<sup>26</sup>.

Unfortunately, several observations from the current study underline the real-world challenges in achieving these goals. First, ED patients who experienced 30-day AMI/PCI/CABG were just as likely to be discharged as they were to be admitted to the hospital (8.3% vs. 9.8%,  $p=0.8$ ), including for two patients adjudicated to have experienced an AMI during the index visit. To the extent that ED disposition decisions reflected lower 30-day adverse events in discharged vs. admitted patients (11% vs. 17%), this was driven almost entirely by fewer non-ischemic adverse events among discharged patients and not by a difference in ischemic events (Figure 2). Second, despite excluding cardiogenic shock and STEMI, we observed a 9% rate of AMI at the index visit (Table 1–2). This is similar to rates in multinational AHF registries dating back over a decade<sup>7,8</sup>, which reinforces that acute ischemia in AHF remains common. Third, around half of all cardiac catheterizations performed during the study were negative (Table 2), further suggesting the difficulty in non-invasively selecting patients for gold-standard work-up and treatment for ischemic heart disease. Fourth, AMI presentation was frequently atypical with regards to chest pain in the ED, which was both insensitive (44.8%) and non-specific (62.8%). Overall, differentiating patients with ischemic events vs. non-ischemic cTn elevations in AHF remains challenging.

### Limitations

This study was limited as it was a secondary analysis of previously collected data, however this data set was prospectively collected as part of other AHF research and the hypotheses pre-planned. Verifying and adjudicating 90-day outcomes was performed by independent reviewers and subject to human error. However, each outcome was compared after blinded review, and adjudicated by a third party to resolve conflicts. The prior troponin values were only those that were available in the system EMR, and the time frame between the prior value and the ED varied as much as a few days to nearly two years. It is plausible that differential timing (inpatient vs. outpatient, end of hospitalization vs. beginning) of the historical troponin may affect clinical ramifications. However, these discrepancies between available information for different patients are a clinical reality that clinicians face every day. The same caveats, and rationale, apply to the fact that troponin assays changed throughout the enrollment period. The 99<sup>th</sup> percentile URL, while imperfect for reasons previously discussed, is the current international standard by which both cs-cTn and hs-cTn are benchmarked. Multiple sensitivity analyses did not show a difference in results by troponin assay, including between cs-cTn and hs-cTn. The lack of a difference between ischemic adverse events among admitted vs. discharged patients was based on a relatively number of events, and

thus we cannot rule out that random error or errors in adjudication led to this result. An event rate of 24% for COMP90 also may have limited statistical modeling for all possible confounders. Lastly, while discharge from the ED was positively associated with elevated historical cTn but not IHD history, we cannot say that this was a causative relationship for physician decision making based on the non-experimental design of the study (i.e. we can only state association).

## Conclusions

AHF patients with historical cTn elevation, in the absence of a prior IHD workup, may benefit from hospital admission given an association with greater adverse events. Urgent coronary evaluation may be beneficial given that adverse event risk appears driven by ischemic outcomes. It may be reasonable to arrange an outpatient ischemic workup for some of these patients with close follow-up, but with a likely self-selected group for poor access to care, feasibility of avoiding admission may be limited. When IHD history is already known, comparison to historical cTn does not appear to reliably distinguish high vs. low-risk patients or ischemic vs. non-ischemic cTn elevation during the current ED visit. These findings directly contradict current disposition practices in the ED, and do not support the common belief that cTn elevation in AHF is safer when accompanied by historical cTn elevation. Opportunity for improvement is highlighted by the discordance between clinical outcomes we observed and current practices, with ischemic adverse events particularly common but frequently missed in the ED.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

<b>AHF</b>	Acute heart failure
<b>ED</b>	Emergency department
<b>cTn</b>	cardiac troponin
<b>AMI</b>	Acute myocardial infarction
<b>PCI</b>	percutaneous coronary intervention
<b>CABG</b>	coronary artery bypass graft
<b>ECG</b>	electrocardiogram
<b>CPR</b>	cardiopulmonary resuscitation
<b>eGFR</b>	estimated glomerular filtration rate
<b>LVEF</b>	left ventricular ejection fraction

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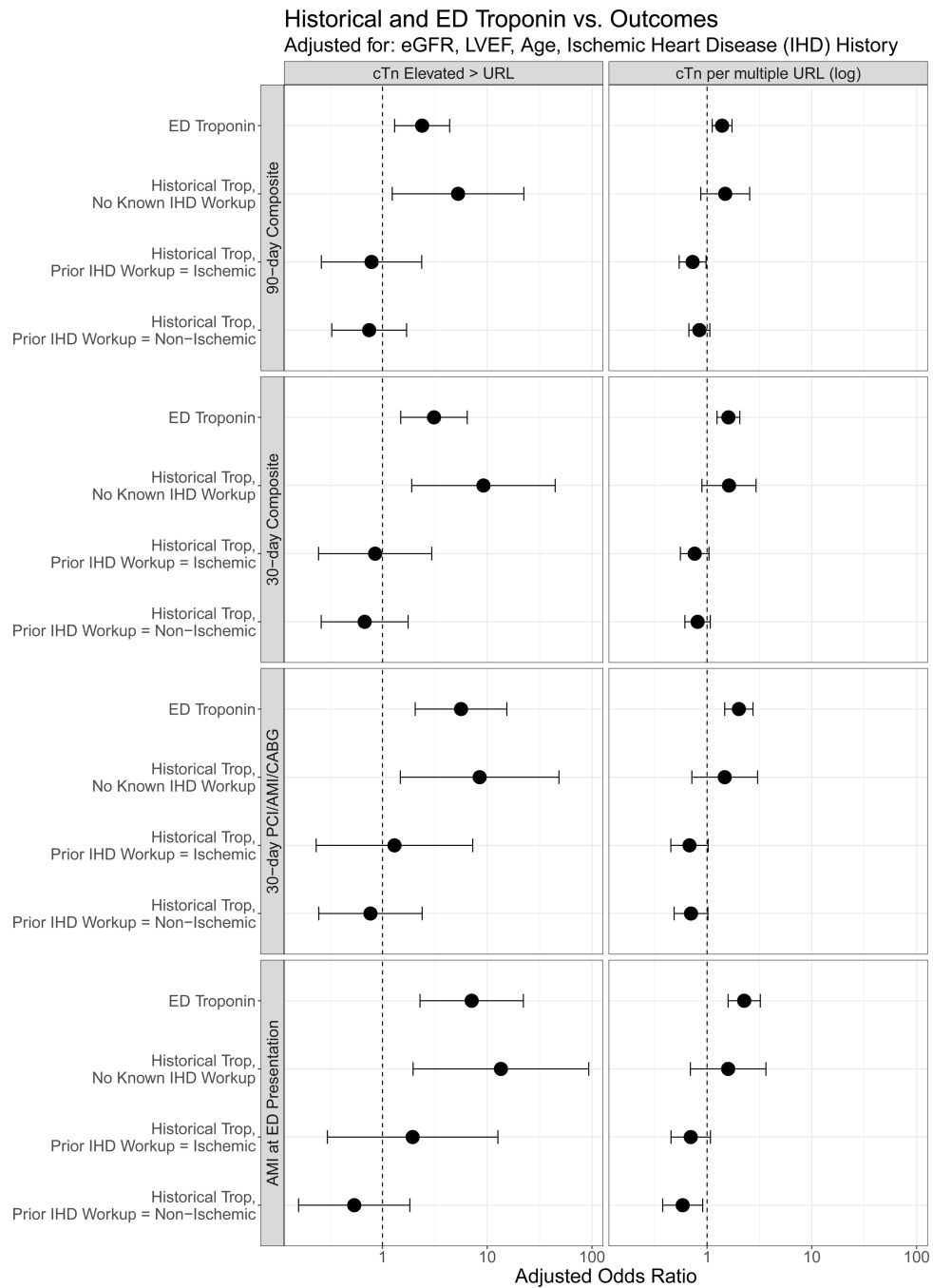
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**Figure 1: Multivariable-Adjusted Prognostic Value of Historical Troponin vs. ED Troponin Alone**

Forest plot of multivariable model results (adjusted odds ratios {aOR, points} and 95% confidence intervals {whiskers}). Results presented are stratified by outcome (rows) and whether troponin (cTn) was modeled as binary (elevated > URL, yes vs. no) or continuous (columns). The composite outcome was death, cardiopulmonary resuscitation, mechanical cardiac support, intubation, new or emergent dialysis, AMI/PCI/CABG.

Statistical notes: Continuous covariates were transformed using restricted cubic splines to maintain linearity to the logit. Multicollinearity was assessed via VIF, and all covariates

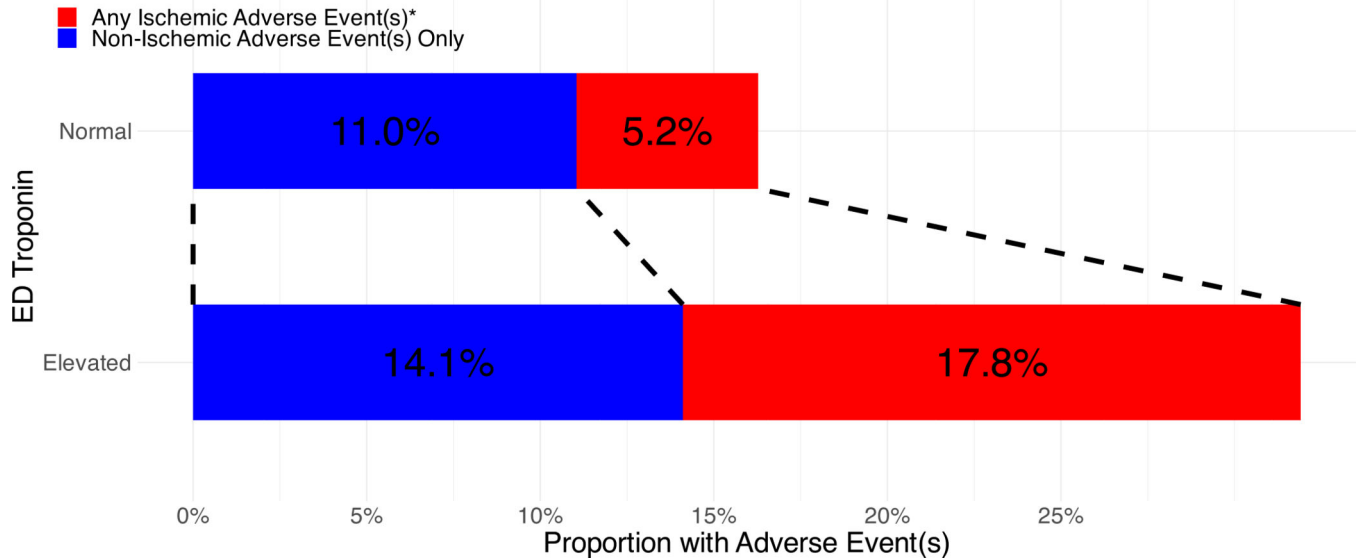
showed  $VIF < 10$ . Goodness of fit testing was performed via the le Cessie-van Houwelingen goodness of fit test, implemented in the *rms* package in  $R^{22}$ , yielding  $p = 0.42$  for lack-of-fit. ED = Emergency Department; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; IHD = ischemic heart disease; cTn = troponin; URL = upper reference limit; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; VIF = variance inflation factor.

### 90-day Outcomes Stratified by Ischemic vs. Non-Ischemic Adverse Events\*

Ischemic adverse events: Acute MI, Percutaneous Coronary Intervention, and/or Coronary Artery Bypass Graft

Non-ischemic adverse events: Intubation, New or Emergent Dialysis, Mechanical Cardiac Support, Death

\*Occurrence of any ischemic adverse event(s), with or without non-ischemic event(s), counted here as 'Ischemic' (e.g. PCI + Death = Ischemic)

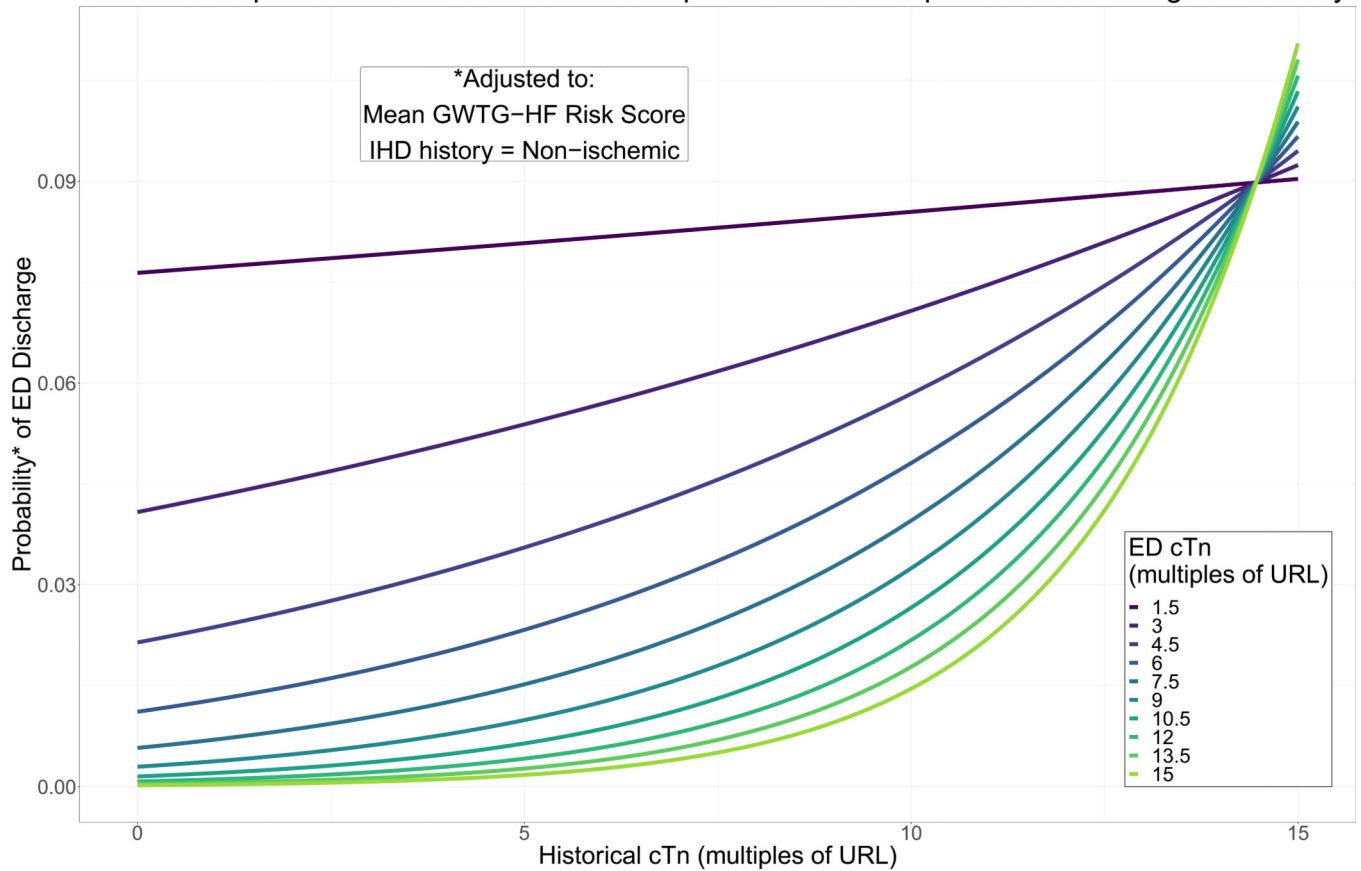


**Figure 2: 90-day adverse events stratified by emergency department troponin and ischemic vs. non-ischemic**

Patients experiencing the 90-day composite are stratified by 1) elevated vs. normal troponin, and 2) whether 1 ischemic adverse event occurred for the patient (AMI/PCI/CABG).

AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

### Historical Troponin Moderates the Relationship Between ED Troponin and Discharge Probability



#### Figure 3: Historical Troponin Moderates the Relationship Between ED Troponin and Discharge Probability

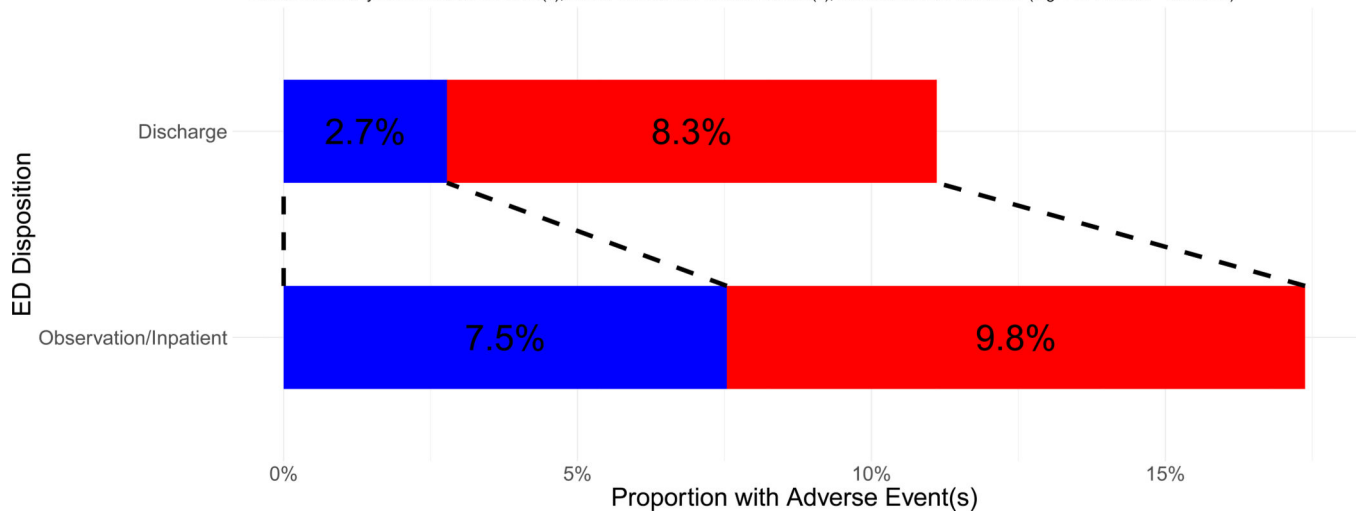
Higher ED troponin (cTn) was associated with significantly lower odds of ED discharge overall (aOR 1.51 per multiple URL; 95% CI: 1.05–2.19), but this relationship was significantly moderated ( $p$  interaction < 0.05) by historical cTn. For any given value of ED cTn, the multivariable-adjusted odds of ED discharge increased as historical troponin rose. ED = emergency department; cTn = cardiac troponin; GWTG-HF risk score = Get With The Guidelines Heart Failure Risk Score; IHD = ischemic heart disease; URL = upper reference limit.

### 30-day Outcomes Stratified by Ischemic vs. Non-Ischemic Adverse Events\*

Ischemic adverse events (Red): Acute MI, Percutaneous Coronary Intervention, and/or Coronary Artery Bypass Graft

Non-ischemic adverse events (Blue): Intubation, New or Emergent Dialysis, Mechanical Cardiac Support, Death

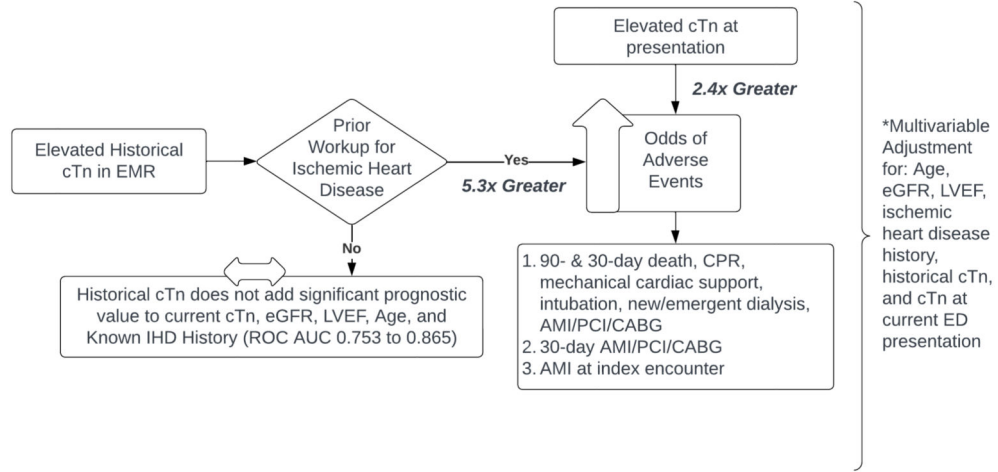
\*Occurrence of any ischemic adverse event(s), with or without non-ischemic event(s), counted here as 'Ischemic' (e.g. PCI + Death = Ischemic)



**Figure 4: 30-day adverse events stratified by emergency department disposition and ischemic vs. non-ischemic**

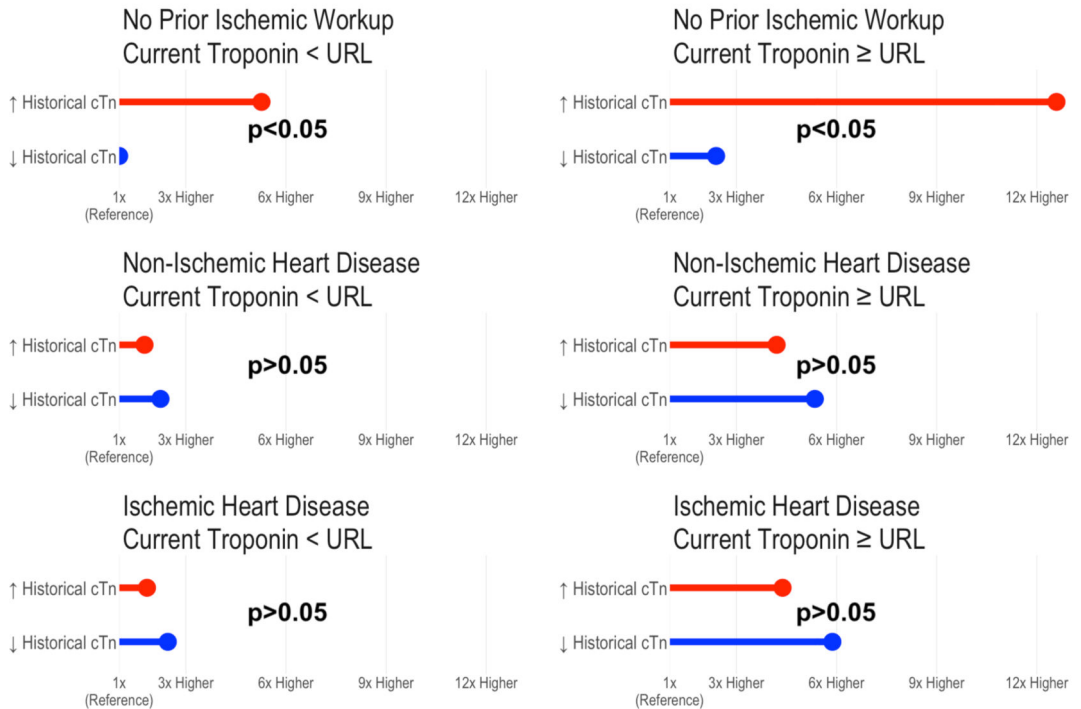
Patients experiencing the composite outcome at 30-days are stratified by 1) emergency department (ED) disposition (discharge vs. observation/inpatient), and 2) whether 1 ischemic adverse event occurred for the patient (AMI/PCI/CABG).

**Central Illustration: Incremental Prognostic Value of Historical (EMR) cTn Compared to cTn and Other Baseline Factors at Time of Presentation For Acute Decompensated Heart Failure**



**Odds of 90-day Adverse Event Composite\* in Acute Decompensated Heart Failure**

Multivariable Adjusted for Age, eGFR, LVEF, Ischemic Heart Disease status at index presentation, ED Troponin (cTn) elevation, and Historical (EMR) cTn elevation



\*Composite of Death, CPR, Mechanical Cardiac Support, Intubation, New or Emergent Dialysis, AMI, PCI, or CABG

**Figure 5 /. Central Illustration:**

After considering baseline characteristics at time of presentation for ADHF (including current cTn, eGFR, LVEF, Age, and IHD history), the incremental prognostic value of historical cTn in the EMR is dependent on the patient’s IHD history. In those without a prior IHD workup, elevated historical cTn increases risk of multiple adverse events. When IHD history has already been established (whether ischemic or non-ischemic) historical cTn does not add incremental prognostic value beyond current cTn and the other baseline variables on their own.

cTn = troponin; AHF = acute heart failure; ED = Emergency Department; EMR = electronic medical record; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; IHD = ischemic heart disease; URL = upper reference limit; ROC AUC = receiver operating characteristic area under curve; CPR = cardiopulmonary resuscitation; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

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Table 1:

## Patient Characteristics by Primary Outcome

Characteristic	Primary Outcome (90-day composite)			p-value <sup>2</sup>
	Overall (N=341) <sup>1</sup>	No (n=258) <sup>1</sup>	Yes (n=83) <sup>1</sup>	
<b>Troponin Characteristics</b>				
<i>Initial ED cTn Elevated</i>	163 (49%)	111 (44%)	52 (65%)	<0.01
<i>Historical cTn Elevated</i>	114 (33%)	79 (31%)	35 (42%)	0.05
<i>Highest ED cTn (multiples URL)</i>	1.06 (0.99, 2.25)	1.00 (0.98, 1.77)	1.74 (0.99, 3.53)	<0.01
<i>ED cTn (multiples URL)</i>	0.99 (0.99, 2.00)	0.99 (0.99, 1.75)	1.61 (0.94, 2.76)	<0.01
<i>Delta cTn in ED (Proportion Change)</i>	0.00 (0.00, 0.25)	0.00 (0.00, 0.14)	0.11 (0.00, 0.50)	<0.01
<i>ED:Historical cTn Ratio</i>	1.00 (0.82, 2.13)	1.00 (0.84, 1.80)	1.25 (0.78, 3.04)	0.06
<b>ED Presentation and Disposition Characteristics</b>				
<i>Age (y)</i>	61 (52, 68)	59 (51, 67)	63 (56, 70)	0.02
<i>eGFR</i>	61 (37, 82)	65 (42, 85)	45 (20, 74)	<0.01
<i>LVEF (%)</i>	35 (21, 55)	35 (21, 55)	39 (22, 54)	0.7
<i>ED Chest Pain</i>	129 (38%)	97 (38%)	32 (39%)	0.9
<i>ED Dyspnea</i>	297 (87%)	225 (87%)	72 (87%)	>0.9
<i>Systolic Blood Pressure (mmHg)</i>	153 (132, 177)	154 (133, 177)	153 (129, 180)	>0.9
<i>Heart Rate</i>	92 (80, 105)	91 (80, 105)	94 (80, 106)	0.3
<i>Sodium, serum (mEq/L)</i>	139 (137, 141)	139 (137, 141)	138.0 (136, 141)	0.08
<i>Blood Urea Nitrogen (mEq/L)</i>	21 (16, 32)	20 (16, 28)	27 (17, 40)	<0.01
<i>History of COPD</i>	146 (43%)	110 (43%)	36 (43%)	>0.9
<i>Get With The Guidelines HF Risk Score</i>	32 (28, 38)	31 (27, 37)	35 (30, 42)	<0.01
<i>ED Disposition = Discharge</i>	36 (11%)	30 (12%)	6 (7.2%)	0.3
<b>ECG Characteristics</b>				
<i>New T wave inversions</i>	63 (18%)	41 (16%)	22 (27%)	0.03
<i>New ST depression</i>	27 (7.9%)	13 (5.0%)	14 (17%)	<0.01
<i>New Pathologic Q</i>	22 (6.5%)	11 (4.3%)	11 (13%)	<0.01
<i>OMI ECG Criteria</i>	34 (10.0%)	11 (4.3%)	23 (28%)	<0.01
<b>Ischemic Heart Disease History at ED Presentation</b>				
<i>Known Prior Workup</i>	250 (73%)	184 (71%)	66 (80%)	0.01
<i>Positive Ischemic History (vs. Known Non-ischemic)</i>	145 (58%)	103 (56%)	42 (64%)	0.35
<b>Utilization of Coronary Angiography</b>				
<i>In-hospital</i>	11 (3.2%)	6 (2.3%)	5 (6.0%)	0.14
<i>30 days</i>	28 (8.2%)	13 (5.0%)	15 (18%)	<0.01
<i>90 days</i>	36 (11%)	15 (5.8%)	21 (25%)	<0.01

<sup>1</sup>Median (IQR); n (%)

<sup>2</sup>Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Composite outcome = Death/cardiopulmonary resuscitation, mechanical cardiac support, intubation, new or emergent dialysis, AMI/PCI/CABG.

AMI = Acute myocardial infarction; PCI = percutaneous coronary intervention; ED = emergency department; cTn = cardiac troponin; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; HF = Heart Failure; OMI = occlusion MI

**Table 2:**

Patient Characteristics by Secondary Outcomes

Characteristic	<i>Secondary Outcomes</i>								
	Composite Outcome at 30 days			Acute MI, PCI, and/or CABG at 30-days			Acute MI at index presentation		
	No (n=284) <sup>I</sup>	Yes (n=57) <sup>I</sup>	p-value <sup>2</sup>	No (n=308) <sup>I</sup>	Yes (n=33) <sup>I</sup>	p-value <sup>2</sup>	No (n=312) <sup>I</sup>	Yes (n=29) <sup>I</sup>	p-value <sup>2</sup>
<u>Troponin Characteristics</u>									
<i>Initial ED cTn Elevated</i>	125 (45%)	38 (69%)	<0.01	137 (45%)	26 (81%)	<0.01	140 (46%)	23 (79%)	<0.01
<i>Historical cTn Elevated</i>	88 (31%)	26 (46%)	0.03	98 (32%)	16 (48%)	0.05	99 (32%)	15 (52%)	0.03
<i>Highest ED cTn (multiples URL)</i>	1.00 (0.96, 2.00)	1.73 (0.99, 4.09)	<0.01	0.99 (0.95, 1.76)	2.12 (1.30, 5.90)	<0.01	0.99 (0.95, 1.78)	2.25 (1.30, 5.90)	<0.01
<i>ED cTn (multiples URL)</i>	0.99 (0.97, 1.78)	1.65 (0.99, 3.28)	<0.01	1.00 (0.95, 2.00)	2.25 (1.63, 7.86)	<0.01	1.00 (0.95, 2.00)	2.25 (1.63, 7.86)	<0.01
<i>Delta cTn in ED (Proportion Change)</i>	0.00 (0.00, 0.17)	0.12 (0.00, 0.53)	<0.01	0.00 (0.00, 0.17)	0.33 (0.00, 1.33)	<0.01	0.00 (0.00, 0.17)	0.42 (0.11, 1.65)	<0.01
<i>ED:Historical cTn Ratio</i>	1.00 (0.80, 1.84)	1.53 (0.85, 3.05)	0.01	1.00 (0.79, 1.95)	2.02 (1.00, 5.71)	<0.01	1.00 (0.80, 1.95)	2.24 (1.04, 6.76)	<0.01
<u>ED Presentation and Disposition Characteristics</u>									
<i>Age (y)</i>	59 (51, 67)	64 (57, 69)	0.07	60 (51, 67)	65 (59, 69)	0.02	60 (51, 68)	65 (59, 69)	0.02
<i>eGFR</i>	64 (41, 85)	39 (19, 73)	<0.01	62 (38, 83)	48 (20, 74)	0.04	62 (38, 83)	44 (20, 64)	0.02
<i>LVEF (%)</i>	35 (22, 55)	37 (21, 55)	>0.9	35 (21, 55)	37 (24, 55)	0.9	35 (21, 55)	39 (24, 55)	0.8
<i>ED Chest Pain</i>	105 (37%)	24 (42%)	0.5	114 (37%)	15 (45%)	0.3	116 (37%)	13 (45%)	0.4
<i>ED Dyspnea</i>	247 (87%)	50 (88%)	0.9	268 (87%)	29 (88%)	>0.9	272 (87%)	25 (86%)	0.8
<i>Systolic Blood Pressure (mmHg)</i>	153 (132, 174)	161 (130, 195)	0.13	153 (132, 175)	161 (130, 195)	0.2	153 (132, 175)	161 (130, 199)	0.2
<i>Heart Rate</i>	91 (80, 104)	98 (81, 109)	0.10	91 (80, 104)	100 (88, 108)	0.07	91 (80, 104)	100 (87, 106)	0.2
<i>Sodium, serum (mEq/L)</i>	139 (137, 141)	138 (135, 140)	0.02	139 (137, 141)	139 (137, 141)	0.9	139 (137, 141)	139 (137, 141)	0.7
<i>Blood Urea Nitrogen (mEq/L)</i>	20 (16, 29)	29 (17, 44)	<0.01	21 (16, 31)	24 (15, 40)	0.3	21 (16, 31)	24 (15, 41)	0.2
<i>History of COPD</i>	122 (43%)	24 (42%)	>0.9	136 (44%)	10 (30%)	0.13	136 (44%)	10 (34%)	0.3
<i>Get With The Guidelines HF Risk Score</i>	32 (28, 37)	34 (29, 40)	0.05	32 (28, 38)	32 (28, 39)	0.7	32 (28, 38)	33 (28, 39)	0.6
<i>ED Disposition = Discharge</i>	32 (11%)	4 (7.0%)	0.3	33 (11%)	3 (9.1%)	>0.9	34 (11%)	2 (6.9%)	0.8
<u>ECG Characteristics</u>									
<i>New T wave inversions</i>	45 (16%)	18 (32%)	0.01	50 (16%)	13 (39%)	<0.01	50 (16%)	13 (45%)	<0.01
<i>New ST depression</i>	15 (5.3%)	12 (21%)	<0.01	16 (5.2%)	11 (33%)	<0.01	17 (5.4%)	10 (34%)	<0.01

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Secondary Outcomes

<i>Characteristic</i>	<u>Composite Outcome at 30 days</u>			<u>Acute MI, PCI, and/or CABG at 30-days</u>			<u>Acute MI at index presentation</u>		
	No (n=284) <sup>1</sup>	Yes (n=57) <sup>1</sup>	p-value <sup>2</sup>	No (n=308) <sup>1</sup>	Yes (n=33) <sup>1</sup>	p-value <sup>2</sup>	No (n=312) <sup>1</sup>	Yes (n=29) <sup>1</sup>	p-value <sup>2</sup>
<i>New Pathologic Q</i>	12 (4.2%)	10 (18%)	<0.01	14 (4.5%)	8 (24%)	<0.01	16 (5.1%)	6 (21%)	<0.01
<i>OMI ECG Criteria</i>	14 (4.9%)	20 (35%)	<0.01	14 (4.5%)	20 (61%)	<0.01	16 (5.1%)	18 (62%)	<0.01
<u>Ischemic Heart Disease History at ED Presentation</u>									
<i>Known Prior Workup</i>	205 (72%)	45 (79%)	0.3	225 (73%)	25 (75%)	0.84	228 (73%)	22 (76%)	0.83
<i>Positive Ischemic History (vs. Known Non-ischemic)</i>	117 (57%)	28 (62%)	0.64	127 (56%)	18 (72%)	0.19	129 (57%)	16 (73%)	0.18
<u>Utilization of Coronary Angiography</u>									
<i>In-hospital</i>	6 (2.1%)	5 (8.8%)	0.02	6 (1.9%)	5 (15%)	<0.01	6 (1.9%)	5 (17%)	<0.01
<i>30 days</i>	14 (4.9%)	14 (25%)	<0.01	15 (4.9%)	13 (39%)	<0.01	18 (5.8%)	10 (34%)	<0.01
<i>90 days</i>	20 (7.0%)	16 (28%)	<0.01	23 (7.5%)	13 (39%)	<0.01	25 (8.0%)	11 (38%)	<0.01

<sup>1</sup>Median (IQR); n (%)

<sup>2</sup>Wilcoxon rank sum test; Pearson’s Chi-squared test; Fisher’s exact test

Composite outcome = Death/cardiopulmonary resuscitation, mechanical cardiac support, intubation, new or emergent dialysis, AMI/PCI/CABG.

AMI = Acute myocardial infarction; PCI = percutaneous coronary intervention; ED = emergency department; cTn = cardiac troponin; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; HF = Heart Failure; OMI = occlusion MI

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