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Original Article

Comparison of Troponin Elevation, Prior Myocardial Infarction, and Chest Pain in Acute Ischemic Heart Failure

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ABSTRACT

Background: Patients with heart failure (HF) with concomitant ischemic heart disease (IHD) have not been well characterized. We examined survival of patients with ischemic HF syndrome (IHFS), defined as presentation with acute HF and concomitant features suggestive of IHD.

Methods: Patients were included if they presented with acute HF to hospitals in Ontario, Canada. IHD was defined by any of the following criteria: angina/chest pain, prior myocardial infarction (MI), or troponin elevation that was above the upper limit of normal (mild) or suggestive of cardiac injury. Deaths were determined after hospital presentation.

Results: Of 5353 patients presenting with acute HF, 4088 (76.4%) exhibited features of IHFS. Patients with IHFS demonstrated a higher

RÉSUMÉ

Contexte : Les patients présentant une insuffisance cardiaque et une cardiopathie ischémique (CI) concomitante ne sont pas bien caractérisés. Nous avons examiné les données sur la survie de patients atteints d'un syndrome d'insuffisance cardiaque ischémique (SICI), caractérisé par la présence d'une insuffisance cardiaque aiguë et de manifestations concomitantes évoquant une CI.

Méthodologie : Les données examinées concernaient des patients atteints d'insuffisance cardiaque aiguë reçus en consultation dans des hôpitaux de l'Ontario, au Canada. Un patient était réputé atteint de CI s'il répondait à l'un des critères suivants : angine/douleur thoracique, antécédents d'infarctus du myocarde (IM) ou élévation de la concentration de troponine se situant au-delà de la limite supérieure de la

Heart failure (HF) is a major public health issue with a current prevalence of more than 26 million people affected worldwide, a 20% lifetime risk of developing HF, and increasing numbers of people living with the disease.[1-3] Mortality is also high, with up to 50% of those diagnosed with HF dying within 5 years.[4] HF is also responsible for substantial healthcare costs, and a major contributor to the costs and morbidity of HF is acute HF decompensation, which often leads to hospital admission. Further, each decompensation leading to HF hospitalization is associated with an incremental risk of subsequent death.[5]

Prior studies have highlighted that patients with HF with concomitant ischemic heart disease (IHD) are at heightened risk for adverse events.[6] However, outcomes in this heterogeneous group of patients have not been fully characterized in the acute setting. Generally, the importance of IHD in patients with HF is assessed by comparing outcomes in those with an ischemic etiology or history of myocardial infarction

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Ethics Statement: This research adheres to ethical guidelines and was approved by research ethics boards at all study hospitals.

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rate of 30-day (hazard ratio [HR], 1.89; 95% confidence interval [CI], 1.33-2.68) and 1-year death (HR, 1.16, 95% CI, 1.00-1.35) compared with those with nonischemic HF. Troponin elevation demonstrated the strongest association with mortality. Mildly elevated troponin was associated with increased hazard over 30-day (HR, 1.77; 95% CI, 1.12-2.81) and 1-year (HR, 1.63; 95% CI, 1.38-1.93) mortality. Troponins indicative of cardiac injury were associated with increased hazard of death over 30 days (HR, 2.33; 95% CI, 1.63-3.33) and 1 year (HR, 1.40; 95% CI, 1.21-1.61). The association between elevated troponin and higher mortality at 30 days was similar in left ventricular ejection fraction subcategories of HF with reduced ejection fraction, HF with mildly reduced ejection fraction, or HF with preserved ejection fraction (P interaction = 0.588). After multivariable adjustment, prior MI and angina were not associated with higher mortality risk.

Conclusions: In acute HF, elevated troponin, but not prior MI or angina, was associated with a higher risk of 30-day and 1-year mortality irrespective of left ventricular ejection fraction.

Résultats : Parmi 5 353 patients atteints d'insuffisance cardiaque aiguë reçus en consultation, 4 088 (76,4 %) présentaient des caractéristiques de SICI. Chez les patients atteints d'un SICI, un taux plus élevé de mortalité à 30 jours (rapport des risques instantanés [RRI] : 1,89, intervalle de confiance [IC] à 95 % : 1,33-2,68) et à 1 an (RRI : 1,16, IC à 95 % : 1,00-1,35) a été noté comparativement aux patients atteints d'insuffisance cardiaque non ischémique. L'élévation de la concentration de troponine présentait la plus forte association avec la mortalité. Une légère élévation de la concentration de troponine se trouvait associée à un risque accru de mortalité à 30 jours (RRI : 1,77, IC à 95 % : 1,12-2,81) et à 1 an (RRI : 1,63, IC à 95 % : 1,38-1,93). Les concentrations de troponine témoignant de lésions cardiaques étaient associées à une augmentation du risque de mortalité à 30 jours (RRI : 2,33, IC à 95 % : 1,63-3,33) et à 1 an (RRI : 1,40, IC à 95 % : 1,21-1,61). L'association entre une concentration élevée de troponine et une augmentation du taux de mortalité à 30 jours était semblable dans les sous-catégories d'insuffisance cardiaque avec fraction d'éjection ventriculaire gauche réduite, légèrement réduite ou préservée (p = 0,588 pour l'interaction). Après correction multivariée, les antécédents d'IM et d'angine n'étaient pas associés à un risque accru de mortalité.

Conclusions : Dans un contexte d'insuffisance cardiaque aiguë, l'élévation de la concentration de troponine était associée à un risque plus élevé de mortalité à 30 jours et à 1 an indépendamment de la fraction d'éjection ventriculaire gauche; les antécédents d'IM ou d'angine ne l'étaient toutefois pas.

(MI). However, some patients may present with symptomatic myocardial ischemia, troponin elevation, or both, and outcomes in these subsets of patients are less well characterised, especially when they decompensate.

Although angina in patients with HF studied in an ambulatory clinical trial setting was associated with increased risk of cardiovascular events, the frequency and impact of angina in patients presenting with acute HF are unknown.[7] In addition, there are conflicting reports about the relationship between troponin, a biomarker of myocardial injury, and outcomes in acute HF. Higher troponin was associated with higher risk in the Serelaxin, Recombinant Human **Relax**in, for Treatment of **A**cute **H**eart **F**ailure (RELAX-AHF) trial, whereas no such relationship was observed in **A**cute **S**tudy of **C**linical **E**ffectiveness of **N**esiritide in **D**ecompensated **H**eart **F**ailure (ASCEND-HF).[8,9]

The relationship between IHD and outcomes may be modified by left ventricular ejection fraction (LVEF).[10] In the Framingham Heart Study, coronary heart disease was a more common cause of death in those with HF with reduced ejection fraction (HFrEF), compared with those with HF with preserved ejection fraction (HFpEF).[10] In the present study, we examined mortality and processes of care in patients with ischemic HF syndrome (IHFS), defined by the presence of anginal symptoms, prior MI, or troponin elevation compared with those without ischemic heart syndrome. We further examined these associations according to LVEF category: HFrEF, HF with mildly reduced ejection fraction (HFmrEF), and HFpEF.

Methods

Patient cohort

To select cases for detailed chart abstraction, we identified patients who (1) were aged $\geq$ 18 years; (2) presented to the emergency department (ED) with a primary diagnosis of HF as encoded in the National Ambulatory Care Reporting System; and (3) met the clinical Framingham criteria for HF.[11] Patients were excluded if brain natriuretic peptide or NT-pro brain natriuretic peptide levels were not indicative of HF as published in the guidelines of the Canadian Cardiovascular Society (ie, $<$ 100 pg/mL and $<$ 300 pg/mL, respectively).[12] We also excluded patients who (1) had HF as a secondary diagnosis developing after admission, (2) had an acute MI hospitalization within 14 days before presentation, (3) were considered for palliative treatment only or deemed "do not resuscitate" before ED arrival, or (4) visited for a nonacute condition that could have been managed in ambulatory care, as determined by a Canadian Triage Acuity Score of 5.[13,14]

Data sources

We identified eligible patients who presented to the ED using National Ambulatory Care Reporting System and those subsequently hospitalized with a primary diagnosis of HF using the Canadian Institute for Health Information Discharge Abstract Database and the International Classification of Diseases and Related Health Problems 10th Revision Canada (ICD-10-CA) code I50. The Canadian Institute for

Health Information Discharge Abstract Database and Same-Day Surgery Databases were used to identify cardiac procedures performed in hospital. The Registered Persons Database was used to identify deaths and the Ontario Registrar General Database provided information on cardiovascular vs non-cardiovascular causes of death.

Sampling and data abstraction

We used stratified cluster sampling of patients admitted to hospitals in Ontario that had an ED on-site and a yearly volume of greater than 50 patients with acute HF per year. Patients who presented to teaching, medium-sized (51-150 annual HF ED visits), and large (>150 annual HF ED visits) community hospitals, from April 1, 2010, to March 31, 2013, were eligible. If a patient had multiple visits during in this period, only the first visit was included. Highly trained, specialized nurse or physician abstractors collected data on approximately 140 patients from each of 13 teaching and 30 large hospitals and approximately 50 patients from each of 27 medium-sized hospitals. Data were collected from hospital medical records using electronic case report forms with automated range checks, double-data entry for key variables, and preloaded medical record numbers to minimize errors in administrative database linkage. To ensure greater representation of patients with IHFS, we oversampled patients who underwent cardiac catheterization (approximately one-third of our total cohort) within 14 days of hospital admission. Research ethics board approval was obtained from all hospitals before data abstraction. Information was retrieved on demographics, clinical characteristics (including cardiac and noncardiac conditions), medications, and laboratory tests, including biomarkers (eg, troponin, brain natriuretic peptide), electrocardiogram, evaluations of left ventricle function, and findings on invasive and noninvasive diagnostic tests. Information on revascularization procedures was also collected.

IHD subgroups

A patient with a primary admission diagnosis of HF was deemed, broadly, to have concomitant IHD syndrome if he/she fulfilled any of the following criteria before index ED presentation: (1) concurrent or prior diagnosis of MI based on the presence of ICD-10 codes I21-I23 or atherosclerotic/IHD (ICD-10 codes I20, I24-25) in any of the primary or secondary diagnosis codes in the previous 5 years; (2) troponin elevation (troponin I, T, or high-sensitivity) above the upper limit of normal (ULN) (including grey zone values of conventional troponin) or exceeding the ULN on peak sample drawn within the first 24 hours; or (3) angina within 48 hours before admission. All other patients were classified as having non-IHFS.

We further stratified troponin elevations as mildly elevated or cardiac injury based on the reference ranges provided by the clinical biochemistry laboratory at participating hospitals. The cardiac injury threshold was defined as the troponin value corresponding to an older definition of MI using creatine kinase-MB and was ascertained for each participating hospital.[15] Mildly elevated troponin was deemed to be present if troponin was higher than the ULN but did not exceed the cardiac injury threshold.[15] Both mildly elevated troponin and cardiac injury were included because prior prognostic studies included both together, and a clear threshold for defining ischemic from nonischemic etiologies has yet to be determined.[16,17] To characterize the mildly elevated and cardiac injury groups, we examined the median ratios of peak troponin to the ULN within the initial 24 hours after emergency presentation. We also stratified our analysis by LVEF groupings where HFpEF was defined as LVEF $\geq$ 50%, HFmrEF was defined as LVEF 40% to 49%, and HFrEF was defined as LVEF $<$ 40%.

Statistical analyses

We compared baseline characteristics between the overall ischemic and nonischemic groups using the Kruskal–Wallis test for continuous variables and chi-square test for categorical variables. Multivariable Cox proportional hazards regression models were used to compare the hazard of death between those with ischemic HF and the subcomponent groups of the IHFS (ie, prior MI, angina, troponin elevation) for outcomes over 30 days and 1 year. The multivariable models were adjusted for age, sex, and type of HF (classified as HFpEF, HFmrEF, HFrEF, or unknown ejection fraction if left ventricular function was not measured during the index admission or in the prior 6 months). Multivariable models were also adjusted for components of the Emergency Heart Failure Mortality Risk Grade[18] and other prognostic factors, including diabetes, hypertension, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, prior percutaneous coronary intervention or coronary artery bypass graft surgery, respiratory rate, haemoglobin levels, sodium concentration, left bundle branch block or paced rhythm on 12-lead electrocardiogram, atrial fibrillation/flutter, and QRS duration. To account for clustering of patients within hospitals, robust standard errors were obtained when using the Cox model. Cumulative incidence curves for mortality were compared using Gray's test. Statistical significance was determined as a 2-tailed P value < 0.05. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Patient characteristics

Initially, 6846 patients were evaluated (flow diagram in Fig. 1). After exclusions, there were 4088 patients with IHFS, of whom 65.8% had troponin above the ULN (troponin positive), 45.0% had angina, and 52.7% had a prior MI (Fig. 2). Baseline characteristics are shown in Table 1. Patients with HF with IHFS were more likely to be male, were more often transported via emergency medical services, and had more comorbid diabetes, hypertension, cerebrovascular disease, and peripheral artery disease. Nonischemic patients more often had atrial fibrillation or flutter. Echocardiographic findings demonstrated that patients in the ischemic group more often had a lower LVEF (ie, had HFrEF or HFmrEF) compared with the nonischemic group. Cohort characteristics stratified by angina, prior MI, and troponin elevation are shown in Supplemental Tables S1-S3. The ratios of peak troponin to ULN are shown for troponin I, high-sensitivity troponin I, troponin T, and high-sensitivity troponin T in

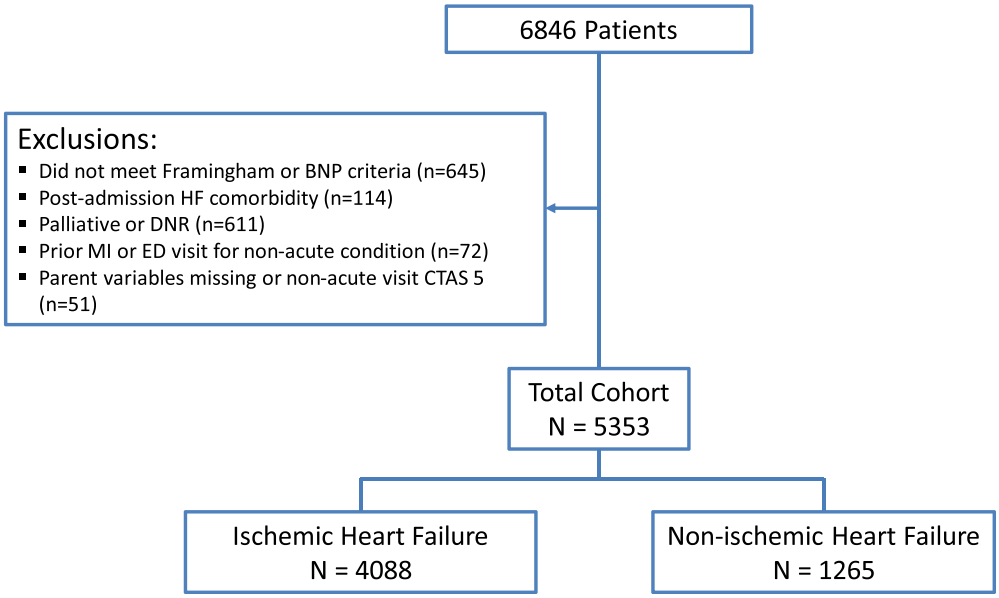

Figure 1. Patient flow diagram. BNP, B-type natriuretic peptide; CTAS, Canadian Triage Acuity Score; DNR, do not resuscitate; ED, emergency department; HF, heart failure; MI, myocardial infarction.

Figure 3. These ratios were further stratified into 3 levels: normal, mildly elevated, and cardiac injury. Interquartile ranges of these ratios are shown in Supplemental Table S4. Those with mildly elevated troponin had values that were approximately 2-fold higher, whereas cardiac injury was 3 to 4 times higher than the ULN independent of the type of troponin test used.

Thirty-day mortality

The 30-day mortality was 6.9% in patients with ischemic HF and 3.9% in patients with nonischemic HF. After adjusting for age and sex, the hazard ratio (HR) for death over 30 days in ischemic HF was 1.92 (95% confidence interval [CI], 1.46-2.55) compared with nonischemic HF ($P < 0.001$). The HR was similar after multivariable adjustment: 1.89 (95% CI, 1.33-2.68; $P < 0.001$). When troponin elevation, angina, and prior MI were entered into the multivariable model in place of any ischemia, only troponin was independently associated with a higher rate of mortality over 30 days. The adjusted HR was 2.19 (95% CI, 1.55-3.10; $P < 0.001$) for elevated vs normal troponin and 0.87 (95% CI, 0.67-1.12; $P = 0.269$) for angina, and the HR was 0.92 (95% CI, 0.74-1.14; $P = 0.433$) for prior MI vs no prior MI.

There was no significant interaction for 30-day mortality between LVEF categories (ie, HFrEF, HFmrEF, or HFpEF) and troponin elevation considered as a binary variable (interaction P value = 0.588). There was also no significant interaction between LVEF category and chest pain (interaction P value = 0.400) or prior MI (interaction P value = 0.612) for the outcome of 30-day mortality.

One-year mortality

One-year mortality was 25.2% in patients with IHFS and 23.6% in patients with nonischemic HF. After adjusting for age and sex, the HR for death over 1 year in ischemic HF vs nonischemic patients was 1.14 (95% CI, 0.99-1.32; $P = 0.064$). The multivariable-adjusted HR was 1.16 (95% CI, 1.00-1.35; $P = 0.046$). In the multivariable model, including troponin, angina, and prior MI in the model, the HR for 1-year mortality was 1.45 (95% CI, 1.27-1.65; $P < 0.001$) for troponin elevation, 0.77 (95% CI, 0.68-0.87; $P < 0.001$) for angina, and 1.13 (95% CI, 1.01-1.28; $P = 0.039$) for prior MI.

There was a significant interaction between LVEF category (ie, HFrEF, HFmrEF, and HFpEF) and troponin elevation at 1-year follow-up ($P = 0.037$). The HR for elevated troponin (vs not elevated) was 1.50 (95% CI, 1.20-1.86; $P < 0.001$) for HFrEF, 1.22 (95% CI, 0.89-1.68; $P = 0.225$) for HFmrEF, and 1.31 (95% CI, 1.03-1.67; $P = 0.028$) for HFpEF. Figure 4A-C illustrates the adjusted cumulative incidence curves for the HFrEF, HFmrEF, and HFpEF

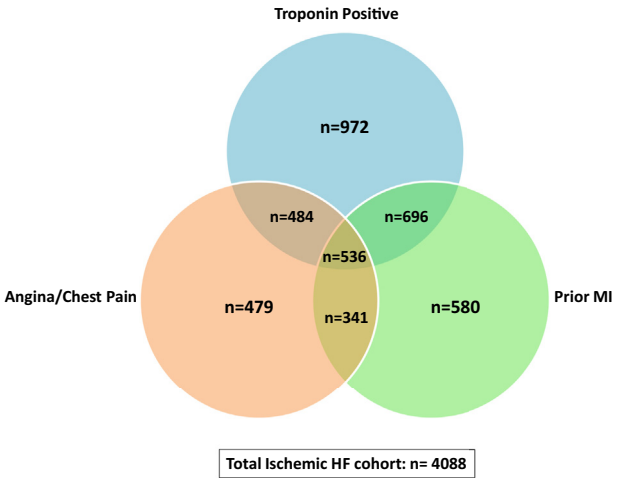

Figure 2. Venn diagram of ischemic HF cohort defining characteristics: prior MI, angina/chest pain, and troponin positivity. HF, heart failure; MI, myocardial infarction.

Table 1. Cohort characteristics

Variable, median (IQR) or n (%)	IHFS (N = 4088)	Nonischemic (N = 1265)	*P* value
Demographic			
Age, y	76 (66-83)	77 (67-85)	0.004
Men	2354 (57.6%)	568 (44.9%)	< 0.001
IHFS features			
Troponin positive	2688 (65.8%)	0 (0%)	< 0.001
Acute angina/chest pain	1840 (45.0%)	0 (0%)	< 0.001
Prior MI	2153 (52.7%)	0 (0%)	< 0.001
Presenting features			
Transport by EMS	1999 (48.9%)	522 (41.3%)	< 0.001
Systolic BP, mm Hg	141 (122-161)	140 (123-158)	0.189
Heart rate, beats/min	90 (74-110)	90 (74-109)	0.523
Oxygen saturation, %	0.96 (0.92-0.98)	0.95 (0.92-0.98)	0.096
Comorbid conditions			
Diabetes	1799 (44.0%)	493 (39.0%)	0.002
Hypertension	3166 (77.4%)	928 (73.4%)	0.003
Cerebrovascular disease	658 (16.1%)	167 (13.2%)	0.013
Peripheral artery disease	478 (11.7%)	86 (6.8%)	< 0.001
Chronic pulmonary disease	875 (21.4%)	304 (24.0%)	0.049
Dementia	210 (5.1%)	94 (7.4%)	0.002
Active cancer	604 (14.8%)	204 (16.1%)	0.241
Laboratory features			
Hemoglobin concentration, g/L	123 (108-139)	120 (106-135)	< 0.001
White blood count, $\times 10^9$ cells/L	9.0 (7.1-11.6)	8.4 (6.6-10.7)	< 0.001
Sodium concentration, mmol/L	138 (135-141)	138 (135-141)	0.231
Potassium concentration, mmol/L	4.2 (3.9-4.6)	4.2 (3.9-4.6)	0.914
Creatinine concentration, µmol/L	106 (82-140)	94 (74-129)	< 0.001
BNP, pg/mL	466 (231-714)	432 (247-612)	0.743
ECG features			
Atrial fibrillation or flutter	1093 (26.7%)	517 (40.9%)	< 0.001
QRS duration, ms	104 (90-136)	96 (84-122)	< 0.001
Echocardiogram, n (%)			
HFrEF	1605 (39.3%)	259 (20.5%)	< 0.001
HFmrEF	634 (15.5%)	121 (9.6%)	
HFpEF	1132 (27.7%)	548 (43.3%)	
LVEF unknown	717 (17.5%)	337 (26.6%)	

BNP, brain natriuretic peptide; BP, blood pressure; EMS, emergency medical services; HF, heart failure; IQR, interquartile range; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHFS, ischemic HF syndrome; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

groups, respectively, stratified by troponin positivity. The incidence of death was higher in those with troponin elevation (troponin positive) compared with those with normal troponin levels (troponin negative). Differences in mortality rates over 1 year were significant in the HFrEF ($P < 0.001$) and HFpEF ($P = 0.034$) groups. However, there was no significant interaction between LVEF category and chest pain (interaction P value = 0.849) or prior MI (interaction P value = 0.090).

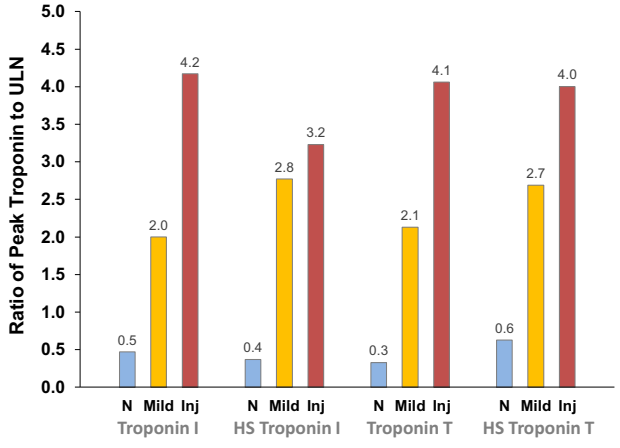

Figure 3. Median ratios of peak troponin to upper limit of normal (ULN) according to classification as normal, mildly elevated, or cardiac injury, stratified by type of troponin test. Inj, cardiac injury; mild, mildly elevated; N, normal.

Effect of the degree of troponin elevation as a multilevel variable

In those with IHFS, we found that crude 30-day mortality increased as troponin levels increased from mildly elevated to values indicative of cardiac injury (Table 2, P trend < 0.001). Mortality rates were significantly higher among patients with troponins that were mildly elevated or indicative of cardiac injury compared with normal levels, even after multivariable adjustment (Table 2). At 30 days, the multivariable-adjusted HR for mildly elevated troponin was 1.77 (95% CI, 1.12-2.81) and for cardiac injury range was 2.33 (95% CI, 1.63-3.33) compared with those with normal levels (Table 2). At 1 year, the multivariable-adjusted HR, for mildly elevated troponin was 1.63 (95% CI, 1.38-1.93) and 1.40 (95% CI, 1.21-1.61) when troponins were indicative of cardiac injury.

When troponin was evaluated as a 3-level variable (normal, mildly elevated, and cardiac injury), there was a significant

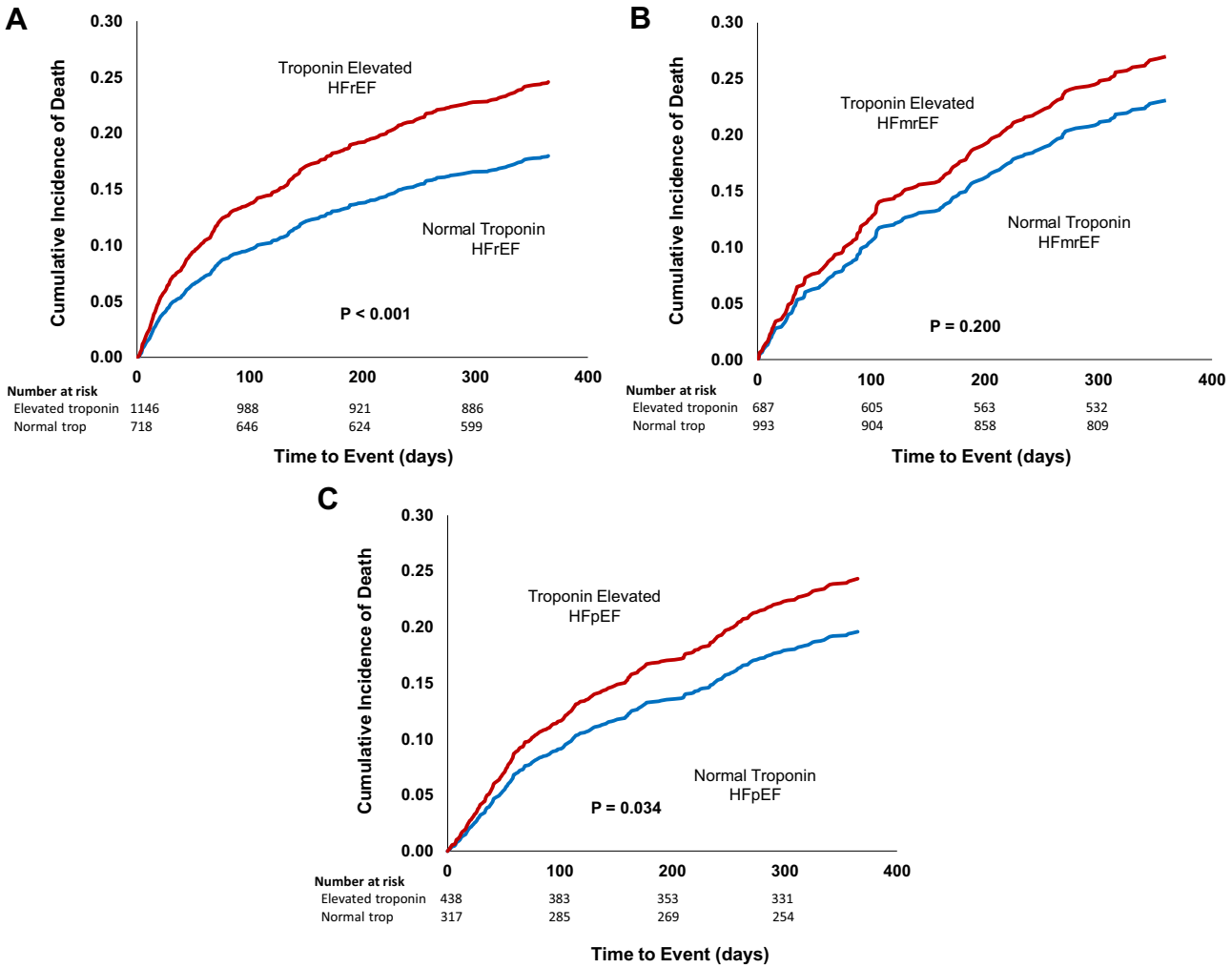

Figure 4. Adjusted cumulative incidence of mortality curves for HFrEF (**A**), HFmrEF (**B**), and HFpEF (**C**) stratified by troponin positivity. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

interaction with LVEF category (HFrEF, HFmrEF, and HFpEF) for the outcome of 30-day mortality (P interaction = 0.036). There was also a significant interaction between LVEF category and 3-level troponin for 1-year mortality (P interaction = 0.028). Multivariable-adjusted HRs stratified by HFrEF, HFmrEF, or HFpEF status are shown in Table 3 for those with troponins that were mildly elevated or indicative of cardiac injury. There was a significantly higher risk of 30-day mortality in those with mildly elevated troponin with HFpEF (HR, 3.25; 95% CI, 1.59-6.67; $P = 0.001$) and higher 1-year mortality in those with HFmrEF (HR, 1.80; 95% CI, 1.19-2.73; $P = 0.006$). Troponins that were mildly elevated or indicative of cardiac injury were associated with higher risks of death at both 30-day and 1-year time points in those with HFrEF (Table 3).

Discussion

The objective of our study was to evaluate prognosis in acutely decompensated patients with IHFS. As a working definition, IHFS was characterized inclusively as the presence of anginal symptoms, history of MI, and biomarkers. We found that those with IHFS had higher short-term and 1-year mortality, and this risk persisted after adjustment for other important predictors of outcome in a multivariable model. However, the excess risk among those with ischemia was confined to the subset of individuals with at least mildly elevated troponin. Troponin was predictive of mortality, irrespective of LVEF category. Angina and prior MI were not associated with increased risk of mortality in the setting of acute HF when entered into a multivariable model including troponin.

There is currently no prognosis-based definition of what constitutes ischemic etiology in HF, although patients with a history of MI or significant coronary stenoses are typically assigned this etiology.[19,20] Several previous studies have examined the prognostic value of chest pain and history of coronary artery disease in stable HF, but have not studied those presenting with an acute hospitalization. In the **Co**ntrolled **Ro**suvastatin Multi**na**tional Trial in Heart Failure (CORONA) study, Badar et al.[7] examined patients with HFrEF randomized to rosuvastatin or placebo. A current or

Table 2. Associations between troponins that were mildly elevated or indicative of cardiac injury with 30-day and 1-year mortality

Outcome		No troponin elevation (N = 2665)	Mildly elevated (N = 618)	Cardiac injury (N = 2070)	*P* value
Death		n (%)	n (%)	n (%)	
No. of 30-d deaths		113 (4.2%)	43 (7.0%)	175 (8.5%)	< 0.001
No. of 1-y deaths		588 (22.1%)	185 (29.9%)	558 (27.0%)	< 0.001
Death 30 d		Adjusted HR (95% CI)	*P* value vs No troponin elevation	Adjusted HR (95% CI)	*P* value vs No troponin elevation
Age, sex*	Reference	1.65 (1.13-2.42)	0.010	2.11 (1.54-2.89)	< 0.001
Age, sex, LVEF†	Reference	1.69 (1.15-2.49)	0.008	2.21 (1.62-3.02)	< 0.001
Multivariable‡	Reference	1.77 (1.12-2.81)	0.015	2.33 (1.63-3.33)	< 0.001
Death 1 y		Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age, sex*	Reference	1.44 (1.21-1.70)	< 0.001	1.31 (1.14-1.51)	< 0.001
Age, sex, LVEF†	Reference	1.45 (1.22-1.72)	< 0.001	1.34 (1.17-1.54)	< 0.001
Multivariable‡	Reference	1.63 (1.38-1.93)	< 0.001	1.40 (1.21-1.61)	< 0.001

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

*Age, sex: adjusted for age and sex.

†Age, sex, LVEF: adjusted for age, sex, HFpEF, HFmrEF, HFrEF, or LVEF unknown (LVEF within past 6 months).

‡Multivariable adjusted: adjusted for age, sex, HFpEF, HFmrEF, HFrEF, or LVEF unknown (LVEF within past 6 months), arrival by emergency medical services, triage systolic blood pressure, triage heart rate, respiratory rate, triage oxygen saturation, diabetes, hypertension, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, prior percutaneous coronary intervention or coronary artery bypass graft, haemoglobin, sodium concentration, potassium concentration, creatinine concentration, active cancer, metolazone, left bundle branch block or paced rhythm on 12-lead electrocardiogram, atrial fibrillation/flutter, and QRS duration.

previous history of chest pain was associated with higher rates of HF hospitalization and a composite ischemic outcome, but not mortality. In a sub-study of **C**andesartan in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity (CHARM), Badar et al.[21] examined patients with both HFrEF and HFpEF randomized to candesartan or placebo. A current or previous history of chest pain was associated with a higher risk of ischemic outcomes, but not HF hospitalization or death. Finally, in the **I**rbesartan in Patients With Heart Failure and **Preserve**d Ejection fraction (I-PRESERVE) trial of patients with HFpEF randomized to irbesartan or placebo, a history of coronary disease was more strongly associated with cardiovascular and all-cause death than angina. The presence of angina alone without coronary disease history was associated with a higher likelihood of MI or unstable angina, but not HF hospitalization and cardiovascular or all-cause death.[22]

There are conflicting data on the prognostic ability of troponin in the setting of acute HF. In the ASCEND-HF study, troponin was not a predictor of in-hospital events requiring treatment in a coronary intensive care unit.[23] The **V**alue of **E**ndothelin **R**eceptor **I**nhibition With **T**ezosentan in **A**cute Heart Failure **S**tudies (VERITAS) trial found that

Table 3. Multivariable-adjusted HRs in those with troponins that were mildly elevated or indicative of cardiac injury by LVEF category: HFrEF, HFmrEF, and HFpEF

Outcome/LVEF category		No troponin elevation	Mildly elevated	Cardiac injury	*P* value
No. of 30-d deaths		n (%)	n (%)	n (%)	
HFrEF		29 (4.0%)	10 (4.3%)	77 (8.4%)	< 0.001
HFmrEF		11 (3.5%)	SC	20 (5.9%)	0.159
HFpEF		28 (2.8%)	17 (9.8%)	22 (4.3%)	< 0.001
No. of 1-y deaths		n (%)	n (%)	n (%)	
HFrEF		133 (18.5%)	60 (25.8%)	221 (24.2%)	0.009
HFmrEF		74 (23.3%)	33 (34.0%)	84 (24.6%)	0.099
HFpEF		205 (20.6%)	45 (26.0%)	126 (24.5%)	0.112
Death 30-d		Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
HFrEF	Reference	1.32 (0.75-2.33)	0.336	2.28 (1.42-3.67)	< 0.001
HFmrEF	Reference	0.96 (0.11-8.48)	0.970	1.72 (0.67-4.43)	0.257
HFpEF	Reference	3.25 (1.59-6.67)	0.001	1.69 (0.78-3.70)	0.186
Death 1 y		Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
HFrEF	Reference	1.73 (1.23-2.44)	0.002	1.44 (1.16-1.79)	0.001
HFmrEF	Reference	1.80 (1.19-2.73)	0.006	1.07 (0.77-1.50)	0.677
HFpEF	Reference	1.32 (0.91-1.92)	0.149	1.31 (0.99-1.72)	0.055

Multivariable adjusted: adjusted for age, sex, arrival by emergency medical services, triage systolic blood pressure, triage heart rate, respiratory rate, triage oxygen saturation, diabetes, hypertension, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, prior percutaneous coronary intervention or coronary artery bypass graft, haemoglobin, sodium concentration, potassium concentration, creatinine concentration, active cancer, metolazone, left bundle branch block or paced rhythm on 12-lead electrocardiogram, atrial fibrillation/flutter, and QRS duration.

CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; SC, small cells (cannot be reported because of privacy regulations).

troponin only marginally improved model discrimination for 90-day mortality.[24] Our study was novel because, unlike in other studies, we demonstrated that the prognostic value of troponin elevation was maintained across the range of LVEF categories.[16,25] An earlier study did report an association between peak troponin in hospital and prognosis, but unlike in our study in which troponins were only captured at initial emergency presentation, elevation of this biomarker could have occurred at any time during the hospital stay.[26] Thus, troponin elevation in this prior study could have occurred after initial presentation and could have been a consequence of acute hemodynamic stress.[26] The prevalence of IHFS was higher in our study than in some population-based studies,[27,28] but was consistent with another prior study.[29] This may have resulted from our intentionally broad inclusion of mildly elevated troponin as part of an IHFS.

The mechanisms by which troponin elevation could confer worsened prognosis include myocyte ischemia or injury, defect in cell membrane integrity, inflammation, and apoptosis.[30] These could be exacerbated by activation of the renin-angiotensin-aldosterone system, adrenergic activity, inflammatory cytokines, and mechanical or oxidative stress.[30] It is still not defined to what extent demand−supply mismatch related to volume overload and decompensated HF or nonischemic mechanisms may contribute to the worsened prognosis of troponin elevation.[26] In our study, angina was associated with lower risk of death at 1 year, and this could have resulted because those with IHFS who have manifest symptoms may enable the detection of ischemia. This hypothesis is supported by the CORONA, CHARM, and I-PRESERVE trials mentioned previously because angina was associated with increased risk of ischemic events, but not mortality. Alternatively, the beneficial effects of anginal symptoms may be mediated by ischemic preconditioning, including via protein kinase C signaling pathways and downstream effects on Akt, PI3 kinase, and ERK.[31] Even brief episodes of angina can promote ischemic preconditioning[32] and could have been responsible for the effects we observed. It should also be noted that although a significant impact of troponin elevation was not observed in those with elevated troponin and HFmrEF, this was the smallest LVEF subgroup with only 35% power to detect a multivariable HR of 1.72.[33,34] In contrast, there was 99% power to detect this effect size in the overall HF cohort of 5353 patients. We would anticipate that a larger number of patients with HFmrEF would have led to a significant association of troponin elevation with mortality.

Our findings highlight the value of troponin as an important predictor of mortality in acute HF, with the risk of death beginning to increase with mildly elevated troponin. Although mortality risk was slightly higher at 30 days in those with MI-range troponin, the risks were comparable to mildly elevated troponin at 1 year, suggesting the possibility that higher intensity of acute medical care in the former group could have attenuated outcome differences. The heightened risk observed irrespective of LVEF advocates for troponin testing upon presentation to the ED.[18] Ischemia testing could be considered even among those with mildly elevated troponin, but before doing so, further research is warranted to elucidate the mechanisms for troponin's role in IHFS.

Study strengths and limitations

This study has several strengths, including a large sample of "real-world" patients with acute HF, characterised in detail and linked to multiple administrative databases. Our study was limited by the absence of a standard definition of IHFS. Thus, our study was designed with a pragmatic definition of IHFS broadly defined by the trio of troponin elevation, anginal symptoms, and prior MI. Additionally, it is conceivable that there is overlap between those with HF and an associated increase in troponin vs those with acute MI with complicating HF. Although similar clinically, there may be pathophysiologic differences between these 2 conditions. Although it has been debated whether HFmrEF is a separate entity,[35] practice guidelines differentiate it separately from HFpEF or HFrEF,[36] and prior work has shown that a 10% decrement in LVEF is associated with significantly increased risk of HF hospitalization, cardiovascular hospitalization, and mortality.[37]

Conclusions

Our study demonstrated the importance of IHFS in acute decompensated HF irrespective of underlying HFrEF, HFmrEF, or HFpEF status. Even a mildly elevated troponin was associated with 30-day and 1-year mortality. Troponin testing may serve as a useful tool to guide medical decision-making in acute HF care.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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