Cardiac troponin and outcome in decompensated heart failure with preserved ejection fraction

Mohammad Thawabi[1], Amer Hawatmeh[1], Sarah Studyvin[1], Habib Habib[2], Fayez Shamoon[2], Marc Cohen[1]

[1]Department of cardiology, Newark Beth Israel Medical Center, Newark, New Jersey, USA; [2]Department of cardiology, St. Joseph's Regional Medical Center, Paterson, New Jersey, USA

Contributions: (I) Concept and design: M Thawabi, A Hawatmeh, F Shamoon, M Cohen; (II) Administrative support: F Shamoon, M Cohen; (III) Provision of study materials or patients: M Thawabi, A Hawatmeh; (IV) Collection and assembly of data: M Thawabi, A Hawatmeh, S Studyvin, H Habib; (V) Data analysis and interpretation: M Thawabi, A Hawatmeh; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mohammad Thawabi, MD. Newark Beth Israel Medical Center, 201 Lyons avenue, Newark, NJ 07112, USA. Email: thawabi@live.com.

Background: Cardiac troponin (cTn) has been established as an effective prognostic marker in acute heart failure (HF) with predominantly reduced ejection fraction. However, its prognostic value in heart failure with preserved ejection fraction (HFpEF) is unclear. The aim of this study is to describe the prognostic role of troponin I in patients hospitalized for HFpEF decompensation.

Methods: We included 363 consecutive patients admitted for HFpEF decompensation that was not associated with acute coronary syndrome (ACS). Patients with troponin level elevation (troponin I level ≥0.04 ng/mL) were compared to patients with normal troponin level. The primary outcome was short-, intermediate-, and long-term all-cause mortality. The secondary outcomes were differences in B-type natriuretic peptide level (BNP), length of stay, and readmission rates between the two groups.

Results: Nearly half of the patients in the Cohort had troponin level elevation. Troponin level elevation was significantly associated with higher 30-day (4.8% *vs.* 0.6%, P=0.014), 1-year (12.2% *vs.* 4.6%, P=0.009), and 2-year mortality (13.8% *vs.* 5.1%, P=0.005) when compared to a normal troponin level. Troponin level elevation was an independent predictor of mortality after adjusting for clinical and laboratory risk factors seen in HFpEF decompensation. Additionally, BNP level >287 pg/mL, age, and history of atrial fibrillation were identified as statistically significant predictors of mortality.

Conclusions: Troponin level elevation, in hospitalized patients with HFpEF decompensation, was associated with higher short-, intermediate-, and long-term mortality.

Keywords: Troponin; heart failure with preserved ejection fraction (HFpEF); diastolic heart failure (HF)

Introduction

Heart failure (HF) is a growing healthcare issue in developed countries due to its high prevalence, mortality, morbidity, and cost of care. In the United States, the population prevalence of HF was 2.42% in 2012 and is projected to increase by 23% in 2030 to 2.97% (1).

Nearly half of the patients with the clinical syndrome of HF have a normal or near-normal left ventricular ejection fraction (LVEF), referred to as heart failure with preserved ejection fraction (HFpEF) (2-6). HFpEF appears to carry a similar short- and long-term mortality to HF with reduced ejection fraction following acute HF hospitalization (3,7-9). This has prompted a search for biomarkers to help risk stratify patients, in order to guide more aggressive in-

hospital management and post-discharge follow up (10).

Cardiac troponin (cTn) has been established as an effective prognostic marker in several arenas, including acute HF exacerbation with a predominantly reduced EF (11-13). Myocardial injury and detectable cTn levels have been previously identified in patients with HFpEF (4,10,14,15). However, studies assessing the prognostic value of cTn level elevation, in hospitalized patients with HFpEF, are limited. The aim of this study is to describe the short-, intermediate-, and long-term outcomes associated with cTn level elevation in patients with acute HFpEF decompensation.

Methods

A retrospective study of consecutive patients admitted for HFpEF decompensation, not associated with acute coronary syndrome (ACS), between January 2010 and December 2013, was performed. HFpEF was diagnosed by the presence of signs and symptoms of HF, normal or near-normal LVEF (≥50%), and evidence of cardiac dysfunction by echocardiography. The diagnosis was confirmed, by an independent cardiologist, after chart review.

Patients with myocardial ischemia (i.e., tachyarrhythmias, illicit drug toxicity, severe hypertension defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg, and shock) or myocardial injury, not secondary to HF, were excluded. Patients who required initiation of, or were previously on, hemodialysis were excluded. In patients with multiple admissions for HFpEF exacerbation, the first admission was used.

Two cTnI levels, within 6 hours of presentation, were required for inclusion in order to detect the rising or falling pattern. Patients with an increase or decrease of more than 20% in cTnI levels were excluded. The peak cTnI level was used. Other lab tests were measured on initial presentation. cTnI level was measured using ADVIA Centaur cTnI assay (Siemens Healthcare Diagnostics, NY). The assay has an analytical measuring range of 0.008 ng/mL to 50 ng/mL, a 99th percentile of 0.04 ng/mL, and a coefficient of variance (CV) of 10% at a level of 0.03 ng/mL.

Patients with troponin level elevation were compared to patients with normal troponin level. Troponin level elevation was defined as a cTnI level of 0.04 ng/mL or greater. Normal troponin level was defined as an undetectable cTnI level or a level <0.04 ng/mL (below the 99th percentile value of the reference population for the test). The primary outcome was short-, intermediate-, and long-term all-cause mortality. The secondary outcomes were differences in B-type natriuretic peptide level (BNP), length of stay, and readmission rates between the two groups.

Clinical and demographic data were retrospectively abstracted from medical records. LVEF was assessed by 2D echocardiography using biplane method of disks (modified Simpson's rule). Survival status was obtained from medical records and social security death index database.

Continuous variables were presented as means ± SDs or medians (interquartile Q1–Q3), depending on their distribution. Categorical variables were presented as frequencies and percentages. Continuous variables were compared using analysis of variance or Mann-Whitney U-test, depending on the distribution of the variable. Categorical variables were compared using chi-squared analysis.

Cox proportional hazard models were used to determine the predictors of the primary outcome and are expressed as hazard ratios (HR) and 95% confidence intervals (CI). Multivariate cox proportional hazard model was adjusted for age, sex, race, history of coronary artery disease, diabetes mellitus, atrial fibrillation, stroke, hypertension, anemia, smoking, creatinine level, BNP level, and statistically significant variables in the univariate models. Kaplan-Meier curves were used to illustrate the difference in survival function between the two groups. Spearman's coefficient of rank correlation (rho) was used to assess the correlation between cTnI level and BNP, length of stay, and number of readmissions.

The areas under the curve (AUC) of the receiver operating characteristics (ROC) were calculated for initial BNP and peak cTnI levels. The optimum cutoff point for BNP level, to predict 2-year mortality, was that with the maximum combined sensitivity and specificity. The statistical significance of the difference between the areas under BNP and cTnI ROC curves was compared using Hanley and McNeil method.

All probabilities were 2-sided and P values <0.05 were considered statistically significant. All data were analyzed using MedCalc version 16.8 (MedCalc Software bvba, Belgium) and SPSS 22 (IBM Corp., USA).

Results

Out of the 432 patients evaluated for study inclusion, 363 patients met the inclusion criteria. Fifty-nine patients were excluded for requiring hemodialysis, 5 for incomplete data, 2 for severe hypertension, 1 for cardiogenic shock,

1 for illicit drug use, and 1 for tachyarrhythmia. Overall, the patients were mostly elderly, female and overweight. There was a high prevalence of systemic hypertension, anemia, diabetes, and atrial fibrillation (*Table 1*). Overall, cardiac cTnI level was detected in 338 patients (93%) and ranged between 0.008–0.76 ng/mL, with a mean level of 0.077±0.11 ng/mL.

One hundred eighty-eight patients (52%) had troponin level elevation (cTnI level of 0.04 ng/mL or more), and 175 patients (48%) had normal troponin level (cTnI level <0.04 ng/mL). Characteristics of the patients, according to whether they had troponin level elevation or normal troponin level, are summarized in *Table 1*. There were small yet statistically significant differences between the two groups. Patients with troponin level elevation were more likely to be males, African Americans, and smokers, and to have higher BNP and serum creatinine levels.

Patients with troponin level elevation had a higher 30-day (4.8% *vs*. 0.6%, P=0.014), 1-year (12.2% *vs*. 4.6%, P=0.009), and 2-year mortality (13.8% *vs*. 5.1%, P=0.005) when compared to patients with normal troponin level (*Figure 1*). Two-year Kaplan-Meier survival curves demonstrate the survival difference between the two groups (*Figure 2*).

BNP levels were higher in patients with troponin level elevation when compared to patients with normal troponin level (820±950 pg/dL *vs*. 478±465 pg/dL, P<0.0001). There was a statistically significant positive correlation between cTnI level and BNP level (Spearman's rho 0.27, 95% CI: 0.17–0.37, P<0.0001,). A BNP level >287 pg/mL was found to be the optimum criterion for predicting 2-year mortality with 91.4% sensitivity and 35.1% specificity. The area under the cTnI ROC curve was higher than that of BNP (*Figure 3*). However, this difference was statistically insignificant (P=0.345).

The median length of stay was 5 days per admission, and had a weak positive correlation with cTnI level (Spearman's rho 0.11, 95% CI: 0.01–0.21, P=0.036). Longer length of stay was seen in patients with troponin level elevation; however, this difference was statistically insignificant. During the study period, more than half of the patients had at least one readmission for HFpEF decompensation. There was no significant difference in the number of readmissions between the two groups. Neither the number of readmissions nor the length of stay were independent predictors of mortality.

Univariate cox proportional-hazard regression models showed that troponin level elevation was associated with an increased risk of 30-day (HR 8.48, 95% CI: 1.07–66.93,

P=0.043), 1-year, (HR 2.82, 95% CI: 1.26–6.31, P=0.012) and 2-year mortality (HR 2.85, 95% CI: 1.33–6.07, P=0.007). It also identified BNP level >287 pg/mL, age, history of atrial fibrillation, diabetes mellitus, and number of readmissions as statistically significant predictors of mortality (*Table 2*).

Multivariate cox proportional-hazard regression model identified troponin level elevation as an independent predictor of 30-day, 1-year, and 2-year mortality. Additionally, BNP level >287 pg/mL, age, and history of atrial fibrillation were identified as independent predictors of 1-year and 2-year mortality (*Table 2*).

Discussion

In the present study, more than half of the hospitalized patients with HFpEF decompensation, not associated with ACS, had troponin level elevation. The presence of troponin level elevation was associated with an 8-fold higher short-term mortality and a 3-fold higher intermediate- and long-term mortality. This association was independent of other clinical and laboratory risk factors seen in HFpEF decompensation. These findings suggest that cTnI measurement, in hospitalized patients with HFpEF decompensation, carries an important prognostic value during patients' early evaluation and is useful for early risk assessment.

The pathophysiological mechanism of myocardial injury and cTn elevation in HFpEF is not fully understood and is probably multifactorial. Potential contributing mechanisms include subendocardial ischemia, neurohormonal activation, inflammatory cytokine release, myocardial stretching, increased wall stress, oxidative stress, and altered myocyte calcium handling. The end result of these mechanisms is myocyte necrosis, apoptosis, or troponin degradation and release from viable cells (16).

The clinical characteristics of the patients in the current study were in agreement with previous studies of patients with HFpEF (2-4,7,9). They were more likely to be elderly, female, and overweight. Also, they were more likely to have hypertension, diabetes, anemia, atrial fibrillation and elevated creatinine levels. On examining the relative prognostic impacts of comorbidities on mortality, we found that age, history of atrial fibrillation, history of stroke, and diabetes were independent predictors of mortality.

Previous studies have reported variable all-cause mortality rates in patients with HFpEF. This variability appears to be dependent on the study design and setting. In population-based observational studies, the reported 1-year

Table 1 Baseline characteristics according to troponin level elevation status

Characteristic	All (n=363)	Negative troponin level elevation (n=175)	Positive troponin level elevation (n=188)	P value
Age (years)	72.51±12.90	71.75±12.71	73.21±13.06	0.201
Male (percentage of patients, %)	135 (37.19)	54 (30.9)	81 (43.1)	0.022
BMI (kg/m^2)	31.42±8.83	32.5±9.79	30.23±7.64	0.140
Race (percentage of patients, %)				
African American	84 (23.14%)	29 (16.57%)	55 (29.26%)	0.004
White	165 (45.45%)	83 (47.43%)	82 (43.62%)	0.452
Other	114 (31.40%)	63 (36%)	51 (27.13%)	0.069
Ejection fraction (%)	57.96±6.08	58.97±5.90	57.18±5.86	0.001
Medical conditions (percentage of patients, %)				
Atrial fibrillation	110 (30.30%)	55 (31.4%)	55 (29.3%)	0.737
Stroke	51 (14.05%)	18 (10.3%)	33 (17.6%)	0.066
Coronary artery disease	126 (34.71%)	57 (32.6%)	69 (36.7%)	0.474
Prior coronary bypass	61 (16.80%)	31 (17.7%)	30 (16%)	0.759
Prior percutaneous intervention	81 (22.31%)	37 (21.1%)	44 (23.4%)	0.696
Prior myocardial infarction	62 (17.08%)	27 (15.4%)	35 (18.7%)	0.490
Systemic Hypertension	317 (87.33%)	150 (85.7%)	167 (88.8%)	0.463
Diabetes mellitus	190 (52.34%)	90 (51.4%)	100 (53.2%)	0.817
Anemia	242 (66.67%)	120 (68.6%)	122 (64.9%)	0.458
Smoker	100 (27.55%)	36 (20.6%)	64 (34%)	0.006
Laboratory test results				
Serum creatinine (mg\dL)	1.38±0.75	1.30±0.70	1.45±0.78	0.007
GFR (mL/min/1.73 m^2)	59.87±29.76	62.7±31.57	57.23±27.79	0.118
GFR < 60 mL/min/1.73 m^2	199 (54.8%)	93 (53.1%)	106 (56.4)	0.536
Blood sugar (mg/dL)	148.66±72.31	146.57±72.03	150.62±72.71	0.335
HDL (mg/dL)	40 [31.25–49]	44 [34–50]	38 [31–48]	0.058
LDL (mg/dL)	83 [64.5–110.25]	87 [60–112]	80 [68–106.75]	0.598
Hemoglobin (g/dL)	11.50±1.94	11.29±1.86	11.69±2.00	0.142
WBC (thousand cells/mcL)	8.47±3.15	8.28±3.13	8.66±3.16	0.146
Peak troponin I (ng/mL)	0.077±0.11	0.01819±0.01126	0.133±0.137	<0.0001
BNP (pg/mL)	666.13±783.60	478.65±465.07	820.33±950.23	<0.0001
Length of stay (days)	5 [3–8]	4 [3–7]	5 [3–8]	0.101
Number of readmissions	1 [0–3]	1 [0–3]	1 [0–3]	0.286
Medications on discharge				
Beta blockers	257 (70.80%)	133 (76.00%)	124 (65.96%)	0.053
ACEi or ARB	187 (51.52%)	85 (48.57%)	102 (54.26%)	0.234

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density-lipoprotein; WBC, white blood cell; BNP, B-type natriuretic peptide level; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate.
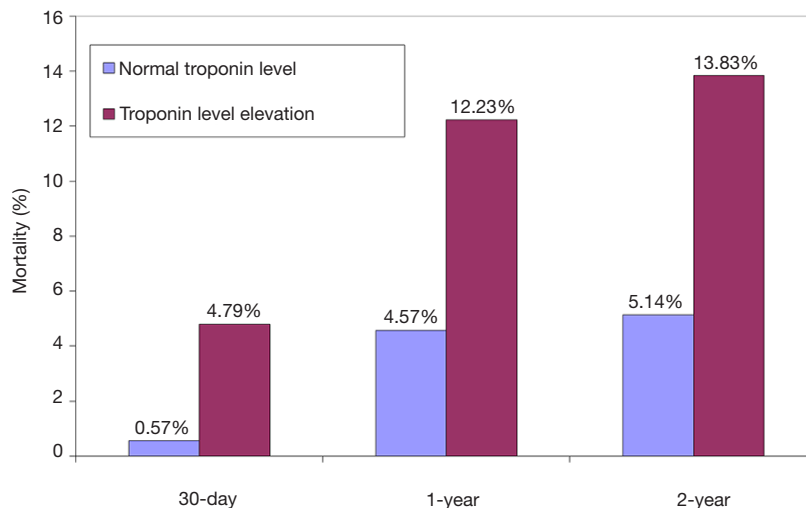
Figure 1 Mortality columns. Thirty-day, 1-year, and 2-year mortality according to troponin level elevation status.
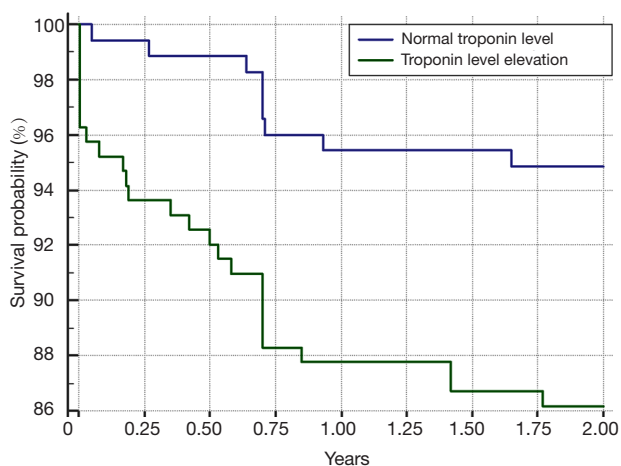

Figure 2 Survival Kaplan-Meyer curves. Kaplan-Meyer curves showing the survival difference between patients with positive and negative troponin level elevation.

Figure 3 Troponin I and BNP, ROC curves: ROC curves showing sensitivity and specificity of cardiac troponin I and BNP values for prediction of 2-year mortality. The AUC for troponin I is 0.67 (95% CI: 0.62–0.72, P=0.045) and the AUC for BNP is 0.61 (95% CI: 0.56–0.66, P=0.012). The cutoff value of 0.04 ng/mL for troponin I had a sensitivity of 74.9% and a specificity of 50.6% in predicting 2-year mortality on using ROC. BNP, B-type natriuretic peptide level; ROC, receiver operating characteristics.

mortality rate was 22–29% (3,7,17). On the other hand, more recent randomized controlled trials (RCTs) reported a 3-time lower 1-year mortality rate of less than 10% (18-24). This difference was confirmed by a meta-analysis of 31 observational studies and RCTs. The mortality rate was 146 deaths per 1,000 patient-years in the non-RCTs alone, and 101 deaths per 1,000 patient-years in the RCTs alone (25). Regardless of this difference, the mortality burden of HFpEF is significant. In the present study, after excluding certain patient subsets, the 30-day mortality
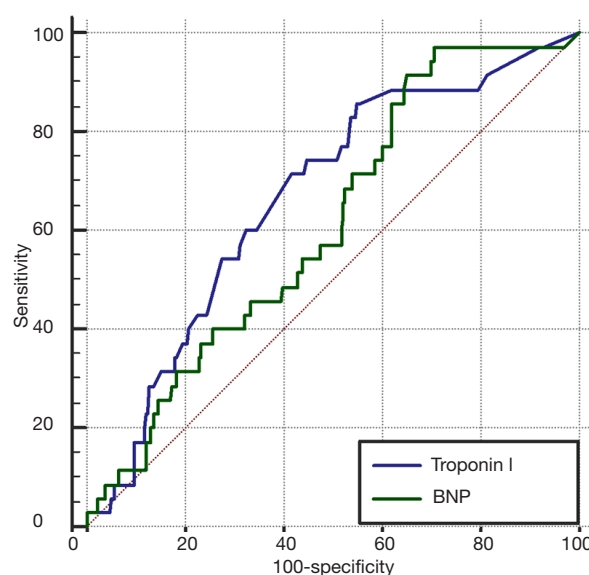
rate was 2.75% and was comparable to the previously reported in-hospital and 30-day mortality (4,7,9,26). The 1-year mortality rate was 8.54%, and was comparable to

Table 2 Statistically significant variables in the univariate and multivariate cox proportional-hazard regression models at 30-day, 1-year, and 2-year (presented as HR, 95% CI, and P value)

Variable	30-day		1-year		2-year	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Positive troponin level elevation	HR: 8.48 (1.07–66.93), P=0.043	HR: 8.84 (1.02–76.34), P=0.048	HR: 2.82 (1.26–6.31), P=0.012	HR: 2.83 (1.16–6.92), P=0.023	HR: 2.85 (1.33–6.07), P=0.007	HR: 2.91 (1.26–6.68), P=0.012
BNP >287 pg/mL			HR: 7.34 (1.75–156.25), P=0.006	HR: 4.58 (1.02–20.62), P=0.047	HR: 5.44 (1.67–17.76), P=0.005	HR: 3.84 (1.10–13.44), P=0.035
Age	HR: 1.19, (1.02–1.10), P=0.0135	HR: 1.10 (1.00–1.21), P=0.047	HR: 1.06 (1.02–1.10), P=0.002	HR: 1.04 (1.01–1.08), P=0.045	HR: 1.05 (1.01–1.08), P=0.005	
Atrial fibrillation			HR: 2.91 (1.43–5.90), P=0.003	HR: 2.34 (1.06–5.00), P=0.035	HR: 2.28, (1.17–4.42), P=0.015	
Diabetes mellitus			HR: 2.36 (1.11–5.01), P=0.0253		HR: 2.47 (1.21–5.04), P=0.013	
Number of readmissions			HR: 1.26 (1.01–1.56), P=0.038		HR: 1.22 (1.01–1.48), P=0.041	

BNP, B-type natriuretic peptide level; HR, hazard ratio; CI, confidence interval.

the mortality rate in the RCTs. Additionally, the 2-year mortality rate was found to be 9.64%.

In the present study, there was a statistically significant positive correlation between BNP and cTnI levels. Additionally, a BNP level >287 pg/mL was found to be an independent predictor of intermediate- and long-term mortality. A similar relationship was previously seen in the acute decompensated HF national registry (ADHERE), where an elevated admission BNP level was found to be an independent predictor of mortality in 18,164 patients with HFpEF decompensation (27). There was also a statistically positive correlation between cTnI level and the length of stay, with a trend towards longer lengths of stay in patients with troponin level elevation. More than half of the patients had at least one readmission for HFpEF decompensation in the study period. This highlights the substantial morbidity and cost of care for such patients.

Currently available pharmacological therapies have failed to demonstrate a meaningful survival benefit in HFpEF despite their success in patients with HF with reduced ejection fraction (28). In our study, there was no significant difference between the medications on discharge between

the two groups. Neither beta blockers nor angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) had a statistically significant effect on mortality.

The findings in our study provide important clinical significance. The presence of troponin level elevation was associated with statistically significant worse short- and long-term mortality, independent of common clinical and laboratory risk factors seen in HFpEF decompensation, including glomerular filtration rate and the presence of chronic kidney disease. Additionally, an elevated BNP level >287 pg/dL was independently associated with higher intermediate- and long-term mortality. Both cTnI and BNP levels provide a valuable tool for early risk stratification in patients with HFpEF decompensation.

Several limitations in our study must be acknowledged. The most important limitation is the retrospective design. The patients evaluated for study inclusion were only those with a discharge diagnosis of HFpEF, at the discretion of the discharging physicians. Hence, the sample size in our study might not represent the actual number of patients hospitalized with this diagnosis due to issues with

documentation and under-diagnosis. Another limitation is that the coronary anatomy was not routinely evaluated, and it is uncertain if some patients with ACS were included. Two cTnI levels were required for inclusion to detect the rising and falling pattern in an attempt to rule out patients with ACS, and the highest troponin I level in our data was only 0.76 ng/mL.

In an effort to decrease the significant effect of end-stage renal disease and extreme fluid overload in patients with acute renal failure on cTnI level elevation, we excluded patients who required or were on hemodialysis; however, such patients represent a substantial proportion of patients with HFpEF. Similarly we excluded patients with severe hypertension and cardiogenic shock. The number of readmissions in our study only represents readmissions to our institution, and might underestimate the actual number of readmissions.

Conclusions

In hospitalized patients with HFpEF decompensation, troponin level elevation was associated with higher short-, intermediate-, and long-term mortality. Additionally, a BNP level >287 pg/dL was associated with higher intermediate- and long-term mortality. This highlights the importance of cTnI and BNP level measurements for early risk stratification. Further prospective studies are needed to assess the relationship between cTnI and BNP levels and outcomes in patients with HFpEF.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Patient's data and outcomes were retrospectively retrieved from hospital's medical records. Informed consent was not required due to the retrospective design. All data were de-identified and secured appropriately.

References

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606-19.

2. Gurwitz JH, Magid DJ, Smith DH, et al. Contemporary prevalence and correlates of incident heart failure with preserved ejection fraction. Am J Med 2013;126:393-400.

3. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.

4. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 2012;126:65-75.

5. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. Circ Heart Fail 2013;6:279-86.

6. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J 2013;34:1424-31.

7. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.

8. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76-84.

9. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768-77.

10. Perna ER, Aspromonte N, Cimbaro Canella JP, et al. Minor myocardial damage is a prevalent condition in patients with acute heart failure syndromes and preserved systolic function with long-term prognostic implications: a report from the CIAST-HF (Collaborative Italo-Argentinean Study on cardiac Troponin T in Heart Failure) study. J Card Fail 2012;18:822-30.

11. Peacock WF 4th, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. N Engl J Med 2008;358:2117-26.

12. Xue Y, Clopton P, Peacock WF, et al. Serial changes in high-sensitive troponin I predict outcome in patients with

decompensated heart failure. Eur J Heart Fail 2011;13:37-42.

13. Pascual-Figal DA, Manzano-Fernández S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail 2011;13:718-25.

14. Jhund PS, Claggett BL, Voors AA, et al. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. Circ Heart Fail 2014;7:953-9.

15. Santhanakrishnan R, Chong JP, Ng TP, et al. Growth differentiation factor 15, ST2, high-sensitivity troponin T, and N-terminal pro brain natriuretic peptide in heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail 2012;14:1338-47.

16. Kociol RD, Pang PS, Gheorghiade M, et al. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol 2010;56:1071-8.

17. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998-1005.

18. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.

19. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268-77.

20. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection

fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781-91.

21. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.

22. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006;114:397-403.

23. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.

24. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.

25. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750-7.

26. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1893-900.

27. Fonarow GC, Peacock WF, Phillips CO, et al. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007;49:1943-50.

28. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. Circ Res 2014;115:79-96.