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A Propensity-Matched Study of New York Heart Association Class and Natural History Endpoints in Chronic Heart Failure

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Abstract

The association between higher New York Heart Association (NYHA) functional classes and poor outcomes in heart failure (HF) is well known. However, to what extent these associations are confounded by covariates such as age, severity of disease and comorbidity burden are unknown. In the Digitalis Investigation Group trial, 2441 of the 7788 chronic HF patients had NYHA class III–IV symptoms. Propensity scores for NYHA class III–IV were calculated for each patient, and were then used to match 1863 NYHA class III–IV patients with 1863 NYHA class I–II patients. Kaplan-Meier and matched Cox regression analyses were used to estimate associations of NYHA class III–IV with mortality and hospitalizations during 37 months of median follow up. Compared with 34% (641/1863) NYHA class I–II patients (mortality rate, 1175/10,000 person-year of follow-up), 42% (777/1863) NYHA class III–IV patients (rate, 1505/10,000 person-year) died from all causes (hazard ratio {HR} =1.29; 95% confidence interval {CI} =1.14–1.45; P<0.0001). Hospitalizations due to all causes occurred in 66% (1232/1863) NYHA class I–II (hospitalization rate, 3898/10,000 person-year) and 71% (1322/1863) (rate, 4793/10,000 person-year) NYHA class III–IV patients (HR =1.16; 95% CI =1.05–1.28; P=0.003). HR (95%CI) for NYHA class III–IV patients, when compared with NYHA class I–II patients, for other outcomes are: cardiovascular mortality, 1.29 (1.12–1.48; P<0.0001), HF mortality, 1.49 (1.20–1.84; P<0.0001), cardiovascular hospitalization, 1.18 (1.06–1.32; P=0.002), and HF hospitalization, 1.17 (1.03–1.34; P=0.017). Baseline NYHA class is a marker of hospitalization, disease progression, and mortality in a wide spectrum of ambulatory chronic HF patients.

Keywords

heart failure; NYHA class; natural history; outcomes

The association of higher New York Heart Association (NYHA) functional class and poor heart failure (HF) outcomes is well known.[1] However, many of these data were derived from advanced HF patients awaiting cardiac transplants, raising concerns for residual confounding by age, severity of disease and comorbidity burden.[2, 3] Studies in ambulatory HF patients are limited by small sample size, short-term follow up, and outcome-based multivariable regression analyses.[4–6] Outcomes studies based on hospitalized HF patients often lack data on NYHA classification.[7–9] The objective of this study was to determine the association between NYHA functional class and broader natural history endpoints such as all-cause and cardiovascular mortality and hospitalizations in ambulatory chronic HF patients using propensity score matching.

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Methods

A public use copy of the DIG data sets was used for the current analysis. The DIG trial enrolled 7788 ambulatory chronic HF patients in normal sinus rhythm from 302 clinical centers in the U.S. and Canada during 1991–1993.[10, 11] Of these patients, 6800 had left ventricular ejection fraction (LVEF) ≤45% and 988 had LVEF >45%. Participants were classified by DIG investigators into one of the four NYHA classes depending on the severity of HF symptoms and the degree of effort needed to elicit those symptoms: class I (n=1103), class II (n=4244), class III (n=2287), and class IV (n=154). Because of functional similarity between class I and II patients and class III and IV patients, and for the convenience of propensity score matching, we categorized patents as having NYHA class I–II (n=5347) and III–IV (n=2441) symptoms. Primary outcomes of interest were mortality and hospitalizations due to all causes, cardiovascular causes, and worsening HF. Data on vital status were 99% complete.[12]

Because of significant imbalance in baseline covariates between NYHA class I–II and III–IV patients, propensity scores to have NYHA III–IV symptoms were calculated for each of the 7788 patients using a non-parsimonious multivariable logistic regression model, adjusting for all available baseline covariates (as shown in Table 1), and incorporating significant two-way interaction terms in the model (Figure 1).[13, 14] The model calibrated (Hosmer-Lemeshow test: $p = 0.303$) and discriminated (area under the ROC curve; $C = 0.80$) well.

Using a SPSS macro, we matched each NYHA III–IV patient with another patient, who had NYHA class I–II symptoms, but had similar propensity score for NYHA III–IV symptoms.[15–19] Overall, 76% (1863/2441) NYHA III–IV patients were matched with 1863 of NYHA I–II patients with similar propensity scores. To assemble a comparable sized pre-match cohort, we randomly selected 1863 NYHA I–II patients from the pre-match file and were paired with 1863 NYHA III–IV in the matched file.

Absolute standardized difference in propensity scores between NYHA I–II and NYHA III–IV patients before and after matching were respectively 84% and 0.1% (Figure 2). Absolute standardized difference after matching between NYHA I–II versus III–IV patients in all measured covariates were <5% (Figure 2). An absolute standardized difference of <10% is considered acceptable reduction of bias.[16–21]

Baseline characteristics of HF patients with NYHA I–II versus III–IV symptoms were compared using Pearson chi-square and Wilcoxon rank-sum tests. Kaplan-Meier analysis and matched Cox regression analyses were used to determine association of NYHA III–IV (relative to class I or II) and various outcomes. Subgroup analyses and first-order interaction were used to test heterogeneity of the association between NYHA class and mortality. All statistical tests were done using SPSS for Windows (Release 14), and two-tailed 95% confidence levels; a $p < 0.05$ was required to reject the null hypothesis.

Results

Overall, patients had a mean age of 65 years, 28% were female, and 14% were nonwhites. Baseline characteristics of patient with NYHA I–II versus III–IV symptoms, before and after matching are displayed in Table 1. There were significant differences in covariates before matching, which was absent from the matched cohort. Quantitative measures of biases before and after matching, and reduction of bias after matching are displayed in Figure 1. Values of absolute standardized differences for all covariates were <5%, suggesting considerable reduction of bias.[16, 17, 20, 21]

Mortality

Overall, 1418 patients (38%) died, including 1114 (30%) deaths from cardiovascular causes and 518 due to HF during the median follow up of 37 months. Kaplan-Meier plots for death due to all causes are displayed in Figure 2a. Compared with 641 deaths from all causes in NYHA I–II patients during 5455 years of follow up (rate, 1175/10,000 person-year), there were 777 death in NYHA III–IV patients during 5162 years (rate, 1505/10,000 person-year; Table 2). NYHA III–IV symptoms were associated with a significant 29% increase in all-cause mortality (hazard ratio, 1.29, 95% confidence interval, 1.14– 1.45; p <0.0001; Table 2). NYHA III–IV was associated with similar increase in mortality due to cardiovascular causes and HF (Table 2). The association between NYHA class III–IV and all-cause mortality were observed across various subgroups of patients, (Figure 3).

Hospitalization

Overall, 2554 patients (69%) were hospitalized due to all causes, including 2040 (55%) due to cardiovascular causes and 1278 (34%) due to worsening HF. Kaplan-Meier plots for hospitalizations due to all causes are displayed in Figure 2b. Compared with 1232 hospitalizations from all causes in NYHA I–II patients during 3161 years of follow up (rate, 3898/10,000 person-year), 1322 NYHA III–IV patients were hospitalized during 2758 years of follow up (rate, 4793/10,000 person-year; Table 2). NYHA III–IV was associated with a significant 16% increase in all-cause hospitalization (hazard ratio, 1.16, 95% confidence interval, 1.05– 1.28; p <0.0001; Table 2). NYHA III–IV was associated with similar increase in hospitalizations due to cardiovascular causes and worsening HF (Table 2).

Discussion

These findings suggest that subjective determination of baseline NYHA classes based on functional capacity and HF symptoms can serve as a marker of important natural history endpoints in a wide spectrum of chronic systolic and diastolic HF patients. This is the first demonstration of a significant association between NYHA class and long-term outcomes in HF using propensity score analysis. NYHA classification can be easily obtained by clinicians and may be used to identify high risk HF patients for appropriate interventions.

NYHA functional classification, although subjective and may vary over time, is a clinical measure of overall symptom burden in HF.[22] However, the findings of the current analysis suggest that higher symptom burden in HF may represent more than worsening clinical symptoms related to noncompliance with medications or salt or fluid. Instead, this may be a marker of disease progression, hospitalization and mortality. NYHA class III–IV HF patients are more likely to be elderly, women, have longer duration of HF, current angina, diabetes, and chronic kidney disease (Table 1). They were also more likely to have symptoms and signs of HF and be receiving diuretics. However, these are unlikely to explain our findings as our propensity score matching reduced bias to <5% absolute standardized differences for all these covariates.[16, 17, 21, 23]

The results of the current study are consistent with those for prior studies. However, most of those studies are based on advanced systolic HF patients awaiting cardiac transplants.[2, 3] Studies of ambulatory HF patients suggesting association between higher NYHA functional class and poor short-term outcomes are limited by small sample size, shorter follow up and residual confounding.[4–6, 24–26] Studies of predictors of HF outcomes based on HF registries typically do not report data on NYHA classification.[7–9] Large sample size, long follow up, cause- specific outcomes and use of propensity score matching distinguishes the current study from previous studies. In particular, as illustrated in Table 1 and Figure 1, propensity score matching allows a more quantitatively assessment of bias reduction.

This study has several limitations. While propensity score technique can account for imbalances in all measured covariates, it may or may not balance unmeasured covariates. However, for such an unmeasured confounder to explain away our finding it must be strongly associated with both NYHA class and outcomes, and be not strongly associated with any of the many baseline covariates in the DIG trial.[11, 16–19] We did not have data on NYHA status during the follow up. It is possible that some patients with NYHA class I–II became III–IV due to disease progression or noncompliance with therapy, and vice-versa. However, such misclassification is likely to be random and could only have underestimated the association observed in our analysis. Finally, the results of this study are based on relatively young male HF patients in normal sinus rhythm from a pre-beta-blocker era and their relevance to contemporary HF patients is unknown.

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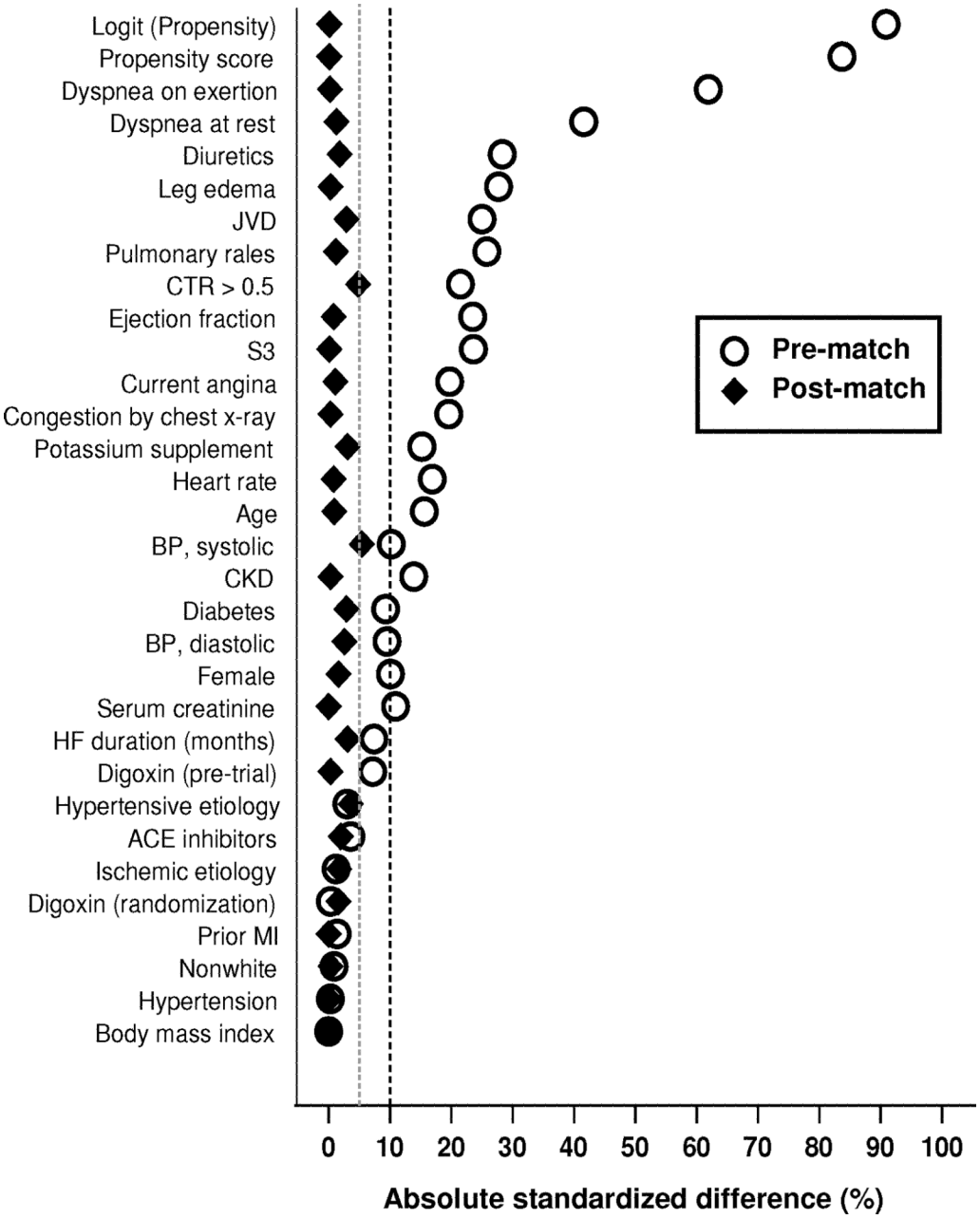

Figure 1.

Absolute standardized differences before and after propensity score matching comparing covariate values for patients with New York Heart Association class I–II versus III–IV
ACE=angiotensin-converting enzyme; BP=blood pressure; CKD=chronic kidney disease; CTR=cardiothoracic ratio; JVD=jugular venous distention; MI=myocardial infarction; S3=third heart sound

Figure 2a

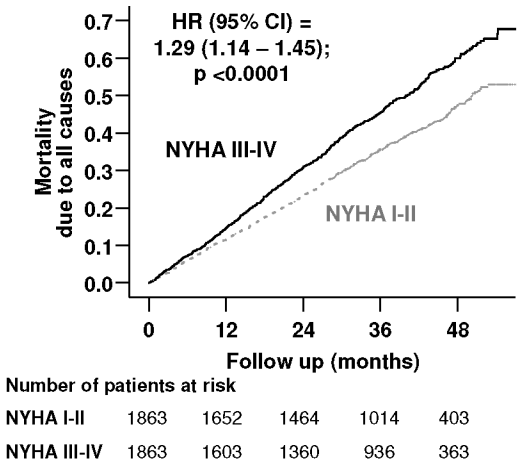

Figure 2b

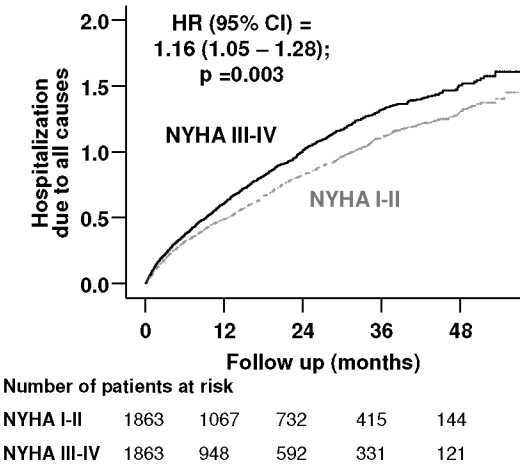

Figure 2.
Kaplan-Meier plots for (a) all-cause mortality and (b) all-cause hospitalization
HR=hazard ratio; CI=confidence interval

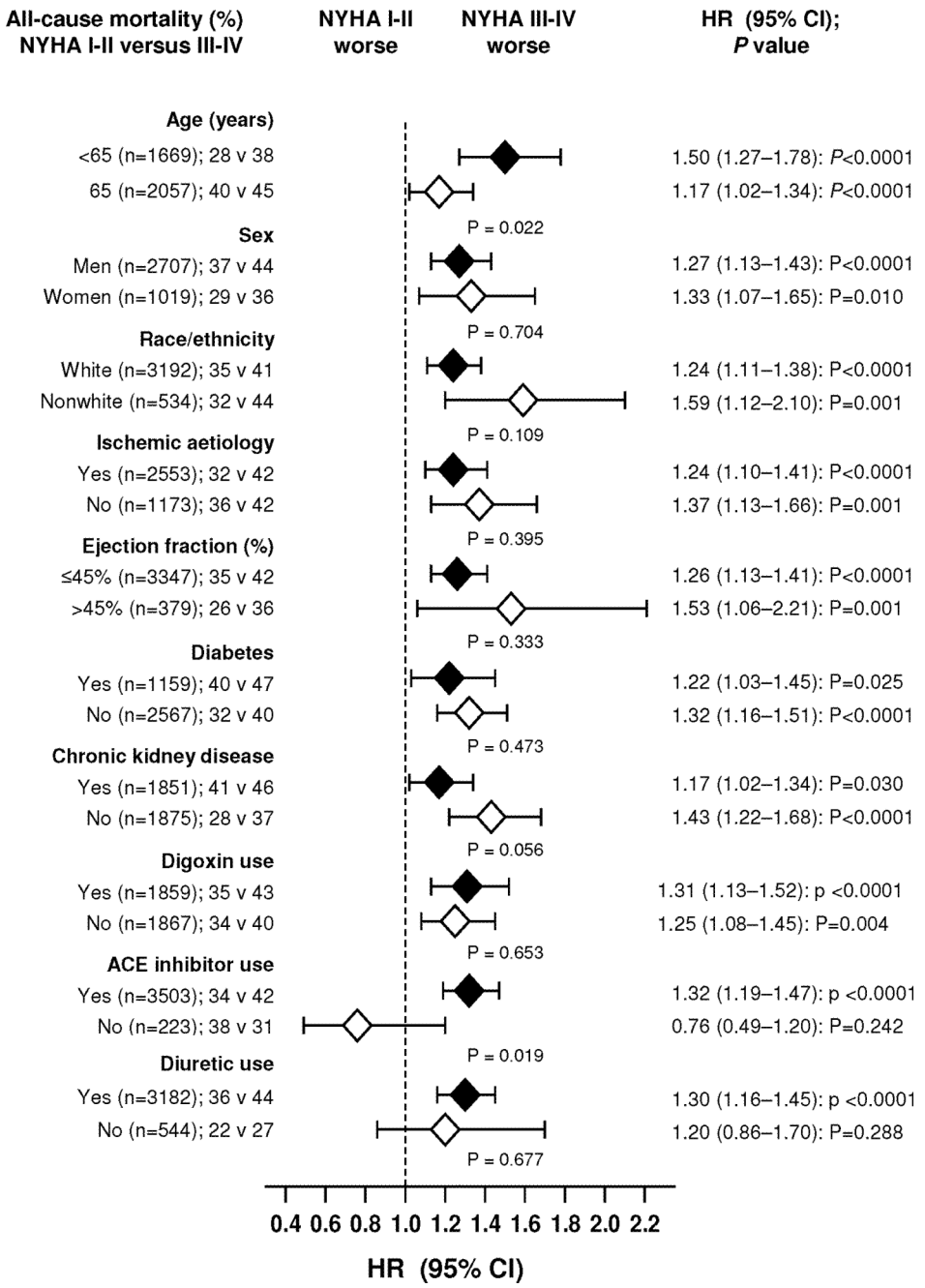

Figure 3.

Hazard ratio and 95% confidence interval (CI) for all-cause mortality in subgroups of heart failure patients matched by propensity scores for New York Heart Association (NYHA) class III–IV

(ACE=angiotensin-converting enzyme; chronic kidney disease=estimated glomerular filtration rate <60 ml/min/1.73m^2)

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Table 1

Baseline patient characteristics, before and after propensity score matching

	Before matching*			After matching	
N (%) or mean (±SD)	**NYHA I – II (N=1,863)**	**P**	**NYHA III – IV† (N=1,863)**	**P Value**	**NYHA I – II (N=1,863)**
Age (years)	63.0 (±10.8)	<0.0001	64.7 (±11.0)	0.734	64.8 (±10.5)
Age ≥65 years	992 (49.5%)	0.012	1000 (53.7%)	0.065	1057(56.7%)
Female	434 (23.3%)	0.002	516 (27.7%)	0.659	503 (27.0%)
Non-white	260 (14.0%)	0.778	266 (14.3%)	0.963	268 (14.4%)
Body mass index, kg/square meter	27.4 (±5.03)	0.923	27.4 (±5.8)	0.786	27.4 (±5.8)
Duration of HF (months)	28.6 (±35.4)	0.022	31.3 (±37.7)	0.474	30.1 (±38.8)
Primary cause of HF					
Ischemic	1274 (68.4%)		1284 (68.9%)		1269 (68.1%)
Hypertensive	196 (10.5%)		179 (9.6%)		199 (10.7%)
Idiopathic	266 (14.3%)	0.830	272 (14.6%)	0.681	272 (14.6%)
Others	127 (6.8%)		128 (6.9%)		119 (6.4%)
Prior myocardial infarction	1158 (62.2%)	0.660	1171 (62.9%)	1.000	1171 (62.9%)
Current angina	431 (23.1%)	<0.0001	594 (31.9%)	0.752	604 (32.4%)
Hypertension	876 (47.0%)	0.922	873 (46.9%)	1.000	872 (46.8%)
Diabetes	489 (26.2%)	0.005	567 (30.4%)	0.377	592 (31.8%)
Chronic kidney disease	798 (42.8%)	<0.0001	927 (49.8%)	0.922	924 (49.6%)
Medications					
Pre-trial digoxin use	769 (41.3%)	0.031	835 (44.8%)	0.947	838 (45.0%)
Trial use of digoxin	940 (50.5%)	0.948	937 (50.3%)	0.646	922 (49.5%)
ACE inhibitors	1740 (93.4%)	0.307	1756 (94.3%)	0.581	1747 (93.8%)
Hydralazine & nitrates	23 (1.2%)	0.882	22 (1.2%)	0.566	27 (1.4%)
Non-potassium sparing diuretics	1374 (73.8%)	<0.0001	1585 (85.1%)	0.610	1597 (85.7%)
Potassium diuretics	134 (7.2%)	0.707	141 (7.6%)	0.542	151 (8.1%)
Potassium supplement	474 (25.4%)	<0.0001	602 (32.3%)	0.360	575 (30.9%)
Symptoms and signs of heart failure					
Dyspnea at rest	265 (14.2%)	<0.0001	583 (31.3%)	0.723	572 (30.7%)
Dyspnea on exertion	1263 (67.8%)	<0.0001	1706 (91.6%)	1.000	1705 (91.5%)

N (%) or mean (±SD)	Before matching* NYHA I – II (N=1,863)	P	NYHA III – IV† (N=1,863)	After matching P Value	After matching NYHA I – II (N=1,863)
Jugular venous distension	170 (9.1%)	<0.0001	327 (17.6%)	0.384	307 (16.5%)
Third heart sound	359 (19.3%)	<0.0001	546 (29.3%)	0.971	547 (29.4%)
Pulmonary râles	223 (12.0%)	<0.0001	401 (21.5%)	0.749	392 (21.0%)
Lower extremity edema	281 (15.1%)	<0.0001	488 (26.2%)	0.881	483 (25.9%)
Heart rate (/minute),	77.4 (±12.5)	<0.0001	79.5 (±12.4)	0.931	79.6 (±12.5)
Blood pressure (mm Hg)					
Systolic	128.0 (±19.9)	0.002	125.9 (±21.2)	0.109	127.0 (±19.7)
Diastolic	75.6 (±11.1)	0.007	74.5 (±12.0)	0.565	74.8 (±11.1)
Chest radiograph findings					
Pulmonary congestion	206 (11.1%)	<0.0001	334 (17.9%)	0.966	332 (17.8%)
Cardiothoracic ratio >0.5	1037 (55.7%)	<0.0001	1231 (66.1%)	0.152	1273 (68.3%)
Serum creatinine (mg/dL)	1.26 (±0.35)	<0.0001	1.30 (±0.38)	0.455	1.31 (±0.39)
Ejection fraction (%)	33.2 (±12.0)	<0.0001	30.3 (±12.7)	0.717	30.4 (±11.6)
Ejection fraction >45%	248 (13.3%)	0.015	199(10.7%)	0.329	180 (9.7%)

*Of the 5347 NYHA I–II patients, 1863 were randomly chosen for pre-match comparison with 1863 NYHA III and IV. This was done to have similar pre-match and post-match sample sizes, and to avoid overestimation of significant p values from a larger sample size.

†Of the 2441 NYHA III–IV patients, 1863 (76%) were matched with 1863 NYHA I–II patients with similar propensity scores

Table 2

Mortality and hospitalizations by causes in heart failure patients before and after matching by propensity scores for NYHA class III–IV

	NYHA I–II (N=1,863)	NYHA III–IV (N=1,863)	Absolute difference* (per 10,000 person-years of follow up)	Hazard ratio (95% confidence interval)	P value
	Mortality Rate, per 10,000 person-years of follow up (Events/total follow up years)				
Mortality					
All-cause	1,175 (641/5,455)	1,505 (777/5,162)	+ 330	1.29 (1.14–1.45)	<0.0001
Cardiovascular	924 (504/5,455)	1,182 (610/5,162)	+ 258	1.29 (1.12–1.48)	<0.0001
Worsening heart failure	409 (223/5,455)	571 (295/5,162)	+ 162	1.49 (1.20–1.84)	<0.0001
Hospitalization**					
All-cause	3,898 (1,232/3,161)	4,793 (1,322/2,758)	+ 895	1.16 (1.05–1.28)	0.003
Cardiovascular	2,580 (965/3,741)	3,227 (1,075/3,331)	+ 647	1.18 (1.06–1.32)	0.002
Worsening heart failure	1,348 (613/4,547)	1,592 (665/4,175)	+ 244	1.17 (1.03–1.34)	0.017
Number of total hospitalizations	12,129	15,105	+ 2,976		

*Absolute differences in rates of events per 10,000 person-year of follow up were calculated by subtracting the event rates in the NYHA class III–IV group from the event rates in the NYHA class I–II group (before values were rounded)

†Data shown include the first hospitalization of each patient due to each cause.