Published in final edited form as:

Am J Cardiol. 2008 February 1; 101(3): 343–347. doi:10.1016/j.amjcard.2007.08.039.

A Propensity-Matched Study of the Association of Cardiothoracic Ratio with Morbidity and Mortality in Chronic Heart Failure

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Abstract

High cardiothoracic ratio (CTR) is a marker of enlarged heart and is associated with poor outcomes in heart failure (HF). However, to what extent this association is independent of other confounders is not well known. To study this, we used propensity score matching to design a study in which HF patients with normal (≤ 0.50) and high (> 0.50) CTR were well-balanced in all measured baseline covariates. In the Digitalis Investigation Group trial (N=7788), 4690 patients had high (> 0.50) CTR. Propensity scores for high CTR were calculated for each patient and were then used to match 2586 pairs of patients with normal and high CTR. Matched Cox regression analyses were used to estimate associations of high CTR with mortality and hospitalization during 37 months of median follow-up. All-cause mortality occurred in 28.5% (rate, 919/10,000 person-years of follow-up) of patients with normal CTR and 34.3% (rate, 1185/10,000 person-years) of patients with high CTR (hazard ratio {HR} 1.35; 95% confidence interval {CI} 1.21–1.51; $p < 0.0001$). All-cause hospitalization occurred in 64.8% (rate, 3513/10,000 person-years) of patients with normal CTR and 66.2% (rate, 3932/10,000 person-years) of patients with high CTR (HR 1.10; 95% CI 1.01–1.20; $p = 0.032$). Respective HR's (95% CI) for other outcomes were: 1.48 (1.30–1.68; $p < 0.0001$) for cardiovascular mortality, 1.57 (1.28–1.92; $p < 0.0001$) for HF mortality, 1.18 (1.08–1.30; $p = 0.001$) for cardiovascular hospitalization and 1.27 (1.13–1.44; $p < 0.0001$) for HF hospitalization. In conclusion, baseline CTR > 0.50 was associated with increased mortality and morbidity in ambulatory chronic HF patients.

Keywords

heart failure; cardiothoracic ratio; mortality; outcomes

High cardiothoracic ratio (CTR), estimated by chest roentgenogram, is a marker of cardiomegaly, and has been shown to be associated with poor outcomes in heart failure (HF).^{1–3} However, to what extent this association is independent of other confounders is not well known. Residual bias due to confounding covariates is a concern for studies based on regression-based risk adjustment methods. Further, most of these studies had relatively small sample sizes, short follow up duration, and mortality was the only outcome studied. The objective of this propensity-matched study was to determine the association of baseline high

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Conflict of Interest Disclosures: None

CTR with a broad spectrum of natural history endpoints in a cohort of ambulatory chronic HF patients where patients with normal (≤ 0.50) and high (> 0.50) CTR were well-balanced in all measured baseline covariates.

Methods

The DIG trial enrolled 7788 ambulatory patients with chronic HF in normal sinus rhythm from 302 clinical centers in the United States and Canada from 1991 to 1993.^{4,5} Of these patients, 6800 had left ventricular ejection fractions of $< 45\%$ and 4690 had high (> 0.50) CTR. The primary end points were mortality and hospitalizations due to all causes, cardiovascular causes, and worsening HF. Data on vital status were 99% complete.⁶

Because of significant imbalance in baseline covariates between patients with normal and high CTR (Table 1), we used propensity score matching to assemble a cohort of patients where patients with normal and high CTR would be well-balanced in all measured baseline covariates.^{7–11} We estimated propensity scores for high CTR for each of the 7788 patients using a non-parsimonious, multivariate logistic regression model, adjusting for all available baseline covariates presented in Table 1. We then used an SPSS macro (SPSS, Inc., Chicago, Illinois) to match 2586 pairs of patients with normal and high CTR who had similar propensity scores. The details of the matching protocol have been described elsewhere.^{12–16} We then objectively estimated bias reduction using absolute standardized differences ($< 10\%$ being inconsequential bias).^{12,14–18}

The baseline characteristics of patients with normal and high CTR were compared using Pearson's chi-square and Wilcoxon's rank-sum tests. Kaplan-Meier analysis and matched Cox regression analyses were used to determine the association of high CTR (relative to normal CTR) with various outcomes. Subgroup analyses and first-order interactions were used to test the heterogeneity of the association between high CTR and mortality. All statistical tests were done using SPSS-14 for Windows (SPSS, Inc., Chicago, Illinois).

Results

Patients had a mean ($\pm$ SD) age of 64 (± 11) years, 19% were women, and 10% were nonwhites. All significant imbalances in baseline covariates before matching were balanced after matching (Table 1). Values of absolute standardized differences for all covariates after matching between patients with normal and high CTR were $< 5\%$ (Figure 1).

Overall, 1625 patients (31%) died, including 1272 (25%) due to cardiovascular causes and 521 (10%) due to progressive HF, during the median follow-up period of 37 months. Kaplan-Meier plots for all-cause mortality are displayed in Figure 2A. All-cause mortality occurred in 738 patients (rate, 919/10,000 person-years) with normal CTR during 8028 years of follow-up and in 887 patients (rate, 1185/10,000 person-years) with high CTR during 7485 years of follow up (hazard ratio {HR}, 1.35; 95% confidence interval {CI}, 1.21–1.51; $p < 0.0001$; Table 2). High CTR was associated with similar increases in cardiovascular and HF mortality (Table 2). High CTR-associated all-cause mortality was observed across various subgroups of patients (Figure 3).

Overall, 3388 patients (66%) were hospitalized for all causes, including 2608 (50%) for cardiovascular causes and 1396 (27%) for worsening HF. Kaplan-Meier plots for all-cause hospitalization are displayed in Figure 2B. All-cause hospitalization occurred in 1676 normal-CTR patients (rate, 3513/10,000 person-years) during 4771 years of follow-up and 1712 high-CTR patients (rate, 3932/10,000 person-years) during 4354 person-years of follow-up (HR, 1.10; 95% CI, 1.01–1.20; $p < 0.0001$; Table 2). High CTR was associated with similar increases in hospitalizations due to cardiovascular causes and worsening HF (Table 2).

Discussion

The results of the current analysis demonstrate that high CTR at baseline as measured by chest x-ray was a marker of poor prognosis for a wide range of major natural history end points in chronic HF. To the best of our knowledge, this is the first demonstration of such association in a large population of propensity-matched chronic systolic and diastolic HF patients with long follow-up of a range of cause-specific mortalities and hospitalizations. These findings are important as despite common use of electrocardiograph and echocardiograph in the evaluation of HF in developed nations, use of chest x-ray is an important element in the initial assessment of patients with chronic HF.^{19,20}

An enlarged heart, often clinically estimated by a radiographic evidence of CTR >0.50 or an electrocardiographic evidence of left ventricular hypertrophy, is considered abnormal, especially in the context of HF. An enlarged heart may be the results of myocardial fibrosis and ventricular remodeling, which may in part explain the high-CTR associated poor prognosis in HF.^{21,22} Recent data suggest that CTR is significantly increased in primary pulmonary hypertension and may predominantly reflect right- rather than left-sided cardiomegaly,^{23,24} both of which are independent predictors of poor outcomes in HF.^{25–29}

The results of our study are consistent with those of reported by other investigators.^{1–3} However, our study is distinguished from prior studies by its large sample size, long follow up of wide spectrum of major naturally history end points, and use of propensity score matching to design the study. Before matching, patients with a high baseline CTR were more likely to be elderly, have ischemic heart disease, hypertension, diabetes, and chronic kidney disease, more severe HF, and lower ejection fraction (Table 1· Figure 1), all characteristics associated with poor outcomes. Because post-match absolute standardized differences for all measured baseline covariates were <5%, it is unlikely that the results of our study can be explained by baseline variations in covariates. The results of our study highlights the importance of routine chest x-ray during initial assessment of HF, and risk stratify patients based on CTR.^{19,20}

Key limitations of our study include those associated with non-randomize design of our study and its inability to account for unmeasured confounders. Our sensitivity analysis suggests that an unmeasured binary covariate could potentially invalidate the results of our study if it would also increase the odds of high CTR by as little as 21%.³⁰ However, for that unmeasured covariate to become a confounder, it should be a strong predictor of mortality and also should not be strongly correlated with any of the measured covariates (Table 1). Of note, the results of sensitivity analysis cannot determine the existence of such a covariate. Other limitations are related to the age of the study data and characteristic of study population (largely young white male systolic HF patients with normal sinus rhythm from pre β -blocker era of HF therapy), which may limit generalizability to contemporary HF patients. In conclusion, baseline CTR >0.5 is associated with increased mortality and hospitalization in chronic HF. Chest x-ray assessment of CTR should be routinely incorporated as a part of initial assessment of HF, and may be used to risk-stratify HF patients.

Acknowledgements

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through grants from the National Heart, Lung, and Blood Institute (1-R01-HL085561-01 and P50-HL077100).

“The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators. This manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI.”

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Figure 1.

Absolute standardized differences before and after propensity score matching comparing covariate values for patients with cardiothoracic ratio ≤ 0.5 and >0.5

Number of patients at risk

CTR ≤ 0.5	2586	2379	2167	1564	645
CTR > 0.5	2586	2292	2026	1383	513

Number of patients at risk

CTR ≤ 0.5	2586	1843	1432	914	346
CTR > 0.5	2586	1698	1258	750	263

Figure 2.

Kaplan-Meier plots for (a) all-cause mortality and (b) cardiovascular (CV) hospitalization by cardiothoracic ratio (CTR)

Figure 3. Hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality for cardiothoracic ratio >0.5 in subgroups of heart failure patients

Chronic kidney disease defined as estimated glomerular filtration rate <60 ml/min/1.73m².
 NYHA=New York Heart Association

Table 1
Baseline patient characteristics of heart failure (HF) patients, by cardiothoracic ratio (CTR), before and after propensity score matching

Variables: N (%) or mean $\pm$ SD	Before matching			After matching		
	CTR ≤ 0.50 (n = 3,098)	CTR > 0.50 (n = 4,690)	p Value	CTR ≤ 0.50 (n = 2,586)	CTR > 0.50 (n = 2,586)	p Value
Age (years)	63 $\pm$ 11	65 $\pm$ 11	<0.0001	64 $\pm$ 10	64 $\pm$ 11	0.611
Age ≥ 65 years	1,500 (48%)	2,536 (54%)	<0.0001	1,324 (51%)	1,292 (50%)	0.389
Female	510 (17%)	1,416 (30%)	<0.0001	492 (19%)	491 (19%)	1.000
Non-white	267 (9%)	861 (18%)	<0.0001	259 (10%)	242 (9%)	0.452
Body mass index, kg/m ²	27 $\pm$ 5	28 $\pm$ 6	<0.0001	27 $\pm$ 5	27 $\pm$ 5	0.650
Duration of HF (months)	30 $\pm$ 35	29 $\pm$ 37	0.385	30 $\pm$ 35	30 $\pm$ 38	0.873
Primary cause of HF						
Ischemic	2,308 (75%)	3,052 (65%)		1,873 (72%)	1,885 (73%)	
Hypertensive	254 (8%)	551 (12%)	<0.0001	231 (9%)	235 (9%)	
Idiopathic	365 (12%)	746 (16%)		324 (13%)	317 (12%)	0.938
Others	171 (6%)	341 (7%)		158 (6%)	149 (6%)	
Prior myocardial infarction	2,119 (68%)	2,789 (60%)	<0.0001	1,717 (66%)	1,733 (67%)	0.329
Current angina pectoris	895 (29%)	1,220 (26%)	0.005	725 (28%)	716 (28%)	0.780
Hypertension	1,290 (42%)	2,384 (51%)	<0.0001	1,145 (44%)	1,163 (45%)	0.634
Diabetes mellitus	818 (26%)	1,400 (30%)	0.001	715 (28%)	719 (28%)	0.901
Chronic kidney disease	1,310 (42%)	2,217 (47%)	<0.0001	1,162 (45%)	1,139 (44%)	0.520
Medications						
Pre-trial digoxin use	1,271 (41%)	2,094 (45%)	0.002	1,091 (42%)	1,114 (43%)	0.536
Trial use of digoxin	1,554 (50%)	2,335 (50%)	0.763	1,303 (50%)	1,286 (50%)	0.637
ACE inhibitors	2,884 (93%)	4,390 (94%)	0.376	2,423 (94%)	2,421 (94%)	0.955
Hydralazine & nitrates	21 (1%)	90 (2%)	<0.0001	21 (1%)	17 (1%)	0.626
Diuretics	2,171 (70%)	3,905 (83%)	<0.0001	1,967 (76%)	1,961 (76%)	0.871
PS diuretics	234 (8%)	362 (8%)	0.828	207 (8%)	220 (9%)	0.544
Potassium supplement	736 (24%)	1,463 (31%)	<0.0001	681 (26%)	687 (27%)	0.850
Symptoms and signs of HF						
Dyspnea at rest	510 (17%)	1,195 (26%)	<0.0001	468 (18%)	485 (19%)	0.542
Dyspnea on exertion	2,236 (72%)	3,626 (77%)	<0.0001	1,898 (73%)	1,911 (74%)	0.705
Limitation of activity	2,236 (72%)	3,667 (78%)	<0.0001	1,925 (74%)	1,920 (74%)	0.899

Variables: N (%) or mean $\pm$ SD	Before matching			After matching		
	CTR ≤ 0.50 (n = 3,098)	CTR > 0.50 (n = 4,690)	p Value	CTR ≤ 0.50 (n = 2,586)	CTR > 0.50 (n = 2,586)	p Value
Jugular venous distension	254 (8%)	766 (16%)	<0.0001	240 (9%)	249 (10%)	0.704
Third heart sound	570 (18%)	1,276 (27%)	<0.0001	529 (21%)	531 (21%)	0.973
Pulmonary rales	334 (11%)	967 (21%)	<0.0001	315 (12%)	327 (13%)	0.643
Lower extremity edema	479 (16%)	1,154 (25%)	<0.0001	444 (17%)	451 (17%)	0.797
Number of symptom/signs	5.1 $\pm$ 2.1	5.7 $\pm$ 2.0	<0.0001	5.3 $\pm$ 2.0	5.3 $\pm$ 2.1	0.527
NYHA functional classes						
Class I	525 (17%)	578 (12%)		398 (15%)	408 (16%)	
Class II	1,844 (60%)	2,400 (51%)	<0.0001	1,505 (58%)	1,483 (57%)	0.824
Class III	710 (23%)	1,577 (34%)		664 (26%)	671 (26%)	
Class IV	19 (1%)	135 (3%)		19 (1%)	24 (1%)	
Heart rate (/minute)	77 $\pm$ 12	79 $\pm$ 13	<0.0001	78 $\pm$ 13	78 $\pm$ 13	0.782
BP, systolic (mm Hg)	127 $\pm$ 20	127 $\pm$ 1	0.864	128 $\pm$ 20	128 $\pm$ 21	0.727
BP, diastolic (mm Hg)	75 $\pm$ 11	75 $\pm$ 12	0.120	75 $\pm$ 11	75 $\pm$ 11	0.590
Pulmonary congestion by chest x-ray	228 (7%)	881 (19%)	<0.0001	226 (9%)	227 (9%)	0.843
Serum creatinine (mg/dL)	1.27 $\pm$ 0.436	1.29 $\pm$ 0.438	0.035	1.28 $\pm$ 0.437	1.28 $\pm$ 0.436	0.807
Serum potassium (mEq/L)	4.4 $\pm$ 0.4	4.3 $\pm$ 0.5	<0.0001	4.4 $\pm$ 0.4	4.4 $\pm$ 0.4	0.377
Estimated glomerular filtration rate, ml/min per 1.73 m ²	65 $\pm$ 21	63 $\pm$ 23	<0.0001	64 $\pm$ 22	64 $\pm$ 20	0.595
Ejection fraction (%)	34 $\pm$ 12	30 $\pm$ 13	<0.0001	33 $\pm$ 12	33 $\pm$ 13	0.944
Ejection fraction $> 45\%$	492 (16%)	496 (11%)	<0.0001	346 (13%)	365 (14%)	0.443

ACE=angiotensin-converting enzyme; BP=blood pressure; NYHA=New York Heart Association; PS=potassium sparing

Mortality and hospitalizations by causes in heart failure patients before and after matching by propensity scores for cardiothoracic ratio (CTR) >0.50

Outcomes	CTR=0.50 (N=2582)		CTR>0.50 (N=2582)		Absolute rate difference (per 10,000 person-years)	Hazard ratio(95% confidence interval)	P value
	Rate, per 10,000 person-years (Events/total follow up years)						
Mortality							
All-cause	919 (738/8028)		1185 (887/7485)		+ 265	1.35 (1.21–1.51)	<0.0001
Cardiovascular	689 (553/8028)		961 (719/7485)		+ 272	1.48 (1.30–1.68)	<0.0001
Progressive heart failure	280 (225/8028)		395 (296/7485)		+ 115	1.57 (1.28–1.92)	<0.0001
Hospitalization†							
All-cause	3513 (1676/4771)		3932 (1712/4354)		+ 419	1.10 (1.01–1.20)	0.032
Cardiovascular	2187 (1250/5715)		2647 (1358/5131)		+ 460	1.18 (1.08–1.30)	0.001
Progressive heart failure	927 (650/7011)		1180 (746/6321)		+ 253	1.27 (1.13–1.44)	<0.0001
Number of total hospitalizations	5932		6779		+ 847		

* Absolute differences in rates of events per 10,000 person-year of follow up were calculated by subtracting the event rates in the normal-CTR group from the event rates in the high-CTR group (before values were rounded).

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