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A Propensity-Matched Study of Outcomes of Chronic Heart Failure in Younger and Older Adults

Christy Wahle^a, Chris Adamopoulos^b, O. James Ekundayo^a, Marjan Mujib^a, Wilbert S. Aronow^c, and Ali Ahmed^{a,d,*}

^a University of Alabama at Birmingham, 1530 3rd Avenue South, CH-19, Ste-219, Birmingham, AL 35294-2041, USA

^b Papageorgiou General Hospital, 56429 Thessaloniki, Greece

^c New York Medical College, Valhalla, NY 10595, USA

^d Veterans Affairs Medical Center, 700 S. 19th Street, Birmingham, AL 35233, USA

Abstract

The majority of heart failure patients are older adults and most heart failure-related adverse events occur in these patients. However, the independent association of age and outcomes in chronic heart failure is not clearly determined. We categorized 7788 ambulatory chronic heart failure patients who participated in the Digitalis Investigation Group trial as younger and older using the cutoff of 65 years. Propensity scores for age were calculated for each patient and used to match 2381 older patients with 2381 younger patients. The impact of age on mortality and hospitalization during a median 40 months of follow-up was assessed using matched Cox regression methods. All-cause mortality occurred in 877 older patients versus 688 younger patients (hazard ratio when older age was compared with younger age (HR) = 1.26, 95% confidence interval (CI) = 1.12–1.41, $p < 0.0001$). Older patients, when compared with propensity-matched younger patients, also had significantly higher mortality rates due to cardiovascular causes (HR = 1.14; 95% CI = 1.00–1.30, $p = 0.044$) and worsening heart failure causes (HR = 1.32; 95% CI = 1.07–1.62, $p = 0.009$). No significant association was found between age and hospitalization due to all causes (HR = 1.08; 95% CI = 0.99–1.18, $p = 0.084$) and cardiovascular causes (HR = 1.03; 95% CI = 0.93–1.13, $p = 0.622$). However, hospitalization due to heart failure was significantly increased in older patients (HR = 1.14; 95% CI = 1.01–1.28, $p = 0.041$). In ambulatory chronic heart failure patients, older age although associated with increased mortality was not associated with increased hospitalizations except for those due to worsening heart failure.

Keywords

Heart failure; mortality; hospitalization; propensity score; older adults

1. Introduction

Aging is associated with multiple morbidities and functional decline that may explain the increased mortality and hospitalization observed in older adults (Sager and Rudberg, 1998; Wolinsky et al., 1993; Yancik et al., 2007). Most heart failure (HF) patients are older adults and most of the HF-related hospitalization and mortality occurs in these patients (Rosamond

*Corresponding author at: University of Alabama at Birmingham, 1530 3rd Ave South, CH-19, Ste-219, Birmingham AL 35294-2041; Telephone: 1-205-934-9632; Fax: 1-205-975-7099; Email address: E-mail: aahmed@uab.edu (A. Ahmed).

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et al., 2007). Previous studies based on multivariable regression-based risk adjustment models have described age as a predictor for mortality (Cowie et al., 2002; Pocock et al., 2006). However, the extent to which aging is independently associated with mortality and morbidity in HF patients is not well known. The purpose of this study was to examine the effect of age on all-cause and cause-specific mortalities and hospitalizations in a propensity-matched population of chronic HF patients.

2. Subjects and methods

2.1. Data Source and Patients

This study was conducted using retrospective analysis of public-use data sets from the Digitalis Investigation Group (DIG) trial, a randomized clinical trial studying the effects of digoxin in HF patients. Between January 1991 and August 1993 the DIG trial enrolled 7788 ambulatory chronic HF patients from 302 clinical centers across the United States (186 centers) and Canada (116 centers). Of these participants, 4036 (52%) were age 65 or older, and overall ages ranged from 21 to 94. Study design and results from the DIG trial have been previously published (The Digitalis Investigation Group, 1996, 1997). For the purpose of this analysis, we categorized patients into younger and older adults based on an age cutoff of 65 years.

2.2. Outcomes

Mortality and hospitalizations attributed to all causes were the outcome measures used to assess the associations of age and outcomes in HF patients. We also examined associations of age with mortality and hospitalization due to cardiovascular causes and worsening HF. End-of-trial vital status was known for 99% (7691) of DIG participants (Collins et al., 2003).

2.3. Estimation of propensity scores

To determine an independence of association between age and outcomes, we used propensity score matching to assemble a cohort of patients who were well balanced in all measured baseline covariates. First, we used a non-parsimonious multivariable logistic regression model to calculate, for each patient, a propensity score for having age ≥ 65 years (Ahmed, 2008; Ahmed et al., 2006a,b; Ahmed et al., 2007a,b; Rosenbaum and Rubin, 1983; Rosenbaum and Rubin, 1984; Rubin, 1997; Rubin, 2001; Rubin, 2004). In the model, age ≥ 65 years was used as the dependent variable, and all covariates shown in Table 1, with the exception of estimated glomerular filtration rate (Levey et al., 1999) and chronic kidney disease (derived values), were entered as covariates into the model.

2.4. Propensity score matching

A propensity score matching technique was utilized to balance available baseline covariates. Although propensity scores are often used to match baseline characteristics between two treatment groups in an observational study, the method can also be used to match baseline characteristics between two groups of patients based on comorbidities or other characteristics such as age or race (Ahmed, 2008; Ahmed et al., 2006a,b; Ahmed et al., 2007a,b). Using an SPSS macro and a greedy matching protocol, each patient ≥ 65 years of age was matched with a younger patient based on propensity score (Levesque, 2005). Overall we matched 2381 (59%) patients ≥ 65 years with 2381 younger patients who had similar propensity scores. The unique aspect of assembling a risk-adjusted well-balanced study cohort using propensity matching is that it can be done without access to outcomes data, thus simulating one key feature of a randomized clinical trial, and therefore adding transparency to study design. However, unlike a randomized clinical trial, this process may or may not balance unmeasured covariates.

2.5. Quantification of bias reduction: standardized differences

To assess the balance between groups achieved through propensity score matching, absolute standardized differences were calculated for each variable. The acceptable level of balance is taken to be a standardized difference under 10% (Ahmed et al., 2006a,b; Normand et al., 2001).

2.6. Statistical Analysis

To compare baseline characteristics between the older and younger age groups we used Pearson Chi square and Wilcoxon rank-sum tests for the pre-matched population and McNemar's test and paired sample t-test for the matched population as appropriate. Kaplan-Meier survival analysis and matched Cox proportional hazard analysis were used to determine the association between age and various outcomes. Log-minus-log scale survival plots were used to check proportional hazards assumptions. We conducted subgroup analyses and tested for interactions to examine if there was any heterogeneity in the association between age and mortality. All statistical tests were evaluated using two-tailed 95% confidence levels, and a $p < 0.05$ was required for significance. SPSS for Windows (Version 14) was used for all data analysis (SPSS, 2006).

3. Results

3.1. Patient characteristics

Overall, 23% of patients in the matched study population were female, 14% were non-white, and the mean ages of the two groups were 71 (± 5.0) years and 56 (± 7.0) years. Baseline characteristics for both age groups before and after matching for are displayed in Table 1. Before matching, patients age ≥ 65 years ($n=4036$) were more likely than younger patients ($n=3752$) to be female, white and have ischemic heart disease, hypertension, cardiomegaly, pulmonary rles, higher serum creatinine and be receiving diuretics. The mean ages ($\pm$ SD) of the older and younger groups were 72 (± 5.4) years and 55 (± 7.9) years, respectively. Interestingly, the duration of HF was similar in young and older patients. After matching, patients were balanced on all measured covariates (Table 1). Absolute standard differences between age groups were $< 5\%$ for all measured covariates after propensity score matching (Figure 1), indicating a substantial reduction of bias (Ahmed et al., 2006a,b; Normand et al., 2001).

3.2. Association of age and mortality

Overall, 1565 (33%) of the 4762 propensity-matched patients died during a median follow-up of 38 months; 1223 of these mortalities were attributed to cardiovascular causes and 516 to worsening HF. All-cause mortality occurred in 877 patients age ≥ 65 years versus 688 younger patients during 6904 and 7125 total years of follow-up, respectively. Mortality rates for older and younger patients were, respectively, 1270 and 966 per 10,000 person-years of follow-up (hazard ratio (HR) = 1.26, 95% confidence interval (CI) = 1.12–1.41, $p < 0.0001$; Table 2). Older patients, when compared with propensity-matched younger patients, also had significantly increased mortality rates due to cardiovascular causes (HR = 1.14; 95% CI = 1.00–1.30; $p = 0.044$; Table 2) and worsening HF causes (HR = 1.32; 95% CI = 1.07–1.62; $p = 0.009$; Table 2). Kaplan-Meier survival curves for all-cause, cardiovascular, and HF mortality are displayed in Figure 2.

3.3. Age and hospitalization

Overall, 3106 patients had hospitalizations due to all causes, including 2421 due to cardiovascular causes and 1379 due to worsening HF. All-cause hospitalization occurred in 1611 patients age ≥ 65 years compared with 1495 younger patients during 3991 and 4307 years

of follow-up, respectively. Rates for all-cause hospitalization per 10,000 person-years were 3471 for younger patients and 4036 for older patients (HR = 1.08; 95% CI = 0.99–1.18; $p = 0.084$; Table 3). There was no significant association between age and hospitalization due to cardiovascular causes. Rates of HF hospitalization per 10,000 person-years were 1058 and 1248 respectively for younger and older patients (HR = 1.14; 95% CI = 1.01–1.28; $p = 0.041$; Table 3). Kaplan-Meier survival curves for all-cause, cardiovascular, and HF hospitalizations are shown in Figure 3.

3.4. Subgroup analyses

The effects of age on mortality were also evident across various subgroups of patients, as shown in Figure 4. There were no significant interactions between older age and any of the subgroups except for diabetes (P for interaction = 0.011).

4. Discussion

4.1. Key study findings

Findings from this study indicate that among ambulatory chronic HF patients, compared to patients younger than 65 years, those ≥ 65 years were more likely to die from all causes, cardiovascular causes and progressive HF, but not more likely to be hospitalized for all causes or cardiovascular causes. Older age was associated with hospitalization due to worsening HF. The findings are interesting as they demonstrate the independent effect of age on the association of older age with mortality and hospitalization. These results are important as most HF patients are ≥ 65 years and HF is the number one reason for hospital admission for population ≥ 65 years (Rosamond et al., 2007). Further, it has been projected that the prevalence of HF may double over the next several decades as the baby-boomer generation ages.

4.2. Explanation of study findings

The association of age with increased mortality is not surprising as aging is associated with increased morbidities and functional decline (Sager and Rudberg, 1998; Wolinsky et al., 1993; Yancik et al., 2007). This is reflected by stronger associations of age with unadjusted mortality (Table 2). However, after matching when all measured baseline characteristics were balanced, these associations became weaker, but remained significant, suggesting an independent association of age with mortality in chronic HF. However, the association of age with mortality was not apparent until after the first 2 years of follow-up (Figure 2). On the other hand, in the case of hospitalization, significant unadjusted associations of age with all-cause and cardiovascular hospitalization became nonsignificant after matching (Table 3). A possible explanation of increased cardiovascular mortality without an associated increase in cardiovascular hospitalization among older adults is that many of these non-HF cardiovascular deaths may be due to lack of symptoms (e.g. silent ischemia) and sudden cardiac deaths (e.g. ventricular arrhythmias), precluding hospital admissions. Older adults are also known to underestimate symptoms, attributing them to aging, and also wishing to avoid emergency room visits and hospital admissions due to long waiting times and prior experience of confusion and delirium (Rothschild et al., 2000). However, that paradigm may not be totally applicable to older adults with symptoms of HF.

In the matched cohort, the association of age with HF hospitalization became weaker but retained a significant independent association. These findings suggest that, although older adults with chronic HF may be less likely to be hospitalized due to other cardiovascular causes, they are more likely to respond to their HF symptoms. This may be due to the fact that unlike other cardiovascular symptoms, such as chest pain, which may be mild or absent in older adults with myocardial ischemia, symptoms of HF, such as shortness of breath or fatigue, are almost never silent.

4.3. Clinical and public health implications

What are the implications for this apparent disconnect between mortality and hospitalizations among elderly HF patients? The results of our study suggest that in older adults with chronic HF, hospitalizations are largely driven by comorbidities and severity of disease and, to a smaller extent, due to aging. Further, our data suggest that older adults may be more likely to ignore non-HF cardiovascular symptoms such as chest pain or palpitation and non-cardiovascular symptoms, but may be more responsive to HF symptoms. HF is the leading cause of hospitalization among older adults (Rosamond et al., 2007) and doubling of the HF population in the coming decades will likely further increase the burden on the health care delivery system. The findings of the current analysis underscore the need for proper outpatient management of older adults with chronic HF in a timely manner. Appropriate patient and family/caregiver education including recognition and treatment of precipitating factors will likely help avoid unnecessary hospitalizations as well as improve quality of life (Sui et al., 2007). An alternate approach might be to improve symptom recognition in outpatient settings and increase appropriate utilization of hospice and palliative care services.

4.4. Literature comparison

Our finding of increased mortality among older HF patients compared with younger patients is consistent with previous studies that show an association between age and HF outcomes (Cowie et al., 2002; Pocock et al., 2006; Roger et al., 2004). These studies have identified age as a predictor for mortality in multivariable regression-based risk adjustment models used for other predictors. However, none of these studies have compared mortality and hospitalization rates between propensity-matched older and younger HF patients.

4.5. Limitations

Although propensity score matching is a powerful technique to provide balance in all measured covariates, it is possible that unmeasured covariates may not be completely balanced. However, for an unmeasured covariate to significantly impact our findings, it must be strongly associated with age and the outcomes, but not be strongly associated with any of the many measured baseline covariates included in the DIG trial.

4.6. Conclusion

In a propensity-matched population of HF patients who were well balanced in all measured covariates, older age was independently associated with increased mortality but not with increased hospitalization except for those due to worsening HF.

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Figure 1.

Love plots for absolute standardized differences before and after propensity score matching comparing covariate values for patients age <65 years and age ≥65 years.

Figure 2a

Number of patients at risk					
Age<65	2381	2137	1921	1341	554
Age≥65	2381	2103	1859	1289	476

Figure 2b

Number of patients at risk					
Age<65	2381	2137	1921	1341	554
Age≥65	2379	2103	1859	1289	476

Figure 2c

Number of patients at risk					
Age<65	2379	2137	1921	1341	554
Age≥65	2367	2103	1859	1289	476

Figure 2.
Kaplan-Meier plots for mortality due to (a) all-causes, (b) cardiovascular causes, and (c) worsening heart failure

Figure 3a **Figure 3b** **Figure 3c**

Figure 3. Kaplan-Meier plots for hospitalization due to (a) all-causes, (b) cardiovascular causes, and (c) worsening heart failure
(Kaplan-Meier plots do not account for matching within the data, but HR estimates are calculated based on matched pairs)

Figure 4. Association of age ≥ 65 years and all-cause mortality in subgroups of propensity score matched heart failure patients (middle p values are for interaction).

Table 1
Baseline patient characteristics, by age, before and after propensity score matching

Variable	Before matching			After matching		
	Age <65 (n = 3752)	Age ≥65 (n = 4036)	p Value	Age <65 (n = 2381)	Age ≥65 (n = 2381)	p Value
N (%) or mean (±S.D.)						
Female	800 (21%)	1126 (28%)	<0.0001	556 (23%)	536 (23%)	0.507
Non-white	679 (18%)	449 (11%)	<0.0001	325 (14%)	331 (14%)	0.828
Body mass index, (kg/m ²)	26 ± 6	26 ± 5	<0.0001	27 ± 5	27 ± 5	0.742
Duration of HF (months)	30 ± 35.7	29.5 ± 37.1	0.025	30 ± 36	30 ± 38	0.724
Primary cause of HF						
Ischemic	2439 (65%)	2921 (72%)		1683 (71%)	1665 (70%)	
Hypertensive	343 (9%)	462 (11%)		231 (9%)	258 (11%)	
Idiopathic	662 (18%)	449 (11%)	<0.0001	333 (14%)	321 (14%)	0.102
Others	308 (8%)	204 (5%)		152 (6%)	137 (6%)	
Prior myocardial infarction	2283 (61%)	2625 (65%)	<0.0001	1541 (65%)	1568 (66%)	0.430
Current angina pectoris	968 (26%)	1147 (28%)	0.010	649 (27%)	657 (28%)	0.820
Hypertension	1689 (45%)	1985 (49%)	<0.0001	1068 (45%)	1088 (46%)	0.575
Diabetes mellitus	1046 (28%)	1172 (29%)	0.258	678 (29%)	695 (29%)	0.606
Medications						
Pre-trial digoxin use	1662 (44%)	1703 (42%)	0.064	1014 (43%)	994 (42%)	0.581
Trial use of digoxin	1885 (50%)	2004 (50%)	0.618	1174 (49%)	1198 (50%)	0.506
Angiotensin converting enzyme inhibitors	3539 (94%)	3735 (93%)	0.002	2229 (94%)	2228 (94%)	1.000
Hydralazine and nitrates	53 (1%)	58 (1%)	1.000	30 (1%)	33 (1%)	0.798
Diuretics	2805 (75%)	3271 (81%)	<0.0001	1857 (78%)	1830 (77%)	0.359
Potassium-sparing diuretics	297 (8%)	299 (7%)	0.418	174 (7%)	188 (8%)	0.472
Potassium supplement	1019 (27%)	1180 (29%)	0.044	685 (29%)	664 (28%)	0.513
Symptoms and signs of HF						
Dyspnea at rest	832 (22%)	873 (22%)	.565	515 (22%)	514 (22%)	1.000
Dyspnea on exertion	2763 (74%)	3099 (77%)	0.001	1785 (75%)	1797 (76%)	0.710
Jugular venous distension	459 (12%)	561 (14%)	0.031	293 (12%)	305 (13%)	0.631
Third heart sound	920 (25%)	926 (23%)	0.104	573 (24%)	544 (23%)	0.342
Pulmonary rales	489 (13%)	812 (20%)	<0.0001	372 (16%)	384 (16%)	0.650

Variable	Before matching			After matching		
	Age <65 (n = 3752)	Age ≥65 (n = 4036)	p Value	Age <65 (n = 2381)	Age ≥65 (n = 2381)	p Value
Lower extremity edema	740 (20%)	893 (22%)	0.010	479 (20%)	495 (21%)	0.586
Number of symptom/signs	5.4 ± 2.1	5.5 ± 2.0	0.060	5.4 ± 2.1	5.4 ± 2.0	0.714
New York Heart Association functional class						
Class I	587 (16%)	516 (13%)		343 (14%)	328 (14%)	
Class II	2093 (56%)	2151 (53%)		1309 (55%)	1348 (57%)	
Class III	1011 (27%)	1276 (32%)	<0.0001	681 (29%)	665 (28%)	0.489
Class IV	61 (2%)	93 (2%)		48 (2%)	40 (2%)	
Heart rate (/minute),	79 ± 13	77 ± 12	<0.0001	78 ± 12	78 ± 12	0.338
Blood pressure (mm Hg)						
Systolic	125 ± 20	130 ± 21	<0.0001	127 ± 21	127 ± 19	0.889
Diastolic	76 ± 11	74 ± 11	<0.0001	75 ± 11	75 ± 11	0.611
Chest radiograph findings						
Pulmonary congestion	492 (13%)	617 (15%)	0.006	324 (14%)	329 (14%)	0.866
Cardiothoracic ratio >0.5	2154 (57%)	2536 (63%)	<0.0001	1408 (59%)	1392 (59%)	0.661
Serum creatinine (mg/dL)	1.20 ± 0.32	1.36 ± 0.40	<0.0001	1.25 ± 0.36	1.26 ± 0.32	0.277
Serum potassium (mEq/L)	4.3 ± 0.4	4.4 ± 0.4	<0.0001	4.3 ± 0.4	4.3 ± 0.4	0.265
Ejection fraction (%)	31 ± 12	33 ± 13	<0.0001	31 ± 12	32 ± 13	0.370

Table 2
Mortality by causes in heart failure patients before and after matching by propensity scores for age ≥ 65 years.

	Rate, per 10,000 person-years (Events/total follow-up years)		Absolute rate difference (per 10,000 person-years)	Hazard ratio [†] (95% confidence interval)	P value
	Age <65	Age ≥ 65			
Pre-match					
All-cause	(N=3752) 901 (1030/11430)	(N=4036) 1377 (1576/11443)	+ 476	1.53 (1.41–1.66)	<0.0001
Cardiovascular	741 (847/11430)	1053 (1205/11443)	+ 312	1.42 (1.30–1.55)	<0.0001
Progressive heart failure	293 (335/11430)	500 (572/11443)	+ 207	1.71 (1.50–1.96)	<0.0001
Post-match					
All-cause	(N=2381) 966 (688/7125)	(N=2381) 1270 (877/6904)	+ 305	1.26 (1.12–1.41)	<0.0001
Cardiovascular	786 (560/7125)	960 (663/6904)	+ 174	1.14 (1.00–1.30)	0.044
Progressive heart failure	305 (217/7125)	433 (299/6904)	+ 129	1.32 (1.07–1.62)	0.009

* Absolute differences in rates of events per 10,000 person-year of follow-up were calculated by subtracting the event rates in the age <65 years group from the event rates in the age ≥ 65 group (before values were rounded).

[†] Hazard ratios and confidence intervals (CI) were estimated from matched Cox proportional hazards models

Table 3
Hospitalizations[†] by causes in heart failure patients before and after matching by propensity scores for age ≥65 years.

	Rate, per 10,000 person-years (Events/total follow-up years)		Absolute rate difference (per 10,000 person-years)	Hazard ratio [‡] (95% confidence interval)	P value
	Age <65	Age ≥65			
Pre-match					
All-cause	(N=3752) 3378 (2333/6906)	(N=4036) 4293 (2795/6510)	+ 915	1.23 (1.17–1.30)	<0.0001
Cardiovascular	2346 (1873/7983)	2705 (2137/7899)	+ 359	1.13 (1.06–1.20)	<0.0001
Worsening heart failure	1033 (1014/9819)	1321 (1273/9634)	+ 289	1.25 (1.15–1.30)	<0.0001
Post-match					
All-cause	(N=2381) 3471 (1495/4307)	(N=2381) 4036 (1611/3991)	+ 565	1.08 (0.99–1.18)	0.084
Cardiovascular	2399 (1197/4989)	2531 (1224/4836)	+ 132	1.03 (0.93–1.13)	0.622
Worsening heart failure	1058 (650/6146)	1248 (729/5842)	+ 190	1.14 (1.01–1.28)	0.041
Number of total hospitalizations	4388	4763	+ 375		

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

^{*} Absolute differences in rates of events per 10,000 person-year of follow-up were calculated by subtracting the event rates in the age ≥65 years group from the event rates in the age >65 years group (before values were rounded).

[‡] Hazard ratios and confidence intervals (CI) were estimated from matched Cox proportional hazards models