Characterization of Hemodynamically Stable Acute Heart Failure Patients requiring Critical Care Unit Admissions

by

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Abstract

Background: It remains unclear which patients with acute heart failure (AHF) may benefit from critical care unit (CCU) versus regular ward-based care when they are admitted to hospital. The purpose of this study was to evaluate the clinical predictors of adverse clinical outcomes and the need for CCU specific therapies in patients with AHF.

Methods and Results: Using data from the ASCEND-HF trial, patients with AHF who did not require critical care related therapies within the preceding 12 hours of randomization were selected. The primary outcome was an in-hospital composite of the requirement of CCU specific therapies, and adverse clinical events (death, myocardial infarction, cardiogenic shock, resuscitated sudden cardiac death, or ventricular arrhythmias requiring intervention). A logistic regression model was developed to identify predictive variables; model discrimination and calibration were evaluated using the c-index and the Hosmer-Lemeshow tests, respectively. The study cohort included 4767 patients and the primary composite outcome occurred in 545 (11.4%) patients including 713 (15.4%) CCU specific therapies and 176 (3.7%) adverse clinical events. A total of 7 variables were predictors of the primary composite outcome: body mass index, chronic respiratory disease, respiratory rate, resting dyspnea, hemoglobin, sodium, and blood urea nitrogen. The simplified clinical prediction model demonstrated modest discrimination (c-index= 0.633) and good calibration (Hosmer-Lemeshow p=0.823).

Conclusions: In a large, international trial of AHF, we identified clinical variables that identify patients who are likely to need a CCU. These findings may provide a more efficient means of triaging patients with AHF.

Preface:

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Abbreviations: PCI: Percutaneous Coronary Intervention, CABG: Coronary artery bypass grafting, NYHA: New York Heart Association (NYHA) Functional Classification, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ACE: angiotensin-converting-enzyme inhibitor, ARB: angiotensin receptor blocker

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Introduction

Heart failure is a leading cause of hospitalization with an approximate 1.1 million annual admissions in the United States alone.[1-4] In contrast to acute coronary syndrome where there are guidelines for critical care units (CCU) admissions, few studies have examined the need for CCU in acute heart failure.[5, 6] This poor understanding is underscored by the substantial hospital variability in the proportion of patients admitted to a CCU versus a non-CCU location. A reported 19 to 51% of European and 0 to 88% of American patients hospitalized with HF are admitted to critical care units. [1, 3, 7-9] In addition, up to 74% of patients with AHF admitted to CCUs do not receive critical care therapies, such as mechanical ventilation or intravenous vasoactive infusions.[10] Given that CCU beds account for 5-10% of all hospital beds and up to 35% of hospital costs in North America, identifying patients who will require a higher level of care at the time of emergency department (ED) triage may help reduce avoidable CCU admissions and reduce health care costs.[11, 12]

Previous studies have described the risk factors associated with early in-hospital mortality among patients with AHF evaluated in the ED. [13] However, little is known about which patients admitted to hospital with acute heart failure (AHF), who do not immediately require critical care therapies, are at risk for in-hospital major adverse cardiovascular events and could potentially benefit from an admission to a higher intensity unit. The purpose of this study was to evaluate the clinical predictors of adverse clinical outcomes or the need for CCU specific therapies in patients with AHF and to develop a simplified clinical prediction model to identify patients AHF who at risk for requiring CCU care.

Methods

Data Sources

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial's methods and results have been described previously ClinicalTrials.gov number NCT00475852 [14]. In summary, it was a randomized, international placebo-controlled trial that compared nesiritide vs. placebo in 7141 patients hospitalized with AHF in between May 2007 and August 2010. The study enrolled patients who were hospitalized with AHF within 24 hours or diagnosed with AHF within 48 hours after being hospitalized for another reason. Key relevant exclusion criteria included uncontrolled hypertension, at high risk for hypotension (systolic blood pressure < 100 mm Hg or <110 mm Hg with intravenous vasodilators), dobutamine ≥ 5μg/kg/min, recent or anticipated inotropic therapy, acute coronary syndrome as a primary diagnosis, and renal replacement therapy. There was no specific requirement for a patient to be admitted to a specific type of hospital unit (e.g. telemetry, CCU) and decisions for hospital unit were at the discretion of the admitting physician. A total of 398 sites in 30 countries enrolled patients into ASCEND-HF.

Written informed consent was provided by all study patients and the ethics review board approved the trial at each site.

Study Population

The ASCEND-HF study population was used as the derivation cohort. In order to mitigate any potential acuity biases, patients requiring the following critical care restricted therapies within 12 hours of randomization were excluded: intravenous vasopressors (dopamine, vasopressin, epinephrine, norepinephrine, phenylephrine), intravenous vasodilators (nitroprusside,

nitroglycerine), intra-aortic balloon pump, mechanical ventilation, non-invasive ventilation (CPAP/BiPAP), pulmonary artery catheter or mechanical circulatory support device (Appendix 1). Only sites with study participants admitted to both CCU and ward units were included in the analysis in order to minimize the risk of critical care restricted treatment biases at sites without an onsite CCU.[15]

Outcomes

The primary outcome of interest was the composite of any in-hospital death, myocardial infarction, resuscitated cardiac death, ventricular tachycardia or fibrillation, cardiogenic shock, or the provision of post-randomization critical care therapies (intra-aortic balloon pump, mechanical ventilation, non-invasive ventilation, mechanical circulatory support device, intravenous vasopressors (epinephrine, norepinephrine, phenylephrine, dopamine, vasopressin) or intravenous vasodilator (nitroglycerine, nitroprusside).

Notably, admission to a CCU during the index hospital stay was <u>not</u> considered an endpoint in the prediction model due to variability in center specific CCU admission practices and that some study sites may have mandated CCU admission while patients were on nesiritide. In a sensitivity analysis, model performance in placebo and the nesiritide treated patients was examined.

Statistical Methods

Continuous variables are presented as median (25th, 75th percentile) and categorical variables are presented as number of patients and row percentage. Select patient characteristics acquired at baseline were presented for the full study cohort and according to occurrence of the primary

composite endpoint; differences between these groups were tested using the Wilcoxon rank sum test and chi-square test, respectively.

The full prediction model for the primary composite endpoint included all of the variables presented in Table 1, ranging from patient demographics to baseline laboratory values. Exceptions to this included race, country, and variables with more than 10% missing data. For those variables with less than 10% missing data, multiple imputation was used. The linearity assumption with the primary composite endpoint was evaluated in continuous variables; if it was not satisfied, restricted cubic splines were applied to assist in choosing the appropriate transformation. Second, the final logistic regression model was determined with the application of stepwise variable selection (entry: $p<0.01$; stay: $p<0.01$). Associations between the covariates and the endpoint are reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The performance of the final model was evaluated for model fit (i.e., Hosmer-Lemeshow Goodness-of-Fit test) and discriminatory power (i.e., c-index). Using Bootstrapping (200 times), internal validation of the final model was assessed by estimating the optimism of the c-index (Harrell macro), and the adjusted c-index was reported.

A simple risk score was then generated from the final model for the primary composite endpoint. Continuous variables were transformed to categorical variables, and the model was then re-run to generate corresponding beta estimates, which were then multiplied by a factor of 10 and the closest whole integer was selected; modifications were made according to sample distribution and clinical reasoning. The fit and discriminatory power for the simple risk score are reported. Based on this simple risk score, a nomogram was constructed.

All statistical tests are two-sided with a significance level of 0.05. All analyses were performed using SAS (version 9.4; SAS Institute, Inc, Cary, NC).

Results

Between May 2007 and August 2010 the ASCEND-HF enrolled 7141 patients with AHF. After excluding patients requiring critical care restricted therapies and interventions within 12 hours of randomization and patients admitted to sites without CCU admissions, the final study cohort included 4767 patients (Appendix 1). A total of 545 (11.4%) patients developed in-hospital adverse clinical event as follows (adverse events are not mutually exclusive): all-cause death (1.9%), myocardial infarction (0.2%), resuscitated sudden cardiac death (0.3%), ventricular arrhythmias (0.9%), cardiogenic shock (0.4%), intra-aortic balloon pump (0.4%), mechanical ventilation (2.7%), non-invasive mechanical ventilation (3.6 %), vasopressors (5.7%) or vasodilators (3.0%).

The baseline characteristics of patients with AHF with and without in-hospital critical care adverse clinical events or therapies are presented in Table 1. Patients with adverse clinical events of interest were more frequently Asian, had chronic respiratory disease, prior New York Heart Association Class II-IV, higher heart rate, lower blood pressure, higher respiratory rate, and dyspnea at rest. Among patients with available laboratory results, median hemoglobin, white blood cell, creatinine, blood urea nitrogen, liver function tests, troponin, and natriuretic peptide levels were higher in patients with the adverse clinical events of interest, while sodium and albumin levels were lower. Patients were well balanced by left ventricular ejection fraction

in both cohorts. The characteristics of patients admitted to CCU and ward environments have been previously described.[15]

Predictors of in-hospital outcomes or critical care restricted therapies

A total of 7 variables were independent predictors of the primary composite outcome and are presented in Table 2. Body mass index, chronic respiratory disease, respiratory rate, dyspnea at rest, hemoglobin, and blood urea nitrogen all were positively associated with the composite adverse clinical events, whereas, serum sodium levels demonstrated a U-shaped association. The model showed modest discrimination (c-index=0.633) and good calibration (Hosmer-Lemeshow Goodness-of-Fit=4.365 p=0.8228). A sensitivity analysis forcing nesiritide or placebo into the regression model showed no impact on study outcomes or on model performance. Bootstrapping was used to internally validate the clinical predictors of adverse clinical events. The results demonstrated minimal over optimism (c-index=0.626).

Risk Nomogram

The clinical, physical exam, and laboratory independent predictors of in-hospital adverse clinical event or critical care restricted therapies were used to create a simplified risk nomogram (Figure 1a). An elevated risk score was associated with a rise in the predicted risk of the adverse clinical event (Figure 1b).

Discussion

In a large international cohort of patients hospitalized with AHF examining the need for CCU care, we identified three main findings. First, using an objective set of clinical and critical care restricted therapeutic endpoints, only 11.4% of hemodynamically stable patients with AHF

would potentially require a CCU admission during their hospitalization. Second, 7 clinical variables were identified as independent predictors of in-hospital major adverse cardiovascular events or the provisions of critical care related therapies. Thirdly, we derived and internally validated a clinical prediction score with modest discrimination and excellent calibration that may help identify patients who may be best cared for in a CCU environment at the time of hospitalization.

A wide variability in the CCU admission rate for patients hospitalized with AHF has been reported in the United States, Europe, and Canada.[1, 3, 7-9] Although it has been hypothesized that remuneration, hospital volumes, and/or physician familiarity may underpin the disparity, the percentage of hemodynamically stable patients with AHF who are at high risk of clinical deterioration and may require higher level of monitoring at the time of hospital admission has not been previously described.[16] Using an objective set of clinical and critical care endpoints, we observed that only 11% of patients with AHF ultimately required CCU level of care and could potentially benefit from higher level of care at the time of hospitalization. Recognizing that some institutions admit up to 88% of AHF to CCU, our results suggest that many institutions may be systematically over-admitting patients with AHF to CCUs or physicians may be over-estimating the risk of significant hemodynamic deterioration. We acknowledge that our results require external validation, but our results could serve as a potential external benchmark in efforts aimed at reducing avoidable – and costlier – CCU admissions.

In this analysis, among the clinical and laboratory triage variables identified as independently associated with the composite of major clinical and critical care restricted therapeutic endpoints, chronic respiratory disease, higher respiratory rates, dyspnea, elevated blood urea nitrogen, and dysnatremias have all been previously associated with AHF in-hospital

mortality[17, 18]. Although lower hemoglobin levels have been traditionally associated with higher mortality rate in patients with chronic and AHF population, our study evidence has emerged that erythrocytes in heart failure is associated with mortality.[19, 20] Studies have showed that elevated hematocrit levels in heart failure can increase blood viscosity and peripheral vascular resistance through increased NO scavenging.[21] We observed that high hemoglobin levels were positively associated with the composite outcome and we hypothesize that erythrocytosis may portent a state of high systemic vascular resistance associated with potential clinical decompensation. Further research is required to further elucidate the pathophysiologic and hemodynamic links and to understand whether erythrocytosis is a risk marker or treatment target in this population.

The wide reported disparity in CCU admission rates coupled with the low use of critical care restricted therapies in patients hospitalized with AHF suggest opportunities the employ evidence-based strategies to reduce AHF CCU admissions. Despite its modest discrimination, the point of care clinical prediction model may help physicians identify the minority patients with AHF at high risk of clinical or hemodynamic deterioration who may benefit from admission to a higher acuity CCU. A universal definition of high risk for this this composite outcome in this patient population is lacking, thus the clinical application of this risk model are subject are somewhat arbitrary. Notwithstanding, if one were to consider a 10% threshold as high risk, our prediction score would suggest that all patients with a score of 11 point or greater should be admitted to a CCU at the time of hospital admission. We acknowledge however, that identifying the optimal risk thresholds along with their cost and resource utilization implications – on both an institutional and national scale - merits further investigation. Future studies should be also be directed at refining and externally validating the risk score and evaluation whether implementation can reduce AHF CCU admission rates, critical care capacity strain and

cost savings.

Strengths and Limitations

First, critically ill patients (including patients with hypotension and patients on vasopressors) were excluded from the ASCEND HF trial. These enrollment criteria, however, are potential study strength as we sought to exclude all patients who immediately required CCU level support. Second, randomization time was used as a surrogate for time of hospital admission; however the median time to randomization in the study cohort was 16.7 hours after admission. Third, we utilized information from a clinical trial which may reduce the generalizability, however, this provides an international snapshot of a variety of health care systems, physician practices, patient preferences and heterogeneity seen in clinical practice. Lastly, no information on individual patient goals of care was available in this dataset, although this may play less of a role globally than anticipated.[22]

Conclusions

In an international dataset of hemodynamically stable patients hospitalized with AHF, we found that only a small percentage of patients ultimately require a CCU admission using a composite of major clinical and critical care restricted therapeutic endpoints. We derived and validated a point-of-care clinical predication model that may help identify patients who may benefit from a CCU admission at the time of hospitalization. Collectively, our findings suggest that very few hemodynamically stable patients with ultimately AHF require CCU level of care after admission and our simplified risk nomogram may aid clinicians appropriately triage patients with AHF at the time of hospitalization.

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Appendix 1: Study population flow chart

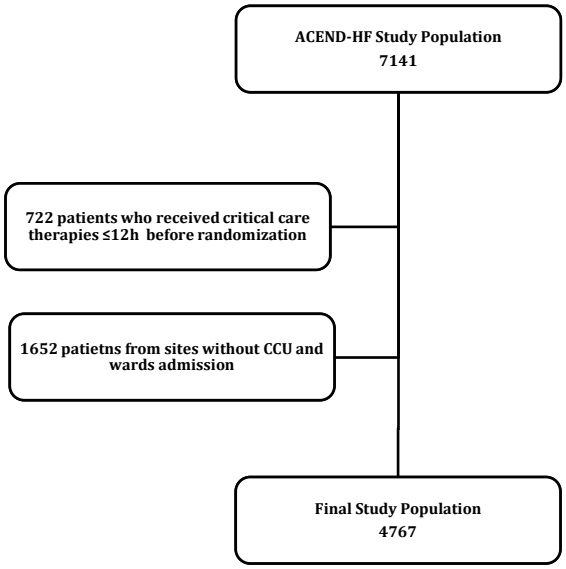

Table 1: Baseline characteristics of patients with acute heart failure with and without the adverse clinical events.

Variable	Adverse Outcomes or Critical Care Therapies		p-value
	No (n=4222)	Yes (n=545)	
Demographics*			
Age, years	66(56-77)	67(56-75)	0.373
Male	2755(65.3)	369(67.7)	0.257
Race			<0.001
Caucasian	2252(53.3)	285(52.3)	
Black/African American	858(20.3)	72(13.2)	
Asian	889(21.1)	168(30.8)	
Other	223(5.3)	20(3.7)	
Region			<0.001
Asia-Pacific	870(20.6)	167(30.6)	
Central Europe	399(9.5)	49(9.0)	
Latin America	299(7.1)	32(5.9)	
North America	2465(58.4)	281(51.6)	
Western Europe	189(4.5)	16(2.9)	
Past Medical History			

Hypertension	3109(73.6)	382(70.1)	0.078
Diabetes	1861(44.1)	256(47.0)	0.201
Coronary artery disease			
Prior myocardial infarction	1405(33.3)	185(33.9)	0.759
Prior Revascularization	1567(37.2)	199(36.5)	0.863
Implantable cardioverter-defibrillator	449(10.6)	47(8.6)	0.148
Atrial fibrillation	1562(37.0)	213(38.9)	0.343
Ventricular fibrillation or tachycardia	416 (9.9)	62(11.3)	0.265
Chronic respiratory disease	730(17.3)	132(24.2)	<0.001
Current smoker	565(13.4)	79(14.5)	0.474
Heart Failure History			
Etiology			0.292
Ischemic	1946(46.1)	248(45.5)	
Non-ischemic	1724(40.8)	237(43.5)	
Unknown	552(13.1)	60(11.0)	
Hospitalization for HF in last year	1708(40.5)	232(42.7)	0.338
NYHA>II[†]	2628(77.1)	394(85.7)	<0.001
Left Ventricular Ejection Fraction	30 (20-37) n(valid)=4785	29.5 (20-39) n(valid)=582	

Presenting features			
Time from hospital arrival to randomization, hours	16.8(5.9-22.3)	16.0(5.6-22.1)	0.078
Dyspnea at rest	2404(56.9)	352(64.7)	<0.001
Paroxysmal nocturnal dyspnea	2601(61.7)	344(63.2)	0.494
Elevated JVP	2452(58.1)	323(59.3)	0.596
Peripheral edema	3206(75.9)	430(78.9)	0.126
Pulmonary edema with rales >1/3 lung	3206(75.9)	430(78.9)	0.126
Weight gain due to fluid retention	2834 (67.3)	382(70.5)	0.140
Body mass index kg/m^2	28.4(24.0-34.4)	28.4(23.9-34.4)	0.105
Presenting vitals			
Heart rate, per minute	80(70-94)	83(73-96)	0.005
Respiratory rate, per minute	23(20-24)	24(22-26)	0.002
Systolic blood pressure, mmHg	123(110-140)	120(110-136)	0.011
Diastolic blood pressure, mmHg	74(66-83)	72(64-80)	0.013
Mean arterial pressure	90(82-101)	89(81-99)	0.005
Body Temperature °C	36.6(36.3-36.9)	36.6(36.3-37)	0.012
Laboratory values at randomization			
Hemoglobin, g/dL (valid n=4441)	12.6(11.2-13.9)	12.8(11.4-14.2)	0.040

White blood cell, x10^9/L(valid n=4389)	7.6(6.1-9.4)	8.3(6.6-10.5)	<0.001
Sodium, mmol/L (valid n=4411)	139(136-141)	138(135-141)	<0.001
Potassium, mmol/L (valid n=4416)	4.0(3.7-4.4)	4.1(3.7-4.5)	0.057
Creatinine, mg/dL (valid n=4488)	1.23(1.00-1.60)	1.30(1.02-1.79)	0.001
BUN, mg/dL (valid n=4395)	24.0(17.0-36.0)	27.0(18.8-45.0)	<0.001
Troponin I, ng/mL (valid n=1983)	0.05(0.03-0.10)	0.06(0.04-0.10)	0.041
Troponin T, ng/mL (valid n=925)	0.02(0.01-0.04)	0.03(0.01-0.08)	0.001
BNP, pg/mL (valid n=1933)	1044(607-1953)	951(571-1730)	0.192
NT-proBNP, pg/mL (valid n=1769)	4535(2186-8804)	5286(2372-11,618)	0.029
AST, U/L (valid n=3138)	28(21-39)	30(22-44)	0.033
ALT, U/L (valid n=3159)	27(18-42)	29(19-46)	0.055
Albumin, g/L (valid n=2849)	36(33-40)	35(32-39)	0.003
Other Investigations			
Chest X-ray with pulmonary edema	2970(70.4)	372(68.3)	0.316
ECG QRS duration, ms (valid n=3648)	106(90-137)	108(92-138)	0.137
Ejection fraction % (valid n=3891)	29(20-37)	30(20-39)	0.430

* Continuous variables expressed as median (interquartile range) and categorical variables expressed as number (%).

† Prior to current hospitalization

Abbreviations: PCI: Percutaneous Coronary Intervention, CABG: Coronary artery bypass grafting, NYHA: New York Heart Association (NYHA) Functional Classification, AST:

Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ACE: angiotensin-converting-enzyme inhibitor, ARB: angiotensin receptor blocker

Table 2: Variables independently predictive of in-hospital outcomes or critical and specific therapies in patients admitted with acute heart failure

Variable	Wald χ^2	Odds Ratio (95% CI)	p value
Body Mass index, per 5 units increase	6.842	1.077 (1.019-1.139)	0.009
Chronic respiratory disease	15.139	1.542 (1.240-1.918)	<0.001
Dyspnea at rest	10.878	1.378 (1.139-1.667)	0.001
Respiratory Rate, per 5/min increase	10.037	1.203 (1.073-1.349)	0.002
Hemoglobin ≥12, per 1 g/L increase	7.064	1.088 (1.022-1.158)	0.008
Blood Urea Nitrogen, per 1 mmol/L increase	42.111	1.013 (1.009-1.016)	<0.001
Sodium<140, per 10 mmol/L decrease	21.950	1.721 (1.372-2.161)	<0.001
Sodium>=140, per 10 mmol/L increase	1.484	1.390 (0.818-2.361)	0.223

Figure Legend:

Figure 1: Simplified risk nomogram to identify acute heart failure patients that require a critical care admission. (A) Simplified nomogram and (B) predicted risk of in-hospital cardiac outcomes or critical are specific therapies.

A)

Background Variables	Score	BMI	Score	Respiratory Rate	Score	Hemoglobin	Score	Sodium	Score	BUN	Score
Chronic Respiratory Disease	4	25-19.9	1	20-29	6	≤ 12	0	<130	9	10-19.9	1
		≥30	2	≥30	10	12.1-13.9	1	130-139	3	20-29.9	1
						14.0-15.9	2	140-144	0	30-39.9	2
				Dyspnea at Rest	3	≥16	5	≥145	4	≥40	9

B)