ONLINE SUPPLEMENT

Title: Late Mortality after Acute Hypoxic Respiratory Failure

Authors: Hallie C. Prescott, MD, MSc; Michael W. Sjoding, MD, MSc; Kenneth M. Langa, MD, PhD; Theodore J. Iwashyna, MD, PhD; Daniel F. McAuley, MD

Supplemental Table 1: Study Definitions

Diagnosis	Definition	Use in Study
Chronic Respiratory Failure	518.83 or 518.84 ICD-9-CM in any diagnosis field.	Exclusion Criteria
Stroke	434.00-434.91 or 436 ICD-9-CM in any diagnosis field.	Exclusion Criteria
Acute Respiratory Failure	518.83 ICD-9-CM in any diagnosis field.	Acute Respiratory Failure Diagnosis
Invasive Mechanical Ventilation	96.70-96.72 ICD-9-CM in any procedural field.	Acute Respiratory Failure Diagnosis
Pneumonia	480.0-480.3; 480.8; 480.9; 481; 482.0 482.1; 482.2; 482.30-482.32; 482.39-482.41; 482.49; 482.81-482.84; 482.89; 482.9; 483.0; 483.1; 483.8; 485; 486; or 487.0 ICD-9-CM in any diagnosis field.	Acute Inciting Event
Aspiration	507.0; 507.1; 507.8 ICD-9-CM in any diagnosis field.	Acute Inciting Event
Non-pulmonary Infection	001.0-005.9; 008.00-018.96; 020.0-027.9; 030.0-041.9; 090.0-092.9; 094.0-104.9; 110.0-118; 320.00-320.99; 322.0-322.9; 324.0-325; 420.0-421.9; 451.0-451.9; 461.0-465.9; 491.21 494 494.0-494.1 510.0-510.9; 513.0-513.1; 540.0-540.9; 541; 542; 562.01; 562.03 562.11; 562.13; 566; 567.0-567.9; 569.5; 569.83; 572.0; 572.1; 575.0; 590.00-590.9; 597.0-597.89; 599.0; 601.0-601.9; 614.0-616.9; 681.00-683; 686.00-686.9; 711.00-711.09; 730.00-730.99; 785.52; 790.7; 995.91; 995.92; 996.60-996.69; 998.51-998.59; 999.3; or 999.31-999.39 ICD-9-CM in any diagnosis field.; OR a sepsis ICD-9-CM in any diagnosis field (038.0-038.9; 785.52; 995.91; or 995.920 and no ICD-9-CM diagnosis code for pneumonia.	Acute Inciting Event
Trauma	An ICD-9-CM diagnosis included in Healthcare Cost and Utilization Project Single-Level Diagnosis Categories 226 “Fracture of Femur”, 227 “Spinal Cord Injury”, 228 “Skull and Face Fracture”, 233 “Intracranial Injury”, 234 “Crushing Injury or Internal Injury”, or 240 “Burns” in any diagnosis field.	Acute Inciting Event
Pancreatitis	577.0 ICD-9-CM in any diagnosis field.	Acute Inciting Event
Congestive Heart Failure	402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93; 428.0-428.9 ICD-9-CM in any diagnosis field.	Matching Variable
COPD/Asthma	493.00; 493.01; 493.02; 493.10; 493.11; 493.12; 493.20; 493.21; 493.22; 493.81; 493.82; 493.90; 493.91; 493.92; 491.0; 491.1; 491.2; 491.20; 491.21; 491.22; 491.8; 491.9; 492.0; 492.8; or 496 ICD-9-CM in any diagnosis field.	Matching Variable

Appendix 1: Validation of Claims-based AHRF definition

We defined AHRF as an ICD-9-CM code for at least one acute inciting event (pneumonia, non-pulmonary infection, aspiration, trauma, or pancreatitis) and an ICD-9-CM code for either acute respiratory failure or invasive mechanical ventilation. We validated this definition in University of Michigan Health System claims adults ≥65 years hospitalized during January 1, 2015 through March 31, 2015 who had at least one acute inciting event and no ICD-9-CM code for either stroke or chronic respiratory failure (1,153 hospitalizations). The clinical standard against which we validated the ICD-9-CM definition was a PaO_2/FIO_2 ratio ≤300 while receiving at least 40% FIO_2. In addition, patient had to receive non-invasive or invasive support for > 12 hours (to exclude routine post-operative ventilation). PaO_2 and FIO_2 were extracted from respiratory flowsheet data in the electronic medical record, including time-stamped recordings of supplemental oxygen (recorded as liters per minute or FIO_2) and respiratory support modality (e.g. nasal cannula, invasive mechanical ventilation). When supplemental oxygen was recorded in liters per minute, conversion to FIO_2 was performed using the following equation: FIO_2=0.21 + 0.03*(flow in L/min). We excluded arterial blood gases with a PaO_2<40 due to concern that the blood gas was venous rather than arterial. FIO_2 and PaO_2 records were aligned to calculate PaO_2/FIO_2 values by carrying forward the most recently recorded FIO_2 value to the time point when the ABG was performed. We report the test characteristics of our definition below.

Table: Comparison of ICD-9-CM identification of AHRF versus PaO2/FIO2<300

	AHRF by ICD-9-CM	No AHRF by ICD-9-CM	Total
PaO_2/FIO_2<300	79	86	165
No PaO_2/FIO_2<300	18	970	988
Total	97	1,056	1,153

Sensitivity: 47.9% (95% CI: 40.1%-55.8%)
Specificity: 98.2% (95% CI: 97.1%-98.9%)
Positive Predictive Value: 81.4% (95% CI: 72.3%-88.6%)
Negative Predictive Value: 91.9% (95% CI: 90.0%-93.4%)

Appendix 2: Methods Supplement on Matching, Proportion of Late Mortality, and Sensitivity Analyses

Matching AHRF to Non-Hospitalized Patients

Because a patient's current age is not available among non-hospitalized adults, we instead matched on age at last HRS survey and number of days since the last HRS survey. We considered adults to be eligible for matching on every 7th day up to 2 years following last HRS survey if he or she was alive and not hospitalized. For the AHRF cohort, we rounded the date of admission for the AHRF hospitalization to the nearest multiple of 7 from last HRS survey. In addition to matching on age at last HRS survey and number of days (rounded to the nearest multiple of 7) since last HRS survey, we also matched on percentile of risk of developing AHRF, total number of hospitalizations in the year prior to index admission (or date of match) and AHRF hospitalizations in the year prior to index admission (or date of match).

Proportion of Late Mortality Attributable to At-Risk Hospitalization versus AHRF

Using the subset of AHRF patients who were matched to both controls, we build a multiple logistic regression model predicting late mortality. To determine the proportion (95% CI) of the odds of late mortality after AHRF that was due hospitalization for acute inciting events, we divided the regression coefficient for at-risk hospitalization by the regression coefficient for AHRF hospitalization[1,2]:

> For Logit (late mortality) = $\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3$,
> where X_1=AHRF, X_2=at-risk, X_3=vector of covariates for age, gender, and risk of AHRF;
> β_0=constant, β_1=regression coefficient for ARHF, β_2=regression coefficient for at-risk, and β_3=vector of regression coefficients for age, gender, and AHRF risk;
> we calculated $\beta_2 \div \beta_1$.

To calculate the proportion (95% CI) of odds of late mortality that is due to the incremental effect of developing AHRF, we calculated $(\beta_1 - \beta_2) \div \beta_1$.

Sensitivity Analyses

First, using the same matched cohorts as the primary analysis, we performed a two-level hierarchical logistic regression in which hospitalizations (and times of non-hospitalization)

were nested within patients[3]. This is an alternate approach to the clustered robust standard errors used in the primary analysis to account for the clustered nature of the data. Second, we examined just first hospitalizations after an HRS survey, adjusting for the nesting of hospitalizations within patients using clustered robust standard errors since patients may still have multiple first hospitalizations (for example, first hospitalizations following both 2008 and 2010 surveys). For this second sensitivity analysis, non-hospitalized adults were required to have no hospitalizations from most recent HRS survey to the date of match. Third, we examined one randomly selected hospitalization (or time of non-hospitalization) per person. For the fourth and fifth sensitivity analyses, we matched AHRF hospitalizations to up to two controls, and up to three controls, respectively, using coarsened exact matching. We did not require each AHRF to have a full two or three matches, as this may increase bias[4]. Rather, the coarsened exact matching required that matches be close—like caliper-based approaches, but with a variable-length caliper[5].

References

1. nlcom — Nonlinear combinations of estimators [Internet]. Available from: http://www.stata.com/manuals13/rnlcom.pdf [accessed 2016 Nov 13].
2. Oehlert GW. A Note on the Delta Method. Am Stat 1992;46(1):27–9.
3. Kreft IGG, Leeuw J de. Introducing multilevel modeling. Sage; 1998.
4. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. Pharmacoepidemiol Drug Saf 2012;21 Suppl 2:69–80.
5. Iacus, Stefano M, Gary King, and Giuseppe Porro. 2009. CEM: Software for Coarsened Exact Matching, Journal of Statistical Software 30. Avaiable at http://j.mp/Te8KP5 (Accessed Jan 31, 2015).

Supplemental Table 2: Covariate Balance between Matched AHRF and Not Currently Hospitalized Cohorts

	AHRF Cohort (N=1,157)	**Not Currently Hospitalized Cohort** (N=1,157)	***p***
Demographics			
Age, years, median (IQR)	79 (72-85)	78 (72-85)	0.22
Male, N (%)	550 (47.5%)	508 (43.9%)	0.08
Race, N (%)			0.34
White/Caucasian	927 (80.1%)	942 (81.4%)	
Black/African American	200 (17.3%)	195 (16.9%)	
Other	30 (2.6%)	20 (1.7%)	
Hispanic, N (%)	98 (8.5%)	107 (9.3%)	0.51
Married or partnered, N (%)	546 (47.2%)	558 (48.2%)	0.62
Economic Status			
Total Wealth			0.92
Quintile 5 positive assets	156 (13.6%)	148 (12.9%)	
Quintile 4 positive assets	171 (14.9%)	174 (15.1%)	
Quintile 3 positive assets	168 (14.6%)	168 (14.6%)	
Quintile 2 positive assets	222 (19.3%)	241 (21.0%)	
Quintile 1 positive assets	298 (25.9%)	294 (25.6%)	
Net negative or zero assets	135 (11.7%)	125 (10.9%)	
Government assistance	107 (9.4%)	99 (8.6%)	0.52
Pre-AHRF Health Status			
Charlson co-morbidity Index, median (IQR)	2 (0-4)	2 (0-3)	0.50
Congestive Heart Failure			
Dementia			
I/ADL limitations, median (IQR)	1 (0-4)	1 (0-5)	0.98
Self-Rating of Health, N (%)			0.14
Excellent	22 (1.9%)	22 (1.9%)	
Very Good	145 (12.5%)	107 (9.3%)	
Good	281 (24.3%)	290 (25.1%)	
Fair	353 (30.5%)	382 (33.0%)	
Poor	356 (30.8%)	356 (30.8%)	
Body Mass Index, N (%)			0.43
Very Severely Obese	50 (4.3%)	44 (3.8%)	
Severely Obese	67 (5.8%)	79 (6.8%)	
Obese	150 (13.0%)	167 (14.4%)	
Overweight	335 (29.0%)	339 (29.3%)	
Normal	448 (38.7%)	445 (38.5%)	
Underweight	84 (7.3%)	69 (6.0%)	
Risk for Developing AHRF	5.7% (3.3%-10.1%)	5.8% (3.4%-10.4%)	0.25
Pre-AHRF Healthcare Use			
Hospitalizations in prior year	1 (0-2)	1 (0-2)	0.08
AHRF in prior year, N (%)	92 (8.0%)	92 (8.0%)	1.00
Residence in a nursing home, N (%)	117 (10.1%)	117 (10.1%)	1.00
Hospitalization Diagnoses			
Risk Factor for Direct AHRF	697 (60.2%)	--	
Pneumonia	519 (44.9%)	--	
Aspiration	208 (18.0%)	--	

Risk Factor for Indirect AHRF	811 (70.1%)	--	
Non-pulmonary infection	758 (65.5%)	--	
Trauma	67 (5.8%)	--	
Pancreatitis	15 (1.3%)	--	

Supplemental Table 3: Covariate Balance between Matched AHRF and At-Risk Hospitalization

	AHRF Cohort (N=1,017)	**At Risk Hospitalization Cohort** (N=1,017)	***p***
Demographics			
Age, years, median (IQR)	78 (72-85)	79 (72-85)	0.88
Male, N (%)	464 (45.6%)	464 (45.6%)	1.00
Race, N (%)			0.56
White/Caucasian	803 (79.0%)	822 (80.8%)	
Black/African American	186 (18.3%)	168 (16.5%)	
Other	28 (2.8%)	27 (2.7%)	
Hispanic, N (%)	84 (8.3%)	72 (7.1%)	0.32
Married or partnered, N (%)	470 (46.2%)	462 (45.4%)	0.72
Economic Status			
Total Wealth			0.14
Quintile 5 positive assets	131 (13.0%)	109 (10.8%)	
Quintile 4 positive assets	152 (15.1%)	125 (12.3%)	
Quintile 3 positive assets	140 (13.9%)	165 (16.3%)	
Quintile 2 positive assets	191 (18.9%)	215 (21.2%)	
Quintile 1 positive assets	276 (27.3%)	284 (28.0%)	
Net negative or zero assets	120 (11.9%)	116 (11.4%)	
Government assistance	103 (10.3%)	101 (10.0%)	0.84
Pre-AHRF Health Status			
Charlson co-morbidity Index, median (IQR)	2 (1-4)	2 (1-4)	0.26
Congestive Heart Failure	323 (31.8%)	353 (34.7%)	0.16
Dementia	70 (6.9%)	84 (8.3%)	0.24
I/ADL limitations, median (IQR)	1 (0-4)	1 (0-5)	0.11
Self-Rating of Health, N (%)			0.45
Excellent	22 (2.2%)	15 (1.5%)	
Very Good	111 (10.9%)	89 (8.8%)	
Good	228 (22.4%)	223 (22.9%)	
Fair	329 (32.4%)	349 (34.3%)	
Poor	325 (32.0%)	330 (32.5%)	
Body Mass Index, N (%)			0.23
Very Severely Obese	48 (4.7%)	35 (3.4%)	
Severely Obese	65 (6.4%)	59 (5.8%)	
Obese	138 (13.6%)	127 (12.5%)	
Overweight	274 (26.9%)	313 (30.8%)	
Normal	405 (39.8%)	411 (40.4%)	
Underweight	69 (6.8%)	62 (6.1%)	
Risk for Developing AHRF	6.3% (3.6%-11.0%)	6.3% (3.6%-11.5%)	0.45
Pre-AHRF Healthcare Use			
Hospitalizations in prior year	1 (0-2)	1 (0-2)	0.34
AHRF in prior year, N (%)	81 (8.0%)	81 (8.0%)	1.00
Residence in a nursing home, N (%)	104 (10.2%)	104 (10.2%)	1.00
Hospitalization Diagnoses			
Risk Factor for Direct AHRF	546 (53.7%)	546 (53.7%)	1.00
Pneumonia	460 (45.2%)	460 (45.2%)	1.00
Aspiration	87 (8.6%)	87 (8.6%)	1.00
Risk Factor for Indirect AHRF	727 (71.5%)	727 (71.5%)	1.00

Non-pulmonary infection	686 (67.5%)	686 (67.5%)	1.00
Trauma	45 (4.4%)	45 (4.4%)	1.00
Pancreatitis	6 (0.6%)	6 (0.6%)	1.00

Supplemental Table 4: Conditional and Unconditional Mortality of Double-Matched Cohorts

	AHRF* (N=952)	At-risk (N=952)	Non-hospitalized (N=952)
Unconditional Mortality, % (95% CI)			
30-Day	41.6% (38.4%-44.8%)	13.1% (11.1%-15.4%)	2.0% (1.2%-3.1%)
90-Day	51.3% (48.0%-54.5%)	21.8% (19.3%-24.6%)	5.0% (3.7%-6.6%)
1-Year	64.0% (60.8%-67.0%)	40.3% (37.2%-43.5%)	16.9% (14.6%-19.4%)
2-Year	71.1% (68.1%-74.0%)	51.4% (48.1%-54.6%)	29.4% (26.5%-32.4%)
Conditional 2-Year Mortality, % (95% CI)			
Conditional on survival to Day 31	50.5% (46.3%-54.8%)	44.0% (40.6%-47.5%)	28.0% (25.1%-31.0%)
Conditional on survival to Day 91	40.7% (36.2%-45.4%)	37.8% (34.2%-41.3%)	25.7% (22.8%-28.6%)
Conditional on survival to Day 366	19.8% (15.7%-24.4%)	18.5% (15.4%-21.9%)	15.0% (12.6%-17.7%)

*This table presents mortality for the 952 AHRF hospitalizations that were matched to both at at-risk hospitalization and a non-hospitalized adult.

Supplemental Table 5: Adjusted Percentage with Mortality by Time Period

Time Period	**AHRF versus Non-Hospitalized**, (Adjusted Percentages[a]) (AHRF 95% CI) (Non-Hosp. 95% CI)	**AHRF versus At-Risk Hospitalization**, (Adjusted Percentages[a]) (AHRF 95% CI) (At Risk 95% CI)
Early Mortality		
0 - 30 day	**42.2% versus 1.8%** (39.5%-45.3%) (0.1%-2.6%)	**42.0% versus 13.2%** (38.9%-45.1%) (11.1%-15.2%)
Late Mortality[b]		
31 day – 2 year	**52.4% versus 28.0%** (48.5%-56.2% (25.3%-30.6%)	**51.5% versus 44.8%** (47.5%-55.5%) (41.4%-48.2%)
Late mortality, by discrete time interval[b]		
31 - 90 day	**17.8% versus 1.8%** (14.8%-20.8%) (0.2%-3.7%)	16.2% versus 10.2%% (13.1%-19.2%) (8.2%-12.3%)
91 - 180 day	**11.9% versus 4.6%** (9.1%-14.7%) (3.4%-5.8%)	11.3% versus 10.1% (8.5%-14.2%) (7.9%-12.3%)
181 day – 1 year	**17.2% versus 8.7%** (7.0%-10.4%) (13.6%-20.8%)	16.0% versus 16.3% (12.5%-19.6%) (13.4%-19.2%)
>1 year – 2 year	**21.0% versus 15.9%** (17.0%-25.0%) (12.6%-17.2%)	22.2% versus 18.4% (17.9%-26.4%) (15.2%-21.5%)

Bolded values are statistically significant, $p<0.05$.

[a]Adjusted for age, gender, and propensity for sepsis. All patients included in the regression were also matched by sepsis propensity, which included age, race, ethnicity, gender, partnership, wealth, use of food stamps, Charlson co-morbidity index, I/ADL limitations, self-rating of health, body mass index, hospitalizations in the prior year, sepsis in the prior year, and residence in a nursing home.

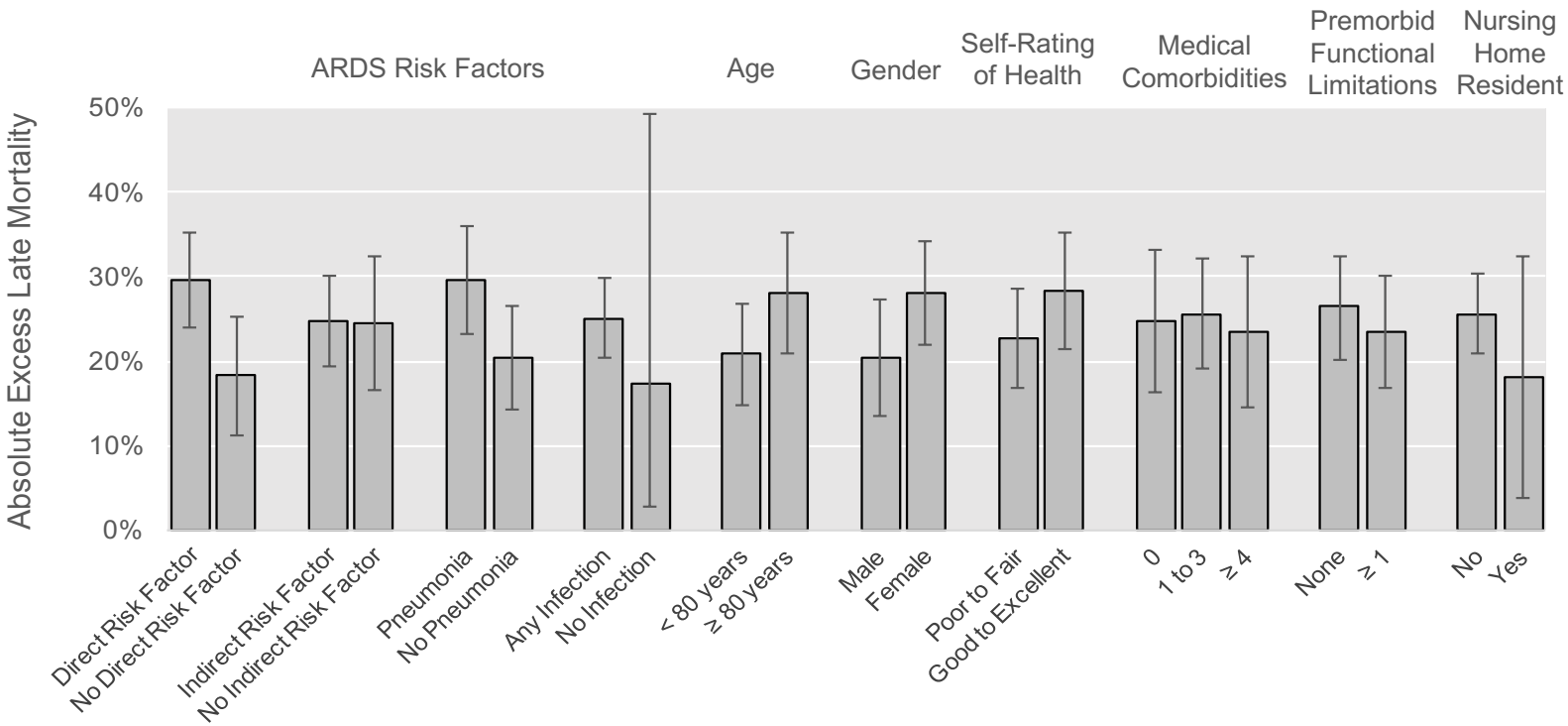
[b]To be included in the models for late mortality, patients had to be alive at the start of the time period.

Supplemental Table 6: Adjusted Odds Ratios for Late Mortality in Primary and Sensitivity Analyses

Analysis	Methodology	Pairs of Matched AHRF to Non-Hospitalized Adults	Adjusted OR for Late Mortality (95% CI)	Pairs of Matched AHRF to "At-risk" Hospitalizations	Adjusted OR for Late Mortality (95% CI)
Principal	All hospitalizations; multivariable logistic regression with robust standard errors	1,157	**3.2** (2.5, 4.0)	1,017	**1.3** (1.1, 1.7)
Sensitivity #1	All hospitalizations; multi-level mixed effects logistic regression with hospitalizations nested within people	1,157	**5.5** (3.7, 8.2)	1,017	**1.7** (2.3, 2.5)
Sensitivity #2	First hospitalizations after HRS survey; multivariable logistic regression with robust standard errors	448	**4.6** (3.2, 6.7)	435	1.4 (1.0, 1.9)
Sensitivity #3	One randomly selected first hospitalization after HRS survey or time of non-hospitalization per person.	407	**5.1** (3.4,7.7)	330	1.3 (0.9, 2.0)
Sensitivity #4	All hospitalizations; 1:2 matching, multivariable logistic regression with robust standard errors	1,157 AHRF; 2,259 Non-Hospitalized Adults	**3.5** (2.5, 4.8)	1,017 AHRF; 1,881 At-Risk Hospitalizations	**1.4** (1.1, 1.7)
Sensitivity #5	All hospitalizations; 1:3 matching, multivariable logistic regression with robust standard errors	1,157 AHRF; 3,321 Non-Hospitalized Adults	**3.4** (2.8, 4.2)	1,017 AHRF; 2,633 At-Risk Hospitalizations	**1.3** (1.1, 1.5)

Bolded values are statistically significant, $p<0.05$.

Supplemental Figure 1: Absolute excess late mortality of AHRF versus non-hospitalized adults, stratified by subgroup.



Supplemental Table 7: Risk for Late Mortality after AHRF, stratified by study time-period.

Early Hospitalizations (1998-2005)		
	AHRF versus Matched Non-Hospitalized Controls N=534 matched pairs	AHRF versus Matched At-Risk Hospitalizations N=489 matched pairs
Adjusted HR for late mortality	2.2 (1.7-2.8)	1.2 (1.0-1.5)
Adjusted probability late mortality after AHRF	47.7% (42.2%, 53.3%)	51.2% (45.0%-57.3%)
Adjusted probability of late mortality in matched control	27.3% (23.5%, 31.0%)	44.4% (39.5%-49.3%)
Late Hospitalizations (2006-2012)		
	AHRF versus Matched Non-Hospitalized Controls N=587 matched pairs	AHRF versus Matched At-Risk Hospitalizations N=508 matched pairs
	2.7 (2.2, 3.4)	1.4 (1.1-1.7)
Adjusted probability late mortality after AHRF	56.3% (50.9%, 61.7%)	57.1% (51.3%-62.9%)
Adjusted probability of late mortality in matched control	27.6% (24.1%, 31.1%)	45.0% (40.4%-49.6%)

Supplemental Table 8: Risk for Late Mortality after AHRF, in patients without AHRF in the prior year

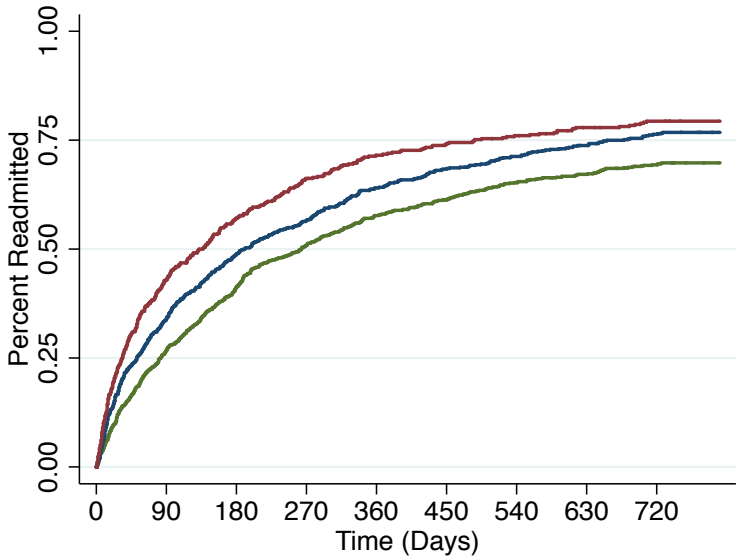
	AHRF versus Not Currently Hospitalized N=1,065 Matched Pairs	AHRF versus At-Risk Hospitalizations N=936 Matched Pairs
Adjusted HR for late mortality	2.6 (2.2, 3.1)	1.3 (1.1-1.5)
Adjusted probability late mortality after AHRF	50.6% (46.9%, 54.4%)	50.0% (45.9%, 54.0%)
Adjusted probability of late mortality in matched cohort	25.6% (23.0%, 28.2%)	42.6% (39.1%, 46.0%)

Supplemental Table 9: Proportion of Patients with a Hospital Readmission

Survivors to 31 days	Non-Hospitalized (N=933)	At-Risk (N=827)	AHRF (N=556)	*p*
Readmitted within 90 days	236 (25.3%)	273 (33.0%)	231 (41.6%)	<0.001
Readmitted within 1year	518 (55.5%)	498 (60.2%)	364 (65.5%)	0.001
Readmitted within 2 year	646 (69.2%)	584 (70.6%)	398 (71.6%)	0.61
Survivors to 2 years	Non-Hospitalized N=672	At-Risk N=364	AHRF N=281	*p*
Readmitted within 90 days	131 (19.5%)	96 (20.7%)	91 (33.1%)	<0.001
Readmitted within 1year	318 (47.3%)	235 (50.8%)	163 (59.3%)	0.004
Readmitted within 2 year	411 (61.2%)	310 (67.0%)	191 (69.5%)	0.02

This analysis examined patients surviving to day 31, and day 31 was considered the starting point for hospital readmissions. Readmissions within 90 days refers to within 90 days of the starting point. We chose to use day 31 as the starting point, rather than discharge day, in order to facilitate comparison to the non-hospitalized cohort.

Supplemental Figure 2: Failure Curve for Hospital Readmissions



Number at risk									
Cohort = Non-hospitalized	933	685	547	456	391	353	313	292	265
Cohort = At Risk	827	508	381	314	252	219	195	176	157
Cohort = AHRF	556	280	200	154	127	116	106	93	84