Published in final edited form as:

Am J Emerg Med. 2015 October ; 33(10): 1483–1488. doi:10.1016/j.ajem.2015.07.033.

Thirty-Day Mortality in Emergency Department Patients With New Onset Atrial Fibrillation and Actively Treated Cancer

Thomas Lardaro, MD, MPH^a, Wesley H. Self, MD, MPH^a, and Tyler W. Barrett, MD, MSCI^a

^aDepartment of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN

Abstract

Objectives—Studies suggest that inflammatory, autonomic and coagulation alterations associated with cancer may increase incident atrial fibrillation (AF). New onset AF is associated with increased mortality in other non-neoplastic disease processes. We investigated the association of active cancer with 30-day mortality in emergency department (ED) patients with new onset AF.

Methods—We conducted an analysis within an observational cohort study at a tertiary care hospital that included ED patients with new onset AF. The exposure variable was presence of active cancer. We defined active cancer as the patient received chemotherapy, radiotherapy, or recent cancer-related surgery within 90 days of the ED visit. The primary outcome was 30-day mortality. Logistic regression was used to analyze the association between cancer status and 30-day mortality adjusting for patient age and sex.

Results—During the 5.5-year study period, 420 patients with new onset AF were included in our cohort, including 37 (8.8%) with active cancer. Patients with active cancer had no clinically relevant differences in their hemodynamic stability. Among the 37 patients with active cancer, 9 (24%) died within 30 days. Of the 383 patients without active cancer, 11 (3%) died within 30 days. After adjusting for age and sex, active cancer was an independent predictor of 30-day mortality, with an adjusted odds ratio of 10.8 (95% confidence interval: 3.8, 31.1).

Corresponding Author Contact Information: Tyler Warren Barrett, MD, MSCI, Vanderbilt University School of Medicine, Department of Emergency Medicine, 703 Oxford House, 1313 21st Ave South, Nashville, TN 37232-4700, Office Phone: 615-936-0253, Fax: 615-936-1316, tyler.barrett@vanderbilt.edu.

Conflicts of Interest/Disclosures: There are no conflicts of interest in connection with this submission or are there any copyright constraints. No industry financial support or compensation has been or will be received for conducting this study. Dr. Barrett serves as a scientific consultant for Red Bull GmbH, Fuschl am See, Salzburg, Austria and Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, Connecticut; and has received research funding from Alere, Boehringer Ingelheim, and Janssen. Dr. Barrett is a member of the American Heart Association's The Guideline Advantage Research Subcommittee and serves on the Editorial Board for *Annals of Emergency Medicine*. Dr. Self is a paid advisor for BioFire Diagnostics, Inc and Venaxis, Inc; and has received research funding from CareFusion, BioMerieux, Affinium Pharmaceuticals, Astute Medical, BRAHMS GmbH, Pfizer, Rapid Pathogen Screening, Venaxis, and BioAegis. Dr. Lardaro has no financial declarations and no potential conflicts of interest.

Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—Among ED patients with new onset AF, active cancer appears to be associated with 11-fold increased odds of 30-day mortality; new-onset AF may represent progressive organ dysfunction leading to an increased risk of short-term mortality in patients with cancer.

Keywords

atrial fibrillation; cancer; epidemiology; prognosis

1. Introduction

In the US, between 3 and 6 million individuals have AF and the prevalence is expected to double by 2050.^{1–3} Among individuals 40 years of age and older, the lifetime risk for developing AF is estimated to be 1 in 4.^{3–5} AF is associated with many adverse sequelae, including heart failure,⁶ a 5-fold increase in the risk of cerebrovascular accident representing an estimated 4 to 13 percent annual risk,^{4,6,7} and a nearly 2-fold increase in mortality.^{6,8,9} AF has been found to occur more frequently in patients with cancer.^{10,11} Studies have suggested that the increased inflammation, autonomic and coagulation alterations associated with cancer may increase patient risk for developing atrial fibrillation (AF).¹⁰ New onset AF is associated with increased mortality in patients with other disease processes such as severe sepsis and chronic kidney disease.^{9,12} Hu et al, using a large Taiwanese population database and ICD-9 code definitions for exposures and outcomes, previously reported that new onset AF did not impact long-term mortality among cancer patients.¹¹ Although AF increases an individual's lifetime risk of death and stroke,^{4,6,7} the 30-day risk following an emergency department (ED) evaluation for AF is relatively low with a combined incidence of 1–3%.^{13–16} We have previously identified several factors that are associated with 30-day adverse events in patients with AF.^{14,15} To our knowledge, no prior study has evaluated whether a pre-existing diagnosis of active cancer is associated with increased short-term mortality among patients diagnosed with new-onset AF. We investigated the association of active cancer with 30-day mortality in ED patients with new onset AF.

2. Methods

We conducted an analysis within an observational cohort study. The cohort combined two databases of patients who presented to our adult ED for evaluation of symptomatic AF. The Risk Estimator Decision aid for Atrial Fibrillation (RED-AF) database was a retrospective cohort of adult ED patients presenting to our center for symptomatic AF or atrial flutter between August 1, 2005 and July 31, 2008.¹⁴ The Atrial fibrillation and flutter outcomes and risk determination (AFFORD) database enrolled a prospective cohort of ED patients with symptomatic AF and atrial flutter from June 8, 2010 to February 28, 2013.¹⁵ The details of both studies have been previously reported.^{14,15,17} The study hospital is an urban, university-affiliated, tertiary care referral center that treats 70,000 adult patients annually. We queried the databases and selected all patients with newly diagnosed AF on their index ED evaluation. The primary exposure variable was presence of active cancer at the time of AF diagnosis in the ED. We documented whether each patient had a history of cancer, active cancer currently undergoing treatment, or no documented cancer. We defined active cancer as the patient having received chemotherapy, radiotherapy, or cancer-related surgery within 90 days of the ED visit when AF was newly diagnosed. The primary outcome was 30-day

mortality obtained through telephone interviews and medical record review. Two investigators (T.L. and T.W.B.) systematically reviewed all records to determine cancer classification with the final classification decided by consensus. The primary outcome was death within 30 days of the index ED presentation. We reviewed medical records and recorded the physician reported cause of death when available. Our hospital's institutional review board reviewed and approved this study.

We calculated descriptive statistics on the baseline characteristics for the cohort stratified by active cancer classification. We analyzed the association between active cancer at the time of new AF diagnosis and 30-day mortality using multivariable logistic regression. We included age and sex as covariates in the regression model. All analyses were done with STATA (StataCorp, College Station, TX).

3. Results

During the 5.5 years of ED evaluations, 420 patients with new onset AF were enrolled, including 37 (9%) with active cancer (Figure A.1). A Table 1 presents the baseline characteristics. Nine of the 37 (24%) patients with active cancer and 11 of the 383 (3%) patients without active cancer died within 30 days of their index ED evaluation. In the multivariable logistic regression model, active cancer (adjusted odds ratio: 10.8; 95% CI: 3.8, 31.1) was significantly associated with 30-day mortality after adjusting for patient age and sex (Table 2). Of the 9 patients with active cancer who died within 30 days, 7 of the deaths were directly related to their cancer. Meanwhile, the majority of deaths in the group without active cancer were attributed to AF-related complications, including stroke and decompensated heart failure. A detailed list of the cause of death for all 20 patients is provided in Table A.1. The median (interquartile range) days until death among the patients with and without active cancer were 17 (12, 23) days and 6 (4, 11) days, respectively. All 20 patients were hospitalized after their index ED visits including 3 patients without active cancer who were admitted to the intensive care unit.

4. Discussion

To our knowledge, this is the first study to investigate whether a pre-existing diagnosis of active cancer is associated with increased 30-day mortality among patients diagnosed with new-onset AF. This investigation found a 11-fold increase in the odds of death within 30-days of a new AF diagnosis among individuals with active cancer compared to those without active cancer. AF is known to have an inflammatory component to its development, similar to other disease states, such as sepsis and post-operative period.^{9,10,18,19} In this study, we found active cancer to be a major risk factor for short term mortality among patients with new-onset AF. We hypothesize that new AF may be an indicator that a patient's cancer has progressed, with increased systemic inflammation triggering the AF. Patients with active cancer had no clinically relevant differences in their hemodynamic stability. A similar percentage of patients with and without active cancer were hospitalized with most admitted to a floor bed. The majority of patients in this cohort had hypertension, nearly 1 in 4 had documented coronary artery disease, and 14% had heart failure at the time of their initial AF

diagnosis. Therefore, these patients had established risk factors for developing AF independent of their cancer status.^{5,18}

Patients with cancer that is being actively treated are clearly at increased risk for developing opportunistic infection related to chemotherapy-induced neutropenia, indwelling central access catheters, and frequent hospital visits.¹⁹ Cancer treatments also have known side effects that might increase an individual's risk of death.²⁰ Patients with active cancer died due to complications of their cancer whereas individuals without active cancer more often died due to AF-related complications. Nearly 1 in 6 of the patients without active cancer had a documented remote history of cancer and may also have been exposed to similar treatments during their lives.

Our conclusions must be interpreted in the context that only 20 patients experienced our primary outcome. Therefore, we could only adjust for a limited number of potential confounders in our multivariable analysis. The study should not be used to prognosticate an individual's 30-day mortality. All of the patients who died within 30 days were hospitalized following their index ED evaluation. There is the potential that hospitalization alone increases the potential mortality for patients with active cancer. This study is an observational cohort analysis and is subject to the inherent limitations of such study designs. There is the potential that patients with an undiagnosed malignancy may have been misclassified as not having active cancer at the time of their AF diagnosis. We did review medical records both at least 90 days prior to and following their ED evaluation to identify any documentation of cancer and related treatment. This study was performed at a single, academic, tertiary care referral center that has a large oncology patient population and our results are limited by the potential selection bias associated with our high acuity patient population. Acknowledging these limitations, our results suggest that new-onset AF may represent progressive organ dysfunction leading to an increased risk of short-term mortality in patients with cancer.

Acknowledgments

Funding Sources: Dr. Barrett and this study are funded by NIH grant K23 HL102069 from the National Heart, Lung and Blood Institute, Bethesda, MD. Dr. Self is supported by NIH grant K23GM110469 from the National Institute of General Medical Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Camm AJ, Lip GY, De Caterina R, et al. Committee for Practice Guidelines. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012; 33:2719–2747. [PubMed: 22922413]
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001; 285:2370–2375. [PubMed: 11343485]
3. Go AS, Mozaffarian D, Roger VL, et al. American Heart Association Statistics, Committee Stroke Statistics, Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014; 129:e28–e292. [PubMed: 24352519]
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991; 22:983–988. [PubMed: 1866765]

5. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004; 110:1042–1046. [PubMed: 15313941]
6. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002; 113:359–364. [PubMed: 12401529]
7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007; 146:857–867. [PubMed: 17577005]
8. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998; 98:946–952. [PubMed: 9737513]
9. Walkey AJ, Wiener RS, Ghobrial JM, et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*. 2011; 306:2248–2254. [PubMed: 22081378]
10. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol*. 2014; 63:945–953. [PubMed: 24361314]
11. Hu YF, Liu CJ, Chang PM, et al. Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. *Int J Cardiol*. 2013; 165:355–357. [PubMed: 22989607]
12. Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. *J Am Soc Nephrol*. 2009; 20:705–711. [PubMed: 19092127]
13. Atzema CL, Austin PC, Chong AS, et al. Factors associated with 90-day death after emergency department discharge for atrial fibrillation. *Ann Emerg Med*. 2013; 61:539–548. e531. [PubMed: 23522608]
14. Barrett TW, Martin AR, Storrow AB, et al. A clinical prediction model to estimate risk for 30-day adverse events in emergency department patients with symptomatic atrial fibrillation. *Ann Emerg Med*. 2011; 57:1–12. [PubMed: 20728962]
15. Barrett TW, Storrow AB, Jenkins CA, et al. The AFFORD Clinical Decision Aid to Identify Emergency Department Patients With Atrial Fibrillation at Low Risk for 30-Day Adverse Events. *Am J Cardiol*. 2015; 115:763–770. [PubMed: 25633190]
16. Scheuermeyer FX, Grafstein E, Stenstrom R, et al. Thirty-day and 1-year outcomes of emergency department patients with atrial fibrillation and no acute underlying medical cause. *Ann Emerg Med*. 2012; 60:755–765. [PubMed: 22738681]
17. Barrett TW, Storrow AB, Jenkins CA, et al. Atrial fibrillation and flutter outcomes and risk determination (AFFORD): design and rationale. *J Cardiol*. 2011; 58:124–130. [PubMed: 21820279]
18. January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014; 64:e1–76. [PubMed: 24685669]
19. Caggiano V, Weiss RV, Rickert TS, et al. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer*. 2005; 103:1916–1924. [PubMed: 15751024]
20. Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*. 2006; 106:2258–2266. [PubMed: 16575919]

Figure A.1.

Study flow diagram

This figure shows the development of the cohort through the merger of the RED-AF and AFFORD databases.

Table 1

Baseline Characteristics of the Cohort (n=420)

Variable	Active Cancer (n=37)	No Active Cancer (n = 383)
Age (years)	67 (62, 78)	64 (52, 76)
Female	7 (19%)	145 (38%)
White, Non Hispanic	32 (87%)	322 (84%)
Black	4 (11%)	53 (14%)
White, Latino or Hispanic	0	3 (1%)
Asian	0	1 (0.3%)
Native American	0	1 (0.3%)
History of Cancer	37 (100%)	63 (16%)
Chemotherapy within 90 days of diagnosis of AF	26 (70%)	0
Radiation therapy within 90 days of diagnosis of AF	9 (24%)	0
Cancer related surgery within 90 days of diagnosis of AF	8 (22%)	0
Type of Cancer		
Bladder	2 (5%)	0
Brain	0	1 (0.3%)
Breast	1 (3%)	7 (2%)
Colorectal	3 (8%)	1 (0.3%)
Gynecologic	1 (3%)	6 (2%)
Liver	1 (3%)	1 (0.3%)
Lung	10 (27%)	3 (1%)
Lymphoma	4 (11%)	4 (1%)
Melanoma	5 (14%)	0
Oropharyngeal	1 (3%)	1 (0.3%)
Pancreas	0	1 (0.3%)
Prostate	3 (8%)	7 (2%)
Skin	0	13 (3%)
Thyroid	0	4 (1%)
Height (meter)	1.8 (1.7, 1.8)	1.8 (1.7, 1.8)
Weight (kg)	78 (69, 92)	84 (71, 100)
BMI	25.4 (22.8, 28.4)	27.5 (23.8, 32.2)
Stroke/Transient ischemic attack	3 (8%)	49 (13%)
Coronary artery disease	8 (22%)	92 (24%)
Heart failure	2 (5%)	55 (14%)
Hypertension	22 (60%)	236 (62%)
Chronic obstructive pulmonary disease	6 (16%)	45 (12%)
Vascular disease	4 (11%)	37 (10%)
Diabetes mellitus	7 (19%)	82 (21%)
CHA ₂ DS ₂ -VASc	3 (1, 4)	3 (1, 4)
Warfarin use	2 (5%)	16 (4%)
Beta Blocker use home medication	11 (30%)	121 (32%)

Variable	Active Cancer (n=37)	No Active Cancer (n = 383)
Calcium Channel Blocker home medication	3 (8%)	44 (12%)
Statin home medication	13 (35%)	116 (30%)
Smoker, Current	2 (5%)	65 (17%)
Smoker, Former	10 (27%)	39 (10%)
Triage ventricular rate at index ED visit (beats per minute),	120 (108, 154)	118 (96, 142)
Systolic Blood Pressure at index ED visit (mm Hg),	126 (101, 141)	134 (119, 154)
Total White Blood Cell Count ($\times 10^3/\text{mL}$) on index ED visit	9.0 (6.1, 16.2)	8.2 (6.7, 10.7)
Hematocrit (%) on index ED visit	35 (31, 40)	42 (38, 45)
Sodium (mmol/L) on index ED visit	137 (132, 140)	139 (136, 141)
Potassium (mmol/L) on index ED visit	4.3 (3.8, 4.5)	3.9 (3.6, 4.3)
Blood Urea Nitrogen (mg/dL) on index ED visit	20 (13.5, 31.5)	17 (13, 24)
Creatinine (mg/dL) on index ED visit	1.1 (1.0, 1.5)	1.1 (0.9, 1.3)
Admitted to Floor Bed on index ED visit	30 (81%)	299 (78%)
Admitted to Intensive Care Unit Bed on index ED visit	3 (8%)	24 (6%)
Diagnosed with Sepsis on index ED visit	0	2 (<1%)
Anemia listed as a Contributing Diagnosis on index ED visit	1 (2.7%)	5 (1.3%)
Discharged Home on index ED visit	4 (11%)	60 (16%)
Palliative care/Hospice consultation within 30 days of index ED visit	11 (30%)	16 (4%)
Median (IQR) Days until Death	17 (12, 23)	6 (4, 11)
Death within 30 days	9 (24%)	11 (3%)

* Categorical data is presented as number of non-missing values (percentage). Continuous variable data is presented as median (interquartile range). IQR: interquartile range

Table 2

Multivariable model for predicting 30-day mortality among patients with new onset atrial fibrillation.

Variable	Adjusted Odds Ratio	95% Confidence Interval
Active Cancer	10.8	(3.8, 31.1)
Age (per year)	1.1	(1.0, 1.1)
Male	1.2	(0.4, 3.4)

Baseline Characteristics and Causes of Death for 20 patients who died within 30-days of index ED visit

Table A.1

Age	Sex	Active Cancer	Type of Cancer	Days until Death	Cause of Death	Palliative Care	CHA ₂ DS ₂ -VAsC	Total White Count (×10 ³ /mcL) at index ED visit	Hematocrit (%) at index ED visit	Creatinine (mg/dL) at index ED visit	Troponin (ng/mL) at index ED visit
70	Male	Yes	Prostate	17	Chronic Kidney Disease	Yes	2	8.9	37	6.3	0.15
72	Male	Yes	Melanoma	17	Cancer Related	No	3	4.3	31	1.3	<0.01
83	Male	Yes	Colon	21	Cancer Related	Yes	3	6.6	32	2	<0.01
58	Male	Yes	Lung	41	Cancer Related	No	0	57.5	31	1.1	0.74
78	Male	Yes	Bladder	20	Cancer Related	No	4	12.4	26	1.2	0.23
67	Male	Yes	Head and Neck	24	Cancer Related	Yes	4	15.4	39	1.2	1.1
81	Male	Yes	Prostate	14	Cancer Related	Yes	6	4.9	30	1	0.02
69	Female	Yes	Breast	9	Sepsis	No	3	7.2	46	2.9	0.05
82	Male	Yes	Lung	8	Cancer Related	Yes	6	1.4	32	1.1	0.05
91	Male	No	History of Prostate	9	Stroke	No	6	13.7	38	1.3	0.02
79	Male	No	History of Lung	4	Sepsis	Yes	6	8.4	37	1.9	<0.01
69	Female	No		11	Stroke	No	5	7.6	33	0.9	0.02
57	Female	No	History of Breast	8	COPD	No	3	11.8	43	0.7	0.03
76	Female	No		30	Stroke	Yes	5	5.9	21	2.2	0.07
85	Female	No		6	Stroke	Yes	4	9.2	29	1	0.01
82	Male	No		6	Sepsis	Yes	7	15.5	27	1.9	0.14
75	Female	No	New diagnosis of Lung on index ED admission	5	Cerebral edema from new brain metastases	Yes	5	8.9	43	0.8	<0.01
93	Female	No		4	Heart failure	Yes	3	5.1	36	0.9	0.2
65	Male	No		2	Aortic aneurysm	No	5	22.8	29	1.8	Not collected
85	Male	No		28	Heart failure	Yes	7	19.7	40	1.6	0.07