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Letter to the Editor

Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients

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Atrial fibrillation (AF), the most common cardiac rhythm disorder, increases cardiovascular mortality, thromboembolism, and heart failure [1]. AF can be induced or exacerbated by anticancer treatments such as various cytostatic agents. Likewise, aging, hypoxia, electrolyte abnormalities and malnourishment—conditions that are common in cancer patients—cause autonomic, metabolic and endocrine abnormalities that contribute to AF [2–4]. Yet it remains unclear exactly how AF complicates outcomes among patients with malignancies. Also, managing AF in cancer patients remains a challenge due to increased risk of bleeding, unpredictable anticoagulant response and lack of controlled studies within this population [2–4]. Using Taiwan's National Health Insurance Research Database (NHIRD), we analyzed the epidemiologic characteristics of new-onset AF in cancer patients, in particular, its relation to the development of thromboembolism, heart failure and mortality.

A population-based, and retrospective cohort study used Taiwan's NHIRD from January 1, 2000 to May 31, 2009. The patients who were hospitalized or sought ambulatory care receiving a first-time primary diagnosis of malignancy were recruited. Major outcome measures were mortality, thromboembolism, and heart failure. Cancer was defined according to diagnostic codes from 140 to 208 of the ICD-9, and AF as code 427.31. New-onset AF was defined as AF that occurred after the diagnosis of cancer. Baseline AF was defined as AF that occurred before or at the same time of cancer diagnosis. Heart failure was identified by codes 428.0 to 428.9, and thromboembolism (stroke, peripheral emboli, and pulmonary emboli) consisted of codes 430 to 438, 444, 415.1, and 416.2. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [5].

We identified 24,125 patients with newly diagnosed malignant diseases during the study period. There were 423 who experienced newly onset AF after their cancer diagnosis (1.8%), and 584 cancer patients with baseline AF (2.4%). The remaining 23,118 patients did not have AF. The baseline characteristics of the three groups (new-onset AF, baseline AF, and non-AF) are shown in Table 1. Binary logistic multivariate analysis was performed to find the independent factors. Comparing patients with new-onset AF and without AF, cancer patients with new-onset AF were independently associated with older age, male, and higher incidence of ischemic heart disease, but lower incidence of diabetes mellitus after the adjustment for the variables of all co-morbidities in Table 1. Comparing patients with baseline and new-onset AF, new-onset AF was independently associated with lower incidence of hypertension, diabetes mellitus, baseline heart failure, hyperthyroidism, and ischemic heart disease.

Compared to non-AF patients, cancer patients with new-onset AF had greater likelihood of thromboembolism and heart failure, but there was no difference in mortality between those with newly onset AF and those without AF, based on Kaplan–Meier analysis (Fig. 1). After adjusting for age, sex and underlying comorbidities, new-onset AF was still independently associated with higher incidence of new thromboembolism and heart failure in cancer

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Table 1
Baseline characteristics of new-onset, baseline AF patients, and those without AF.

	New-onset AF	Baseline AF	Non-AF
Number	423	584	23118
Age (years)	71.98 ± 10.07	75.04 ± 10.21	60.43 ± 15.69
Male (n, %)	284 (67.1%)	386 (66.1%)	12892 (55.8%)
Diabetes mellitus	126 (29.8%)	282 (48.3%)	7605 (32.9%)
Hypertension	270 (63.8%)	502 (86.0%)	12314 (53.3%)
Myocardial infarction	21 (5%)	71 (12.2%)	818 (3.5%)
History of heart failure	80 (18.9%)	348 (59.6%)	2726 (11.8%)
Hyperthyroidism	12 (2.8%)	34 (5.8%)	968 (4.2%)
Ischemic heart diseases	200 (47.3%)	476 (81.5%)	7577 (32.8%)
History of cerebrovascular diseases	117 (27.7%)	276 (47.3%)	4024 (17.4%)
Dyslipidemias	116 (27.4%)	234 (40.1%)	7956 (34.4%)

MI: myocardial infarction, AF: atrial fibrillation.

patients, compared to patients without AF (Table 2). Overall mortality was lower in cancer patients with new-onset AF compared with patients who had baseline AF, while there were no differences in incidence of new thromboembolism and heart failure between these two groups.

In new-onset AF patients, increasing $CHADS_2$ score was associated with higher mortality (25.8%, 33.3%, and 45.2%, p = 0.001, Fig. 2), however, it was not predictive of thromboembolism (29.7%, 27.9%, 54.5%, p = 0.49) and heart failure (18.4%, 25.2%, and 28.3%, p = 0.09). In cancer patients with AF at baseline, increasing $CHADS_2$ score was not associated with differences in mortality (32.0%, 34.2%, and 35.6%, p = 0.56), but was predictive of new thromboembolism (6.7%, 15.8%, 27.0%, p = 0.004) and heart failure (1.6%, 9.0%, and 13.3%, p = 0.02).

This study is the first to show that AF is related to poor prognosis in cancer patients. Specifically, new-onset AF was associated with poor cardiovascular outcomes, such as thromboembolism or heart failure, but it was not associated with higher mortality among cancer patients. The relationship between new-onset AF and heart failure was universal for all cancer types, but a greater tendency to thromboembolism was especially notable in patients with colorectal, breast, head and neck, and cervical cancers (data not shown). Walsh et al. reported that AF correlated with worse two-year survival in 175 colon cancer patients, but it was not an independent predictor of survival after multivariate analysis. That study was limited by the small number of cases, and confined to patients with colon cancer [6]. Our study showed similar results in patients with cancers, in that new-onset AF likewise had no impact on survival. However, we observed a greater tendency to thromboembolism and new heart failure. These findings suggest that prevention or treatment of AF may be important for patients with cancer.

$CHADS_2$ score is widely used to predict the risk of thromboembolism [7]. However, it remains unclear if $CHADS_2$ score can predict outcomes specifically in cancer patients. We found that for cancer patients with baseline AF, $CHADS_2$ score remains predictive of thromboembolism risk. However, for cancer patients with new-onset AF, $CHADS_2$ score could not predict the incidence of thromboembolism, though it was still associated with mortality. According to ACC/AHA guidelines, the $CHADS_2$ score should determine the strategy used for anticoagulation therapy [7]. However, therapeutic strategies guided by the $CHADS_2$ score may not be appropriate for patients with newly onset AF, a possibility that further complicates the treatment of AF in cancer patients.

In conclusion, newly onset AF was associated with more thromboembolism and heart failure, but not with mortality in cancer patients. $CHADS_2$ score lacked power to predict thromboembolism in cancer patients with new-onset AF.

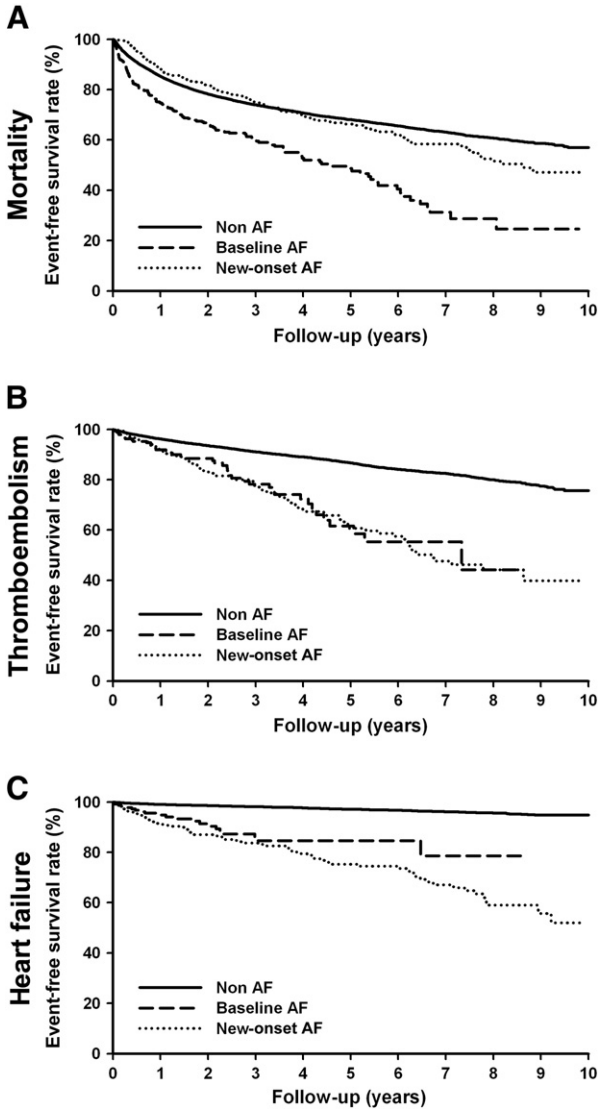

Fig. 1. The event-free incidence of mortality, thromboembolism, and heart failure in cancer patients with new-onset AF, baseline AF, and no AF. (A) Mortality did not differ between new-onset AF and non-AF cancer patients. But baseline AF was associated with higher mortality compared to the other two groups (p<0.001); (B), both new-onset AF and baseline AF were associated with higher incidence of thromboembolism, compared to the non-AF group (p<0.001); (C) both new-onset AF and baseline AF were associated with higher incidence of heart failure, compared to the non-AF group (p<0.001). A log-rank test was used to examine differences of the variables.

Table 2
Association of new-onset AF and adverse outcomes, compared to non-AF and baseline AF patients.

	New-onset AF vs. non-AF		New-onset AF vs. baseline AF	
	HR (CI 95%)	p Value	HR (CI 95%)	p Value
Mortality				
Non-adjusted model	1.07 (0.90–1.27)	0.43	0.49 (0.40–0.62)	<0.001
Adjusted for age, sex and comorbidities			0.51 (0.39–0.66)	<0.001
Thromboembolism				
Non-adjusted model	3.10 (2.51–3.83)	<0.001	1.03 (0.72–1.49)	0.86
Adjusted for age, sex and comorbidities	1.98 (1.60–2.46)	<0.001		
Heart failure				
Non-adjusted model	10.21 (7.95–13.12)	<0.001	1.53 (0.93–2.50)	0.09
Adjusted for age, sex and comorbidities	6.28 (4.83–8.17)	<0.001		

*Cox proportional hazard models were used. Co-morbidities include diabetes mellitus, hypertension, history of heart failure and myocardial infarction, hyperthyroidism, ischemic heart diseases, cerebrovascular diseases, and dyslipidemias.

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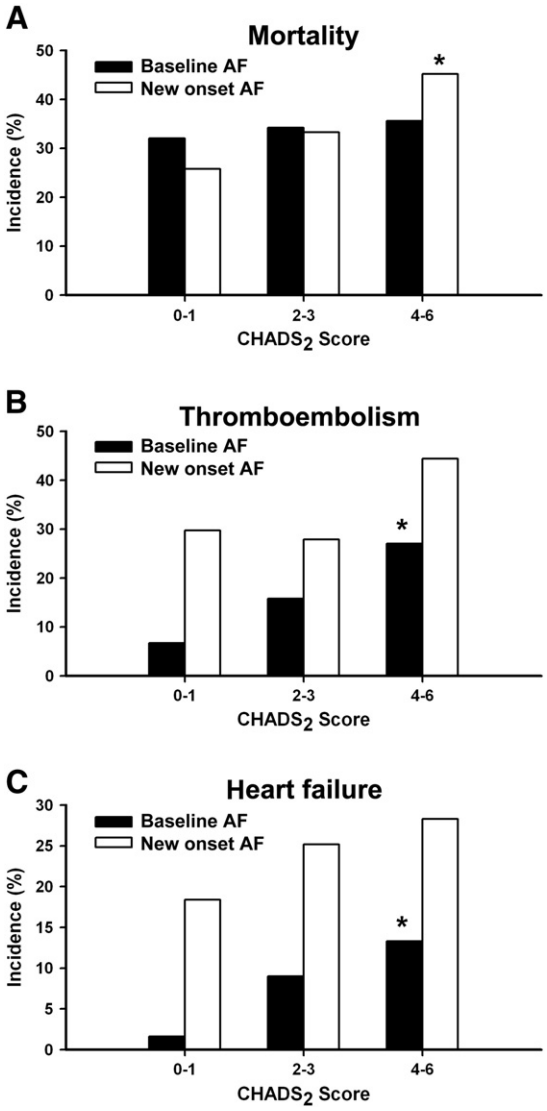

Fig. 2. The incidence of mortality, thromboembolism, and heart failure according to different $CHADS_2$ score in newly onset AF and baseline AF cancer patients. *Chi-square test, $p<0.05$.

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