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Original Article

Atrial fibrillation influences survival in patients with hepatocellular carcinoma: Experience from a single center in Taiwan

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Abstract

Background: It is unclear whether atrial fibrillation (AF) adversely influences the clinical course of patients with hepatocellular carcinoma (HCC).
Methods: During the period from January 1, 2001 to December 31, 2010, 476 patients (mean ± SD age 60.3 ± 12.9 years) diagnosed with HCC were retrospectively enrolled in our study. The HCC stage, treatment, baseline characteristics, underlying cardiovascular diseases, and corresponding drug treatment were systematically reviewed. The primary endpoint was death from any cause.
Results: AF was associated with a significantly reduced survival time in patients with HCC (AF vs. non-AF patients mean ± SD survival time 470.1 ± 89.6 days vs. 1161.2 ± 32.6 days, log-rank $p < 0.001$; probability of survival 0.20, 95% confidence interval 0.10–0.38, $p < 0.001$). After adjustment for sex and age, AF was still associated with poorer survival times (hazard ratio 4.131, 95% confidence interval 2.134–5.733, $p < 0.001$). The causes of death among 22 patients with both HCC and AF included 11 cases of hepatic failure, four cases of ruptured tumor, and two cases of bleeding from esophageal varices. None of these patients with AF used warfarin. Seven bleeding events related to HCC were noted, but none of these patients developed a major thromboembolism. The mean ± SD follow-up period was 645 ± 468 days.
Conclusion: Patients with HCC had a significantly reduced survival time with the comorbidity of AF. Tumor rupture was relatively common among patients with both HCC and AF. The anticoagulation treatment of AF in patients with HCC deviated from the current guidelines without an increase in thromboembolic events.

Keywords: atrial fibrillation; hepatocellular carcinoma; prognosis; survival

1. Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia and has become a growing problem worldwide.[1,2] The remaining lifetime risk for AF at age 40 years has been reported as 25% for both sexes.[2] In addition, several reports have suggested that AF might complicate the clinical course and outcome of patients with cancer during surgical or medical treatment.

Hepatocellular carcinoma (HCC), which originates from liver cells, has tripled in incidence in the past two decades and has become the fastest rising cause of cancer-related death in the USA; the hepatitis C virus (HCV) accounts for most cases.[3,4] It would therefore be expected that there will be increasing numbers of patients with both HCC and AF, the most prevalent arrhythmia. So far, the relationship between arrhythmias and cancer has been somewhat overlooked.[4] It remains unclear whether AF is associated with different outcomes for these patients. The aim of this study was to

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investigate the effects of AF on the overall survival of patients with HCC.

2. Methods

Patients with HCC in Taipei Veterans General Hospital were retrospectively reviewed and a total of 476 patients with HCC were recruited from January 2001 to December 2010. The underlying viral hepatitis status, HCC stages, laboratory tests, electrocardiography, and treatment choice of each patient were meticulously scrutinized. All patients were followed up until December 31, 2011. The primary endpoint was death due to all causes to delineate the survival impact of AF on patients with HCC. Thereafter the causes of death were analyzed further.

Diagnoses of HCC were confirmed based on the guidelines proposed in 2005 by the American Association for the Study of Liver Diseases. By these criteria, HCC is diagnosed if a patient has one or more risk factors [hepatitis B (HBV) or C (HCV) virus infection, or cirrhosis, or both] and one of the following: a serum α-fetoprotein (AFP) level >200 ng/mL and a positive result with at least one of the three typical imaging techniques (triple-phase computed tomography, contrast-enhanced dynamic magnetic resonance imaging, or hepatic angiography); or a serum AFP level of <200 ng/mL and positive findings with at least two of three imaging techniques. A positive result for typical HCC through the use of dynamic computed tomography or magnetic resonance imaging is indicative of arterial enhancement followed by venous washout in the delayed portal/venous phase.[5] Any case of HCC diagnosed before 2005 was confirmed by pathology (either a biopsy or surgical sample).

AF was confirmed by surface 12-lead electrocardiography performed by at least two cardiologists. The AF type was evaluated for all patients by a review of their medical records, with an extensive examination of all the electrocardiographic results for each patient.

The medical records of enrolled patients were reviewed for age, sex, HBV, or HCV infection status, history of alcoholism, dyslipidemia (defined as total cholesterol >200 mg/dL or triglyceride >150 mg/dL), diabetes mellitus, Child–Pugh score, chemistry profiles, AFP level, size and number of tumor, extrahepatic spread of tumor, hepatic or portal vein invasion by tumor, the presence of lymph nodes or distant metastasis, and the Eastern Cooperative Oncology Group performance status. Treatment modalities for HCC for each patient were recorded, including surgery, locoregional treatment (transarterial chemoembolization, percutaneous ethanol injection, and radiofrequency ablation), radiotherapy, and cytotoxic chemotherapy. The retrospective study was performed without violating guidelines for clinical research.

2.1. Statistical analyses

The two-sample *t* tests were used for noncategorical data. Categorical data were compared using a Chi-square test with Yates' correction or Fisher's exact test. The overall survival was determined and compared using a Kaplan–Meier analysis and log-rank test. A Cox regression analysis was used to identify the independent factors associated with mortality. Variables selected for multivariate analysis had $p < 0.1$ on univariate analysis and statistical significance was established if $p < 0.05$.

Table 1
Baseline characteristics of groups of patients with hepatocellular carcinoma with and without atrial fibrillation.

Parameters	Patients with both HCC and AF ($n = 22$)	Patients with HCC without AF ($n = 454$)	p
Age (y)	75.9 ± 10.1	59.5 ± 12.6	<0.001
Male	15 (68.2)	349 (76.9)	0.495
DM	3 (13.6)	85 (18.7)	0.779
HTN	6 (27.3)	119 (26.2)	0.998
Clinical HF	1 (4.5)	19 (4.2)	1.000
Dyslipidemia	2 (9.1)	134 (29.5)	0.050
HBV	8 (36.4)	290 (63.9)	0.012
HCV	9 (40.9)	131 (28.9)	0.236
Alcohol use	2 (9.1)	70 (15.4)	0.554
Child score			0.121
No cirrhosis or A	12 (54.5)	303 (66.7)	
B	9 (40.9)	102 (22.5)	
C	1 (4.5)	49 (10.8)	
BCLC stage			0.062
A	3 (13.6)	126 (27.8)	
B	4 (18.2)	142 (31.3)	
C	11 (50.0)	118 (26.0)	
D, n (%)	4 (18.2)	68 (15.0)	
Major vascular invasion	7 (31.8)	136 (30.0)	0.991
Extrahepatic spread	5 (22.7)	77 (17.0)	0.489
Treatment			
Surgery	5 (22.7)	169 (37.2)	0.157
Locoregional therapy	12 (54.5)	247 (55.4)	0.957

Data are presented as mean ± standard deviation or *n* (%).
AF = atrial fibrillation; BCLC stage = Barcelona Clinic Liver Cancer stage; DM = diabetes mellitus; HCC = hepatocellular carcinoma; HF = heart failure; HTN = hypertension; HBV = hepatitis B virus; HCV = hepatitis C virus.

3. Results

3.1. Baseline characteristics

Twenty-two patients with both HCC and AF were identified and another 454 patients with HCC without AF were enrolled from the same medical center database. The mean ± SD duration of follow-up was 645 ± 468 days. The AF group was older than the non-AF group (75.9 ± 10.1 years versus 59.5 ± 12.6 years, $p < 0.001$) with a lower incidence of HBV infection (36.4% versus 63.9%, $p = 0.012$). Sex, diabetes mellitus, hypertension, dyslipidemia, HCV infection, alcohol use, Child–Pugh score and Barcelona Clinic Liver Cancer (BCLC) staging system, major vascular invasion, extrahepatic spread, and treatment strategies such as locoregional treatment or surgery did not differ between the groups with and without AF (Table 1).

3.2. Characteristics of patients with AF

The clinical courses of all 22 patients with both HCC and AF were carefully examined. All electrocardiographic data

were examined from the time of first medical contact to last follow-up, or until death. Four (18.2%) patients with paroxysmal AF, three (13.6%) patients with persistent AF, and 15 (68.2%) patients with permanent AF were identified. None of these patients was prescribed warfarin. Eleven (50%) of the patients with AF were taking aspirin. One (4.5%), seven (31.8%), 12 (54.6%), and two (9.1%) patients had $CHADS_2$ scores of 4, 2, 1, and 0, respectively (Table 2).

3.3. Association of AF and death from HCC

During a mean follow-up period of 21.5 months, 18 and 131 deaths were identified in the AF and non-AF group, respectively. Using the log-rank test in the Kaplan–Meier analysis, the patients with both HCC and AF were associated with a significantly shorter mean ± SD survival time (AF versus non-AF 470.1 ± 89.6 days vs. 1161.2 ± 32.6 days, log-rank $p < 0.001$; Fig. 1). The relative ratio of survival for patients in the AF compared with the non-AF group was 0.20 (95% confidence interval (CI) 0.10–0.38, $p < 0.00$). Subsequent adjustment for sex and age showed a significantly poorer outcome in the group with both HCC and AF: hazard ratio (HR) for mortality 4.131, 95% CI 2.134–5.733, $p < 0.001$. We also performed age subgroup analysis via stratification of the age groups (Table 3). Significantly worse survival was detected among all patients older than 70 years (HR for mortality 7.306, 95% CI 3.75–14.23, $p < 0.001$, Fig. 1). The main survival difference occurred in the group aged 70–80 years, in which those with both HCC and AF had a significantly higher risk of death from all causes (HR 9.81, 95% CI 4.16–23.12, $p < 0.001$). Among patients older than 80 years of age, AF did not have a significant impact on overall survival (HR 1.96, 95% CI 0.68–5.74, $p = 0.211$). Among patients younger than 70 years of age, no survival difference was detected between groups.

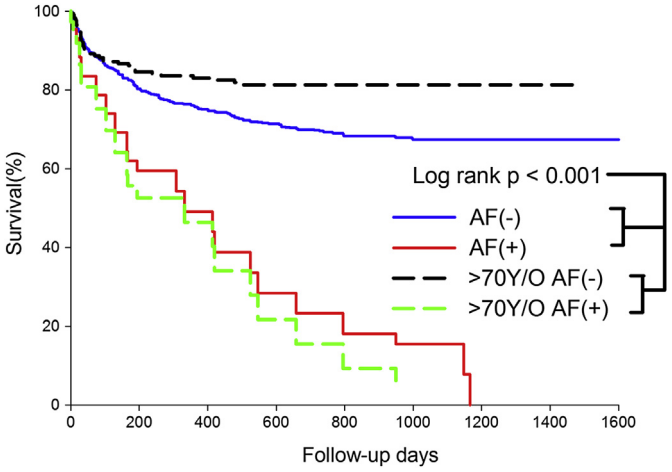

Fig. 1. Kaplan–Meier analysis of overall survival in patients with hepatocellular carcinoma with or without atrial fibrillation and in elderly (>70 years old) patients with hepatocellular carcinoma with or without atrial fibrillation.

3.4. Treatment and outcome of patients with both HCC and AF

The treatment modalities (surgery or locoregional treatment) for HCC did not differ between the AF and non-AF

Table 2
Clinical characteristics of 22 patients with both hepatocellular carcinoma and atrial fibrillation.

Patient no.	Age (y)	Sex	HBV	HCV	BCLC stage	HTN	DM	CS	Tx	Endpoint	Cause of death
1	79	F	+	–	C	+	+	4	S + L	+	HCC, liver failure
2	42	M	+	–	D	–	+	2	S + L	+	HCC, liver failure
3	77	M	–	–	D	+	–	2	BSC	+	Tumor rupture with shock
4	80	M	–	–	C	–	+	2	BSC	+	HCC, liver failure
5	81	M	–	–	B	+	–	2	S + L	+	HCC, liver failure
6	77	M	–	–	B	+	–	2	S + L	+	HCC, liver failure
7	86	F	–	+	A	–	–	2	L	+	Tumor rupture with shock
8	87	M	–	–	D	–	–	2	BSC	–	—
9	72	F	–	+	D	–	–	1	BSC	+	HCC, liver failure
10	83	F	+	+	C	–	–	1	BSC	+	Tumor rupture with shock
11	70	F	–	+	C	+	–	1	L	+	HCC, liver failure
12	85	M	–	+	C	–	–	1	L	+	HCC, liver failure
13	71	M	+	–	C	–	–	1	BSC	+	EVB with shock, MOF
14	76	M	+	–	C	–	–	1	L	+	HCC, liver failure
15	85	M	+	–	C	–	–	1	BSC	+	Tumor rupture, MOF
16	85	F	–	+	B	–	–	1	L	+	HCC, liver failure
17	72	M	+	–	B	+	–	1	L	+	HCC, liver failure
18	80	M	–	+	A	–	–	1	L	+	HCC, liver failure
19	65	M	–	+	C	–	–	1	L	–	—
20	80	F	–	+	C	–	–	1	BSC	–	
21	72	M	–	–	C	–	–	0	L	+	EVB with shock, MOF
22	64	M	+	–	A	–	–	0	S + L	–	

AF = atrial fibrillation; BCLC stage = Barcelona Clinic Liver Cancer stage; BSC = best supportive care; CS = $CHADS_2$ score; DM = diabetes mellitus; EVB = esophageal variceal bleeding; F = female sex; HCC = hepatocellular carcinoma; HTN = hypertension; HBV = hepatitis B virus; HCV = hepatitis C virus; L = locoregional treatment; M = male sex; MOF = multiorgan failure; S = surgery; Tx = treatment.

Table 3
Association between atrial fibrillation and all causes of death among patients with hepatocellular carcinoma in different age groups.

AF	HR	95% CI	*p*
>80	1.96	0.68–5.74	0.211
70–80	9.81	4.16–23.12	<0.001
60–70	0.05	0 to >50	0.603

CI = confidence interval; HR = hazard ratio.

groups. Among the patients with AF, there were eight patients with a $CHADS_2$ score ≥ 2, 12 with a $CHADS_2$ score = 1, and two patients with a $CHADS_2$ score = 0. None of the patients was prescribed warfarin. Eleven patients received antiplatelet drugs (50.0%). Rate control drugs, including beta blockers, calcium channel blockers, and digoxin, and were prescribed in 12 patients (54.5%). One patient received amiodarone. The treatment of patients with AF for thromboembolism was clearly inadequate according to the 2006 American College of Cardiology/American Heart Association guideline.[6]

The total death rate during follow-up in patients with AF was 81.8% ($n = 18$). The cause of death in the patients with AF included 12 cases of hepatic failure, four cases of tumor rupture, and two cases of bleeding from esophageal varices (Table 2). Even when patients with BCLC stage D were excluded, patients with both AF and HCC still had significantly shorter survival times than patients with HCC but no AF (log-rank $p < 0.001$). Thus AF influenced the survival of those so-called relatively manageable patients with HCC (BCLC stages A to C). None of the patients developed a thromboembolic event despite an extremely low rate of use of anticoagulant drugs.

4. Discussion

4.1. Main findings

The present study shows that AF was significantly associated with a poor prognosis in patients with HCC, especially in older patients. The use of anticoagulant drugs deviated from the current guidelines. The causes of death in patients with AF were mostly attributed to hepatic failure and death from tumor rupture was relatively higher among patients with both HCC and AF.

4.2. Association between AF and survival in patients with HCC

It is reasonable to expect that a patient with cancer will have a poorer prognosis if he or she has another disorder of a major organ. However, the mechanism through which AF acts to influence the clinical outcome of patients with HCC is not yet clear. The poorer survival among patients with both HCC and AF may be ascribed to a higher risk of congestive heart failure due to chronic rhythm incompetence. The majority of patients with both AF and HCC died from hepatic failure (61%). Tumor rupture is an uncommon complication of hepatocellular carcinoma. However, we observed a relative higher incidence of tumor rupture in patients with both AF and HCC (18%). The probable explanation for this observation is that AF predisposes a patient to intracardial thrombus formation, and the microthrombi randomly embolize the systemic microcirculation, including that of the HCC, which is artery-dependent. Chronic embolization-related hypoxia may lead to the activation of hypoxia inducible factor-1, which promotes angiogenesis, invasion, and epithelial-mesenchymal transition.[7] Over-promotion of angiogenesis may lead to a clinical picture of tumor rupture.

4.3. Interaction between HCC and AF

Whether or not cancer can induce AF remains an unsettled question. In limited case control studies, cancer was not found to lead to AF *per se*, but did lead to AF due to a high inflammation state.[8–11] AF, exacerbated by anticancer treatments, was suspected to complicate the outcome of patients with cancer during surgical or medical treatment. However, there is a lack of clinical evidence for an association, especially for patients with HCC. The present study first showed that AF was associated with a poorer prognosis in patients with HCC, providing clinical evidence that links AF to clinical outcomes in patients with HCC and implies that treating AF correctly might help patients with HCC. In this study, no obvious correlation was observed between the $CHADS_2$ score and survival.

4.4. Dilemma in the prevention of thromboembolism in patients with AF and HCC

The maintenance of patients with AF depends partially on atrial remodeling and gives rise to a predisposition to thromboembolism.[12] The prevention of thromboembolism in patients with both AF and HCC is difficult, and current American College of Cardiology/American Heart Association guidelines have not yet been validated for patients with HCC.[6] Commonly, patients with HCC are associated with thrombocytopenia, making the standard guidelines for treatment with anticoagulant drugs inapplicable. It remains unclear whether these thromboembolism events would be similar in patients with thrombocytopenia or in patients with HCC. The interaction between chemotherapeutic drugs and warfarin might further prevent the benefit of anticoagulant drugs and contrarily lead to a higher bleeding rate.

In the present study, the use of anticoagulant drugs is discordant with the guideline, which reflects the dilemma in the prevention of thromboembolism in patients with both AF and HCC. None of the patients had, or died of, a major thromboembolism, and most of the deaths could be attributed to cancer. It is possible that most patients would die from cancer before the development of a major thromboembolism. These findings lead us to reconsider the necessity of using anticoagulant drugs in this particular population. The profile of risks and benefits might be different from the profiles of patients without malignancies. We need a larger number of patients with both HCC and AF to further elucidate the issue. It is possible that AF might represent as a prognostic marker.

Further investigation is needed to determine whether treating AF could lead to different outcomes in these patients.

4.5. Limitations

The present study was limited by its retrospective, single-center design as well as by the number of patients with AF studied. A larger prospective cohort might be needed to confirm our findings. The present study could not define the causality between AF and death from HCC. Also, the data related to heart failure, e.g. left ventricular ejection fraction or left atrium size, did not exist for every patient. Thus no further relationship between heart failure and outcome could be determined.

In conclusion, AF was associated with a significantly lower probability of overall survival in patients with HCC, especially elderly patients. Tumor rupture was relatively common among patients with both HCC and AF. The anticoagulation treatment of AF in patients with HCC deviated from the current guidelines, without increasing the incidence of thromboembolic events.

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