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Clinical Research

Perioperative Atrial Fibrillation in Noncardiac Surgeries for Malignancies and One-Year Recurrence

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See editorial by Aguilar and Nattel, pages 1423–1425 of this issue.

ABSTRACT

Background: Perioperative atrial fibrillation (POAF) in noncardiac surgeries is common. However, it is unclear whether such atrial fibrillation (AF) recurs in the long term.

Methods: This study was a prospective, single-center, observational study that included patients who underwent noncardiac surgeries for malignancies. Patients were followed up for 1 year to evaluate the incidence of AF, ischemic stroke, and mortality. An event-triggered recorder was used in patients with POAF. The incidences were compared according to the presence of POAF.

Results: Of 752 consecutive patients, 77 (10.2%) developed POAF and wore an event recorder for 19 (12-30) days. AF and ischemic

RÉSUMÉ

Contexte : Il arrive fréquemment qu'un patient subissant une intervention chirurgicale non cardiaque présente une fibrillation auriculaire périopératoire (FAPO). On ne sait toutefois pas si d'autres épisodes de fibrillation auriculaire (FA) surviennent par la suite.

Méthodologie : Les auteurs ont mené une étude d'observation prospective unicentrique auprès de patients ayant subi une intervention chirurgicale non cardiaque visant à retirer une tumeur. Les patients ont fait l'objet d'un suivi pendant 1 an afin d'évaluer l'incidence des épisodes de FA et des accidents vasculaires cérébraux (AVC) ischémiques, ainsi que la mortalité. Un dispositif d'enregistrement déclenché par la survenue d'un événement a été utilisé chez les

Perioperative (or postoperative) atrial fibrillation (POAF) in the setting of noncardiac surgery is common and has recently attracted the attention of cardiologists because of its complications, such as thromboembolism and subsequent mortality and morbidity.[1] However, the clinical course and management of POAF in noncardiac surgeries have not been investigated in detail, and clinical practice guidelines do not provide any recommendations regarding POAF.[2] A recent retrospective study demonstrated that long-term anticoagulation might be beneficial in patients with POAF to prevent thromboembolism.[3] This result suggests that atrial fibrillation (AF) can recur even in patients with POAF who have undergone noncardiac surgeries; however, the population at risk of recurrence of AF is unknown. This evidence gap should be resolved because a large number of noncardiac surgical procedures are performed throughout the world. The

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stroke at 1 year were observed in 24 patients (31.1%) and 2 patients (2.6%) with POAF and 4 patients (0.6%) and 3 patients (0.4%) without POAF, respectively. Of the 24 patients with POAF and AF recurrence, 22 (92%) were asymptomatic. Anticoagulation was prescribed in 67 patients (87%) with POAF. Multivariate Cox regression analysis demonstrated that a higher AF recurrence rate in patients with POAF was associated with hypertension (hazard ratio, 2.79; 95% confidence interval, 1.06-7.38) and serum creatinine level (hazard ratio for 20 μmol/L increase, 2.32; 95% confidence interval, 1.16-4.62).

Conclusions: AF recurs in approximately 30% of patients with POAF with malignancy in the subsequent year; most recurrences are asymptomatic.

Résultats : Sur 752 patients consécutifs, 77 (10,2 %) ont subi une FAPO et ont porté un dispositif d'enregistrement des événements pendant 19 (12-30) jours. Durant l'année de suivi, des épisodes de FA et des AVC ischémiques ont été observés respectivement chez 24 (31,1 %) et 2 (2,6 %) patients ayant subi une FAPO, et chez 4 (0,6 %) et 3 (0,4 %) des autres patients. Des 24 patients ayant subi une FAPO et présenté un autre épisode de FA par la suite, 22 (92 %) étaient asymptomatiques. Des anticoagulants ont été prescrits à 67 patients (87 %) ayant subi une FAPO. Les résultats d'une analyse multivariée par régression de Cox ont montré qu'un taux d'épisodes de FA supérieur chez les patients ayant subi une FAPO était associé à l'hypertension (rapport des risques instantanés : 2,79; intervalle de confiance à 95 % : de 1,06 à 7,38) et au taux sérique de créatinine (rapport des risques instantanés pour chaque hausse de 20 μmol/l : 2,32; intervalle de confiance à 95 % : de 1,16 à 4,62).

Conclusions : Environ 30 % des patients ayant subi une FAPO lors d'une intervention visant à retirer une tumeur présentent un épisode de FA dans l'année qui suit l'intervention; dans la plupart des cas, la FA est asymptomatique.

aim of this study was to investigate 1-year AF recurrence rate and its clinical impact.

Material and Methods

Study population

The **Pr**ospe**c**tive Cohort Stu**d**y of Surve**i**llan**c**e for Perioperat**i**ve **A**trial **F**ibrillation **Recurrence** (PREDICT AF RECURRENCE) in major noncardiac surgeries for malignancy is an ongoing prospective, single-center, observational study designed to survey the clinical impact of POAF on the mortality and morbidity of these patients. In this study, cardiologists collaborate with the surgical teams and investigate the incidence of AF recurrence after discharge in patients with malignancies. The study protocol has been reported.[4] In brief, patients who underwent noncardiac surgeries for definitive or suspected malignancies between 2014 and 2017 were registered for the present study. A definitive diagnosis of malignancy was confirmed within postoperative day 30.

Inclusion criteria

Patients aged $\geq$ 20 and $\leq$ 90 years with definitive diagnoses of malignancies who underwent surgeries were included. The malignancies included head and neck (pharyngeal, laryngeal, tongue, mandibular, buccal mucosal, gingival, and glottic cancers), chest (esophageal and lung cancers, and lung metastasis), and abdominal cancers (gallbladder, pancreatic, and duodenal cancers, extra- and intra-hepatic cholangiocarcinomas, carcinoma of the ampulla of Vater, hepatic cell carcinoma, and liver metastasis).

Exclusion criteria

Patients without a confirmative diagnosis of malignancy or those with a medical history of prior AF, which was confirmed on the basis of medical records, at the time of the surgery were excluded from the present analysis.

Sample size

Of the 812 registered patients, 14 with a medical history of AF and 46 whose final diagnoses were not malignancies were excluded. Finally, 752 patients were included in the analyses.

Data collection

A baseline survey was conducted preoperatively using a study-specific questionnaire for collecting information. The operative data included the stage of malignancy and type of surgery. At least 2 pathologists provided the diagnosis. If their opinions conflicted, a decision was reached by consensus. The stage of each surgery was determined on the basis of the Union of International Cancer Control TNM classification, seventh edition.[5] All patients were scheduled to be observed with an electrocardiogram (ECG) monitoring device in the wards for a minimum of 24 hours and up to 30 days postoperatively; the monitoring started from the induction of anaesthesia, and the duration was based on the surgeon's discretion.

Follow-up

The follow-up began on postoperative day 31. The entire data in the present study were collected by December 31, 2018. The follow-up was completed on the last medical interview date, the last examination date, or the date when an end point event was observed, whichever came first. Follow-up data, including the incidence of AF, ischemic stroke, mortality, and cause of death at 1 year were collected from the outpatient visits or telephone interviews. The cause of death was confirmed by surgeons and cardiologists according to autopsy or clinical data.

SPIDER FLASH-t AFib (LivaNova, London, UK), an event-triggered recorder, was used for the surveillance of AF recurrence in patients with POAF. This device has 2 leads and provides a simplified and patient-centric method of ECG follow-up and an accurate diagnosis of the rhythm. The

detailed algorithm, including setup of the device, has been reported.[4] Monitoring was performed throughout the day, except during bathing time, for approximately 2 weeks in the postoperative months 1 and 12. Additionally, follow-up was performed after 6 months, if required. Patients who were unable to handle the event recorder were evaluated with 24-hour Holter ECG 2 to 3 times at some point in the postoperative months 1, 6, or 12. If AF recurrence was documented once, subsequent event monitoring was not implemented. The records acquired by SPIDER FLASH-t AFib were assessed by an external expert organization, and the final decision was confirmed by 2 cardiologists. In cases of a difference in opinion, consensus was achieved by discussion.

Definitions

AF was defined as irregular heart rhythm without a repetitive pattern and distinct P wave for at least 30 seconds. POAF was defined as AF during or after the surgery but before postoperative day 30. For the analysis of AF, "1-year AF development" was defined as recurrence of AF in those with POAF—or new-onset AF in those without POAF—that was observed within 1 year after the follow-up began on the postoperative day 31. The CHA_2DS_2-VASc score includes a single point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex, and 2 points each for age $\geq$ 75 years and prior stroke, transient ischemic attack, and thromboembolism. The score ranges from 0 to 9.[6] AF recurrence was defined as repetitive AF for $\geq$ 30 seconds on or after postoperative day 31, which was documented by any ECG monitoring device. Each patient's self-assessment and symptoms did not contribute to the definitive diagnosis.

Indications for anticoagulation

Anticoagulation therapy was prescribed to men and women who developed AF with CHA_2DS_2-VASc score of $\geq$ 1 and $\geq$ 2, respectively.[7] If the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, and drugs/alcohol concomitantly (HAS-BLED) score[8] was $\geq$ 3, the anticoagulation was prescribed when the expected advantages assessed by the $CHAD_2S_2$-VASc score overweighed the disadvantages evaluated by the HAS-BLED score.

End points

The primary end point was the 1-year recurrence rate of AF in patients with POAF. The secondary end points were ischemic stroke and mortality (including cardiac, noncardiac, and cancer-related deaths) at 1 year in all the patients.

Ethical principles

This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Japanese government. This study was approved by the ethics committee of Kyorin University Hospital (approval number: 488) and is registered with the University Medical Information Network (UMIN ID: UMIN000016146). Written informed consent was obtained from each patient preoperatively by the physicians.

Statistical analysis

Numerical data were presented as mean $\pm$ standard deviation if the data had normal distribution. Otherwise, the data were presented as median and interquartile ranges (Q1-Q3). Categorical variables were expressed as absolute numbers or percentages. Continuous variables were analyzed using the unpaired Student t test or Mann−Whitney U test, and categorical variables were analyzed using the Fisher exact test or chi-square test, as appropriate. The primary and secondary end points except for 1-year ischemic stroke, were evaluated by Kaplan−Meier survival curves with log-rank tests. The risk of each end point was assessed using univariate and multivariate Cox regression analyses and expressed as hazard ratio (HR), 95% confidence interval (CI), and P value. Variables with a P value < 0.10 in the univariate analysis were included in the multivariate Cox regression analysis, with the least absolute shrinkage and selection operator to identify the significant factors. The multivariate model in the analysis of the primary end point included hypertension, concomitant coronary artery disease, and serum creatinine level at discharge. Regarding the secondary end points, the multivariate model to assess the mortality included 1-year AF development, diabetes mellitus, stage of malignancy, and hemoglobin level at discharge, whereas the multivariate analysis on ischemic stroke was not performed because the incidence of ischemic stroke was too small to perform analyses. Statistical significance was set at $P < 0.05$. All statistical analyses were carried out using Stata software, version 14 (StataCorp LP, College Station, TX) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and follow-up duration

The consecutive 752 patients (mean age, 68 $\pm$ 11 years; male, 62%) were observed with continuous ECG monitors for a median of 72 (48-120) hours in the perioperative period. Of those, 77 patients (10%) developed POAF. AF was observed 48 (27-80) hours postoperatively. The first episode of POAF was sustained for 2.3 (0.2-14.0) hours, and the cumulative time during hospitalization was 6.0 (0.5-16.5) hours. The patient characteristics are summarized in Table 1. Notably, 97 patients (13%) were prescribed anticoagulants (67 patients with POAF [87%]; 30 patients without POAF [4%]; $P <$ 0.001). Antiarrhythmic drugs and β-blockers were discontinued 3 days before the first examination with the event recorder in all of the patients with POAF (none of the patients were treated with amiodarone). The overall follow-up durations were 690 (385-1051) days and 625 (385-970) days in patients with POAF.

Incidence of AF recurrence

Of the 77 patients with new-onset POAF, 24 (31%) developed AF within 1 year of the surgery. An event recorder was used for 19 (12-30) days (recurrence group, 14 [12-22] days and no recurrence group, 26 [14-32] days; $P =$ 0.046). The first AF recurrence was documented at a median of the 47th (39-61) postoperative day. Of the 24 patients, 22 (92%) were asymptomatic. Kaplan−Meier survival curve for

Table 1. Patient characteristics

	Total (n = 752)	New-onset POAF‡				No POAF§	
		Total (n = 77)	Recurrence* (n = 24)	No recurrence† (n = 53)	*P* value (* vs †)	Total (n = 675)	*P* value (‡ vs §)
Age, y	68 ± 11	72 ± 7	73 ± 7	72 ± 7	0.406	68 ± 11	< 0.001
Male, n (%)	468 (62)	50 (65)	19 (79)	31 (58)	0.121	418 (62)	0.606
Body mass index, kg/m^2	23 ± 15	23 ± 3	24 ± 4	22 ± 3	0.163	23 ± 4	0.541
Hypertension, n (%)	346 (46)	37 (48)	18 (75)	19 (36)	0.003	309 (46)	0.704
Diabetes mellitus, n (%)	143 (19)	18 (23)	6 (25)	12 (23)	1.000	125 (19)	0.303
History of heart failure, n (%)	5 (1)	0 (0)	0 (0)	0 (0)	NA	5 (1)	1.000
History of cardiogenic stroke, n (%)	1 (0)	1 (0)	0 (0)	1 (2)	1.000	0 (0)	0.102
Coronary artery disease, n (%)	42 (6)	4 (5)	3 (13)	1 (2)	0.087	38 (6)	1.000
Chronic obstructive pulmonary disease, n (%)	199 (27)	27 (35)	11 (46)	16 (30)	0.206	172 (26)	0.075
CHA_2DS_2 VASc score	2 (1-3)	2 (2-3)	3 (2-3)	2 (1-3)	0.200	2 (1-3)	0.030
Brinkman index	360 (0-890)	560 (0-986)	670 (120-1350)	380 (0-900)	0.130	340 (0-870)	0.177
Alcohol consumption, g/d	0 (0-20)	0 (0-17)	0 (0-24)	0 (0-15)	0.417	0 (0-20)	0.262
Stage of malignancy					0.484		0.070
Stage 0, n (%)	39 (5)	1 (1)	0 (0)	1 (2)		38 (6)	
Stage 1, n (%)	333 (44)	39 (51)	16 (67)	23 (43)		294 (44)	
Stage 2, n (%)	142 (19)	19 (25)	4 (17)	15 (28)		123 (18)	
Stage 3, n (%)	78 (10)	9 (12)	2 (8)	7 (13)		69 (10)	
Stage 4, n (%)	160 (21)	9 (12)	2 (8)	7 (13)		151 (22)	
Head and neck cancer, n (%)	35 (5)	1 (1)	1 (1)	0 (0)	0.312	34 (5)	0.246
Chest, n (%)	492 (65)	55 (71)	20 (83)	35 (66)	0.174	437 (65)	0.242
Lung cancer, n (%)	407 (54)	51 (66)	18 (75)	33 (62)	0.310	356 (53)	0.024
Metastatic lung cancer, n (%)	60 (8)	1 (1)	0 (0)	1 (2)	1.000	59 (9)	0.023
Esophagus cancer, n (%)	25 (3)	3 (4)	2 (8)	1 (2)	0.228	22 (3)	0.735
Abdomen, n (%)	228 (30)	21 (27)	3 (13)	18 (34)	0.058	207 (31)	0.539
Pancreatic cancer, n (%)	108 (14)	7 (9)	1 (4)	6 (11)	0.424	101 (15)	0.164
Carcinoma of the ampulla of Vater, n (%)	8 (1)	2 (3)	0 (0)	2 (4)	1.000	6 (1)	0.193
Duodenal cancer, n (%)	2 (0)	0 (0)	0 (0)	0 (0)	NA	2 (0)	1.000
Intrahepatic cholangiocarcinoma, n (%)	4 (1)	1 (1)	1 (4)	0 (0)	0.312	3 (0)	0.351
Cholangiocarcinoma, n (%)	30 (4)	2 (3)	1 (4)	1 (2)	0.529	28 (4)	0.759
Gallbladder cancer, n (%)	7 (1)	1 (1)	0 (0)	1 (2)	1.000	6 (1)	0.532
Hepatic cell carcinoma, n (%)	29 (4)	2 (3)	0 (0)	2 (4)	1.000	27 (4)	0.759
Liver metastasis, n (%)	42 (6)	6 (8)	0 (0)	6 (11)	0.169	36 (5)	0.427
Laboratory data at postoperative day 30							
Hemoglobin, g/L	118 ± 14	117 ± 15	115 ± 14	118 ± 15	0.632	119 ± 14	0.349
Creatinine, µmol/L	58 (48-70)	60 (50-74)	65 (54-90)	59 (49-73)	0.095	57 (48-69)	0.131
Medication at discharge							
β-Blocker, n (%)	59 (8)	8 (10)	6 (25)	2 (4)	0.010	51 (8)	0.371
β-Stimulant, n (%)	66 (9)	11 (14)	1 (4)	10 (19)	0.157	55 (8)	0.087
Renin-angiotensin system inhibitor, n (%)	179 (24)	20 (26)	9 (38)	11 (21)	0.162	159 (24)	0.637
Calcium channel blocker, n (%)	236 (31)	27 (35)	12 (50)	15 (28)	0.076	209 (31)	0.462
Levothyroxine, n (%)	20 (3)	0 (0)	0 (0)	0 (0)	NA	20 (3)	0.251
Anticholinergic agent, n (%)	49 (7)	7 (9)	2 (8)	5 (9)	1.000	42 (6)	0.329
Anticoagulation, n (%)	97 (13)	67 (87)	21 (88)	46 (87)	1.000	30 (4)	< 0.001

The Brinkman index is defined as the number of cigarettes smoked per day times smoking years. Malignancies at 2 different organs were simultaneously resected in 5 patients.

CHA_2DS_2VASc, congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex, and 2 points each for age ≥ 75 years and prior stroke, transient ischemic attack, and thromboembolism; NA, not applicable; POAF, perioperative atrial fibrillation.

*POAF patients with atrial fibrillation recurrence.

†POAF patients without atrial fibrillation recurrence.

‡Patients with new-onset POAF.

§Patients without POAF.

estimating the incidence of AF recurrence is demonstrated in Figure 1. β-Blockers were prescribed in patients who had a longer duration of AF (duration in those who received β-blockers, 15.8 hours [4.4-132.3]; duration in those who did not receive β-blockers, 3.0 hours [0.5-12.0]; $P = 0.063$). Univariate Cox regression analysis demonstrated that a higher AF recurrence rate was associated with higher serum creatinine level (HR for 20 µmol/L increase, 1.13; 95% CI, 1.05-1.21; $P = 0.001$), hypertension (HR, 3.78; 95% CI, 1.50-9.54; $P = 0.005$), concomitant coronary artery disease (HR, 3.93; 95% CI, 1.16-13.31; $P = 0.028$), maximum duration of POAF (HR for 1-hour increase in duration, 1.01; 95% CI, 1.00-1.01; $P = 0.009$), and prescription of β-blockers at discharge (HR, 4.38; 95% CI, 1.72-11.11; $P = 0.002$) (Table 2). Kaplan–Meier survival curve for estimating the incidence of AF recurrence according to the presence of hypertension is demonstrated in Figure 2. Multivariate analysis revealed similar results regarding the serum creatinine level at discharge and hypertension (Fig. 3).

Incidence of AF in patients without POAF

Of the 675 patients without POAF, AF within 1 year was observed in only 4 patients (0.6%). There was a significant difference in the incidence of AF between patients with and without POAF (POAF group, 31%; non-POAF group, 0.6%;

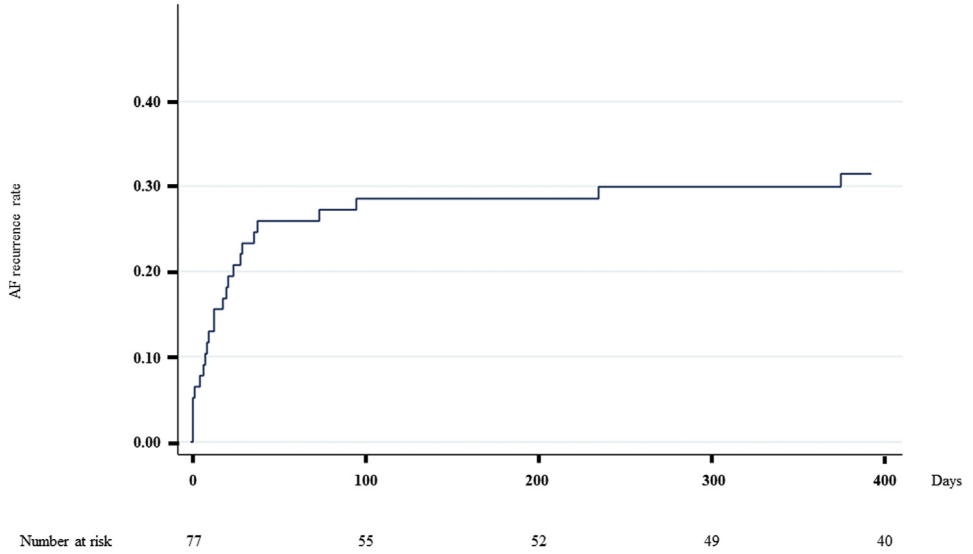

Figure 1. AF recurrence rate 1 year after noncardiac surgery for malignancy. Kaplan–Meier survival curve demonstrated AF recurrence rate of 30% at 1 year in patients with POAF. AF, atrial fibrillation; POAF, perioperative atrial fibrillation.

$P < 0.001$). However, it should be noted that patients without POAF were not subjected to routine postoperative monitoring; therefore, the recurrence rate of AF was likely underestimated in them.

Table 2. Cox regression analysis for AF recurrence in patients with POAF

	Univariate		
	HR	95% CI	*P* value
Age	1.03	0.97-1.09	0.348
Male	2.15	0.80-5.76	0.128
Body mass index (an increase of 1 kg/m^2)	1.09	0.97-1.23	0.140
Hypertension	3.78	1.50-9.54	0.005
Diabetes mellitus	1.13	0.45-2.86	0.791
Coronary artery disease	3.93	1.16-13.31	0.028
Chronic obstructive pulmonary disease	1.71	0.77-3.83	0.188
CHA_2DS_2-VASc score	1.28	0.92-1.78	0.143
Stages of malignancy (an increase of 1 stage)	0.74	0.48-1.15	0.183
Alcohol consumption (an increase of 10 g)	1.07	0.96-1.20	0.238
AF duration at the first onset (an increase of 1 h)	1.01	1.00-1.02	0.020
The longest duration of AF (an increase of 1 h)	1.01	1.00-1.01	0.009
Hemoglobin at discharge (an increase of 10 g/L)	0.90	0.69-1.19	0.475
Creatinine at discharge (an increase of 20 μmol/L)	1.13	1.05-1.21	0.001
Medication at discharge			
β-Blocker	4.38	1.72-11.11	0.002
β-Stimulant	0.42	0.06-3.14	0.401
Renin-angiotensin system inhibitor	1.65	0.72-3.76	0.238
Calcium channel blocker	1.97	0.88-4.38	0.098
Anticholinergic agent	0.89	0.21-3.79	0.876
Anticoagulation	1.03	0.31-3.45	0.963

AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex, and 2 points each for age ≥ 75 years and prior stroke, transient ischemic attack, and thromboembolism; CI, confidence interval; HR, hazard ratio; POAF, perioperative atrial fibrillation.

Incidence of stroke

Overall, 5 patients (2 with POAF and 3 without POAF) developed ischemic stroke at a median of the 38th (33-167) postoperative day. Anticoagulation was prescribed in 2 patients with POAF and 1 patient without POAF. The causes of stroke included embolic stroke due to AF (n = 2), embolic stroke of undetermined source (n = 2), and lacunar infarction (n = 1). Univariate Cox regression analysis revealed that 1-year AF development was associated with ischemic stroke (HR, 18.97; 95% CI, 3.16-113.76; $P = 0.001$), and POAF demonstrated a similar result, which was not statistically significant (HR, 5.88; 95% CI, 0.98-35.20; $P = 0.052$).

Relationship between AF and 1-year mortality in the setting of malignancy

At the end of 1 year, 35 patients (5%) died (1 cardiac death and 34 noncardiac deaths). Of them, 28 died of malignancies. Table 3 summarizes some of the variables related to mortality. In univariate Cox regression analysis, 1-year AF development was associated with 1-year all-cause mortality (HR, 4.78; 95% CI, 1.85-12.32; $P = 0.001$) and 1-year mortality due to malignancy (HR, 3.49; 95% CI, 1.05-11.55; $P = 0.041$), but POAF was not (all-cause mortality: HR, 0.82; 95% CI, 0.25-2.68; $P = 0.742$; mortality due to malignancy: HR, 0.67; 95% CI, 0.16-2.84; $P = 0.592$). These results persisted even after adjustment for diabetes mellitus, stage of malignancy, and hemoglobin level at discharge (all-cause mortality: HR, 6.01; 95% CI, 2.26-15.98; $P < 0.001$; mortality due to malignancy: HR, 4.94; 95% CI, 1.43-17.06; $P = 0.012$).

Discussion

To our knowledge, the present study is the first prospective cohort study that demonstrated the recurrence rate of AF in patients with POAF who underwent noncardiac surgeries for malignancies. The high AF recurrence rate and the asymptomatic nature are worthy of special mention. AF recurrence—rather

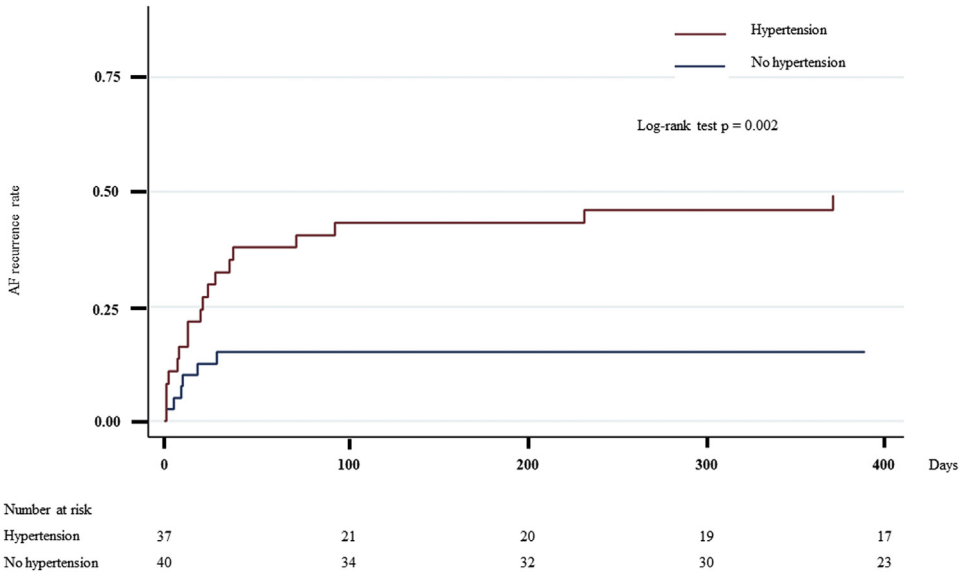

Figure 2. Hypertension as a predictor of higher 1-year AF recurrence rate. Log-rank test demonstrated that hypertension was associated with higher incidence of AF recurrence in patients with perioperative AF. AF, atrial fibrillation.

than POAF itself—is an important predictor of long-term adverse events. However, documentation of POAF is essential and should not be underestimated because of the subsequent high recurrence rate of AF.

Prediction of AF recurrence

The present study revealed that 1-year AF recurrence episodes were mostly asymptomatic as well as were observed in patients with malignancies who developed POAF.[9] Therefore, a follow-up based on symptoms such as palpitation would result in overlooking the recurrent episodes. The best way to detect AF recurrence would be by providing an event-triggered recorder for a long-term period. Patients with hypertension or renal impairment may be monitored more closely. Hypertension activates renin-angiotensin aldosterone system and sympathetic outflow, which result in left ventricular hypertrophy, diastolic dysfunction, and atrial stiffness, all of which contribute to AF.[10] Patients with chronic kidney disease are likely to have poor control of blood pressure, which

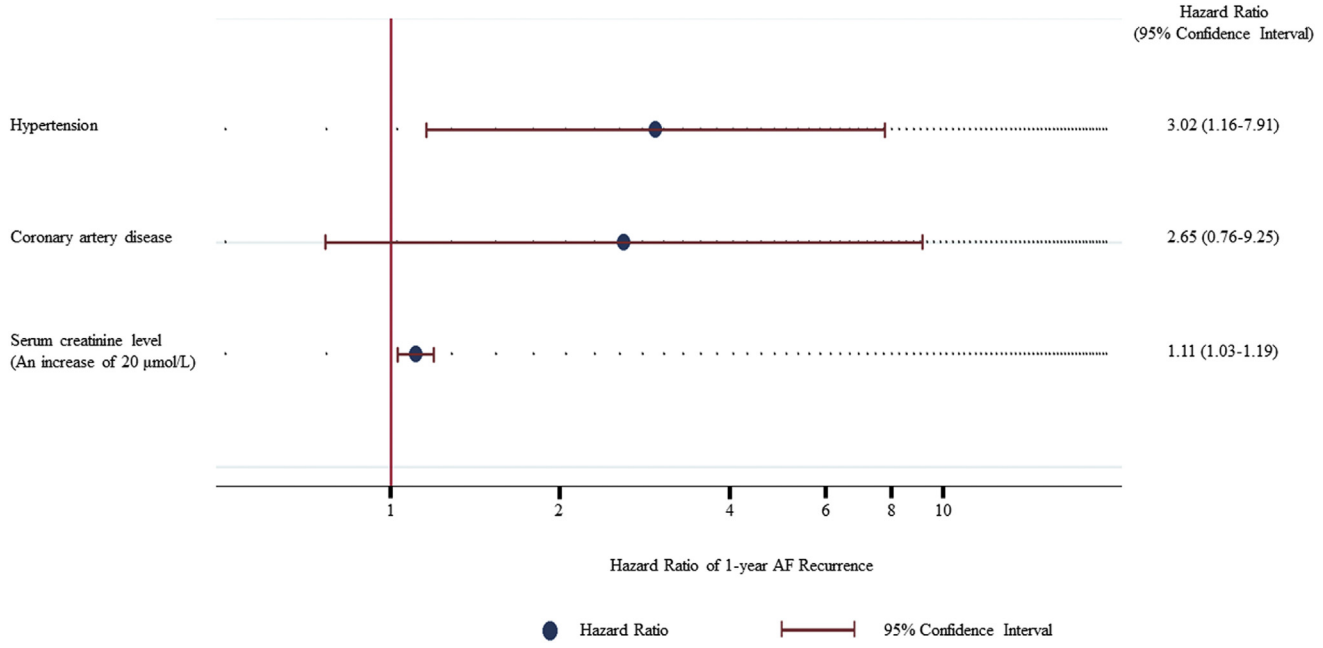

Figure 3. Predictors of 1-year AF recurrence. Multivariate Cox regression analysis demonstrated that hypertension and higher serum creatinine level were related to 1-year AF recurrence. Variables with a *P* value of < 0.10 in the univariate analysis were included in the multivariate Cox regression analysis, with the least absolute shrinkage and selection operator to identify the significant factors. AF, atrial fibrillation.

Table 3. Univariate Cox regression analysis for 1-year all-cause mortality

	HR	95% CI	*P* value
Age	1.02	0.99-1.06	0.231
Male	0.72	0.37-1.40	0.332
Body mass index (an increase of 1 kg/m^2)	0.98	0.89-1.08	0.653
Hypertension	0.77	0.39-1.51	0.447
Diabetes mellitus	2.70	1.36-5.35	0.005
Coronary artery disease	2.41	0.85-6.83	0.098
Chronic obstructive pulmonary disease	0.56	0.23-1.35	0.198
CHA_2DS_2-VASc score	1.29	1.00-1.67	0.052
Stages of malignancy (an increase of 1 stage)	1.45	1.13-1.87	0.004
POAF	0.82	0.25-2.68	0.742
Hemoglobin at discharge (increase of 10 g/L)	0.68	0.54-0.86	0.001
Creatinine at discharge (increase of 20 μmol/L)	0.99	0.79-1.25	0.964
Medication at discharge			
β-Blocker	1.60	0.57-4.54	0.374
β-Stimulant	0.37	0.05-2.67	0.322
Renin-angiotensin system inhibitor	0.52	0.20-1.33	0.170
Calcium channel blocker	0.63	0.29-1.39	0.255
Anticholinergic agent	0.42	0.06-3.05	0.389
Anticoagulation	0.40	0.10-1.68	0.211
1-y AF development	4.78	1.85-12.32	0.001

AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex, and 2 points each for age $\geq$ 75 years and prior stroke, transient ischemic attack, and thromboembolism; CI, confidence interval; HR, hazard ratio; POAF, perioperative atrial fibrillation.

results in the pathological activation of intra-renal renin-angiotensin aldosterone system, atrial fibrosis, and electrical remodeling.[11]

Anticoagulation

We should consider anticoagulation for a certain number of patients with POAF for a long-term period. One of the significant features in our study was a higher prescription rate of anticoagulation compared with those in previous studies.[12] This prescription rate may have resulted in the low incidence of stroke.

Long-term clinical impacts of POAF and 1-year AF development

The present study demonstrated that not POAF, but 1-year AF development, was associated with 1-year all-cause mortality, despite the significant relationship between POAF and AF recurrence. Because 1-year AF development was significantly higher in those with POAF, it is reasonable that the apparent association between POAF and long-term adverse events has been reported in previous studies. Otherwise, the result may be due to β error because of the small number of patients. The backgrounds of patients with POAF may be heterogeneous. Some factors that result in 1-year AF development may also affect the subsequent clinical course. It is plausible that AF does not accelerate the progression of malignancy. Inflammation may be a key factor in explaining the clinical impact of 1-year AF development.[13-15] Inflammation plays an important role in carcinogenesis[16] and both electrical and structural atrial remodeling.[17] A previous study suggested that malignancy does not directly lead to AF but does so via inflammation.[18] The association between AF recurrence and noncardiac mortality might be explained through chronic inflammation due to carcinogenesis, paraneoplastic syndromes, and the intrinsic characteristics of patients with malignancy.[19]

Study limitations

First, this study was a prospective single-center study. The types of malignancies and surgeries may be biased. However, the study included consecutive patients who underwent surgeries with various degrees of invasiveness for common malignancies. Second, some of the recurrences of AF in those with POAF might have been overlooked because of insufficient duration of wearing the event recorder. Although an implantable loop recorder would be more useful and precise, it also has considerable ethical and impractical issues. Third, AF burden was not assessed by SPIDER FLASH-t AFib because of its incapability. AF burden for anticoagulation cannot be determined in this study. Finally, 1-year AF development in the patients without POAF would have been underestimated because they did not routinely wear an event recorder. However, according to a Japanese survey, the annual incidence of AF in healthy subjects aged $\geq$40 years was 0.9%,[20] which was similar to the incidence in those without POAF in our study. Another study indicated that the incidence of AF after cancer diagnosis was 1.8% over 9 years.[21] Although their backgrounds differed, there might be slight underestimation in those without POAF, who were observed with continuous ECG monitors as well as those with POAF and did not develop AF even after highly invasive surgeries. It would be reasonable that the non-POAF group demonstrated a low incidence of AF recurrence.

Conclusions

POAF in noncardiac surgeries for malignancies is not a temporal arrhythmia, and its recurrence rate is relatively high. Most episodes of recurrence are asymptomatic, and recurrence is associated with subsequent adverse events. Further studies are needed to assess the value of anticoagulation for recurrent AF in this population.

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Disclosures

The authors have no conflicts of interest to disclose.

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