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*World J Clin Cases* 2022 April 16; 10(11): 3321-3638



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Hua-Ge Yin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

April 16, 2022

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**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>





Retrospective Study

## Predictors and prognostic impact of post-operative atrial fibrillation in patients with hip fracture surgery

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**Specialty type:** Cardiac and cardiovascular systems

**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Sawalha K, United States; Xie M, China

**Received:** October 15, 2021

**Peer-review started:** October 15, 2021

**First decision:** December 17, 2021

**Revised:** December 18, 2021

**Accepted:** February 17, 2022

**Article in press:** February 27, 2022

**Published online:** April 16, 2022



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### Abstract

#### BACKGROUND

Atrial fibrillation (AF) is the most common arrhythmia developing in post-operative patients. Limited data are available regarding pre-operative risk factors and prognostic impact of post-operative AF (POAF) following hip fracture surgery (HFS) in Korean population.

#### AIM

We aimed to investigate the incidence, predictors, and hospital prognosis of POAF in HFS patients.

#### METHODS

This study included 245 patients without history of AF who underwent HFS between August 2014 and November 2016. POAF was defined as new-onset AF that occurred during hospitalization after HFS.

#### RESULTS

Twenty patients (8.2%) experienced POAF after HFS. POAF developed on median post-operative day 2 (interquartile range, 1–3). Multivariable logistic regression analysis showed that age [odds ratio (OR), 1.111; 95% confidence interval (CI), 1.022–1.209], chronic obstructive pulmonary disease (COPD) (OR, 6.352; 95% CI, 1.561–25.841) and E/e' ratio (OR, 1.174; 95% CI, 1.002–1.376) were significant predictors of POAF. Patients with POAF had a significantly higher intensive care unit admission rate (55.0% vs 14.7%,  $P < 0.001$ ) and incidence of congestive heart failure (45.0% vs 10.7%,  $P < 0.001$ ). In multivariable logistic regression analysis, POAF was significantly associated with increased incidence of congestive heart

failure (OR, 4.856; 95%CI, 1.437–16.411) and intensive care unit admission (OR, 6.615; 95%CI, 2.112–20.718).

### CONCLUSION

POAF was frequently developed in elderly patients following HFS. Age, COPD and elevated E/e' ratio were found as significant predictors of POAF in HFS patients. Patients with POAF significantly experienced intensive care unit admission and incident congestive heart failure during hospitalization.

**Key Words:** Atrial fibrillation; Post-operative; Predictor; Prognosis; Hip fracture surgery

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**Core Tip:** This study is a retrospective study to evaluate the predictors and prognosis of post-operative atrial fibrillation (POAF) following hip fracture surgery (HFS) in elderly patients. Atrial fibrillation (AF) was developed in 8.2% following HFS. Patients with older age, COPD, or elevated E/e' ratio were shown as high risk of suffering POAF following HFS. Moreover, Patients with POAF significantly experienced intensive care unit admission and incident heart failure rather than those without POAF. Therefore, physicians have to carefully observe the occurrence of AF after HFS in elderly patients.

**Citation:** Bae SJ, Kwon CH, Kim TY, Chang H, Kim BS, Kim SH, Kim HJ. Predictors and prognostic impact of post-operative atrial fibrillation in patients with hip fracture surgery. *World J Clin Cases* 2022; 10(11): 3379-3388

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i11/3379.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v10.i11.3379>

## INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is independently associated with increased risks of mortality and morbidity[1,2]. Incidence of post-operative AF (POAF) has been reported as 15%–45% of patients after cardiac surgery[3,4], and 0.4%–3% after non-cardiac surgery[5,6]. POAF after cardiac surgery is associated with increased length of hospital stay, early stroke risk, morbidity, and 30-d mortality[7-9]. In addition, a recent study has shown that patients with POAF after non-cardiac surgery have a significantly higher risk of stroke, myocardial infarction, and death at 1 year than patients without developing POAF[10].

Approximately 300000 individuals are hospitalized with hip fractures in the United States per year, and about one-third of these patients go on to receive a hip fracture surgery (HFS)[11,12]. Hip fractures occur frequently with aging in patients older than 65 years[13], and substantially increase the risk of death and major morbidity in elderly patients[14,15]. Moreover, HFS is associated with post-operative cardiovascular complications including AF[16-18]. Therefore, we aimed to investigate the incidence, predictors, and clinical impact of POAF in HFS patients.

## MATERIALS AND METHODS

### Study patients

This retrospective study involved 435 patients who underwent HFS in the Konkuk University Medical Center between August 2014 and November 2016. We excluded 190 patients who met the following exclusion criteria: (1) Patients with preoperative acute coronary syndrome (ACS) or acute decompensated congestive heart failure (CHF) ( $n = 18$ ); (2) Patients with AF documented in a preoperative evaluation ( $n = 35$ ); and (3) Patients with insufficient preoperative clinical or laboratory data ( $n = 138$ ). Finally, 245 patients were included in this analysis. We evaluated the occurrence of POAF during hospitalization after HFS.

### Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of the Konkuk University Medical Center (protocol No. KUMC 2019-07-053). The requirement for informed consent was waived because de-identified information was retrieved retrospectively.

### Study outcomes and definitions

The primary outcome was the new-onset POAF during hospitalization after HFS. POAF was defined as AF of any duration on 12-lead electrocardiography (ECG) during the post-operative period. We evaluated the incidence of clinical adverse events including ACS, CHF, pulmonary thromboembolism, and death according to the occurrence of POAF. Post-operative ACS was defined as the appearance of appropriate clinical symptoms representing unstable angina or evidence of myocardial infarction defined as creatine kinase-myocardial band levels that increased to > 2 times the upper normal limit in association with at least one of the following ECG findings: New Q wave ( $\geq 30$  ms in 2 continuous leads), persistent significant ST elevation or depression, or a new regional wall motion abnormality. Post-operative CHF was defined as the appearance of appropriate clinical symptoms and signs of CHF that required diuretics or post-operative ventilation regardless of left ventricular ejection fraction. Pulmonary thromboembolism was diagnosed if there was a thrombus in the pulmonary arteries on computed tomographic angiography. We also compared the incidence of transfusion, admission duration, and rate of intensive care unit admission according to the occurrence of POAF.

### Statistical analysis

Statistical analyses were performed using SPSS 17 software (SPSS Inc., Chicago, IL, the United States). The data were expressed as the mean  $\pm$  SD for continuous variables and as frequencies with percentages for categorical variables. Continuous variables were compared by using a Student's *t*-test or Mann-Whitney test, and categorical variables using a chi-square test or Fisher's exact test. The associations of clinical, echocardiographic, or laboratory variables with the development of POAF were assessed by using univariable and multivariable logistic regression models. All variables with *P* values < 0.10 in univariable analysis were included in the multivariable analysis. A multivariable logistic regression model with stepwise backward elimination was used to test the independent correlations of these variables with POAF. Significant predictors for incident heart failure and intensive care unit admission were assessed by using univariable and multivariable logistic regression models. All *P* values were two-tailed, and a *P* < 0.05 was considered statistically significant.

## RESULTS

**Figure 1** shows incidence, risk factors, and prognostic impact of POAF following HFS. The mean age of the study patients was  $76.4 \pm 13.1$  years, and 64.9% were female. Among the 245 HFS patients enrolled in this analysis, POAF developed in 20 patients (8.2%) during post-operative hospitalization. POAF occurred on median post-operative day 2 (interquartile range[1-3]). Baseline characteristics of the patients according to occurrence of POAF are shown in **Table 1**. Patients with POAF were more likely to be older, to have history of previous myocardial infarction, previous CHF, or chronic obstructive pulmonary disease (COPD), and to have higher *e/e'* ratio levels significantly.

In the univariable logistic regression analysis, age, previous myocardial infarction, previous CHF, and COPD were significantly associated with development of POAF after HFS (**Table 2**). However, in multivariable logistic regression analysis with stepwise backward elimination, age, COPD, and *E/e'* ratio level were left as significant predictors of POAF (**Table 2**).

**Table 3** shows clinical adverse events during hospitalization according to occurrence of POAF. Patients with POAF required more transfusion and longer hospitalization than those without POAF, but the difference was not statistically significant. The incidences of intensive care unit admission and CHF were significantly increased in patients with POAF. Median time of CHF incidence was post-operative day 3 (interquartile range[2-4]). The incidences of pulmonary thromboembolism, ACS, or death during hospitalization were not different significantly between two groups. All death events were developed in patients without POAF. Two patients died from cardiac arrest and one patient died from hypovolemic shock.

**Table 4** shows the results of logistic regression analyses to evaluate independent predictors of incident CHF following HFS. Lower hemoglobin levels and POAF were found as significant predictors of incident CHF following HFS in multivariable analysis. Independent predictors of intensive care unit admission following HFS are shown in **Table 5**. History of previous stroke, elevated creatinine levels, and POAF were significantly associated with intensive care unit admission following HFS.

## DISCUSSION

The major findings of the present study are as follows: (1) The incidence of POAF was 20 (8.2%) among 245 patients with HFS; (2) Age, COPD, and elevated *E/e'* ratio were significant predictors of POAF in these patients; (3) Incidences of intensive care unit admission and CHF during hospitalization were significantly higher in patients with POAF; and (4) POAF was significantly associated with intensive care unit admission and incident CHF following HFS.



**Table 1** Baseline characteristics of study patients according to occurrence of post-operative atrial fibrillation

Variables	Sinus rhythm (n = 225)	POAF (n = 20)	P value
Age (yr)	75.3 ± 13.3	84.3 ± 5.7	< 0.001
Male	79 (35.1)	7 (35.0)	0.992
Medical history			
Hypertension	153 (68.0)	14 (70.0)	0.854
Diabetes	68 (30.2)	5 (25.0)	0.625
Chronic kidney disease	30 (13.3)	5 (25.0)	0.153
Coronary artery disease	15 (6.7)	3 (15.0)	0.171
Previous MI	6 (2.7)	3 (15.0)	0.005
Previous CHF	9 (4.0)	3 (15.0)	0.029
Previous stroke	27 (12.0)	1 (5.0)	0.346
COPD	14 (6.2)	6 (30.0)	< 0.001
Echocardiographic parameter			
LVEF, %	59.1 ± 6.9	56.3 ± 9.2	0.096
LVEF < 50%	18 (8.0)	2 (10.0)	0.754
E/e'	10.9 ± 3.2	12.6 ± 2.8	0.047
Laboratory parameter			
Hemoglobin, g/dL	11.8 ± 2.0	11.2 ± 2.1	0.227
Creatinine, mg/dL	1.0 ± 1.1	1.2 ± 0.8	0.634
CK-MB, ng/mL	2.9 ± 3.9	2.8 ± 4.3	0.863
hsTn-I, ng/L	30.3 ± 155.2	24.1 ± 29.1	0.858
NT-proBNP, pg/dL	598.8 ± 1923.4	1172.7 ± 1844.5	0.251

Data are expressed as the mean ± standard deviation, or as a number (percentage). CHF: Congestive heart failure; CK-MB: Creatine kinase-myocardial band; COPD: Chronic obstructive pulmonary disease; hsTn-I: High-sensitivity troponin I; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; NT-proBNP: N-terminal pro-brain natriuretic peptide; and POAF: Post-operative atrial fibrillation.

The 8.2% incidence of POAF was consistent with previous results[5,6,10]. Among various types of non-cardiac surgery, abdominal, thoracic and vascular surgeries have been associated with higher incidence rates of POAF[5,10,19]. Although HFS is orthopedic surgery, most patients with hip fractures are elderly and commonly have impaired functional status and medical comorbidities[15,20]. Moreover, in elderly patients receiving HFS, perioperative atrial arrhythmias were reported to be common (5.6%) and to be associated with greater mortality[21]. Rhythm monitoring might be used only for selected patients after surgery, and patients do not always feel AF symptoms. Therefore, the incidence of POAF in this study might be underestimated. So, we have to monitor rhythm status actively in elderly patients as having high risk of POAF during the perioperative period.

In this analysis, age, COPD, and elevated e/e' ratio were significant predictors of POAF after HFS. Old age, pre-existing AF, CHF, ischemic heart disease, hypertension, chronic renal failure, sepsis, shock, asthma, and valvular heart disease are associated with increased risk of POAF[5,22-24]. The pathophysiology of the development of POAF after non-cardiac surgery is not fully understood. Potential mechanisms may be explained by a combination of multiple factors including increased sympathetic activity, autonomic stimulation, electrolyte imbalance, anemia, underlying cardiac disease, metabolic alterations, hypothermia, inflammation, hypoxia, and intraoperative adverse events like hypotension[25]. The prevalence and incidence of AF are elevated among patients with COPD[26,27]. Although we did not evaluate lung function in this study, patients with COPD history might have reduced lung function compared to those without COPD. Therefore, these patients are more likely to experience hypoxia in stress situations caused by surgery, which may cause hypoxia-driven POAF. In addition, E/e' ratio is well known marker for high left ventricular filling pressure[28]. In this analysis, elevated E/e' ratio was a significant predictor of POAF. Elevated E/e' ratio has been reported as significant predictor of POAF following non-cardiac surgery[29-31]. Elevated E/e' ratio presents left ventricular diastolic dysfunction, which is related to increased left atrial filling pressures. With increasing pressure in left atrium, pathological changes including increased atrial afterload, myocyte

**Table 2 Independent predictors of post-operative atrial fibrillation following hip fracture surgery**

Variables	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Age (yr)	1.100 (1.031-1.172)	0.004	1.111 (1.022-1.209)	0.014
Male	0.995 (0.382-2.596)	0.992		
Hypertension	1.098 (0.405-2.974)	0.854		
Diabetes mellitus	0.770 (0.269-2.202)	0.625		
Chronic kidney disease	2.167 (0.734-6.397)	0.162		
Coronary artery disease	0.405 (0.107-1.537)	0.184		
Previous MI	6.441 (1.479-28.046)	0.013		
Previous CHF	4.235 (1.048-17.120)	0.043		
Previous stroke	0.386 (0.050-3.000)	0.363		
COPD	6.459 (2.153-19.380)	0.001	6.352 (1.561-25.841)	0.010
LVEF (%)	0.952 (0.899-1.009)	0.098		
E/e'	1.151 (0.999-1.327)	0.051	1.174 (1.002-1.376)	0.047
Hemoglobin (g/dL)	0.870 (0.694-1.091)	0.228		
Creatinine (mg/dL)	1.083 (0.778-1.506)	0.636		
CK-MB (ng/mL)	0.988 (0.872-1.120)	0.853		
hsTn-I (ng/L)	1.000 (0.996-1.003)	0.859		
NT-proBNP (pg/dL)	1.000 (1.000-1.000)	0.279		

CHF: Congestive heart failure; CK-MB: Creatine kinase-myocardial band; COPD: Chronic obstructive pulmonary disease; hsTn-I: High-sensitivity troponin I; LVEF: Left ventricular ejection fraction; MI: myocardial infarction; NT-proBNP: N-terminal pro-brain natriuretic peptide; and OR: Odds ratio.

**Table 3 Clinical adverse events during hospitalization according to occurrence of post-operative atrial fibrillation**

	Sinus rhythm (n = 225)	POAF (n = 20)	P value
Transfusion	190 (84.4)	19 (95.0)	0.201
Transfused packed RBC count	3.4 ± 4.4	4.1 ± 2.4	0.508
Admission day	23.0 ± 33.8	29.6 ± 18.4	0.391
Intensive care unit admission	33 (14.7)	11 (55.0)	< 0.001
Congestive heart failure	24 (10.7)	9 (45.0)	< 0.001
Pulmonary thromboembolism	4 (1.8)	0 (0.0)	0.548
Acute coronary syndrome	7 (3.1)	2 (10.0)	0.117
Death	3 (1.3)	0 (0.0)	0.548

Data are expressed as the mean ± SD, or as a number (percentage). POAF: Post-operative atrial fibrillation; RBC: Red blood cell.

stretch, and atrial wall stress are developed[32]. This consequent left atrial remodeling is believed as main mechanism of POAF following HFS.

Patients with POAF required a longer hospital stay, had a higher intensive care unit admission, and experienced more development of CHF during hospitalization. Our results are consistent with previous findings that POAF leads to increased length of hospital stay and subsequently elevated health care costs[22,23,33]. Moreover, recent cohort including large number ( $n = 2922$ ) of patients underwent HFS reported that patients with POAF experienced not only higher length of hospital stay but also higher 1-year mortality in comparison to control group[34]. The present study only showed significant association between POAF and in-hospital complications, but this study revealed poor long-term prognosis of POAF patients. AF and CHF often occur together, and each can precede and follow the other[35]. In this study, POAF occurred on median day 2 after surgery, but CHF developed on median post-operative day 3. Thus, CHF might not result in POAF in these patients. Even then, we cannot

**Table 4 Independent predictors of incident congestive heart failure following hip fracture surgery**

Variables	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Age (yr)	1.060 (1.015-1.107)	0.008		
Male	1.238 (0.583-2.629)	0.579		
Hypertension	0.924 (0.424-2.015)	0.843		
Diabetes mellitus	0.724 (0.310-1.690)	0.455		
Chronic kidney disease	3.917 (1.692-9.066)	0.001	2.570 (0.946-6.980)	0.064
Coronary artery disease	1.951 (0.601-6.333)	0.266		
Previous MI	5.710 (1.450-22.495)	0.013		
Previous CHF	5.230 (1.554-17.602)	0.008		
Previous stroke	1.080 (0.350-3.339)	0.893		
COPD	5.333 (1.989-14.303)	0.001	3.408 (0.898-12.934)	0.072
LVEF (%)	0.971 (0.925-1.020)	0.243		
E/e'	1.088 (0.967-1.224)	0.159		
Hemoglobin (g/dL)	0.688 (0.565-0.838)	< 0.001	0.753 (0.597-0.949)	0.016
Creatinine (mg/dL)	1.266 (0.997-1.608)	0.053		
CK-MB (ng/mL)	1.042 (0.969-1.121)	0.268		
hsTn-I (ng/L)	1.001 (0.999-1.003)	0.334		
NT-proBNP (pg/dL)	1.000 (1.000-1.000)	0.050		
Post-operative AF	6.852 (2.579-18.209)	< 0.001	4.856 (1.437-16.411)	0.011

AF: Atrial fibrillation; CHF: Congestive heart failure; CK-MB: Creatine kinase-myocardial band; COPD: Chronic obstructive pulmonary disease; hsTn-I: High-sensitivity troponin I; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; NT-proBNP: N-terminal pro-brain natriuretic peptide; and OR: Odds ratio.

conclude that POAF directly causes CHF after surgery. Because patients with POAF had more chronic comorbidities like COPD and CKD, the poor outcomes might be the consequence of their comorbidities rather than the result of POAF. Even we cannot explain complex mechanism between POAF and post-operative CHF development, we need to pay more attention to the development of CHF when patients experience POAF following surgery.

### Limitations

This study had several inherent limitations. First, the study design was retrospective and observational, and thus we could not adjust potential confounding factors. Second, evaluation of 12-lead ECG after HFS was not consistent and uniform because it was left to the discretion of attending physician. Third, diagnosis of POAF was based only on 12-lead ECG. Therefore, the incidence of new-onset POAF might have been underestimated because paroxysmal AF, especially asymptomatic episodes, could not be diagnosed. Fourth, a large population ( $n = 138$ ) with insufficient laboratory data including high-sensitivity troponin I and/or N-terminal pro-brain natriuretic peptide were excluded from this study because pre-operative biomarker evaluation was not performed in all patients. Therefore, there would be a selection bias associated with this factor. Fifth, frailty is a strong indication for mortality, intensive care unit admission, and AF. But, we could not incorporate frailty score in our analysis. Finally, because study patients and incident POAF patients ( $n = 20$ ) were relatively small, the statistical power for the predictors of POAF might have been low. Moreover, for this reason, we only evaluated the association between POAF and in-hospital complications, but not long-term prognosis of POAF. Despite these limitations, the present study may have clinical significance because this analysis showed real-world observational results in elderly Korean patients who underwent HFS.

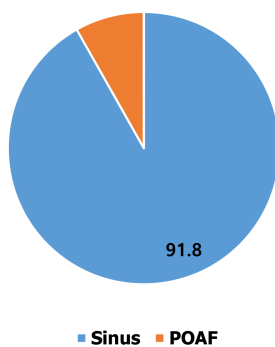
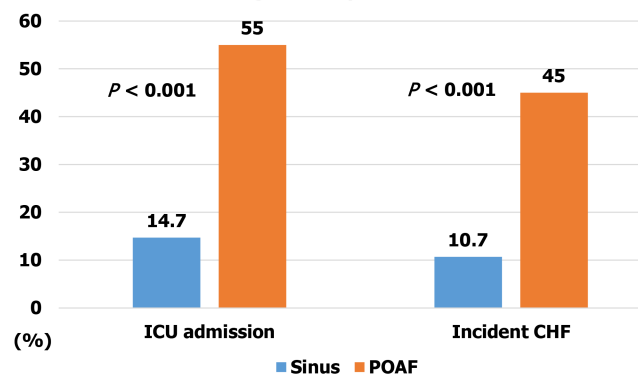
### CONCLUSION

The incidence of POAF was 8.2% in patients with HFS. Age, COPD and elevated E/e' ratio were potential predictors of POAF in these patients. Patients with POAF significantly experienced intensive care unit admission and incident CHF during hospitalization. POAF was revealed as significant

**Table 5 Independent predictors of intensive care unit admission following hip fracture surgery**

Variables	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Age (yr)	1.017 (0.989-1.046)	0.242		
Male	0.836 (0.417-1.678)	0.615		
Hypertension	0.781 (0.394-1.546)	0.477		
Diabetes mellitus	1.444 (0.727-2.868)	0.295		
Chronic kidney disease	2.458 (1.100-5.496)	0.028		
Coronary artery disease	1.336 (0.418-4.271)	0.626		
Previous MI	2.378 (0.571-9.900)	0.234		
Previous CHF	5.132 (1.571-16.763)	0.007	3.295 (0.860-12.632)	0.082
Previous stroke	2.463 (1.030-5.889)	0.043	3.718 (1.326-10.420)	0.013
COPD	2.109 (0.762-5.837)	0.151		
LVEF (%)	0.979 (0.937-1.024)	0.358		
E/e'	1.032 (0.928-1.148)	0.557		
Hemoglobin (g/dL)	0.853 (0.724-1.004)	0.057		
Creatinine (mg/dL)	1.348 (1.054-1.725)	0.018	1.416 (1.085-1.848)	0.011
CK-MB (ng/mL)	1.033 (0.963-1.108)	0.368		
hsTn-I (ng/L)	1.002 (1.000-1.004)	0.112		
NT-proBNP (pg/dL)	1.000 (1.000-1.000)	0.019		
Post-operative AF	7.111 (2.736-18.484)	<0.001	6.615 (2.112-20.718)	0.001

AF: Atrial fibrillation; CHF: Congestive heart failure; CK-MB: Creatine kinase-myocardial band; COPD: Chronic obstructive pulmonary disease; hsTn-I: High-sensitivity troponin I; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; NT-proBNP: N-terminal pro-brain natriuretic peptide; and OR: Odds ratio.

**Incidence (%) of POAF following HFS****Prognostic impact of POAF****Risk factors of POAF**

	Adjusted OR (95%CI)	P value
Age (yr)	1.111 (1.022-1.209)	0.014
COPD	6.352 (1.561-25.841)	0.010
E/e' ratio	1.174 (1.002-1.376)	0.047

**Prognostic impact of POAF**

	ICU admission	Incident CHF
Adjusted OR (95%CI)	6.615 (2.112-20.718)	4.856 (1.437-16.411)

DOI: 10.12998/wjcc.v10.i11.3379 Copyright © The Author(s) 2022.

**Figure 1 Incidence, risk factors, and prognostic impact of post-operative atrial fibrillation following hip fracture surgery.** POAF: Post-operative atrial fibrillation; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; ICU: Intensive care unit.

predictor of intensive care unit admission and incident CHF. Therefore, physicians have to observe closely the incidence of POAF in old HFS patients.

## ARTICLE HIGHLIGHTS

### **Research perspectives**

Physicians have to carefully observe the occurrence of atrial fibrillation (AF) after hip fracture surgery (HFS) in elderly patients.

### **Research conclusions**

Age, chronic obstructive pulmonary disease (COPD) and elevated E/e' ratio were found as significant predictors of post-operative AF (POAF) in HFS patients. Patients with POAF significantly experienced intensive care unit admission and incident congestive heart failure during hospitalization.

### **Research results**

The major findings of the present study are as follows: (1) The incidence of POAF was 20 (8.2%) among 245 patients with HFS; (2) Age, chronic obstructive pulmonary disease, and elevated E/e' ratio were significant predictors of POAF in these patients; (3) Incidences of intensive care unit admission and congestive heart failure during hospitalization were significantly higher in patients with POAF; and (4) POAF was significantly associated with intensive care unit admission and incident congestive heart failure following HFS.

### **Research methods**

This retrospective study involved 245 patients who underwent HFS in the Konkuk University Medical Center between August 2014 and November 2016. We evaluated the incidence, risk factors, and prognosis impact during hospitalization following HFS.

### **Research objectives**

We aimed to investigate the incidence, predictors, and hospital prognosis of POAF in HFS patients.

### **Research motivation**

People are getting older, and many elderly patients have been undergoing HFS. Atrial fibrillation is the most common arrhythmia developing in post-operative patients. So, we were wondering if POAF may affect in-hospital outcomes in patients underwent HFS.

### **Research background**

Limited data are available regarding pre-operative risk factors and prognostic impact of post-operative atrial fibrillation following hip fracture surgery in Korean population.

## FOOTNOTES

**Author contributions:** Kwon CH conceived and designed the research study; Bae SJ acquisitioned the data; Bae SJ and Kwon CH analysed and interpreted the data; Bae SJ and Kwon CH prepared the manuscript; Kwon CH, Bae SJ, Kim TY, Chang H, Kim BS, Kim SH, and Kim HJ revised the manuscript.

**Institutional review board statement:** The present study protocol was reviewed and approved by the Institutional Review Board of the Konkuk University Medical Center (protocol No. KUMC 2019-07-053). The requirement for informed consent was waived because de-identified information was retrieved retrospectively.

**Conflict-of-interest statement:** The authors declare that there is no conflict of interest.

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S-Editor: Xing YX

L-Editor: A

P-Editor: Xing YX

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