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The impact of sustained new-onset atrial fibrillation on mortality and stroke incidence in critically ill patients: A retrospective cohort study

Takuo Yoshida [a,*], Shigehiko Uchino [a], Taisuke Yokota [b], Tomoko Fujii [c], Shoichi Uezono [a], Masanori Takinami [a]

[a] Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan
[b] Department of Anesthesiology, Dokkyo Medical University, Koshigaya Hospital, Saitama, Japan
[c] Epidemiology and Preventive Medicine, Graduate School of Medicine Kyoto University, Kyoto, Japan

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ABSTRACT

Purpose: The purpose of the study is to evaluate the impact of sustained new-onset AF on mortality and the incidence of stroke in critically ill non-cardiac surgery patients.
Material and methods: This was a retrospective cohort study of non-cardiac surgery patients with new-onset AF conducted in a general intensive care unit. We compared patients remaining in AF with those restored to sinus rhythm (SR) at 6 h after the onset of AF and conducted multivariable logistic regression analysis for in-hospital mortality. We also examined the impact of the cumulative time of AF duration in the first 48 h on hospital outcomes.
Results: New-onset AF occurred in 151 of 1718 patients (9%). Patients with sustained AF after 6 h (34% of 151 patients included) experienced greater in-hospital mortality than patients with SR at 6 h (37% vs. 20%, $p = 0.033$). Multivariable logistic regression analysis confirmed the association between AF at 6 h and in-hospital mortality (adjusted odds ratio, 3.14; 95% confidence intervals, 1.28–7.69; $p = 0.012$). Patients with longer AF duration had greater in-hospital mortality ($p = 0.043$) and in-hospital ischemic stroke incidence ($p = 0.041$).
Conclusion: Sustained new-onset AF is associated with poor outcomes.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in critically ill patients [1-3], with a reported incidence ranging between 4.5 and 15% among patients in the general intensive care unit (ICU) [1,4-11]. Multiple previous studies have shown that the development of new-onset AF in critically ill patients is associated with increased mortality [4,6, 12-14]. Several studies have also reported the association between the development of new-onset AF in critically ill patients and thromboembolic events [13,15-17].

Despite the amount of information available for the development of new-onset AF in critically ill patients, data on the impact of duration of sustained new-onset AF on patient outcomes are scarce [18-20]. Therefore, it is unclear whether the sustained new-onset AF contributes to poor outcomes or is only a marker of severe disease [21-24]. With respect to cardiac surgery, results of a clinical trial showed that the administration of antiarrhythmic drugs did not affect patient outcomes once patients develop new-onset AF in the early postoperative period [25, 26]. In non-cardiac surgery patients, however, there are insufficient data on even epidemiology of patient outcomes of sustained new-onset AF [20,27,28].

Therefore, we conducted a retrospective cohort study to evaluate the impact of sustained new-onset AF on mortality and stroke incidence in critically ill non-cardiac surgery patients.

2. Material and methods

2.1. Study design and patients

This was a retrospective cohort study in a 20-bed ICU at Jikei University Hospital in Tokyo, Japan. The study protocol was approved by the Jikei University Institutional Review Board (27-062[7947]). Written informed consent was waived in view of the observational nature of this study.

We enrolled non-cardiac surgery patients aged 18 years or older, who were admitted to the ICU between January 1, 2010, and December

Abbreviations: AF, atrial fibrillation; SR, sinus rhythm; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPSII, Simplified Acute Physiology Score II; OR, odds ratio; CI, confidence interval; ACE, angiotensin converting enzyme; ARBs, Angiotensin II receptor blockers; CRRT, continuous renal replacement therapy.

* Corresponding author at: Intensive Care Unit, Department of Anesthesiology, The Jikei University School of Medicine, 3-19-18, Nishi-Shinbashi Minato-ku, Tokyo 105-8471, Japan.
E-mail addresses: hawaii28981@jikei.ac.jp (T. Yoshida), tofujii-tky@umin.net (T. Fujii).

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31, 2013, and who remained longer than 24 h in the ICU. New-onset AF was defined as the development of AF in the ICU in a patient with no prior history of AF.

We first screened for the development of AF based on interpretations of continuous electrocardiographic monitoring by the ICU staff (who then recorded their findings in the electrical medical records every 2 h) or documentation of any occurrence of arrhythmia in the nursing records, which included the following words: "atrial fibrillation," "atrial flutter," "tachycardia," "supraventricular," and "cardioversion." We also retrieved chart records of antiarrhythmic agents and screened patients' charts for the administration of any of the following: "amiodarone," "diltiazem," "pilsicainide," "magnesium," and "propranolol." Patients without any related records, or who experienced any AF during the first 2 h in the ICU were excluded because the timing of AF development before ICU admission was unclear. After the initial screening, we manually reviewed all medical records and excluded patients with a previous history of AF on ICU admission note, those with any rhythm abnormality other than AF, or those who had decision to withhold or withdraw medical therapy at the time of onset of new-onset AF.

2.2. Data collection

We reviewed interpretations of continuous electrocardiographic monitoring by the ICU staff at 6, 12, 18, 24, 30, 36, 42, 48 h after the onset of AF. If patients were discharged from the ICU within 48 h after the onset of AF, we also reviewed medical records including electrocardiographic monitoring in the general ward. The following information was collected from the medical records and ICU patient database: age, sex, body mass index, past medical history (hypertension, diabetes, congestive heart failure, prior stroke or transient ischemic attack, chronic hemodialysis, liver failure, hematological cancer, and immunosuppression), previous medication (calcium-channel blockers, β-blocking agents, angiotensin converting enzyme inhibitors, Angiotensin II receptor blockers, and anticoagulants), patient category at ICU admission (non-scheduled surgical, scheduled surgical, medical), Acute Physiology and Chronic Health Evaluation (APACHE) II score [29], Simplified Acute Physiology Score (SAPS) II [30], infection on ICU admission, ICU readmission, number of days between the onset of AF and ICU admission, and treatment in ICU (central venous catheter, pulmonary artery catheter, usage and duration of mechanical ventilation, tracheotomy, continuous renal replacement therapy, drug treatment for AF). History of diabetes or hypertension was determined based on patients' medications. We calculated the CHADS2 score [31], which was used to estimate the risk of stroke, by adding one point for each of the following conditions: recent congestive heart failure, hypertension, age 75 years or older, or diabetes mellitus; two points were added for a prior transient ischemic attack or a prior stroke. We also collected physiological status at the onset and interventions for AF after the onset: mechanical ventilation and hemodynamic status (mean arterial pressure, norepinephrine use, vasopressin use, dobutamine use) at the onset of AF, interventions for AF and anticoagulation therapy within 24 h after the onset of AF. Interventions for AF were defined as initiation of amiodarone, diltiazem, pilsicainide, magnesium, propranolol, or direct-current cardioversion. We also examined the proportion of the interventions given within 1 h after the onset of AF. Anticoagulation therapy was defined as initiation of intravenous unfractionated heparin or warfarin or direct oral anticoagulants. We also examined the number of rhythm transition from AF to SR and from SR to AF within 48 h after the onset of AF among patients who survived the period. Primary outcomes were in-hospital mortality and any event of ischemic stroke during the hospital stay. Outcome data, including ICU mortality and length of ICU and hospital stay, were also retrieved. In-hospital stroke was defined as symptomatic cerebral infarction with ischemic findings, as determined using new computed tomography or magnetic resonance imaging findings after the onset of AF. The CHADS2 score, anticoagulation therapy within 24 h after the onset of AF, incidence of in-hospital ischemic stroke, and duration from the onset of AF to stroke onset were evaluated only for patients without cerebrovascular disease, cerebral trauma and post-neurosurgery as the reason for ICU admission, with consideration for those with potential risks for developing stroke.

2.3. Statistical analysis

Data are presented as medians, interquartile ranges, or percentages. We compared patients who converted to sinus rhythm (SR) and those who remained in AF at 6 h after the onset of AF to evaluate whether the early restoration to SR was associated with hospital outcomes. The Fisher's exact test or chi-squared test was used for nominal variables, and the Mann-Whitney test was used for numerical variables. We conducted multivariable logistic regression analysis to determine the association between AF at 6 h and in-hospital mortality/the incidence of in-hospital stroke. Variables in the model were selected according to clinical relevance and their importance in previous studies. Results of the regression analysis are presented as odds ratios (ORs) and 95% confidence intervals (CIs). To further examine the impact of the duration of sustained new-onset AF on patient outcomes, we calculated the cumulative time of AF duration in the first 48 h after the onset of AF among patients who survived the period. We excluded patients who died within 48 h after the onset for this analysis, because we could not examine the cumulative time within 48 h for those patients. We assumed that the cardiac rhythms observed at each time point had been sustained since the previous observation. For example, if a patient had AF at 6 h, AF at 12 h, SR at 18 h, SR at 24 h, SR at 30 h, SR at 36 h, AF at 42 h and AF at 48 h, the cumulative duration of AF for this patient was calculated as: $(6-0)*1+(12-6)*1+(18-12)*0+(24-18)*0+(30-24)*0+(36-30)*0+(42-36)*1+(48-42)*1=24$ h. If patients converted from AF to SR within 6 h after the onset and did not have a recurrence of AF later than 6 h, we assumed the cumulative time of AF duration for these patients as 0 h. We classified AF patients into nine categories according to the cumulative time of AF duration (0, 6, 12, 18, 24, 30, 36, 42, and 48 h), and evaluated in-hospital mortality and the incidence of in-hospital stroke for each duration. If we included the cumulative time of AF duration after the adverse events that happened within 48 h, we could not adequately evaluate the association between the cumulative time of AF duration and the adverse events. Thus, we excluded patients with these events within 48 h after the onset of AF for this analysis. We used the Cochran-Armitage test to assess the association of the cumulative duration of AF and patient outcomes. Commercially available statistical packages (SPSS 19.0, IBM Corp., Armonk, NY, USA and JMP® Pro 11.2.0, SAS Institute Inc.) were used for all statistical analyses.

3. Results

A total of 1718 adult non-cardiac surgery patients were admitted to the ICU and remained there for over 24 h during the study period. We screened these patients using electronic medical records for any record related to AF, and found 297 patients with possible new-onset AF. Of these, 151 patients developed new-onset AF during their ICU stay (Fig. 1).

Patient demographics and clinical characteristics are shown in Table 1. Among the 151 patients, 52 patients (34%) remained in AF (AF group) and 99 patients (66%) converted to SR (SR group) at 6 h after the onset of AF. In each group, there were seven patients who developed acute cerebrovascular disease and/or cerebral trauma and/or post neurosurgery on ICU admission. Warfarin was the only anticoagulant prescribed before ICU admission, and was mostly for past medical history of pulmonary embolism or deep vein thrombosis. 107 of 151 patients (71%) were male sex. Postoperative state accounted for approximately 70% (99/151) of all study patients. Calcium-channel blockers were the most commonly prescribed antihypertensive agents (71/151, 47%).

ICU: intensive care unit; AF: atrial fibrillation.

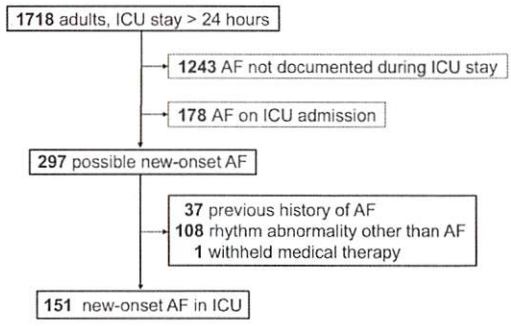

Fig. 1. Study flow chart. ICU: intensive care unit; AF: atrial fibrillation.

None of the patient characteristics showed statistically significant differences between the AF group and the SR group.

Physiological status at the onset of AF and interventions for new-onset AF after the onset of AF are summarized in Table 2. The proportion of patients with mechanical ventilation at the onset of AF was significantly higher in the AF group than in the SR group. Mean arterial pressure at the onset of AF was lower in the AF group than in the SR group and the proportion of patients with norepinephrine use at the onset of AF was higher in the AF group than in the SR group, although not statistically significant. Eighty-six percent (130/151) of all study patients received any interventions for AF. There were no statistically significant differences between the AF group and the SR group for any AF interventions despite the significant difference for Ca-channel blocker usage. Diltiazem was the only Ca-channel blocker administered. In addition, approximately 80% of all patients treated with any interventions for AF received medication within 1 h after AF onset. There was no difference in the proportion of the interventions given within 1 h between the SR and AF groups. Anticoagulants were administered to six patients (4.3%) and intravenous unfractionated heparin was the only anticoagulant administered during the first 24 h of AF onset. The number of rhythm transitions was significantly less in the AF group than in the SR group. On the other hand, the cumulative time of AF duration was significantly longer in the AF group than in the SR group.

Outcomes of patients remained in AF at 6 h after the onset are shown in Table 3. Of the 52 patients who remained in AF at 6 h after the onset, 19 (37%) died during hospitalization, while 20 of the 99 patients (20%) with SR died ($p = 0.033$). ICU mortality (11/52 vs. 11/99, $p = 0.144$) and the incidence of in-hospital stroke (6/52 vs. 5/99, $p = 0.177$) were numerically higher in the AF group, although not significant. After adjusting for the significant confounding factors (APACHE II score, infection on ICU admission), multivariable logistic regression analysis confirmed that AF at 6 h remained significantly associated with an increased risk of in-hospital mortality (adjusted OR 3.14; 95% CI, 1.28–7.69; $p = 0.012$) (Table 4). With regard to the association between the incidence of in-hospital stroke and AF at 6 h, only 11 patients had an in-hospital stroke; therefore, we did not conduct multivariable regression analysis.

Table 1
Demographic and clinical characteristics of patients with new-onset atrial fibrillation.

	SR (n = 99)	AF (n = 52)	*p* Value
Age, years	72 (66–80)	72 (67–76)	0.729
Male sex, n (%)	66 (67)	41 (79)	0.135
Body mass index, kg/m^2	22 (20–24)	22 (20–24)	0.445
Hypertension, n (%)	59 (60)	34 (65)	0.598
Diabetes, n (%)	12 (12)	7 (13)	0.801
Congestive heart failure, n (%)	2 (2)	3 (6)	0.340
Prior stroke or TIA, n (%)	11 (11)	8 (15)	0.451
CHADS2 score[a]	1 (0–2)	1 (1–2)	0.178
Chronic hemodialysis, n (%)	4 (4)	5 (10)	0.276
Liver failure, n (%)	4 (4)	0 (0)	0.299
Hematological cancer, n (%)	4 (4)	3 (6)	0.692
Immunosuppression, n (%)	10 (10)	3 (6)	0.544
Previous medication			
Calcium-channel blockers, n (%)	42 (42)	29 (56)	0.127
β-Blocking agents, n (%)	21 (21)	7 (13)	0.278
ACE inhibitors, n (%)	6 (6)	3 (6)	>0.999
ARBs, n (%)	29 (29)	17 (33)	0.712
Anticoagulants, n (%)	9 (9)	7 (13)	0.416
Patient category			
Non-scheduled surgical, n (%)	19 (19)	14 (27)	
Scheduled surgical n (%)	41 (41)	25 (48)	0.182
Medical, n (%)	39 (39)	13 (25)	
APACHE II	21 (15–26)	20 (15–27)	0.998
SAPS II	39 (28–50)	42 (29–51)	0.531
Infection on ICU admission, n (%)	23 (23)	17 (33)	0.246
Readmission to ICU, n (%)	11 (11)	3 (6)	0.382
Central venous catheter, n (%)	95 (96)	50 (96)	>0.999
Pulmonary artery catheter, n (%)	1 (1)	2 (4)	0.273
Mechanical ventilation, n (%)	65 (66)	40 (77)	0.193
Mechanical ventilation hours	12 (0–120)	38 (3–197)	0.056
Tracheotomy in ICU, n (%)	17 (17)	6 (12)	0.476
CRRT, n (%)	20 (20)	13 (25)	0.537

SR: sinus rhythm, AF: atrial fibrillation, TIA: transient ischemic attack, CHADS2: one point: recent congestive heart failure, hypertension, age at least 75 years, diabetes mellitus; two points: transient ischemic attack or a prior stroke, ACE: angiotensin converting enzyme, ARBs: Angiotensin II receptor blockers, APACHE II: Acute Physiology and Chronic Health Evaluation II, SAPS II: Simplified Acute Physiology Score II, ICU: intensive care unit, CRRT: continuous renal replacement therapy.

[a] Patients with cerebrovascular disease or neurosurgery or trauma were excluded (seven patients each in SR and AF).

Table 2
Physiological status and interventions of patients with new-onset atrial fibrillation.

	SR (n = 99)	AF (n = 52)	*p* Value
AF onset from ICU admission, days	1.6 (1.0–2.8)	1.5 (0.8–2.1)	0.192
MV at the onset of AF, n (%)	31 (31)	26 (50)	0.034
Hemodynamic status at the onset of AF			
Mean arterial pressure (mm Hg)	82 (73–96)	78 (71–89)	0.109
Norepinephrine use, n (%)	25 (25)	20 (39)	0.097
Vasopressin use, n (%)	3 (3.0)	1 (1.9)	1.000
Dobutamine use, n (%)	3 (3.0)	3 (5.8)	0.415
Intervention for AF[a], n (%)	83 (84)	47 (90)	0.329
Calcium-channel blockers, n (%)	10 (10)	20 (39)	<0.001
β-Blocking agents, n (%)	2 (2)	3 (6)	0.340
Magnesium sulfate, n (%)	59 (60)	32 (62)	0.862
Amiodarone, n (%)	3 (3)	7 (13)	0.032
Pilsicainide, n (%)	51 (52)	28 (54)	0.864
Direct-current cardioversion, n (%)	2 (1.3)	1 (0.7)	1.000
Intervention within 1 h after onset, n (%)	64 (64)	38 (73)	0.361
Anticoagulant therapy[b], n (%)	7 (5)	1 (1)	0.272
Number of rhythm transitions[c]	1.0 (1.0–2.0)	1.0 (1.0)	<0.001
Cumulative time of AF duration[c], hours	0 (0–12)	6.0 (0–20)	<0.001

SR: sinus rhythm, AF: atrial fibrillation, ICU: intensive care unit, MV: mechanical ventilation.

[a] Rhythm control and/or rate control for AF.

[b] Patients with cerebrovascular disease or neurosurgery or trauma were excluded (seven patients each in SR and AF).

[c] Patients who died within 48 h after the onset of AF were excluded (three patients in AF and two patients in SR).

Table 3
Outcomes of patients with new-onset atrial fibrillation.

	SR (n = 99)	AF (n = 52)	*p* Value
ICU length of stay, days	5.4 (2.8–10.0)	5.7 (2.7–11.5)	0.798
Hospital length of stay, days	46 (24–78)	40 (23–70)	0.524
ICU mortality, n (%)	11 (11)	11 (21)	0.144
Hospital mortality, n (%)	20 (20)	19 (37)	0.033
In-hospital stroke[a], n (%)	5 (5)	6 (13)	0.177
Days from AF to stroke[a], days	6 (5–36)	4 (3–13)	0.267

SR: sinus rhythm, AF: atrial fibrillation, ICU: intensive care unit.

[a] Patients with cerebrovascular disease or neurosurgery or trauma were excluded (seven patients each in SR and AF).

Table 4
Multivariable logistic regression analysis for hospital mortality in patients with new-onset atrial fibrillation.

	Adjusted odds ratio (95% CI)	*p* Value
APACHE II, points	1.18 (1.10–1.25)	<0.001
Infection on ICU admission	1.30 (0.52–3.29)	0.578
AF at 6 h after onset	3.14 (1.28–7.69)	0.012

APACHE II: Acute Physiology and Chronic Health Evaluation II, AF: atrial fibrillation, CI: confidence interval.

The numbers of patients with AF or SR at 0, 6, 12, 18, 24, 30, 36, 42, and 48 h after the onset of AF are shown in Fig. 2. The proportion of patients with AF decreased over time; the restoration rate at 6, 12, 18, 24, 30, 36, 42, and 48 h after the onset of AF was 66% (99/151), 73% (110/151), 81% (123/151), 85% (128/151), 82% (124/151), 83% (126/151), 84% (127/151), and 80% (121/151), respectively. Two and three patients died before 24 and 48 h, respectively, after the onset of AF.

In-hospital mortality and the incidence of in-hospital stroke for various cumulative duration of AF are shown in Table 5. In this table, in-hospital mortality was evaluated excluding five patients who died within 48 h after the onset and in-hospital stroke was evaluated excluding 14 patients with new-onset cerebrovascular disease and/or cerebral trauma and/or post neurosurgery on ICU admission. There were no patients with in-hospital stroke occurred within 48 h after the onset of AF. Patients with longer AF duration had greater in-hospital mortality ($p = 0.043$) and ischemic stroke incidence ($p = 0.041$).

4. Discussion

4.1. Key findings

We conducted a retrospective cohort study to assess the association between sustained new-onset AF and outcomes in critically ill non-cardiac surgery patients. Although there was no statistically significant difference in patient characteristics between the AF and SR groups, patients with AF at 6 h had approximately twice as high in-hospital mortality as patients with SR at 6 h. Multivariable logistic regression analysis confirmed the association between AF at 6 h and in-hospital mortality. In addition, longer AF duration was associated with higher in-hospital mortality and the incidence of in-hospital stroke.

4.2. Relationship with previous studies

There have been several studies that have evaluated the association between the development of new-onset AF and outcomes in critically ill patients [11,14,32]. For example, Shaver et al. reported that the development of new-onset AF in a diverse population of critically ill patients was an independent risk factor for in-hospital mortality (OR 1.60; 95%

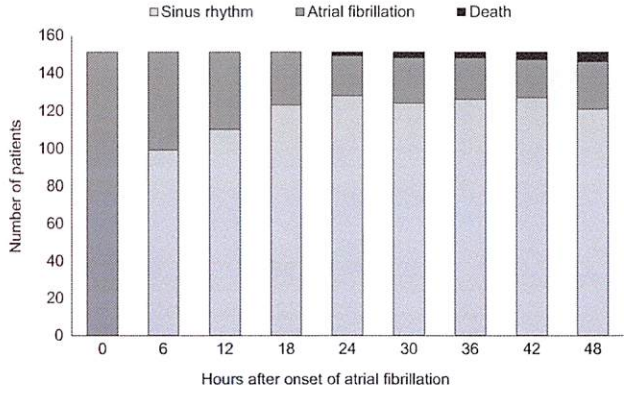

Fig. 2. Transition of cardiac rhythms within 48 h after new-onset atrial fibrillation.

Table 5
In-hospital mortality and stroke incidence for various cumulative duration of new-onset atrial fibrillation.

Cumulative duration, hours	In-hospital mortality, % (n)[a]	In-hospital stroke, % (n)[ab]
0	13 (9/67)	3 (2/62)
6	33 (10/30)	14 (4/28)
12	18 (3/17)	6 (1/16)
18	31 (4/13)	0 (0/12)
24	60 (3/5)	40 (2/5)
30	50 (1/2)	0 (0/2)
36	0 (0)	0 (0)
42	50 (1/2)	0 (0/1)
48	30 (3/10)	20 (2/10)
p Value[c]	0.043	0.041

[a] Patients who died within 48 h after the onset of AF were excluded.
[b] Patients with cerebrovascular disease or neurosurgery or trauma were excluded.
[c] By the Cochran-Armitage test to assess the association of the cumulative duration of AF and patient outcomes.

CI, 1.03–2.48; $p = 0.036$) [14]. On the other hand, only a few studies have focused on the association between the time duration after the development of new-onset AF and outcomes in critically ill patients. In a recent study, Liu et al. evaluated the prognostic impact of restored SR in patients with sepsis and new-onset AF [33]. They reported that patients remained in AF had greater in-hospital mortality than patients who restored to SR (61.3% vs. 26.1%, $p < 0.01$), and multivariate logistic regression analysis revealed that failure to restore to SR was independently associated with increased in-hospital mortality (OR 2.22; 95% CI, 1.02–4.83; $p = 0.045$). These results were consistent with our findings that sustained new-onset AF might be associated with in-hospital death.

The development of new-onset AF in critically ill non-cardiac surgery patients has also been reported as a risk factor for stroke. Walkey et al. also indicated that the development of new-onset AF in severe sepsis increased the risk of in-hospital stroke (2.6% with new-onset AF vs. 0.6% without new-onset AF; adjusted OR 2.70; 95% CI, 2.05–3.57; $p < 0.001$) [13]. Additionally, Gialdini et al. examined the association between new-onset perioperative AF, including cardiac surgery, and the long-term risk of stroke [16]. They reported that perioperative AF was associated with subsequent stroke after non-cardiac and cardiac surgery (non-cardiac surgery, hazard ratio [HR], 2.0; 95% CI, 1.7–2.3; cardiac surgery, HR, 1.3; 95% CI, 1.1–1.6), and that the strength of this association was significantly greater in non-cardiac surgery than in cardiac surgery ($p < 0.001$ for interaction). The association between the time course after the development of new-onset AF and in-hospital stroke has never been explored. Our study suggests that sustained new-onset AF might be associated with in-hospital stroke.

4.3. Significance and implications

To understand rhythm control strategy for new-onset AF, firstly we need to know the association between the sustained new-onset AF and outcomes. Subsequently, we need to evaluate the causality between the sustained new-onset AF and outcomes. In our study, remaining in AF at 6 h after the onset of AF was an independent risk factor for in-hospital mortality. Additionally, patients with the longer AF duration had greater in-hospital mortality and incidence of ischemic stroke. These findings suggest that sustained new-onset AF may be associated with poor outcomes. In the post-cardiac surgery setting, Gillinov et al. evaluated the efficacy of rhythm control for patients with new-onset AF in a randomized control study, and reported that in comparison with the rate control strategy, the rhythm control strategy did not reduce thromboembolism significantly (0.4% vs. 0.8%, $p = 0.40$) [26]. Whether this is also the case for critically ill non-cardiac surgery patients is uncertain. Therefore, further prospective studies are warranted to investigate outcomes of these patients with new-onset AF treated with rhythm

control strategies. Such studies might be able to set the stage for a trial of comparing rhythm control and rate control strategies.

4.4. Strengths and limitations

We evaluated the new-onset AF in a diverse ICU population who did not undergo cardiac surgery. To the best of our knowledge, there have been no studies that focused on the association between the sustained new-onset AF and patient outcomes. Since the types and timing of AF interventions were similar in both groups, our study highlights the association between sustained AF and adverse hospital outcomes.

However, this study also contains several limitations. First, we cannot mention the causality between the sustained new-onset AF and poor outcomes because of nature of the retrospective cohort study, although our findings suggest that sustained new-onset AF is associated with poor outcomes. Thus, sustained new-onset AF may be only a severity marker. Second, the sample size was small (N = 151) and our analyses might not have enough power to detect the association between AF at 6 h and in-hospital stroke. Third, we observed cardiac rhythms only at specific time points (6, 12, 18, 24, 30, 36, 42 and 48 h after the onset of AF) and calculated assumed duration of AF for each patient. Therefore, we could not assess the true "persistence" of cardiac rhythms that lasted for <6 h and measure the accurate duration of AF. However, we regarded that the time interval of 6 h might be adequate in the clinical context. Fourth, since we retrospectively reviewed medical records and drug charts to diagnose new-onset AF, we might have missed some AF that were not clinically recognized. The identification of AF occurrence by nursing staff could be also flawed. However, in a recent study using automated analysis of continuous ECG to detect AF, new-onset subclinical AF (detected by the algorithm but missed, or at least never documented, by the clinicians) was reported not to be associated with adverse hospital outcomes [34]. Fifth, we could not analyze the effectiveness of pharmacological interventions for AF because of its various ways and timings. Finally, we could not control for unmeasured or unknown confounding factors that may have influenced the results.

5. Conclusion

We analyzed the association between sustained new-onset AF and outcomes in critically ill non-cardiac surgery patients. We found that more than one third of new-onset AF patients remained in AF at 6 h after onset, which was associated with increased in-hospital mortality. We also found that longer AF duration was associated with higher in-hospital mortality and incidence of in-hospital stroke. Further research is warranted to investigate outcomes of critically ill non-cardiac surgery patients with new-onset AF.

Authors' contributions

T. Yoshida extracted the data, analyzed the data, and wrote the first draft of the manuscript. S. Uchino designed the study, supervised the analysis of the data, and critically revised the manuscript. T. Yokota extracted the data with T. Yoshida and interpreted the data and critically revised the manuscript. TF was in charge of statistical analysis and critically revised the manuscript. S. Uezono interpreted the data and critically revised the manuscript. MT interpreted the data and critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The hospital ethics committee of Jikei University School of Medicine approved the study protocol, and the need for informed consent was waived because of the retrospective design of the study.

Competing interests

The authors declare that they have no competing interests.

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References

[1] Bender JS. Supraventricular tachyarrhythmias in the surgical intensive care unit: an under-recognized event. Am Surg 1996;62:73–5.
[2] Knotzer H, Mayr A, Ulmer H, Lederer W, Schobersberger W, Mutz N, et al. Tachyarrhythmias in a surgical intensive care unit: a case-controlled epidemiologic study. Intensive Care Med 2000;26:908–14.
[3] Annane D, Sebille V, Duboc D, Le Heuzey JY, Sadoul N, Bouvier E, et al. Incidence and prognosis of sustained arrhythmias in critically ill patients. Am J Respir Crit Care Med 2008;178:20–5.
[4] Seguin P, Signouret T, Laviolle B, Branger B, Malledant Y. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. Crit Care Med 2004;32:722–6.
[5] Seguin P, Laviolle B, Maurice A, Leclercq C, Malledant Y. Atrial fibrillation in trauma patients requiring intensive care. Intensive Care Med 2006;32:398–404.
[6] Christian SA, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. J Crit Care 2008;23:532–6.
[7] Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bogelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. Crit Care 2010;14:R108.
[8] Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L, Canadian Critical Care Trials Group. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. J Crit Care 2012;27:326.
[9] Tongyoo S, Permpikul C, Haemin R, Epichath N. Predicting factors, incidence and prognosis of cardiac arrhythmia in medical, non-acute coronary syndrome, critically ill patients. J Med Assoc Thai 2013;96(Suppl. 2):S238–45.
[10] Makrygiannis SS, Margariti A, Rizikou D, Lampakis M, Vangelis S, Ampartzidou OS, et al. Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients. J Crit Care 2014;29:697.
[11] Yoshida T, Fujii T, Uchino S, Takinami M. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. J Intensive Care 2015;3:19.
[12] Arora S, Lang I, Nayyar V, Stachowski E, Ross DL. Atrial fibrillation in a tertiary care multidisciplinary intensive care unit—incidence and risk factors. Anaesth Intensive Care 2007;35:707–13.
[13] Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA 2011;306:2248–54.
[14] Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard GR, et al. Atrial fibrillation is an independent predictor of mortality in critically ill patients. Crit Care Med 2015;43:2104–11.
[15] Champion S, Lefort Y, Gauzere BA, Drouet D, Bouchet BJ, Bossard G, et al. CHADS2 and CHA2DS2-VASc scores can predict thromboembolic events after supraventricular arrhythmia in the critically ill patients. J Crit Care 2014;29:854–8.
[16] Gialdini G, Nearing K, Bhave PD, Bonuccelli U, Iadecola C, Healey JS, et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. JAMA 2014;312:616–22.
[17] Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. Chest 2014;146:1187–95.
[18] Sleeswijk ME, Van Noord T, Tulleken JE, Ligtenberg JJ, Girbes AR, Zijlstra JG. Clinical review: treatment of new-onset atrial fibrillation in medical intensive care patients—a clinical framework. Crit Care 2007;11:233.
[19] Kanji S, Stewart R, Fergusson DA, McIntyre L, Turgeon AF, Hebert PC. Treatment of new-onset atrial fibrillation in noncardiac intensive care unit patients: a systematic review of randomized controlled trials. Crit Care Med 2008;36:1620–4.
[20] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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.
[21] Brathwaite D, Weissman C. The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest 1998;114:462–8.
[22] Rivero-Ayerza M, Scholte Op Reimer W, Lenzen M, Theuns DA, Jordaens L, Komajda M, et al. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. Eur Heart J 2008;29:1618–24.
[23] Seguin P, Launey Y. Atrial fibrillation is not just an artefact in the ICU. Crit Care 2010;14:182.
[24] Yucel E, Hollenberg S. Atrial fibrillation in critical illness: innocent bystander or guilty party? Crit Care Med 2015;43:2254–5.
[25] Frendl G, Sodickson AC, Chung MK, Waldo AL, Gersh BJ, Tisdale JE, et al. American Association for Thoracic Surgery. 2014 AATS guidelines for the prevention and

management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. J Thorac Cardiovasc Surg 2014;148:e153-3.
[26] Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, et al. CTSN. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. N Engl J Med 2016;374:1911–21.
[27] Lim HS, Hamaad A, Lip GY. Clinical review: clinical management of atrial fibrillation - rate control versus rhythm control. Crit Care 2004;8:271–9.
[28] Danelich IM, Lose JM, Wright SS, Asirvatham SJ, Ballinger BA, Larson DW, et al. Practical management of postoperative atrial fibrillation after noncardiac surgery. J Am Coll Surg 2014;219:831–41.
[29] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
[30] Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270: 2957–63.
[31] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
[32] Kuipers S, Klein Klouwenberg PM, Cremer OL. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review. Crit Care 2014;18:688.
[33] Liu WC, Lin WY, Lin CS, Huang HB, Lin TC, Cheng SM, et al. Prognostic impact of restored sinus rhythm in patients with sepsis and new-onset atrial fibrillation. Crit Care 2016;20:373.
[34] Moss TJ, Calland JF, Enfield KB, Gomez-Manjarres DC, Ruminski C, DiMarco JP, et al. New-onset atrial fibrillation in the critically ill. Crit Care Med 2017;45:790–7.