Prevalence, Outcomes, and Risk Factors of New-Onset Atrial Fibrillation in Critically Ill Patients
A Systematic Review

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Summary
The purpose of this article is to systematically evaluate the prevalence, outcomes, and risk factors of new-onset atrial fibrillation (AF) in critically ill patients.

Medline, Embase, Science Citation Index, Wanfang, CNKI, and Wiley Online Library were thoroughly searched to identify relevant studies. Studies were assessed for methodological quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Odds ratio (OR) and weighted mean difference (WMD) with 95% confidence interval (CI) were used to assess the strength of the association. Heterogeneity, subgroup, sensitivity analyses, and publication bias were conducted.

A total of 25 studies were included. The prevalence of new-onset AF ranged from 4.1% to 46%. The random-effects pooled prevalence was 10.7%. The pooled result jumped up to 35.8% in patients with septic shock. Pooled analysis showed significant associations between new-onset AF with intensive care unit (ICU) mortality and in-hospital mortality over those patients without AF (OR = 3.11; 95%CI 2.45-3.96 and OR = 1.63; 95%CI 1.27-2.08). The pooled analysis also indicated that both ICU and hospital length of stay are longer in patients with new-onset AF than those without AF (WMD = 1.87; 95%CI 0.89-2.84 and WMD = 2.73; 95%CI 0.77-4.69). Independent risk factors included increasing age, shock, sepsis, use of a pulmonary artery catheter and mechanical ventilation, fluid loading, and organ failures.

New-onset AF incidence rate is high in critically ill patients. New-onset AF is associated with worse outcomes. Further studies should be done to explore how to prevent and treat new-onset AF in critically ill patients.

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Key words: Intensive care unit

Critical illness can induce the development of AF in patients without previous history of arrhythmia. New-onset AF is the most common complication in critically ill patients, with reported incidence ranging from 4% to 15% in general intensive care unit (ICU), even up to 46% in septic shock patients. In critically ill patients, new-onset AF can cause hemodynamic instability, acute heart failure, and thromboembolism. Multiple studies demonstrated that new-onset AF during critical illness is associated with poor outcome. Several studies also found that development of new-onset AF in the ICU indicates increased mortality. However, it is unclear whether the association between poor outcomes and AF in critical illness is due to AF itself or is only a marker of severity of disease. Despite the large number of studies reported the development of new-onset AF in critically ill patients, data on the risk factors to development of new-onset AF in critically ill patients is scarce. The higher susceptibility of new-onset AF is probably due to critical illness and concurrent presence of predisposing and precipitating risk factors. In addition, identification of patients at high risk for new-onset AF in critically ill patients is also important.

This meta-analysis aims to evaluate the prevalence, outcome (ICU and in-hospital mortality, ICU and hospital length of stay, stroke incidence), and prognostic factors (age, comorbidities, severity of ill, gender) of new-onset AF in critically ill patients.

Methods
The PRISMA guidelines for systematic reviews and meta-analysis (Supplemental Figure 1) and the Cochrane Handbook were followed.

Search strategy: A comprehensive electronic search of Medline, Embase, Science Citation Index, Wanfang, CNKI, and Wiley Online Library was undertaken. All resources were searched from inception to May 2019. The search terms were “intensive care” or “intensive care unit” or “critical illness” or “critically ill patient” and “atrial fibril-
The reference list of included articles and systematic reviews were searched for additional studies.

Inclusion and exclusion criteria:

Types of studies: All types of studies were included if written in English or Chinese.

Type of patients: Adult patients admitted to ICU for greater than 24 hours.

Contents: We included studies describing the prevalence, risk factors, and outcomes of new-onset AF during ICU stay in adult patients. Studies were excluded if there is no any description of settings as ICU or no clear definition of new-onset AF. We also excluded reviews and commentaries that contained no original data and reports that were published only in abstract form.

Types of outcome measures: The primary outcome was mortality measured at ICU and during in-hospital stay. The secondary outcomes were length of stay (ICU and hospital), risk of stroke incidence at ICU discharge, and the survival rates at hospital discharge more than 6 months of follow-up.

Study selection and data extraction: Two authors (JYF and YW) performed the screening of titles and abstracts, reviewed full-text articles, and confirmed their eligibility. Data were extracted by two independent authors (ZSW and FHC). Disagreements were resolved using consensus and by a third author (YW) if necessary. When the data extraction was unclear or required further details, studies’ authors were contacted by e-mail for clarification of results.

Quality assessment: Studies were evaluated for their methodological quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines. The following items were assessed: study design, risk of bias, sample size, and indirectness, which included details of diagnosis of new-onset AF, applicability of each study population, and reported outcome. We scored all items on a four-point scale from very low to high.

Data analysis: Odds ratios (ORs), or prevalence ratios, were used to estimate effect size. The risk ratios and hazard ratios were directly considered equivalent to OR. For continuous variables such as length of stay in ICU or hospital were carried out using the weighted mean difference (WMD) as the summary statistic. The ORs for the relations between new-onset AF and mortality were calculated based on the crude data provided in the article, and then the adjusted effect results and the rough ones were pooled in separately. Risk factors were considered to have a high level of evidence if a significant association ($P < 0.05$) was reported in two studies using multivariable analyses.

Clinical heterogeneity was checked by Q-test. If the heterogeneity was high ($I^2 > 50\%$), the random-effects model was used for meta-analysis. Otherwise, the fixed-effects model was used. Subgroup and sensitivity analyses were done to examine the effect of heterogeneity on the estimated effect size. Egger’s test and Begg’s funnel plot were used for diagnosis of potential publication bias, and $P < 0.05$ was considered statistically significant.

Results

The flowchart of the studies selected is shown in Figure 1. We identified 1,016 potential articles from our search of published work, and 971 were rejected after review of title and abstract. After full-text-level selection, 25 studies which consist of 78,877 patients were included in this meta-analysis. Two studies did not specify whether the patients were managed in ICU or in general ward. However, the conditions of included patients were
were included in this meta-analysis. The vast majority suffered severe sepsis and acute respiratory distress syndrome patients, so the two studies were included in this meta-analysis.

Overall characteristics of included studies were summarized in Table I. Fourteen studies used a method of prospective collection, while the remaining studies were
The prevalence of new-onset AF ranges from 4.5% to 31.9% in 12 studies performed in the medical ICU.2,26,27,29,31,34,35,39) The prevalence of new-onset AF ranges from 5.3% to 7.8% in three studies performed in the surgical ICU.4,7,22) The prevalence of new-onset AF ranges from 7.4%, 17.3%, and 35.8% in patients with non-sepsis, sepsis, and septic shock, respectively. Subgroup analyses were done by setting and study design, and we found that new-onset AF incidence was increasing in medical ICU and retrospective studies. Five studies were multi-center study designed, whereas the others were single-center. The number of included patients in each study ranges from 61 to 49,082. Due to retrospective study designs, small sample sizes, flawed diagnosis of new-onset AF, and lack of mortality evaluation, the overall methodological quality of the studies was very low to moderate (GRADE scores 1.7 to 4.9, 108). Due to retrospective study designs, small sample sizes, flawed diagnosis of new-onset AF, and lack of mortality evaluation, the overall methodological quality of the studies was very low to moderate (GRADE scores 1.7 to 4.9, 108).

Table II shows the prevalence of new-onset AF and severity scores in critically ill patients. The prevalence of new-onset AF ranges from 5.3% to 7.8% in three studies performed in the surgical ICU.4,7,22) The prevalence of new-onset AF ranges from 4.1% to 44% in eight studies in the medical ICU.2,26,27,29,31,34,35,39) The prevalence of new-onset AF ranges from 4.5% to 31.9% in 12 studies performed in the mixed ICU.3,9,11,12,23-25,28,32,33,36-38) The prevalence of new-onset AF ranges from 5.9% to 23.5% in septic patients.9,10,28,33,35) The incidence is even higher in patients with septic shock, and 46% of patients with septic shock developed new-onset AF. As shown in Figure 2, the pooled prevalence of new-onset AF was 10.7%, 95%CI 9.1-12.4, heterogeneity was observed (P < 0.05; I² = 97.7%). The pooled prevalence of new-onset AF was 7.4%, 17.3%, and 35.8% in patients with non-sepsis, sepsis, and septic shock, respectively. Subgroup analyses were done by setting and study design, and we found that new-onset AF incidence was increasing in medical ICU and retrospective study designs (Supplemental Table II). The severity of illness was reported in most studies by Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation II/III/IV; OASIS, Oxford Acute Severity of Illness Score; ISS, injury severity score; and NR, no report.

Table II. The Prevalence of New-onset AF and Severity Scores in Critically Ill Patients

| Name          | Year | Case | Incidence of AF (no.) | Severity index | Severity score |
|---------------|------|------|-----------------------|----------------|---------------|
| Seguin        | 2004 | 453  | 5.3% (24)             | SAPS II        | 45 ± 20/31 ± 17|
| Seguin        | 2006 | 293  | 5.5% (16)             | SAPS II        | 47 ± 12/31 ± 16|
| Arora         | 2007 | 61   | 29.5% (18)            | APACHE II      | 25.4 ± 6.4/20 ± 6.4 |
| Goodman       | 2007 | 611  | 9% (52)               | APACHE II      | 23 ± 8/16 ± 8   |
| Christian     | 2008 | 272  | 5.9% (16)             | APACHE II      | NR             |
| Salman        | 2008 | 81   | 31% (25)              | APACHE III     | 106 ± 31/95 ± 33|
| Meierhenrich  | 2010 | 628  | All patients 7.8% (49/628) | NR             | NR             |
| Walkin        | 2011 | 49082 | 5.9% (2896)        | NR             | NR             |
| Wells         | 2011 | 1466 | 22.7% (328)          | NR             | NR             |
| Della Ayed    | 2012 | 377  | 7% (26)               | APACHE II      | 19 ± 7/15 ± 9   |
| Kanji         | 2012 | 3081 | 4.5% (139)            | APACHE II      | 22.6 ± 9.0/N    |
| Makrygiannis  | 2014 | 133  | 15% (20)              | APACHE II      | 17.9 ± 5/15 ± 6.8|
| Chen          | 2015 | 741  | 7.2% (53)             | APACHE II      | 27 ± 7/22 ± 9.2 |
| Ambrus        | 2015 | 282  | 10% (28)              | APACHE III     | 91 ± 28/97 ± 32 |
| Guenancia     | 2015 | 66   | 44% (29)              | SAPS II        | 56 ± 45/71/50 (39-57) |
| Gupta         | 2015 | 2018 | 12.6% (254)           | APACHE II      | 19 (15-23)/16 (11-19) |
| Shaver        | 2015 | 1770 | 7% (123)              | APACHE II      | 27 (21-33)/25 (20-31) |
| Klouwenberg   | 2016 | 1782 | 23.5% (418)           | APACHE IV      | 89 (72-108)/74 (58-94) |
| Tseng         | 2016 | 285  | 21.8% (62)            | APACHE II      | 18.6 ± 4.2/18.0 ± 5.1 |
| Liu           | 2016 | 503  | All patients 47.7% (240) | APACHE II | NR |
| NeOAF to SR   | (31.1%) | APACHE II | 22.8 ± 5.8/21.6 ± 5.5 |
| NeOAF to AF   | (14.9%) | APACHE II | 24.6 ± 6.1/21.6 ± 5.5 |
| Moss          | 2017 | 8556 | 9% (749)              | OASIS          | NR             |
| New subclinical AF | New subclinical AF (626) | OASIS | 30 (24-36)/26 (21-32) |
| New clinical AF | New clinical AF (123) | OASIS | 32 (28-38)/26 (21-32) |
| Duby          | 2017 | 506  | 4.1% (106)            | ISS            | 20.5 ± 14.2/15.8 ± 10.9 |
| Arrigo        | 2018 | 1841 | 12% (212)             | SAPS II        | NR             |
| Fu            | 2018 | 1673 | 4.5% (75)             | APACHE II      | 27.7 ± 8/23.4 ± 7.1 |

AF indicates atrial fibrillation; SAPS II, Simplified Acute Physiologic Score II; APACHE II/III/IV, Acute Physiology and Chronic Health Evaluation II/III/IV; OASIS, Oxford Acute Severity of Illness Score; ISS, injury severity score; and NR, no report.
from 1.07 (95% CI 1.04-1.11) to 3.31 (95% CI 1.54-7.13). As shown in Figure 3, the pooled analysis of adjusted OR showed a significant association between new-onset AF and in-hospital mortality (adjusted OR, 1.63; 95% CI 1.27-2.08, \( P < 0.05 \)), and substantial heterogeneity was observed \( (P < 0.05; \chi^2 = 74.2\%) \). The pooled analysis of crude OR was 2.69 (Supplemental Figure 3). Subgroup analysis was done in all of the outcome by severity of illness, setting, and study design. (Supplementary Table II)

Table III shows the length of stay in ICU and hospital. Nineteen studies were compared between patients with and without new-onset AF. As shown in Figure 4 (Supplemental Figure 4), the pooled analysis indicated that both
Table III. Hospital and ICU Length of Stay

| Name          | Year | ICU LOS (days) AF/without AF | Hospital LOS (days) AF/without AF | Stroke (%) | Follow-up (year, mean) |
|---------------|------|-----------------------------|----------------------------------|------------|------------------------|
| Seguin       | 2004 | 16 ± 14/7 ± 9               | 34 ± 30/22 ± 21                  |            |                        |
| Seguin       | 2006 | 22 ± 23/10 ± 10             | 32 ± 28/25 ± 26                  |            |                        |
| Arora        | 2007 | 10 (5-18)/4 (2-13)          | 47 (12-63)/22 (10-50)            |            |                        |
| Goodman      | 2007 | 15 ± 13/11 ± 17             | 34 ± 36/21 ± 21                  |            |                        |
| Christian    | 2008 | 17.7/8.3                    | 32.1/28.5                        |            | 4-year survival        |
| Salman       | 2008 | 8 (5-13)/3 (2-11)           | NR                               |            |                        |
| Meierhenrich | 2010 | 30 (9-125)/17 (4-48)        | NR                               |            |                        |
| Walkey       | 2011 | NR                          | NR                               |            | 2.6% (75/2896)/0.6% (306/46186), P < 0.01 |
| Wells        | 2011 | NR                          | NR                               |            |                        |
| Della Ayed   | 2012 | 13 ± 12/7 ± 10              | 15 ± 11/10 ± 10                  |            |                        |
| Kanji        | 2012 | 10 (1-117)/NR               | 24 (1-165)/NR                    |            |                        |
| Chen         | 2015 | 6 ± 10.2/3 ± 3.6            | 15 ± 19/7 ± 9                    |            |                        |
| Guenancia    | 2015 | 10 (4-17)/7 (4-14)          | NR                               |            |                        |
| Gupta        | 2015 | 4.1 (1.9-8.1)/1.23 (0.9-2.8) | 17.5 (10.8-33)/10.7 (6.4-20.9)  | 6.3% (16/254)/4.1% (6/145), P = 0.32 |
| Shaver       | 2015 | 6 (3-13)/5 (2-11)          | 12 (7-22)/11 (6-19)              |            |                        |
| Klouwenberg  | 2016 | 7.6 (4.0-14.8)/4.1 (2.2-8.2) | NR                               |            | 1-year survival        |
| Tseng        | 2016 | 24.7 ± 16.0/20.7 ± 15.4     | 65.6 ± 47.4/51.8 ± 45.7          |            |                        |
| Liu          | 2016 | NR                          | NR                               |            |                        |
| NeOAF to SR  | 2016 | 16.7 ± 13.6/11.4 ± 11.1     | NR                               |            |                        |
| NeOAF to AF  | 2016 | 17.3 ± 23.3/11.4 ± 11.1     | NR                               |            |                        |
| Duarte       | 2017 | NR                          | NR                               |            | 0.8-year survival      |
| New subclinical AF | 2017 | 4.5 (2.1-10.1)/1.8 (1.0-3.4) | 11 (6-21)/7 (4-12)               |            |                        |
| New clinical AF | 2017 | 7.4 (3.9-14.5)/1.8 (1.0-3.4) | 16 (10-25)/7 (4-12)              |            |                        |
| Arrigo       | 2018 | 15 (9-28)/12 (7-21)         | NR                               |            | 1-year survival        |

AF indicates atrial fibrillation; NR, no report; and LOS, length of stay.

ICU and hospital length of stay are longer in patients with new-onset AF than those without AF (WMD =1.87; 95% CI 0.89-2.84 and WMD =2.73; 95%CI 0.77-4.69, respectively). Two studies reported the in-hospital ischemic stroke incidence, and one study found that patients with new-onset AF have increased risk for in-hospital stroke (adjusted OR, 2.70; 95% CI 2.05-3.57, P < 0.05).\textsuperscript{10} In contrast, another study did not find significant
Table IV. Risk Factors for New-onset Atrial Fibrillation in Critically Ill Patients

| Risk factor category      | Variables                                | Reference1# (P < 0.05) | Reference2# (P > 0.05) |
|---------------------------|------------------------------------------|------------------------|------------------------|
| Demographics              | Increased age                            | 3, 4, 7, 10, 11, 22-25, 27, 29, 31-34, 39 | 9, 30, 36              |
|                           | Male sex                                 | 11, 33                 | 3, 4, 7, 10, 22-25, 29, 30, 34, 36 |
|                           | White race                               | 10, 26, 30, 33         | 25, 29                 |
| Past history              | Diabetes mellitus                        | 24, 33                 | 3, 10, 11, 25-27, 29-31, 34, 36 |
|                           | Cardiovascular disease                   | 7, 33                  | 3, 22-24, 30, 39       |
|                           | Coronary artery disease                  | 24, 29                 | 4, 11, 22, 25-27, 31, 34, 36 |
|                           | Myocardial infarction                    | 11                     | 10, 24                 |
|                           | COPD                                     | 24                     | 4, 10, 22, 25-27, 36   |
|                           | Stroke                                   | 10.25                  | 34                     |
|                           | Hypertension                             | 3, 4, 11, 25           | 10, 22, 25, 27, 30, 34, 36 |
|                           | Cancer                                   | 33                     | 10, 30, 34, 36         |
|                           | Heart failure                            | 10, 24                 | 4, 11, 29              |
|                           | Smoking                                  | 10                     | 3, 11, 23, 24, 31, 34, 36 |
|                           | Alcohol use                              | 23, 36                 |                        |
| Severity of ill           | APACHE II                                | 23-25, 27, 32, 33      | 3, 11, 29, 30, 34, 36, 39 |
|                           | SAPS II                                  | 7, 22, 23, 27          | 9, 4, 31               |
|                           | Shock                                    | 7, 9, 11, 22, 24, 27, 39|                        |
|                           | Organ failures                           | 9, 10, 33              | 11                     |
| Infection                 | Primary blood stream                     |                        |                        |
|                           | Respiratory tract                        | 10                     |                        |
|                           | Abdominal                                | 10                     |                        |
|                           | Urinary tract                            | 10                     |                        |
|                           | Skin or soft tissue                      | 10                     |                        |
|                           | Sepsis                                   | 3, 9, 10, 24-26, 31, 33, 35 |
| Intervention             | Pulmonary artery catheter                | 7, 9, 10, 27           |                        |
|                           | Mechanical ventilation                   | 9, 33, 34, 36          |                        |
| Fluid loading             | Increased loading                        | 7, 22                  |                        |

COPD indicates chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiologic Score II; and APACHE II, Acute Physiology and Chronic Health Evaluation II.

Discussion

New-onset AF occurred frequently in critically ill patients. Meierhenrich’s study reported a high rate of new-onset AF among septic shock patients (46.0%). Echahidi’s study even found that the incidence of AF was as high as 50%. This study has shown that the prevalence of new-onset AF is 10.7% in pooled analysis. The pooled prevalence is higher than the 5 to 8% occurrence rates reported for surgical ICU populations and consistent with the 9 to 11% rates in mixed ICU populations but far lower than the 23 to 46% rates in sepsis patients. Moreover, we found that the incidence of new-onset AF in critically ill patients varies widely between studies, which may be due to sample sizes of included studies, difference of patient populations, severity of illness, and study design. So, we also carried out a subgroup analysis based on above factors and found that the incidence of new-onset AF was higher in septic shock patients, medical ICU, and prospective study design. Reinelt’s study reported that up to about 15% of medical ICU patients show periods of AF, and Sleeswijk’s review carried out special analysis on the incidence and treatment of new-onset AF in medical ICU. Prospective studies use strict and continuous monitoring methods that can detect even short episodes of new-onset AF that may have only mild clinical symptoms, while retrospective studies definition of AF based on available administrative databases will likely lead to underestimating the incidence of AF. A standardized approach to the definition and method of timely detection of new-onset AF is likely needed.

Previous studies have shown that critically ill patients with new-onset AF have higher mortality. However,
in a large, retrospective, cohort study in cardiac surgery patients, new-onset AF was not an independent predictor for in-hospital mortality.49 Two systematic reviews by Yoshida et al. and Kuipers et al.44,46 reported higher mortality in critically ill patients with new-onset AF, but pooled analysis was not performed in two studies. Gandhi’s study also found that new-onset AF is significantly increased in-hospital mortality in critically ill patients with sepsis (pooled relative risk (RR): 1.45).50 The latest meta-analysis by Kanjanahattakij et al.48 reported that there has been significant association between new-onset AF and in-hospital mortality (pooled OR: 2.70), but the meta-analysis only pooled the crude OR. Our study found 1.63-fold increase in-hospital mortality in critically ill patients with new-onset AF compared with patients without AF by pooled adjusted OR. The pooled crude OR was 2.69, which is consistent with Kanjanahattakij’s result. Liu et al.51 found that the new-onset AF group has higher in-hospital mortality rate (61.3%) compared with no new-onset AF groups (17.5%) in critically ill patients with sepsis (adjusted OR: 3.31). However, there are not enough studies that reported adjusted OR in critically ill patients with sepsis. Notwithstanding, many studies have reported that new-onset AF was associated with higher ICU mortality in critically ill patients, but only two studies reported adjusted OR.33,34 We found 3.11-fold increase ICU mortality in critically ill patients with new-onset AF by pooled crude OR. However, we were unable to explore if this association is because of confounders that were not adjusted.

The lengths of stay in ICU and hospital were longer in critically ill patients with new-onset AF across all studies. Prior studies in ICU population10,44-48 have found a 1.8-3.1-fold increase in both the mean ICU and hospital lengths of stay in patients with new-onset AF, similar to our observed 1.9- and 2.7-fold increase in the ICU and hospital lengths of stay, respectively. Furthermore, patients who developed new-onset AF are at an increased risk of systemic embolization and stroke.50 Walkey’s study presented increased risks of stroke associated with new-onset AF in septic shock patients.50 However, the relationship may also result from the indiscriminate use of anticoagulants in patients with AF, particularly in an ICU setting.50 On the other hand, Kanji’s study found that the incidence of stroke was 0% in new-onset AF patients who have received systemic anticoagulation during the course of AF.50 So, an evidence-based guidelines for the use of anticoagulant prophylaxis in critically ill patients with new-onset AF are urgently needed.

Multiple studies have reported risk factors for the development of AF in the critically ill patients, but only six studies used multivariate analyses to evaluate risk factors.7,10,22-24,27 Advanced age is the important determinant factor for developing AF. The incidence and prevalence rise with age (> 60 years: 1%; > 80 years: 5-15%).7,15,42,50 Issac’s study found systemic inflammatory response syndrome (SIRS) associated with the occurrence of AF,51 and they suggest that SIRS might be a significant predictor of AF occurrence. Moreover, known risk factors for new-onset AF in the critically ill patients are pulmonary artery catheter, mechanical ventilation, and increased fluid load-
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Supplemental Files
Supplemental Tables I-IV
Supplemental Figures 1-5
Please see supplemental files; https://doi.org/10.1536/ihj.19-511