Journal of Critical Care 53 (2019) 169–175

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Risk factors for new-onset atrial fibrillation on the general adult ICU: A systematic review

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ARTICLE INFO

Keywords:
Atrial fibrillation
Risk factors
Critical illness
Intensive care units

ABSTRACT

Purpose: This study was performed to systematically review the available evidence for the risk factors for new-onset atrial fibrillation (NOAF) on the general adult intensive care unit (ICU) and provide a semi-quantitative evidence synthesis.

Methods: We searched the MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and the CENTRAL databases from 1970 to 2018.

We included studies of adults based in general ICUs that evaluated potential risk factors for NOAF. We excluded studies involving patients with a history of atrial fibrillation (AF).

We semi-qualitatively evaluated the strength of evidence for each identified variable.

Results: We screened 1447 studies. Seventeen studies were included in the final analysis. We identified strong evidence for age, male sex, preceding cardiovascular disease, acute renal failure, acute respiratory failure, APACHE score and the use of vasopressors as risk factors for the development of NOAF on the ICU. Modifiable risk factors had not been studied in detail.

Conclusions: We provide the first systematic review with evidence synthesis of risk factors for NOAF on the general adult ICU. Evidence for modifiable risk factors was limited. Further research is therefore required and may contribute towards the evidence-based prevention and management of this important condition.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia in critically ill patients [1,2]. Observational data suggest new-onset AF (NOAF) occurs in 4.5–11% of all patients admitted to the intensive care unit (ICU) [3-7], rising to 23% of those patients with septic shock [8].

New onset AF in critically ill patients is associated with increased length of both ICU and hospital stay [5]. It is also associated with increased mortality [9,10]. Whether AF is an independent risk factor or merely a marker of disease severity is uncertain. NOAF is temporally associated with a reduction in cardiac index and raised filling pressures [11] and precedes haemodynamic instability and organ failure in critically ill patients [7]. AF is also associated with early thromboembolic complications during critical illness [12]. An aetiological association between NOAF and poor outcomes is therefore feasible and is supported by studies demonstrating an independent association with mortality [13,14].

New-onset AF during critical illness carries a significant long-term burden. Patients who develop AF during sepsis have poorer 5-year survival and 50% will have AF at 5 years post-admission [15].

AF in critical care differs from AF in the general population regarding its risk factors, incidence and clinical course [16-19]. Given its associated morbidity and mortality in this environment, identification of at-risk patients is vital.

We therefore performed a comprehensive systematic review and semi-quantitative data synthesis investigating risk factors for NOAF in the general adult ICU population.

2. Materials and methods

2.1. Search and identification of studies

We registered this systematic review with PROSPERO (CRD42017074221). We published the protocol [20] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21,22]. The PRISMA checklist of recommended items is included in the supplemental material (SDC-1).

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https://doi.org/10.1016/j.jcrc.2019.06.015

We identified papers by searching the Medical Literature Analysis and Retrieval System Online (MEDLINE) database, the Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1970 to August 2018.

We developed a search strategy with input from an experienced medical librarian (TP). A full description of the search strategy is outlined in the supplemental material (SDC-2).

2.2. Inclusion criteria

We included studies that evaluated adults (≥16 years of age) admitted to an ICU, where at least one risk factor for the development of AF was investigated. We included studies if they reported both a cohort of patients who developed NOAF and a cohort who did not, providing statistical relationships between patient-derived variables and the development of AF could be extracted.

We included studies investigating supraventricular arrhythmias (SVAs) if AF constituted at least 70% of arrhythmia episodes. We included studies that grouped atrial fibrillation and atrial flutter providing no other arrhythmia types were included. We included studies of cohorts defined by a single disease or narrow group of diseases (e.g. acute respiratory distress syndrome or sepsis). We also included studies focussing on patients with severe sepsis or septic shock (though not sepsis or septicaemia) that were not specifically restricted to the ICU as they were likely to contain a high proportion of ICU patients.

2.3. Exclusion criteria

We excluded studies that did not explicitly exclude or separate patients with a history of AF. We excluded studies of cohorts defined by a single procedure or narrow group of procedures (e.g. appendicectomy or thoracic surgery). We also excluded studies based on service-specific (e.g. cardiac, cardiothoracic surgical or neurosurgical) ICUs. Exclusion criteria were applied at study level. Cardiac, cardiothoracic surgical or neurosurgical patients were not individually excluded from studies based in non-service-specific ICUs. We excluded non-English-language papers where no translation was available.

2.4. Study selection and data extraction

We used Covidence (Veritas Health Innovation Ltd., Melbourne, Australia) software to identify duplicate records and for relevance screening. Two reviewers (JB and MH) independently undertook initial relevance screening of titles and abstracts. We then independently rescreened all potentially relevant studies in full-text form. We also screened the reference lists of all relevant articles including reviews to identify additional citations not identified through our search strategy. We contacted four authors for further information and all responded with the required data. The study team then reached a final consensus regarding studies to include in the final analysis. We generated a flow diagram outlining the stages of study selection and the reasons for exclusion for those studies that underwent full text review (Fig. 1). We used a reference manager program (EndNoteX8, Clarivate Analytics, Philadelphia, USA) to store identified citations and their electronic text.

One review author (JB) extracted data from included studies using a standardised collection form. The following data were extracted: (1) Characteristics of study setting and patient population; (2) study methodology (including ascertainment of risk factors, definition and assessment of outcome and control of confounding variables) (3) risk factor estimates including relative risk, odds ratios, confidence intervals and *p*-values for statistical significance. Where studies did not report these, but provided sufficient raw data, we calculated risk ratios with confidence intervals and/or p-values as necessary. We performed these calculations using R Core v3.4.3 [23] using χ^2 for statistical significance. Where values were calculated rather than transcribed, we identified these as such in the presented data.

2.5. Risk of bias assessment

We assessed the risk of bias of identified studies using the Newcastle-Ottawa Scale (NOS) [24]. We incorporated adaptations from a previous systematic review of risk factors [25]. We modified this a priori [20] to better evaluate studies investigating AF risk factors in the ICU. The scoring system employed is outlined in the supplemental material (SDC-3). This scale assessed the studies across three domains: (1) the selection of study groups, (2) the comparability of the groups and (3) the assessment of the outcome. A maximum of 9 points were available for each study. We defined a high-rating study as one with 8 or 9 points, an acceptable-rating study as one with 6 or 7 points and a low-rating study as one with 5 points or fewer.

2.6. Data synthesis

We synthesised available data using a semi-quantitative method established a priori [20]. We employed a method previously described by Zaal et al. [26] and adapted by Dettmer et al. [27]. We reviewed each article and identified all variables that were associated with the development of NOAF on the ICU. We included those risk factors with associated *p*-values of ≤0.05 or 95% confidence intervals that did not cross 1. We included risk factors derived through multivariate and univariate analysis. This was performed to gain a broad understanding of risk and to reduce bias related to the differences in variables included in multivariable analyses between studies. Each identified variable was allocated a relative strength. This was based on the composite of the number of articles in which the variable was identified and the rating of those articles as defined by the adapted NOS. The criteria for strength of associations is outlined in Table 1. If a study subdivided the NOAF cohort into patients who remained in AF and a cohort who reverted to sinus rhythm, we included risk factor data for the cohort who remained in AF.

3. Results

3.1. Study identification

The search of MEDLINE, EMBASE and Cochrane databases generated 1447 unique studies. Of these, 1378 were rejected after title and abstract screening. Of the 69 remaining studies, 52 were excluded after full text review leaving 17 studies for inclusion [28-44]. Studies excluded after full text review and rationale for exclusion are detailed in the supplemental material (SDC-4). The study identification process is outlined in Fig. 1.

3.2. Study characteristics

The study characteristics are summarised in the supplemental material (SDC-5). Of the 17 studies selected for review, 8 were retrospective studies and 9 were prospective studies. The number of participants ranged from 66 to 39,096. The ICU setting varied with 12 studies based in mixed ICUs, 4 in medical ICUs and 1 in a surgical ICU. Nine studies investigated unselected patients, 7 studies patients with sepsis and 1 study patients with trauma.

AF diagnosis in the retrospective studies was made using either diagnostic codes, patient record review or continuous ECG data. ECG verification was performed in 3/7 of these studies with 1 study performing this independently. One study employed an automated detection algorithm. AF diagnosis in the prospective studies was made through

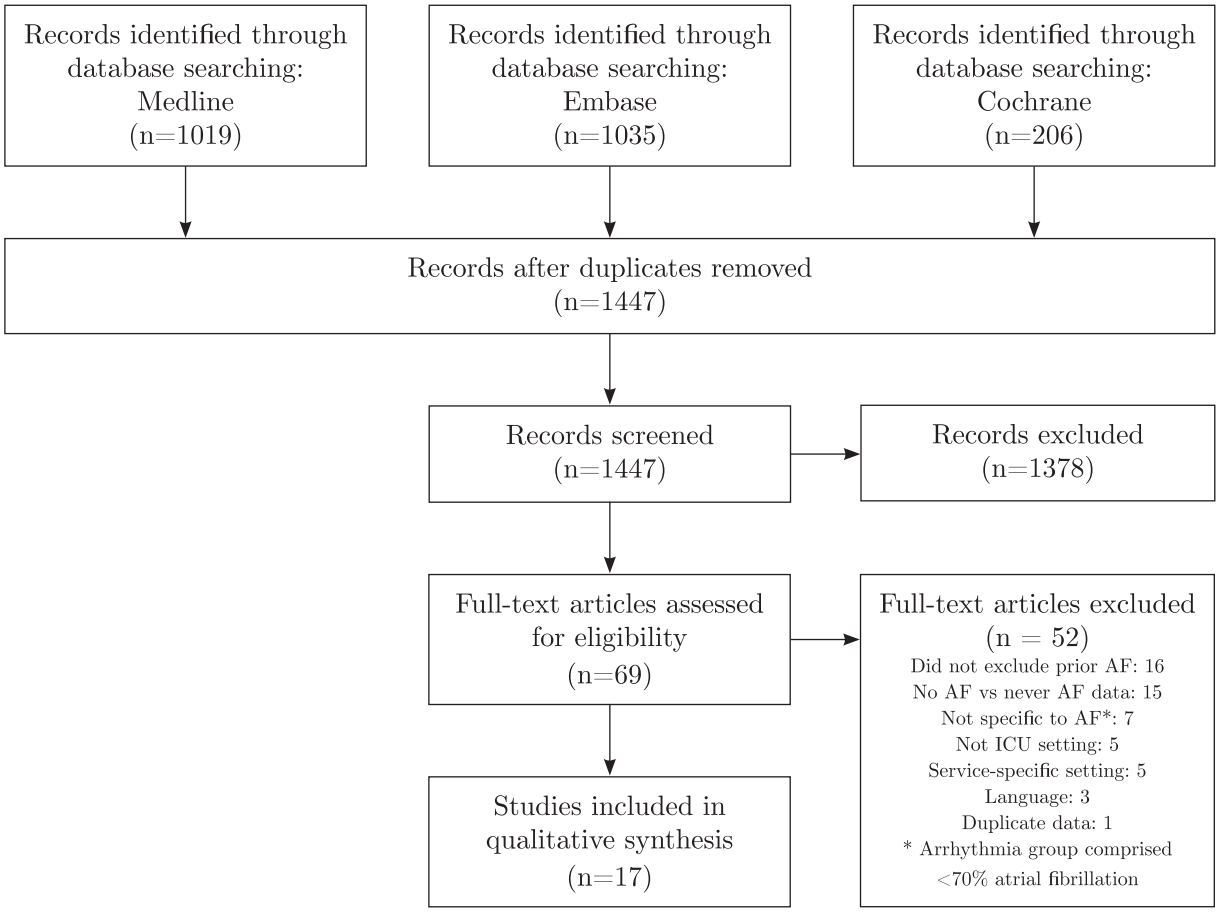

Fig. 1. Flow diagram of study selection process.

identifying the rhythm from the patient monitor with ECG confirmation, Holter monitor analysis or patient record review. One of these studies employed independent rhythm classification.

Nine studies investigated laboratory test results as potential risk factors for NOAF [28,29,34,36,37,39-41,44]. A temporal relationship between these results and AF onset was only made clear in 3 of these studies, with 1 study providing results from within the preceding 24 h [37], and 2 studies providing results at AF onset [40,41]. The studies providing results at AF onset did not provide matching control results so no statistical comparison was possible.

3.3. Risk of bias

The results of the risk of bias assessment for each study are presented in the supplemental material (SDC-6). The median (range) rating was 6 (5–8) out of a possible 9 points. 3 studies achieved a high rating, 10 moderate, and 4 low.

Table 1
Level of evidence for risk factors for new-onset atrial fibrillation.

Level of evidence	Criteria
Strong evidence	Consistent findings in ≥2 high-rating studies AND no conflicting studies
Moderate evidence	Consistent findings in 1 high-rating study AND ≥ 1 acceptable-rating study AND no conflicting studies
Weak evidence	Consistent findings in ≥3 low-rating studies OR ≥ 2 acceptable-rating studies OR 1 high-rating study in isolation

3.4. Synthesis of results

The strength of evidence for identified antecedents of NOAF on the ICU is presented in Table 2. Effect sizes and/or *p*-values for all identified risk factors are displayed in the supplementary data (SDC-7).

We identified 7 variables with strong evidence and a further 15 with moderate evidence from the 17 studies included. There was strong evidence supporting increasing age, male sex, preceding cardiovascular disease, acute renal failure, acute respiratory failure and the use of vasopressors as variables associated with the development of NOAF in the ICU. There was also strong evidence supporting increasing Acute Physiology And Chronic Health Evaluation (APACHE) score including the abbreviated OASIS (Oxford Acute Severity of Illness Score) [45].

There was moderate evidence supporting white ethnicity, chronic lung disease, valvular heart disease, stroke, chronic heart failure, diabetes mellitus, increasing BMI, malignancy, sepsis, shock and pulmonary embolism. Raised troponin, BNP and inflammatory markers along with reduced baseline left ventricular ejection fraction (LVEF) also had had moderate strength of evidence. We identified an additional 14 variables with weak evidence of association.

Evidence for reversible risk factors was limited. No vital sign data met criteria for inclusion in the final evidence synthesis. One study identified a U-shaped association of AF risk with plasma potassium concentration [37] and one study identified an association with lower magnesium levels [34] but overall this area was poorly studied and scarcely reported. Plasma potassium concentration was the only laboratory result to be included in our synthesis, with a weak level of evidence. The presence of a pulmonary artery catheter was identified as a risk factor in 2 studies [32,44] but this did not meet strength of evidence criteria (Table 1) for inclusion in the final synthesis.

Table 2
Evidence synthesis of variables associated with the development of new-onset AF in critically ill patients.

Variable	High-rating positive association	Moderate-rating positive association	Low-rating positive association	Overall strength of evidence
Demographics				
Age ↑	36°,37°,42°	33,35,39,40°,41,44°,28,43	29,31	Strong
Sex: male	37,42°	44°,28,30,43,		Strong
Ethnicity: white	37	44°,43		Moderate
Comorbidities				
Cardiovascular disease	37,42	28,30,39,43	31,34	Strong
BMI ↑/obesity	37°	44°,28		Moderate
Chronic lung disease	42°	28,35		Moderate
Diabetes mellitus	37	44°,28,30		Moderate
Heart failure	42	39,44°,28,30,43	29,34	Moderate
Malignancy	37	44°		Moderate
Valvular heart disease	42°	28	29	Moderate
Stroke	42	44°,43	29°	Moderate
Charlson comorbidity index	37			Weak
Immunocompromise	37°			Weak
Thyroid disease		28,35	29	Weak
Disease/disease severity factors				
APACHE score ↑ (II/III/IV/OASIS)	37 (IV), 42° (OASIS)	30 (III),39 (II)	31 (II) 29,(II)	Strong
Renal failure	37°42,	33°,35,39,44°,43		Strong
Respiratory failure	37,42°	44°		Strong
Sepsis	42°	35,40°,44°,28,	43	Moderate
Circulatory failure/Shock	37°	39,43	32	Moderate
Pulmonary embolism	42	40		Moderate
Haemorrhage	42°			Weak
Postoperative state	42°			Weak
Respiratory tract infection		33,44°		Weak
SOFA score ↑		28,39,41		Weak
Time since ICU admission ↓	37			Weak
Investigations				
LVEF ↓	36°	39,40		Moderate
Inflammatory markers ↑	37°	28		Moderate
Troponin ↑	36	28,39		Moderate
NT ProBNP ↑	36	28	29°	Moderate
Abnormal potassium level	37°			Weak
Left atrial diameter ↑		39,40		Weak
Bilirubin ↑	37			Weak
QRS duration ↑	36			Weak
NSVT day 1	36			Weak
Interventions				
Vasopressor use	37,42°	28,33,35,39		Strong
Renal replacement therapy		28,33		Weak

° - identified through multivariate analysis, BMI – body mass index, APACHE - Acute Physiology and Chronic Health Evaluation, OASIS - Oxford Acute Severity of Illness Score (abbreviated acute physiology score derived from APACHE IV hence included in category), SOFA – sequential organ failure assessment, ICU – intensive care unit; LVEF – left ventricular ejection fraction, NT ProBNP - N-terminal prohormone of brain natriuretic peptide, NSVT – non-sustained ventricular tachycardia.

Seven studies used multivariate analysis to identify independent predictors of NOAF [29,33,36,37,42,44,46]. Seven risk factors were identified in more than one study through multivariate analysis, namely increasing age, male sex, obesity, previous stroke, acute renal failure, acute respiratory failure and sepsis.

4. Discussion

We provide the first systematic evidence synthesis of risk factors for NOAF in the general adult ICU population. Previous systematic reviews in this area have focussed on patients with sepsis [8] or provided no evidence synthesis [47]. Previous reviews have also included studies where patients with a history of AF have not been excluded [17,48,49].

NOAF in critically ill patients is a common and important complication. It is associated with poorer short- and long-term outcomes including stroke and mortality [15,28,30,31,37,42-44]. Given its impact, understanding those variables that predict the onset of NOAF in critically ill patients is vital to gain a better understanding of the phenomenon itself. Furthermore, the ability to identify at-risk patients and address modifiable risk factors may improve patient outcomes.

Our review has several strengths. We developed the search strategy with an experienced medical librarian and searched multiple databases. It was designed with reference to the PRISMA guidelines [21,22] and strictly adhered to a protocol published in advance [20].

This review has some limitations. We decided a priori that a pooled statistical analysis would not be appropriate given the anticipated heterogeneity in methodology and study settings. We therefore performed a semi-quantitative analysis by matching variables across studies.

This method has been used previously to analyse heterogeneous ICU data [26,27] and requires grouping of risk factors across studies. These risk factors were not always homogenous. For example, we pragmatically grouped the data on different APACHE scores and the abbreviated OASIS score into a single category to demonstrate the body of evidence for these scoring systems as predictors of AF.

Our methods enabled us to provide a synthesis on strength of evidence but not strength of association. Furthermore, the identified associations do not confirm causality. We acknowledge the heterogeneity of study cohorts which limits the strength of our analysis. We did not individually exclude cardiothoracic surgical patients providing they were managed on a non-service-specific ICU. Whilst the substrate for NOAF in these patients may differ, the results remain relevant for the general

ICU. It was not possible to check for publication bias given the study types included. There is little reason for publication bias to affect these study types.

Definitions of NOAF varied between studies. This highlights the need for the development of standardised definitions for use in future research.

Age and male sex are well established risk factors for NOAF in the community [50-53] and our review supports their association with NOAF in the critically ill. Our review identified many comorbid factors in ICU patients which are also known to increase AF risk in the community. These include cardiovascular disease [54], valvular heart disease [55], chronic heart failure [56], diabetes mellitus [57] and obesity [58,59]. Hypertension is a likely risk factor in both settings [60] however one study in our review identified a negative association therefore hypertension did not qualify for inclusion in our evidence synthesis.

Whilst sharing certain demographic and comorbid risk factors, the development of NOAF in ICU patients seems strongly associated with acute factors including inflammation [8,16,37]. Systemic inflammation may trigger and perpetuate AF in the community [61-63]. Our findings support this association in critically ill patients. Sepsis, raised inflammatory markers and higher APACHE score had strong or moderate evidence of association in our synthesis. C-reactive protein was noted to increase prior to the onset of AF [41]. Furthermore, hydrocortisone therapy was associated with a lower risk of developing AF in patients with septic shock [38]. Pivotal trials of steroids in sepsis did not report comparative arrhythmia rates [64-66] or reported only life-threatening arrhythmias [64]. Inflammation seems to play a role in the development of NOAF in general ICU patients and the role of steroids in unclear in its prevention and management.

Maintaining plasma potassium concentration in the high normal range is often considered routine practice for prevention and treatment of NOAF after cardiac surgery [67]. This practice is frequently observed in the general adult ICU [68], yet evidence for this approach is limited [69]. Our review identified one study demonstrating a relationship between plasma potassium concentration and NOAF. Intravenous potassium supplementation confers clinical risk [70,71]. Our review therefore highlights the need for further research in this area before adopting high normal potassium concentration targets into routine practice.

Our study demonstrates echocardiographic predictors of NOAF in ICU patients. Reduced baseline LVEF and increased baseline left atrial diameter were identified in our evidence synthesis. These findings are consistent with echocardiographic predictors of NOAF in the general population [72].

Pulmonary artery (PA) catheters may increase the risk of NOAF in ICU patients however evidence is limited. Our review did not identify sufficient evidence to include PA catheter use in the final evidence synthesis. Two pivotal PA catheter controlled trials did not compare rates of NOAF between intervention and control groups [73,74]. One study demonstrated an increased risk of arrhythmias with a smaller study demonstrating no difference [75,76]. It remains unclear whether jugular central venous catheters are independently associated with an increased NOAF risk.

Our study has provided evidence to support a number of demographic and comorbid risk factors for the development of NOAF in ICU patients. Many of these factors are shared with AF acquired in the community. It is likely, however, that NOAF during critical illness differs in its mechanism from NOAF in the community and NOAF acquired after cardiac surgery. Systemic inflammation and organ failure play an important role in NOAF development in critically ill patients although the mechanisms are unclear. Modifiable risk factors have not been studied adequately and certain aspects of current clinical practice including electrolyte supplementation seem unfounded.

5. Conclusions

We identified strong evidence for age, male sex, preceding cardiovascular disease, acute renal failure, acute respiratory failure, APACHE score and the use of vasopressors as risk factors for the development of NOAF in patients on an ICU. We found that modifiable risk factors have not been studied in detail.

NOAF in critically ill patients confers significant morbidity and mortality. Its prevention and management therefore deserves considerable attention. Further research in this area is needed and will contribute towards the evidence-based prevention and management of this important condition. Future research should also focus on developing standardised definitions and core outcome measures for NOAF in critically ill patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions

JB, MH, DY and PW have substantially contributed to the design of the systematic review protocol. TP developed the search strategy. JB and MH performed study screening. JB, DY and PW wrote this manuscript. All authors read and approved the final manuscript. The funders have not been involved in the study design or reporting. PW is guarantor of this review.

Acknowledgements

The authors would like to thank the following people for kindly responding to requests for additional data/information:

Professor Ciara Shaver [77], Professor Allan Walkey [78], Dr. Peter Klein Klouwenberg [79], Dr. Travis Moss & Professor Randall Moorman [80].

Financial support

This work has been funded by the National Institute for Health Research (NIHR) and by the NIHR Biomedical Research Centre (Oxford). These funders played no role in developing the review. All views expressed are those of the authors and not necessarily those of the Department of Health or NIHR.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.015.

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