

BMJ Open Risk factors for new-onset atrial fibrillation on the general adult ICU: protocol for a systematic review

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ABSTRACT

Introduction Atrial fibrillation (AF) is a common arrhythmia in the critical care environment. New-onset AF is associated with increased mortality and intensive care unit (ICU) length of stay. Observational studies have identified several epidemiological and disease severity-related factors associated with developing new-onset AF on the ICU. However, there are limited data on the modifiable risk factors in the general adult ICU population. We describe a protocol for a systematic review of modifiable and non-modifiable risk factors for new-onset AF in the general adult ICU population. The results of this review will aid the development of risk prediction tools and inform future research into AF prevention on the ICU.

Methods and analysis Medical Literature Analysis and Retrieval System Online, Excerpta Medica database and the Cochrane Library, including Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials will be searched for studies that assess the association of patient variables, investigation results, interventions and diagnoses associated with subsequent new-onset AF on the ICU. Only studies involving adult patients admitted to non-service-specific ICUs will be included. We will extract data relating to the statistical association between reversible and non-reversible factors and AF, the quality of the studies and the generalisability of the results. This systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Ethics and dissemination This proposed systematic review will be based on published data, and therefore ethical approval is not required. The findings of this study will be disseminated through publication in a peer reviewed journal and will be presented at conferences.

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INTRODUCTION

New-onset atrial fibrillation (AF) in intensive care is defined for the purposes of this protocol as AF occurring after admission to ICU in a patient with no known history of chronic or paroxysmal AF. It is the most common arrhythmia in critically ill patients.^{1 2} It is particularly common after cardiac surgery, with a prevalence ranging from 10%–65% depending on the nature of

Strengths and limitations of this study

- New-onset atrial fibrillation in intensive care is a common and important condition.
- This protocol will ensure a targeted and comprehensive analysis of this poorly understood phenomenon.
- This protocol provides a framework for a clinically useful data synthesis.
- This protocol will guide an unbiased systematic review based on agreed best practice principles.
- The results of this review will inform current practice and aid the development of risk prediction tools.

the surgery.³ Data regarding new-onset AF in non-service-specific intensive care units (ICUs) are more limited. Observational data suggest new-onset AF occurs in 4.5%–15% of patients in this setting^{4–9} and up to 46% of patients with septic shock.¹⁰

New-onset AF in critically ill patients is associated with increased mortality and length of stay.^{1 8 11} It is unclear whether AF itself is an independent contributor to poor outcome, or rather a marker of disease severity.⁷ However, given the detrimental effects of AF on cardiac output and filling pressures, it is feasible that the arrhythmia itself contributes to increased mortality.¹² Furthermore, AF in critically ill patients is associated with thromboembolic complications, and these may contribute to poorer outcomes.¹³

Risk factors for developing AF on the ICU include patient factors such as increasing age or presence of comorbidities and ICU interventions including renal replacement therapy, vasopressor use and the use of pulmonary artery catheters.^{7 9 13} The risk of developing new-onset AF also increases with increasing disease severity.⁷ While a systematic review of AF risk factors in sepsis has been undertaken,¹⁴ this included studies that did not exclude patients with potential prior or paroxysmal AF.^{15–17} A systematic review has also been undertaken in the general adult

ICU population.¹⁸ However, this again did not focus on true new-onset AF and did not provide an evidence synthesis.

There is a paucity of data around reversible/modifiable antecedents in this context. Current practice of preventing AF in critically ill patients is variable and not based on robust evidence. Given the potential morbidity and mortality associated with new-onset AF on the ICU, a better understanding of modifiable and non-modifiable risk factors may improve patient care and outcomes.

OBJECTIVE

We will conduct a systematic review to identify studies of factors that are associated with an increased risk of new-onset AF in adult patients on non-service-specific ICUs.

METHODS

This protocol will adhere to the requirements of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol¹⁹ (online supplementary appendix 1).

Patient and public involvement

We have involved the Oxford ICU patient forum. This is a cohort of participants previously managed on Oxford ICUs and their relatives. They are recruited from the ICU follow-up clinic. Within this group are members who experienced AF during their stay. They stressed the importance of producing evidence to guide the prevention and management strategies for new-onset AF on the ICU. They felt the phenomenon was poorly understood, including investigations and management after discharge.

Search strategy

Papers will be identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials. MEDLINE and EMBASE will be accessed via the Ovid platform. We will include additional papers from other sources including the references of review articles or studies identified during screening. A full description of the search strategy is outlined in online supplementary appendix 2.

Study selection

Two reviewers will independently undertake initial relevance screening of titles and abstracts. The researchers will not be blinded to the journal titles or to the study authors or institutions. If there is disagreement or uncertainty regarding eligibility, the article will be included in the next stage of screening for further analysis for inclusion/exclusion. The full text will be retrieved for all articles not excluded by the initial screening. These papers will be assessed against the inclusion and exclusion criteria. Disagreements about eligibility will be resolved

by discussion between the screening researchers or a third party.

Data management

We will use Covidence (Veritas Health Innovation) software to identify duplicate records and for relevance screening. We will use a reference manager program (EndNote V.X8, Clarivate Analytics) to store identified citations and their electronic text.

Inclusion criteria

Types of studies

Quantitative studies published in peer reviewed journals assessing adults will be eligible for inclusion in this review. Studies are likely to be prospective or retrospective cohort or case-control studies.

Study characteristics

Eligible studies must include both a cohort of patients who developed new-onset AF and a cohort who did not. They must include at least one risk factor that was investigated. The studies must be based in non-service-specific ICUs. These will include general medical, surgical or mixed ICUs. Studies of cohorts defined by a single disease or narrow group of diseases (eg, myocardial infarction or sepsis) will be included. Identified studies published from January 1970 until the day of search completion will be included.

Phenomenon of interest

Studies must describe a statistical relationship between a patient-derived variable (eg, age, blood pressure or serum potassium level) and the development of new-onset AF. 'Diagnosis' may be included as a variable. We will include studies that group AF with atrial flutter, and we will include studies investigating new-onset supraventricular arrhythmias, providing AF constituted at least 70% of arrhythmia episodes.

Population

Studies that sample adult patients admitted to the ICU types specified above will be considered for inclusion.

For the purpose of this review, an adult is defined as ≥ 16 years of age. There will be no other restrictions.

Exclusion criteria

Types of studies

Qualitative studies, case studies, editorials, letters, practice guidelines and abstract only reports will be excluded.

Study characteristics

Studies of cohorts defined by a single procedure or narrow group of procedures (eg, appendicectomy or hepatobiliary surgery) will be excluded. Studies based on service-specific (eg, cardiac, cardiothoracic surgical or neurosurgical) ICUs will also be excluded. Studies published in a language other than English will be excluded.

Phenomenon of interest

Studies will be excluded if no risk factors are analysed. Studies that do not explicitly exclude or separate patients with a history of chronic or paroxysmal AF will be excluded. Studies that do not specify arrhythmia type will also be excluded.

Population

Studies of participants under 16 years old will be excluded.

Data extraction

Data will be extracted from identified full text articles and supplementary material. One researcher (JB) will be responsible for data extraction. All uncertainties regarding data extraction will be resolved by discussion among the study team. Extracted data will include: (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) and (3) risk factor estimates including measures quantifying risk, confidence intervals and p values for statistical significance. Where available we will extract β coefficients and the units of measurement to which they refer. We will extract risk estimates identified through both univariate and multivariate analysis and record the analysis method. We will populate prespecified data extraction tables. Where insufficient data are presented, we will request additional data from the authors.

Risk of bias assessment

We will assess risk of bias using an adapted Newcastle-Ottawa Scale (NOS).²⁰ The NOS is a scoring system designed to assess the quality of non-randomised studies in meta-analyses. Scores are attributed to each paper after assessing domains including the selection of study groups, the comparability of the groups and the ascertainment of the outcome of interest. We have incorporated adaptations from a previous systematic review of risk factors.²¹ We have further modified this with the intention of best evaluating our phenomenon of interest. The scoring system used in this systematic review will allocate scores from zero to nine and is outlined in online supplementary appendix 3.

Data synthesis and analysis

We will extract summary comparison data as measures of risk (eg, ORs or risk ratios) where possible. Where sufficient original data are presented, we will calculate these measures if required. We will then conduct a semiquantitative synthesis of results from included studies using a method previously described by Zaai *et al.*²² and adapted by Dettmer *et al.*²³ This method requires grouping of risk factors across studies. Grouped risk factors may be heterogeneous in terms of variable type (eg, continuous or categorical) or cut-off value. Identified variables with associated p values of ≤ 0.05 or 95% CI that do not cross 1 will be allocated a relative strength. This will be based on a composite of the number of articles in which an

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

Level of evidence	Criteria
Strong evidence	Consistent findings in ≥ 2 high quality studies (adapted NOS score 8–9) AND no conflicting studies
Moderate evidence	Consistent findings in 1 high quality study AND ≥ 1 acceptable quality study (adapted NOS score 6–7) AND no conflicting studies
Weak evidence	Consistent findings in ≥ 3 low quality studies (adapted NOS score ≤ 5) OR ≥ 2 acceptable quality studies OR 1 high quality study in isolation

NOS, Newcastle-Ottawa Scale.

association is identified, and the methodological quality of those articles as defined by our adapted NOS. Adjustment for confounding variables contributes to a study's risk of bias score. Risk factors identified through multivariate analysis will therefore be prioritised in the data synthesis. Criteria for strength of evidence is outlined in table 1.

DISCUSSION

Several epidemiological and disease severity-related factors have been associated with new-onset AF on the ICU in observational studies. These have not yet been investigated in the general adult ICU population in a systematic review with an evidence synthesis. Data are also limited regarding modifiable or reversible risk factors; available evidence is scarce regarding specific patient vital signs, laboratory results or ICU procedures that may increase the risk of AF. Current clinical practice is therefore variable and not evidence based.

We will synthesise the weight of evidence behind identified risk factors using a semiquantitative analytical technique. This method will not provide a synthesis of strength of association for each risk factor. However, this information, along with study-level data such as cut-off values, will be provided in the supplementary material.

The findings from this review will contribute towards an improved understanding of the modifiable and non-modifiable antecedents of new-onset AF on the ICU. It may lead to a clinically useful risk prediction model and inform future research into AF prevention on the ICU. Given the high prevalence and significant associated morbidity and mortality of new-onset AF on the ICU, optimal prevention strategies may result in improved patient outcomes.

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contributed to the design of the systematic review protocol. TP developed the search strategy. JB, DY, PJW wrote the manuscript. All authors read and approved the final manuscript. PJW is guarantor of this manuscript.

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REFERENCES

- Annane D, Sébille V, Duboc D, *et al.* Incidence and prognosis of sustained arrhythmias in critically ill patients. *Am J Respir Crit Care Med* 2008;178:20–5.
- Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: epidemiologic study. *Crit Care Med* 1990;18:1383–8.
- Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med* 2001;135:1061–73.
- Kanji S, Williamson DR, Yaghchi BM, *et al.* Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. *J Crit Care* 2012;27:326.e1–326.e8.
- Bender JS. Supraventricular tachyarrhythmias in the surgical intensive care unit: an under-recognized event. *Am Surg* 1996;62:73–5.
- Knotzer H, Mayr A, Ulmer H, *et al.* Tachyarrhythmias in a surgical intensive care unit: a case-controlled epidemiologic study. *Intensive Care Med* 2000;26:908–14.
- Carrera P, Thongprayoon C, Cheungpasitporn W, *et al.* Epidemiology and outcome of new-onset atrial fibrillation in the medical intensive care unit. *J Crit Care* 2016;36:102–6.
- Chen AY, Sokol SS, Kress JP, *et al.* New-onset atrial fibrillation is an independent predictor of mortality in medical intensive care unit patients. *Ann Pharmacother* 2015;49:523–7.
- Makrygiannis SS, Margariti A, Rizikou D, *et al.* Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients. *J Crit Care* 2014;29:697.e1–e5.
- Meierhenrich R, Steinhilber E, Eggermann C, *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.
- Salman S, Bajwa A, Gajic O, *et al.* Paroxysmal atrial fibrillation in critically ill patients with sepsis. *J Intensive Care Med* 2008;23:178–83.
- Pozzoli M, Cioffi G, Traversi E, *et al.* Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardiol* 1998;32:197–204.
- Walkey AJ, Wiener RS, Ghobrial JM, *et al.* Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–54.
- 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.
- Arora S, Lang I, Nayyar V, *et al.* Atrial fibrillation in a tertiary care multidisciplinary intensive care unit—incidence and risk factors. *Anaesth Intensive Care* 2007;35:707–13.
- Seguin P, Signouret T, Laviolle B, *et al.* Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. *Crit Care Med* 2004;32:722–6.
- Seguin P, Laviolle B, Maurice A, *et al.* Atrial fibrillation in trauma patients requiring intensive care. *Intensive Care Med* 2006;32:398–404.
- Yoshida T, Fujii T, Uchino S, *et al.* Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. *J Intensive Care* 2015;3:19.
- Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
- Wells G, Shea B, O'Connell D, *et al.* *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* Ottawa Hospital Research Institute: Oxford, 2015.
- Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005;330:565.
- Zaal IJ, Devlin JW, Peelen LM, *et al.* A systematic review of risk factors for delirium in the ICU. *Crit Care Med* 2015;43:40–7.
- Dettmer MR, Damuth E, Zarbiv S, *et al.* Prognostic factors for long-term mortality in critically ill patients treated with prolonged mechanical ventilation: a systematic review. *Crit Care Med* 2017;45:69–74.