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Published in:
Journal of Critical Care

DOI:
10.1016/j.jcrc.2019.11.011

Publication date:
2020

Journal of Critical Care 56 (2020) 26–30

Contents lists available at ScienceDirect

Journal of Critical Care

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

Low serum albumin levels and new-onset atrial fibrillation in the ICU: a prospective cohort study

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ARTICLE INFO

Available online xxxx

Keywords:
Serum albumin
Atrial fibrillation
Intensive care
Prediction
Outcome

ABSTRACT

Purpose: The aim was to determine if a low serum albumin (SA) level was associated with the occurrence of new onset atrial fibrillation (NOAF) during the first 48 h of intensive care unit (ICU) admission.
Methods: Overall, 97 patients admitted to the ICU were included in this prospective study. NOAF during the first 48 h was defined as irregularity and absence of p-waves on the continuous electrocardiogram, lasting longer than 2 min. Association were analysed using logistic regression with correction for confounding variables in multivariable analysis.
Results: The incidence of NOAF during the first 48 h of ICU admission was 18%. SA levels at ICU admission were significantly associated with NOAF after correction for confounders (odds ratio [OR] 0.86, 95%CI 0.77–0.97, $p = .010$). SA levels were also significantly associated with the number of episodes of NOAF in multivariate analysis (−0.09 episodes, 95%CI [−0.15/−0.04], $p = .001$), but not with the presence of sinus rhythm at 48 h (OR 1.05, 95%CI [0.93–1.12], $p = .46$).
Conclusion: In this small hypothesis generating study low levels of SA were associated with the occurrence of NOAF. It remains to be shown if increasing SA levels lowers the incidence of NOAF.

1. Introduction

Atrial fibrillation (AF) is often encountered in the Intensive Care Unit (ICU) with a reported incidence ranging from 4.5% to 31%, depending of the ICU setting to be surgical, mixed, or medical [1,2,3,4,5,6,7]. Episodes of new-onset AF (NOAF) during ICU stay have been independently associated with longer length of hospital stay (LOS), higher in-hospital morbidity and higher in-hospital mortality [2,3,6,8,9,10].

Because NOAF increases morbidity and mortality in the critically ill, efforts have been made to predict which patients are most at risk for developing NOAF. Several factors have been independently associated with the occurrence of NOAF including higher age, sepsis and cardiovascular morbidity [11].

Several studies have included hypovolemia, or the amount of fluid administered as substitute, as a possible predictor of the occurrence of NOAF [8,11,12]. Serum albumin (SA) is a protein with multiple biochemical properties of interest, especially with regard to effects on intravascular volume expansion in the critically ill [12,13,14]. Also, albumin was thought to affect the cardiovascular integrity by effects mimicking those of ACE-inhibitors [15]. After off-pump coronary artery bypass grafting ACE has been associated with the occurrence of AF [16]. In the outpatient clinic, low SA has been established as a risk factor for paroxysmal atrial fibrillation (pAF) [17].

The aim of this study was to determine if low SA levels were also associated with the occurrence of NOAF during the first 48 h of ICU admission.

2. Methods

This observational study comprised a single-centre cohort study within an adult (≥18 years), level II, medical and surgical (non-cardiac) Intensive Care Unit (ICU) containing 13 beds. For patients admitted to this ICU from January 1st 2016 with an expected stay of >24 h, serum albumin was determined as standard measure. For the patients admitted from January1st 2016 until June 5th, 2016 the electronical patient data were retrospectively analysed. The Maxima Medical Center (MMC) works with an opt-out system in which patients can object against using their anonymized medical data obtained for standard care for research purposes, therefore institutional review board (IRB) approval was not required.

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https://doi.org/10.1016/j.jcrc.2019.11.011
0883-9441/

With a presumed incidence of NOAF of 20% (based on the available literature [1,2,3,4,5,6,7]) to test the association between SA and NOAF using logistic regression a sample size with ten outcomes per variable in the analysis a total of (1*10)/0.2 = 50 patients in total (10 with NOAF) would need to be included in this hypothesis generating study. For the multivariable logistic regression with 5 variables in the analysis, a sample size of (5*10)/0.2 = 250 patients would have ideally been included (250 patients in total of which 50 patients would have had NOAF). Considering the hypothesis generating nature of this study, we wanted to have enough power to test for the primary hypothesis in univariable analysis. We accepted the increased risk of a type II error in multivariable analysis resulting from a loss of power.

Patients were excluded from the study if their medical history contained chronic AF and if no SA was measured within 3 h of ICU admission.

The first measured SA level upon ICU admission was used for analysis. SA was determined by the in-hospital laboratory using a calibrated colorimetric endpoint assay analyser (Roche Diagnostics, Mannheim, Germany). SA is presented in g/l with a reference range of 35-50 g/l. A SA concentration below 35 g/l was considered hypoalbuminemia.

The primary outcome of this study was the occurrence of new-onset atrial fibrillation (NOAF) within the first 48 h of ICU admission. Secondary outcomes were the number of separate episodes of NOAF and having sinus rhythm at the timepoint of 48 h after admission. Rhythm monitoring consisted of a continuous 5-lead electrocardiogram in all patients. An episode of NOAF was defined as a sudden change in heart rhythm showing irregularity and absence of p-waves on the continues electrocardiogram, lasting longer than 2 min. To be counted as separate episodes, a minimum period of 15 min of sinus rhythm was required between two episodes of AF.

The patient characteristics (age, gender, Body Mass Index [BMI]) were documented. Additional baseline factors (medical history of pAF and the use of anti-arrhythmic drugs of any class prior to admission) were derived from prior medical correspondence. At admission, the presence of severe sepsis was registered, and the APACHE-II score was calculated. Severe sepsis was defined according to the definitions identified by the Surviving Sepsis Campaign in the guideline published in 2012.[19]

If available the arterial potassium, serum magnesium and ionized calcium level at ICU admission were documented. Hypokalaemia was defined as a level <3.5 mmol/L and hyperkalaemia as >5.0 mmol/L, hypocalcaemia was defined as a level <1.15 mmol/L and hypercalcaemia as >1.30 mmol/L, and hypomagnesemia was defined as a level <0.71 mmol/L and hypermagnesemia as a level >0.93 mmol/L.

2.1. Statistical analysis

Statistical analysis was performed using IBM SPSS statistics, version 24. Categorical patient data are presented as percentages. Numerical data was presented using means and standard deviations (SD) or medians and interquartile ranges [25th – 75th percentile] dependant on distribution. We tested for normal distribution of the data using QQ plots and the Shapiro-Wilk test for both patients with and without AF. Associations between serum albumin (linearly) and NOAF during the first 48 h of ICU admission were analysed using the univariable and multivariable logistic regression to correct for potential confounders. Poisson regression was used for assessing the association between SA (linearly) and the consecutive number of NOAF episodes. Logistic regression was used for SA (linearly) and sinus rhythm after 48 h. We conducted a sensitivity analysis regarding severity of disease by evaluating the relationship between APACHE II and NOAF using binary logistic regression. During all multivariable analyses, we included the confounding variables with a $p < 0.30$ in univariable analysis using an enter approach. The included confounding variables were: age, medical history of AF, use of anti-arrhythmic drugs prior to admission, severe sepsis at admission and binary yes/no if all three electrolytes (potassium, magnesium and calcium) were normal (not low, not high) at ICU admission. Missing electrolytes at ICU admission were considered to be normal. All patients were included in all analyses. A two-tailed significance with an $\alpha \leq 0.05$ was considered significant for all analyses.

3. Results

During the inclusion period of this study, a total of 227 patients were admitted to the ICU. In 109 (48%) of these patients, SA level at admission was available. See supplementary tables 1 and 2 for the characteristics of the patients in whom SA was not available. Of these 109 patients, 12 patients (9.1%) were excluded because of chronic AF in their medical history. The characteristics of the patient population with or without NOAF within the first 48 h of ICU admission is summarized in Table 1 (for further information on the electrolytes see supplementary table 3).

3.1. New-onset atrial fibrillation

A total of 17 out of 97 patients (18%) developed new-onset AF within the first 48 h of ICU admission. Mean SA level at admission was 30.8 (± 7.3) g/L for the entire population, with a mean of 32.0 (± 7.0) g/L in patients without NOAF and 25.0 (± 8.0) g/L in patients with NOAF within the first 48 h of ICU admission (see Fig. 1). Univariate logistic regression revealed a significant association between serum albumin at ICU admission and the occurrence of NOAF within the first 48 h of admission (odds ratio [OR] 0.87, 95%CI 0.79–0.95, $p = .002$). After correction for potential confounders the association remained significant (OR 0.86, 95%CI 0.77–0.97, $p = .010$), indicating that for every gram increase of SA level the odds for developing NOAF decreased by 14% (see Fig. 2). For the complete multivariable logistic regression analysis see supplementary table 4.

The occurrence of NOAF was not associated with the APACHE II score (OR 1.01, 95% CI 0.98–1.05, $p = .553$).

Table 1
Baseline characteristics for patients with or without new-onset AF within the first 48 h of ICU admission. Mean with standard deviation (SD) or median with interquartile ranges [IQR] for continuous variables and count with percentage for categorical variables.

	Without AF $N = 80$	With AF $N = 17$
Age (years)	65 [51–74]	73 [67–80]
Male gender	42 (53%)	9 (53%)
BMI (kg/m^2)	25 [23–29]	26 [24–28]
pAF in medical history	7 (9%)	4 (24%)
Prior use of anti-arrhythmic drugs	27 (34%)	13 (77%)
• Digoxin	• 1 (4%)	• 0
• Amiodaron	• 2 (7%)	• 1 (8%)
• Beta-blocker	• 25 (93%)[a]	• 12 (92%)[b]
• Other	• 1 (4%)	• 0
APACHE II score	22 [15–28]	25 [18–29]
Potassium in mmol/L at ICU admission	4.2 [3.7–4.6]	3.8 [3.6–4.1]
Magnesium in mmol/L at ICU admission	0.83 [0.73–0.92]	0.81 [0.75–0.90]
Calcium in mmol/L at ICU admission	1.17 [1.10–1.23]	1.15 [1.10–1.23]
Severe sepsis	18 (23%)	9 (53%)
Cumulative fluid balance after 48 h (ml)	2674 (±2800)	5274 (±4609)
Administration of diuretics during the first 48 h	14 (18%)	3 (17%)

pAF: paroxysmal atrial fibrillation.

[a] The beta-blockers used were: atenolol daily dose 50 mg ($n = 1$), bisoprolol daily dose 2.5 mg ($n = 1$), bisoprolol daily dose 5 mg ($n = 2$), carvedilol 6.25 mg ($n = 1$), metoprolol daily dose 25 mg ($n = 1$), metoprolol daily dose 50 mg ($n = 10$), metoprolol daily dose 100 mg ($n = 6$), propranolol daily dose 40 mg ($n = 1$), sotalol daily dose 80 mg ($n = 1$), sotalol daily dose 160 mg ($n = 1$).

[b] The beta-blockers used were: bisoprolol daily dose 5 mg ($n = 1$), metoprolol daily dose 50 mg ($n = 5$), metoprolol daily dose 100 mg ($n = 4$), metoprolol daily dose 200 mg ($n = 1$), sotalol daily dose 80 mg ($n = 1$).

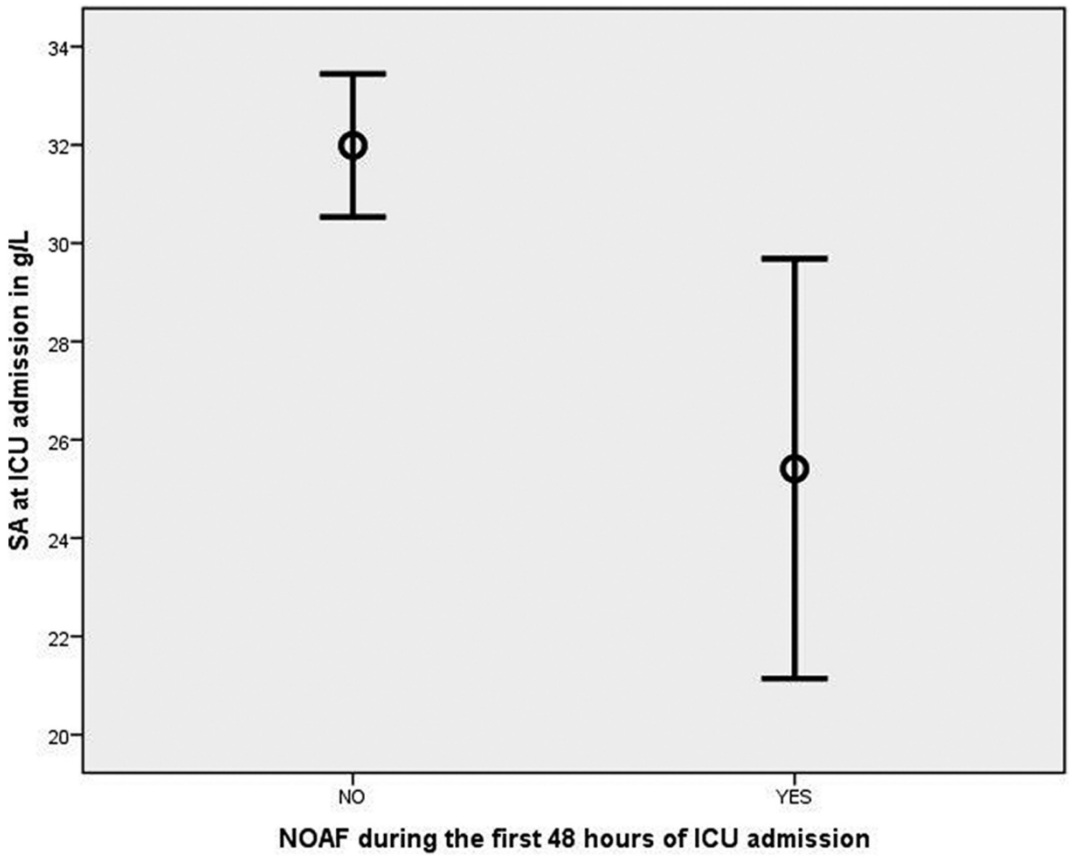

Fig. 1. The mean SA at ICU admission with the 95% confidence interval for patients without and with NOAF.

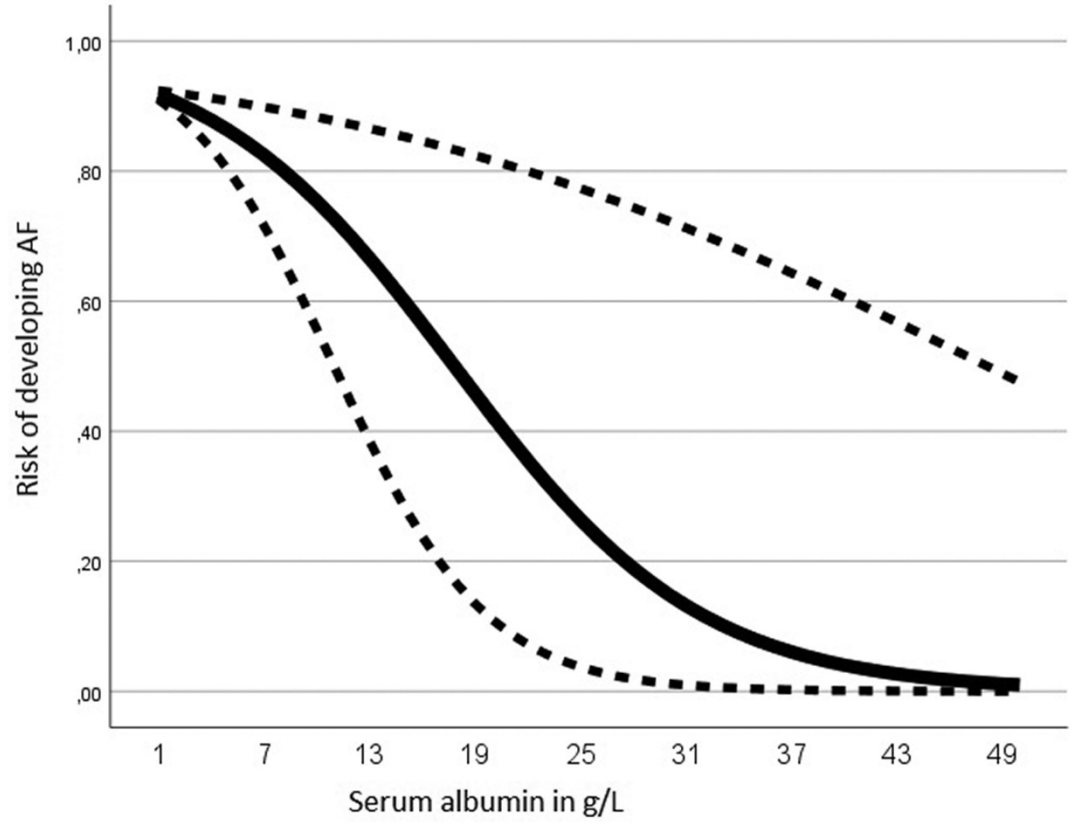

Fig. 2. Multivariable logistic regression the risk for AF based on the SA level at ICU admission with the 95% confidence interval.

3.2. Number of new-onset AF episodes

The average time between two successive AF episodes was 10 h and 20 min (range 30 min to 18 h). In univariable analysis, every g/L increase in SA level at ICU admission was associated with 0.12 less episodes of NOAF (95%CI [−0.18/−0.06], $p < .0005$). After correction for potential confounders, the association remained significant showing 0.09 less episodes of NOAF (95%CI [−0.15/−0.04], $p = .001$) per g/L increase in SA. For the complete multivariable Poisson regression analysis see supplementary table 5.

3.3. Sinus rhythm at 48u hours after admission

SA level at ICU admission was not significantly predictive for the presence of sinus rhythm at 48 h after admission to the ICU (OR 1.05, 95%CI [0.93-1.12], $p = .46$) in the univariable analysis.

4. Discussion

In this small hypothesis generating study, we found that low serum albumin levels at ICU admission were significantly associated with new onset AF during the first 48 h of ICU admission and with the number of episodes of AF during the first 48 h. These associations remained significant after correction for potential confounders. SA levels were not predictive of the presence of sinus rhythm after 48 h.

We found an incidence of AF in the first 48 h of 18%, which is similar to the incidence reported in literature during the entire ICU stay (1.7%–43.9%) [11]. These results indicate that if a patient develops NOAF during ICU stay, he/she will likely develop it already during the first 48 h of ICU admission.

One previous study, performed in patients with Acute Respiratory Distress Syndrome (ARDS), did not find an association between SA and NOAF [4]. However, the timing of SA measurement in that study was not specified.

It can be debated if AF in the ICU is a causal factor for poor outcome, or merely a marker of the severity of the underlying disease [7]. In line with the latter, a recent systematic review found APACHE score (II/III/IV/Oxford Acute Severity of Illness Score [OASIS]) as strongly associated with the development of NOAF in the ICU and the SOFA score only weakly [18]. In our study, the APACHE II score was not associated with NOAF. In addition, a study reported that treatment of AF did have no significant effect on mortality (29% mortality in treated patients compared to 34% mortality in untreated patient) [9]. However, not all treatments were effective and no analysis was conducted on effective treatment versus no-treatment or ineffective treatment. There is also currently no evidence available which management strategy for NOAF in the ICU is optimal [11]. We found that low SA levels were not only associated with NOAF, but also with the number of episodes of NOAF, indicating that SA level could play a role in the effectiveness of treatment. Once the association between SA and NOAF in the ICU has been validated sufficiently, it would be interesting to test whether normalizing SA before cardioversion could improve the effectiveness of this therapeutic strategy. Even more so, it is plausible that a preventative measure would be more beneficial for patient outcome than any treatment, although we can provide no evidence for this assumption.

This study has several limitations; first, this was a small sample size study aimed to be hypothesis generating. We did not reach the calculated ideal sample size and therefore we could not adequately adjust for confounding factors. The results of this study should therefore be interpreted with great caution and the results do not have any direct clinical implications. Ideally the results of this study would be validated in a larger cohort. Second, as mentioned in the method section, SA was only measured in those patients with an expected stay in the ICU of >24 h. This might create a population bias towards preferentially including sicker ICU patients and therefore decreases the generalizability of the results. Third, this study was conducted without a prewritten study protocol. Fourth, we used a binary variable to assess the effect of the electrolytes (all three measured normal / not all three measured normal). Chancing continuous variables to binary variables results in a loss of power for detecting the effect of that particular variable.

5. Conclusion

In this small hypothesis generating study, an increased SA level at ICU admission did not only significantly lower the odds for developing NOAF during the first 48 h of ICU admission, but also significantly lowered the number of NOAF episodes in this time period. This association remained significant after correction for confounding variables.

Funding

Departmental funding only

Declaration of Competing Interest

None to declare

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.11.011.

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