Research Square

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The Association between Serum Potassium Level and 30-day Mortality for Patients with Cardiac Arrhythmias in the Emergency Department: Secondary Analysis of a Cohort Study

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Original investigation

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Abstract

Background: Clinical evidence shows that mortality in relation to the potassium ranges was U-shaped in patients with hypertension, heart failure and cardiovascular disease. However, evidence is lacking for patients with cardiac arrhythmias in the emergency department. Present study aimed to clear the relationship between serum potassium level and mortality for patients with cardiac arrhythmias in the emergency department.

Methods: Using data from a retrospective cohort study, we identified 7532 visits involving 3882 patients with cardiac arrhythmias referred for any reason to the emergency department (ED) between January 1, 2010, and December 31, 2015. All-cause mortality within 30-days after the date of visit to the ED. We estimated the risk of mortality using multivariable logistic-regression model.

Results: There were 448 deaths (5.9%). The probability of mortality rose rapidly when potassium higher than the turning point (potassium ≥ 4.3 mmol/L) with a adjusted OR of 1.13 (95% CI:1.09, 1.16) for every 0.1 mmol/L increment of potassium. Moreover, the probability of mortality decreased when potassium lower than the turning point (potassium < 4.3 mmol/L) with a adjusted OR of 0.95 (95% CI:0.91, 0.98).

Conclusions: Higher serum potassium, even at a low level, was associated with a higher risk of 30-day mortality for patients with cardiac arrhythmias in the emergency department. The probability of mortality rose rapidly when potassium higher than the turning point (may at 4.3 mmol/L).

Background

Heart rhythm disorders are responsible for considerable morbidity and mortality, particularly in developed nations. Atrial fibrillation (AF) is the leading cause of stroke and a common contributor to overall morbidity and mortality[1].

Clinical evidence shows that mortality in relation to the potassium ranges was U-shaped in patients with hypertension[2, 3], chronic heart failure (HF) [4, 5], acute HF and cardiovascular disease (CVD)[2], and even high and low potassium levels within the accepted normal range of potassium were associated with increased mortality suggesting a narrower safe level for these patients.

However, robust evidence is lacking to guide the emergency management of patients with cardiac arrhythmias[6]. Serum potassium levels of > 6.0 or > 6.5 mmol/L[7] or electrocardiogram (ECG) manifestations of hyperkalemia (regardless of serum potassium level) have been recommended as thresholds for initiation of emergency therapy due to the risk of acute life-threatening cardiac rhythm disorders[6].

Exploring the threshold potassium level where risk of death significantly increases is a high priority in patients with cardiac arrhythmias. We used a emergency department (ED) database from a retrospective cohort study to investigate association between serum potassium levels and 30-day mortality. In our

observational study, we hypothesized that in patients with cardiac arrhythmias even high and low potassium is associated with a higher risk of all-cause mortality within 30-days after the date of visit to the ED.

Methods

Data Source

Data from a retrospective cohort study were used for the present study[8]. All relevant data are available in the Dryad Digital Repository and this website permitted users to freely download the raw data. According to Dryad Terms of Service, we cited Dryad data package in the present study. (Dryad data package: Tazmini, Kiarash et al. (2019), Data from: Electrolyte imbalances in an unselected population in an emergency department: a retrospective cohort study, Dryad, Dataset, https://doi.org/10.5061/dryad.f3h26j3).

Complete information regarding data collection is publicly available from the original paper[8]. Briefly, data were extracted from the Diakonhjemmet Hospital's Department of Medical Biochemistry database and the patient administrative system in Oslo, Norway.

Study population

Tazmini, Kiarash et al.[8] completed the entire study. Briefly, the original cohort is an unselected population in an emergency department. All patients ≥ 18 years referred for any reason to the ED between January 1, 2010, and December 31, 2015, who had measured blood electrolytes were included. Who were diagnosed with cardiac arrhythmias (see ICD-10 codes in Supplementary material online, *S1*) were included. The following exclusion criteria were applied: (i) dehydration, sepsis or cancer; (ii) missing serum potassium; (iii) with an extreme high potassium measurement (> 7 mmol/L). In total, 7532 visits involving 3882 patients with cardiac arrhythmias were included. The study flow chart is presented in Fig. 1.

In the previously published article[8], Tazmini, Kiarash et al. Has clearly stated that: the study was approved by the institutional review board (The Research Committee, Diakonhjemmet Hospital). The data are anonymous, and the requirement for informed consent was therefore waived.

Variables

Measurement of serum levels of potassium, sodium, calcium, albumin and glucose are performed routinely in all medical patients in the ED (serum levels of calcium, albumin and glucose are not measured in surgical patients). For every visit to the ED, age, sex, serum-electrolyte values and serum-albumin and glucose levels were registered. The time at which the patients have a serum potassium measurement represents the baseline of our study.

Serum-sodium levels were corrected for serum-glucose by lowering the sodium concentration by 2.4 mmol/L for every 5.5 mmol/L increase in glucose to account for the diluting effect of hyperglycemia[9].

Albumin-corrected calcium levels (mmol/L) [= measured serum-calcium level + 0.020 × (41.3 – serum-albumin) where 41.3 g/L is the albumin median] [10].

Concomitant diseases, and conditions

We identified clinical relevant comorbidities, and conditions used as covariates in the analysis. Hospital discharge diagnoses (primary or secondary) were classified by the International Classification of Diseases, 10th revision (ICD-10). Patients with hypertension, diabetes, pneumonia, coronary heart disease, heart failure, atrial fibrillation/flutter, chronic obstructive pulmonary disease (COPD), kidney failure, dehydration, sepsis or cancer were identified from the Danish National Patient Registry based on ICD-10 (see ICD-10 codes in Supplementary material online, *S1*).

Outcomes

The outcome of the study was all-cause mortality within 30 days after the date of visit to the Emergency department. In supplementary analyses, we also analyzed 60-days mortality.

Statistical analysis

Continuous variables are described as means ± SD and categorical data are presented as number and percentage. The difference according to the tertiles of potassium was compared using one-way analysis of variance (ANOVA) for continuous data and Chi-squared tests for categorical variables.

We applied a generalized additive model (GAM) to investigate dose-response relationships between potassium and 30-day mortality (Fig. 1). We applied logistic-regression model to estimate the association between potassium and 30-day mortality. The results were presented as odds ratios (ORs) with their 95% confidence intervals (95% CIs). Crude regression estimates are presented, as well as estimates adjusted for covariates. We selected these confounders on the basis of their associations with the outcomes of interest or a change in effect estimate of more than 10%.[11] Adjusted for the following potential confounders: age (as a continuous variable), sex, glucose-corrected sodium (as a continuous variable), albumin-corrected calcium (as a continuous variable), glucose (as a continuous variable), albumin (as a continuous variable) and comorbid conditions (no, yes): hypertension, diabetes, pneumonia, coronary heart disease, heart failure, atrial fibrillation/flutte, COPD and kidney failure.

We further applied two-piece-wise linear regression model to examine the threshold effect of potassium on mortality (Table 2). The turning point of potassium was determined using "exploratory" analyses, which is to move the trial turning point along the pre-defined interval and pick up the one which gave maximum model likelihood. We also conducted log likelihood ratio test comparing one-line linear regression model with two-piece-wise linear model. As described in previous analyses[12, 13].

To examine the robustness of our results, we conducted stratified analyses according to covariates. Dummy variables were used to indicate missing covariate values. The multiple visits per patient were analyzed with generalized estimating equation (GEE) model[14]. The two-sided alpha level was set at 0.05.

All the statistical analysis was performed using the Empower Stats (www.empowerstats.com, X&Y solutions, Inc. Boston MA) and R software version 3.6.1 (http://www.r-project.org).

Results

Baseline characteristics

A total of 7532 visits involving 3882 patients with cardiac arrhythmias were included in the study. The median age of all visits was 76.2 years (IQR 68–87 years). 3788 visits (50.3%) were female. Around 92% had a atrial fibrillation/flutter. No significant statistical difference in coronary heart disease was detected across the tertiles of potassium (see Table 1).

Table 1
Characteristics and 30-day mortality according to the tertiles of potassium (mmol/L) for 7532 visits involving 3882 patients with cardiac arrhythmias

		Serum potassium tertiles			
Parameters	**Total**	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P-value**
		2.1–3.9	**4.0-4.3**	**4.4-7.0**	
No. of visits	7532	2104	2714	2714	
No. of patients*	3882	1483	1881	1803	
Sex, male, n(%)	3744 (49.7)	851 (40.4)	1361 (50.1)	1532 (56.4)	
Sex, female, n(%)	3788 (50.3)	1253 (59.6)	1353 (49.9)	1182 (43.6)	< 0.001
Age, years	76.2 ± 14.2	76.6 ± 14.3	75.1 ± 14.9	76.9 ± 13.4	< 0.001
Sodium, mmol/L	139.6 ± 4.1	139.7 ± 4.2	139.7 ± 3.7	139.3 ± 4.4	< 0.001
Glucose, mmol/L	7.0 ± 2.3	7.0 ± 2.0	6.8 ± 2.0	7.0 ± 2.7	0.002
Potassium, mmol/L	4.2 ± 0.5	3.7 ± 0.3	4.2 ± 0.1	4.7 ± 0.3	< 0.001
Albumin, mmol/L	38.5 ± 4.4	38.3 ± 4.8	38.9 ± 4.2	38.4 ± 4.3	< 0.001
Calcium, mmol/L	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	< 0.001
Comorbidity					
Hypertension, n(%)	1099 (14.6)	363 (17.3)	379 (14.0)	357 (13.2)	< 0.001
Diabetes, n(%)	489 (6.5)	119 (5.7)	154 (5.7)	216 (8.0)	< 0.001
COPD, n(%)	303 (4.0)	72 (3.4)	99 (3.6)	132 (4.9)	0.019
Atrial fibrillation/flutter, n(%)	6914 (91.8)	1918 (91.2)	2450 (90.3)	2546 (93.8)	< 0.001
Pneumonia, n(%)	905 (12.0)	252 (12.0)	287 (10.6)	366 (13.5)	0.004
Coronary heart disease, n(%)	850 (11.3)	245 (11.6)	289 (10.6)	316 (11.6)	0.424
Heart failure, n(%)	1508 (20.0)	381 (18.1)	462 (17.0)	665 (24.5)	< 0.001
Kidney failure, n(%)	644 (8.6)	109 (5.2)	170 (6.3)	365 (13.4)	< 0.001
30-day Mortality	448 (5.9)	134 (6.4)	113 (4.2)	201 (7.4)	< 0.001

Data are mean ± SD, n (%). p values comparing groups are from one-way analysis of variance (ANOVA) for continuous data and Chi-squared tests for categorical variables. Among the 7532 visits, the amount of missing values for the covariates were:699 (9.3%) for glucose corrected sodium and serum-glucose, 454 (6.0%) for seum-albumin, 794 (10.5%) for albumin corrected calcium. *Patients meet combined conditions.COPD, Chronic obstructive pulmonary disease.

Table 2
Threshold effect analysis of potassium (per 0.1 mmol/L) and 30-day mortality in all visits with cardiac arrhythmias

Threshold	Crude		Model 1		Model 2	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
potassium < 4.3	0.90 (0.88, 0.93)	< 0.001	0.91 (0.88, 0.94)	< 0.001	0.95 (0.91, 0.98)	0.0037
potassium ≥ 4.3	1.18 (1.15, 1.21)	< 0.001	1.14 (1.11, 1.17)	< 0.001	1.13 (1.09, 1.16)	< 0.001

Model 1: adjusted for age, sex and comorbid conditions (hypertension, diabetes, pneumonia, coronary heart disease, heart failure, atrial fibrillation/flutter, chronic obstructive pulmonary disease and kidney failure). Model 2: Adjusted 1 + sodium (glucose-corrected), calcium (albumin-corrected), glucose and albumin. Among the 7532 visits, the amount of missing values for Model 2 were: 805 (10.7%). CI, confidence interval; OR, odds ratio.

30-Day Mortality

Among 7532 visits involving 3882 patients, there were 448 (5.9%) patients died within 30 days after the date of visit to the Emergency department. The 30-day mortality in the lowest tertiles of potassium (K: 2.1–3.9 mmol/L) to the highest (K: 4.4-7.0 mmol/L) were 134 (6.4%), 113 (4.2%) and 201 (7.4%) respectively (Table 1).

Identification of non-linear relationship

We observed a nonlinear dose-response relationship between potassium and mortality (Fig. 2 and Table 2). The probability of mortality rose rapidly when potassium higher than the turning point (potassium ≥ 4.3 mmol/L) with a adjusted OR of 1.13 (95% CI:1.09, 1.16) for every 0.1mmol/L increment of potassium. Moreover, the probability of mortality decreased when potassium lower than the turning point (potassium < 4.3 mmol/L) with a adjusted OR of 0.95 (95% CI:0.91, 0.98) for every 0.1 mmol/L increment of potassium.

Using the generalized additive model, the non-linear association between potassium and 30-day mortality was detected (Table 2). The linear regression model and a two-piece-wise linear regression model were compared, and the *P* value for the log-likelihood ratio test is < 0.001. This result demonstrates that the two-piece-wise linear regression model should be used to fit the model.

Additional analyses

We performed five sensitivity analyses to test the robustness of our results.

First, we analyzed 60-days mortality. These analyses showed that different outcome did not change the overall results. See Supplementary material online, *S2* for these analyses.

Secondly, we considered two approaches which incorporate multiple ED visit per patient, both restricting to the first visit and including all visit. The multiple visits per patient were analyzed with generalized estimating equation (GEE) model. (see Supplementary material online, *S3*). We observed that the results were generally similar to our main analysis.

Third, dummy variables were used to indicate missing covariate values. Similar results were obtained after considering the impact of missing data. See Supplementary material online, *S4* for the analysis.

Fourth, we performed an additional analysis including visits with atrial fibrillation/flutter. The result is generally similar to our main results (see Supplementary material online, *S5*).

Fifth, we performed subgroup analyses for patients with and without heart failure. These analyses both show the same trend as the main analysis. See Supplementary material online, *S6*.

Discussion

This study showed that higher serum potassium, even at a low level, was associated with a higher risk of 30-day mortality among patients with cardiac arrhythmias in the emergency department. The major finding was that the probability of mortality rose rapidly when potassium higher than the turning point (potassium ≥ 4.3 mmol/L) with a adjusted OR of 1.13 (95% CI:1.09, 1.16) for every 0.1 mmol/L increment of potassium. Moreover, the probability of mortality decreased when potassium lower than the turning point (potassium < 4.3 mmol/L) with a adjusted OR of 0.95 (95% CI:0.91, 0.98). To our knowledge, this is the first study to report the relation between potassium and 30-day mortality in an unselected adult ED patients with cardiac arrhythmias.

Previous studies have demonstrated that mortality in relation to the potassium ranges was U-shaped. In a Danish National Registries-based study of 44 799 hypertensive patients, potassium levels outside the interval of 4.1–4.7 mmol/L were associated with increased mortality risk[2]. Krogager *et al*. also demonstrated that potassium levels outside the interval 3.9–4.5 mmol/L were associated with a substantial risk of death in patients requiring diuretic treatment after an myocardial infarction[15]. Moreover, in HF patients, potassium levels of < 4 and ≥ 5 mEq/L have been shown to be associated with poor outcomes when compared with 4–5 mEq/L[5, 16]. These findings are in agreement with our study. We observed that higher serum potassium, even at a low level, was associated with a higher risk of 30-day mortality among patients with cardiac arrhythmias.

Hypokalemia has traditionally been defined as serum potassium < 3.5 mEq/L, in patients with HF, and in some study defined hypokalemia as potassium < 4 mEq/L [17]. Several retrospective analyses from the digitalis investigation group trial[17],[18] all suggest that a potassium level below 4 mmol/L was associated with excess mortality and diuretic induced potassium depletion has been suggested as a potential cause of arrhythmic death in chronic heart failure patients[19]. Similarly, our study demonstrated that the probability of mortality decreased when potassium lower than the turning point (potassium < 4.3

mmol/L) with a adjusted OR of 0.95 (95% CI:0.91, 0.98) for every 0.1mmol/L increment of potassium. In the present study, patients with HF in about 20% of cases. We performed an additional sensitivity analysis (see Supplementary material online, *S6*) and these analyses both show the same trend as the main analysis.

Hyperkalemia is a potentially serious condition that can result in life-threatening cardiac arrhythmias and is associated with an increased mortality risk[20]. Hyperkalemia is a potentially life-threatening condition that is defined as a serum potassium level above a reference range, usually greater than 5.0 mEq/L; severe hyperkalemia is often defined as a level greater than 6.0 mEq/L[21]. In some retrospective analyses, moderate hyperkalemia defined as serum potassium level ≥ 5.5 mg/dL and < 6.0 mg/dL[22] and severe hyperkalemia defined as ≥ 6.0 mg/dL[23]. Hyperkalemia is encountered frequently in patients with established CVD who are taking antihypertensive drugs and is associated with increases in all-cause mortality[24]. If not treated rapidly, the mortality rate for patients with severe hyperkalemia can be over 30%[25]. Similarly, we observed that the probability of mortality rose rapidly when potassium higher than the turning point (potassium ≥ 4.3 mmol/L) with a adjusted OR of 1.13 (95% CI:1.09, 1.16) for every 0.1mmol/L increment of potassium. The probability of mortality rose rapidly when potassium higher than the turning point (may at 4.3 mmol/L).

The current study is based on a emergency department data, included both patients with abnormal and normal potassium levels, of high age, with comorbid conditions. Explored the threshold potassium level where risk of death significantly increases is a high priority in patients with cardiac arrhythmias.

Study limitations

One limitation of this study is inherent to the observational nature of the study design which lends itself subject to limitations that should be considered including confounding by indication.

In our analysis, we adjusted for likely confounders, including age, sex, sodium, calcium, glucose, albumin and comorbid conditions (hypertension, diabetes, coronary heart disease, heart failure, COPD, pneumonia, kidney failure, dehydration, diabetes and pneumonia). Despite this adjustment, it is still possible that some amount of unmeasured confounding remains. Additional limitations of our study include missing data for some variables. Nonetheless, we used contemporary methods to deal with missing data to minimize bias.

Another limitation relates to the fact that the diagnoses were based on the ICD-10 coding which the responsible physician found relevant, and we did not have information concerning causes of death. Since we are examining mortality over a short period after the date of visit to the ED, we did not find it beneficial to distinguish between cardiovascular and non-cardiovascular death. Furthermore, we lacked information about interventions during the initial stabilization, which may have influenced potassium levels and survival. It is noteworthy that the potential resulting from interventions would bias toward to the null and thus result in an underestimation of the association between potassium level and mortality.

Further, we did not have electrocardiogram data available. Consequently, we were not able to examine whether the arrhythmia patient had malignant ventricular arrhythmias such as torsades de pointes (TdP) ventricular tachycardia and other lethal ventricular arrhythmias. Nevertheless, we performed an additional analysis including visits with atrial fibrillation/flutter. The result is generally similar to our main results (see Supplementary material online, *S5*).

Moreover, we were unable to obtain the variables, including past medical history, reason for visiting and vital status in the ED, and history of chronic electrolyte imbalances and treatment. Although the routine at Diakonhjemmet Hospital is to take blood samples shortly after the patient has arrived in the ED, we cannot exclude that blood from some patients was collected after initiation of treatment. Finally, we also acknowledge that as our participants were patients referred for any reason to the emergency department, which limits the generalizability of the findings to other population.

Conclusions

Using data from a retrospective cohort study, we identified 7532 visits involving 3882 patients with cardiac arrhythmias referred for any reason to the emergency department. This study identifies a nonlinear dose-response relationship between potassium and 30-day mortality. The probability of mortality rose rapidly when potassium higher than the turning point (may at 4.3 mmol/L).
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Abbreviations

AF: atrial fibrillation; ANOVA: one-way analysis of variance; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; ECG: electrocardiogram; ED: emergency department; GEE: generalized estimating equation; HF: heart failure; ICD-10: International Classification of Diseases, 10th revision; IQR: interquartile range; K: potassium; ORs: odds ratios; TdP: torsades de pointes; 95% CIs: 95% confidence intervals.

Declarations

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(Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway; Center for Heart Failure Research, University of Oslo, Oslo, Norway).

Authors' contributions

XLC performed statistical analysis. LC cleaned the data. CL conceived and designed the research. XLC and LC drafted the manuscript. CL made critical revision of the manuscript for key intellectual content.

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Availability of data and materials

Data are available in the Dryad Digital Repository at https://doi.org/10.1371/journal.pone.0215673.

Ethics approval and consent to participate

In the previously published article[8], Tazmini, Kiarash et al. Has clearly stated that: the study was approved by the institutional review board (The Research Committee, Diakonhjemmet Hospital). The data are anonymous, and the requirement for informed consent was therefore waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

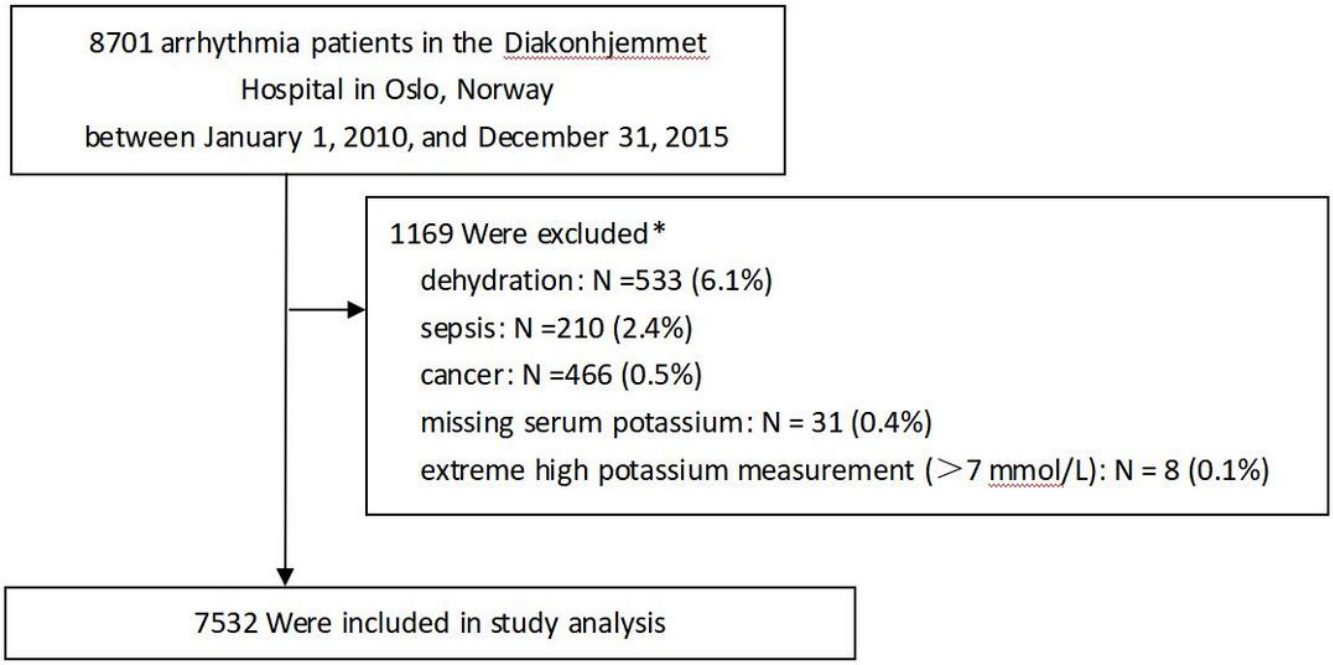

Figure 1 Study flowchart. *Subjects meet combined conditions

Figure 1

Study flow chart. *Subjects meet combined conditions

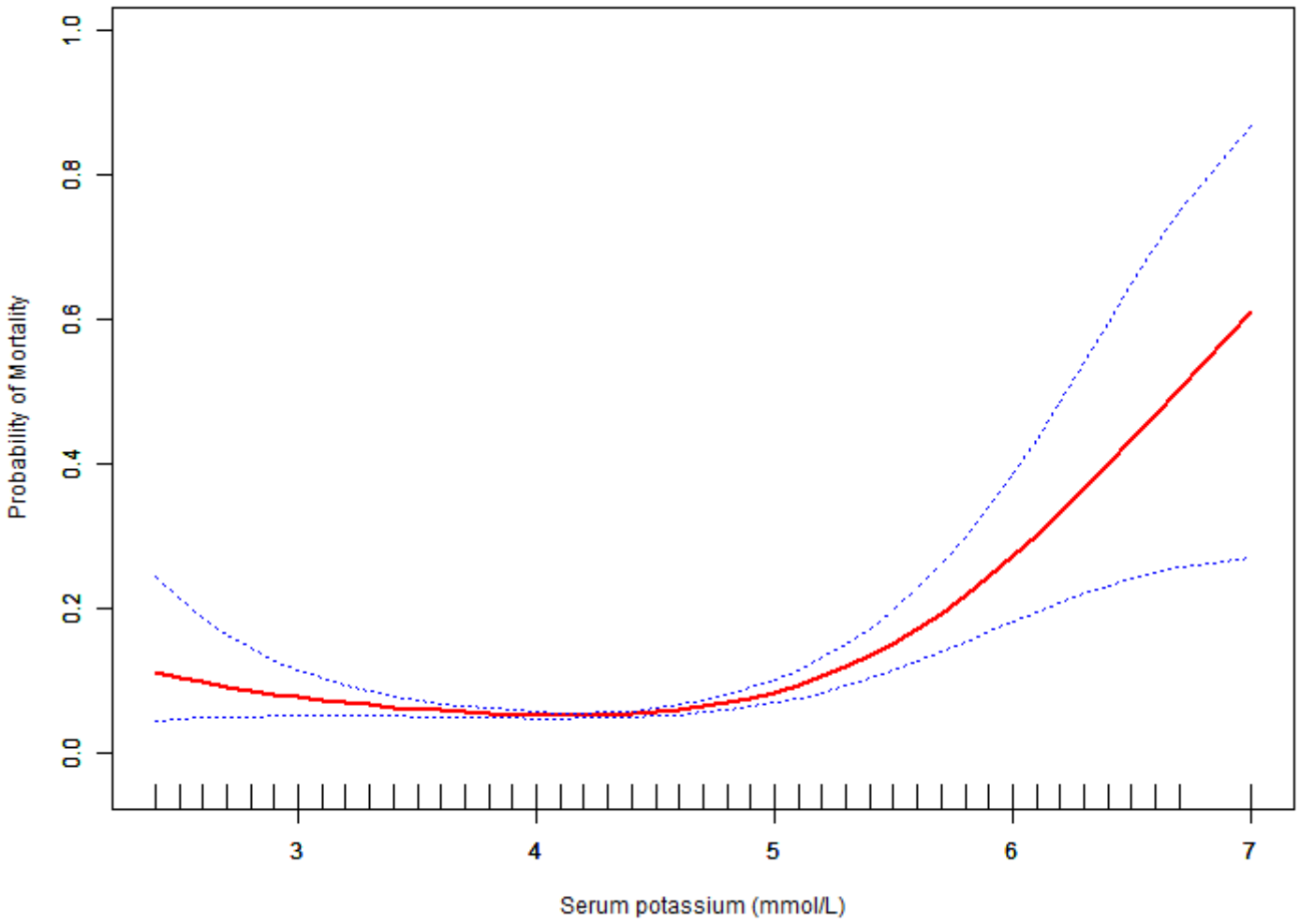

Figure 2

Associations between potassium (mmol/L) and 30-day mortality in all visits with cardiac arrhythmias. A threshold, nonlinear association between potassium levels and 30-day mortality was found in a generalized additive model (GAM) . Solid rad line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Adjusted for age, sex, sodium (glucose-corrected), calcium (albumin-corrected), glucose, albumin and comorbid conditions (hypertension, diabetes, pneumonia, coronary heart disease, heart failure, atrial fibrillation/flutter, chronic obstructive pulmonary disease and kidney failure).

Supplementary Files

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