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Clinical paper

Potassium disorders at intensive care unit admission and functional outcomes after cardiac arrest

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ABSTRACT

Background: Abnormal serum potassium levels are commonly found in the intensive care unit (ICU) population. We aimed to determine the prevalence of potassium disorders at ICU admission and its association with functional outcomes in comatose patients resuscitated from cardiac arrest.

Methods: We performed a post hoc analysis of pooled data from four randomised clinical trials involving comatose post-cardiac arrest patients admitted to ICU after return of spontaneous circulation (ROSC). Reference serum potassium levels were defined as between 3.0 and 4.9 mmol/L. An unfavourable functional outcome was defined as a cerebral performance category of 3 to 5 at 180 days. We compared potassium disturbances categorically in a mixed effects logistic regression model including initial rhythm, delay from collapse to return of spontaneous circulation, bystander cardiopulmonary resuscitation, lactate and urea at ICU admission, with normokalaemia set as the reference group.

Results: We included 1133 patients (557 from the HYPERION, 346 from the TTH48, 120 from the COMACARE, and 110 from the Xe-HYPOTHECA trials) with a median age of 64 years (interquartile range 55–72) and a predominance of males (72 %); a total of 712 (64 %) patients had unfavourable functional outcomes. On admission, 221 patients (19.5 %) experienced hyperkalaemia and 35 (3.1 %) patients experienced hypokalaemia. Fewer patients in the normokalaemia group (513/877, 58.5 %) had an unfavourable functional outcome compared to the hypokalaemia (24/35, 68.6 %) and hyperkalaemia groups (180/221, 81.4 %; $p < 0.001$). Hyperkalaemia was associated with higher odds for an unfavourable functional outcome (adjusted odds ratio (OR) 1.85, 95 % confidence interval (CI) 1.10–3.12, $p = 0.02$), while hypokalaemia was not (OR 1.36 95 % CI 0.51–3.60, $p = 0.53$). The associations were not significant in a subgroup analysis adjusted for the modified cardiac arrest hospital prognosis score in 833 patients (OR 1.74, 95 % CI 0.91–3.34, $p = 0.10$ for hyperkalaemia and OR 1.48, 95 % CI 0.40–5.44, $p = 0.55$ for hypokalaemia).

Conclusions: Of the comatose patients admitted to ICU after cardiac arrest, one in five experienced a potassium disorder on ICU admission. Hyperkalaemia was associated with unfavourable functional outcomes at 180 days, while hypokalaemia was not.

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Introduction

Achieving survival in cardiac arrest is still a significant difficulty. Despite progress in prehospital interventions, achieving favourable functional outcomes remains a considerable challenge, with survival rates ranging from 0–18 % for out-of-hospital cardiac arrest (OHCA) to 15–34 % for in-hospital cardiac arrest at hospital discharge.[1] Previous research on cardiac arrest outcomes have focused on both mortality[2,3] and functional outcomes.[4] One large study reported that 95 % of patients and members of the public prioritised long-term survival with favourable functional outcome over short-term survival (hours to days).[5].

Potassium disorders, encompassing hyperkalaemia and hypokalaemia, represent common electrolyte abnormalities encountered in critically ill patients admitted to intensive care units (ICUs). The significance of potassium disorders extends beyond their mere biochemical derangements, as previous studies have suggested their association with clinical outcomes, particularly in populations vulnerable to cardiac events, such as those with myocardial infarction or those resuscitated from cardiac arrest.[6,7] While potassium disorders were associated with 28-day mortality in a previous study,[3] the authors did not include any data on long-term functional outcomes. Interestingly, in a large study that included more than 40,000 patients with acute myocardial infarction, a U-shaped relationship between potassium and in-hospital mortality was observed.[6] In addition, another recent study that focused on cardiac arrest patients found that mortality was the lowest in the quartile of potassium, ranging between 4.0 and 4.2 mmol/L, and the highest in the quartile of elevated potassium levels.[8].

Understanding the prevalence and prognostic implications of potassium disorders in comatose post-cardiac arrest patients could contribute to optimising patient care. The primary aim of this *post hoc* study is to determine the occurrence of early ICU potassium disorders and their link with long-term functional outcomes after cardiac arrest. Despite some previous suggestions that low potassium could be associated with favourable functional outcomes,[9–11] we hypothesise that hypokalaemia and hyperkalaemia are both associated with unfavourable functional outcomes.[6].

Materials and Methods

Study Design

This was a retrospective observational study that utilised pooled data from four randomised clinical trials conducted in comatose post-cardiac arrest patients admitted to the ICU after return of spontaneous circulation (ROSC). The included trials were HYPERION[12], TTH48[13], COMACARE[14], and Xe-HYPOTHECA,[15] selected based on their relevance to the research question and the availability of data pertaining to potassium disorders and functional outcomes. This cohort was also gathered to assess other electrolyte disturbances.[16] The four studies collectively enrolled a total of 1,172 ICU patients between August 2009 and January 2018. For our analysis, we included patients who were admitted to the ICU and were alive, with available laboratory results.

Study population

The inclusion criteria across the trials were patients aged 18 years or older (up to 80 years in the TTH48 and COMACARE trials) who were comatose (Glasgow Coma Scale score $\leq$ 8) following ROSC after OHCA and subsequently admitted to the ICU. Additionally, some patients with in-hospital cardiac arrest were included in the HYPERION trial (around one quarter of the patients in the HYPERION study). The exclusion criteria were patients who withdrew consent after initial inclusion. The patient selection criteria, interventions and follow-up were described in detail in the original studies.[12–15].

Data Collection and variables

Data regarding patient demographics, clinical characteristics, laboratory parameters and outcomes were extracted from the individual trial databases. Potassium disorders were defined based on serum potassium levels measured at ICU admission. Hyperkalaemia was defined as serum potassium levels exceeding 4.9 mmol/L, while hypokalaemia was defined as serum potassium levels below 3.0 mmol/L. Normokalaemia was defined as serum potassium levels within the range of 3.0 to 4.9 mmol/L, as proposed in the Simplified Acute Physiology Score II.[17].

The primary outcome of interest was functional outcomes assessed at 180 days post-CA using the Cerebral Performance Category (CPC) scale.[18] A favourable functional outcome was defined as a CPC score of 1 or 2, indicating no to mild or moderate neurological disability, and an unfavourable functional outcome was defined as a CPC score of 3–5, indicating severe disability or death. In the HYPERION trial, the primary outcome was the CPC score on day 90, and the functional outcome for day 180 from this study was collected using the last observation carried forward method.

The relationships between urea and lactate levels at ICU admission and potassium were independently analysed and displayed in separate figures to highlight their potential influence on potassium levels and how they might indirectly impact patient outcomes.

Subgroup analysis

We pre-planned a multivariable mixed effects logistic regression model adjusted on modified cardiac arrest prognosis (mCAHP) score. The mCAHP was incorporated into the model as a continuous variable. This tool is a summary statistic designed to predict brain damage early after cardiac arrest with ROSC, allowing for comparisons across different cardiac arrest patient populations. [19–21] The mCAHP score includes age, initial rhythm, no-flow and low-flow time combination, location of arrest, epinephrine dose and pH. Thescore could not be calculated due to missing data for patients from the COMACARE trial and for few patients from other trials and we therefore performed a subgroup mixed effects logistic regression model adjusted with the mCAHP score on patients from only the TTH48, HYPERION and Xe-HYPOTHECA trials. This subgroup analysis had lower statistical power, as the mCAHP score was missing for 300 (25.8 %) patients.

Statistical analysis

Descriptive statistics were used to summarise patient characteristics, potassium disorder prevalence and functional outcomes. Categorical variables are presented as frequencies and percentages. The distribution was initially assessed using the Shapiro–Wilk test for normality and manual evaluation. Because only two factors (temperature and SAPS II score) were normally distributed, we decided to report all continuous variables as medians with interquartile ranges (IQR) for clarity and consistency. We performed the comparisons with the chi-square test for categorical data and the Mann–Whitney U and Kruskal–Wallis tests for continuous data. P-values below 0.05 were considered significant. We report log odds with confidence intervals for unfavourable functional outcome in restricted cubic spline models for linear visualisation of association.

We used mixed effects logistic regression models to further investigate the association between hypokalaemia, normokalaemia, hyperkalaemia and functional outcome. The dependent variable was unfavourable functional outcome at 180 days after ICU admission. The original source study was included as a random intercept, and while we modelled potassium as a categorical variable, we also used restricted cubic splines with 3 knots (at 10th, 50th and 90th percentile) to model the effect of non-linearity. The p-values of the terms in the mixed-effects models were calculated using Satterthwaite denominator degrees of freedom. In the plots of the non-linear models, the confidence intervals were calculated using adjusted bootstrap percentile intervals with 1000 bootstrap samples. We included three mixed effects logistic regression models, where potassium was modelled categorically with normokalaemia as the reference group: (1) potassium as an independent variable; (2) an a priori decided model including potassium, initial rhythm, delay from collapse to ROSC (no-flow + low-flow sum) as a continuous variable, bystander cardiopulmonary resuscitation[22] and lactate[23] and urea[24] levels; and (3) a subgroup analysis adjusted with the mCAHP score.[19] The factors were selected based on the previous literature and data availability. The association between potassium disorders and functional outcomes was evaluated, adjusting for relevant prognostic factors, including mCAHP scores. Patients with missing data were excluded. We conducted additional sensitivity analyses to adjust for the effects of pH, previous cardiac and pulmonary diseases, the differences in no-flow and low-flow times, sex and cardiac arrest location (in-hospital cardiac arrest patients excluded).

All analyses were conducted using IBM SPSS Statistics for Windows, Version 29.0. (IBM Corporation, Armonk, NY, USA) and R software version 4.3.2 using the rms, lme4 and lmerTest packages.[25–28].

Results

Patients

We included 1133 patients (557 from HYPERION, 346 from TTH48, 120 from COMACARE and 110 from Xe-HYPOTHECA) with a median age of 64 years (IQR 55–72) and a predominance of males (72 %).

Demographic and resuscitation factors are reported separately for the normokalaemia, the hypokalaemia and hyperkalaemia groups (Table 1). In addition, the same demographic and resuscitation factors are reported for the favourable and unfavourable outcome groups (Supplementary Table 1).

Potassium and functional outcomes

A total of 712 (64 %) patients had unfavourable functional outcomes. The distribution of patients with unfavourable functional outcome is presented in Supplementary Table 2. When potassium was modelled categorically in a mixed effects logistic regression model, hyperkalaemia was associated with higher odds for unfavourable functional outcome (adjusted odds ratio (OR) 1.85, 95 % confidence interval (CI) 1.10–3.12, p = 0.02), whereas the association for hypokalaemia was not statistically significant (OR 1.36, 95 % CI 0.51–3.60, p = 0.53). However, in the mCAHP-adjusted subgroup mixed effects regression model, hyperkalaemia was not significantly associated with functional outcome score (OR 1.74, 95 % CI 0.91–2.23, p = 0.10).

The results of the regression models are shown as a forest plot in Fig. 1. Excluding the in-hospital cardiac arrest patients did not significantly change the results. In a sensitivity model including potassium, initial rhythm, no-flow time, low-flow time, whether bystander cardiopulmonary resuscitation was performed or not, lactate, urea, sex, previous chronic cardiac disease and previous chronic pulmonary disease

Table 1
Demographic factors according to potassium category.

	Normokalaemia n = 877		Hypokalaemia n = 35		Hyperkalaemia n = 221	
Demographics						
Males	659	75 %	20	57 %	146	66 %
Age, years	63	[55–71]	66	[54–72]	66	[56–73]
Height, cm	175	[167–180]	168	[164–173]	170	[165–180]
Weight, kg	80	[70–92]	72	[67–88]	81	[69–90]
Body mass index, kg/m^2	26.3	[23.9–29.8]	26.7	[23.8–30.3]	27.0	[24.0–31.4]
Chronic heart disease	379	43 %	10	29 %	124	56 %
Chronic pulmonary disease	164	19 %	9	26 %	72	33 %
Resuscitation factors						
Shockable rhythm	458	54 %	15	44 %	63	30 %
Bystander witnessed cardiac arrest	832	95 %	32	91 %	206	93 %
Bystander performed CPR	667	76 %	27	77 %	153	69 %
Location of cardiac arrest						
Place of residence	450	51 %	20	57 %	115	52 %
Public place	319	36 %	9	26 %	66	30 %
Hospital	108	12 %	6	17 %	40	18 %
SAPS II score	68	[56–79]	79	[70–86]	79	[66–91]
No-flow duration minutes	0	[0–5]	1	[0–5]	0	[0–5]
Low-flow duration minutes	18	[12–25]	20	[12–30]	19	[12–29]
Time to ROSC, minutes	20	[15–28]	24	[15–37]	21	[15–32]
Epinephrine given	588	76 %	27	82 %	186	91 %
Epinephrine dose, mg	2	[0–4]	3	[1–4]	3	[1–5]
Amiodarone injection	200	26 %	10	30 %	39	19 %
Bicarbonate injection	36	5 %	5	15 %	16	8 %
ICU characteristics						
Coronary angiography	466	53 %	16	46 %	105	48 %
Successful angioplasty	213	24 %	5	14 %	40	18 %
Admission pH	7.27	[7.20–7.34]	7.31	[7.24–7.40]	7.21	[7.08–7.28]
Lactate, mmol/L	3.3	[1.8–6.3]	4.6	[2.5–11.1]	4.9	[2.5–9.5]
Serum creatinine, μmol/L	97	[78–124]	90	[76–109]	123	[98–166]
Blood glucose, mmol/L	11.1	[8.1–14.5]	12.6	[9.5–17.7]	11.9	[7.7–17.6]
PaO_2, mmHg	127	[90–205]	120	[91–221]	140	[87–241]
$PaCO^2$, mmHg	43	[37–51]	42	[36–47]	45	[38–57]
Urea, mmol/L	7.0	[5.2–9.0]	5.9	[4.7–7.6]	8.7	[6.2–12.4]
mCAHP score	88	[71–103]	91	[79–107]	102	[87–113]

The results are presented in either n(%) or median and [interquartile range], CPR = cardiopulmonary resuscitation, SAPS II = Simplified acute physiology score, ROSC = return of spontaneous circulation, mCAHP score = modified cardiac arrest hospital prognosis score. Temperature and Glasgow coma scale were also compared with no significant differences between groups.

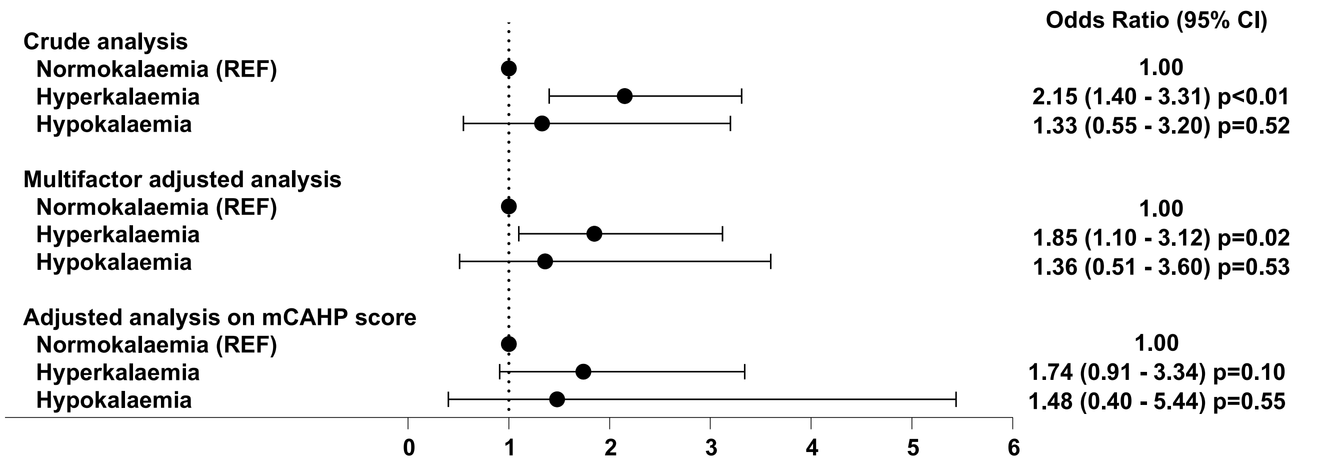

Fig. 1. Forest plot of the association between unfavourable functional outcomes and potassium categories. The results are from a mixed effects logistic regression model. Multifactor adjusted analysis included: potassium as categorial variable, initial rhythm, delay from collapse to ROSC (no-flow + low-flow sum) as a continuous variable, bystander cardiopulmonary resuscitation and lactate and urea levels at ICU admission.

the direction for potassium effect did not change. The results of the sensitivity analyses are provided in Supplementary Table 2.

The association of potassium disorders with unfavourable functional outcomes varied significantly between the trials, of which TTH48 seemed to have the strongest association. We present the functional outcomes separately for each study in Supplementary Table 3 and the log odds for unfavourable functional outcomes at different potassium levels in **Supplementary** Figure 1.

The association between potassium levels and unfavourable functional outcomes followed a U-shaped curve, with values around 4.2 corresponding to the lowest odds of an unfavourable functional outcome in all models. The results of the mixed effects regression models are shown in Fig. 2. Relative risks for unfavourable outcome are presented in **Supplementary** Figure 2. Changing the amount or position of the knots did not significantly change the results. The independent associations of lactate and urea levels with unfavourable are illustrated in **Supplementary Figure 3** and **Supplementary Figure 4**. STROBE Checklist for included items is included as Supplementary Table 4.

Discussion

This study aimed to explore the relationship between potassium disorders and long-term functional outcomes in comatose patients post cardiac arrest. We found an association between hyperkalaemia and higher odds of unfavourable functional outcomes. Hypokalaemia did not show a significant association with functional outcomes in any of our models, although the trend was leaning towards unfavourable functional outcomes.

Our results are partially in line with the findings of previous studies. In line with our results, Shida et al. observed in an observational

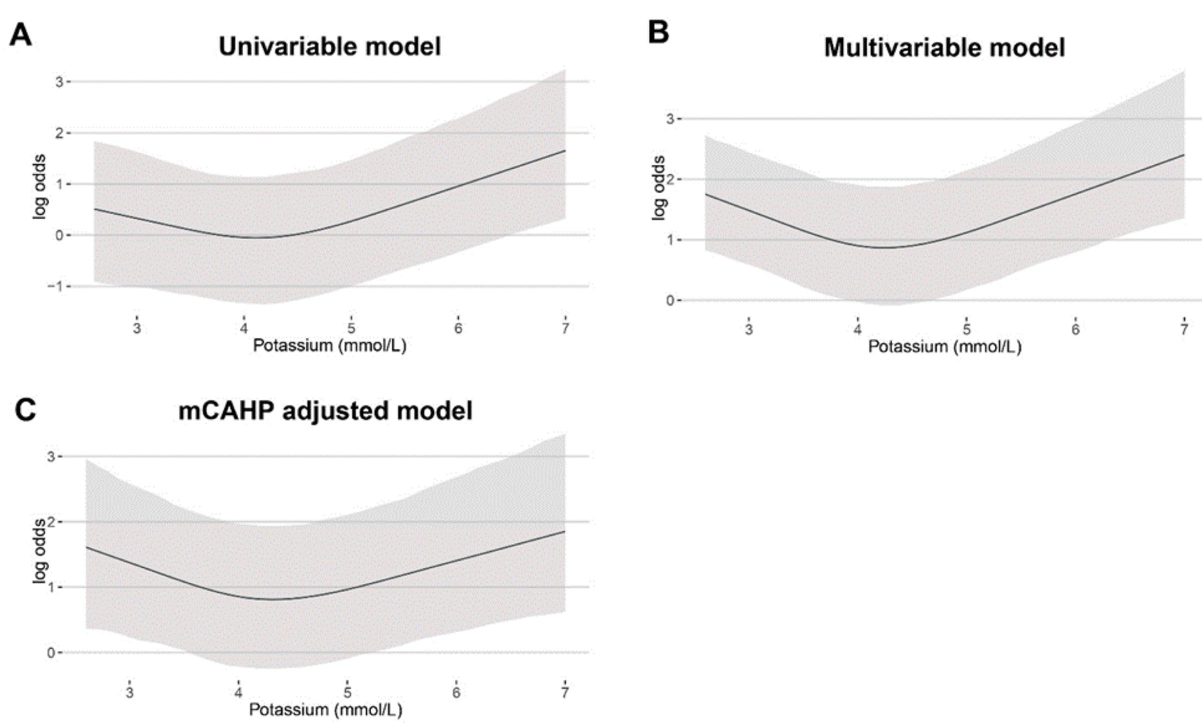

Fig. 2. Log odds for unfavourable functional outcomes according to potassium levels. Modelled with mixed effects logistic regression models using restricted cubic splines with 3 knots.

multicentre study that high serum potassium levels on hospital arrival were associated with unfavourable functional outcomes in OHCA patients.[10] However, Choi et al. reported a negative association between hypokalaemia and favourable functional outcomes in OHCA patients, while hyperkalaemia was negatively associated with survival to hospital discharge and not with functional outcomes. Nevertheless, their hypokalaemia group had better prognostic resuscitation factors, such as higher rates of shockable rhythm, bystander CPR and public cardiac arrest locations, which could explain the favourable functional outcome results.[9] Of the previous studies, only that by Shida et al. focused on the magnitude-dependent association of serum potassium levels and functional outcomes.[10] However they did not include data on previous medical conditions, and the hypokalaemia group was significantly younger than other groups considered, which could explain the differences in functional outcomes in our results. Furthermore, all of these studies focused on short-term outcomes, while we observed long-term functional outcomes. The variation in findings across these studies can be attributed to differences in study populations. While some studies employed broader inclusion criteria and controlled for a wider range of confounding factors, others focused on more specific patient groups, resulting in differing associations between potassium levels and outcomes in out-of-hospital cardiac arrest patients.[7–11].

Given the U-shaped relationship between potassium levels and functional outcomes, the current study suggests that hyperkalaemia, and potentially also hypokalaemia, could associate with functional outcomes. Although hypokalaemia was not statistically associated with functional outcomes, its low prevalence in our sample limits the power of the analysis, making its impact less statistically significant and harder to assess compared to hyperkalaemia. It remains unknown whether potassium disorders contribute to increased mortality or are merely markers for cardiac arrest patients' abnormal homeostasis. The current findings are in line with an earlier study by Skrifvars et al., in which hyperkalaemia seemed to be associated with mortality.[8] However, CPR may increase potassium levels per se, and therefore, hyperkalaemia during CPR may not necessarily refer to elevated potassium levels before cardiac arrest.[29] Severe potassium disorders can cause myocardial conduction delays, arrythmias and even cardiac arrest. [30–34] Therefore, monitoring and managing potassium levels in post-cardiac arrest patients appears to be important in identifying patients at risk of unfavourable functional outcomes.

Acute kidney injury and chronic kidney disease are apparently important contributing factors to hyperkalaemia after cardiac arrest.[5] This is supported by earlier reports of high incidences of acute kidney injury after cardiac arrest.[35–37] In the TTH48 population, nearly half of the patients developed acute kidney injury (using modified KDIGO AKI classification), which was also independently associated with worse outcomes.[37] In addition, the current results revealed higher creatinine and urea levels in hyperkaliaemic patients. On the other hand, previous studies have demonstrated an association between high mortality and hyperkalaemia, especially in patients with kidney disease, but also in patients with other severe comorbidities.[38,39] This is further supported by current findings regarding a higher prevalence of chronic pulmonary and heart disease in patients with hyperkalaemia compared with the other patients.

However, hyperkalaemia can also be a secondary phenomenon caused by a shift of potassium from the intracellular space to the extracellular space in acidosis. In our study, patients with hyperkalaemia had a lower pH than normokalaemic and hypokalaemic patients and in some patients acidosis may have been the reason for hyperkalaemia. Also, bleeding and medications such as digoxin and potassium-sparing antihypertensive drugs influence the probability of acidosis and hyperkalaemia.[36] Furthermore, temperature may play a role in potassium excretion and serum levels. This is supported by an earlier study in which potassium levels increased during rewarming after targeted temperature management in out-of-hospital cardiac arrest patients.[40] There is a possibility that the use of cold fluids[41], extended targeted temperature management (TTM) or fever after TTM[42,43] in the TTH48 study may have influenced the renal function, temperature changes and ultimately potassium levels and outcomes. This could also explain the clearest U-shape curve findings in the TTH48 dataset.

Our study has several strengths, including a large sample size and the use of data from four multinational randomised clinical trials. This diverse dataset provides a robust basis for understanding the association of potassium disorders on long-term functional outcomes in specific cardiac arrest populations. Additionally, our focus on baseline characteristics and long-term outcomes adds valuable insights to the existing body of literature, which predominantly emphasises short-term survival and the independent effects of potassium.

However, our study also has limitations. Variability in electrolyte and fluid treatment protocols across the included trials could have introduced heterogeneity in the patient population.[44] In addition, the serum potassium level could have been influenced by other blood parameters or medications, and we did not include extensive analyses adjusted for all relevant biomarkers or medications. Furthermore, this study included only the initial measurement of potassium and was not controlled for potassium supplementation and changes over time. The data were collected from ambulance records and especially no-flow times may be subject to bias as bystander reports are often inaccurate. There was heterogeneity among the selection criteria and patient populations in the original studies, which may have affected the outcome results, and our study only focused on subpopulation of cardiac arrest patients comatose at ICU arrival and do not represent all cardiac arrest patients.[45] Hypokalaemia was very uncommon, and the small population reduced the power of our analysis, and our analyses do not differentiate patients between no-flow and low-flow times. Lastly, this was a retrospective observational analysis of merged high-quality randomised controlled trial data and cannot assess causality between potassium disorders and functional outcomes.

Conclusions

One-fifth of cardiac arrest patients in four major randomised controlled trials experienced potassium disorders. Hyperkalaemia was associated with unfavourable functional outcomes while hypokalaemia was not. However, the association was no longer statistically significant after adjustment for the mCAHP score.

CRediT authorship contribution statement

Holm Aki: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lascarrou Jean Baptiste:** Investigation, Writing – review & editing. **Cariou Alain:** Investigation, Writing – review & editing. **Reinikainen Matti:** Investigation, Writing – review & editing. **Laitio Timo:** Investigation, Writing – review & editing. **Kirkegaard Hans:** Investigation, Writing – review & editing. **Søreide Eldar:** Investigation, Writing – review & editing. **Taccone Fabio Silvio:** Investigation, Writing – review & editing. **Lääperi Mitja:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **B. Skrifvars Markus:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [J. B. Lascarrou reports lecture fees from Masimo and BD. Markus Skrifvars reports lectue fees from BARD Medical (Ireland) in 2021 and 2022.].

All other authors report no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2024.110439.

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