Admission plasma potassium and length of hospital stay: a meta-analysis

Hugh Logan Ellis, David Llewellyn, Jeewaka Mendis, Martin Whyte

ABSTRACT

Objective Hypokalaemia and hyperkalaemia (‘dyskalaemia’) are commonly seen in patients requiring emergency hospital admission. The adverse effect of dyskalaemia on mortality is well described but there are few data for the effect on hospital length of stay. We sought to determine the association of serum potassium concentration with in-hospital length of stay.

Design Systematic review and meta-analysis.

Data sources A structured search of MEDLINE, PubMed and SCOPUS databases to 19 March 2021.

Eligibility criteria Observational cohort studies defining exposure of interest as serum potassium levels (at admission or within the first 72 hours) and with outcome of interest as length of hospital stay. Studies had to provide estimates of length of stay as a comparison between normokalaemia and defined ranges of hyperkalaemia or hypokalaemia.

Data extraction and synthesis We identified 39 articles published to March 2021 that met the inclusion and exclusion criteria. Study selection, data extraction and quality assessment were carried out by two reviewers working independently and in duplicate, to assess eligibility and risk of bias, and extract data from eligible studies. Random effects models were used to pool estimates across the included studies. Meta-analyses were performed using Cochrane-RevMan.

Results Five studies were included in the meta-analysis. Compared with the reference group (3.5–5.0 mmol/L), the pooled raw differences of medians were 4.45 (95% CI 2.71 to 6.91), 1.99 (95% CI 0.03 to 3.94), 0.98 (95% CI 0.91 to 1.05), 1.51 (95% CI 1.03 to 2.0), 1.95 (95% CI 0.75 to 1.25) and 2.76 (95% CI 1.24 to 4.29) for patients with potassium levels of <2.5, 2.5 to <3.0, 3.0 to <3.5, <3.5 to 5.5, <5.5 to 6 and ≥6.0 mmol/L, respectively.

Conclusion Hospital length of stay follows a U-shaped curve against plasma potassium concentration: increased mortality has also been seen in a number of subpopulations. A U-shaped mortality curve against plasma potassium concentration evident in populations with myocardial infarction, hypertension, heart failure, diabetes and chronic kidney disease. As well as mortality, hyperkalaemia leads to high economic burden, in part mediated by the requirement for frequent hospital admissions. Whether the hospital admissions are more prolonged in dyskalaemia—compared with their eukalaemic counterparts—is unknown. This information would allow for a more accurate assessment of the economic and societal burden of dyskalaemia. To our knowledge, there are no previous systematic reviews of dyskalaemia and length of stay. In this systematic review, we determined whether dyskalaemia on admission is associated with significant differences in length of hospital admission.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used rigorous methodology in accordance with the Cochrane handbook and the results were reported as stated by Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

⇒ The search algorithm was applied to the largest medical databases.

⇒ The certainty of the evidence of this meta-analysis may be limited by the limited number of studies available.

⇒ Data were not analysed separately by organ pathology; however, patients rarely present to hospital with single organ disease states.
and was registered with PROSPERO (International Prospective Register of Systematic Reviews; registration identification CRD42021244454).\textsuperscript{18} Comprehensive literature searches of the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), and SCOPUS databases from were performed up to 19 March 2021 using the following combinations of keywords and medical subject heading terms without language restriction: ‘hyperkalaemia’ OR ‘hyperkal*’ OR ‘hypokalaemia’ OR ‘hypokal*’ OR ‘potassium’, AND ‘length of stay’, ‘emergency’, ‘cohort’, ‘admission’ and ‘outcome’. In addition, the reference sections of the included studies and review articles were reviewed to identify other relevant articles (online supplemental appendix 1).

**Study selection criteria**

A modified framework (Population, Intervention, Comparison, Outcome), whereby ‘intervention’ and ‘outcome’ were replaced with ‘phenomenon of interest’, was used to develop the inclusion and exclusion criteria.

**Inclusion criteria**

Observational cohort studies that defined the exposure of interest as serum potassium levels on admission, or within the first 72 hours of admission and with the outcome of interest defined as length of hospital stay. Studies had to provide estimates of median length of stay and IQR as a comparison between normokalaemia and defined ranges of hyper or hypokalaemia. For publications examining a cohort more than once, we selected only the article with the largest number of participants from that dataset. The reference lists of studies that examine the topic of interest were checked for additional publications.

**Exclusion criteria**

Narrative reviews, systematic review protocols, case reports, abstracts, data from unpublished research or incomplete articles were excluded. We also excluded articles not written in English.

Identification, screening and eligibility assessments were performed independently in an unblinded, standardised manner by two reviewers (HLE and DL) using Rayyan, a web application designed for the purpose. Disagreements between reviewers were discussed with a third researcher (MW).

**Data extraction and quality assessment**

Using a standardised data extraction sheet, the following information (if available) was extracted and recorded from studies: author name, year of publication, reference ranges of potassium, number of cases in each reference range, lower IQR, median and upper IQR of length of stay for each reference range. If length of stay was reported in weeks or months, it was multiplied by 7 and 30, respectively.

Risk of bias was evaluated separately by two reviewers, using the Newcastle-Ottawa Scale. This considers the selection of participants, comparability of groups and ascertainment of outcomes.\textsuperscript{19} Studies that achieved a full rating in at least two categories of selection, comparability or outcome assessment were considered to have a low risk of bias and were included.

**Statistical analysis**

Studies included different dyskalaemia comparison groups (table 1). We evaluated outcomes with comparison to serum potassium of 3.5–5.0 mmol/L as the reference category in each of the five studies. Heterogeneity of design and participant populations was anticipated between studies; therefore, we conducted a linear random effects meta-analysis. As length of stay is not normally distributed, the median and IQRs were reported in all studies. We used the R package ‘metamedian’ which uses the quantile estimation method of McGrath et al.\textsuperscript{20} to estimate the pooled raw difference of medians across groups.

We measured the inconsistency (the proportion of total variation across studies due to heterogeneity) of effects across interventions using the I\(^2\) statistic. I\(^2\) value of 25\% or more represented heterogeneity.\textsuperscript{21} Risk of bias across studies was assessed by inspection of funnel plots for asymmetry. All statistical analyses were performed using R statistical software V.4.0.5. Analyses were made from published data. No additional data available for public repository.

**Patient and public involvement**

No patients were involved in this systematic review study.

**RESULTS**

**Characteristics of the included studies**

A total of 517 unique articles were retrieved from the database searches (figure 1). Of the 517 studies, 478 were excluded based on the contents of their abstract. The full text of the remaining 39 papers was reviewed according to the inclusion criteria, which led to the identification of 5 studies.\textsuperscript{16–22,24}

The studies were published between 2015 and 2021 and contained between 20421 and 73938 individuals (table 1). Two studies were from the USA\textsuperscript{6} and three from Western Europe.\textsuperscript{22–24} Three studies analysed all patients who attended an emergency department and had electrolyte measurement,\textsuperscript{6,23,24} and two studies only considered patients admitted acutely under the care of the medical team.\textsuperscript{16,25} Patients had a range of principal diagnoses including cardiovascular, haematological/oncological, infectious, respiratory, gastrointestinal, injury/poisoning and endocrinological.\textsuperscript{1}

In all studies the Newcastle-Ottawa score was 9, and therefore, no studies were considered at high risk of bias (online supplemental appendix 2).

**Association of admission serum potassium levels with length of stay**

The median length of hospital admission ranged from 3 to 6 days. There was a U-shaped association between admission potassium concentration and length of stay.
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Country</th>
<th>Study design</th>
<th>Year of inclusion</th>
<th>Patients (n)</th>
<th>Age years</th>
<th>Sex (M/F)</th>
<th>Hypokalaemia definition (mmol/L)</th>
<th>Hyperkalaemia definition (mmol/L)</th>
<th>Study design</th>
<th>Year of inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheungpasitporn2017</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>1 January 2011–31 December 2013</td>
<td>73983</td>
<td>61 (SD 18)</td>
<td>Male 38973 (63%)</td>
<td>Not defined.</td>
<td>Reference group 4.0–4.5</td>
<td></td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td>Spjeger2017</td>
<td>Norway</td>
<td>Retrospective cohort study</td>
<td>December 2013</td>
<td>47089</td>
<td>49 (SD 22)</td>
<td>Male 21573 (46%)</td>
<td>&lt;3.5</td>
<td>&gt;5.0</td>
<td></td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td>Tazmini2019</td>
<td>Denmark</td>
<td>Retrospective cohort study</td>
<td>February 2019</td>
<td>42355</td>
<td>69</td>
<td>Male 20800 (47%)</td>
<td>Not defined.</td>
<td>Reference group 4.0–4.5</td>
<td></td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td>Ravelli2020</td>
<td>Norway</td>
<td>Retrospective cohort study</td>
<td>January 2017</td>
<td>59 (SD 22)</td>
<td>69</td>
<td>Male 32700 (47%)</td>
<td>Not defined.</td>
<td>Reference group 4.0–4.5</td>
<td></td>
<td>Retrospective cohort study</td>
</tr>
</tbody>
</table>

DISCUSSION

This is the first meta-analysis to provide evidence for a U-shaped association between the first potassium value, taken at hospital admission and subsequent length of stay. The pooled median length of stay in the reference group was 3.1 days, rising to 7.6 days in patients with severe hypokalaemia (<2.5 mmol/L) and 5.9 days in patients with severe hyperkalaemia (>6.0 mmol/L), hence hospitalisation was prolonged by a factor of two.

Electrolyte disturbance is often attributable to significant comorbidity, for example, hypokalaemia is associated with malnutrition, long-term diuretic therapy or diarrhoea and hyperkalaemia with acidosis and renal impairment. In frail individuals with dyskalaemia, a prolonged length of stay may represent greater propensity to be discharged to hospice or to a nursing facility, as has been seen with hyponatraemia. Hyperkalaemia may restrict prescribing of drugs for other pathologies, for example, digoxin for atrial fibrillation or beta-agonist inhalers for asthma. It is uncertain whether the electrolyte dysfunction is independently associated with length of stay.

In-hospital correction of hypokalaemia has been reported to reduce mortality, or to have no effect. Whether correction of hypokalaemia reduces length of stay is uncertain. Correction of the hypokalaemia itself may take time. A reduction in serum potassium of 0.3 mmol/L below normal is representative of approximately 100 mmol reduction in total body potassium stores. Hence, the deficit can be considerable in moderate or severe hypokalaemia and careful, gradual intravenous replacement is needed. Intravenous potassium substitution may increase potassium variability and cause hyperkalaemia. Cation exchange resins are used for hyperkalaemia, but show no reduction in serum potassium within 4 hours. The new potassium binders, patiromer (Veltassa) and sodium zirconium cyclosilicate (Lokelma) are finding their place in therapy. Sodium zirconium cyclosilicate is a non-polymer compound that exchanges potassium for sodium and hydrogen ions whereas patiromer is a polymer that exchanges potassium for calcium ions. Both act in the bowel and neither are typically used for acute treatment of hyperkalaemia, as their onset of action may take several hours to days. Conversely, whereas insulin-dextrose has onset of action...
within 15–30 min, its duration of action is only up to 6 hours, often necessitating additional treatment. Renal replacement therapy requires time for HDU transfer and to initiate the dialysis.

There are some limitations to our meta-analysis. The systematic search found that there were relatively few studies to examine the relationship between admission potassium and length of stay. Within the studies that exist, there were differences in methodology and result reporting which limited our ability to directly compare the results. Although papers used same thresholds for hyperkalaemia and hypokalaemia, the subcategories, for reporting results, differed. Singer et al. explicitly mention that they only included patients who were discharged alive within their analysis, but the other papers do not address this potential confounder within their results or methods text. Given the U-shaped association between in-hospital mortality and admission potassium, when considering the relationship of admission potassium to length of stay, our results may have the effect of underestimation of length of stay. The studies included within this review were from disparate healthcare systems (Ireland, Norway, Switzerland, USA) and although they are of similar patient types, the results may not be generalisable outside of the country of study. Dyskalaemia is associated with comorbid states. This analysis does not seek to examine outcomes in disease-specific states but in the current era, patients rarely present to hospital with single organ disease. For example, heart failure and chronic kidney disease often coexist and share common risk factors in their development, and both heart and kidney disease can worsen each other’s prognosis. We, therefore, feel that our analysis is highly applicable to everyday clinical practice in general medicine. As a meta-analysis of observational data, we report an association but not necessarily a causation of dyskalaemia on length of stay. Dyskalaemia may be a surrogate marker of more general illness severity. However, data suggest that correction of hyperkalaemia improves outcomes.

New, effective potassium binders (patiromer and sodium zirconium
cyclosilicate) are available. They do not directly treat underlying pathologies of drivers for hyperkalaemia and it will be of interest as to whether they influence hospital length of stay. Future studies should evaluate whether the effect of potassium levels on duration of hospital admission varies between age groups.

In conclusion, in this meta-analysis, we have shown that hospital length of stay follows a U-shaped distribution, with duration of admission being twofold greater at the extremes of the potassium range.

**Acknowledgements** The authors wish to thank the librarians at The University of Surrey.

**Contributors** The work was conceived by MW and HLE. Paper searches and identification were made by HLE and DL with MW arbitrating. Statistical support was provided by JM. All authors contributed equally to the writing and review of the manuscript. MW is the guarantor of the integrity of this work.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** MBW has received investigator-led funding from AstraZeneca and Sanofi. HLE, LD and JM have no conflicts of interest.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Ethical approval was not required as no new data or patient-level data were collected.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iD**

Martin Whyte [http://orcid.org/0000-0002-2897-2026](http://orcid.org/0000-0002-2897-2026)

**REFERENCES**


10. Khan SS, Campia U, Chioncel O, et al. Changes in serum potassium levels during hospitalization in patients with worsening heart failure...
and reduced ejection fraction (from the EVEREST trial). Am J Cardiol 2015;115:S0022-9149(14)02327-3:790–6.;


Appendix 1

Search Strategy

**Databases: Embase®, MEDLINE®**

S1 - Pubmed
("hyperkalaemia"[All Fields] OR "hyperkalemia"[MeSH Terms] OR "hyperkalemia"[All Fields]) OR ("hypokalaemia"[All Fields] OR "hypokalemia"[MeSH Terms] OR "hypokalemia"[All Fields]) OR "potassium"[All Fields] OR ("dyskalaemia" [All fields] or "dyskalaemia" [All Fields]) AND ("hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields] OR "length of stay" [All Fields]) AND “cohort”[All Fields]

S2- Scopus
("hyperkalaemia" OR "hyperkalemia") OR ("hypokalaemia" OR "hypokalemia") OR "potassium" OR ("dyskalaemia" or "dyskalaemia" ) AND ("hospitalisation" OR "hospitalization" OR "length of stay") AND “cohort”

In All fields (Keywords, Title, Abstract, Text)
Appendix 2. Length of hospital admission, per potassium stratum, per study

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Overall number in study</th>
<th>number with K &lt;2.5 mM</th>
<th>Length of stay (days) in group &lt;2.5 mM</th>
<th>number with K 2.5-3 or &lt;3 mM</th>
<th>Length of stay (days) in group 2.5 to &lt;3 mM</th>
<th>number with K 3-3.5 or &lt;3.5 mM</th>
<th>Length of stay (days) in group 3-3.5 mM</th>
<th>number with K &gt;3.5 mM</th>
<th>Length of stay (days) in group &gt;3.5 mM</th>
<th>number with K &gt;5 mM</th>
<th>Length of stay (days) in group &gt;5 mM</th>
<th>number with K &gt;5.5 mM</th>
<th>Length of stay (days) in group &gt;5.5 mM</th>
<th>number with K &gt;6 mM</th>
<th>Length of stay (days) in group &gt;6 mM</th>
<th>number with K &gt;7 mM</th>
<th>Length of stay (days) in group &gt;7 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conway (2015)</td>
<td>60864</td>
<td></td>
<td>8811</td>
<td>5.8 (2.7 - 10.6)</td>
<td>49087</td>
<td>4.8 (2.0 - 9.0)</td>
<td>2966</td>
<td>6.6 (3.0 - 11.9)</td>
<td>26 (2 - 10)</td>
<td>6.6 (2 - 8)</td>
<td>197</td>
<td>4 (2 - 7)</td>
<td>49</td>
<td>4 (1 - 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tazmini (2019)</td>
<td>62730</td>
<td>49</td>
<td>6 (2 - 11)</td>
<td>396</td>
<td>5 (2 - 9)</td>
<td>4931</td>
<td>3 (2 - 6)</td>
<td>55274</td>
<td>2 (1 - 5)</td>
<td>1834</td>
<td>4 (2 - 7)</td>
<td>197</td>
<td>4 (2 - 7)</td>
<td>49</td>
<td>4 (1 - 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ravioli (2021)</td>
<td>20421</td>
<td>38</td>
<td>7 (3 - 12)</td>
<td>2338</td>
<td>2 (1 - 4)</td>
<td>17633</td>
<td>2 (1 - 4)</td>
<td>366</td>
<td>4 (2 - 10)</td>
<td>46</td>
<td>7 (4 - 13)</td>
<td>49</td>
<td>4 (1 - 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheungpasitporrn (2017)</td>
<td>73983</td>
<td>700</td>
<td>5 (3 - 9)</td>
<td>3943</td>
<td>5 (3 - 8)</td>
<td>63511</td>
<td>4 (3 - 7)</td>
<td>4463</td>
<td>5 (3 - 7)</td>
<td>1366</td>
<td>5 (3 - 9)</td>
<td>49</td>
<td>4 (1 - 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer (2017)</td>
<td>47089</td>
<td>2574</td>
<td>3.79 (1.83 - 7.08)</td>
<td>42818</td>
<td>2.91 (1.58 - 5.96)</td>
<td>1058</td>
<td>3.83 (2 - 7.75)</td>
<td>448</td>
<td>3.92 (1.92 - 8.71)</td>
<td>191</td>
<td>5.17 (0.48 - 10.04)</td>
<td>49</td>
<td>4 (1 - 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2. Funnel plots of bias, based upon potassium concentration

<2.5mmol/l vs ref (3.5-5.0 mmol/l)

<3mmol/l or 2.5-3mmol/l vs ref (3.5-5.0 mmol/l)