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 assessed 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), 1.9 (95% CI 0.75 to 2.76) and 0.76 (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, <5 to 5.5, <5.5 to 6 and >6.0 mmol/L, respectively.

Conclusion Hospital length of stay follows a U-shaped distribution, with duration of admission being twofold greater at the extremes of the potassium range.

INTRODUCTION

Dyskalaemias, disorders of potassium homeostasis, are a common occurrence in patients requiring emergency hospital treatment, with the prevalence of dyskalaemia in hospitalised patients reported to be as high as 48%. Mild hypokalaemia can lead to patients feeling tired and weak and to the development of muscle cramps. However, significant deficiency (<3 mmol/L) or elevations (>6.5 mmol/L) in plasma potassium may cause life-threatening cardiac arrhythmias and sudden death. Unsurprisingly, therefore, within the emergency department both hyperkalaemia and hypokalaemia have been associated with risk for both admission to hospital and mortality.

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.

METHODS

Data sources and search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
and was registered with PROSPERO (International Prospective Register of Systematic Reviews; registration identification CRD42021244454). 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 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. 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. 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 I² statistic. I² value of 25% or more represented heterogeneity. 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, 22–24 25

The studies were published between 2015 and 2021 and contained between 20 421 and 73 938 individuals (table 1). Two studies were from the USA and three from Western Europe. Three studies assessed all patients who attended an emergency department and had electrolyte measurement, and two studies only considered patients admitted acutely under the care of the medical team. Patients had a range of principal diagnoses including cardiovascular, haematological/oncological, infectious, respiratory, gastrointestinal, injury/poisoning and endocrinological.

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>
</tr>
</thead>
<tbody>
<tr>
<td>Conway 2015</td>
<td>Ireland</td>
<td>Retrospective cohort study</td>
<td>January 2002–December 2012</td>
<td>60864</td>
<td>Not specified. Inclusion criteria 10–85+</td>
<td>Male 29854 (49%) Female 31010 (51%)</td>
<td>&lt;3.5</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>Cheungpasitporn 2017</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 (53%)</td>
<td>Not defined. Reference group 4.0–4.5 mmol/L, against which, outcomes were compared</td>
<td></td>
</tr>
<tr>
<td>Singer 2017</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>All visits during 2014</td>
<td>47089</td>
<td>49 (SD 22)</td>
<td>Male 21573 (46%)</td>
<td>Not defined. Reference group 4.0–4.5 mmol/L, against which, outcomes were compared</td>
<td></td>
</tr>
<tr>
<td>Tazmini 2019</td>
<td>Norway</td>
<td>Retrospective cohort study</td>
<td>1 January 2010–31 December 2015</td>
<td>44255</td>
<td>69 (IQR 51–82)</td>
<td>Male 20800 (47%)</td>
<td>&lt;3.5</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>Ravioli 2021</td>
<td>Switzerland</td>
<td>Retrospective cohort study</td>
<td>1 January 2017 and 31 December 2018</td>
<td>20421</td>
<td>59 (SD 22)</td>
<td>50.7% Male 33203 (approx. as data only given as %)</td>
<td>&lt;3.5</td>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This is the first meta-analysis to provide evidence for a U-shaped association between the first potassium value and hospital length of stay. A lower first potassium value (<2.5 mmol/L) is associated with increased hospital stay, which is independently associated with length of stay and comorbidities. Hypokalaemia may restrict the efficacy of digoxin and other medications, particularly in patients with severe comorbidities. Whether correction of hypokalaemia reduces length of stay is uncertain. Correction of hypokalaemia reduces length of stay is associated with increased hospitalisation and readmission rates. In frail individuals with dyskalaemia, a prolonged hospital length of stay may represent greater frailty and a need for further intervention.

**Conclusions**

Electrolyte disturbance is often attributable to significant comorbidities and hospital length of stay. A U-shaped association between the first potassium value and hospital length of stay was prolonged by a factor of two.

**References**

1. Singer. 2017
2. Cheungpasitporn. 2017
3. Ravioli. 2021
4. Conway. 2015
5. Tazmini. 2019

As compared with the differences of means (3.5–5.0 mmol/L), the pooled sample size of all studies (3.5–5.0 mmol/L) was larger than that of studies with smaller sample sizes. A comparison of the pooled sample sizes with the sample sizes of the included studies is provided in Figure 2. The funnel plots showed no clear evidence of publication bias, though the utility was limited by the small sample sizes (online supplemental appendix 3).
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...
extremes of the potassium range.

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sion varies between age groups.

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length of stay. Future studies should evaluate whether the

it will be of interest as to whether they influence hospital

underlying pathologies of drivers for hyperkalaemia and

hospital


...closilylate) 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.

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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.

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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.

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Figure 3 Forest plot for the estimated effect size. RE, Random Effects.
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