


# Association of hyponatremia with outcomes after geriatric trauma: a systematic review and meta-analysis

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## ABSTRACT

**Background** Trauma is a major cause of mortality in the elderly population. Hyponatremia is the most common electrolyte imbalance in geriatric patients and has been demonstrated to be a risk factor for altered cognition, low bone density, falls, and death. We systematically and critically reviewed the literature to ascertain the association between hyponatremia and geriatric trauma outcomes.

**Methods** We searched seven databases for articles published from inception to October 2023. Studies included reported on geriatric trauma, hyponatremia, and clinical outcomes. Two investigators independently reviewed 6535 abstracts, 235 full-text articles, and critically appraised each study. Study details, patient characteristics, and outcomes were independently extracted by two reviewers. Data quality assessment was performed using the Grading of Recommendations Assessment, Development, and Evaluation approach. Publication bias was assessed using funnel plot-based methods. A meta-analysis of risk ratios (RR) was performed using the random effects method.

**Results** Four retrospective cohort studies involving 11 894 geriatric patients were included. Among these, 492 (21.4%) were classified as trauma patients due to a fall and 1806 (78.6%) were classified as a trauma patient due to the presence of a fracture. In total, 2298 (19.3%) patients were classified as hyponatremic (125–135 mmol/L) while 9596 (80.7%) were classified as normonatremic. The pooled RR for in-hospital mortality for hyponatremic patients was 2.23 (95% CI 1.51 to 3.74) with high heterogeneity across the studies ( $I^2=82.17\%$ ).

**Conclusions** Geriatric trauma patients presenting with hyponatremia appear to have an increased risk of in-hospital mortality. Given this association, national trauma registries should consider collecting serum sodium values for geriatric patients and providers should work to address hyponatremia as a possible contribution to falls. Given the paucity of published literature on this topic, there is a need for prospective studies evaluating the association between hyponatremia and geriatric trauma outcomes.

**Level of evidence** Level III, systematic review with meta-analysis

## INTRODUCTION

Trauma is the fifth leading cause of death in the elderly population, and geriatric trauma accounts for about 25% of trauma admissions nationally.<sup>1</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Hyponatremia is the most common electrolyte deficiency in geriatric patients and has been demonstrated to be a risk factor for altered cognition, low bone density and osteoporosis, falls and death.
- ⇒ While we know that hyponatremic geriatric patients are more likely to be admitted for falls than normonatremic geriatric patients, the risk of this electrolyte disturbance on clinical outcomes in the geriatric trauma population is not clear.

## WHAT THIS STUDY ADDS

- ⇒ This study systematically and critically reviews the literature demonstrating that very few high-quality studies have been published on this important topic in a vulnerable population. From the studies that have been published, there is a clear association between hyponatremia and worse outcomes in geriatric trauma patients.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Geriatric trauma providers should place great importance on and work to address hyponatremia as a possible contributing or exacerbating factor in geriatric falls.
- ⇒ Further research is necessary to develop evidence-based guidelines for geriatric trauma patients.

Falls are the most common cause of injury in the elderly. In 2020, falls in the geriatric population resulted in 3 million emergency department visits, 36 000 deaths, and \$50 billion in healthcare costs.<sup>2</sup> This is expected to increase, considering that the US geriatric population is anticipated to double in size over the next two decades.<sup>3</sup> The definition of a geriatric trauma patient remains elusive as varying age cut-offs of between 55 and 80 years have been reported.<sup>4–8</sup> Yet, these patients warrant special consideration because of their significant differences from younger injured patients, including medical comorbidities, prescription medications, physiological differences, and diminished physiologic reserve.<sup>9–10</sup> Geriatric patients admitted after major trauma have a mortality rate almost four times greater than their younger counterparts.<sup>11</sup>

In 2003, the Eastern Association for the Surgery of Trauma published practice guidelines to underscore the need for standardized care for geriatric trauma patients.<sup>12</sup> Since then, there has been a paucity of prospective studies evaluating the prognostic values of age, biochemical abnormalities, or injury severity on outcomes after geriatric trauma. Fall prevention has garnered attention with focuses mainly on physical therapy, pharmacology, nutrition, and comorbidities, including electrolyte disturbances.<sup>2–13</sup> Hyponatremia is the most common electrolyte imbalance in the elderly population, with a prevalence as high as 50% in hospitalized patients.<sup>14</sup> Symptoms of hyponatremia include lethargy, dizziness, confusion, and ataxia.<sup>15</sup> Hyponatremia is a risk factor for altered cognition, low bone density and osteoporosis, falls, and death.<sup>16–19</sup> Even in patients without underlying osteoporosis, hyponatremia has been shown to be a modifiable risk factor for falls and hip fractures.<sup>20–21</sup> Hyponatremic geriatric patients are also more likely to be admitted for falls than non-hyponatremic patients.<sup>22–23</sup>

In addition to increasing fall risk for elderly individuals, hyponatremia has been associated with hospital length of stay (LOS), need for inpatient rehabilitation, and 30-day mortality.<sup>24–26</sup> It has been suggested that electrolyte disturbances such as hyponatremia can be an indicator of underlying illnesses and comorbidities that can adversely affect clinical outcomes.<sup>27</sup> Most of the published literature on this topic has been limited to single-institution retrospective analyses and failed to explore the downstream clinical effects of hyponatremia on geriatric trauma patients. To more clearly define the risks of hyponatremia in the geriatric trauma population, we sought to systematically review the literature to ascertain if and how hyponatremia impacts clinical outcomes.

## METHODS

The Institutional Review Board deemed this study protocol exempt as all data were publicly available. This systematic review was not registered, but our protocol developed based on the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) checklist is available in online supplemental appendix 1. This review was conducted in accordance with the PRISMA guidelines and our checklist is available in online supplemental appendix 2.<sup>28</sup>

## Search strategy

A medical librarian (LHY), with significant expertise in conducting systematic reviews, developed a comprehensive search strategy to find published articles reporting on falls, trauma, and hyponatremia. The librarian created search strategies using a combination of keywords and controlled vocabulary in Embase.com 1947, Ovid Medline 1946, Scopus 1823, Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews, The Cumulated Index to Nursing and Allied Health Literature Plus 1937, and Clinicaltrials.gov 1997. Fully reproducible search strategies are found in online supplemental appendix 3. Studies were not restricted by language or full text.

## Study selection

Screening was completed using Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia) and adhered to the PRISMA guidelines. All citations obtained from the literature search were imported into Covidence. First, two reviewers (AN and ST) independently evaluated the titles and abstracts of articles. Screened studies were then subjected

to full-text review for eligibility. The senior author (MWS) adjudicated decisions regarding study inclusion or exclusion in discrepant cases.

We included articles that focused on geriatric or elderly trauma patients and reported on clinical outcomes such as mortality and LOS. Given the limited amount of published literature on the topic, fractures, falls, and fracture repairs were included as surrogates for traumatic injury. For articles reporting on a surrogate for trauma, we searched for specific language within the manuscript body to delineate that the study population included traumatic, non-pathologic fractures. Randomized or non-randomized controlled trials as well as prospective and retrospective studies were included. We excluded studies reporting on non-geriatric patients, case reports/series, review articles, or articles that did not report on clinical outcomes. Additionally, articles reporting on traumatic brain injury, spinal cord injury, or burns were excluded given the well-recognized role of hyponatremia in the management of these injuries.

## Data abstraction

Two reviewers (ST and AN) independently conducted data abstraction. A data extraction template was designed a priori. Abstracted data included study characteristics (title, lead author, publication year, country of publication), study aims, study design, patient demographics, comparator groups, hyponatremia type (ie, acute vs chronic), definition of hyponatremia used, traumatic injury or surrogate for trauma, hospital setting, statistical methods, primary outcomes, and study results.

## Data analysis

Statistical analyses were performed using Stata V.18 (StataCorp LLC, College Station, Texas). Statistical significance was set at a *p* value of <0.05. A random effect meta-analysis was performed for the primary outcome of in-hospital mortality. For the purposes of the meta-analysis, studies that reported subgroups of hyponatremia (ie, acute and chronic) were collapsed into one group of hyponatremic patients to maintain consistent exposure and outcome reporting among the selected studies. Heterogeneity was assessed using the inconsistency statistic (*I*<sup>2</sup>, with an *I*<sup>2</sup> value greater than 50% considered to represent considerable heterogeneity).

## Assessing methodological quality and bias

Quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach by two independent reviewers (ST and AN).<sup>29</sup> Evidence was ranked from 'very low' to 'high' quality based on risk of bias and publication bias. The senior author (MWS) then adjudicated decisions regarding grades of evidence in discrepant cases.

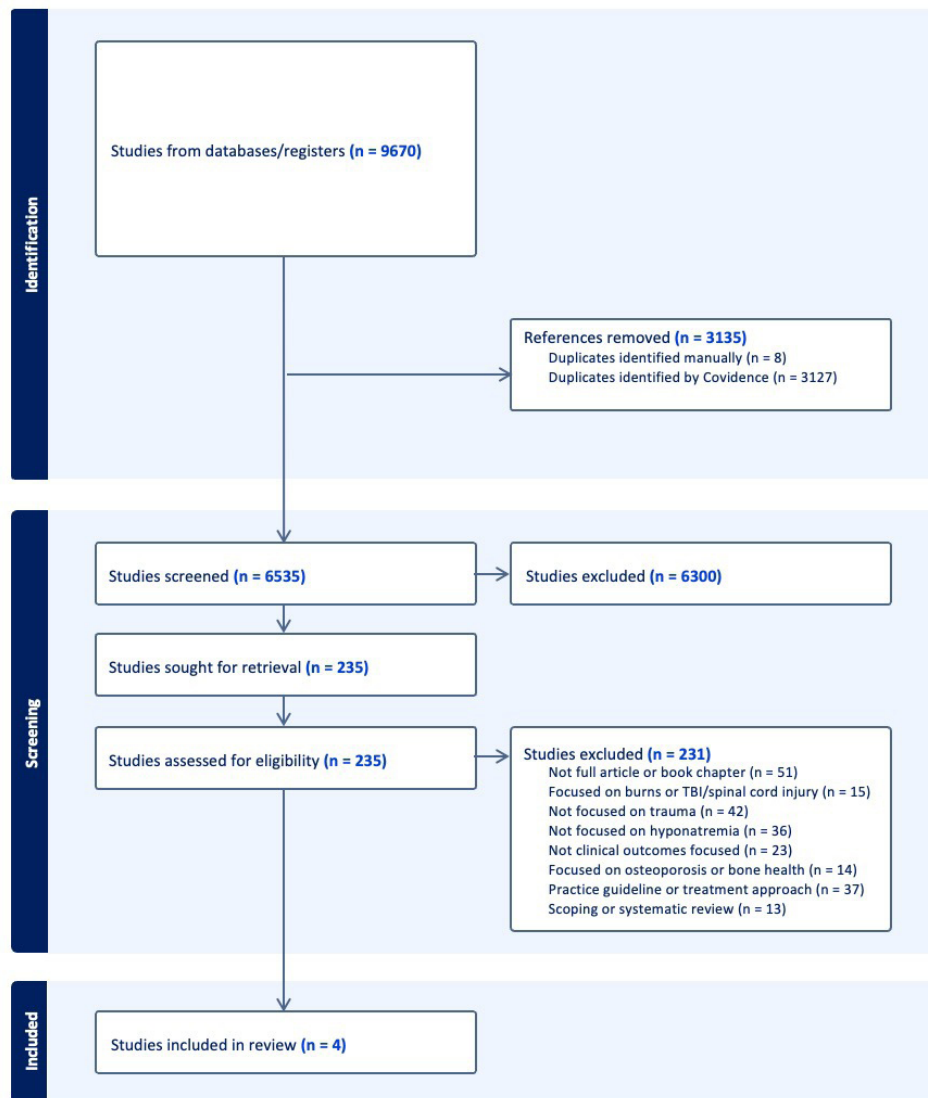
## Assessing publication bias

Publication bias among the reviewed studies was described using funnel plot-based methods.<sup>30</sup> Statistical assessment of publication bias was performed using the Harbord test.<sup>31</sup>

## RESULTS

### Literature search

The literature search yielded 9670 articles that met the inclusion criteria. Of these, 3135 duplicate articles were removed yielding 6535 articles eligible for screening. Following title and abstract screening, we excluded 6300 articles and performed full-text review on 235 studies. 231 articles were excluded during



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing selection process of included articles.

full-text review, leaving four studies that met final eligibility criteria (figure 1).

### Study and patient characteristics

In total, 11 894 geriatric trauma patients were included in the analysis. Of these, 2298 patients were hyponatremic (chronic or acute) while 9596 were normonatremic. Kuo *et al* reported on 125 adult hyponatremic patients (ages 20–64) as a third comparator group, and Madsen *et al* included 122 hypernatremic patients as a third comparator group.<sup>32–33</sup> The studies were performed between 2013 and 2020 in four different countries. Trauma patients were defined as those who underwent hip fracture repair (Ayus, Hagino, and Madsen) or experienced a ground-level fall (Kuo).<sup>34–35</sup> Hyponatremia was defined as acute/recent, chronic, persistent, or corrected during admission. Ayus *et al* defined chronic hyponatremia as greater than or equal to two consecutive plasma sodium values <135 mmol/L over greater than 90 days prior to admission, while acute/recent hyponatremia was defined by one plasma sodium value <135 mmol/L within 30 days of admission with a previously recorded normal plasma sodium. All studies categorized hyponatremia as

<135 mEq/L or mmol/L. Only patients with a serum sodium measure prior to admission or at presentation were eligible for inclusion in all four studies. Normonatremia comparison groups were defined as sodium values between 135 and 145 mEq/L. Clinical outcomes assessed included LOS, postoperative complications, 30-day readmission, in-hospital mortality, long-term mortality, and trauma bay procedures (table 1). Patient characteristics from the included studies are reported in table 2.

### In-hospital mortality

Results of the meta-analysis for in-hospital mortality are displayed in figure 2. Three of the four extracted studies (Hagino, Kuo, Ayus) included in-hospital mortality as an outcome. In the meta-analysis, in-hospital mortality was significantly higher in the hyponatremic group compared with the normonatremic group (risk ratio (RR) 2.23; 95% CI 1.51 to 3.74;  $I^2=82.17\%$ ).

### Hospital LOS

Three of the four studies (Ayus, Hagino, Kuo) reported on hospital LOS. However, Ayus *et al* did not include the SD values

**Table 1** Characteristics of included studies

Study	Year	Study design	Definition of geriatric	Hyponatremia groups	Definition of trauma	Clinical outcomes collected
Ayus <i>et al</i>	2020	Retrospective cohort	Did not specify, included all adult patients	Recent and chronic hyponatremia, normonatremia	Traumatic hip fracture repair	Length of stay (LOS), in-hospital mortality, post-operative complications, 30-day readmission and long-term mortality
Hagino <i>et al</i>	2013	Retrospective cohort	>60 years of age	Hyponatremia and normonatremia	Hip fracture repair	LOS, in-hospital mortality
Kuo <i>et al</i>	2017	Retrospective cohort	>65 years of age	Hyponatremia (elderly and adult (20–64)) and normonatremia elderly	Fall<1 meter	LOS (ICU and hospital), in-hospital mortality, trauma bay procedures
Madsen <i>et al</i>	2016	Retrospective cohort	>60 years of age	Hyponatremia (including persistent and corrected during admission) and normonatremia	Hip fracture repair	30-day mortality

ICU, intensive care unit.

for LOS. Additionally, Hagino *et al* reported that their hospital was a combined inpatient and rehabilitation facility, which led their reported LOS values being considerably higher than the other studies due to the inclusion of postoperative recovery and rehabilitation days. Therefore, we had limited ability to perform an outcome-specific meta-analysis. In an unadjusted analysis, Ayus *et al* reported no significant difference in median LOS in both the chronic prolonged hyponatremia (CPH) (8 days,  $p=0.15$ ) and acute hyponatremia (AH) group (8 days,  $p=0.78$ ) compared with the normonatremia group (7 days). After propensity score adjustment, the lack of significant association held. Hagino *et al* found that the hyponatremia group had a longer LOS than the normonatremia group (58.2 vs 54.4,  $p=0.395$ ). Similarly, Kuo *et al* demonstrated that elderly hyponatremic patients had a significantly longer LOS than normonatremic patients (11.1 vs 9.1,  $p<0.001$ ). There was no difference in LOS between elderly patients with hyponatremia and adult patients with hyponatremia (11.1 vs 11.6,  $p=0.663$ ).

### Readmission

Only Ayus *et al* included 30-day readmission as an outcome. In their study, the crude risk of all-cause readmission at 30 days following discharge was significantly higher in patients with CPH compared with the normonatremic patients (18% vs 12.9%,  $p=0.04$ ). This association was not present when comparing patients with AH and normonatremic patients (12.5% vs 12.9%,  $p=0.90$ ). After adjustment for potential confounders, there was no significant association with either hyponatremia group and 30-day readmission (CPH: adjusted OR (aOR): 1.29, 95% CI 0.86 to 1.60, AH: aOR: 0.93, 95% CI 0.54 to 1.60).

### Trauma bay procedures

Only Kuo *et al* included trauma bay procedures as a clinical outcome. They found that hyponatremic patients were significantly more likely to undergo intubation (OR: 2.4, 95% CI 1.15 to 4.83) compared with normonatremic patients, but no association was present between the two groups with respect to chest tube insertion or receiving a blood transfusion. There was no significant difference in trauma bay procedures between the adult and elderly hyponatremic groups.

### Intensive care unit admission and LOS

Only Kuo *et al* reported on intensive care unit (ICU) admission and LOS. Their results demonstrated that a higher proportion of hyponatremic geriatric patients were admitted to the ICU than those without (20.9% vs 16.2%; OR: 1.40, 95% CI 1.07 to 1.76). However, ICU LOS was not significantly different between the hyponatremic and normonatremic groups. There was no significant difference in ICU admission or LOS between elderly and adult patients with hyponatremia.

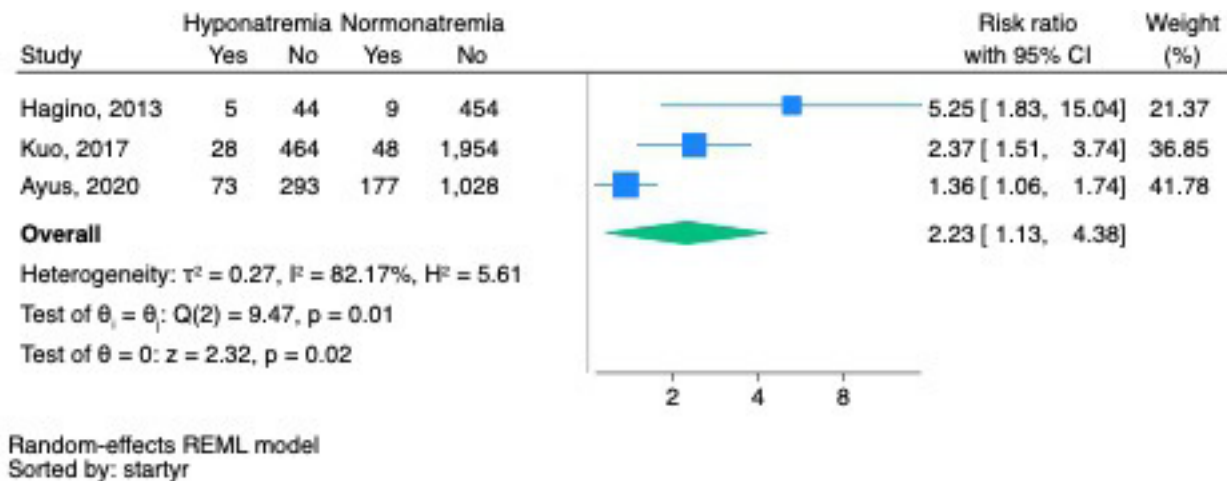
### Long-term mortality

Two studies reported on long-term mortality. Madsen *et al* analyzed all-cause 30-day mortality while Ayus *et al* analyzed all-cause mortality during a 6-year follow-up period. Ayus *et al* demonstrated that unadjusted survival was lower in patients who initially presented with CPH or AH. In their adjusted Cox proportional hazards regression, patients with CPH had a higher rate of death (adjusted HR (aHR) 1.53, 95% CI 1.12 to 2.09) compared with normonatremic patients, while there

**Table 2** Patient characteristics in included studies

Study	Total number of geriatric patients	Total number of hyponatremic geriatric patients	Age (mean, SD)	Female gender	Mean sodium level in geriatric hyponatremia group
Ayus <i>et al</i>	1571	366 (chronic=222, acute=144)	Chronic (median, IQR): 86 (81–89) Acute (median, IQR): 83 (78–87)	Chronic: 183 (82.4%) Acute: 119 (82.6%)	Chronic: 131 Acute: 133
Hagino <i>et al</i>	512	49	86.7±6.6	28 (75.5%)	132±2.3 (127–134)
Kuo <i>et al</i>	2494	492	Not reported	311 (63.2%)	130.5±4.1
Madsen <i>et al</i>	7195	1391	81.8 (8.8)	1092 (78.5%)	Not reported





**Figure 2** Forest plot results of meta-analysis comparing in-hospital mortality among geriatric patients with and without hyponatremia. REML, Restricted Maximum Likelihood.

was no association between AH and long-term survival (aHR: 1.29, 95% CI 0.86 to 1.93). Madsen *et al* reported that 30-day mortality was significantly higher in hyponatremic patients than those with normonatremia (12.2% vs 9.6%,  $p=0.005$ ). After subdividing patients into quartiles based on severity of hyponatremia, there was no difference in 30-day mortality between the quartiles. In their analysis, hyponatremia was associated with an increased risk of mortality (aHR 1.28, 95% CI 1.08 to 1.52).

### Quality assessment

All included studies were categorized as very low quality per the GRADE approach.

### Publication bias

Results of the Harbord test revealed that the risk of publication bias was high ( $p=0.0003$ ). The contour-enhanced funnel plot is exhibited in online supplemental figure 1 and demonstrates a noticeable lack of publications with non-significant findings and small sample sizes. A trim-and-fill analysis demonstrated a decreased and non-significant RR for in-hospital mortality (1.36, 95% CI 0.61 to 3.01) compared with the observed RR of 2.23 (95% CI 1.13 to 4.38).

### DISCUSSION

Geriatric trauma patients experience increased morbidity and mortality compared with younger adults.<sup>36–39</sup> This difference in outcomes may be attributable to the decreased physiologic reserve that occurs concurrently with aging, a higher prevalence of medical comorbidities and prescription medication use in elderly patients, or other factors yet to be identified. Electrolyte abnormalities, namely hyponatremia, have been found to be one such factor.<sup>16–23</sup> Our systematic review and meta-analysis, including nearly 12 000 patients from four retrospective cohort studies, corroborates this. We found that geriatric trauma patients with hyponatremia have significantly higher risk of in-hospital mortality than those with normal serum sodium levels. Hyponatremia in geriatric trauma patients was also associated with a greater LOS and a higher risk of trauma bay procedures (primarily intubation), readmission, and long-term mortality. These findings are remarkable as hyponatremia may be a modifiable risk factor for adverse outcomes in geriatric trauma patients, and perhaps a key factor overlooked for fall prevention strategies. Hyponatremia requires particular attention as a

potential cause and/or exacerbating factor in geriatric trauma, as opposed to an unrelated entity.

Hyponatremia is extremely common in hospitalized geriatric patients with an incidence of 22.2% compared with 6% in younger adults.<sup>15</sup> It is also associated with increased morbidity and mortality in numerous medical conditions, including myocardial infarction, renal insufficiency, liver cirrhosis and hip fractures.<sup>15</sup> Hyponatremia can have multiple various etiologies and primary treatment focuses on addressing the underlying cause. It remains unclear if the impact of hyponatremia on clinical outcomes is also dependent on the underlying etiology of the hyponatremia, if it is an independent driver, or both. Whether the effects of hyponatremia influence outcomes at the physiological level or if hyponatremia, especially chronic hyponatremia, serves as a marker of decreased physiologic reserve or high comorbidity burden in elderly patients remains uncertain. An interesting finding from our review is that one study reported geriatric trauma patients presenting with chronic hyponatremia had significantly higher risk-adjusted in-hospital mortality compared with their normonatremic counterparts.<sup>34</sup> This association did not hold between patients with AH and normonatremia, suggesting that chronic hyponatremia may be a major contributor to adverse outcomes and should be specifically investigated in geriatric trauma patients.

Given the complex medical and social needs of geriatric trauma patients, surgical leaders have advocated that elderly patients may benefit from multidisciplinary clinical care involving experienced geriatricians.<sup>40–43</sup> Multiple studies have shown that adoption of multidisciplinary care of geriatric trauma patients can help reduce hospital-acquired complications such as functional decline, falls, delirium, and death.<sup>40–42</sup> In relation to hyponatremia, trauma providers may benefit from leveraging the expertise of geriatricians to help determine its etiology and address contributing factors such as polypharmacy, heart failure, renal disease, liver dysfunction, or malnutrition.

A significant takeaway from our systematic review is that only four retrospective cohort studies met inclusion criteria, all of which were published outside of the United States (US). Many trauma-focused retrospective studies performed in the US rely on institutionally or nationally maintained databases, which typically lack laboratory values. As such, studying the clinical impact of hyponatremia is not feasible using most national trauma registries. In contrast, Denmark maintains a national registry, which

contains demographic information, details regarding all hospital admissions, and outpatient visits for all citizens. This system is highly beneficial for evaluating national trauma data, as it permits extraction of laboratory values and complete follow-up over time.<sup>33</sup> Given the association between hyponatremia and geriatric trauma outcomes, US trauma registries should consider collecting serum sodium values for elderly patients to aid in future analyses.

We also noted substantial heterogeneity within the published literature on this topic. Major sources of heterogeneity included the lack of a consensus regarding the age limit for geriatric trauma patients as well as variable comparator groups, clinical outcome measures, and patient populations across all studies. While there has been a push towards developing evidence-based recommendations for geriatric trauma care, there is no consensus regarding the age cut-off or standardized outcome metrics for geriatric trauma patients. Additionally, we found that the outcomes of interest varied among all four studies. Even when evaluating in-hospital mortality, an outcome in all four included studies, the meta-analysis revealed a high  $I^2$  value, suggesting that considerable heterogeneity is present. We believe that this presents an opportunity for the field to standardize the age criterion for geriatric trauma and the outcomes measured in geriatric trauma research to enable generation of quality data for research and quality improvement. Higher quality data are needed to enhance our understanding of the complex association between hyponatremia and trauma outcomes as well as inform the development of evidence-based recommendations for geriatric trauma care.

A limitation of this work is the low number of included studies, all of which provide very low-quality evidence of the association between hyponatremia and geriatric trauma outcomes. Our systematic review only revealed four retrospective cohort studies, even after broadening our inclusion criteria to include surrogates for traumatic injuries (eg, patients undergoing hip fracture repair). Furthermore, across all studies, the mean sodium level of patients was between 130 mEq/L and 135 mEq/L, indicating that a large majority of the patients discussed had mild hyponatremia and limiting the generalizability of these findings in trauma patients with moderate and severe hyponatremia. Given the paucity of published articles on this topic, there is a critical need for well-designed, prospective studies evaluating the impact of hyponatremia on geriatric trauma outcomes. Future research should investigate the etiology of hyponatremia in geriatric trauma patients and its relationship to syncopal versus mechanical falls.

## CONCLUSIONS

Our findings, while limited by significant heterogeneity and publication bias, demonstrate that hyponatremia significantly increases the risk of in-hospital mortality among geriatric trauma patients, primarily those with hip fractures. In individual studies, hyponatremia also increases the likelihood for trauma bay intubation, higher LOS, and long-term mortality. Lack of available, high-quality studies limits definitive conclusions and recommendations that can guide clinical practice, but a clear association exists between hyponatremia and adverse outcomes in geriatric trauma. Trauma providers should be aware of this association and work to address hyponatremia as a possible contributing and/or exacerbating factor after injury, as opposed to an unrelated chronic medical problem. Focusing on and addressing hyponatremia in the clinical setting could be a key factor in prevention of future falls. Further study is critically needed to

improve our understanding of the impact of hyponatremia on the clinical outcomes of geriatric trauma patients.

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**Contributors** Conception and study design: AN, ST, MWS. Literature review: AN, ST, LHY. Data acquisition: AN, ST, LHY. Data analysis and interpretation: AN, ST, CS, CL, MHH, GAC, MWS. Drafting of the manuscript: AN, ST, MWS. Critical revision: AN, ST, CS, CL, LHY, MHH, GAC, MWS. AN and MWS accept full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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**Data availability statement** Data are available upon request. Data discussed in the article including template data collection forms, data extracted from included studies, data used for all analyses, and analytic code will be made available upon request with appropriate institutional review board approval and data use agreements.

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