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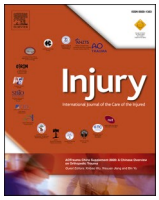

In-hospital hypernatremia prior to discharge to primary care hospitals predicts 90-day mortality in older hip fracture patients

L.Matias Pehkonen [a,*,1], Sanna Collin [b], Päivi Korhonen [b], Maria S. Nuotio [a]

[a] Department of Geriatric Medicine, Turku University Hospital and University of Turku, Finland
[b] Department of General Practice, University of Turku and Southwest Finland Wellbeing Services County, Turku, Finland

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ABSTRACT

Purpose: Discharge is a critical time point in the care pathway of geriatric hospital patients, and post-acute care facilities often have less monitoring possibilities. Active medical issues such as electrolyte disturbances should be treated before transfer. We studied the impact of in-hospital hypernatremia of older hip fracture patients to mortality at 90 days.

Methods: A retrospective study population of 2240 hip fracture patients from 2015 to 2019 was collected from the Hospital District of Southwest Finland data pool. In the present study we included patients aged ≥65 years who were transferred from the operating hospital to primary health care wards after surgery ($n = 1,125$). Laboratory results were collected on admission and before discharge. The main outcome was mortality at 90 days.

Results: Hypernatremia, defined as serum sodium ≥144 mmol/l, was present in 6.8 % ($n = 91$) before discharge. For patients with hypernatremia the crude mortality at 90 days was 35.8 % (95 % CI 27.1 to 46.3) and for patients with normal serum sodium 9.6 % (95 % CI 8.0 to 11.6). The age- and sex-adjusted hazard ratio of hypernatremia compared to normal serum sodium was 3.91 (95 % CI 2.62 to 5.82).

Conclusion: In-hospital hypernatremia had predictive value for 90-day mortality. We recommend active screening for and prompt treatment of perioperative hypernatremia in hip fracture patients. Local guidelines and discharge checklists are recommended to secure the discharge period.

Introduction

Hip fracture is among the most common and serious injuries in older adults, often leading to severe impairments in functional ability, decreased quality of life and excess mortality [1–3]. One-year mortality after hip fracture ranges from 15 to 25 % in global studies [4]. Multimorbidity and geriatric syndromes such as frailty, malnutrition, functional and cognitive deficits are prevalent in this patient group, predisposing hip fracture patients to a wide range of medical complications and increased postoperative mortality [5,6]. In addition to existing pathologies, normal physiological changes of aging make older hip fracture patients more susceptible to fluid and electrolyte disorders in the perioperative period [7].

Discharge from the operating hospital is a critical transition point in the care pathway of this high-risk patient group. In many countries hip fracture patients are transferred to primary care facilities after only a few days in the operating hospital. Transfer in a suboptimal medical condition can lead to adverse outcomes, such as complications, readmissions, and increased mortality [8,9]. Electrolyte disturbances and other common complications should be actively screened and standardized treatment protocols are recommended to secure a safe discharge.

Water homeostasis is maintained by thirst, arginine vasopressin, and the kidneys [10]. Dysnatremia – either in the form of low or high plasma sodium – is a sign of a disruption in the body water homeostasis, and a potentially dangerous condition if left untreated. It is among the most common medical problems in all older hospitalized patients, also in hip fracture patients. Normal sodium concentration range is between 135 and 145 mmol/l [11], with slight variation between countries.

Hyponatremia is by far the most common electrolyte imbalance; as much as every fourth older patient has sodium below 135 mmol/l on hospital admission [12,13]. In hip fracture patients the reported prevalence is 10 to 20 % [14,15]. New-onset hyponatremia develops in every fourth hip fracture patients in the acute postoperative period [16].

* Corresponding author.
E-mail address: lamapeh@utu.fi (L.Matias Pehkonen).
[1] Present address: University of Turku, Department of Clinical Medicine, Geriatric Medicine, Medisiina B-C, Kiinamyllynkatu 10, 20,520 Turku, Finland.

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Hyponatremia is associated with higher 30-day mortality and longer length of stay [14,16]. Hyponatremia can also be an underlying factor in the hip fracture incident [17,18].

Hypernatremia is a less frequent finding, also with far less published data available. The reported prevalence is ca. 2 % in all hospitalized patients [19] and 1,5 % to 3 % in hip fracture patients [15,20]. Any dysnatremia on admission is associated with increased 30-day mortality, however, hypernatremia seems to be even more dangerous, especially if

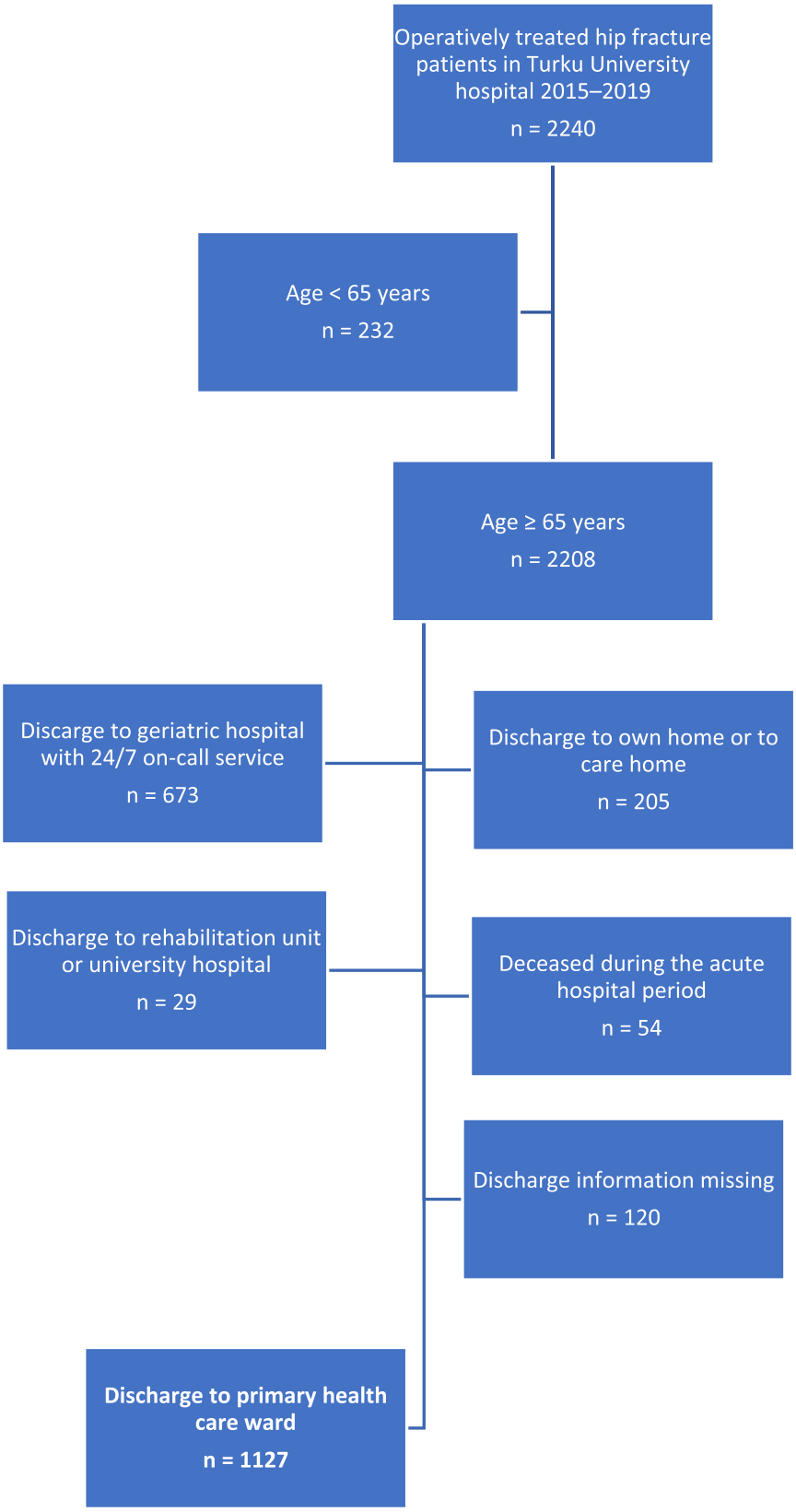

Fig. 1. Flow chart of the selection process of study participants.

it is not successfully corrected [15,21]. During the acute postoperative period, higher plasma sodium trends are seen in patients with cognitive disorders and functional impairment [22].

In-hospital hypernatremia could be managed before discharge from the acute operating hospital. Our hypothesis was that hypernatremia at the time of discharge from the acute operating hospital predicts post-operative mortality in this patient group. We focused specifically on patients who were transferred to primary care wards. These facilities do not have 24 h on-call services or weekend laboratory possibilities, therefore their capacity to manage electrolyte imbalances properly is weaker.

We aimed to examine in-hospital hypernatremia as measured during the acute hospital period after hip fracture and the impact it has on the patients' 90-day mortality. The 90-day time point was chosen to study short-term mortality, which could be influenced by care during the perioperative period.

Methods

Study design and population

We performed a retrospective register-based study of older hip fracture patients. The study population was collected retrospectively from the Hospital District of Southwest Finland data pool. Altogether 2240 patients with a hip fracture were managed operatively in the Turku University Hospital during the years 2015–2019. Of them, 2208 (99 %) were at least 65 years of age. Reoperations were excluded from the study, therefore each patient in this study appears in the data only once. For the present analysis we included only patients aged ≥65 years who were transferred from the operating hospital to primary health care wards after the surgery ($n = 1125$) (Fig. 1). These primary care units did not have physicians on call, nor did they have the possibility to take laboratory tests during the weekend.

Data collection procedures

For each patient, information on age, gender, the American Society of Anesthesiologists (ASA) grade, delay from admission to surgery, length and type of surgery, length of stay at the operating hospital, fracture type, and laboratory test results were gathered from the data pool (Table 1). Fracture types included in the study were fracture of femoral neck (S72.0), pertrochanteric fracture (S72.1) and sub-trochanteric fracture (S72.2), diagnostic codes according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). For the laboratory results we included the last available plasma sodium sample before discharge to a primary care health care unit. The main outcome was 90-day post-fracture mortality. The comorbidities were assessed using ASA physical status classification system (grades I-V), which determines the health of the patients before the surgery. ASA grade I denotes good health, grade II, mild systemic disease, grade III, severe nonincapacitating systemic disease, grade IV, severe incapacitating systemic disease with a constant threat to life, and grade V, severe, life-threatening condition.

The institutional review board of the Hospital District of Southwest Finland gave authorization for this register-based study. Since the data used are routinely recorded in administrative health records, informed consent was not required, nor were the patients contacted. Legal grounds for data handling are public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6).

Statistical analysis

Descriptive statistics are presented as means with standard deviation (SD), as medians with interquartile range (IQR) or as counts with percentages. Statistical differences between sexes were evaluated using unpaired Student's *t*-test, Mann-Whitney U test, chi-squared test, or Fisher's exact test, as appropriate. Mortality curves were plotted using the Kaplan–Meier method and the log-rank test was used to analyze the statistical differences between groups. A possible nonlinear relationship between 90-day mortality and the sodium level was assessed by using 3-knot restricted cubic spline logistic regression model. The multivariable adjusted model included covariate terms for age, gender, and ASA score. Receiver-operating characteristic (ROC) curve was used for the determination of thresholds for the sodium levels to predict mortality. The best cutoff value (144 mmol/l) was defined as the value with the highest accuracy that maximizes the Youden's index.

Table 1
Characteristics of the patients and treatment at the operating hospital according to gender.

	Women N = 784	Men N = 341	P-value
Age, mean (SD)	84 (7)	81 (8)	<0.001
ASA grade			0.56
I	2 (0)	1 (0)	
II	46 (6)	24 (7)	
III	517 (66)	222 (66)	
IV	216 (28)	91 (27)	
V	2 (0)	0 (0)	
Delay from admission to surgery, h, median (IQR)	21 (13,28)	22 (14,30)	0.24
Length of the surgery, h, mean (SD)	1.1 (0.5)	1.1 (0.4)	0.45
Type of surgery (NOMESCO* codes) n (%)			0.63
Total hip arthroplasty (1)	30 (4)	14 (4)	
Hemiarthroplasty (2)	367 (47)	149 (44)	
Internal fixation (3)	387 (49)	178 (52)	
Length of stay at hospital, days, median (IQR)	3 (3,5)	4 (3,6)	0.037
Diagnostic code, n (%)			0.47
Femoral neck fracture (S72.0)	476 (61)	216 (63)	
Pertrochanteric fracture (S72.1)	260 (33)	101 (30)	
Subtrochanteric fracture (S72.2)	48 (6)	24 (7)	
Sodium, mean (SD)	139 (4)	139 (4)	0.12

* NOMESCO indicates Nordic Medico-Statistical Committee Classification of Surgical Procedures.

1) Including hybrid total hip arthroplasty and cemented primary total hip arthroplasty. 2) Including cemented hemiarthroplasty. 3) Including internal fixation of a fracture of the neck of the femur with a nail or screw, internal fixation of a fracture of the upper femur with screws and a side plate, internal fixation of a fracture of the upper femur with intramedullary nails, and other internal fixation of other parts of the femur.

Results

We evaluated 1125 patients aged ≥65 years who underwent hip fracture surgery and were transferred from the operating hospital to primary health care wards during the years 2015–2019. Table 1 shows the characteristics of the studied population. Of the patients, 70 % were women. Compared to male patients, women were on average older but their median stay at the operating hospital was shorter. The median length of stay in the operating hospital was 3 and 4 days in women and men, respectively. The median delay from admission to surgery was below 24 h in the whole study population. Before discharge 6.8 % ($n = 91$) of the patients had hypernatremia, defined as plasma sodium 144 mmol/l or higher.

The optimal cut-off point for plasma sodium according to ROC curve was 144 mmol/l (overall accuracy 86 %). Crude mortality at 30 days after hip fracture surgery was 3,8 % in women (95 % CI 2.7 to 5.4) and 8,2 % in men (95 % CI 5.7 to 11.7). At 90 days crude mortality was 9.9 % in women (95 % CI 8.1 to 12.3) and 16.1 % (95 % CI 12.6 to 20.5) in men, $p = 0.002$. The age-adjusted hazard ratio (HR) for all-cause mortality in men was 1.93 (95 % CI 1.36 to 2.74, $p < 0.001$) compared to female patients at 90 days after the surgery.

For patients with hypernatremia (defined as plasma sodium at least 144 mmol/l) crude mortality at 90 days was 35.8 % (95 % CI 27.1 to

46.3) and for patients with normal plasma sodium 9.6 % (95 % CI 8.0 to 11.6) Hypernatremia showed predictive value for identifying patients with a high mortality risk (Fig. 2). The age- and sex-adjusted hazard ratio of hypernatremia compared to normal serum sodium was 3.91 (95 % CI 2.62 to 5.82). According to the cubic spline regression, adjusted with age, gender, and ASA score, there was a sharp increase in mortality at the plasma sodium cut-off point of 144 mmol/l (Fig. 3).

Discussion

In our retrospective study of older hip fracture patients, men had higher crude mortality than women in all time points up to 90 days. Most importantly, in-hospital hypernatremia had predictive value for 90-day mortality.

The gender distribution of hip fractures in our study matches local and international studies, the female incidence being slightly over 70 % [23,24]. The overall mortality in our study was similar than those reported in previous hip fracture studies [25]. For the 90-day mortality, a large Danish register study reported a result of 16 % at 90 days, which is slightly higher than our crude mortality [26]. In our study men had higher mortality than women, which is also well in line with previous hip fracture research. In fact, the difference in the risk of mortality between the two genders in hip fracture cohorts is well established. Two large population-based cohort studies report increased 30-day [27] and 1 year mortality [28] in men compared to women with similar ratios than in our study. The reasons for this sex-related difference are not well known. The difference in comorbidity does not seem to fully explain this. However, it has been hypothesized that men suffer more greatly from the fracture event, postoperative complications, and common geriatric risk factors such as malnutrition, sarcopenia, and functional impairment [28].

Hypernatremia in hip fracture patients has not been widely studied. In the few studies available, the reported prevalence has been between 1.5 to 3 % [15,20]. Thus, our study adds to the previous research. We found hypernatremia in 8.5 % of subjects on admission and 6.8 % of subjects before discharge. This prevalence is higher than in previous studies. Our results focusing on the in-hospital period highlight the detrimental effect of chronic or uncorrected new-onset hypernatremia before discharge. In general hospital population, hypernatremia on admission is known to increase mortality [19]. Persistent hypernatremia

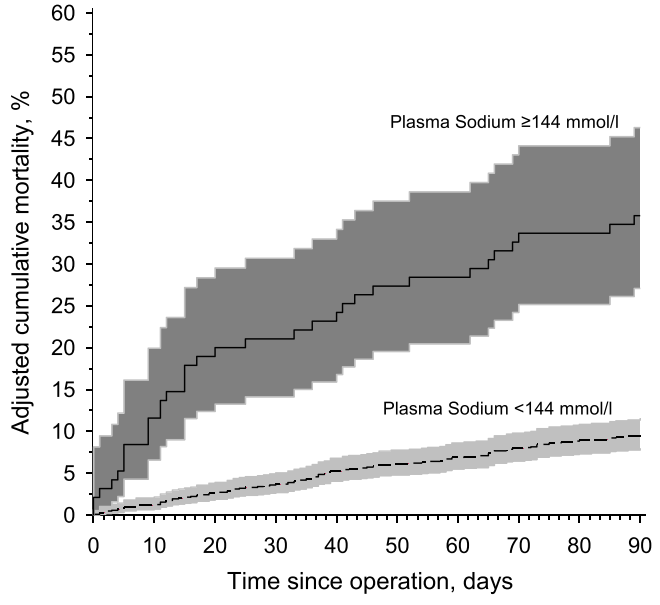

Fig. 2. Cumulative mortality according to sodium levels during the follow-up. Age- and sex-adjusted hazard ratio in hypernatremia compared to normal serum sodium (HR = 3.91, 95 % CI 2.62 to 5.82).

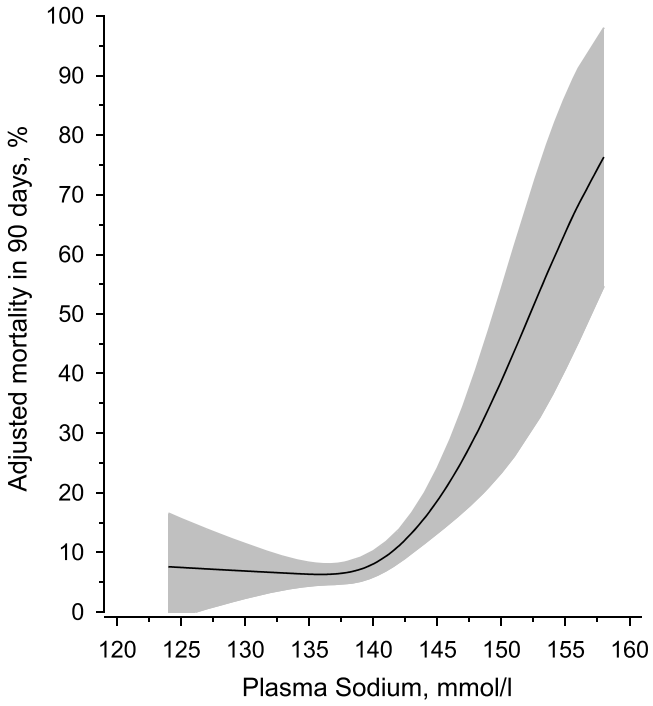

Fig. 3. Adjusted all-cause mortality in 90 days after hip fracture surgery according to plasma sodium level. The curve was derived from a 3-knot restricted cubic spline logistic regression model. The model was adjusted for age, sex, and ASA score. The grey area represents a 95 % confidence interval.

in the acute hospital period has also showed an increasing effect on mortality [21]. To our knowledge, only two larger studies have reported hypernatremia in patients undergoing orthopedic surgery, both of which were retrospective studies [15,29]. Of these two, a Danish registry study of over 7000 hip fracture patients reported a 1.7 % prevalence of hypernatremia on admission and increased 30-day mortality (15.5 % vs 9.6 %, $p = 0.03$) compared to patients with normal serum sodium concentration [15]. Mortality was decreased if sodium concentration was normalized, emphasizing diligent perioperative treatment of hypernatremia. In the same study, however, similar decrease in mortality was not seen with persistent hyponatremia.

An Israeli study of 155 hip fracture patients investigated the in-hospital trends of sodium levels in relation to functional and mental status. They reported a trend towards postoperative hypernatremia in patients with decreased prefracture mobility and impaired cognition [22]. A small Italian study reported a 1.4 % prevalence of hypernatremia on admission but did not investigate mortality [20].

It is known that hypernatremia marks a sign of a disruption in the body water balance. Dehydration is the main reason of hypernatremia in the older population. Other causes are sodium loading and excessive renal excretion of electrolyte free water, both of which are rare mechanisms [30]. As much as over one-third-of older patients are known to be in a state of dehydration when admitted to hospital [31], and every fifth hip fracture patient acquires clinically detectable dehydration in the perioperative period [32]. Geriatric patients have multiple predisposing factors to this electrolyte disorder, and hip fracture surgery brings additional stress to the fluid homeostasis.

Most previous studies have focused on the time of admission to hospital. We are not aware of a previous study focusing on in-hospital electrolyte disturbances of hip fracture patients prior to discharge to a primary health care ward. It is known that acute medical issues at discharge such as desaturation, hypotension and fever predict short- and long-term readmissions [8,9]. A large American study found that discharge to inpatient care facilities was associated with post-discharge complications, re-operations and readmissions compared to those

discharged to home [33]. The authors concluded that this might reflect the baseline functional status and comorbidities of those needing post-acute care in a hospital setting, rather than the harmful effect of discharge destination care per se.

The strengths of this study include the relatively large and representative study population. Our study focused on a specific group of hip fracture patients, who were transferred to primary health care facilities after the acute postoperative period. Those discharged to their own home or to a care home were excluded from the analyses. Thus, the study population was representative of the largest group among hip fracture patients, and relevant to the study hypothesis. The study population was relatively large, so that analyses yield enough statistical power. The mortality rates and gender differences in our study correspond well to earlier research, thus our data can be considered representative and reliable for the analysis in question. Our study has also several limitations. Firstly, it was a register-based retrospective study, therefore confounding factors do not allow for direct causative deduction. We could extract only a limited number of data elements from the hospital database. For this reason, we do not know what kind of fluid regimens were prescribed or e.g., what proportion of the patients received blood transfusions during the perioperative period. Another limitation is the lack of knowledge about the exact timing of the laboratory tests taken after admission. As the length of stay varied between patients, there is also marked variation in when the last recorded sodium measurement was taken. Also, if no additional laboratory tests were taken before discharge, the admission test results counted as the last results.

Dysnatremia cannot always be fully corrected before transfer, but proper diagnosis should be made, and treatment protocols prescribed and initiated. As the length of stay in the operating hospital is generally short, the primary care facilities receiving hip fracture patients should also have sufficient resources to treat electrolyte imbalances. Recommended approach to hypernatremia includes calculation of fluid deficit and ongoing losses, and administration of appropriate, usually hypotonic, fluids [34]. Specialized care protocols have been developed to manage the multitude of medical issues of hip fracture patients. Orthogeriatric care models represent an advanced and holistic development in the care of fragility fracture patients, strongly recommended for implementation in all hip fracture units [35]. Importantly, orthogeriatric care has been shown to reduce complications and decrease the risk of mortality [36]. In our study, all patients received usual care at the orthopedic and trauma ward with orthopedic surgeons and residents mainly in charge. Nowadays, orthogeriatric care model has been implemented also in the acute care period. We recommend active screening for perioperative hypernatremia as part of an orthogeriatric assessment of hip fracture patients. Local guidelines and discharge checklists help to secure the vulnerable period of discharge.

Conclusion

Most older hip fracture patients are transferred to primary care facilities after the acute postoperative period. Any active medical issues should be corrected before discharge. We found that hypernatremia is a common postoperative finding in older hip fracture patients. It is associated with increased 90-day mortality, with a rapidly increasing mortality rate after exceeding sodium concentration of 144 mmol/l.

CRediT authorship contribution statement

L.Matias Pehkonen: Writing – review & editing, Writing – original draft. **Sanna Collin:** Writing – review & editing, Data curation, Conceptualization. **Päivi Korhonen:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Maria S. Nuotio:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

LMP and MSN have been part of an advisory board for Amgen. SC and PK have no conflicts of interest to state.

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