International Orthopaedics (2019) 43:2825–2829
https://doi.org/10.1007/s00264-019-04368-0

ORIGINAL PAPER

Altered seric levels of albumin, sodium and parathyroid hormone may predict early mortality following hip fracture surgery in elderly

Alejandro Lizaur-Utrilla[1,2] · Blanca Gonzalez-Navarro[1] · Maria F. Vizcaya-Moreno[3] · Fernando A. Lopez-Prats[2]

Received: 15 December 2018 / Accepted: 19 June 2019 / Published online: 29 June 2019

Abstract

Purpose To analyse a wide set of routine laboratory parameters at admission to predict mortality within 30 post-operative days in elderly patients with hip fracture, as well as calculate the critical values of those biomarkers.

Method Data of 994 patients older than 65 years with hip fracture were analysed of which 89 (8.2%) died within 30 post-operative days. Variables described in the literature with potential influence on early mortality were collected, including demographics, fracture type, American Society of Anesthesiologists score, Charlson's comorbidity index and pre-operative Hodkinson's mental test and the Katz index for activities of daily living. In addition, an exhaustive collection of biomarkers from routine blood testing at admission was performed. Critical levels of biomarkers were calculated by the method of area under ROC curve.

Results At admission, early mortality group had significantly higher Charlson's index ($p = 0.001$) and lower the Katz index ($p = 0.001$). The surgical delay also was significantly longer in that group ($p = 0.001$). In univariate analyses, serum concentration at admission of total protein ($p = 0.004$), albumin ($p = 0.001$), sodium ($p = 0.001$), and parathyroid hormone (PTH) ($p = 0.001$) were significantly different between both groups. In multivariate analysis, serum albumin < 2.9 g/dL ($p = 0.013$), sodium < 127 mEq/L ($p = 0.035$) and PTH > 65 pg/mL ($p = 0.005$) were predictors of early mortality. The three biomarkers together accounted for 67% of the variability in early mortality.

Conclusion The association of altered levels at admission of serum concentration of albumin, sodium and PTH was predictor of early mortality following hip fracture surgery in elderly patients.

Keywords Early mortality · Biomarkers · Routine blood testing · Hip fracture · Elderly

Introduction

Hip fractures in elderly are associated with increased morbidity and mortality despite advances in surgical and anaesthetic techniques [1]. Numerous studies have investigated clinical risk factors associated with mortality following hip fracture surgery, especially demographic factors and comorbidities, in addition to other factors such as surgical delay, type of surgery and anaesthesia, post-operative management and complications [2–5]. However, laboratory factors, especially biochemical, have been few considered. Some studies have reported influence on mortality of some biochemical parameters, as low serum albumin [6] or high serum creatinine [7]. Likewise, several studies have analysed the value of routine blood testing to predict early mortality [8]. However, only one study carried out a comprehensive analysis of the biomarkers on routine laboratory analysis [9], and none has reported the critical values of the biochemical parameters influencing mortality.

The objective of this study was to analyse a wide set of routine laboratory parameters at admission to predict early mortality in elderly patients with hip fracture, as well as calculate the critical values of those biomarkers.

✉ Alejandro Lizaur-Utrilla
lizaur1@telefonica.net

[1] Department of Orthopaedic Surgery, Elda University Hospital, Ctra Sax s/n, Elda, 03600 Alicante, Spain

[2] Traumatology and Orthopaedics, Miguel Hernandez University, Avda Universidad s/n, San Juan de Alicante, 03202 Alicante, Spain

[3] Clinical Research Group, Faculty of Health Sciences, University of Alicante, Ctra San Vicente Raspeig s/n, San Vicente Raspeig, 03690 Alicante, Spain

Material and methods

The study was approved by the institutional review board, and informed consent was not required because it was considered a department evaluation. Consecutive patients admitted at our centre for hip fracture between January 2013 and December 2017 were prospectively evaluated. The inclusion criteria were patients with age 65 years or older and low-trauma fracture. The exclusion criteria were multiple trauma, periprosthetic fracture and malignant condition. Patients who received conservative treatment of their fractures were also excluded. Conservative treatment was indicated for ASA-V patients or decision to palliative care.

Patient management

A standardised protocol for co-management of these patients between orthopaedic surgeons and a specific team of geriatrics was used at our hospital from admission to discharge. Pre-operative stabilisation, suitability of previous medical treatments and patient control were performed by surgeons and geriatrics from admission to death or discharge. After surgery, ambulation with walker was authorised at second post-operative day if they tolerated. All patients received antibiotic prophylaxis with first-generation cephalosporin for 24 hours (started 1 hour prior to skin incision) and thromboembolic prophylaxis with low-molecular-weight heparin for 30 days.

Evaluations

Pre-operative and post-operative clinical evaluation and laboratory data of the patients were standardised at our department. Data were prospectively recorded in an electronic database.

In each patient, 20 routine laboratory metabolic parameters collected at admission were analysed: biochemistry (glucose, urea, cholesterol, total serum protein, albumin); liver enzymes (GGT gamma-glutamyl transferase, ALT alanine aminotransferase, ALP alkaline phosphatase, total bilirubin); electrolytes (sodium, potassium, total calcium, phosphate, magnesium); renal function (estimated glomerular filtration rate, creatinine, urea); parathyroid hormone (PTH); thyroid-stimulating hormone (TSH); and 25 (OH) vitamin D. Haematological parameters included haemoglobin, haematocrit, erythrocytes, white blood cell count, neutrophils, platelets and haemostasis tests. Clinical and demographic characteristics were also recorded.

Comorbidity at admission was assessed by the ASA score [10] and Charlson's comorbidity index (CCI) [11]. According to the author, Charlson's index was categorised into three groups: absent or mild (0–2 points), moderate (3–4 points) and severe (5 or more points). Mental status at admission was measured by the Hodkinson's abbreviated mental test 0–10 score [12], where 6 or less suggested dementia. Preinjury physical function was assessed using the Katz Index [13] for activities of daily living (ADL), where full independence was defined as the ability to do all six ADL without assistance, partial dependence as the ability to do four or five activities without assistance, and total dependence as the ability to do three activities or fewer without assistance. Time from admission to surgery was categorised as either less than or more than 48 hours.

Statistical analysis

Statistical analyses were conducted with IBM-SPSS v.15 software. Normal distribution was assessed by the Kolmogorov-Smirnov test. For univariate analysis, categorical variables were analysed by the chi-square test or the non-parametric Fisher exact and Mantel-Haenszel tests, and continuous variables by Student *t* test or Mann-Whitney *U* test. Multivariate analysis was conducted by a logistic regression model with in-hospital mortality as a dependent variable. An odds ratio (OR) with 95% confidence interval for risk factors was used. The coefficient of multiple determination (adjusted R^2) was used to indicate how much of the variability of the early mortality was explained for by the dependent variables (0 poor, 100 the best) in the multiple regression model.

The cut point of the biomarker levels with influence on early mortality was calculated by the method of area under the ROC curve (AUC), assuming that an AUC of 0.70 was considered acceptable discrimination. The Youden index was used to identify the best relationship between sensitivity and specificity.

A p value less than 0.05 or was considered significant in all tests.

Results

Among 1083 patients who met the inclusion criteria, 89 (8.2%) died within 30 post-operative days. Comparative characteristics between survivor patients and those with early mortality are shown in Table 1. Comparing the admission data between groups, there were no significant differences between groups in age ($p = 0.176$), gender ($p = 0.112$), place of residence ($p = 0.789$) or BMI ($p = 0.581$). Likewise, there were no significant differences between groups in the mental test ($p = 0.055$), but the preinjury physical function as assessed by the Katz index was significantly lower in the mortality group ($p = 0.001$). The mean ASA score was not significantly different ($p = 0.152$). However, mean Charlson's index was significantly higher in the mortality group ($p = 0.001$). In the mortality group, 22 (68.2%) patients had 3 or more active comorbidities at admission, while in the control group it was in 375 (52.0%) patients. The most common comorbidities in both groups were hypertension history, diabetes, chronic

Table 1 Patient characteristics at admission

	Mortality group $n = 89$	Survivor group $n = 994$	p
Age (year)	85.0 (7.4)	83.1 (9.6)	0.176
Gender (F/M)	57/32	716/278	0.112
Residence (H/G)	66/23	748/246	0.789
BMI (gr/m2)	27.2 (3.9)	26.8 (4.2)	0.581
Mental test	5.6 (2.7)	6.6 (3.6)	0.055
Katz index	3.1 (1.2)	4.2 (2.7)	0.001
Charlson's index	3.1 (1.7)	1.9 (1.4)	0.001
ASA score	3.7 (1.5)	3.3 (1.1)	0.152
Fracture type (C/T)	28/61	308/686	0.505
Time to surgery (days)	3.8 (1.8)	2.4 (1.6)	0.001

Continuous data are shown as mean (SD). Residence: home, geriatric; fracture type: cervical, trochanteric

obstructive pulmonary disease and heart disease. There was no difference in the type of fracture ($p = 0.505$). However, the surgical delay was significantly longer in the in-hospital mortality group ($p = 0.001$).

Logistic regression models adjusted for hip fracture type, age and gender were performed. All the clinical and laboratory parameters with $p < 0.10$ in univariate analysis were included. The final model (Table 2) identified independent factors associated with early mortality low serum levels at admission of albumin (OR 0.7; 95% CI 0.2–0.8; $p = 0.002$) and sodium (OR 0.6; 95% CI 0.2–0.9; $p = 0.012$) and high PTH level (OR 1.2; 95% CI 1.1–2.7; $p = 0.015$). High Charlson's index was also a significant predictor (OR 1.3; 95% CI 1.4–4.9; $p = 0.023$).

Using ROC curve analysis, the cut-off points for those three biomarkers with influence on early mortality were albumin < 2.9 g/dL (AUC = 0.74), sodium < 127 mEq/L (AUC = 0.77) and PTH > 65 pg/mL (AUC = 0.72). Categorising the biomarkers according to those cut-off points, albumin < 2.9 g/dL (OR 1.6; 95% CI 1.2–2.4; $p = 0.013$), sodium < 127 mEq/L (OR 1.4; 95% CI 1.1–2.4; $p = 0.035$) and PTH > 65 pg/mL (OR 1.3; 95% CI 1.0–3.4; $p = 0.005$) were significant predictors of early mortality. The three biomarkers together accounted for 67% of the variability in early mortality (adjusted $R^2 = 0.674$).

Discussion

The main finding of the present study was that the association of low levels of serum albumin and sodium and high level of PTH at admission was a significant predictor of early mortality within 30 days after surgery. To our knowledge, this is the first study that describes this association as a risk factor of early mortality. Some authors have previously reported the levels of albumin [7, 14], sodium [15] and PTH [16, 17] as independent predictors of early mortality. However, those studies had not analysed the combined influence of these three biomarkers. Moreover, the critical levels of those biomarkers for early mortality in the elderly with hip fracture had not been described.

Serum albumin concentration is the most commonly used biomarker of malnutrition [14]. Lee et al. [18] reported that hypoalbuminemia and low level of total serum protein were significantly associated with pulmonary and heart complications within 30 days after hip fracture surgery. Bohl et al. [14] reported that the risk of post-operative complication and death in fracture hip patients was significantly and inversely associated with pre-operative serum albumin concentration. Another

Table 2 Independent predictors of in-hospital mortality in multivariate analysis adjusted for hip fracture type, age and gender

	Mortality group	Survivor group	Univariate p value	Multivariate analysis	
				OR (95% CI)	p
Charlson's index	3.1 (1.7)	1.9 (1.4)	0.001	1.3 (1.4–4.9)	0.023
Mental test	5.6 (2.7)	6.6 (3.6)	0.055	0.8 (0.4–7.6)	0.132
Katz score	3.1 (1.2)	4.2 (2.7)	0.001	1.2 (0.6–1.9)	0.841
Surgical delay (days)	3.8 (1.8)	2.4 (1.6)	0.001	1.1 (0.5–6.3)	0.069
Bs total protein (g/dL)	6.1 (1.2)	6.8 (2.3)	0.004	0.6 (0.1–8.5)	0.394
Bs albumin (g/dL)	3.7 (0.5)	4.1 (0.9)	0.001	0.7 (0.2–0.8)	0.002
Bs albumin < 3.5 g/dL	89%	68%	0.028	1.6 (1.2–2.4)	0.013
Bs PTH (pg/mL)	67.2 (9.1)	54.6 (8.2)	0.001	1.2 (1.1–2.7)	0.015
Bs PTH > 65 pg/mL	80%	52%	0.001	1.3 (1.0–3.4)	0.005
Bs Na (mEq/L)	131.3 (14.7)	141.2 (12.6)	0.001	0.6 (0.2–0.9)	0.012
Bs Na < 135 mEq/L	71%	37%	0.001	1.4 (1.1–2.4)	0.035

Continuous variables as mean (SD). *Bs*, baseline; *OR*, odds ratio; *CI*, confidence interval. The logistic regression models included all the clinical and laboratory parameters. Only variables with $p < 0.10$ in univariate analysis are shown in the table

study found that nutritional supplementation decreased post-operative complication rate after hip fractures [9]. However, a recent Cochrane review reported some evidence that oral nutritional supplements in patients with hip fractures could prevent complications but had no clear effect on mortality [19]. Like us, a recent study focused on the use of simple biomarkers to predict early mortality [9] showed that serum albumin level < 33 g/L and parathyroid hormone > 6.8 pmol/L were significant predictors. However, these authors also reported that a low level of serum vitamin D was a significant predictor which was not found in our study. Menéndez-Colino et al. [3] reported that secondary hyperparathyroidism associated with vitamin D deficiency was a predictor of one year mortality.

On the other hand, anaemia and dehydration are also usually present in many of the elderly with hip fracture [20], and serum sodium concentration is a good marker of dehydration. However, the influence of hyponatremia on mortality has been little studied. To our knowledge, only one study has also reported the association between alterations in serum sodium concentration and early mortality in hip fracture patients [15].

Other several factors have been suggested in the literature to predict one year mortality following hip fracture surgery [1], but there are many conflicts in the literature about the risk factors for early mortality. Several studies have confirmed the association between three or more active comorbidities and early mortality after hip fracture surgery. Most authors agree that ASA grade is greater than a three grade [21], renal insufficiency [21], cardiac disease [22] and cancer [5] are risk factors for early mortality. However, ASA score was not a predictive factor for early mortality in the present study, although the presence of three or more major comorbidities was an independent predictor of early mortality. Influence of the surgery delay more than two days on mortality has been established in several studies [22, 23]. However, we found in a previous study that waiting time for hip fracture surgery more than two days was not associated with higher complication or mortality rate if waiting was to stabilise patients with active comorbidities at admission [24]. In a recent study, Wong et al. [25] reported no increase in mortality rate at six months and two years in patients having small delays in surgery because of holidays.

In the present study, surgical delay was significantly associated to early mortality in univariate analysis, but it was not a significant predictor in multivariate analysis. Other studies found that both multidisciplinary orthogeriatric models for the treatment of these patients and informal caregivers were effective in reducing time to surgery and mortality [26–28].

Strengths of the study were consecutive patients and the number and exhaustive collection of variables studied, including demographic, peri-operative and blood parameters. There was no loss of patient data. In addition, the cut-off point for the mortality risk of the biomarkers was calculated. Our study also has potential limitations. The variables analysed were mainly those observed at admission, and other variables of interest such as complications were not included. However, the study was designed to determine the effect of baseline characteristics, differentiating those from the effects of clinical course, which can be confounding factors in a predictive analysis. On the other hand, the significant risk predictors had adjusted ORs with small wide of their 95% CIs. According to other authors, this suggested that residual confounding was negligible [29, 30].

In conclusion, the present study demonstrated that the association of altered levels at admission of serum concentration of albumin, sodium and PTH was a predictor of early mortality following hip fracture surgery in elderly patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not required by our institutional review board.

References

1. Hu F, Jiang C, Shen J, Tang P, Wang Y (2012) Preoperative predictors for mortality following hip fracture surgery: a systematic review and meta-analysis. Injury 43:676–685. https://doi.org/10.1016/j.injury.2011.05.017
2. Khan MA, Hossain FS, Ahmed I, Muthukumar N, Mohsen A (2013) Predictors of early mortality after hip fracture surgery. Int Orthop 37:2119–2124. https://doi.org/10.1007/s00264-013-2068-1
3. Menéndez-Colino R, Alarcon T, Gotor P, Queipo R, Ramírez-Martín R, Otero A, González-Montalvo JI (2018) Baseline and pre-operative 1-year mortality risk factors in a cohort of 509 hip fracture patients consecutively admitted to a co-managed orthogeriatric unit (FONDA cohort). Injury 49:656–661. https://doi.org/10.1016/j.injury.2018.01.003
4. Nkanang B, Parker M, Parker E, Griffiths R (2017) Perioperative mortality for patients with a hip fracture. Injury 48:2180–2183. https://doi.org/10.1016/j.injury.2017.07.007
5. Omari A, Madsen CM, Lauritzen JB, Jørgensen HL, Vojdeman FJ (2019) Comorbidity and mortality after hip fracture in nineteen thousand six hundred and eighty two patients aged eighteen to sixty five years in Denmark from 1996 to 2012. Int Orthop. https://doi.org/10.1007/s00264-019-04323-z
6. Aldebeyan S, Nooh A, Aoude A, Weber MH, Harvey EJ (2017) Hypoalbuminaemia-a marker of malnutrition and predictor of post-operative complications and mortality after hip fractures. Injury 48:436–440. https://doi.org/10.1016/j.injury.2016.12.016
7. Laulund AS, Lauritzen JB, Duus BR, Mosfeldt M, Jørgensen HL (2012) Routine blood tests as predictors of mortality in hip fracture patients. Injury 43:1014–1020. https://doi.org/10.1016/j.injury.2011.12.008

8. Seyedi HR, Mahdian M, Khosravi G, Bidgoli MS, Mousavi SG, Razavizadeh MR, Mahdian S, Mohammadzadeh M (2015) Prediction of mortality in hip fracture patients: role of routine blood tests. Arch Bone Jt Surg 3:51–55
9. Fisher A, Fisher L, Srikusalanukul W, Smith PN (2018) Usefulness of simple biomarkers at admission as independent indicators and predictors of in-hospital mortality in older hip fracture patients. Injury. https://doi.org/10.1016/j.injury.2018.03.005
10. American Society of Anesthesiologists (2017) Relative value guide. Online http://www.asahq.org. Accessed 26 June 2017
11. Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. J Clin Epidemiol 47:1245–1251
12. Hodkinson HM (1972) Evaluation of a mental test score for assessment of mental impairment in the elderly. Age Ageing 4:233–238
13. Katz S, Ford A, Moskowitz R, Jackson B, Jaffe M (1963) Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. JAMA 185:914–919
14. Bohl DD, Shen MR, Hannon CP, Fillingham YA, Darrith B, Della Valle CJ (2017) Serum albumin predicts survival and postoperative course following surgery for geriatric hip fracture. J Bone Joint Surg Am 99:2110–2118. https://doi.org/10.2106/JBJS.16.01620
15. Madsen CM, Jantzen C, Lauritzen JB, Abrahamsen B, Jorgensen HL (2016) Hyponatremia and hypernatremia are associated with increased 30-day mortality in hip fracture patients. Osteoporos Int 27:397–404. https://doi.org/10.1007/s00198-015-3423-4
16. Di Monaco M, Vallero F, Di Monaco R, Tappero R, Cavanna A (2006) 25-Hydroxyvitamin D, parathyroid hormone, and functional recovery after hip fracture in elderly patients. J Bone Miner Metab 24:42–47. https://doi.org/10.1007/s00774-005-0644-1
17. Fisher A, Goh S, Srikusalanukul W, Davis M (2009) Elevated serum PTH is independently associated with poor outcomes in older patients with hip fracture and vitamin D inadequacy. Calcif Tissue Int 85:301–309. https://doi.org/10.1007/s00223-009-9283-1
18. Lee HP, Chang YY, Jean YH, Wang HC (2009) Importance of serum albumin level in the preoperative tests conducted in elderly patients with hip fracture. Injury 40:756–759. https://doi.org/10.1016/j.injury.2009.01.008
19. Avenell A, Smith TO, Curtain JP, Mak JC, Myint PK (2016) Nutritional supplementation for hip fracture aftercare in older people. Cochrane Database Syst Rev 11:CD001880. https://doi.org/10.1002/14651858.CD001880.pub6
20. Bhaskar D, Parker MJ (2011) Haematological indices as surrogate markers of factors affecting mortality after hip fracture. Injury 42:178–182. https://doi.org/10.1016/j.injury.2010.07.501
21. Jiang HX, Majumdar SR, Dick DA, Moreau M, Raso J, Otto DD, Johnston DW (2005) Development and initial validation of a risk score for predicting in-hospital and 1-year mortality in patients with hip fractures. J Bone Miner Res 20:494–500. https://doi.org/10.1359/JBMR.041133
22. Belmont PJ Jr, Garcia EJ, Romano D, Bader JO, Nelson KJ, Schoenfeld AJ (2014) Risk factors for complications and in-hospital mortality following hip fractures: a study using the National Trauma Data Bank. Arch Orthop Trauma Surg 134:597–604. https://doi.org/10.1007/s00402-014-1959-y
23. Chatterton BD, Moores TS, Ahmad S, Cattell A, Roberts PJ (2015) Cause of death and factors associated with early in-hospital mortality after hip fracture. Bone Joint J 97:246–251. https://doi.org/10.1302/0301-620X.97B2.35248
24. Lizaur-Utrilla A, Gonzalez-Navarro B, Vizcaya-Moreno MF, Miralles Muñoz FA, Gonzalez-Parreño S, Lopez-Prats FA (2019) Reasons for delaying surgery following hip fractures and its impact on one year mortality. Int Orthop. https://doi.org/10.1007/s00264-018-3936-5
25. Wong SHJ, Fang XC, Yee KHD, Wong TM, Pun CTT, Lau TW, Leung KLF (2018) Hip fracture time-to-surgery and mortality revisited: mitigating comorbidity confounding by effect of holidays on surgical timing. Int Orthop 42:1789–1794. https://doi.org/10.1007/s00264-017-3737-2
26. Civinini R, Paoli T, Cianferotti L, Cartei A, Boccaccini A, Peris A, Brandi ML, Rostagno C, Innocenti M (2019) Functional outcomes and mortality in geriatric and fragility hip fractures-results of an integrated, multidisciplinary model experienced by the "Florence hip fracture unit". Int Orthop 43:187–192. https://doi.org/10.1007/s00264-018-4132-3
27. Moyet J, Deschasse G, Marquant B, Mertl P, Bloch F (2019) Which is the optimal orthogeriatric care model to prevent mortality of elderly subjects post hip fractures? A systematic review and meta-analysis based on current clinical practice. Int Orthop 43:1449–1454. https://doi.org/10.1007/s00264-018-3928-5
28. Forni C, Gazineo D, D'Alessandro F, Fiorani A, Morri M, Sabattini T, Ambrosi E, Chiari P (2019) Predictive factors for thirty day mortality in geriatric patients with hip fractures: a prospective study. Int Orthop 43:275–281. https://doi.org/10.1007/s00264-018-4057-x
29. Ayubi E, Safiri S (2018) Comments on "mortality and cardiorespiratory complications in trochanteric femoral fractures: a ten year retrospective analysis". Int Orthop 42:441–442. https://doi.org/10.1007/s00264-017-3668-y
30. Carow J, Carow JB, Coburn M, Kim BS, Bücking B, Bliemel C, Bollheimer LC, Werner CJ, Bach JP, Knobe M (2018) Response to "comments on mortality and cardiorespiratory complications in trochanteric femoral fractures: a ten year retrospective analysis". Int Orthop 42:967–968. https://doi.org/10.1007/s00264-017-3755-0
31. Eneroth M, Olsson UB, Thorngren KG (2006) Nutritional supplementation decreases hip fracture-related complications. Clin Orthop Relat Res 451:212–217. https://doi.org/10.1097/01.blo.0000224054.86625.06