Injury, Int. J. Care Injured xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Usefulness of simple biomarkers at admission as independent indicators and predictors of in-hospital mortality in older hip fracture patients

Alexander Fisher[a,b,d,*], Leon Fisher[c], Wichat Srikusalanukul[a], Paul N. Smith[b,d]

[a] Department of Geriatric Medicine, The Canberra Hospital, ACT Health, Canberra, Australia
[b] Department of Orthopaedic Surgery, The Canberra Hospital, ACT Health, Canberra, Australia
[c] Frankston Hospital, Peninsula Health, Melbourne, Australia
[d] Australian National University Medical School, Canberra, ACT, Australia

ARTICLE INFO

Article history:
Accepted 7 March 2018

Keywords:
Hip fracture
In-hospital mortality
Biomarkers
Prediction

ABSTRACT

Introduction: The data on predictive value of the routinely obtained preoperative biochemical parameters in hip fracture (HF) patients are limited. The aims of this study were to examine in older HF patients (1) the relationships between a broad set of routine laboratory parameters at admission and in-hospital mortality, and (2) evaluate the prognostic value the biomarkers and clinical characteristics (alone or in combination) provide to predict a fatal outcome.
Patients and methods: In 1820 consecutive patients with low-trauma osteoporotic HF aged >60 years (mean age 82.8 ± 8.1 years; 76.4% women; 65% community-dwelling) 35 laboratory variables along with 20 clinical and socio-demographic characteristics at admission were analysed. The validation cohort included data on 455 older (≥60 years of age) HF patients (mean age 82.1 ± 8.0 years, 72.1% women).
Results: The mortality rate was 6% (n = 109). On univariate analysis 14 laboratory and 8 clinical parameters have been associated with in-hospital mortality. Multiple regression analyses determined 7 variables at admission as independent indicators of a fatal outcome: 4 biomarkers (albumin <33 g/L; alanine aminotransferase/gamma-glutamyl transferase ratio [GGT/ALT] >2.5; parathyroid hormone [PTH] >6.8 pmol/L; 25(OH)vitamin D < 25 nmol/L) and 3 pre-fracture clinical conditions (history of myocardial infarction, chronic kidney disease [GFR <60 ml/min/1.73 m^2] and chronic obstructive pulmonary disease); the area under the receiver operating characteristic curve (AUC) was 0.75 (95%CI 0.70–0.80). The risk of in-hospital death was 1.6–2.6 times higher in subjects with any of these risk factors (RFs), and increased by 2.6–6.0-fold in patients with any two RFs (versus no RFs). The mortality rate increased stepwise as the number of RFs increased (from 0.43% –none RF to 16.8%- ≥4RF). The prognostic value of a single RF was low (AUC ≤0.635) but combination of 2 or more RFs improved the prediction significantly; AUC reached 0.84(95%CI 0.77–0.90) when ≥4 RFs (versus 0–1RF) were present. In the validated and main cohorts the number of predicted by 1, 2, 3 or ≥4 RFs and observed deaths were practically similar.
Conclusions: In HF patients, seven easily identifiable at admission characteristics, including 4 biomarkers, are strong and independent indicators of in-hospital mortality and can be used for risk stratification and individualised management.

Introduction

The number of hip fractures (HF), one of the most common and challenging clinical conditions in the elderly, is expected to rise worldwide from 1.66 million in 1990 to 6.26 million in 2050 [1], despite declines (mainly among western populations) in the incidence rates [2,3]. The reported one-year mortality rates range between 12%–37% [4–9], and 3.3%–19.5% of HF patients die during hospitalization or in the first month following injury [4,10] –19.5%, [6,11–17]. Early prediction of outcome and the ability to identify at admission patients at a higher risk of morbidity and mortality can help optimise their management and reduce the burden of this disease.

Numerous studies on mortality following a HF focussed predominantly on clinical characteristics [4,6,15,18–24] and rarely

* Corresponding author at: A/Prof Alexander Fisher, Department of Geriatric Medicine, The Canberra Hospital, PO Box 11, Woden, ACT 2606, Australia.
E-mail address: alex.fisher@act.gov.au (A. Fisher).

https://doi.org/10.1016/j.injury.2018.03.005
0020-1383/

took into consideration laboratory, especially biochemical, data [25–28].

Among hepatic-related markers only low serum albumin concentration has been found to be a prognostic factor for mortality [6,26,29–36], and one study documented a positive association between alanine aminotransferase (ALT) levels and mortality within 3 months [37]. The pathophysiologic and prognostic input of the available on admission spectrum of biochemical markers has not been studied, and systematic characterization of metabolic, specifically liver-related factors, in regard to survival in a large cohort of patients with HF has not been performed. However, there are numerous reports linking all-cause mortality in community-dwelling older adults and various groups of hospitalised patients with serum activities (even in the normal range) of gamma-glutamyl transferase (GGT), ALT and alkaline phosphatase (ALP) [38–46]. Recently, combined indices (ratios and scores) – serum GGT/ALT [47], albumin/bilirubin [48–51], albumin/GGT [52], and ALT/ALP [53,54], were proposed as simple and objective tools for evaluation of hepatic reserve function and prediction survival and therapeutic outcomes in different settings including non-liver disease-related mortality, especially in various malignancies. None of these ratios which represent simultaneous changes of two liver function indices have been intended for HF patients.

Among routine biochemical factors as potential predictors of early mortality in HF patients should also be noted vitamin D, parathyroid hormone (PTH), indices of iron metabolism and thyroid function, vitamin B12 and folate. These candidate biomarkers have pluripotent metabolic effects, play a vital role in a myriad of biologic functions, are often abnormal in the elderly, particularly in subjects with a HF, and, most importantly, have been shown to interfere with survival in different diseases. However, these biomarkers remain outside the models proposed for predicting mortality in HF patients. It is unknown whether any of abovementioned metabolic parameters (alone or in combination) may present an objective and reliable prognostic guide for prediction in HF patients the short-term outcome.

Given the potential effects of metabolic characteristics on outcomes, the aims of the present study were: (1) to examine in a large, well-characterised cohort of older patients with HF the relationships between a broad set of routine biochemical, mainly liver-related, parameters at admission and in-hospital mortality, and (2) to evaluate the prognostic value such biomarkers provide alone or in combination to predict a fatal outcome. We analysed in total 35 laboratory variables along with 20 clinical and socio-demographic characteristics at admission to ascertain their feasibility to predict in-hospital death.

Patients and methods

Patients

Data for this study were obtained from a prospective electronic database on all adult patients with fracture of the upper femur admitted to the Department of Orthopaedic Surgery of The Canberra Hospital (university-affiliated tertiary care centre) from January 2000 to January 2013. Patients who had subtrochanteric and shaft fracture, high trauma and pathological HF due to primary or metastatic bone cancer, multiple myeloma, Paget disease or primary hyperparathyroidism, or who had incomplete data on admission were excluded. In total, 1820 consecutive older (≥60 years of age) patients (mean age 82.8 ± 8.1 years; 76.4% women; 94.6% Caucasian) with low-trauma osteoporotic HF were finally included into the study. Socio-demographic, anthropometric, clinical (HF type, comorbidities, complications, medication use) and laboratory data as well as outcomes were recorded.

The study was conducted according to the standards of the Declaration of Helsinki and was approved by the Australian Capital Territory Health Human Research Ethical Committee. As only routinely collected patient data (anonymized before analysis) were used and none of the patients had a blood test for the purposes of the study itself, the need for informed consent was waived.

Validation dataset

A retrospective analysis of a second cohort included data (obtained from electronic medical and administrative records) from 455 consecutive older (≥60 years of age) patients (mean age 82.1 ± 8.0 years, 72.1% women) with osteoporotic HF who were treated at the Canberra Hospital between 2013 and 2015.

Laboratory tests

In each patient fasting venous blood samples were collected on admission and the following assays performed: complete blood count, GGT, ALT, ALP (all 3 enzymes measured enzymatically using the Abbott Architect CI16200 automatic analyser), total bilirubin (measured using diazonium salt), albumin (analysed using bromcresol green), total protein (Biuret method), iron (direct colorimetric determination), ferritin (two-step chemiluminescence microparticle immunoassay),transferrin (immunoturbidimetric procedure), vitamin B12 (two step chemiluminescence microparticle intrinsic factor assay),folate (chemiluminesence microparticle folate binding protein assay), 25 (OH) vitamin D (25(OH)D, radioimmunoassay kit, Dia Sorin, Stillwater, MN, USA), intact PTH (2-site chemiluminescence enzyme-linked immunoassay on DPC Immulite 2000, Diagnostic Products, Los Angeles, CA), electrolytes (sodium, potassium, total calcium, phosphate and magnesium), renal (creatinine, urea) and thyroid function tests (thyroid stimulating hormone, [TSH], thyroxine,T4). All biochemical parameters were measured using commercially available kits according to the manufacturers' protocols. The serum calcium level was corrected for albumin concentration. The mean inter–assay and intra-assay CV for these tests were within 1.1%–12.7%. In all patients the GGT/ALT, ALT/ALP, GGT/ALP, albumin/GGT, albumin/ALT, albumin/ALP, albumin/bilirubin ratios were calculated, and serum transferrin saturation (using the IFCC protein standards) and glomerular filtration rate (GFR, by standardized serum creatinine-based formula normalized to a body surface area of 1.73 m^2) estimated. All reference ranges used are the ranges used by the Pathology Department of our hospital. Continuous variables were converted to categorical groups based on generally accepted cutoffs. For the analyses, deficiency of vitamin D was defined as 25(OH)D <25 nmol/L and insufficiency as 25(OH)D <50 nmol/L based on current recommendations. Secondary hyperparathyroidism (SHPT) was defined as elevated serum PTH (>6.8 pmol/L, the upper limit of the laboratory reference range). Chronic kidney disease (CKD ≥stage 3) was defined as a GFR <60 ml/min/1.73 m^2, which represents a loss of half or more of the normal adult renal function level [55].

In total, 27 metabolic and haematological variables (albumin, ALT, GGT, ALP, bilirubin, 25(OH)D, PTH, calcium, phosphate, magnesium, TSH, T4, urea, creatinine, GFR, iron, ferritin, transferrin, transferrin saturation, vitamin B12, folate, haemoglobin, erythrocytes, white blood cell count, neutrophils, mean corpuscular volume, and haematocrit) along with 8 ratios (GGT/ALT, GGT/ALP, GGT/bilirubin, ALT/ALP, albumin/GGT, albumin/ALT, albumin/ALP and albumin/bilirubin) were analysed.

Statistical analyses

Statistical analyses were performed using the Stata software version 10 (StataCorp, College Station, TX, USA). Descriptive statistics

Please cite this article in press as: A. Fisher, et al., Usefulness of simple biomarkers at admission as independent indicators and predictors of in-hospital mortality in older hip fracture patients, Injury (2018), https://doi.org/10.1016/j.injury.2018.03.005