Markers of renal function at admission and mortality in hip fracture patients - a single center prospective observational study

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ABSTRACT

Plasma cystatin C and shrunken pore syndrome (SPS) are associated with increased mortality in older adults. The objective was to assess the association between these markers of kidney function at admission and mortality in hip fracture patients. Hip fracture patients presenting at Lund University Hospital were eligible for inclusion. Cox regression was used to assess association between plasma cystatin C, creatinine, cystatin C- or creatinine-based estimations of glomerular filtration rate (eGFR\(_{\text{CYS}}\) and eGFR\(_{\text{CREA}}\)), or SPS (defined as eGFR\(_{\text{CYS}}\)/eGFR\(_{\text{CREA}}\) < 0.7) and mortality during one year follow up. Improvement in discrimination relative to the Nottingham Hip fracture score was assessed by Receiver Operational Characteristics (ROC) analysis and calculation of Net Reclassification Index (NRI). 996 patients were included in the study. Cystatin C, creatinine, eGFR\(_{\text{CYS}}\) and eGFR\(_{\text{CREA}}\) were associated with one-year mortality in both unadjusted and adjusted analyses. The association with mortality was stronger for cystatin C and for eGFR\(_{\text{CYS}}\) than for creatinine and eGFR\(_{\text{CREA}}\). Patients with SPS had doubled one-year mortality compared with patients without SPS (43.7 and 20.2%, respectively, \(p < .001\)). Hazard ratio for SPS in the adjusted analysis was 1.66 (95\%CI: 1.16–2.39, \(p = .006\)). None of the markers improved discrimination compared to the Nottingham Hip Fracture Score using ROC analysis whereas eGFR\(_{\text{CYS}}\) and eGFR\(_{\text{CREA}}\) improved NRI. Our conclusion is that plasma concentrations of creatinine or cystatin C, eGFR\(_{\text{CYS}}\) or eGFR\(_{\text{CREA}}\) or SPS at admission in hip fracture patients are associated with mortality when known risk factors are accounted for. Identification of high risk patients may be improved by eGFR\(_{\text{CYS}}\) or eGFR\(_{\text{CREA}}\).

Introduction

A hip fracture in older adults is a serious condition and early identification of the high-risk patient may offer the opportunity for interventions which may improve outcome. Impaired kidney function is an independent risk factor for perioperative mortality and cardiovascular complications [1–3]. Also in hip fracture patients, urea and creatinine are associated with mortality [3–9] but discrimination has generally been reported to be low with area under the Receiver Operational Characteristics (ROC) curve below 0.7 [6].

While plasma concentration of the small molecule creatinine (113 Da) remains the most common marker of kidney function it rises relatively late in the course of diminishing kidney function and plasma concentration is influenced by factors other than glomerular filtration rate, such as gender, muscle mass and diet [10]. This may be particularly relevant in hip fracture patients because of the high incidence of malnourishment [11]. Cystatin C is a 13 300 Da protease inhibitor which is produced by all nucleated cells at a constant rate and has been deemed equal or superior to serum creatinine as a plasma biomarker for estimation of glomerular filtration rate [12–16]. Moreover, plasma cystatin C has been shown to be a stronger predictor of death in community dwelling elderly patients than creatinine [17,18].

Recently it was suggested that the association between death and cystatin C could be linked to the shrunken pore syndrome (SPS) which is characterized by a 60–70% lower glomerular filtration rate as estimated by cystatin C (eGFR\(_{\text{CYS}}\)) than glomerular filtration rate estimated by creatinine (eGFR\(_{\text{CREA}}\)) [18–22]. SPS is associated with increased long term mortality in healthy seniors as well as in patients undergoing coronary artery bypass surgery [19]. It has been shown that SPS was associated with increased mortality also in patients with normal GFR as measured with plasma clearance of iohexol [19] suggesting that SPS reflects important aspects of kidney function that are not captured with more common measures of GFR.
The objectives of the present study were to assess the association between creatinine, cystatin C or SPS, and mortality in patients suffering from out of hospital hip fractures and to assess if these measures of renal function add clinically useful information to other predictors of poor outcome in hip fracture patients.

Methods

Study design

This study was based on prospectively collected data from a cohort of hip fracture patients admitted to Skåne University Hospital, Lund, Sweden between January 31st 2011 and August 30th 2014. The manuscript was prepared according to the STROBE guidelines for reporting of observational studies [23]. The cohort has previously been described in detail [24,25].

Ethics and trial registration

The study was approved by the regional ethical review board in Lund (application numbers 2010/218 and 2011/506). The study was conducted according to the Declaration of Helsinki and was monitored by external monitors from the Clinical Research Unit, Skåne University hospital, Lund. Consent was sought from patients or next of kin within 72 h of admission. The study was registered at Clinicaltrials.gov (NCT01280253) on January 18th, 2011.

Inclusion and exclusion criteria

Ambulance and emergency department nurses performed patient screening. Inclusion criteria were out-of-hospital cervical, trochanteric or subtrochanteric fracture of the neck of the femur and blood sampling within 3 h from first contact with health care providers. Patients were excluded if informed consent was not obtained, if non-operative management was chosen, if the fracture was pathological, part of multitrauma or if follow up was not possible within the Swedish National Hip Fracture Database.

Laboratory analysis

Venous blood samples were drawn at admission, centrifuged to isolate plasma in EDTA and frozen at −80 ºC until analysis. The plasma concentration of cystatin C was determined by an automated particle-based immunoassay, and that of creatinine by an enzymatic colorimetric assay with an IDMS-traceable calibrator [26]. Both assays were run on a Cobas c-system (Roche Diagnostics, Basel, Switzerland). All assays were performed according to the manufacturer’s instructions. GFR-estimating equations, traceable to international reference materials, were used to determine eGFR_CYS (CAPA) and eGFR_CREA (LMrev) [26,27]. SPS was defined as eGFR_CYS/eGFR_CREA ≤ 0.7 [21].

Data collection

Demographic data was retrieved from ambulance charts, anaesthesia and patient charts and mortality data from the Swedish National Hip Fracture Database. Cognitive function was assessed by the Short Portable Mental Status Questionnaire as described previously [24]. External monitors checked the accuracy of the database against source data in a sample of 31 randomly selected patients and the fraction of wrong entries was found to be < 0.1%. Mortality data were collected for the first year after inclusion.

Statistics

In a first step we performed unadjusted Cox regression analysis for the one year follow up with the following variables divided into quartiles: cystatin C, creatinine, eGFR_CYS, eGFR_CREA and Shrunken Pore Syndrome. In a second step we adjusted the Cox regression for age, gender, hemoglobin concentration, cognitive function, living conditions, number of co-morbidities and history of malignancy (except non-invasive skin cancer) as these variables are used in the Nottingham Hip Fracture Score (NHFS) which is the best validated risk assessment tool available for patients suffering a hip fracture [28]. We also adjusted the cystatin C variables for creatinine levels. Proportional hazards assumptions were checked both graphically and using Schoenfeld’s test.

To assess discrimination, Receiver Operational Characteristics (ROC) analysis for one-year mortality for the markers of kidney function was performed. The markers of kidney function were added to the NHFS model which was used as a reference model to see if the area under the curve (AUC) could be improved. Finally we calculated the net reclassification improvement (NRI) after adding the biomarkers to the Nottingham Hip Fracture Score. NRI is the sum of the reclassification improvement of events (the difference between the percentage of patients that are classified with the new model as a high-risk patient and experience an outcome and percentage of patients that were classified as high risk patients and experience an outcome by the old model) and the reclassification improvement of non-events (percentage of patients that are reclassified as low-risk and do not experience the outcome minus the percentage of patients previously classified as low risk and not experiencing the outcome). High risk patients were defined as patients with predicted double or higher risk compared with mean mortality on a national level during the study period as suggested previously [29,30]. The 95% confidence intervals for the NRI were calculated using bootstrap analysis. In the bootstrap analysis, a random sample of the same number of patients as in the cohort was drawn from the cohort and an NRI was calculated. This was repeated 10 000 times and the 95% confidence intervals were defined as the 2.5th and 97.5th percentile of all 10 000 bootstrapped values. A 95% confidence interval not including zero was considered to reflect a significant NRI.

Statistical significance was defined as p value < .05. No adjustment for multiple comparisons was performed.
analyses were performed R v. 3.5.2 (R Core Team (2018)) and Stata SE16 (StataCorp).

Results

Demographics

During the study period 1845 patients were admitted to Lund University hospital with a hip fracture of which 1556 fulfilled inclusion criteria and none of the exclusion criteria. A total of 996 of these patients (64%) were included in the study. Majority of the non-included patients were screening failures in which blood samples for the study were not collected within 3 hrs. A flowchart of patients is presented in Figure 1. Patient demographics are presented in Table 1. All the components of the NHFS were associated mortality at one year (Table 2).

Cox regression

The results of the Cox regression are shown in Table 3. All investigated markers of kidney function were associated with one-year mortality when divided into quartiles and remained significant after adjustment for the variables included in NHFS. The cystatin C and SPS variables remained statistically significant after adjustment for creatinine variables. In a post hoc sensitivity analysis we performed unadjusted and adjusted cox regression with 90-day mortality as an outcome. This analysis yielded similar point estimates but with wider 95% CI (supplement table 1). The Kaplan Meier survival plot for patients with and without SPS are shown in Figure 2. One-year mortality for patients with SPS was twice that of patients without SPS (43.7 and 20.2%, respectively).

ROC analysis and reclassification

The Nottingham Hip Fracture Score was used as a reference model and provided moderate discrimination for one-year mortality with AUC of 0.76 (95% CI; 0.72 – 0.79). Adding the biomarkers for kidney function to the reference model did not improve the AUC (Table 4).

One-year mortality during the study period was 23.9% in the Swedish National Hip Fracture Database and a high-risk patient was therefore defined as a patient with an expected risk of death of 48% or higher [29]. This was used to assess Net Reclassification Improvement. There was an improvement of identification of high-risk patients as measured by NRI for eGFR$_\text{CYS}$ and eGFR$_\text{CREA}$.

Discussion

The results in this exploratory study show that cystatin C and eGFR$_\text{CYS}$ are associated with an increased mortality at one year in hip fracture patients in analyses adjusted creatinine and for established risk factors of a poor outcome in

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| Table 1. Flowchart of patients included in the study. |
|---|---|

| Number of patients | 996 |
|---|---|
| Age (years) | 84 (77–90) |
| Female | 71% |
| ASA PS 1 | 5% |
| ASA PS 2 | 29% |
| ASA PS 3 | 62% |
| ASA PS 4 | 4% |
| Cervical fracture | 53% |
| Trochanteric fr. | 41% |
| Subtrochanteric fr. | 6% |
| Time from admission to operation (hrs) | 17 (10–23) |
| eGFR$_\text{CREA}$ ≥90 (ml/min/1.73m$^2$) | 1% |
| eGFR$_\text{CREA}$ 60–89 (ml/min/1.73m$^2$) | 16% |
| eGFR$_\text{CREA}$ 30–59 (ml/min/1.73m$^2$) | 45% |
| eGFR$_\text{CREA}$ 15–29 (ml/min/1.73m$^2$) | 35% |
| eGFR$_\text{CREA}$ < 15 (ml/min/1.73m$^2$) | 3% |

Continuous data are presented as median and interquartile range. ASA-PS: American Society of Anesthesiologists physical status classification. eGFR$_\text{CREA}$: estimated glomerular filtration rate based on plasma concentration of creatinine using the Lund-Malmo Revised GFR estimating equation.

| Table 2. Nottingham hip fracture score variables and cox regression analysis in the cohort. |
|---|---|---|---|
| Alive | Dead | HR (95 % CI) |
|---|---|---|---|
| NHFS-variables |
| n = 765 | n = 231 | Unadjusted |
| --- | --- | --- | --- |
| Age |
| 0–65 | 8.6 (66) | 2.2 (5) | Ref. |
| 65–85 | 52.9 (405) | 35.5 (82) | 2.51 (1.02–6.18) |
| > 85 | 38.4 (294) | 62.4 (144) | 5.37 (2.20–13.10) |
| Male |
| 26.7 (204) | 36.9 (85) | 1.52 (1.16–1.99) | .002 |
| Malignancy |
| 14.3 (109) | 19.9 (46) | 1.42 (1.03–1.96) | .033 |
| Co-morbidities* |
| 32.9 (252) | 48.1 (111) | 1.71 (1.32–2.22) | <.001 |
| Institutional living |
| 17.9 (137) | 48.1 (111) | 3.39 (2.62–4.39) | <.001 |
| SPMSQ score ≤ 6$^b$ |
| 33.9 (259) | 67.3 (156) | 3.40 (2.58–4.48) | <.001 |

$^a$Diabetes, malignancy (excluding non-invasive skin cancer), cardiovascular, cerebrovascular, respiratory or renal disease.

$^b$Short portable mental status questionnaire.
this patient category. Creatinine and eGFRCREA were also associated with mortality but not as strongly as the cystatin C derived variables. Shrunken Pore Syndrome as a categorical variable was a strong risk factor for one-year mortality. None of the markers of kidney function improved the area under the ROC curve whereas the NRI was improved by eGFRCYS and eGFRCREA when added to the Nottingham Hip Fracture Score for prediction of 1-year mortality.

Several studies have shown an association between increased plasma creatinine concentrations at admission and postoperative mortality both in adjusted and unadjusted analyses and our results confirm these previous findings in a large prospectively collected cohort of hip fracture patients [4,6,8,9,31,32]. Interestingly this association does not translate to improved discrimination and our result that creatinine does not improve discrimination as assessed by ROC analysis aligns with previous studies showing that urea or creatinine influence plasma creatinine independent of kidney function [35]. The optimal cut-off, defined by the highest sum of sensitivity and specificity, for detection of patients with an increased 1-year mortality in that study was found to be 0.69 [35].

Recently published data refutes the hypotheses that the association of increased mortality and cystatin C or eGFRCYS is solely explained by better estimation of true GFR [36]. In fact, SPS is associated with increased mortality also in analyses adjusted for measured GFR, eGFRCREA, eGFRCYS and without albuminuria, suggesting that the syndrome may reflect a previously unrecognized disturbance in kidney function [37]. SPS is associated with increased plasma concentrations not only of cystatin C, but also of other 5–40 kDa proteins linked to development of cardiovascular disease and mortality [18,38,39]. Although the increased levels of these signal proteins might be causally linked to increased mortality or morbidity, it has also been speculated that the syndrome is a marker of a more widespread endothelial dysfunction as is seen, for example, in patients with preeclampsia [16]. Another potential explanation for the association between SPS and mortality in our patient cohort could be that patients with SPS represent a subgroup of frail and sarcopenic patients which would have relatively low levels of creatinine and therefore a falsely high

#### Table 3. Cox regression for all-cause one year mortality (n = 996).

| Variable | Unadjusted | Adjusted for NHFS* | Adjusted for creatinine** |
|----------|------------|--------------------|--------------------------|
| Cystatin C | HR (95 % CI) | p Value | HR (95 % CI) | p Value | HR (95 % CI) | p Value |
| Q1 | 1.303 (0.821–2.069) | .001 | 1.018 (0.635–1.630) | .925 (0.751–1.996) |
| Q2 | 1.801 (1.162–2.794) | .001 | 1.118 (0.709–1.762) | .586 (0.918–2.740) |
| Q4 | 4.082 (2.747–6.066) | .001 | 2.045 (1.322–3.164) | 2.091 (1.622–5.516) |
| Creatinine | <.001 | .013 | <.001 | .001 |
| Q1 | 1.707 (1.099–2.652) | 1.034 (0.653–1.637) | 1.560 (0.878–2.769) |
| Q3 | 1.210 (0.756–1.937) | 0.909 (0.562–1.471) | 1.147 (0.691–1.903) |
| eGFRCYS | <.001 | .001 | <.001 | .001 |
| Q1 | 5.509 (1.795–3.736) | 1.277 (0.843–1.934) | 2.925 (1.534–5.756) |
| Q2 | 1.307 (0.868–1.969) | 0.723 (0.463–1.127) | 1.560 (0.878–2.769) |
| Q3 | 1.064 (0.693–1.632) | 0.691 (0.441–1.084) | 1.147 (0.691–1.903) |
| SPS | 2.475 (1.747–3.505) | <.001 | 1.661 (1.155–2.393) | .006 | 1.669 (1.157–2.406) | .006 |

*Nottingham Hip Fracture Score: Adjusted analysis, adding to each predictor, respectively, to a model including, age, gender, blood hemoglobin concentration, Short Portable Mental Status Questionnaire, living conditions, co-morbidities and a history of malignancy.

**: same as *, but the cystatin C/eGFRCYS models are also adjusted for creatinine/eGFRCREAA respectively. SPS model adjusted for eGFRCREA.

eGFRCREAA Estimated glomerular filtration rate based on cystatin C or creatinine plasma levels respectively.
eGFRCREA. This has not been the case in other studies of SPS [19,20,22], but unfortunately, we did not have access to the body mass index of the patients in our cohort.

As the specific underlying pathophysiological mechanism for the increased mortality in patients with SPS is not known, it is uncertain if any therapeutic intervention could be applied to improve outcome in hip fracture patients suffering from the syndrome. However, it has been shown in previous studies that chronic kidney disease is a risk factor for development of acute kidney injury which in turn is associated with an increased mortality [40,41] although this does not seem to be universal [42].

The value of a novel biomarker is commonly assessed by calculating the increase in AUC of the ROC curve compared with a base model. However, this approach has limitations and hence we choose to assess discrimination also by calculating improvement in identification of the high-risk patients [43,44]. Our results, showing that both eGFR$_{\text{CYS}}$ and eGFRCREA improved NRI, suggest that these measures of renal function may improve discrimination when added to the Nottingham Hip Fracture Score and that the improvement in NRI was driven by improvement of correct classification of high-risk patients. Given that NRI values below 0.2 have been suggested to reflect a small improvement [45] we believe that the clinical relevance of this finding is uncertain and should be evaluated in future studies.

**Limitations**

This is a single centre study and despite our efforts we included about two thirds of eligible patients. However, we have previously shown that demographics and outcome for included patients is similar to those of patients fulfilling entry criteria on a national level supporting the external validity of our results [24]. The last patient was included in mid 2014 and it could be argued that the time passed since then could limit the validity of our results. To assess if any major changes in outcome had occurred we recently assessed 30-day mortality on a national level for the year of 2017 and found it to be 7.7%. During the inclusion period the 30-day mortality on a national level was 7.6%. This value is similar to the mortality in the present cohort and indicates that our results are likely to be valid also in a current setting. Another limitation is that we did not establish cause of death for patients dying during the observation period. Such data could have been valuable in establishing underlying pathophysiological mechanisms of the excess mortality in patients with small pore syndrome.

### Table 4. Reclassification and improvement in AUC for 1-year mortality.

|          | AUC (95% CI) | AUC improvement | p Value | NRI (95% CI) | RI Event (95% CI) | RI Non-event (95% CI) |
|----------|--------------|-----------------|---------|--------------|--------------------|-----------------------|
| Cystatin C | 0.78 (0.75–0.81) | 0.023 (–0.025;0.071) | 0.350 | 0.051 (–0.001;1.103) | 0.069 (0.0190;1.120) | –0.018 (–0.032; –0.005) |
| Creatinine | 0.77 (0.64;0.80) | 0.011 (–0.037;0.059) | 0.648 | 0.004 (–0.033;0.040) | 0.013 (–0.022;0.048) | –0.009 (–0.020; 0.001) |
| eGFRCYS | 0.78 (0.75;0.81) | 0.024 (–0.021;0.069) | 0.322 | 0.060 (0.003;0.117) | 0.082 (0.0280;0.138) | –0.022 (–0.038; –0.008) |
| eGFRCREA | 0.77 (0.74;0.81) | 0.016 (–0.017;0.064) | 0.510 | 0.040 (0.001;0.080) | 0.065 (0.0280;0.104) | –0.025 (–0.037; –0.014) |
| SPS | 0.76 (0.73;0.80) | 0.005 (–0.236;0.246) | 0.853 | –0.001 (–0.031;0.031) | 0.004 (–0.026;0.035) | –0.005 (–0.013; 0.001) |

$\text{p-value}$ refers to improvement in area under the curve (AUC) compared to reference model. Ref. model AUC: 0.76 (0.72–0.79) for the Nottingham Hip Fracture Score.

eGFRCYS/CREA: Estimated glomerular filtration rate based on cystatin C or creatinine plasma levels respectively.

SPS: Shrunken pore syndrome.
Conclusion
Our data suggest that plasma concentration of cystatin C, creatinine, eGFR_CYS, eGFR_CREA and the Shrunken Pore Syndrome are associated with increased mortality when other established risk factors for mortality are accounted for in hip fracture patients. Discrimination is improved when eGFR_CYS or eGFR_CREA are added to the Nottingham Hip Fracture Score when one-year mortality is being assessed. Further studies are needed to investigate the implications of these novel findings on clinical care.

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Author contributions
MHJ: Study design, data analysis, patient recruitment, data collection and drafting of manuscript. ÅÅ: Study design, statistical analysis, critical revision of the manuscript. AH: Study design, data collection, critical revision of the manuscript. AG: Study design, data collection, critical revision of the manuscript. PB: Study initiation and design, data analysis, patient recruitment drafting and critical revision of the manuscript.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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