INTRODUCTION

Hip fractures in older persons in Europe have an incidence of about 150-250 per 100 000 inhabitants and the number of patients is expected to rise.\(^1\)\(^2\) Complications occur in about 40% of these patients and the 30-day mortality is reported to be 6%-10%.\(^3\)\(^-\)\(^5\) Risk prediction at admission to hospital could be valuable to allocate resources to patients whom may benefit from further workup.

Background: Little is known about the value of biomarkers for prognostication in hip fracture patients. The main objective of the present study was to assess if biomarkers add useful information to an existing risk score for prediction of 30-day mortality in patients suffering from out of hospital hip fractures.

Methods: In a prospective observational single centre study, association between plasma concentration of ninety-two biomarkers at admission and 30-day mortality was analysed using logistic regression adjusted for risk factors included in Nottingham Hip Fracture Score (NHFS). Biomarkers associated with the outcome in the adjusted analysis were further evaluated by calculating the net reclassification improvement (NRI) and the change in area under the receiver operating characteristics curve (AUC) relative to the NHFS.

Results: 997 patients were included. Sixty-two patients died within 30 days (6.2%). Eleven biomarkers were associated with 30-day mortality in adjusted analysis. Of these biomarkers Growth Differentiation Factor-15 (GDF-15) had NRI for the primary outcome (12.1%; 95% CI: 1.2-23.3) and Carbohydrate Antigen 125 (CA-125) improved the AUC relative to NHFS (improvement: 0.05; 95% CI: 0.01-0.10, \(P = .027\)). Both CA-125 and GDF-15 improved the AUC for a composite outcome of 30-day mortality and cardiovascular complications.

Conclusions: Adding GDF-15 or CA-125 to the Nottingham Hip Fracture Score improves the discrimination with regard to predicting 30-day mortality and may help to identify a subgroup of hip fracture patients with a particularly poor prognosis. The value of these biomarkers should be explored in further studies to confirm clinical utility.
perioperative monitoring or increased postoperative vigilance. For this purpose, risk prediction scores specifically intended for hip fracture patients have been designed. Of these scores the Nottingham Hip Fracture Score (NHFS) is the most validated and broadly used. Unfortunately, accuracy of NHFS is moderate in many settings and improved predictive ability is desirable.

While cardiovascular complications are common and constitute a major cause of mortality in hip fracture patients, little is known about the value of cardiovascular biomarkers in this setting. In smaller studies, N-terminal-pro Brain Natriuretic Peptide (NT-proBNP) and BNP, markers of heart failure, were measured at various time points after admission in selected patients and were shown to predict post-operative mortality and complications. Plasma lactate at admission which reflects adequacy of organ perfusion has been evaluated in two large studies with conflicting results. Moreover, it is currently unclear if biomarkers add prognostic information to existing risk scoring systems for hip fracture patients.

The present study was designed to test the hypothesis that plasma concentration of biomarkers of cardiovascular risk at admission can be used to predict 30-day mortality and non-fatal cardiac complications during admission in a cohort of patients suffering from out of hospital hip fractures and that such biomarkers add clinically useful information to existing scoring systems.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was based on prospectively collected data from a cohort of hip fracture patients. The cohort has been described in two manuscripts evaluating performance of the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM), the Nottingham Hip Fracture Score (NHFS) and lactate for prediction of mortality and morbidity.

2.2 | Ethics and trial registration

The study was approved by the regional ethical review board in Lund, Sweden; application number 2010/218 and application number 2011/506. The study was conducted according to the Declaration of Helsinki. Consent was sought from patients or next of kin within 72 hours of admission. The study was registered at Clinicaltrials.gov (NCT01280253) on January 18th, 2011.

2.3 | Participants

Ambulance and emergency department staff performed screening on patients admitted to Skåne University Hospital, Lund, Sweden between 31 January 2011 and 30 August 2014. Inclusion criteria were out-of-hospital cervical, trochanteric or subtrochanteric fracture of the neck of the femur and blood sampling within 3 hours 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 Registry. The rationale for excluding patients with pathological fractures was that these patients were considered to represent a separate group of patients with particularly poor prognosis.

Editorial Comment

Valid risk prediction in perioperative medicine could be used to tailor the perioperative care of the patient. In this study, the authors have tested multiple potential biomarkers sampled at admittance to hospital for association with 30-day mortality. Of 11 with an association only one changed the prediction value of the Nottingham hip fracture score when evaluated as net reclassification improvement and area under the receiver operating characteristic curve (AUC).
2.6 | Data collection

Demographic information, mortality and cardiovascular complications were retrieved from ambulance charts, anaesthesia and patient charts and the Swedish National Hip Fracture Registry. Cognitive function was assessed by the Short Portable Mental Status Questionnaire. Cognitive impairment was defined as a Short Portable Mental Status Questionnaire of ≤seven.²⁴ The accuracy of the data in the database was checked against source data by the external monitors in a sample of 31 randomly selected patients and the fraction of wrong entries was found to be <0.1%. The 30-day mortality data for patients fulfilling inclusion criteria on a national level during the study period was extracted from the Swedish National Hip Fracture Registry. To assess if our cohort is similar to more recent data we also extracted demographic data and mortality data on patients fulfilling inclusion criteria on a national level in 2017.

2.7 | Statistics

No power analysis was performed. Based on historical annual admission rates of patients fulfilling the inclusion criteria of about 500, a 50% inclusion rate and an inclusion period of about 2 years we pragmatically aimed to include 1000 patients. In a first analytical step, univariable logistic regression was performed to identify biomarkers which were associated with the primary outcome. In a second step, such biomarkers were included in a multivariable logistic regression model including clinical variables which have previously been associated with outcome in the Nottingham Hip Fracture Score (NHFS).²⁵ These variables were: age, gender, cognitive function, haemoglobin value at admission, number of comorbidities and malignancy excluding non-invasive skin cancer. Both models were corrected for false discovery rates using the Bonferroni method.

In a third step, the clinical utility of biomarkers which were associated with the primary outcome in the adjusted analysis was assessed by calculating the net reclassification improvement (NRI) after adding the biomarker 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 experienced 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.²⁶,²⁷ 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 calculated based on these samples. A 95% confidence interval not including zero was considered to reflect a significant NRI. NRI analysis was not performed for the secondary outcome because risk estimation using the Nottingham Hip Fracture Score for this outcome is not validated.

To further assess discrimination, Receiver Operational Characteristics (ROC) analysis for the biomarkers in the reclassification analysis was performed. Biomarker plasma concentrations were dichotomized and area under the curve (AUC) of NHFS with or without each biomarker was compared using the DeLongs test. Calibration of the models was assessed using the Hosmer-Lemeshow (HL) test.

Statistical significance was defined as a P ≤ .05. Demographic data are expressed as median and interquartile range unless stated otherwise. Analyses were performed using SAS 9.4 (SAS Institute Inc, SAS Campus Drive).

3 | RESULTS

3.1 | 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 997 of these patients (64%) were included in the study. Majority of the non-included patients were screening failures in which study blood samples for the biomarker study were not collected within 3 hours. A flowchart of patients is presented in the Figure S1. Demographics for included patients are presented in Table 1. Mortality was 6.2% and 23 patients experienced a cardiovascular event (Table 2). Of these 23 patients, 11 were still alive at thirty days (1.1% of all patients). Thus, the primary outcome was reached in 6.2% of the patients and secondary outcome in 7.3% (Table 2).

3.2 | Association between biomarkers and outcome

Analysis of two of the biomarkers in the assay was successful in less than 130 samples and these biomarkers were not included in the subsequent analysis (Table S1). Number of patients included in the analysis for the other 90 biomarkers ranged from 839 to 971. Univariable analysis corrected for false discovery rates using the Bonferroni method with P values below .05, identified 19 biomarkers that predicted primary outcome (Table S1). When age, gender, haemoglobin value, cognitive function, living conditions, number of comorbidities and history of malignancy excluding non-invasive skin cancer were added in a multivariable logistic regression model a total of 11 of the biomarkers remained associated with primary outcome and were included in subsequent steps of the analysis (Table S2).
During the study period the 30-day mortality was 7.6% in the Swedish National Hip Fracture Registry and a high-risk patient was therefore defined as a patient with an expected risk for the primary endpoint of 15.2% or higher. To assess if mortality in our cohort was similar to a more recent cohort, we retrieved data from the Swedish National Hip Fracture Registry on thirty-day mortality for the year 2017 and the mortality for this period was 7.7% (Table 1).

Reclassification tables were created for the biomarkers which were associated with the primary outcome. Adding growth differentiation factor-15 (GDF-15) to the NHFS resulted in a net reclassification improvement (NRI) of 12.1% (95% CI 1.2-23.3) (Table 3).

3.4 | ROC analysis

ROC analysis using the NHFS score to predict primary outcome resulted in area under the curve value (AUC) of 0.70 (95% CI 0.63-0.76). When biomarkers were added to the model as a dichotomous variable only CA-125 increased significantly the AUC for prediction of the primary outcome with an AUC improvement of 0.05 (95% CI; 0.01-0.10, \( P = .027 \)). The change in AUC for GDF-15 was 0.05 (95% CI; 0.00-0.11, \( P = .062 \)).

In the ROC analysis for the secondary outcome GDF-15 and CA-125 both improved the AUC when added to the NHFS (0.06 95% CI; 0.00-0.11, \( P = .036 \)) and (0.05 95% CI; 0.01-0.09, \( P = .017 \), respectively). In this analysis CTSL1, IL27-A, CXCL16, TF and IL-8 also improved the AUC (Table S3).

Models with and without biomarkers were well calibrated with Hosmer-Lemeshow \( P \) values above .05 in all analyses except for CA-125. Kaplan-Meier-survival-curves for mortality in the respective tertiles of GDF-15 and CA-125 plasma concentrations are shown in Figure 1. Unadjusted and adjusted odds ratios for the two higher tertiles of plasma concentration of GDF-15 and CA-125 relative to the lowest tertile are presented in Table 4.

4 | DISCUSSION

In a broad search for novel biomarkers as risk markers of mortality and cardiovascular morbidity in hip fracture patients we identified 11 biomarkers that were associated with 30-day mortality. Only one of these biomarkers, GDF-15, changed risk prediction as evaluated by NRI. ROC analysis revealed that only CA-125 improved the AUC for prediction of 30-day mortality whereas both CA-125 and GDF-15 improved the AUC for the secondary outcome when added to the Nottingham Hip Fracture Score.

The added value of a novel biomarker is often analysed by the increase in AUC of the ROC curve compared with the base model. However, it is increasingly recognized that this approach has limitations and clinical value of a biomarker should also be measured by other means.
assessed by other metrics such as the NRI.28,29 One of the clinically most important reasons for using risk prediction tools is to identify those patients which are at greatest risk for a poor outcome.27

When new variables or biomarkers are added to existing prognostication tools NRI provides a measure for the improved classification and for this reason emphasis was placed on NRI in our analysis of biomarkers. The calculation of NRI requires that risk categories are defined. Although there is no consensus on the definition on what constitutes a high-risk patient, a predicted mortality twice as high as the average mortality is commonly used.26 For the purpose of the present analysis we chose the national average during the inclusion period to define average mortality. Our finding that mortality is very similar in a more recent sample from the national hip fracture registry and that 30-day mortality from hip fractures is reported to be in the range of 6%-10% in recent datasets from other developed countries support the external validity of our definition of a high-risk patient.3,4 It could be argued that other clinical risk factors than those used in the NHFS could have been used in our analyses. However, we believe that NHFS serves as clinically relevant baseline for risk prediction, given that it is the most validated and widely used risk prediction score for hip fracture patients.7-10,12,25

Our finding that GDF-15 was a promising biomarker in our cohort adds to a growing literature suggesting that increased plasma concentrations of this molecule are associated with a poor outcome in various pathologies.30-32 Growth differentiation factor-15, also called macrophage inhibitory cytokine 1, is a member of the human transforming growth factor β superfamily. GDF-15 is expressed in most organs in low concentrations under normal conditions and therefore likely to take part in basic cellular functions.33 It is believed that GDF-15 has a broad anti-inflammatory and immunosuppressive action. Increased plasma concentrations have been associated with cardiac infarction, heart failure, malignant tumour phenotypes

| Biomarker | NRI | Base model | Biomarker model | HL | AUC difference | P value for difference |
|-----------|-----|------------|----------------|----|----------------|-----------------------|
| GDF-15    | 0.121 | 0.695      | 0.748          | 0.440 | 0.053           | −0.003; 0.109          |
| CA-125    | 0.116 | 0.692      | 0.744          | 0.023 | 0.052           | 0.006; 0.097           |
| TF        | 0.102 | 0.695      | 0.743          | 0.829 | 0.048           | 0.002; 0.0989          |
| TRAIL-R2  | 0.094 | 0.695      | 0.728          | 0.760 | 0.033           | −0.017; 0.084          |
| IL27-A    | 0.066 | 0.695      | 0.742          | 0.955 | 0.046           | 0.002; 0.095           |
| FGF-23    | 0.058 | 0.695      | 0.728          | 0.571 | 0.033           | 0.011; 0.077           |
| BNP       | 0.057 | 0.690      | 0.725          | 0.834 | 0.035           | 0.012; 0.082           |
| U-PAR     | 0.046 | 0.695      | 0.736          | 0.887 | 0.041           | 0.006; 0.088           |
| IL-8      | 0.043 | 0.695      | 0.742          | 0.959 | 0.047           | 0.009; 0.102           |
| CTSL1     | 0.013 | 0.695      | 0.729          | 0.790 | 0.033           | 0.004; 0.071           |
| EN-RAGE   | 0.012 | 0.694      | 0.736          | 0.084 | 0.042           | 0.010; 0.094           |

Note: The biomarker model includes the variables from the basemodel and respective biomarker. The 95% confidence interval is shown within parentheses. P value refers to the difference in area under the curve (AUC) of the biomarker model compared to a base model including, age, gender, blood hemoglobin concentration, Short Portable Mental Status Questionnaire, living conditions, co-morbidities and a history of malignancy (excluding skin cancer). As only patients in whom biomarker analysis was successful were included in the base model for respective biomarker number of patients and hence base model performance varies slightly. See Table S1 for full names of biomarkers.

Abbreviations: HL, Hosmer-Lemeshow goodness of fit test with regard to the biomarker model; NRI, net reclassification improvement.
as well as development of renal failure.\textsuperscript{31,33} GDF-15 has been associated with all-cause as well as cardiovascular mortality in older clinically healthy subjects\textsuperscript{32,34,35} and to be a stronger predictor of all-cause mortality than NT-proBNP in community dwelling older adults.\textsuperscript{34} To our knowledge, the present study is the first study suggesting that GDF-15 is associated with outcome in older hip fracture patients. Given that we do not have access to plasma samples prior to the trauma we cannot determine if the increase in concentrations reflects a response to tissue injury or if the increased GDF-15 is reflects an underlying baseline pathology. The finding that GDF-15 can increase 3-fold within a few hours following a surgical trauma suggests that the former is at least a possibility.\textsuperscript{35} Taken together, our results and previous data showing an association between GDF-15 and cardiovascular complications and mortality suggest increased GDF-15 identifies a subgroup of hip fracture patients with a particularly poor prognosis. To improve outcome these patients could be considered for higher level of care and/or routine perioperative cardiovascular work-up.

Carbohydrate Antigen 125 (CA-125), which also is known as mucin\textsuperscript{16}, was described in the 1980’s and has been used clinically for some time as a tumour marker; mostly in ovarian cancer.\textsuperscript{37} Beyond malignancies CA-125 is elevated in non-cancerous conditions such as pleural effusions, peritoneal trauma, ascites and in heart failure.\textsuperscript{38} The mechanism of this rise is likely multifactorial and mechanical stress on the mesothelium in the epicardium, the pleura and the peritoneum as well as inflammatory processes may trigger it’s release.\textsuperscript{38} In recent studies serum CA-125 has been correlated to larger left atrial volume in heart failure patients\textsuperscript{39} and to confer high risk of death within 3 months in these patients.\textsuperscript{40} Interestingly Serum CA-125 levels have also been used as a treatment goal in treating heart failure patients and the patients randomized to CA-125 goal directed therapy showed fewer heart failure readmissions.\textsuperscript{41}

As mentioned above, the biologically active peptide BNP and the inactive N-terminal fragment of BNP (NT-proBNP) are both correlated to outcome in heart failure and have also been shown to predict an increase in short and long term mortality in smaller cohorts of hip fracture patients.\textsuperscript{16,17,19} Our finding that BNP and NT-proBNP were associated with the primary endpoint in the unadjusted analysis thus aligns with these previous data. Interestingly, the adjusted analysis suggests that only BNP adds predictive information to that available in the NHFS and indicates that in this setting the two biomarkers may not be used interchangeably. Interestingly, BNP has previously been suggested to be more sensitive to changes in heart function than NT-proBNP because of differences in degradation and half-lives.\textsuperscript{42,43} It is therefore possible than in hip fracture patients BNP better reflects rapid changes in heart function induced by the trauma and/or the initial treatment. However, it should be noted that we did not include heart failure as an outcome except when overt pulmonary oedema was confirmed by chest x-ray. It is in the setting of heart failure that the Natriuretic peptides have gained most clinical use.\textsuperscript{44} Our analysis indicate that several other biomarkers may be superior to BNP in hip fracture patients.

### 4.1 Limitations

The present study suffers from several limitations. This is a single centre study and given that only 64% of eligible patients were
included the external validity of our data could be questioned. However, we have previously shown that our cohort is similar to all eligible patients at our institution and to all eligible patients nationally, suggesting that our cohort is a representative sample and supporting the external validity of our results. The last patient was recruited 5 years ago and it could be argued this may limit the validity of our results in a more current setting. However, our observation that mortality in 2017 for eligible patients nationally was 7.7% compared with the national average mortality during the study period of 7.6% indicate that no major changes in care have occurred (Table 1).

Given the high number of biomarkers that was assessed in the study it could be argued that there is a high risk of false positive results. To address this concern, we corrected the logistic regression analysis for multiple comparisons by using the highly conservative Bonferroni method. However, it should be noted that we did not have access to an independent cohort and future studies will have to assess the external validity of our findings.

Another limitation is that we only sampled blood at admission. Biomarker sampling at later time points would have yielded results reflecting the overall response to both the initial trauma, the surgical trauma, the anaesthesia and other aspects of the resuscitation.

Lastly, similar to other risk scores in hip fracture patients we chose a 30-day window to assess performance of the biomarkers. It is possible that other biomarkers than those identified in the present study would be superior for risk assessment for more long-term outcomes.

4.2 | Conclusion

The results of our study exploring a large set of potential biomarkers suggest that adding GDF-15 or CA-125 to the Nottingham Hip Fracture Score improved discrimination in our dataset with regard to prediction of 30-day mortality. The value of these biomarkers should be explored in further studies to confirm clinical utility before a regular use can be recommended.

CONFLICT OF INTEREST
The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS
The following persons contributed greatly with data collection and registration: Susann Schrey, Lena Jönsson, Anne Adolfsen, Carina Lilja. We are also deeply grateful to ambulance staff of Region Skåne, emergency ward staff and the staff at the orthopaedic wards at Skåne University hospital (Lund) for recruiting patients to this study. We would like especially like to thank Tommy Schyman and Anna Åkesson for assistance with the statistical analysis.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the Supporting Information section.

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