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ORIGINAL ARTICLE

History of cardiovascular disease and cardiovascular biomarkers are associated with 30-day mortality in patients with hip fracture

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Abstract

Summary Hip fractures are associated with increased mortality and it is important to identify risk factors. This study demonstrates that preexisting cardiovascular disease as well as cardiovascular biomarkers that are associated with increased 30-day mortality. These findings can be used to identify high-risk patients who might benefit from specialized care.

Introduction This study investigates the association between cardiovascular disease (CVD), cardiovascular biomarkers, and 30-day mortality following a hip fracture.

Methods The Danish National Patient Registry was used to investigate the association between CVD and mortality following hip fracture in a nationwide population-based cohort study. In a subset of the included patients ($n = 355$), blood samples were available from a local biobank. These samples were used for analyzing the association between specific biochemical markers and mortality. The primary outcome was 30-day mortality.

Results A total of 113,211 patients were included in the population-based cohort study. Among these, heart failure was present in 9.4%, ischemic heart disease in 15.9%, and ischemic stroke in 12.0%. Within 30 days after the hip fracture, 11,488 patients died, resulting in an overall 30-day mortality of 10.1%. The 30-day mortality was significantly increased in individuals with preexisting CVD with multivariably adjusted odds ratios of 1.69 (95% confidence interval, 1.60–1.78) for heart failure, 1.23 (1.17–1.29) for ischemic heart disease, and 1.06 (1.00–1.12) for ischemic stroke. In the local database including 355 patients, 41 (11.5%) died within 30 days. The multivariably adjusted odds ratio for 30-day mortality increased with increasing NT-proBNP (2.36 [1.53–3.64] per quartile) and decreased with increasing HDL cholesterol (0.58 [0.41–0.82] per quartile). On this basis, we established a model for predicting the probability of death based on the biochemical markers.

Conclusion Preexisting CVD was associated with increased 30-day mortality after a hip fracture. Furthermore, high levels of NT-proBNP and low levels of HDL cholesterol were associated with increased 30-day mortality.

Keywords HDL-C · Heart failure · Ischemic heart disease · Ischemic stroke · NT-proBNP

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Introduction

Hip fractures are common among the elderly and they are associated with both high morbidity and mortality. Within the first month after the fracture, mortality has been reported to be as high as 16.3% [1].

Several risk factors for mortality such as high age, male gender, low body mass index (BMI), and comorbidities have been identified [2–4]. Additionally, several commonly used biochemical markers such as hemoglobin, creatinine, potassium, and sodium have been shown to be associated with mortality [5–9]. Cardiovascular diseases (CVDs) are very common among elderly hip fracture patients [3, 10] and have also been associated with an increased incidence of hip fracture [11, 12].

Several studies have indicated an association between atherosclerosis with low bone mineral density (BMD) in the hip [13–15]. Severe osteoporosis in the hip may indicate advanced atherosclerosis and thereby an increased risk of not only hip fractures but also of coronary heart disease [13].

Major surgery, including hip fracture surgery, has been associated with increased risk of major vascular complications [16]. Indeed, perioperative myocardial infarction is a severe complication that increases morbidity and mortality of patients undergoing non-cardiac surgery, e.g., orthopedic surgery [10, 16, 17]. It has been shown that the vast majority of patients undergoing non-cardiac surgery with postoperative heart failure also have preoperative heart failure [18]. Patients with preoperative heart failure are at substantially higher risk of postoperative mortality than patients with coronary artery disease [12].

The presence of CVD could thus have an impact on mortality in hip fracture patients. However, little is known about the outcome after a hip fracture in patients with CVD and about the possible utility of cardiovascular biomarkers in the prediction of mortality in hip fracture patients.

B-type natriuretic peptide (BNP) and its prohormone, N-terminal fragment of BNP (NT-proBNP), are secreted mainly by the ventricular myocytes in response to cardiac wall tension [19] and have a vasodilatory and natriuretic function. The circulating concentrations of peptides are highly increased in patients with congestive heart failure [20]. Studies have shown NT-proBNP to be useful in predicting cardiac complications after hip fracture [21–23].

Cardiac troponins T (TnT) and I (TnI) rise in response to myocardial injury [24, 25] and thus, the two biomarkers are used for diagnosing acute myocardial infarction. A few studies have demonstrated elevated cardiac troponin levels in hip fracture patients after surgery [10, 26, 27] and one study found 50% of the patients to have elevated TnT before surgery [28]. In addition, this study demonstrated that elevation of perioperative TnT levels constituted an independent predictor of mortality in hip fracture patients [28].

The purpose of this study was to investigate the association between previous CVD, cardiovascular biomarkers (NT-proBNP, TnI, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoproteins cholesterol (LDL-C)), and 30-day mortality using a nationwide population-based cohort and a local patient cohort with information on biochemical measurements. The paper aims to establish a model for predicting the probability of death based on the biochemical markers using stepwise logistic regression analysis.

Methods

Study population

The Danish National Patient Registry (NPR) [29] was used to investigate the association between history of CVD and mortality following hip fracture in a nationwide population-based cohort study based on routinely collected healthcare data. In a subset of the included patients, biological material and blood samples were available from a local hip fracture biobank from Bispebjerg Hospital (Copenhagen, Denmark). These samples from the cohort nested within the population-based cohort were used for analyzing the association between specific biochemical markers and mortality following a hip fracture.

Nationwide population-based cohort study

The Danish civil registration number (CRN) [30] is a unique 10-digit personal identifier that serves as the social security number. The CRN was used in the study to obtain information such as the date of birth, gender, and vital status. Combining the CRN with the NPR [29], information on discharge diagnoses and comorbidities was collected. All Danish patients above 18 years, sustaining a hip fracture (ICD-10 codes DS720 (femoral neck), DS721 (pertrochanteric), and DS722 (subtrochanteric)) during the period January 1st, 2000, to December 31st, 2012, were identified using the NPR and included in the study. For patients sustaining more than 1 hip fracture during the period, only the first was included and used as an index fracture for survival analysis. All hip fracture patients were included regardless of the nature of the trauma, since this information was not available for analysis.

Medical history of CVD was defined as a hospital contact due to heart failure (ICD-10: I50), ischemic heart disease (ICD-10: I20-25), or ischemic stroke (ICD-10: I63-64) within 5 years preceding the hip fracture date.

Local patient cohort study

The local biobank contains whole blood, serum, and plasma drawn preoperatively from hip fracture patients at Bispebjerg

Hospital. The samples were consecutively collected over a period of 2.5 years from 2008 to 2011 with no patient dropout, as all gave written informed consent to use the biological material for research purposes. Patients were included in the present study if their fractures had been treated surgically. Patients who died before surgery were excluded.

All samples were stored at – 80 °C and thawed immediately before performing the analyses.

All samples for each individual biomarker were analyzed as one single batch to reduce analytical variation. Plasma levels of NT-ProBNP, TC, TG, HDL-C, and LDL-C were analyzed using Cobas 8000 (Roche Diagnostics International Ltd.), blood levels of hemoglobin were analyzed using Sysmex XE-2100 (Sysmex Cooperation), and plasma levels of TnI were analyzed using Vitros 5.1 (Ortho Clinical Diagnostics). The limit of detection for TnI was 12 ng/L. Therefore, levels < 12 ng/L were coded as 11 ng/L in the analyses used for Table 1.

Data and covariates

Data on comorbidity, medication, and death were retrieved unbiasedly from national registries [29, 31]. Using ICD-10 codes, we extracted the 19 comorbidities used in the Charlson comorbidity index (CCI) [32]. The CCI was calculated using all hospital contacts prior to the hip fracture index admission. Because CVD is part of the full CCI, we subtracted points for heart failure, ischemic heart disease, and ischemic stroke before using the CCI in the regression analyses to avoid over-adjustment. In the local patient cohort, information on body mass index (BMI) was available.

The Danish National Prescription Registry (DNPR) [33] contains information on all prescription drugs sold in Denmark. Data on the following groups of pharmaceuticals (ATC codes) primarily used to treat or prevent CVD were included: beta-blockers (ATC code: C07); angiotensin-converting enzyme (ACE) inhibitors (ATC code: C09AA); diuretics including potassium-sparing diuretics (ATC code: C03D), thiazides (ATC code: C03AA), and loop diuretics (ATC code: C03C); acetylsalicylic acid (ATC code: B01AC06); clopidogrel (ATC code: B01AC04); statins (ATC code: C10AA); steroids (ATC code: H02A); and insulin (ATC code: A10A). Use was defined as at least two redeemed prescriptions for individual drugs within the last year before the fracture.

Endpoint

The primary endpoint was 30-day all-cause mortality and was ascertained using the Danish Civil Registration system.

Statistics

Baseline characteristics

The differences between continuous variables were tested using Mann-Whitney U tests. The differences in the distribution of categorical variables were tested using χ^2 test or Fisher's exact test as appropriate.

Kaplan-Meier analyses were used to examine 30-day mortality according to quartiles of NT-proBNP, TC, TG, HDL-C, TG/HDL-C ratio, and LDL-C. The differences between strata in the Kaplan-Meier analyses were tested using log-rank statistics. The distribution of TnI made it unfit for quartiles, since half of the TnI results were < 12 ng/L. Therefore, we used this level to define the first group. The rest of the results were divided into two groups according to their median. As a result, the three groups were 1, < 12 ng/L; 2, 12–34.9 ng/L; and 3, > 34.9 ng/L.

Logistic regression was used to test the association between previous CVD, preoperative biomarkers, and 30-day mortality based on odds ratios (OR) with 95% confidence intervals (CI). Analyses were either unadjusted or multivariably adjusted for age, sex, comorbidities, and BMI (only in the local cohort). p values < 0.05 were considered statistically significant.

Receiver operating characteristics (ROCs) were used to compare the relation between sensitivity and specificity of each biomarker as well as to determine the cutoff optimizing both these factors. The area under the curve (AUC) was used to compare the discriminative abilities of the biomarkers.

In order to construct a prediction model, a stepwise multivariate logistic regression was carried out. Variables with a statistically significant association with 30-day mortality were included in the model. In a stepwise manner, variables were removed one at a time from the model if p values were greater than 0.05, starting with the least significant variable. The results of the stepwise logistic regression analysis were used to assess the probability of death within 30 days after hip fracture (P_{d30}) according to the following equation:

$$ln\frac{P_{d30}}{1-P_{d30}} = \text{intercept} + \text{estimate 1} \times \text{covariate 1} + \text{estimate 2} \times \text{covaritate 2} + .$$

By isolating P_{d30} in this equation, the probability of death within 30 days after hip fracture based on the covariates can be estimated.

All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC) through a secure remote connection provided by Statistics Denmark.

Table 1 Basic characteristics in the local patient cohort

	Alive at 30 days	Dead within 30 days	*p* value
n (%)	314 (88.5%)	41 (11.5%)	NA
Age (years)	83.0 [13.4]	87.2 [7.2]	0.02
Sex (female/male)	242 (77.1%) / 72 (22.9%)	26 (63.4%) / 15 (36.6%)	0.06
BMI (kg/m^2)	22.2 [4.4]	21.1 [3.9]	0.2
CCI	1 [3]	2 [2]	0.1
ASA	2 [1]	3 [1]	0.01
Length of admission	12 [11]	9 [26]	0.01
NT-ProBNP (pmol/L)	84.6 [139.4]	247 [409]	< 0.0001
TnI (ng/L)	11 [23.7]	23.2 [44.4]	0.001
TC (mmol/L)	4.5 [1.4]	4.0 [1.6]	0.2
TG (mmol/L)	0.9 [0.5]	1.1 [0.4]	0.003
HDL-C (mmol/L)	1.6 [0.7]	1.4 [0.7]	0.002
TG/HDL-C ratio	0.6 [0.4]	0.9 [0.7]	0.0002
LDL-C (mmol/L)	2.4 [1.3]	2.3 [1.2]	0.7
Hemoglobin	7.7 [1.6]	7.3 [1.8]	0.2

Note: Values are *n* (%) or median (interquartile range [IQR]). *NA*, not applicable; *IQR*, interquartile range; *BMI*, body mass index; *CCI*, Charlson comorbidity index; *NT-proBNP*, N-terminal pro B-type natriuretic peptide; *TnI*, troponin I; *TC*, total cholesterol; *TG*, triglycerides; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol

Results

Nationwide population-based cohort study

A total of 113,211 hip fracture patients were included and of these, 77,893 were female. The median age was 81 years (interquartile range (IQR), 74–88 years). Among the hip fracture patients, heart failure was present in 9.4%, ischemic heart disease in 15.9%, and ischemic stroke in 12.0% prior to admission. Within 30 days after the hip fracture, 11,488 patients died, resulting in an overall 30-day mortality of 10.1%. For patients with known CVD, the 30-day mortality was increased compared with that in patients without CVD. The unadjusted ORs with 95% CIs were 2.46 (2.34–2.59) for heart failure, 1.75 (1.67–1.83) for ischemic heart disease, and 1.27 (1.20–1.34) for ischemic stroke. Corresponding age- and sex-adjusted ORs were 1.98 (1.88–2.09), 1.47 (1.41–1.55), and 1.18 (1.11–1.24), respectively. Adjusted for age, sex, and CCI, the ORs were 1.69 (1.60–1.78), 1.23 (1.17–1.29), and 1.06 (1.00–1.12) for heart failure, ischemic heart disease, and ischemic stroke, respectively. Figure 1 shows the ORs for 30-day mortality for CVD and for the relevant individual comorbidities from the CCI (chronic pulmonary disease, renal disease, liver disease, diabetes, dementia, malignancy, and solid metastatic tumor) as well as for age (per 5-year increase) and sex.

Local patient cohort study

This study included 355 patients. The baseline characteristics are presented in Table 1. Of the included patients, 41 (11.5%) died within 30 days. The median age at the time of the fracture, among the patients who died within 30 days (87.2 years), was significantly higher than for those who did not (83.0 years) ($p = 0.02$). Additionally, both the median ASA score and the median length of stay were significantly higher for those who died. The difference in sex between the two groups did not reach statistical significance ($p = 0.06$). Regarding the biomarkers, the concentrations of NT-proBNP, TnI, TG, and HDL-C, as well as the ratio between TG and HDL-C, were statistically different between the two groups. Table 2 shows the medical history and medication use in the local patient cohort. The presence of ischemic heart disease was greater among patients who died ($p < 0.0001$) and they had a greater use of all medications except for steroids and insulin, reaching significance for beta-blockers ($p = 0.01$) as well as diuretics ($p = 0.008$).

Unadjusted 30-day mortality Kaplan-Meier plots of the biomarkers are shown in Fig. 2, showing increased mortality with increasing quartiles of NT-proBNP, increasing levels of TnI, increasing quartiles of TG, decreasing quartiles of HDL-C, and increasing quartiles of TG/HDL-C ratio.

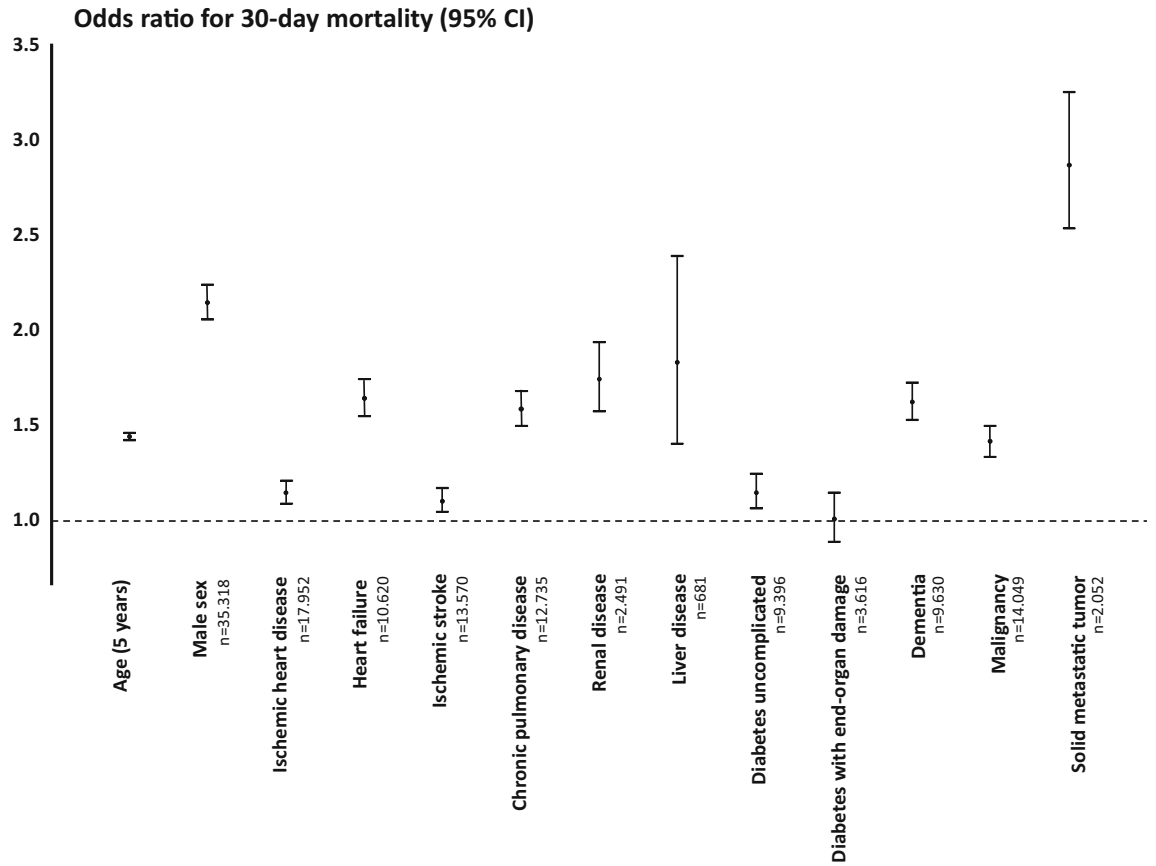

Fig. 1 Odds ratios (ORs) for 30-day mortality for cardiovascular disease (CVD) and for the relevant individual comorbidities from the Charlson comorbidity index (CCI) as well as for age (per 5-year increase) and sex. ORs are illustrated by the solid symbols and the 95% confidence intervals (CI) are illustrated as vertical lines. The dashed line at OR = 1 indicates no difference in odds for mortality. The number of patients is noted under the respective variables

NT-proBNP and 30-day mortality

The NT-proBNP levels ranged from 2.3 to 4500 pmol/L with a median (IQR) of 99.7 (164.7) pmol/L. NT-proBNP was elevated above the corresponding age and sex-dependent reference intervals in 221 patients. Of these, 90 patients (40.7%) had a history of CVD ($p = 0.003$). When analyzing the CVDs according to the NT-proBNP quartiles, we found that patients in the highest quartile (Q4) had a greater presence of heart failure ($p = 0.0002$) and ischemic heart disease ($p = 0.0001$) prior to admission than patients in the lowest quartile (Q1). No statistically significant association between the quartiles and the presence of ischemic stroke was found.

Univariate analysis revealed an almost threefold increased 30-day mortality per quartile increase of NT-proBNP (OR 2.66, 95% CI [1.81–3.93], $p < 0.0001$). Multivariable logistic regression showed that after adjusting for age, sex, CCI, and BMI, the association between 30-day mortality and increasing quartiles of NT-proBNP levels remained (OR 2.36, 95% CI [1.53–3.64], $p = 0.0001$) (Fig. 3). From the ROC analysis, the optimal cutoff was 146.2 pmol/L. In a univariate analysis using this cutoff, the unadjusted OR for 30-day mortality was 3.89 (95% CI [1.96–7.74], $p = 0.0001$). Adjusting for the same covariates as above the association between 30-day mortality and NT-proBNP (above versus below the cutoff) remained significant (OR 2.74, 95% CI [1.28–5.88], $p = 0.009$).

TnI and 30-day mortality

Half of the included patients ($n = 183$) had a TnI level > 12 ng/L at admission. Of these, 40 patients (21.9%) had a history of ischemic heart disease which was more frequent than for patients with TnI < 12 ng/L, $n = 19$ (11.0%) ($p = 0.006$).

Univariate analysis showed increased 30-day mortality per increasing TnI groups (OR 1.81, 95% CI [1.23–2.68], $p = 0.003$). However, when adjusting for age, sex, CCI, and BMI in the multivariable logistic regression, the association between 30-day mortality and elevated TnI levels disappeared (OR 0.85, 95% CI [0.92–2.22], $p = 0.1$) (Fig. 3). From the ROC analysis, the optimal cutoff was 18.5 ng/L. In a

Table 2 Medical history and medication in the local patient cohort

	Alive at 30 days	Dead within 30 days	*p* value
Medical history			
Heart failure	31 (9.9%)	8 (19.5%)	0.1
Ischemic heart disease	43 (13.7%)	16 (39.0%)	< 0.0001
Ischemic stroke	53 (6.7%)	9 (4.9%)	0.4
Chronic pulmonary disease	47 (15.0%)	7 (17.1%)	0.7
Renal disease*	12 (3.8%)	3 (7.3%)	0.3
Liver disease*	7 (2.2%)	0 (0%)	0.3
Diabetes, uncomplicated	37 (11.8%)	3 (7.3%)	0.4
Diabetes with end-organ damage	12 (3.8%)	0 (0%)	0.2
Dementia	47 (15.0%)	8 (19.5%)	0.4
Malignancy	49 (15.6%)	10 (24.4%)	0.2
Metastatic solid tumor	3 (1.0%)	1 (2.4%)	0.4
Medication			
Beta-blocker	44 (14.0%)	12 (29.3%)	0.01
ACE inhibitors	63 (20.1%)	9 (22.0%)	0.8
Diuretics	109 (34.7%)	23 (56.1%)	0.008
Acetylsalicylic acid	81 (25.8%)	16 (39.0%)	0.07
Clopidogrel	5 (1.6%)	1 (2.4%)	0.5
Statin	58 (18.5%)	8 (19.5%)	0.9
Steroid	20 (6.4%)	1 (2.4%)	0.5
Insulin	12 (3.8%)	0 (0%)	0.4

Note: Values are *n* (%). *ACE*, angiotensin-converting-enzyme. *Moderate to severe

univariate analysis using this cutoff, the unadjusted OR for 30-day mortality was 2.67 (95% CI [1.37–5.20], $p = 0.004$). Adjusting for the same covariates as above, the association between 30-day mortality and TnI (above versus below the cutoff) disappeared (OR 2.09, 95% CI [0.99–4.42], $p = 0.05$).

Lipids and 30-day mortality

Both univariate and multivariable analyses showed increasing 30-day mortality with increasing quartiles of TG (OR 1.53, 95% CI [1.12–2.09], $p = 0.008$ and OR 1.68, 95% CI [1.18–2.41], $p = 0.004$) and decreasing mortality with increasing quartiles of HDL-C (OR 0.58, 95% CI [0.41–0.82], $p = 0.002$ and OR 0.5, 95% CI [0.33–0.74], $p = 0.0007$). Neither TC nor LDL-C showed a statistically significant association with mortality (Fig. 3). A subanalysis of men separately showed no significant association between neither TG nor HDL-C with 30-day mortality whereas the association between the biomarkers and 30-day mortality for women yielded similar ORs as in the total population. A further analysis using the ratio between TG and HDL-C showed a significant association between this ratio and 30-day mortality with an unadjusted OR of 1.74 (95% CI [1.26–2.40], $p = 0.0007$) and an adjusted OR of 1.97 (95% CI [1.36–2.86], $p = 0.0003$) both per quartile increase of this ratio.

From the ROC analyses, the optimal cutoff points for the lipids were as follows: TG 1.0 mmol/L, HDL-C 1.4 mmol/L, TC 4.3 mmol/L, and LDL-C 2.4 mmol/L. For the TG/HDL-C ratio, the optimal cutoff was 0.6. Univariate analyses using these cutoffs revealed significant unadjusted ORs for 30-day mortality for TG (OR 2.78, 95% CI [1.42–5.42], $p = 0.003$), HDL-C (OR 0.36, 95% CI [0.18–0.70], $p = 0.003$), and TC (OR 0.45, 95% CI [0.23–0.86], $p = 0.02$). After adjustment for age, sex, CCI, and BMI, the association for the three biomarkers remained statistically significant with OR 3.15 (95% CI [1.51–6.60], $p = 0.002$), OR 0.31 (95% CI [0.14–0.67], $p = 0.003$), and OR 0.41 (95% CI [0.20–0.86], $p = 0.02$) for TG, HDL-C, and TC, respectively. In addition, the TG/HDL-C ratio reached significance with an adjusted OR 2.74 (95% CI [1.28–5.87], $p = 0.01$). Analyses using the cutoff for LDL-C showed no statistically significant associations with mortality.

Stepwise logistic regression

The stepwise multivariable logistic regression resulted in a final model including age, sex, NT-proBNP, HDL-C, and BMI (Table 3). TnI, TG, TC, LDL-C, and the TG/HDL-C ratio did not reach significance and were therefore not included in the model.

The results of the stepwise logistic regression analysis were used to assess the probability of death within 30 days after hip fracture (P_{d30}):

$$\ln\frac{P_{d30}}{1-P_{d30}} = -2.805 + 0.0659 \times \mathrm{AGE} + 1.3615 \times \mathrm{SEX} + 0.0008 \times \mathrm{NT-proBNP} - 1.5036 \times \mathrm{HDLC} - 0.1434 \times \mathrm{BMI}$$

where AGE is the patient age in years, SEX is coded 0 for females and 1 for males, NT-proBNP is NT-proBNP in pmol/L, HDLC is HDL-C in mmol/L, and BMI is kilograms/square meter.

By isolating P_{d30} in this equation, the probability of death within 30 days after hip fracture based on the patient's age, sex, NT-proBNP level, HDL-C, and BMI can be estimated and hence work as a risk assessment tool.

$$P_{d30} = \frac{e^{(-2.805+0.0659\times\mathrm{AGE}+1.3615\times\mathrm{SEX}+0.0008\times\mathrm{NT-proBNP}-1.5036\times\mathrm{HDLC}-0.1434\times\mathrm{BMI})}}{1+e^{(-2.805+0.0659\times\mathrm{AGE}+1.3615\times\mathrm{SEX}+0.0008\times\mathrm{NT-proBNP}-1.5036\times\mathrm{HDLC}-0.1434\times\mathrm{BMI})}}$$

Example : An 80 year old male patient with $\mathrm{NT-proBNP} = 75\ \mathrm{pmol/L}$, $\mathrm{HDL-C} = 1.3\ \mathrm{mmol/L}$ and $\mathrm{BMI} = 20$

$$P_{d30} = \frac{e^{(-2.805+0.0659\times80+1.3615\times1+0.0008\times75-1.5036\times1.3-0.1434\times20)}}{1+e^{(-2.805+0.0659\times80+1.3615\times1+0.0008\times75-1.5036\times1.3-0.1434\times20)}} = 0.28$$

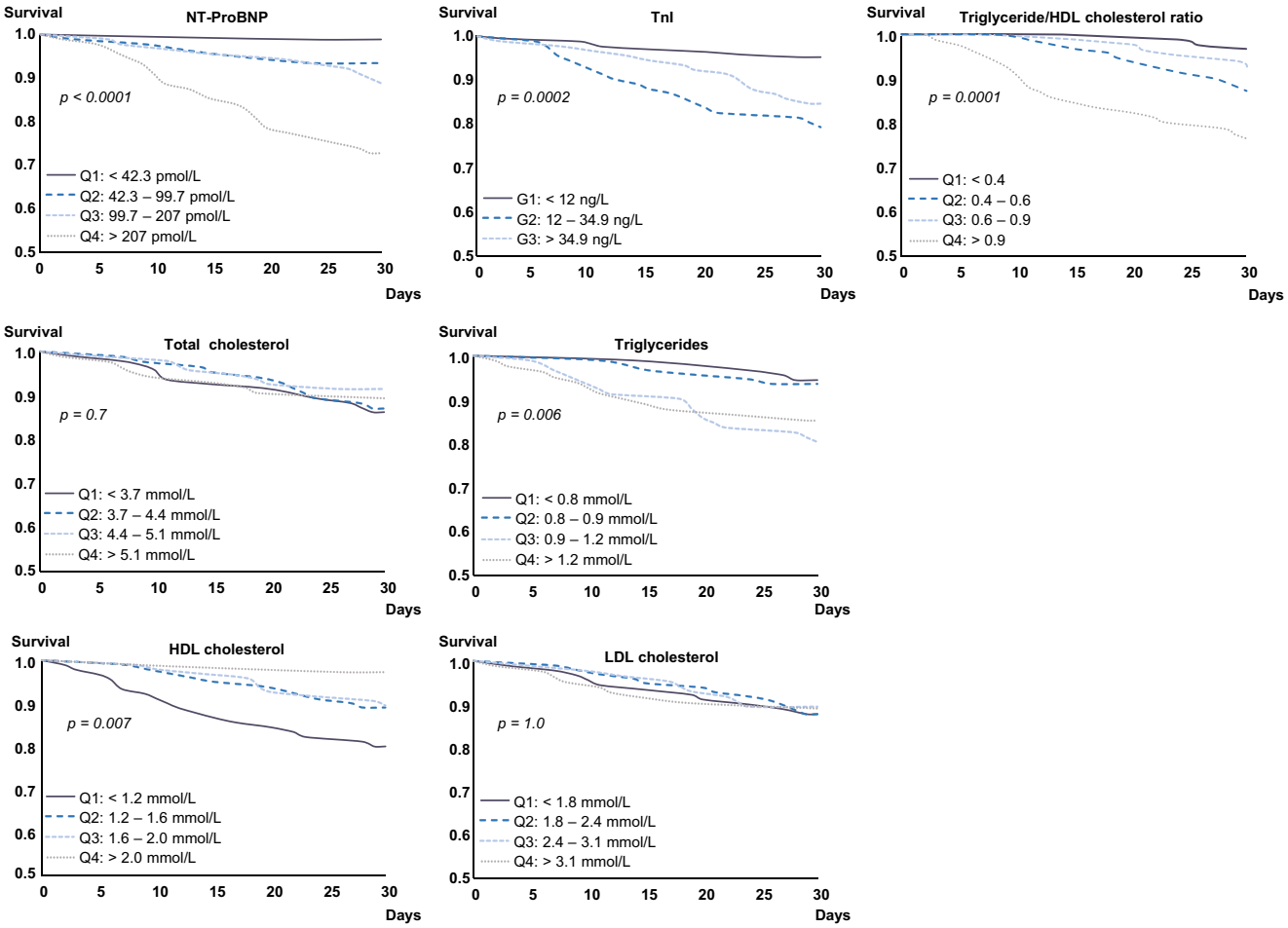

Fig. 2 Kaplan-Meier plots: 30-day mortality in relation to N-terminal pro B-type natriuretic peptide (NT-proBNP), total cholesterol, triglycerides, high-density lipoprotein (HDL), ratio between triglycerides and HDL cholesterol (TG/HDL ratio), and low-density lipoprotein (LDL) cholesterol divided into quartiles (Q1-Q4) as well as troponin I (TnI) levels divided into groups (G1–G3). Differences between the strata were tested using log-rank statistics

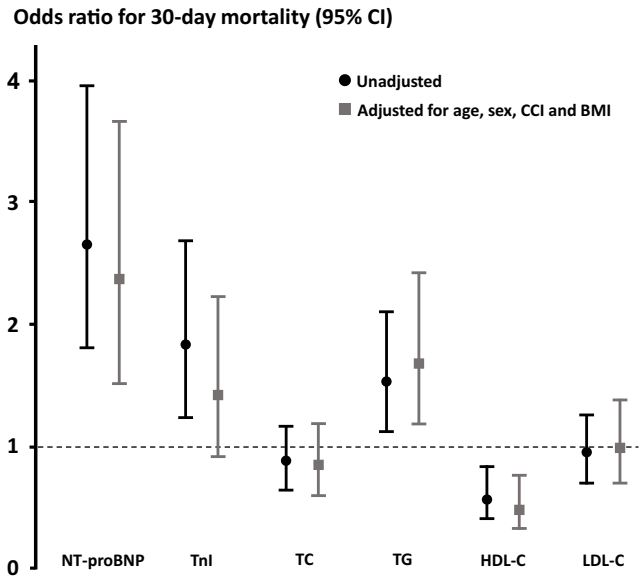

Fig. 3 Odds ratios (OR) for 30-day mortality related to N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin I (TnI), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). ORs are illustrated by the solid symbols and the 95% confidence intervals (CI) are illustrated as vertical lines. The dashed line at OR = 1 indicates no difference in odds for mortality. CCI, Charlson comorbidity index; BMI, body mass index

The risk of dying within 30 days after fracture for this patient would thus be 28% based on this algorithm.

Diagnostic performance of the individual biomarkers and the predictive algorithm

Combined ROC curves for the individual markers and the algorithm are shown in Fig. 4. The algorithm achieved the highest AUC of 0.79, slightly higher than for NT-proBNP alone (0.76). Optimizing both sensitivity and specificity in the algorithm resulted in a sensitivity as well as specificity of 65% at a cutoff of 10% risk. Accepting a specificity of only 50% would increase sensitivity to 73% at a cutoff of 6% risk.

Table 3 Final model after stepwise logistic regression

Variable	Odds ratio	95% CI	*p* value
NT-ProBNP (per 50 pmol/L)	1.04	1.01–1.07	0.01
HDL-C (mmol/L)	0.22	0.09–0.52	0.0006
Age (per 5 years)	1.39	1.12–1.73	0.003
Sex	3.90	1.66–9.15	0.002
BMI (kg/m^2)	0.87	0.77–0.98	0.02

Note: *CI*, confidence interval, *NT-ProBNP*, N-terminal pro B-type natriuretic peptide; *HDL-C*, high-density lipoprotein cholesterol; *BMI*, body mass index

Discussion

Our study shows that preexisting CVD and cardiovascular biomarkers are strong predictors of mortality within 30 days after hip fracture. The cohort study shows that the most frequent CVD among the patients was a history of ischemic heart disease; however, among the CVDs, heart failure was found to have the strongest association with increased 30-day mortality. The biobank study furthermore found that elevated plasma levels of NT-proBNP at admission were common (found in 62.3% of the patients) and associated with increased risk of 30-day mortality, supporting that heart failure is an important factor in predicting mortality. Interestingly, more than half of the patients with elevated NT-proBNP had no prior medical history of CVD.

Preexisting CVD in hip fracture patients has previously been investigated in smaller studies with findings comparable to ours. Heart failure, ischemic heart disease, and stroke have all been reported as common comorbidities in this group of patients. Indeed, CVD has been identified as a general risk factor for falls [34]. Furthermore, studies have found that patients with preexisting heart failure have a greater risk of a prolonged hospital stay and that they more often experience cardiac complications [35, 36]. In addition, patients sustaining a hip fracture often develop asymptomatic and unrecognized perioperative myocardial infarctions [10]. This was not possible to investigate in the present study since we do not have data available for postoperative follow-up or cause of death.

Only a few studies have assessed NT-proBNP levels in hip fracture patients. Two studies ($n = 262$ [36] and $n = 69$ [22]) found an association between NT-proBNP levels and cardiac complications. However, only one previous study ($n = 182$), in agreement with our findings, demonstrated that elevated perioperative NT-proBNP is an independent predictor of both short-term and long-term mortality [21]. In this study, the patients were divided into tertiles according to the NT-proBNP levels and high NT-proBNP was defined as > 2370 ng/L (corresponding to 280 pmol/L), which is somewhat higher than our cutoff for the upper quartile at 207 pmol/L. Indeed, the patients in the study generally had higher NT-proBNP levels with a median (IQR) of 1415 (2232) ng/L corresponding to 167 (347) pmol/L. In the present study, the median (IQR) was only 99.7 (164.7) pmol/L.

Triglycerides and HDL cholesterol are inversely associated and both have been associated with CVD and mortality in the general population. To our knowledge, no previous studies have investigated the association between lipids and mortality in hip fracture patients. We found a strong association between decreasing levels of HDL-C and increased risk of mortality. As low levels of HDL-C are a known risk factor for developing atherosclerotic CVD [37, 38], this supports the association of CVD with increased risk of death in elderly with hip fracture. HDL-C has several potentially anti-atherogenic

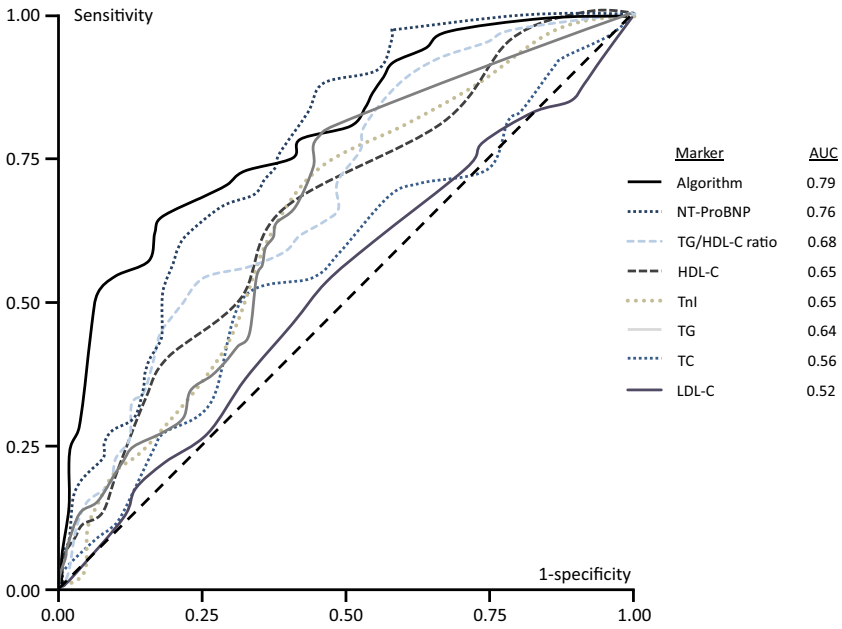

Fig. 4 Receiver operating characteristics (ROC) curves used to compare the relation between sensitivity and specificity of each biomarker used. The areas under the curve (AUC) are listed in descending order

properties, the best known of which is the ability to remove cholesterol from the cells, such as macrophages in the artery wall, in the first step of the reverse cholesterol transport pathway [39, 40], thus preventing atherosclerotic lesion progression [39]. The TG/HDL-C ratio has been found to be a potential atherogenic marker [41] as well as a strong predictor of myocardial infarction [42]. Additionally, a high TG/HDL-C ratio has been found to be a predictor of mortality from coronary heart disease and CVD in men [43]. In accordance with this, we found a significant association between 30-day mortality in hip fracture patients and increasing quartiles of TG/HDL-C ratios.

A limited number of studies have studied the occurrence of elevated cardiac troponins in hip fracture patients and report that this is associated with increased risk of cardiac complications [36] and mortality [28, 44]. In our study, half of the patients had TnI > 12 ng/L. However, we did not find a statistically significant association with mortality when performing the multivariable logistic regression analysis. Elevated levels of TnI reflect myocardial damage but this is not synonymous with coronary heart disease. Other factors are known to be associated with increased levels of cardiac troponins such as sepsis, renal failure, and rhabdomyolysis. Also, heart failure can cause acute elevations of cardiac troponins [45].

Based on the multivariable logistic regression analysis, we developed an algorithm (including age, sex, NT-proBNP, HDL-C, and BMI) as a prognostic tool for identifying patients at increased risk of 30-day mortality following hip fracture. Several other scoring systems have been used to predict 30-day mortality following hip fracture surgery. The study by Karres et al. [46] compared six of these, finding AUCs in ROC analyses of 30-day mortality ranging from 0.69 for O-POSSUM [47] to 0.78 for the model developed by Jiang et al. [48]. The latter AUC is similar to the one found in this study (0.79). However, the two scoring systems are very different. The model by Jiang et al. is based on a long range of comorbidities such as chronic obstructive lung disease, malignancies, renal failure, heart disease, and arrhythmias, whereas the algorithm developed in the present study focuses primarily on cardiovascular biomarkers. A higher prediction might be achieved combining factors from all these risk models. However, it is important to keep such algorithms as simple and as easy to use as possible to facilitate the identification of patients who could potentially benefit from an intensified perioperative care.

With our study, we have demonstrated that preexisting CVD is associated with an increased risk of mortality in patients sustaining a hip fracture. This is supported by the biochemical results. The specific cause of death is still unknown; however, one possible cause could be a worsening of preexisting CVD due to the trauma sustained or the following prolonged period of immobilization. Indeed, the initial fall leading to the hip fracture could for some patients be due to preexisting CVD, making these patients more susceptible to a negative outcome. In fact, a recent review demonstrated that several CVDs were associated with falls, including low blood pressure, heart failure, and arrhythmia [49]. This is supported by the fact that the patients, who died within 30-days, used more cardiovascular medications.

Strength and limitations

This study is partly based on routinely collected health care data from nationwide Danish registries. These registers,

unfortunately, do not contain information on possible confounders such as smoking habits, alcohol consumption, and BMI. Due to the observational nature of the study, we cannot exclude the possibility that the associations with 30-day mortality are due to residual confounding despite adjustment for different covariates.

Further, the biobank only contains 1 sample from each patient. Thus, we had no opportunity to evaluate the progression of the biomarkers over time. Clinical information on newly diagnosed CVDs and treatment during admission were not available either. However, the aim of this study was not to determine if there was a causal relationship between CVD and mortality or to assess the development of cardiovascular events during hospitalization. Rather, we intended to investigate the degree of excess mortality in individuals with preexisting CVD and the association between specific cardiovascular biomarkers and mortality.

Another limitation of this study is the retrospective design. Additionally, the Danish Register of Causes of Death is very useful for investigating all-cause mortality. However, the data on causes of death are, unfortunately, not of a high quality. In Denmark, the autopsy rate is only around 10%. Hence, the quality of data on causes of death relies mainly upon the correctness of the physicians' notification [31]. Furthermore, the registration and coding have changed over time and, as the mortality statistics are not regularly validated, we did not use this data in the present study.

Finally, the validity of the diagnoses available from the NPR depends on the coding process. Data completeness depends on hospitalization patterns and diagnostic accuracy [50], which may be considered a limitation of NPR. Risk of misclassification could be a potential risk of information bias.

The strengths of this study are the large number of patients included, the biobank material available for analysis, and the ability to use CRN [30]. The latter provides a unique opportunity to gather information on comorbidities and time of death as well as to avoid any lost to follow-up by combining the national registers via the CRN.

Conclusion

In this study, we demonstrate that previous CVD is associated with increased 30-day mortality in patients with hip fracture. This is supported by the biochemical results, showing that high levels of NT-proBNP and low levels of HDL-C are associated with increased 30-day mortality.

Authors' contributions All authors have contributed significantly to the manuscript. Study design: All authors. Processing and preparation of raw data for subsequent analyses: HLJ. Preparation of biobank material: DNA. Data analysis: DNA, CMM, and HLJ. Interpretation of data: All authors. Drafting of the manuscript: DNA. Critical review of the manuscript for intellectual content and approval of the final version: All authors. Guarantor: DNA.

Compliance with ethical standards

This study was approved by the Danish Data Protection Agency (2012-58-0004)/local number BBH-2014-050, by Statistics Denmark (project number 704670) and by the ethics committee of the Capital Region of Denmark (H-B-2007-103 / 61361).

Conflicts of interest None.

Human and animal rights and informed consent Most of the data is derived from registers and the data was anonymized prior to our use. In this case, informed consent from the individual patients is not required according to Danish law. Informed consent was obtained for all the patients included in the biobank. Animals were not used in this study.

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