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Predicting the outcome of hip fracture patients by using N-terminal fragment of pro-B-type natriuretic peptide

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Key words: NT-proBNP, troponin T, hip fracture, prognosis, mortality.

Word count: 2516

ABSTRACT

Objective: To examine the prognostic value of perioperative N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) in hip fracture patients.

Design: Blinded prospective cohort study.

Setting: Single centre trial at Turku University Hospital in Finland.

Participants: Inclusion criterion was admittance to the study hospital due to hip fracture during the trial period of October 2009 - May 2010. Exclusion criteria were the patient's refusal and inadequate laboratory tests. The final study population consisted of 182 patients**.**

Primary and secondary outcome measures: NT-proBNP was assessed once during the perioperative period and later if clinically indicated, and troponin T (TnT) and ECG recordings repeatedly. The short- (30-day) and long-term (1000-days) mortalities were studied.

Results: Median [IQR] follow-up time was 3.1 [0.3] years. The median [IQR] NT-proBNP level was 1260 [2298] ng/l in preoperative and 1600 [3971] ng/l in postoperative samples (P=0.001). TnT was elevated in 66 (36 %) patients, and was significantly more common in patients with higher NT-proBNP. Patients with high (>2370 ng/L) and intermediate (806 – 2370 ng/L) NT-proBNP level had significantly higher short-term mortality compared to patients with low (<806 ng/L) NT-proBNP level (15 vs. 11 vs. 2 %, P=0.04), and the long-term mortality remained higher in these patients (69 % vs. 49 % vs. 27 %, P<0.001). Intermediate or high NT-proBNP level (HR 8.30, 95%Cl 1.10-62.57, P=0.04) was the only independent predictor of short-term mortality, while intermediate or high NT-proBNP level (HR 3.23, 95%CI 1.80-5.80, P<0.001), the presence of dementia (HR 2.28, 95%CI 1.45-3.56, P<0.001) and higher preoperative ASA classification (HR 2.44, 95%CI 1.59-3.74, P<0.001) were independent predictors of long-term mortality.

Conclusions: Elevated perioperative NT-proBNP level is common in hip fracture patients and it is an independent predictor of short- and long-term mortality superior to the commonly used clinical risk scores.

Trial registration: www.ClinicalTrials.gov, identifier NCT01015105.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of our knowledge, there is no prior data on the combined effect of TnT and NT-proBNP on top of clinical preoperative risk evaluation in hip fracture patients.

-All consecutive patients admitted to hospital due to an acute hip fracture during the trial period were initially included in the study and the only exclusion criteria were the patient's refusal and inadequate laboratory testing.

-Complete follow-up data was available of all the study patients

-The blinded setting of the trial prevents acquiring information on the effect of possible pharmacological treatment on the outcome

INTRODUCTION

History of cardiovascular diseases and heart failure is common amongst hip fracture patients.(1, 2) However, clinical preoperative cardiac risk assessment of hip fracture patients is often complicated and inaccurate and can lead to delays in surgery.(3) This has led to search for alternative ways to identify patients at high risk for complications. Brain natriuretic peptide (BNP) is a vasoactive hormone secreted mainly by the ventricular myocytes in response to cardiac wall tension,(4, 5) and the level of the N-terminal fragment of its prohormone (NT-proBNP) correlates with the extent of ventricular dysfunction.(6) Increased preoperative BNP and NT-proBNP levels have been shown to predict cardiovascular complications in non-cardiac surgery.(7-12) An earlier small study on orthopaedic patients has found preoperative BNP elevation to be superior to American Society of Anesthesiologists' (ASA) physical status classification in independently predicting postoperative cardiac complications.(13) Increased preoperative NT-proBNP has also been shown to independently predict short-term cardiovascular complications and cardiac death in non-cardiac surgery,(9, 14) and in older patients high perioperative NT-proBNP has also predicted long-term mortality.(7) However, to our knowledge only one small study has assessed the role of NT-proBNP in the prediction of peri- and early postoperative cardiac complications in high-risk hip fracture patients.(8) We recently showed that troponin T (TnT) is a strong independent predictor of short- and long-term mortality in hip fracture patients,(15) but there is no data on the combined effect of TnT and NT-proBNP on top of

clinical preoperative risk evaluation in hip fracture patients. The purpose of this study was to evaluate whether NT-ProBNP together with TnT provides useful additive prognostic information on the short- and long-term outcome of unselected hip fracture patients.

METHODS

The study (www.ClinicalTrials.gov, identifier NCT01015105) is part of a wider protocol in progress to assess thrombotic and bleeding complications of invasive procedures in Western Finland.(16-18) All consecutive hip fracture patients referred to Turku University hospital during a period of 6 months (from October 19th 2009 to May 19th 2010) were asked consent to be included in this study. One patient declined. This resulted in 200 consecutive hip fracture patients. NT-proBNP measurements were missing in 18 patients and these were excluded and the final study population consisted of 182 hip fracture patients. An anaesthesiologist clinically evaluated the patients preoperatively. A lumbar epidural catheter was placed for pain control, and the patients received a mixture of a local anaesthetic and opiate from the admission to the second postoperative morning. A chest x-ray study and basic blood chemistry tests were performed on admission and later according to the clinical need. The patients were operated under spinal anaesthesia with isobaric bupivacaine. Significant postoperative blood loss was substituted with red blood cell transfusions. Hypotension (blood pressure <100/60) was treated with rapid fluid challenge, vasopressors and atropine as appropriate. Patient's cardiac medications (excluding diuretics) were continued throughout the hospital period. Blinded NT-proBNP measurements were performed once during the hospitalization. Blinded TnT measurements and ECG recordings were performed on admission, before operation and on 1st and 2nd postoperative days. Physicians were unaware of these results but additional tests were performed when clinically indicated.

NT-ProBNP and TnT levels were determined by electrochemiluminescence immunoassay (ECLIA) on Modular E170 automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany), which detects a NT-proBNP level of ≥50 ng/l. The patients were divided into tertiles according to the measured NT-proBNP level. When multiple NT-proBNP measurements were available, the highest of them was

considered. The recommended diagnostic threshold of 0.03 µg/l was used to evaluate TnT elevation. Data on medical history, medication and cardiac risks were collected from the electronic medical records. These data were also used to evaluate the Revised Cardiac Risk Index value (RCRI, the Lee's score) for each patient.(19) Furthermore, each patient was assigned an ASA physical status class. The patients were followed until April 2013. The Ethics Committee of the Hospital District of Southwest Finland reviewed and approved the study protocol, all study patients gave their informed consent and the principles of the Helsinki declaration were followed.

Normality was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Skewed variables presented as median and interquartile range [IQR], and categorical variables as percentage. ANOVA, Mann-Whitney U-test and Chi-square test were used for comparison of variables as appropriate. Survival analysis was performed using Kaplan-Meier's method and Cox proportional hazards method. A Cox regression analysis with backward selection was performed to analyse the independent predictors of short- and long-term mortality. A p-value < 0.05 was considered statistically significant. All computations were carried out with SPSS software (V22, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics are presented in Table 1. Median [IQR] age of the patients was 84 [11] years. A history of heart failure was known in 26 (14 %) patients and coronary artery disease in 56 (31 %). Surgery was performed on the day of admission in 34 (19 %) patients, 1 day after admission in 109 (60 %), 2 days after admission in 24 (13 %) and 3-5 days after admission in 12 (7 %) patients. One patient died before the operation.

Table 1. Baseline clinical characteristics of the study population

Variable	All patients	NT-proBNP level			*P*-value
		Low	Intermediate	High	
	n = 182	n = 60	n = 61	n = 61	
NT-proBNP level	1415 [2932]	441 [342]	1390 [860]	5170 [6045]	

Men	59 (32 %)	20 (33 %)	18 (30 %)	21 (34 %)	0.83
Age (years)	81.2 ± 11.0	74.7 ± 12.8	83.0 ± 9.2	85.8 ± 7.4	<0.001
History of any cardiovascular disease	130 (71 %)	36 (60 %)	43 (70 %)	51 (83 %)	0.02
History of heart failure	26 (14 %)	3 (5 %)	5 (8 %)	18 (30 %)	<0.001
Coronary artery disease	56 (31 %)	12 (20 %)	19 (31 %)	25 (41 %)	0.04
Prior myocardial infarction	19 (10 %)	3 (5 %)	6 (10 %)	10 (16 %)	0.12
Prior coronary revascularization	14 (8 %)	2 (3 %)	4 (7 %)	8 (13 %)	0.12
Hypertension	91 (50 %)	22 (37 %)	31 (51 %)	38 (62 %)	0.02
Diabetes mellitus	32 (18 %)	10 (17 %)	9 (15 %)	13 (21 %)	0.62
Atrial fibrillation	39 (21 %)	3 (5 %)	10 (16 %)	26 (43 %)	<0.001
Renal failure	10 (6 %)	0 (0 %)	1 (2 %)	9 (15 %)	<0.001
Dementia	73 (40 %)	16 (27 %)	32 (53 %)	25 (41 %)	0.02
Prior TIA or stroke	30 (17 %)	11 (18 %)	11 (18 %)	8 (13 %)	0.68
Preoperative ASA class	2.28 ± 0.82	2.05 ± 0.87	2.23 ± 0.82	2.56 ± 0.70	0.002
Revised cardiac risk index	0.72 ± 0.91	0.53 ± 0.83	0.64 ± 0.86	0.98 ± 0.99	0.017
Preoperative haemoglobin	113 ± 17	116 ± 14	111 ± 16	113 ± 19	0.32
Received red blood cell units	1.51 ± 1.53	1.68 ± 1.70	1.66 ± 1.54	1.18 ± 1.30	0.125
Perioperative TnT elevation	66 (36 %)	7 (12 %)	18 (30 %)	41 (67 %)	<0.001

Data are presented as median [IQR], count (%) or mean ± standard deviation. NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; TIA, transient ischaemic attack; ASA class, American Society of Anesthesiologists' physical status classification; Revised cardiac risk index, Lee's score.

NT-ProBNP was measured during hospitalization in all 182 patients, preoperatively in 117 (64 %) and postoperatively in 86 (47 %) patients; in 96 patients preoperative only, in 21 both pre- and postoperatively and in 65 postoperatively only. NT-ProBNP levels ranged from 50 to 72100 ng/l, with a median [IQR] of 1415 [2932] ng/l. The median [IQR] NT-proBNP level was 1260 [2298] ng/l in preoperative samples and 1600 [3971] ng/l in postoperative samples (P = 0.001). Those 21 patients who had both pre- and postoperative NT-proBNP measurements had a median preoperative proBNP level of 2220 [2964] ng/l and postoperative proBNP level of 3370 [5520] ng/l (P = 0.001). Comparison of the NT-ProBNP tertiles is presented in Table 1. There was no significant gender difference in NT-proBNP levels. Increasing age, history of hypertension, coronary artery disease, atrial fibrillation, heart failure, renal failure and

dementia were significantly associated with higher NT-proBNP levels. However, high NT-proBNP levels were detected even in patients with no prior cardiac morbidity, and 10 (16 %) patients in the highest NT-proBNP tertile had no history of cardiovascular diseases. Multivariate logistic regression showed that age, renal failure and atrial fibrillation were the independent predictors of higher NT-proBNP. Chest x-ray showed signs of congestive heart failure already on admission to hospital in 1 (2 %) patient with low NT-proBNP (<806 ng/L), in 2 (3 %) patients with intermediate NT-proBNP (806 – 2370 ng/L) and in 5 (8 %) patients with high NT-proBNP (>2370 ng/L). Median [IQR] duration of hospitalization was 6.0 [4.0] days and there was no difference in the duration between patients with low vs. intermediate vs. high NT-proBNP.

TnT was elevated in 7 (12 %) patients with low NT-proBNP, in 18 (30 %) patients with intermediate NT-proBNP and in 41 (67 %) patients with high NT-proBNP (P < 0.001).

Cardiac symptoms were infrequent in all NT-proBNP groups during hospitalization. Shortness of breath was experienced by 10 (17 %) patients with low, 10 (16 %) patients with intermediate, and 19 (31 %) patients with high NT-proBNP (P = 0.08) and chest pain by 2 (3 %) vs. 2 (3 %) vs. 3 (5 %) (P = 0.87). Disorientation was observed in 23 (38 %) vs. 36 (59 %) vs. 46 (75 %) of the patients in low, intermediate and high NT-proBNP groups, respectively (P < 0.001).

At 30 days follow-up, 17 (9 %) patients had died (Table 2).

Table 2. Comparison of the patients who died within 30 days of hospital admission and patients who survived.

Variable	Died during 30 days n = 17	Alive after 30 days n = 165	*P*-value
NT-ProBNP level	2700 [10435]	1230 [2736]	0.01
Men	9 (53 %)	50 (30 %)	0.058
Age (years)	84.7 ± 6.3	80.8 ± 11.4	0.17
History of any cardiovascular disease	15 (88 %)	115 (70 %)	0.11
History of heart failure	2 (12 %)	24 (15 %)	0.76
Coronary artery disease	5 (29 %)	51 (31 %)	0.90
Prior myocardial infarction	3 (18 %)	15 (9 %)	0.31
Prior coronary revascularization	2 (12 %)	12 (7 %)	0.51

Hypertension	10 (59 %)	81 (49 %)	0.45
Diabetes mellitus	6 (35 %)	26 (16 %)	0.04
Atrial fibrillation	6 (35 %)	33 (20 %)	0.14
Renal failure	2 (12 %)	8 (5 %)	0.23
Dementia	9 (53 %)	64 (39 %)	0.26
Prior TIA or stroke	2 (12 %)	28 (17 %)	0.58
Preoperative ASA score	2.5 ± 0.6	2.3 ± 0.8	0.20
Revised cardiac risk index	0.8 ± 1.0	0.7 ± 0.9	0.83
Perioperative troponin T elevation	11 (65 %)	55 (33 %)	0.01

Data are presented as median [IQR], count (%) or mean ± standard deviation. NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; TIA, transient ischemic attack; ASA class, American Society of Anesthesiologists' physical status classification; Revised cardiac risk index, Lee's score.

Patients with high and intermediate NT-proBNP had significantly higher 30-day mortality compared to patients with low NT-proBNP (15 % vs. 11 % vs. 2 %, P = 0.04), as shown in figure 1. The patients who died during the first 30 days had a median [IQR] proBNP level of 2700 [10435] ng/l compared to 1230 [2736] ng/l in patients who survived the first 30 days (P = 0.002). Out of the patients with no TnT elevation, 5 % died during the first 30 days; no patients with low proBNP vs. 6 (10 %) of the patients with intermediate or high NT-proBNP (P = 0.02). Of the 66 patients with a perioperative TnT elevation 11 (17 %) died during the first 30 days, with no difference in mortalities regarding the NT-proBNP levels in these patients. Intermediate/high vs. low NT-proBNP levels (HR 8.30, 95%Cl 1.10-62.57, P = 0.04) remained the only independent predictor of short-term mortality in a Cox regression model including age, renal impairment, TnT elevation, NT-proBNP levels, ASA and Lee scores.

Complete follow-up data up to 1000 days was available in all 182 patients. Median [IQR] follow-up time was 3.12 [0.28] years. The overall mortality at 1000 days was 48 % (Table 3).

Table 3. Comparison of the patients who died within 1000 days of hospital admission and patients who survived.

Variable	Died during 1000 days n = 88	Alive after 1000 days n = 94	*P*-value
NT-ProBNP level	2295 [4403]	913 [1679]	<0.001

Men	32 (36 %)	27 (29 %)	0.27
Age (years)	84.1 ± 9.7	78.5 ± 11.6	<0.001
History of any cardiovascular disease	71 (81 %)	59 (63 %)	0.008
History of heart failure	18 (20 %)	8 (9 %)	0.02
Coronary artery disease	34 (39 %)	22 (23 %)	0.03
Prior myocardial infarction	11 (13 %)	8 (9 %)	0.38
Prior coronary revascularization	9 (10 %)	5 (5 %)	0.21
Hypertension	48 (55 %)	43 (46 %)	0.24
Diabetes mellitus	18 (20 %)	14 (15 %)	0.33
Atrial fibrillation	27 (31 %)	12 (13 %)	0.003
Renal failure	7 (8 %)	3 (3 %)	0.16
Dementia	45 (51 %)	28 (30 %)	0.003
Prior TIA or stroke	17 (19 %)	13 (14 %)	0.32
Preoperative ASA score	2.6 ± 0.7	2.0 ± 0.8	<0.001
Revised cardiac risk index	0.9 ± 1.0	0.6 ± 0.9	0.02
Troponin T elevation	40 (45 %)	26 (28 %)	0.01

Data are presented as median [IQR], count (%) or mean ± standard deviation. NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; TIA, transient ischemic attack; ASA class, American Society of Anesthesiologists' physical status classification; Revised cardiac risk index, Lee's score.

The mortality remained constantly higher in patients with high and intermediate NT-proBNP compared to patients with low NT-proBNP (69 % vs. 49 % vs. 27 %, $P < 0.001$), as shown in figure 2. Intermediate/high NT-proBNP levels (HR 3.23, 95%CI 1.80-5.80, P < 0.001), the presence of dementia (HR 2.28, 95%CI 1.45-3.56, P<0.001) and higher preoperative ASA class (HR 2.44, 95%CI 1.59-3.74, P < 0.001) remained independent predictors of long-term mortality in a Cox regression model including NT-proBNP levels, TnT elevation, age, renal impairment, the presence of dementia, atrial fibrillation and coronary artery disease, preoperative ASA and Lee's scores. Intermediate/high NT-proBNP (HR 2.78, 95%CI 1.42-5.46, P = 0.003) and preoperative ASA class (HR 2.91, 95%CI 1.70-4.98, P < 0.001) were the independent predictors of

1000-day mortality in patients with no perioperative TnT elevation, but in patients with a perioperative TnT elevation NT-proBNP did not carry significant predictive value.

DISCUSSION

The present study showed that high NT-proBNP levels are common in hip fracture patients, and that there is a significant graded association between increasing NT-proBNP level and short- and long-term mortality. Furthermore, measurement of this natriuretic peptide provided useful independent prognostic information on top of currently used risk scores and troponin levels. While perioperative NT-proBNP level was the only independent predictor of short-term mortality, perioperative NT-proBNP level, preoperative ASA class and the presence of dementia were independent predictors of long-term mortality. Of note, none of the clinical characteristics of the patients or currently used risk scores provided useful information on the short-term mortality in these fragile acute patients.

When patients with a perioperative TnT elevation were analysed separately, the short-term mortality was not affected by the perioperative NT-proBNP level, but the long-term mortality was higher if the patient also had high NT-proBNP level. However, high NT-proBNP level did not remain a significant predictor of long-term mortality in this relatively small patient group with a poor overall prognosis.

In elective non-cardiac surgery, a low NT-proBNP level of 201 ng/l has been shown to have a high sensitivity and specificity to predict perioperative cardiovascular complications,(9) while in emergency orthopaedic surgery patients a preoperative NT-proBNP level of ≥741 - 842 ng/l was the best cut-off level in evaluating the risk of in-hospital and long-term cardiac complications.(7, 20) In line with these observations the best cut-off level for the prediction of short-term mortality was low also in this old patient group with frequent co-morbidities, and most of the difference in short-term mortality was observed already between the low and intermediate NT-proBNP groups. The increase in long-term mortality between the NT-proBNP groups was, however, more stable and not unexpectedly dementia and poor ASA group were the other independent predictors of long-term mortality.

Unexpectedly, some patients with no prior history of cardiovascular diseases or renal failure had a high NT-proBNP level supporting the view that major trauma and surgery, or heavy use of intravenous fluids in the perioperative period may cause stress on the heart and lead to elevated NT-proBNP levels. High co-incidence of TnT elevation also suggests that a perioperative myocardial injury is a major cause of elevated NT-proBNP levels in this patient group.

To our knowledge there has only been one earlier study assessing NT-proBNP levels in hip fracture patients. In this study of only 69 frail hip fracture patients with a high ASA class preoperative NT-proBNP level exceeding 3984 ng/l was an independent predictor of perioperative cardiac complications, but did not find an association between increased NT-proBNP and mortality at 3 months follow-up.(8) On the contrary to these findings, our study showed that high NT-proBNP is an independent predictor of both short- and long-term mortalities, and that there is 5-fold increase in short-term mortality already at NT-proBNP level exceeding 805 ng/l.

This study has some limitations that should be considered. The study population of 182 patients, although bigger than in earlier similar studies, is relatively small. Secondly, the idea was to obtain NT-proBNP samples preoperatively in all patients, but due to weekends and public holidays, preoperative tests were obtained in 64 % of the patients only. Since this was a blind evaluation it is not possible to assess how pharmacological treatments may have affected the outcome. The strengths of this study are the prospective nature of the registry, inclusion of all consecutive hip fracture patients and complete follow-up data of all 182 patients.

In conclusion, elevated perioperative NT-proBNP level is common in surgically treated hip fracture patients and an independent predictor of short- and long-term mortality superior to the commonly used clinical risk scores, and an efficient tool in detecting the patients in greater risk of death. Measurement of NT-proBNP and TnT in hip fracture patients could lead to the detection of patients at high risk of early and later death after the operation. The prognosis of high risk patients might be improved with appropriate cardiac care especially in those patients with no previous cardiovascular history or medications.

AUTHOR CONTRIBUTION

All authors participated in designing this study. MS recruited the patients. NS operated on the patients. PN collected the data. PN and TK analyzed the data and PN, TK, MS and KEA interpreted the data. PN wrote the first draft and all other authors reviewed it and provided further contributions and suggestions. All authors read and approved the final version.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pd and declare: authors had financial support from the Finnish Foundation for Cardiovascular Research for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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DATA SHARING

Data is available upon request to the corresponding author.

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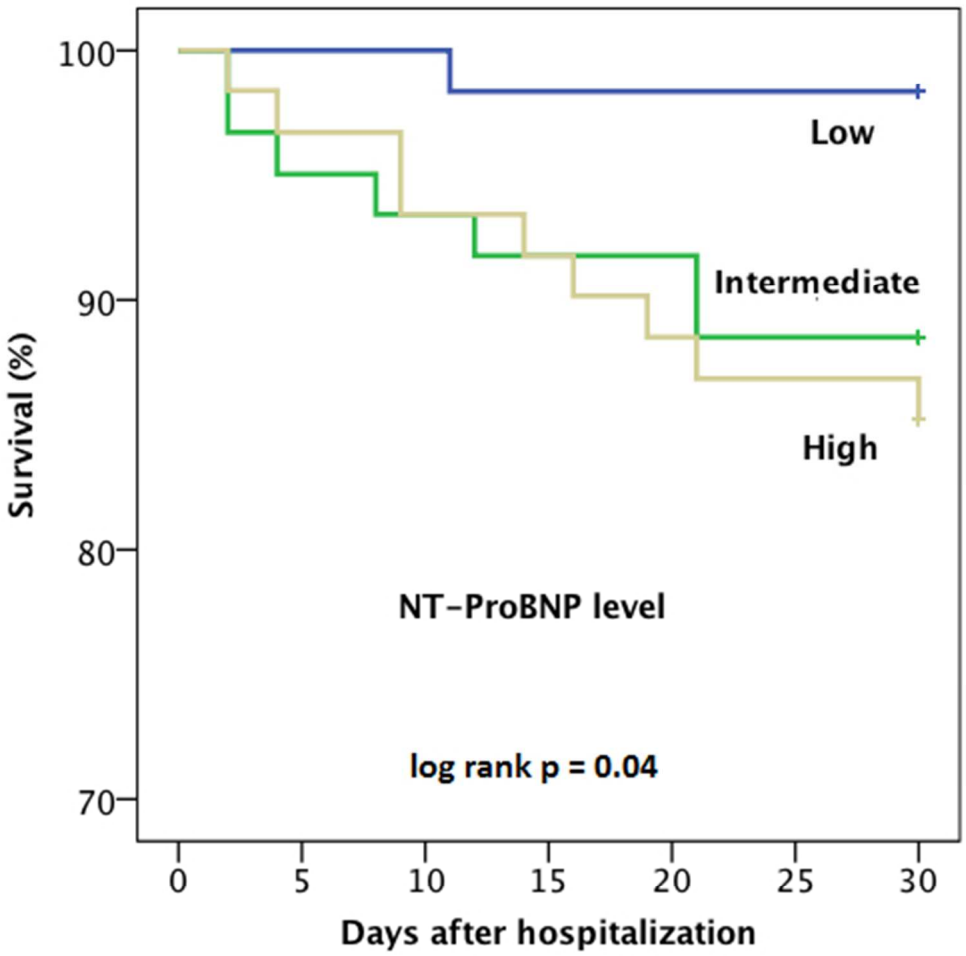
LEGENDS

Figure 1. Kaplan-Meier estimates for survival in 30 days follow-up in patients with low, intermediate and high NT-proBNP level during index hospitalization.

Figure 2. Kaplan-Meier estimates for survival in 1000 days follow-up in patients with low, intermediate and high NT-proBNP level during the index hospitalization.



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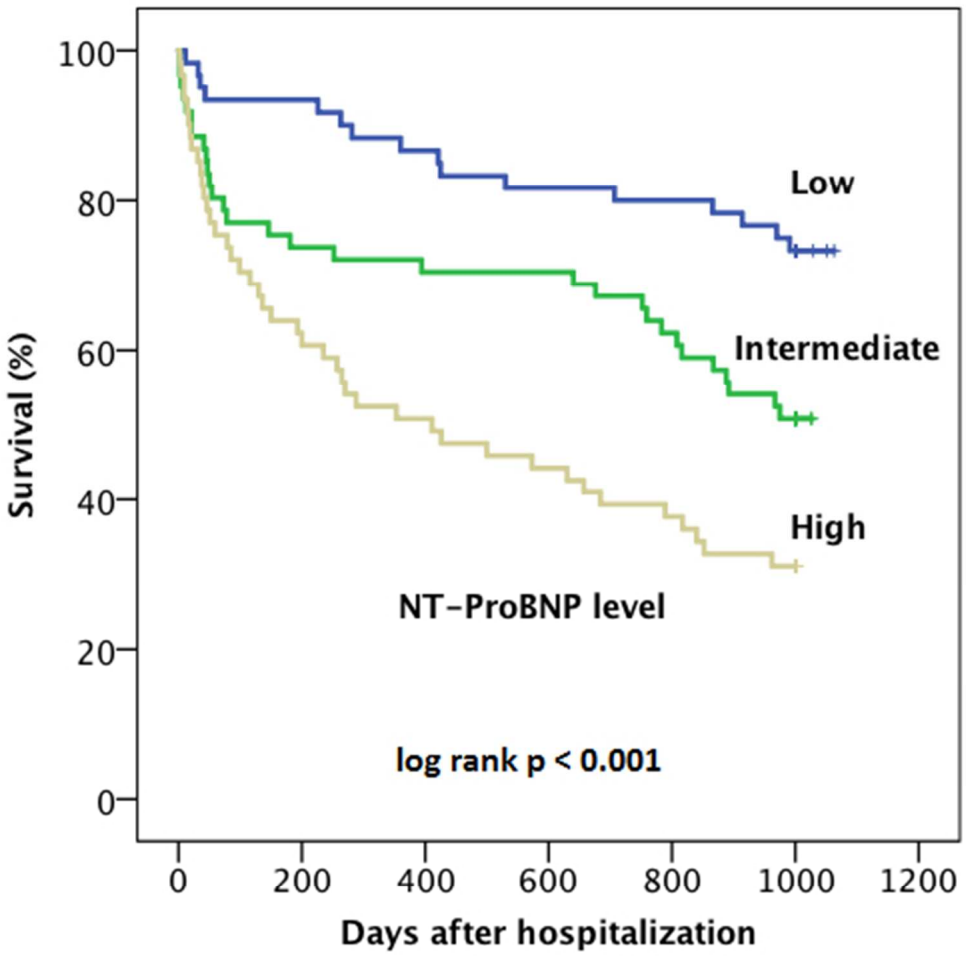

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-5
		(b) Indicate number of participants with missing data for each variable of interest	4-7
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predicting the outcome of hip fracture patients by using N-terminal fragment of pro-B-type natriuretic peptide

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Predicting the outcome of hip fracture patients by using N-terminal fragment of pro-B-type natriuretic peptide

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Key words: NT-proBNP, troponin T, hip fracture, prognosis, mortality.

Word count: 2516

ABSTRACT

Objective: To examine the prognostic value of perioperative N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) in hip fracture patients.

Design: Blinded prospective cohort study.

Setting: Single centre trial at Turku University Hospital in Finland.

Participants: Inclusion criterion was admittance to the study hospital due to hip fracture during the trial period of October 2009 - May 2010. Exclusion criteria were the patient's refusal and inadequate laboratory tests. The final study population consisted of 182 patients**.**

Primary and secondary outcome measures: NT-proBNP was assessed once during the perioperative period and later if clinically indicated, and troponin T (TnT) and ECG recordings repeatedly. The short- (30-day) and long-term (1000-days) mortalities were studied.

Results: Median [IQR] follow-up time was 3.1 [0.3] years. The median [IQR] NT-proBNP level was 1260 [2298] ng/l in preoperative and 1600 [3971] ng/l in postoperative samples (P=0.001). TnT was elevated in 66 (36 %) patients, and was significantly more common in patients with higher NT-proBNP. Patients with high (>2370 ng/L) and intermediate (806 – 2370 ng/L) NT-proBNP level had significantly higher short-term mortality compared to patients with low (<806 ng/L) NT-proBNP level (15 vs. 11 vs. 2 %, P=0.04), and the long-term mortality remained higher in these patients (69 % vs. 49 % vs. 27 %, P<0.001). Intermediate or high NT-proBNP level (HR 7.8, 95%Cl 1.03-59.14, P<0.05) was the only independent predictor of short-term mortality, while intermediate or high NT-proBNP level (HR 2.27, 95%CI 1.30-3.96, P=0.004), the presence of dementia (HR 1.74, 95%CI 1.13-2.66, P=0.01) and higher preoperative ASA classification (HR 1.59, 95%CI 1.06-2.38, P=0.02) were independent predictors of long-term mortality.

Conclusions: Elevated perioperative NT-proBNP level is common in hip fracture patients and it is an independent predictor of short- and long-term mortality superior to the commonly used clinical risk scores.

Trial registration: www.ClinicalTrials.gov, identifier NCT01015105.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of our knowledge, there is no prior data on the combined effect of TnT and NT-proBNP on top of clinical preoperative risk evaluation in hip fracture patients.

-All consecutive patients admitted to hospital due to an acute hip fracture during the trial period were initially included in the study and the only exclusion criteria were the patient's refusal and inadequate laboratory testing.

-Complete follow-up data was available of all the study patients

-The blinded setting of the trial prevents acquiring information on the effect of possible pharmacological treatment on the outcome

INTRODUCTION

History of cardiovascular diseases and heart failure is common amongst hip fracture patients.(1, 2) However, clinical preoperative cardiac risk assessment of hip fracture patients is often complicated and inaccurate and can lead to delays in surgery.(3) This has led to search for alternative ways to identify patients at high risk for complications. Brain natriuretic peptide (BNP) is a vasoactive hormone secreted mainly by the ventricular myocytes in response to cardiac wall tension,(4, 5) and the level of the N-terminal fragment of its prohormone (NT-proBNP) correlates with the extent of ventricular dysfunction.(6) Increased preoperative BNP and NT-proBNP levels have been shown to predict cardiovascular complications in non-cardiac surgery.(7-12) An earlier small study on orthopaedic patients has found preoperative BNP elevation to be superior to American Society of Anesthesiologists' (ASA) physical status classification in independently predicting postoperative cardiac complications.(13) Increased preoperative NT-proBNP has also been shown to independently predict short-term cardiovascular complications and cardiac death in non-cardiac surgery,(9, 14) and in older patients high perioperative NT-proBNP has also predicted long-term mortality.(7) However, to our knowledge only one small study has assessed the role of NT-proBNP in the prediction of peri- and early postoperative cardiac complications in high-risk hip fracture patients.(8) We recently showed that troponin T (TnT) is a strong independent predictor of short- and long-term mortality in hip fracture patients,(15) but there is no data on the combined effect of TnT and NT-proBNP on top of

clinical preoperative risk evaluation in hip fracture patients. The purpose of this study was to evaluate whether NT-ProBNP together with TnT provides useful additive prognostic information on the short- and long-term outcome of unselected hip fracture patients.

METHODS

The study (www.ClinicalTrials.gov, identifier NCT01015105) is part of a wider protocol in progress to assess thrombotic and bleeding complications of invasive procedures in Western Finland.(16-18) All consecutive hip fracture patients referred to Turku University hospital during a period of 6 months (from October 19th 2009 to May 19th 2010) were asked consent to be included in this study. One patient declined. This resulted in 200 consecutive hip fracture patients. NT-proBNP measurements were missing in 18 patients and these were excluded and the final study population consisted of 182 hip fracture patients. An anaesthesiologist clinically evaluated the patients preoperatively, and assigned each patient an ASA physical status class. A lumbar epidural catheter was placed for pain control, and the patients received a mixture of a local anaesthetic and opiate from the admission to the second postoperative morning. A chest x-ray study and basic blood chemistry tests were performed on admission and later according to the clinical need. The patients were operated under spinal anaesthesia with isobaric bupivacaine. Significant postoperative blood loss was substituted with red blood cell transfusions. Hypotension (blood pressure <100/60) was treated with rapid fluid challenge, vasopressors and atropine as appropriate. Patient's cardiac medications (excluding diuretics) were continued throughout the hospital period. Blinded NT-proBNP measurements were performed once during the hospitalization. Blinded TnT measurements and ECG recordings were performed on admission, before operation and on 1st and 2nd postoperative days. Physicians were unaware of these results but additional tests were performed when clinically indicated.

NT-ProBNP and TnT levels were determined by electrochemiluminescence immunoassay (ECLIA) on Modular E170 automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany), which detects a NT-proBNP level of ≥50 ng/l. The patients were divided into tertiles according to the measured NT-proBNP level. When multiple NT-proBNP measurements were available, the highest of them was

considered. The recommended diagnostic threshold of 0.03 µg/l was used to evaluate TnT elevation. Data on medical history, medication and cardiac risks were collected from the electronic medical records. These data were also used to evaluate the Revised Cardiac Risk Index value (RCRI, the Lee's score) for each patient.(19) The patients were followed until April 2013. The Ethics Committee of the Hospital District of Southwest Finland reviewed and approved the study protocol, all study patients gave their informed consent and the principles of the Helsinki declaration were followed.

Normality was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Skewed variables presented as median and interquartile range [IQR], and categorical variables as percentage. ANOVA, Mann-Whitney U-test and Chi-square test were used for comparison of variables as appropriate. Survival analysis was performed using Kaplan-Meier's method and Cox proportional hazards method. A Cox regression analysis with backward selection was performed to analyse the independent predictors of short- and long-term mortality. A p-value < 0.05 was considered statistically significant. All computations were carried out with SPSS software (V22, SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics are presented in Table 1. Median [IQR] age of the patients was 84 [11] years. A history of heart failure was known in 26 (14 %) patients and coronary artery disease in 56 (31 %). Surgery was performed on the day of admission in 34 (19 %) patients, 1 day after admission in 109 (60 %), 2 days after admission in 24 (13 %) and 3-5 days after admission in 12 (7 %) patients. One patient died before the operation.

Table 1. Baseline clinical characteristics of the study population

Variable	All patients	NT-proBNP level			*P*-value
		Low	Intermediate	High	
	n = 182	n = 60	n = 61	n = 61	
NT-proBNP level	1415 [2932]	441 [342]	1390 [860]	5170 [6045]	
Men	59 (32 %)	20 (33 %)	18 (30 %)	21 (34 %)	0.83

Age (years)	81.2 ± 11.0	74.7 ± 12.8	83.0 ± 9.2	85.8 ± 7.4	<0.001
History of any cardiovascular disease	130 (71 %)	36 (60 %)	43 (70 %)	51 (83 %)	0.02
History of heart failure	26 (14 %)	3 (5 %)	5 (8 %)	18 (30 %)	<0.001
Coronary artery disease	56 (31 %)	12 (20 %)	19 (31 %)	25 (41 %)	0.04
Prior myocardial infarction	19 (10 %)	3 (5 %)	6 (10 %)	10 (16 %)	0.12
Prior coronary revascularization	14 (8 %)	2 (3 %)	4 (7 %)	8 (13 %)	0.12
Hypertension	91 (50 %)	22 (37 %)	31 (51 %)	38 (62 %)	0.02
Diabetes mellitus	32 (18 %)	10 (17 %)	9 (15 %)	13 (21 %)	0.62
Atrial fibrillation	39 (21 %)	3 (5 %)	10 (16 %)	26 (43 %)	<0.001
Renal failure	10 (6 %)	0 (0 %)	1 (2 %)	9 (15 %)	<0.001
Dementia	73 (40 %)	16 (27 %)	32 (53 %)	25 (41 %)	0.02
Prior TIA or stroke	30 (17 %)	11 (18 %)	11 (18 %)	8 (13 %)	0.68
Preoperative ASA class	3.28 ± 0.57	3.10 ± 0.63	3.27 ± 0.52	3.48 ± 0.50	0.001
Revised cardiac risk index	0.72 ± 0.91	0.53 ± 0.83	0.64 ± 0.86	0.98 ± 0.99	0.017
Preoperative haemoglobin	113 ± 17	116 ± 14	111 ± 16	113 ± 19	0.32
Received red blood cell units	1.51 ± 1.53	1.68 ± 1.70	1.66 ± 1.54	1.18 ± 1.30	0.125
Perioperative TnT elevation	66 (36 %)	7 (12 %)	18 (30 %)	41 (67 %)	<0.001
Cardiovascular medication at hospital admission					
Aspirin	68 (37 %)	20 (33 %)	22 (36 %)	26 (43 %)	0.55
Low molecular weight heparin	2 (1 %)	0 (0 %)	0 (0 %)	2 (3 %)	0.14
Warfarin	28 (15 %)	3 (5 %)	11 (18 %)	14 (23 %)	0.018
Beta-blocker	70 (38 %)	14 (23 %)	25 (41 %)	31 (51 %)	0.007
ACE inhibitor or ARB	48 (26 %)	9 (15 %)	20 (33 %)	19 (31 %)	0.05
Calcium channel blocker	29 (16 %)	7 (12 %)	10 (16 %)	12 (20 %)	0.48
Diuretic	61 (34 %)	13 (22 %)	17 (28 %)	31 (51 %)	0.002
Digoxin	14 (8 %)	4 (7 %)	3 (5 %)	7 (11 %)	0.38
Statin	46 (25 %)	14 (23 %)	17 (28 %)	15 (25 %)	0.84

Data are presented as median [IQR], count (%) or mean ± standard deviation. NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; TIA, transient ischaemic attack; ASA class, American Society of Anesthesiologists' physical status classification; Revised cardiac risk index, Lee's score; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

NT-ProBNP was measured during hospitalization in all 182 patients, preoperatively in 117 (64 %) and postoperatively in 86 (47 %) patients; in 96 patients preoperative only, in 21 both pre- and postoperatively and in 65 postoperatively only. NT-ProBNP levels ranged from 50 to 72100 ng/l, with a median [IQR] of 1415 [2932] ng/l. The median [IQR] NT-proBNP level was 1260 [2298] ng/l in preoperative samples and 1600 [3971] ng/l in postoperative samples (P = 0.001). Those 21 patients who had both pre- and postoperative NT-proBNP measurements had a median preoperative proBNP level of 2220 [2964] ng/l and postoperative proBNP level of 3370 [5520] ng/l (P = 0.001). Comparison of the NT-ProBNP tertiles is presented in Table 1. There was no significant gender difference in NT-proBNP levels. Increasing age, history of hypertension, coronary artery disease, atrial fibrillation, heart failure, renal failure and dementia were significantly associated with higher NT-proBNP levels. However, high NT-proBNP levels were detected even in patients with no prior cardiac morbidity, and 10 (16 %) patients in the highest NT-proBNP tertile had no history of cardiovascular diseases. Multivariate logistic regression showed that age, renal failure and atrial fibrillation were the independent predictors of higher NT-proBNP. Chest x-ray showed signs of congestive heart failure already on admission to hospital in 1 (2 %) patient with low NT-proBNP (<806 ng/L), in 2 (3 %) patients with intermediate NT-proBNP (806 – 2370 ng/L) and in 5 (8 %) patients with high NT-proBNP (>2370 ng/L). Median [IQR] duration of hospitalization was 6.0 [4.0] days and there was no difference in the duration between patients with low vs. intermediate vs. high NT-proBNP.

TnT was elevated in 7 (12 %) patients with low NT-proBNP, in 18 (30 %) patients with intermediate NT-proBNP and in 41 (67 %) patients with high NT-proBNP (P < 0.001).

Cardiac symptoms were infrequent in all NT-proBNP groups during hospitalization. Shortness of breath was experienced by 10 (17 %) patients with low, 10 (16 %) patients with intermediate, and 19 (31 %) patients with high NT-proBNP (P = 0.08) and chest pain by 2 (3 %) vs. 2 (3 %) vs. 3 (5 %) (P = 0.87). Disorientation was observed in 23 (38 %) vs. 36 (59 %) vs. 46 (75 %) of the patients in low, intermediate and high NT-proBNP groups, respectively (P < 0.001).

At 30 days follow-up, 17 (9 %) patients had died (Table 2).

Table 2. Comparison of the patients who died within 30 days of hospital admission and patients who survived.

Variable	Died during 30 days n = 17	Alive after 30 days n = 165	*P*-value
NT-ProBNP level	2700 [10435]	1230 [2736]	0.01
Men	9 (53 %)	50 (30 %)	0.058
Age (years)	84.7 ± 6.3	80.8 ± 11.4	0.17
History of any cardiovascular disease	15 (88 %)	115 (70 %)	0.11
History of heart failure	2 (12 %)	24 (15 %)	0.76
Coronary artery disease	5 (29 %)	51 (31 %)	0.90
Prior myocardial infarction	3 (18 %)	15 (9 %)	0.31
Prior coronary revascularization	2 (12 %)	12 (7 %)	0.51
Hypertension	10 (59 %)	81 (49 %)	0.45
Diabetes mellitus	6 (35 %)	26 (16 %)	0.04
Atrial fibrillation	6 (35 %)	33 (20 %)	0.14
Renal failure	2 (12 %)	8 (5 %)	0.23
Dementia	9 (53 %)	64 (39 %)	0.26
Prior TIA or stroke	2 (12 %)	28 (17 %)	0.58
Preoperative ASA score	3.4 ± 0.5	3.3 ± 0.6	0.25
Revised cardiac risk index	0.8 ± 1.0	0.7 ± 0.9	0.83
Perioperative troponin T elevation	11 (65 %)	55 (33 %)	0.01

Data are presented as median [IQR], count (%) or mean ± standard deviation. NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; TIA, transient ischemic attack; ASA class, American Society of Anesthesiologists' physical status classification; Revised cardiac risk index, Lee's score.

Patients with high and intermediate NT-proBNP had significantly higher 30-day mortality compared to patients with low NT-proBNP (15 % vs. 11 % vs. 2 %, P = 0.04), as shown in figure 1. The patients who died during the first 30 days had a median [IQR] proBNP level of 2700 [10435] ng/l compared to 1230 [2736] ng/l in patients who survived the first 30 days (P = 0.002). Out of the patients with no TnT elevation, 5 % died during the first 30 days; no patients with low proBNP vs. 6 (10 %) of the patients with intermediate or high NT-proBNP (P = 0.02). Of the 66 patients with a perioperative TnT elevation 11 (17 %) died during the first 30 days, with no difference in mortalities regarding the NT-proBNP levels in these patients.

Intermediate/high vs. low NT-proBNP levels (HR 7.8, 95%Cl 1.03-59.14, P < 0.05) remained the only independent predictor of short-term mortality in a Cox regression model including age, renal impairment, TnT elevation, NT-proBNP levels, ASA and Lee scores.

Complete follow-up data up to 1000 days was available in all 182 patients. Median [IQR] follow-up time was 3.12 [0.28] years. The overall mortality at 1000 days was 48 % (Table 3).

Table 3. Comparison of the patients who died within 1000 days of hospital admission and patients who survived.

Variable	Died during 1000 days n = 88	Alive after 1000 days n = 94	*P*-value
NT-ProBNP level	2295 [4403]	913 [1679]	<0.001
Men	32 (36 %)	27 (29 %)	0.27
Age (years)	84.1 ± 9.7	78.5 ± 11.6	<0.001
History of any cardiovascular disease	71 (81 %)	59 (63 %)	0.008
History of heart failure	18 (20 %)	8 (9 %)	0.02
Coronary artery disease	34 (39 %)	22 (23 %)	0.03
Prior myocardial infarction	11 (13 %)	8 (9 %)	0.38
Prior coronary revascularization	9 (10 %)	5 (5 %)	0.21
Hypertension	48 (55 %)	43 (46 %)	0.24
Diabetes mellitus	18 (20 %)	14 (15 %)	0.33
Atrial fibrillation	27 (31 %)	12 (13 %)	0.003
Renal failure	7 (8 %)	3 (3 %)	0.16
Dementia	45 (51 %)	28 (30 %)	0.003
Prior TIA or stroke	17 (19 %)	13 (14 %)	0.32
Preoperative ASA score	3.4 ± 0.5	3.2 ± 0.6	0.003
Revised cardiac risk index	0.9 ± 1.0	0.6 ± 0.9	0.02
Troponin T elevation	40 (45 %)	26 (28 %)	0.01

Data are presented as median [IQR], count (%) or mean ± standard deviation. NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; TIA, transient ischemic attack; ASA class, American Society of Anesthesiologists' physical status classification; Revised cardiac risk index, Lee's score.

The mortality remained constantly higher in patients with high and intermediate NT-proBNP compared to patients with low NT-proBNP (69 % vs. 49 % vs. 27 %, $P < 0.001$), as shown in figure 2. Intermediate/high NT-proBNP levels (HR 2.27, 95%CI 1.30-3.96, P = 0.004), the presence of dementia (HR 1.74, 95%CI 1.13-2.66, P=0.01) and higher preoperative ASA class (HR 1.59, 95%CI 1.06-2.38, P = 0.02) remained independent predictors of long-term mortality in a Cox regression model including NT-proBNP levels, TnT elevation, age, renal impairment, the presence of dementia, atrial fibrillation and coronary artery disease, preoperative ASA and Lee's scores. In patients with no perioperative TnT elevation, intermediate/high NT-proBNP (HR 3,17; 95% CI 1.64-6.10, p=0.001) was the only independent predictor of 1000-day mortality, while in patients with a perioperative TnT elevation NT-proBNP did not carry a significant predictive value.

DISCUSSION

The present study showed that high NT-proBNP levels are common in hip fracture patients, and that there is a significant graded association between increasing NT-proBNP level and short- and long-term mortality. Furthermore, measurement of this natriuretic peptide provided useful independent prognostic information on top of currently used risk scores and troponin levels. While perioperative NT-proBNP level was the only independent predictor of short-term mortality, perioperative NT-proBNP level, preoperative ASA class and the presence of dementia were independent predictors of long-term mortality. Of note, none of the clinical characteristics of the patients or currently used risk scores provided useful information on the short-term mortality in these fragile acute patients.

When patients with a perioperative TnT elevation were analysed separately, the short-term mortality was not affected by the perioperative NT-proBNP level, but the long-term mortality was higher if the patient also had high NT-proBNP level. However, high NT-proBNP level did not remain a significant predictor of long-term mortality in this relatively small patient group with a poor overall prognosis.

In elective non-cardiac surgery, a low NT-proBNP level of 201 ng/l has been shown to have a high sensitivity and specificity to predict perioperative cardiovascular complications,(9) while in emergency orthopaedic surgery patients a preoperative NT-proBNP level of ≥741 - 842 ng/l was the best cut-off level in

evaluating the risk of in-hospital and long-term cardiac complications.(7, 20) In line with these observations the best cut-off level for the prediction of short-term mortality was low also in this old patient group with frequent co-morbidities, and most of the difference in short-term mortality was observed already between the low and intermediate NT-proBNP groups. The increase in long-term mortality between the NT-proBNP groups was, however, more stable and not unexpectedly dementia and poor ASA group were the other independent predictors of long-term mortality.

Unexpectedly, some patients with no prior history of cardiovascular diseases or renal failure had a high NT-proBNP level supporting the view that major trauma and surgery, or heavy use of intravenous fluids in the perioperative period may cause stress on the heart and lead to elevated NT-proBNP levels. High co-incidence of TnT elevation also suggests that a perioperative myocardial injury is a major cause of elevated NT-proBNP levels in this patient group.

To our knowledge there has only been one earlier study assessing NT-proBNP levels in hip fracture patients. In this study of only 69 frail hip fracture patients with a high ASA class preoperative NT-proBNP level exceeding 3984 ng/l was an independent predictor of perioperative cardiac complications, but did not find an association between increased NT-proBNP and mortality at 3 months follow-up.(8) On the contrary to these findings, our study showed that high NT-proBNP is an independent predictor of both short- and long-term mortalities, and that there is 5-fold increase in short-term mortality already at NT-proBNP level exceeding 805 ng/l.

This study has some limitations that should be considered. The study population of 182 patients, although bigger than in earlier similar studies, is relatively small. Secondly, the idea was to obtain NT-proBNP samples preoperatively in all patients, but due to weekends and public holidays, preoperative tests were obtained in 64 % of the patients only. Since this was a blind evaluation it is not possible to assess how pharmacological treatments may have affected the outcome. The strengths of this study are the prospective nature of the registry, inclusion of all consecutive hip fracture patients and complete follow-up data of all 182 patients.

In conclusion, elevated perioperative NT-proBNP level is common in surgically treated hip fracture patients and an independent predictor of short- and long-term mortality superior to the commonly used clinical risk scores, and an efficient tool in detecting the patients in greater risk of death. Measurement

of NT-proBNP and TnT in hip fracture patients could lead to the detection of patients at high risk of early and later death after the operation. The prognosis of high risk patients might be improved with appropriate cardiac care especially in those patients with no previous cardiovascular history or medications.

AUTHOR CONTRIBUTION

All authors participated in designing this study. MS recruited the patients. NS operated on the patients. PN collected the data. PN and TK analyzed the data and PN, TK, MS and KEA interpreted the data. PN wrote the first draft and all other authors reviewed it and provided further contributions and suggestions. All authors read and approved the final version.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pd and declare: authors had financial support from the Finnish Foundation for Cardiovascular Research for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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DATA SHARING

No additional data available

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LEGENDS

Figure 1. Kaplan-Meier estimates for survival in 30 days follow-up in patients with low, intermediate and high NT-proBNP level during index hospitalization.

Figure 2. Kaplan-Meier estimates for survival in 1000 days follow-up in patients with low, intermediate and high NT-proBNP level during the index hospitalization.

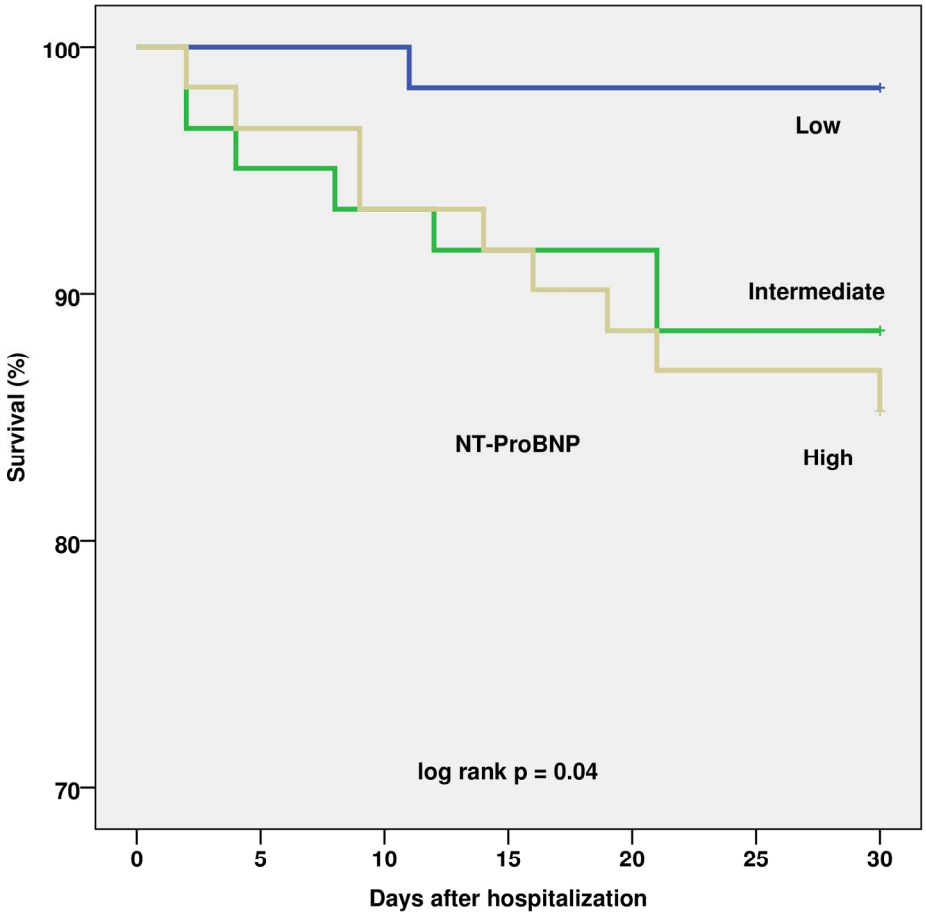

Figure 1. Kaplan-Meier estimates for survival in 30 days follow-up in patients with low, intermediate and high NT-proBNP level during index hospitalization.
173x173mm (300 x 300 DPI)

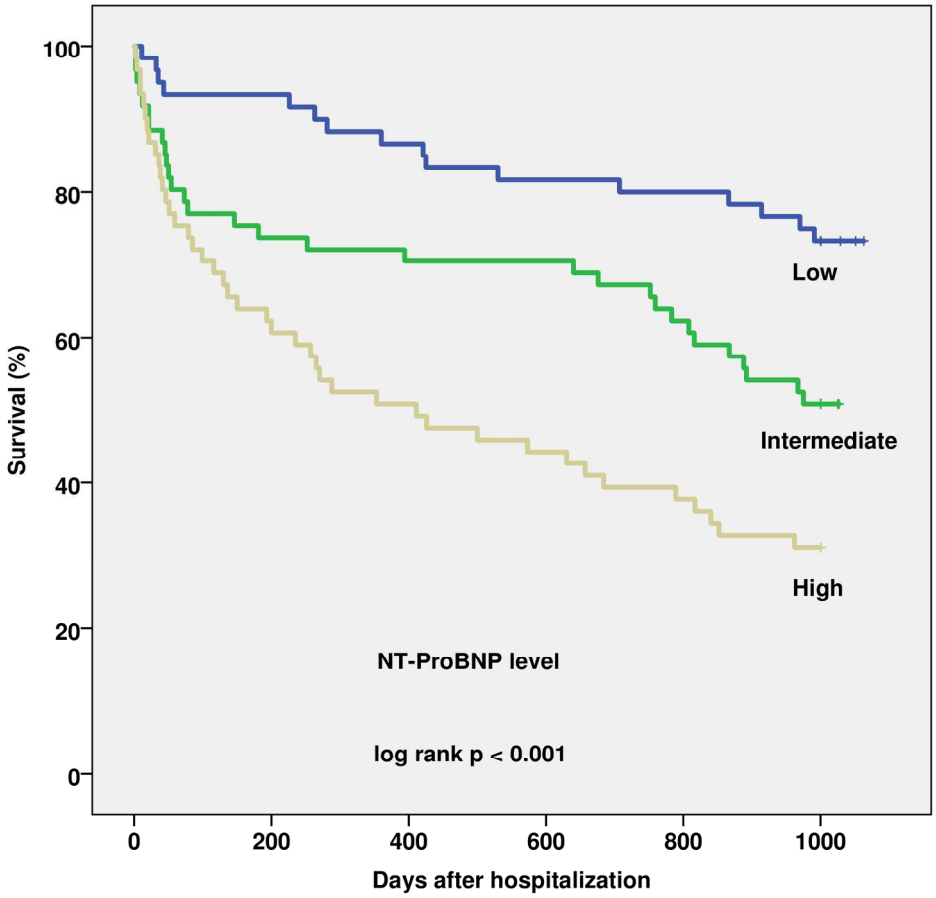

Figure 2. Kaplan-Meier estimates for survival in 1000 days follow-up in patients with low, intermediate and high NT-proBNP level during index hospitalization.
173x173mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-5
		(b) Indicate number of participants with missing data for each variable of interest	4-7
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.