Urinary N-terminal pro-brain natriuretic peptide: prognostic value in patients with acute chest pain

Stefanie Reynen1*, Michael Schlossbauer1,2, Ute Hubauer1, Julian Hupf3, Arno Mohr1,4, Evelyn Orso5, Markus Zimmermann3, Andreas Luchner6, Lars S. Maier1, Stefan Wallner5† and Carsten G. Jungbauer1†

1Department of Internal Medicine II (Cardiology), University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg, 93053, Germany; 2Department of Anesthesiology, Hospital Barmherzige Brüder Regensburg, Regensburg, Germany; 3Department of Pneumology, Donaustauf Hospital, Donaustauf, Germany; and 4Department of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Regensburg, Germany

Abstract

Aims The objective of this study was to investigate the prognostic value of urinary N-terminal pro-brain natriuretic peptide (NT-proBNP) compared with plasma NT-proBNP in patients presenting with acute chest pain in the emergency department.

Methods and results We measured simultaneously plasma and urinary NT-proBNP at admission in 301 patients with acute chest pain. In our cohort, 174 patients suffered from acute coronary syndrome (ACS). A follow-up (median of 55 months) was performed regarding the endpoints all-cause mortality and major adverse cardiac events (mortality, congestive heart failure, ACS with the necessity of a coronary intervention, and stroke). Fifty-four patients died during follow-up; 98 suffered from the combined endpoint. A significant positive correlation of urinary and plasma NT-proBNP was found (r = 0.87, P < 0.05). Patients with troponin positive ACS had significantly elevated levels of plasma and urinary NT-proBNP compared with those with unstable angina pectoris or chest wall syndrome (each P < 0.05). The highest levels of both biomarkers were found in patients with congestive heart failure (each P < 0.05). According to Kaplan–Meier analysis, plasma and urinary NT-proBNP were significant predictors for mortality and the combined endpoint in the whole study cohort and in the subgroup of patients with ACS (each P < 0.05). Regarding Cox regression analysis, plasma and urinary NT-proBNP were independent predictors for mortality and the combined endpoint (each P < 0.05).

Conclusions Urinary NT-proBNP seems to provide a significant predictive value regarding the endpoints all-cause mortality and major adverse cardiac events in patients with acute chest pain and those with ACS.

Keywords Urinary NT-proBNP; Acute chest pain; Cardiac markers; Natriuretic peptides

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*Correspondence to: Stefanie Reynen, Department of Internal Medicine II (Cardiology), University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg, 93053, Germany; Tel: +49 941 944 17264; Fax: +49 941 944 7280. Email: stefanie.reynen@klinik.uni-regensburg.de
†These authors contributed equally to this publication.

Introduction

N-terminal pro-brain natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are established biomarkers especially for heart failure diagnosis and prognosis.1–5 Particularly in the emergency department, both markers offer important diagnostic information as patients with normal plasma concentrations of natriuretic peptides are ruled out of suffering from heart failure.6 N-terminal pro-brain natriuretic peptide (NT-proBNP) is mainly kidney-associated eliminated, and therefore, it can also be measured in urine. Previous studies have examined the validity and prognostic value of urinary NT-proBNP in patients with heart failure.7–10 In former studies, urinary NT-proBNP was comparable with plasma NT-proBNP regarding diagnosis of acute and chronic heart failure.11,12 To our knowledge, the diagnostic and prognostic value of urinary NT-proBNP in patients with chest pain as well as acute coronary syndrome (ACS) has not been examined yet. In contrast, a prognostic value in regard to mortality has been previously demonstrated for plasma NT-proBNP in patients with ACS.13,14

The aim of the current study was to investigate the prognostic value of urinary NT-proBNP compared with plasma NT-proBNP in patients presenting with acute chest pain in
the emergency department. Therefore, we measured plasma and urinary NT-proBNP at admission and also performed a median follow-up of 55 months in regard to the endpoints all-cause mortality and major adverse cardiac events.

**Methods**

**Study population**

Four hundred two patients presenting with acute chest pain in the emergency department of the University Hospital Regensburg between February and October 2015 were included in this study. Due to limited personal resources, there was no patient inclusion possible from the middle of July to the end of August 2015 during the study period. Exclusion criteria were age less than 18 years, pregnancy or breastfeeding, inability to deliver urine, and absence of written informed consent. Plasma and urinary NT-proBNP were measured at admission. Depending on electrocardiogram and cardiac markers, patients were diagnosed with an ACS [unstable angina pectoris, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI); NSTEMI and STEMI were summarized as troponin positive ACS] according to the European Society of Cardiology guidelines\textsuperscript{15,16} or non-ischaemic chest pain (e.g. chest wall syndrome). Patients classified as congestive heart failure suffered from chest pain symptoms due to fluid overload and not due to relevant coronary artery disease, especially ACS and unstable angina pectoris. Median follow-up was 55 months [interquartile range (IQR) 52–57 months]. From 301 patients, blood and urine samples as well as follow-up information were present and were included in the current analysis (Figure 1). We evaluated both urinary and plasma NT-proBNP regarding mortality as well as a combined endpoint of major adverse cardiac events (mortality, congestive heart failure, ACS with the necessity of a coronary intervention, and stroke).

All patients enrolled confirmed written informed consent. The study was approved by the institutional ethics committee and carried out in agreement with good clinical practice guidelines and with the standards established for human experimentation by the Declaration of Helsinki.

**Biochemical analyses**

At admission to the emergency department, blood and urine samples were taken and sent to the central laboratory immediately. All biomarkers were determined on Siemens Dimension Vista 1500 autoanalysers. Blood samples were

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![Flow chart](image)

**Figure 1.** Flow chart.
analysed on the same day. Urine samples were taken from spontaneous void, and sterile cups were used for collection. The urine sample was centrifugated. Urinary creatinine was determined with an enzymatic method (ECREA, Siemens Healthcare Diagnostics). Urinary NT-proBNP was measured also on the same day with the Siemens PBNP serum and plasma method and normalized to urinary creatinine in order to minimize dilution effect.

Statistics

Descriptive data are presented as mean ± standard deviation (normally distributed data) or as medians and IQR. Correlation coefficients were evaluated according to Spearman. Mann–Whitney U test was performed for continuous non-normally distributed variables. Box plot analyses were used to analyse and visualize biomarker levels according to the different entities of chest pain. Kaplan–Meier curves were constructed for follow-up analysis, representing the time of follow-up and the likelihood of reaching the endpoint mortality and the combined endpoint of major adverse cardiac events. This was performed for the overall study cohort as well as for the subgroup of patients with ACS. The median of each marker was chosen as binary cut-off. Cox regression was used to evaluate possible associations between biomarker and endpoint. Further, age, glomerular filtration rate (GFR), troponin I, arterial hypertension, and diabetes mellitus were included to the analysis. All data were analysed by using a commercially available statistical software package (SPSS 25.0, SPSS Inc., IL, USA; MedCalc 19.6.4, MedCalc Software, Mariakerke, Belgium).

Results

In Table 1, the baseline characteristics are presented. A total of 301 patients were included in the current analysis. The average age was 62.2 years, and two-thirds were male. Forty per cent of the patients had a history of coronary artery disease, 63% of hypertension, and 26% of diabetes. Fifty-four patients died during follow-up. Patients who died during follow-up were significantly older and suffered more often from diabetes and hypertension (each \( P < 0.05 \)). A total of 174 patients initially presented with an ACS.

A significant and positive correlation between urinary NT-proBNP and plasma NT-proBNP was found \( (r = 0.87, P < 0.05) \). For both urinary and plasma NT-proBNP, a significant and positive correlation with creatinine (plasma NT-proBNP \( r = 0.42 \), urinary NT-proBNP \( r = 0.39 \), each \( P < 0.05 \)) and age (plasma NT-proBNP \( r = 0.57 \), urinary NT-proBNP \( r = 0.49 \), each \( P < 0.05 \)) as well as a significant and negative correlation with GFR (plasma NT-proBNP \( r = -0.58 \), urinary NT-proBNP \( r = -0.54 \), each \( P < 0.05 \)) could be demonstrated.

Plasma and urinary N-terminal pro-brain natriuretic peptide and acute chest pain

There was no significant difference between urinary and plasma NT-proBNP in patients with STEMI \( (87.1 \text{ (IQR 15.9; 634.6)} \text{ pg/mg Crea} \text{ and } 531.5 \text{ (IQR 81.5; 3496.7)} \text{ pg/mL}, \text{ respectively}) \) compared with those with NSTEMI \( (77.8 \text{ (IQR 31.8; 193.7)} \text{ pg/mg Crea} \text{ and } 952.0 \text{ (IQR 385.5; 2316.7)} \text{ pg/mL}, \text{ respectively}) \) were significantly elevated compared with patients with unstable angina pectoris \( (\text{plasma: } 278.5 \text{ (IQR 126.0; 889.5)} \text{ pg/mL, } \text{urine: } 19.2 \text{ (IQR 8.6; 47.0)} \text{ pg/mg Crea}, \text{ each } P < 0.05) \). Patients with troponin positive ACS as well as unstable angina pectoris showed significantly higher urinary and plasma NT-proBNP concentrations than patients with chest wall syndrome \( (\text{plasma NT-proBNP } 60.0 \text{ (IQR 31.0; 151.0)} \text{ pg/mL, urinary NT-proBNP } 0.12 \text{ (IQR 0.06; 0.22)} \text{ pg/mg Crea, each } P < 0.05) \).

Patients with congestive heart failure showed the highest concentrations of urinary and plasma NT-proBNP \( (\text{plasma NT-proBNP: } 7831.0 \text{ (IQR 3757.5; 24 274.5)} \text{ pg/mL, urinary NT-proBNP: } 643.4 \text{ (IQR 299.0; 22 969.8)} \text{ pg/mg Crea; compared with all other groups: each } P < 0.05; \text{Figure 2A and 2B}) \).

Receiver operating characteristic analysis for the overall study group and the subgroup of patients with chest wall syndrome

For the overall study cohort, receiver operating characteristic (ROC) analysis regarding the endpoint all-cause mortality showed very satisfying values for urinary NT-proBNP \( (\text{area under the curve (AUC) } 0.85, \text{ at a cutpoint of } 63.2 \text{ pg/mg creatinine: } \text{sensitivity } 81\%, \text{ specificity } 74\%; \text{ } P < 0.001) \) and plasma NT-proBNP \( (\text{AUC } 0.83, \text{ at a cutpoint of } 755 \text{ pg/mL: } \text{sensitivity } 81\%, \text{ specificity } 73\%; \text{ } P < 0.001) \). ROC analysis regarding the combined endpoint revealed slightly worse values for urinary NT-proBNP \( (\text{AUC } 0.76, \text{ at a cutpoint of } 38.8 \text{ pg/mg creatinine: } \text{sensitivity } 73\%, \text{ specificity } 70\%; \text{ } P < 0.001) \) and plasma NT-proBNP \( (\text{AUC } 0.76, \text{ at a cutpoint of } 447 \text{ pg/mL: } \text{sensitivity } 73\%, \text{ specificity } 70\%; \text{ } P < 0.001) \). There was no significant difference between the AUC of plasma and urinary NT-proBNP in regard to the endpoint all-cause mortality \( (P = 0.25) \) and the combined endpoint \( (P = 0.91) \) (Figure 3). According to ROC analysis regarding ACS detection, urinary NT-proBNP showed an AUC of 0.59 \( (\text{at a cutpoint of } 89.1 \text{ pg/mg creatinine: } \text{sensitivity } 83\%, \text{ specificity } 30\%; \text{ } P = 0.008) \) and plasma NT-proBNP an AUC of 0.65 \( (\text{at a cutpoint of } 87.5 \text{ pg/mL: } \text{sensitivity } 83\%, \text{ specificity } 46\%; \text{ } P < 0.001) \).

In patients presenting with chest wall syndrome, ROC analysis for the endpoint all-cause mortality showed satisfying values for urinary NT-proBNP \( (\text{AUC } 0.87, \text{ at a cutpoint of} \)
Diagnosis at discharge, History of stroke, Hyperlipidaemia, Diabetes, Acute treatment, Blood work, median (IQR)

| Baseline characteristics | All (n = 301) | Survived (n = 247) | Deceased (n = 54) | P-value |
|--------------------------|--------------|-------------------|------------------|---------|
| Age (years)              | 62.2 (SD 15.56) | 59.4 (SD 14.97) | 75.2 (SD 11.02) | <0.001  |
| Male, n (%)              | 216 (72%)     | 177 (72%)         | 39 (72%)         | 0.934   |
| BMI (kg/m²)              | 28.3 (SD 4.63) | 28.4 (SD 4.76)   | 28.0 (SD 4.01)  | 0.767   |
| History of coronary artery disease, n (%) | 117 (39%)     | 93 (38%)          | 24 (44%)         | 0.354   |
| Ejection fraction < 35%, n (%) | 15 (5%)       | 7 (3%)            | 8 (15%)          | 0.002   |
| Hypertension, n (%)      | 191 (63%)     | 149 (60%)         | 42 (78%)         | 0.016   |
| Diabetes, n (%)          | 79 (26%)      | 57 (23%)          | 22 (41%)         | 0.008   |
| Hyperlipidaemia, n (%)   | 173 (57%)     | 147 (59%)         | 26 (48%)         | 0.127   |
| History of stroke, n (%) | 17 (6%)       | 15 (6%)           | 2 (4%)           | 0.495   |
| Diagnosis at discharge, n (%) |                |                   |                  |         |
| STEMI                    | 50 (17%)      | 37 (15%)          | 13 (24%)         | 0.104   |
| NSTEMI                   | 52 (17%)      | 43 (17%)          | 9 (17%)          | 0.896   |
| Unstable angina pectoris | 72 (24%)      | 62 (25%)          | 10 (18%)         | 0.305   |
| Congestive heart failure | 10 (3%)       | 4 (2%)            | 6 (11%)          | <0.001  |
| Chest wall syndrome      | 55 (18%)      | 49 (20%)          | 6 (11%)          | 0.133   |
| Acute treatment, n (%)   |                |                   |                  |         |
| PCI                      | 117 (39%)     | 91 (37%)          | 26 (48%)         | 0.346   |
| CABG                     | 5 (2%)        | 5 (2%)            | 0 (0%)           | 0.257   |
| Blood work, median (IQR) |                |                   |                  |         |
| Plasma NT-proBNP (pg/mL) | 296 (69; 1516) | 206 (58; 841)   | 2426 (1079.7; 8392.2) | <0.001  |
| Urinary NT-proBNP (pg/mg Crea) | 31.8 (10.7; 159.1) | 22.2 (7.7; 74.0) | 396.4 (30.8; 2254.2) | <0.001  |
| Plasma creatinine (mg/dL) | 0.92 (0.78; 1.1) | 0.9 (0.77; 1.02) | 1.28 (1.01; 1.7) | <0.001  |
| eGFR MDRD (ml/min/1.73 m²) | 84 (60; 98)   | 88 (69; 100)     | 49.5 (35.0; 68.2) | <0.001  |
| Troponin I (ng/mL)       | 0.01 (0.0; 0.4) | 0.01 (0.0; 0.02) | 0.36 (0.23; 0.53) | 0.041   |
| CK (U/L)                 | 127 (73.7; 248) | 132 (81.2; 251.5) | 93.5 (56.5; 242.2) | 0.142   |
| CK-MB (U/L)              | 2 (1; 6)      | 2.5 (1.0; 6.5)   | 2 (1.0; 29.5)    | 0.643   |
| Drugs at admission, n (%) |                |                   |                  |         |
| Aspirin                  | 111 (37%)     | 89 (36%)          | 22 (41%)         | 0.517   |
| Clopidogrel              | 19 (6%)       | 14 (6%)           | 5 (9%)           | 0.326   |
| Ticagrelor               | 7 (2%)        | 6 (2%)            | 1 (2%)           | 0.799   |
| Prasugrel                | 3 (1%)        | 3 (1%)            | 0 (0%)           | 0.416   |
| Beta-blocker             | 132 (44%)     | 103 (42%)         | 29 (54%)         | 0.108   |
| ACE-i/ARB                | 133 (44%)     | 107 (43%)         | 26 (48%)         | 0.518   |
| Ca-channel blockers      | 54 (18%)      | 42 (17%)          | 12 (22%)         | 0.366   |
| Diuretics                | 92 (31%)      | 61 (25%)          | 31 (57%)         | <0.001  |
| Aldosterone antagonists  | 16 (5%)       | 9 (4%)            | 7 (13%)          | 0.006   |
| Phenprocoumon/NOAK       | 28 (9%)       | 19 (8%)           | 9 (17%)          | 0.356   |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CK, creatine kinase; CK-MB, creatine kinase myocardial band; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NOAK, novel oral anticoagulants (non-vitamin-K dependent anticoagulants); NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

20.3 pg/mg creatinine: sensitivity 83%, specificity 78%; P = 0.003) and plasma NT-proBNP (AUC 0.88, at a cutpoint of 95 pg/mL: sensitivity 83%, specificity 74%; P = 0.003). Similar results were found for the combined endpoint (urinary NT-proBNP: AUC 0.87, at a cutpoint of 20.3 pg/mg creatinine: sensitivity 83%, specificity 78%; P = 0.003; plasma NT-proBNP: AUC 0.88, at a cutpoint of 95 pg/mL: sensitivity 83%, specificity 74%; P = 0.003).

Prognostic value of urinary and plasma N-terminal pro-brain natriuretic peptide

Patients were followed for a median of 55 months (IQR 52–57 months). Fifty-four of 301 patients died during the follow-up period, and 98 of 301 patients reached the combined endpoint. In particular, 21 patients suffered from an ACS with the necessity of a coronary intervention, 31 from heart failure, and 11 from stroke during the follow-up period. Regarding Kaplan–Meier analysis, levels of urinary and plasma NT-proBNP ≥ median were significant predictors for mortality (each P < 0.05; Table 2A and Figures 4 and 5). In Cox regression analysis, urinary and plasma NT-proBNP were independent predictors for mortality and the combined endpoint beside age (each P < 0.05), opposite to history of diabetes or hypertension, GFR, and troponin I (each P = n.s.; Tables 3A and 4A).

In the subgroup of patients with ACS, 32 of 174 patients died and 67 of 174 patients reached the combined endpoint. Both urinary and plasma NT-proBNP were significant predictors for mortality and the combined endpoint (each P < 0.05; Table 2B). In Cox regression analysis, urinary and plasma NT-proBNP were significant and independent predictors for mortality beside age (each P < 0.05), opposite to history of diabetes or hypertension, GFR, and troponin I (each P = n.s.; Table 3B). In addition, urinary and plasma NT-proBNP were significant and independent predictors for the combined endpoint (each P < 0.05), opposite to age,
Figure 2  (A) Box plots representing logarithm of plasma NT-proBNP according to the different entities of chest pain at admission. *$P < 0.05$ vs. chest wall syndrome, §$P < 0.05$ vs. unstable angina pectoris, #$P < 0.05$ vs. troponin positive ACS. (B) Box plots representing logarithm of urinary NT-proBNP according to the different entities of chest pain at admission. *$P < 0.05$ vs. chest wall syndrome, §$P < 0.05$ vs. unstable angina pectoris, #$P < 0.05$ vs. troponin positive ACS. ACS, acute coronary syndrome; NT-proBNP, N-terminal pro-brain natriuretic peptide.
Figure 3 (A) Receiver operating characteristic curves for urinary and plasma NT-proBNP in regard to the endpoint all-cause mortality for the overall study cohort (plasma vs. urinary NT-proBNP $P = 0.25$). (B) Receiver operating characteristic curves for urinary and plasma NT-proBNP in regard to the combined endpoint for the overall study cohort (plasma vs. urinary NT-proBNP $P = 0.91$). NT-proBNP, N-terminal pro-brain natriuretic peptide.
history of diabetes or hypertension, GFR, and troponin I (each \( P = \text{n.s.}; \) Table 4B).

**Discussion**

The aim of the current study was to investigate the prognostic value of urinary NT-proBNP in patients presenting with acute chest pain in the emergency department compared with plasma NT-proBNP. In our cohort, both urinary and plasma NT-proBNP revealed similar distribution patterns of concentrations according to the different entities of chest pain. In particular, the highest concentrations of urinary and plasma NT-proBNP were found in patients with troponin-positive ACS and congestive heart failure. Urinary and plasma NT-proBNP were significant and independent predictors for all-cause mortality beside age.

Plasma NT-proBNP is a well-established biomarker for heart failure and also provides predictive value in other cardiac conditions.\(^1\)\(^-\)\(^3\)\(^,\)\(^17\)\(^-\)\(^20\) In contrast to BNP, which is removed by enzymatic degradation via neutral endopeptidase, receptor-mediated clearance, and renal elimination, NT-proBNP is mainly excreted via the kidneys and can be measured in urine.\(^21\)\(^,\)\(^22\) Urinary NT-proBNP seems to be not dependent from GFR but to be related to renal plasma flow.\(^23\)\(^,\)\(^24\) The diagnostic value of urinary NT-proBNP has been predominantly investigated in patients with heart failure.\(^7\)\(^,\)\(^9\)\(^,\)\(^25\)\(^,\)\(^26\) Roselló-Lletí et al. examined urinary NT-proBNP in patients with essential hypertension. They found higher levels of plasma and urinary NT-proBNP in patients with left ventricular hypertrophy than in a group of patients with essential hypertension and no left ventricular hypertrophy as well as a control group.\(^27\) Further, urinary NT-proBNP was shown to be a significant and independent predictor for all-cause mortality in patients with chronic heart failure.\(^10\) And even in paediatrics, urinary NT-proBNP might be a valuable biomarker, for example, in preterm infants with patent ductus arteriosus.\(^28\) However, data of urinary NT-proBNP are still rare, especially in regard to its prognostic potential.

In the current study, both plasma and urinary NT-proBNP levels revealed similar distribution patterns according to the different forms of ACS and non-ischaemic chest pain. Patients with troponin positive coronary syndrome showed significantly elevated levels of urinary and plasma NT-proBNP compared with those with unstable angina pectoris or chest wall syndrome. The highest levels of both markers were measured in patients with congestive heart failure. Omland et al. found in a cohort of patients with ACS the highest median concentrations of plasma NT-proBNP in patients with STEMI \((n = 204)\) compared with those with NSTEMI \((n = 220)\) and unstable angina pectoris \((n = 185)\). These findings may be explained by myocardial ischaemia causes ventricular dysfunction with an increase in wall stress and consecutive release of NT-proBNP.\(^14\) Ventricular dysfunction normally leads to secretion of natriuretic peptides, but also hypoxic damage of the myocytes as demonstrated by Goetze et al. in an animal experimental study. In this porcine model, surgical induced myocardial hypoxia led to an increase of plasma NT-proBNP concentrations.\(^29\) For the first time, we showed an association between urinary NT-proBNP and the different entities of the ACS, similar to plasma NT-proBNP in the current chest pain cohort. In the current cohort, ROC analysis for detecting ACS showed no satisfying values for urinary and plasma NT-proBNP. Therefore, regarding acute myocardial ischaemia, natriuretic peptides seem to incorporate no relevant diagnostic value. In general, patients with congestive heart failure show the highest levels of urinary and plasma NT-proBNP, which also might be a confounder for diagnosis of ACS.

Previous studies revealed the impact of plasma NT-proBNP on the prognosis in patients with ACS.\(^13\)\(^,\)\(^14\)\(^,\)\(^30\) Galvani et al. evaluated the short-term prognostic outcome of plasma NT-proBNP measured early after symptom onset in a large cohort of patients with STEMI and no ST-segment elevation ACS in regard to death within 30 days. In both groups, plasma NT-proBNP was independently related to death. In addition, NT-proBNP was found to be an independent predictor of heart failure.\(^13\) Omland et al. proved plasma NT-proBNP as a strong predictor of long-term mortality in a cohort of 609 patients with ACS. In their study, the median follow-up was 51 months and median plasma NT-proBNP concentrations were significantly higher in patients who died.\(^14\) Van der Zee et al. investigated the prognostic value of plasma NT-proBNP not only in patients with ACS but also in patients with non-ACS chest pain. In both cohorts, plasma NT-proBNP was found to be a predictor for cardiovascular mortality in the long term.\(^31\) To our knowledge, the current study evaluates for the first time the prognostic value of urinary NT-proBNP in patients with acute chest pain. In the current study, the median follow-up was 55 months, and regarding

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**Table 2A** Kaplan–Meier analysis according to plasma and urinary NT-proBNP regarding all-cause mortality and combined endpoint in all study cohorts.

| All study cohort | All-cause mortality | Combined endpoint |
|------------------|---------------------|-------------------|
|                  | Plasma NT-proBNP    | Urinary NT-proBNP | Plasma NT-proBNP | Urinary NT-proBNP |
| < Median         | 6/150               | 6/150             | 25/150           | 24/150             |
| > Median         | 48/151              | 48/151            | 73/151           | 74/151             |
| \( P \)          | \(<0.001\)          | \(<0.001\)        | \(<0.001\)       | \(<0.001\)         |

NT-proBNP, N-terminal pro-brain natriuretic peptide.
Figure 4 Kaplan–Meier curves regarding the endpoint all-cause mortality for plasma NT-proBNP (A) and urinary NT-proBNP (B) in all patients ($n = 301$). NT-proBNP, N-terminal pro-brain natriuretic peptide.
Figure 5  Kaplan–Meier curves regarding the combined endpoint for plasma NT-proBNP (A) and urinary NT-proBNP (B) in all patients (n = 301). NT-proBNP, N-terminal pro-brain natriuretic peptide.
the endpoints all-cause mortality and major adverse cardiac events, urinary NT-proBNP presented as promising and independent predictor comparable with plasma NT-proBNP in a cohort of patients presenting with chest pain as well as in the subgroup of patients with ACS. The diagnostic and prognostic value of urinary NT-proBNP appears to be comparable with plasma NT-proBNP. According to ROC analysis regarding the endpoint all-cause mortality in the overall study cohort, plasma and urinary NT-proBNP revealed satisfying values. This finding underlines the prognostic capability of plasma and urinary NT-proBNP in patients with acute chest pain.

In the current cohort, according to ROC analysis, urinary and plasma NT-proBNP showed significantly larger AUC values for the endpoint all-cause mortality and the combined endpoint than troponin I (data not shown). These findings underline the prognostic value of urinary and plasma NT-proBNP regarding both endpoints and might accentuate the rationale for measuring urinary or plasma NT-proBNP in chest pain patients. Therefore, in the future, the measurement of urinary NT-proBNP might provide a simple and cost-effective examination method without the need of venipuncture and also feasible for medical facilities without own

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**Table 2A** Kaplan–Meier analysis according to plasma and urinary NT-proBNP regarding all-cause mortality and combined endpoint in patients with acute coronary syndrome

| ACS cohort | Plasma NT-proBNP | Urinary NT-proBNP | Combined endpoint |
|------------|-----------------|------------------|-------------------|
|            | All-cause mortality |                  |                   |
|            | Plasma NT-proBNP | Urinary NT-proBNP | Plasma NT-proBNP | Urinary NT-proBNP |
| Median     | 4/87            | 4/87             | 21/87             | 21/87             |
| Median     | 28/87           | 28/87            | 46/87             | 46/87             |
| P          | <0.001          | <0.001           | <0.001            | <0.001            |

ACS, acute coronary syndrome; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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**Table 3A** Cox regression analysis for plasma and urinary NT-proBNP regarding the endpoint all-cause mortality in all study cohort

| Marker | Plasma NT-proBNP | Urinary NT-proBNP |
|--------|-----------------|------------------|
|        | P-value HR 95% CI | P-value HR 95% CI |
| Marker | 0.001 3.72 1.67; 8.28 | <0.001 4.12 2.19; 7.76 |
| GFR    | 0.562 0.57 0.09; 3.78 | 0.253 3.44 0.41; 28.69 |
| Troponin I | 0.835 0.97 0.70; 1.33 | 0.505 0.89 0.64; 1.24 |
| Age    | 0.029 1.04 1.00; 1.08 | 0.011 1.05 1.01; 1.08 |
| Diabetes | 0.761 0.89 0.43; 1.86 | 0.632 0.83 0.39; 1.76 |
| Hypertension | 0.139 2.58 0.73; 9.03 | 0.134 2.37 0.75; 8.85 |

CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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**Table 2B** Kaplan–Meier analysis according to plasma and urinary NT-proBNP regarding all-cause mortality and combined endpoint in patients with acute coronary syndrome

| ACS cohort | Plasma NT-proBNP | Urinary NT-proBNP |
|------------|-----------------|------------------|
|            | All-cause mortality |                 |
|            | Plasma NT-proBNP | Urinary NT-proBNP |
| Median     | 4/87            | 4/87             |
| Median     | 28/87           | 28/87            |
| P          | <0.001          | <0.001           |

ACS, acute coronary syndrome; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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**Table 3B** Cox regression analysis for plasma and urinary NT-proBNP regarding the endpoint all-cause mortality in patients with acute coronary syndrome

| Marker | Plasma NT-proBNP | Urinary NT-proBNP |
|--------|-----------------|------------------|
|        | P-value HR 95% CI | P-value HR 95% CI |
| Marker | 0.001 3.72 1.67; 8.28 | <0.001 4.12 2.19; 7.76 |
| GFR    | 0.562 0.57 0.09; 3.78 | 0.253 3.44 0.41; 28.69 |
| Troponin I | 0.835 0.97 0.70; 1.33 | 0.505 0.89 0.64; 1.24 |
| Age    | 0.029 1.04 1.00; 1.08 | 0.011 1.05 1.01; 1.08 |
| Diabetes | 0.761 0.89 0.43; 1.86 | 0.632 0.83 0.39; 1.76 |
| Hypertension | 0.139 2.58 0.73; 9.03 | 0.134 2.37 0.75; 8.85 |

ACS, acute coronary syndrome; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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**Table 4A** Cox regression analysis for plasma and urinary NT-proBNP regarding the combined endpoint in all study cohort

| Marker | Plasma NT-proBNP | Urinary NT-proBNP |
|--------|-----------------|------------------|
|        | P-value HR 95% CI | P-value HR 95% CI |
| Marker | <0.001 2.13 1.45; 3.14 | <0.001 1.79 1.31; 2.45 |
| GFR    | 0.562 0.57 0.09; 3.78 | 0.253 3.44 0.41; 28.69 |
| Troponin I | 0.835 0.97 0.70; 1.33 | 0.505 0.89 0.64; 1.24 |
| Age    | 0.029 1.04 1.00; 1.08 | 0.011 1.05 1.01; 1.08 |
| Diabetes | 0.761 0.89 0.43; 1.86 | 0.632 0.83 0.39; 1.76 |
| Hypertension | 0.139 2.58 0.73; 9.03 | 0.134 2.37 0.75; 8.85 |

CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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**Table 3B** Cox regression analysis for plasma and urinary NT-proBNP regarding the combined endpoint in patients with acute coronary syndrome

| Marker | Plasma NT-proBNP | Urinary NT-proBNP |
|--------|-----------------|------------------|
|        | P-value HR 95% CI | P-value HR 95% CI |
| Marker | 0.001 2.13 1.45; 3.14 | <0.001 1.79 1.31; 2.45 |
| GFR    | 0.562 0.57 0.09; 3.78 | 0.253 3.44 0.41; 28.69 |
| Troponin I | 0.835 0.97 0.70; 1.33 | 0.505 0.89 0.64; 1.24 |
| Age    | 0.029 1.04 1.00; 1.08 | 0.011 1.05 1.01; 1.08 |
| Diabetes | 0.761 0.89 0.43; 1.86 | 0.632 0.83 0.39; 1.76 |
| Hypertension | 0.139 2.58 0.73; 9.03 | 0.134 2.37 0.75; 8.85 |

ACS, acute coronary syndrome; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.
laboratories. Further prospective studies are necessary to confirm the current findings.

In the subgroup of patients presenting with chest wall syndrome, ROC analysis showed satisfying values for urinary and plasma NT-proBNP regarding the endpoint all-cause mortality and the combined endpoint. This leads to the hypothesis that patients diagnosed with chest wall syndrome and low levels of urinary and plasma NT-proBNP might be discharged due to a relevant better prognosis. Also, the number of patients with chest wall syndrome in our cohort was very small. Therefore, in this subgroup, the informative value in regard to the prognostic value of both biomarkers is limited. Further studies with a larger number of participants are necessary to confirm our findings. Especially for urinary NT-proBNP, this might be a possible use in the future, as patients with low risk could be identified by a simple urine test.

Limitations

Four hundred two patients were originally recruited in the overall study cohort, but only 301 patients could be included in the current analysis due to the absence of blood and/or urine samples and patients lost to follow-up. The main limitation was the absence of a urine sample. According to the study protocol, it was required that the collection of the blood and urine sample has to take place in the chest pain unit. Especially patients who needed urgent treatment, for example, coronary angiography, were not able to deliver urine samples prior or directly after the coronary angiography. The failure to obtain a blood and urine sample in these most severe patients might be a limitation in the analysis of the prognostic value of plasma and urinary NT-proBNP in regard to a potential selection bias. Because of inability to urinate, it might be also difficult to correlate the time of sampling to symptom onset.

Also, 24 patients who presented at least twice with acute chest pain in the emergency department could only be included once in the current analysis regarding the prognostic capability of plasma and urinary NT-proBNP. Therefore, only the first admission was included in the Kaplan–Meier analysis if blood and urine sample and a follow-up were present. Due to limited personal resources, there was no patient inclusion possible from the middle of July to the end of August 2015 during the study period. One hundred five patients presented with acute chest pain in the emergency department and denied written informed consent. Therefore, these patients could not be recruited for the study. This resulted in a reduced number of participants in this study. A major number of subjects would have made the results more consistent.

In the subgroup of patients with chest wall syndrome, six patients died during the follow-up period. The interpretation of this surprising finding is limited due to the fact that the cause of death is unknown.

Conclusions

Urinary NT-proBNP was assessed prospectively in a cohort of patients presenting with acute chest pain in the emergency department and compared with plasma NT-proBNP. Regarding the endpoints all-cause mortality and major adverse cardiac events, it seems to provide a relevant and predictive value in a long-term follow-up in patients presenting with acute chest pain and in the subgroup of patients with ACS. So, in the future, urinary NT-proBNP might help detect patients with acute chest pain at high risk by using a simple urine test stripe. But further studies with a larger number of participants are necessary to confirm our findings.

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Conflict of interest

None declared.

Table 4B Cox regression analysis for plasma and urinary NT-proBNP regarding the combined endpoint in patients with acute coronary syndrome

| ACS cohort | Plasma NT-proBNP | P-value | HR | 95% CI | Urinary NT-proBNP | P-value | HR | 95% CI |
|------------|------------------|---------|----|--------|-------------------|---------|----|--------|
| Marker     | 0.033            | 1.69    | 1.04; 2.75 | 0.003 | 1.95 | 1.26; 3.03 |
| GFR        | 0.206            | 0.42    | 0.11; 1.61 | 0.891 | 1.12 | 0.23; 5.43 |
| Troponin I | 0.742            | 0.96    | 0.78; 1.19 | 0.384 | 0.91 | 0.72; 1.13 |
| Age        | 0.143            | 1.02    | 0.99; 1.04 | 0.052 | 1.02 | 1.00; 1.05 |
| Diabetes   | 0.794            | 0.75    | 0.45; 1.28 | 0.324 | 0.77 | 0.45; 1.30 |
| Hypertension | 0.170          | 1.64    | 0.81; 3.33 | 0.140 | 1.70 | 0.84; 3.44 |

ACS, acute coronary syndrome; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.
References

1. Nielsen LS, Svanegaard J, Klitgaard NA, Egebald H. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. *Eur J Heart Fail* 2004; 6: 63–70.

2. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Dougherty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. *Clin Endocrinol (Oxf)* 1997; 47: 287–296.

3. Hammerer-Lercher A, Ludwig W, Falkensammer G, Müller S, Neubauer E, Puschendorf B, Pachinger O, Mair J. Natriuretic peptides as markers of mild forms of left ventricular dysfunction: effects of assays on diagnostic performance of markers. *Clin Chem* 2004; 50: 1174–1183.

4. Gustafsson F, Steensgaard-Hansen F, Badskjær J, Poulsen AH, Corell P, Hildebrandt P. Diagnostic and prognostic performance of N-terminal proBNP in primary care patients with suspected heart failure. *J Card Fail* 2005; 11: 15–20.

5. Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P, Corell P, Tendra M, Castaigne A, Anker SD, Amann-Zalan I, Hoersch S, Katus HA. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. *Circulation* 2004; 110: 1780–1786.

6. Ponikowski P, Voors AA, Anker SD, Bueno H, Celldin JG, Coats AJ, Falk V, González-Juantej AE, Harjola VP, Jankowska EA, Jessup M, Corrêa A, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Schumacher A, Soria F, Portolés M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.

7. Ng LL, Geeranavar S, Jennings SC, Loke I, O’Brien RJ. Diagnosis of heart failure using urinary natriuretic peptides. *Clin Sci* 2004; 106: 129–133.

8. Michielsen ECH, Bakker JA, van Kammenade RRJ, Pinto YM, van Dieijen-Visser MP. The diagnostic value of serum and urinary NT-proBNP for heart failure. *Ann Clin Biochem* 2008; 45: 389–394.

9. Jungbauer CG, Buchner S, Birner C, Resch M, Heinicke N, Debl K, Buesing M, Biermeier D, Schmitz G, Riegger G, Luchner A. N-terminal pro-brain natriuretic peptide from fresh urine for the biochemical detection of heart failure and left ventricular dysfunction. *Eur J Heart Fail* 2010; 12: 331–337.

10. Jungbauer CG, Stadler S, Birner C, Resch M, Ücer E, Fredersdorf S, Maier LS, Luchner A. Urinary NT-proBNP is independently associated with long-term prognosis of mortality in chronic heart failure. *J Dis Markers* 2015; 2: 1027.

11. Cortés R, Rivera M, Salvador A, Bertomeu V, de Burgos FG, Roselló-Lleti E, Portolés M, Payá R, Martínez-Dolz L, Climent V. Variability of NT-proBNP plasma and urine levels in patients with stable heart failure: a 2-year follow-up study. *Heart* 2007; 93: 957–962.

12. Ng LL, Loke J, Davies J, Geeranavar S, Khunti K, Stone MA, Squire IB. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspepsia. *Eur J Gastroenterol Hepatol* 2005; 17: 389–394.

13. Galvani M, Ottani F, Oltrona L, Drissi S, Geraci G, Maggioni AP, Magnani PM, Mininni N, Prando MD, Turbiano F, Vernocchi A, Vecchio C; on behalf of the Italian Working Group on Atherosclerosis, Thrombosis, and Vascular Biology and the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004; 110:128–134.

14. Omland T, Persson A, Ng L, O’Brien R, Karlsson T, Herlitz J, Hartford M, Caidahl K. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002; 106: 2913–2918.

15. Ibanez B, James S, Argewall S, Antunes MJ, Buccionitte-Ducci C, Bueno H, Colomer-Dorta CM, Cuerdenovos JA, Haverkoren S, Hindricks G, Kastrati A, Lenzen MJ, Prescot E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39: 119–177.

16. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Baix J, Bojer MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Muhkerjee D, Storey RF, Windecker S, ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37: 267–315.

17. Luchner A, Hengstenberg C, Löwel H, Buchner S, Schunkert H, Rieger GA, Holmer S. NT-ProBNP in outpatients after myocardial infarction: interaction between symptoms and left ventricular function and optimized cut-points. *J Card Fail* 2005; 11: 21–27.

18. Luchner A, Hengstenberg C, Löwel H, Trawinski J, Baumann M, Rieger GA, Schunkert H, Holmer S. N-terminal pro-brain natriuretic peptide after myocardial infarction: a marker of cardiorenal function. *Hypertension* 2002; 39: 99–104.

19. Galvani M, Ferrini D, Ottani F. Natriuretic peptides for risk stratification of patients with acute coronary syndromes. *Eur J Heart Fail* 2004; 6: 327–333.

20. Kang Q, Wan Z, Huang Z. N-terminal pro-brain natriuretic peptide in patients with acute coronary syndrome. *Int J Clin Pharmaco Ther* 2017; 55: 78–84.

21. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 2004; 6: 257–260.

22. Goetze JP, Jensen G, Møller S, Bendsen F, Reinholdt JH, Henriksen JH. BNP and N-terminal proBNP are both extracted in the normal kidney. *Eur J Clin Invest* 2006; 36: 8–15.

23. Linsen GCM, Damman K, Hillega HL, Navis G, Veldhuisen DJ, Voors AA. Urinary N-terminal prohormone brain natriuretic peptide excretion in patients with chronic heart failure. *Circulation* 2009; 120: 35–41.

24. van Kammenade RRJ, Januzzi JL, Bakker JA, Houben AJ, Rennenberg R, Kroon A, Crisp HJGM, van Dieijen-Visser MP, Pinto YM. Renal clearance of B-type natriuretic peptide and amino terminal pro B-type natriuretic peptide: a mechanistic study of hypertensive subjects. *J Am Coll Cardiol* 2009; 53: 884–890.

25. Cortés R, Portolés M, Salvador A, Bertomeu V, García de Burgos F, Martínez-Dolz L, Roselló-Lleti E, Climent V, Jordán A, Payá R, Sogorb F, Rivera M. Diagnostic and prognostic value of urine NT-proBNP levels in heart failure patients. *Eur J Heart Fail* 2006; 8: 621–627.

26. Toufan M, Namdar H, Abbasnezhad M, Habibzadeh A, Esmaeili H, Yaraghi S, Samani Z. Diagnostic values of plasma, fresh and frozen urine NT-proBNP in heart failure patients. *J Cardiovasc Thorac Res* 2014; 6: 111–115.

27. Roselló-Lleti E, Rivera M, Cortés R, Grigorian L, Miró V, Soria F, Portolés M, Bertomeu V. Urinary NT-proBNP: a valuable marker in the assessment of
patients with essential hypertension. *Rev Esp Cardiol* 2009; 62: 1322–1325.

28. Khan S, Sithisarn T, Bada H, Vranicar M, Westgate PM, Hanna M. Urinary NT-proBNP levels and echocardiographic parameters for patent ductus arteriosus. *J Perinatol* 2017; 37: 1319–1324.

29. Goetze JP, Gore A, Møller CH, Steinbrüchel DA, Rehfeld JF, Nielsen LB. Acute myocardial hypoxia increases BNP gene expression. *FASEB J* 2004; 18: 1928–1930.

30. Kavsak PA, Ko DT, Newman AM, Palomaki GE, Lustig V, MacRae AR, Jaffe AS. Risk stratification for heart failure and death in an acute coronary syndrome population using inflammatory cytokines and N-terminal pro-brain natriuretic peptide. *Clin Chem* 2007; 53: 2112–2118.

31. van der Zee PM, Cornel JH, Bholasingh R, Fischer JC, van Straalen JP, De Winter RJ. N-terminal pro B-type natriuretic peptide identifies patients with chest pain at high long-term cardiovascular risk. *Am J Med* 2011; 124: 961–969.