European Journal of Heart Failure (2016)
doi:10.1002/ejhf.604

Natriuretic peptide levels taken following unplanned admission to a cardiology department predict the duration of hospitalization

Marte Asphaug[1], Øyvind Skadberg[1], Ingvild Dalen[1], and Kenneth Dickstein[1,2]*

[1]Stavanger University Hospital, Stavanger, Norway ; and [2]University of Bergen, Bergen, Norway

Received 11 January 2016; revised 7 June 2016; accepted 7 June 2016

Aims Natriuretic peptide (NP) levels are routinely employed as useful diagnostic and prognostic tools in the evaluation of patients with heart failure (HF). As hospitalization is the major consumer of healthcare resources, the prognostic power of admission NPs with regard to the duration of hospitalization deserves further investigation.

Methods and results We assessed retrospectively the association between NP values sampled shortly following unplanned admission and the duration of hospitalization in 2978 patients admitted to a cardiology department. Duration of hospitalization (hours) and survival were determined by interrogation of the electronic medical records system. Associations with peptide levels were estimated using regression models and receiver operating characteristic (ROC) analysis. The results demonstrate a significant positive relationship between NP levels and the duration of hospitalization, after adjusting for age ($P < 0.001$). The median duration of hospitalization for the lowest BNP and NT-proBNP quintiles were 80 and 97 h, respectively, vs. 224.5 and 236 h for the highest quintiles. Using cut-off levels of 115 pmol/L for BNP and 390 pmol/L for NT-proBNP, the peptides have a positive predictive value of 78% and 85% for a stay >4 days. During follow-up, NP levels were strongly predictive of all-cause mortality.

Conclusion The results quantify the strong relationship between NP levels taken following an unplanned admission to a cardiology department and the duration of hospitalization. This information permits improved identification of a patient population likely to require a prolonged hospital stay and consume more healthcare resources. Such patients may require a more aggressive diagnostic, treatment, and management strategy.

Keywords Natriuretic peptides • Heart failure • Duration of hospitalization

Introduction

The prevalence of heart failure (HF) according to 2013 data is 6.2% in patients aged 60–79 years, with a marked rise to 10% in patients aged >80 years. The incidence is projected to increase 25% by 2030,[1] mainly due to an increase in the total population and increasing average age due to improved survival for patients with both cardiovascular and non-cardiovascular morbidity. HF is a major cause of hospitalization, and in Europe it represents 5% of all acute hospital admissions.[2] HF represents a major economic burden on western healthcare systems, and 50–60% of the HF costs are estimated to be associated with hospitalization.[2–4]

Natriuretic peptide (NP) levels are important diagnostic tools in confirming and staging cardiac disease and HF. In response to volume and pressure overload, a prohormone is secreted from the myocardium and cleaved into two biologically active fragments: BNP and the biologically inactive NT-proBNP.[5] Both BNP and NT-proBNP are significantly increased in patients with HF secondary to LV dilatation and wall stress.[6,7] Serum concentrations

*Corresponding author. Cardiology Division, Stavanger University Hospital, Gerd Ragna Block Thorsensgate 8, 4003 Stavanger, Norway. Tel: +47 5151 8000, Fax: +47 5151 9921, Email: kenneth.dickstein@med.uib.no

are moderately influenced by demographic factors such as age, gender, renal dysfunction, and obesity.[8,9]

The literature confirms that high NP levels are associated with prolonged hospital stays;[10] however, the prognostic power of NPs with regard to predicting duration of hospitalization deserves further investigation. This is of topical interest as a readily available biomarker able to predict extended hospital stay will help identify patients in need of an aggressive approach and treatment, which may serve to improve the treatment strategy and optimize the use of hospital resources.[11,12] The objective of this analysis was to evaluate the degree to which NP levels predict the duration of hospitalization in unplanned admissions to a cardiology department. We also evaluated cut-off values for the peptides' ability to predict stays >4 days.

Methods

Study design

In this retrospective, single-centre analysis we collected data from the electronic medical records (EMR) in a Norwegian University teaching hospital. The data were anonymized, and the Regional Health Trust and the local Data Protection Authority approved the collection of data.

Study population

This study included 3194 consecutive patients with a registered NP value taken following unplanned admission to a cardiology department at Stavanger University Hospital during the period April 2005–June 2013. Admission diagnoses were not available. A total of 216 patients who died during the index admission were excluded, leaving a final study population of 2978. A flow chart of patients included in the study is shown in *Figure 1*.

In January 2011, NT-proBNP sampling was replaced by BNP sampling due to change in hospital routines. A total of 1040 patients were included in the final NT-proBNP group and 1938 patients were included in the final BNP group, 35% and 65%, respectively, of the total study population. Only the first NP value registered following the index admission (first registered admission) was used in this analysis. Age was registered for all patients. The indication for ordering an NP assay was based on conventional clinical practice. The sample of patients should be representative for the general population admitted acutely to a cardiology department.

Collection of data

We interrogated the EMR of Stavanger University Hospital. Patients with a registered NP value during the period of April 2005–June 2013 were given a fictive identification number. For each patient, the first registered NP value, the corresponding length of hospitalization (in hours), and age were recorded. Duration of hospitalization was calculated from the hour of admission until the hour of discharge, both registered routinely by nursing staff. In cases where patients were registered with more than one hospitalization, we only collected data from the first event (index admission). The primary discharge diagnoses were registered. Mortality data until 3 August 2013 were also collected from the EMR, which is automatically synchronized with the Norwegian death register. We assumed a minimal loss to follow-up. It is essential to note that all NP values are reported using the SI unit pmol/L. For conversion to pg/mL, multiply by 8.46 for NT-proBNP and by 3.47 for BNP. For NT-proBNP, 21 values were registered as above the upper quantitation limit (>4000); these values were changed to the fictive value of 4010 in this study.

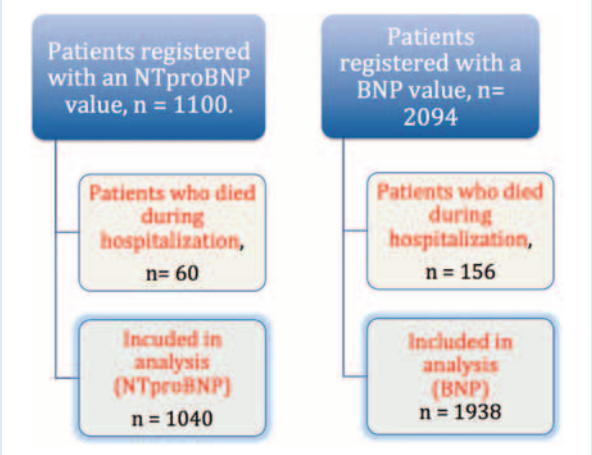

Figure 1 Flow chart of patients included in the study with a registered NT-proBNP (2005–2011) and BNP (2011–2013).

N-terminal pro brain natriuretic peptide assays

The Elecsys proBNP II assay was used for measuring NT-proBNP on the Roche Modular Analytics E170 analyser. The measuring range was 5–35 000 pg/mL or 0.6–4130 pmol/L. Studies of this NT-proBNP assay have shown a clinical sensitivity and specificity of 88% and 92%, respectively, in patients with diagnosed stable HF, using a threshold of 125 pg/mL.

Brain natriuretic peptide assays

The Architect BNP assay was used for measuring BNP in EDTA plasma on the Architect iSystem (Abbott Diagnostics Division). The measuring range was 10–5000 pg/mL; after dilution the range was 1–25 000 pg/mL. Studies of this BNP assay have shown a clinical sensitivity and specificity of 74.2% and 91.5%, respectively, in patients with diagnosed stable HF, using a threshold of 100 pg/mL.

Statistical analysis

All statistical analysis was performed using the IBM SPSS Statistics 22. Median hospitalization durations (days) with confidence intervals (CIs) were plotted for each decile group of NP values in bar charts. Spearman's rho was used to estimate the correlation between NP values and duration of hospitalization. Multivariable linear regression analysis was done to model parametrically the relationship between the duration of hospitalization (hours) and the NP values. Owing to heavily skewed distributions that affected the residual distributions, hospitalization durations were log transformed. Furthermore, log transformations of NP values improved the fit of the regression models as measured by the R^2 statistic. The effect estimates were adjusted for age. Receiver operating characteristic (ROC) analysis was used to assess the

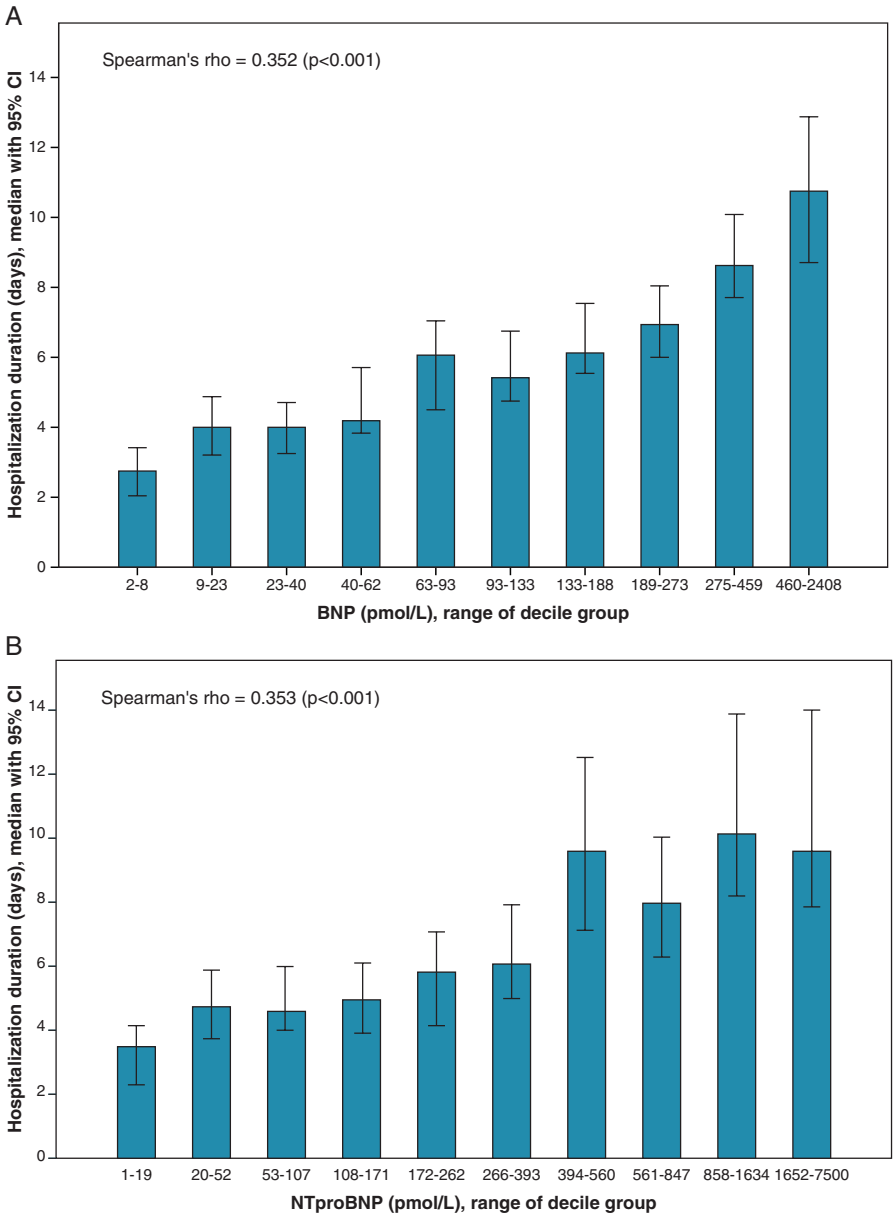

Figure 2 Duration of hospitalization in days for deciles of (*A*) BNP values ($n = 1938$) and (*B*) NT-proBNP values ($n = 1040$). CI, confidence interval.

discriminating power of NP values with regard to patients requiring prolonged stays, defined as stays >4 days. Kaplan–Meier survival curves were derived to assess all-cause mortality stratified by quartiles of BNP and NT-proBNP, and hazard ratios were estimated for the quartiles using Cox regression.

Results

Of the 3194 patients first included in the study, 216 were censored from further analysis due to death during the index hospitalization. These patients had a median BNP level of 289 pmol/L and a median NT-proBNP level of 1520 pmol/L. The final study group consisted of 2978 patients, out of whom 35% were registered with an NT-proBNP value and 65% were registered with a BNP value. The relationship between NP levels and the duration of hospitalization was significant, with substantial increases in hospitalization duration with increasing NP values (*Figure 2*). *Figure 2* shows that patients in the higher NP deciles had substantially longer hospitalizations. The median duration of hospitalization for the lowest BNP quintile (BNP values 2.3–23.1, median 8.7 pmol/L) was 3.3 days (80 h), vs. 9.4 days (224.5 h) for the highest quintile (BNP values 275.4–2407.5, median 458.6 pmol/L). The median duration of hospitalization for the lowest NT-proBNP quintile (NT-proBNP values 1.0–52.0, median 19.0 pmol/L) was 4 days (97 h), vs. 9.8 days

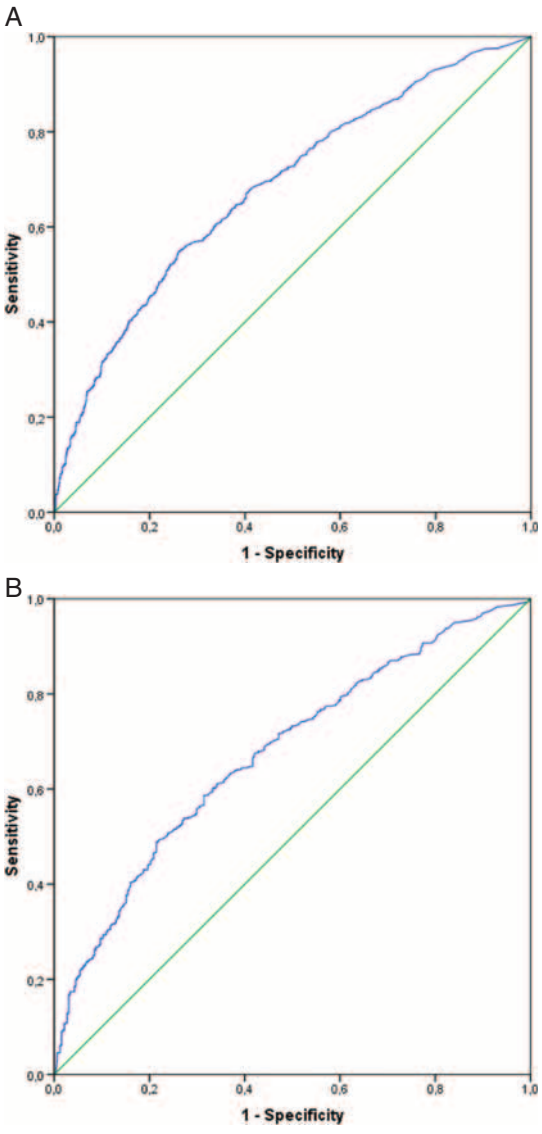

Figure 3 Receiver operating characteristic curve displaying sensitivities and specificities with regard to discriminating between patients requiring long stays (>4 days) and patients with shorter stays for (*A*) BNP ($n = 1938$) and (*B*) NT-proBNP ($n = 1040$).

(236 h) for the highest quintile (NT-proBNP values 858–7500, median 1643 pmol/L).

Linear regression analyses confirmed that both NT-proBNP and BNP were strong and comparable predictors for the duration of hospitalization ($P < 0.001$). The effect estimate from a linear model with predictor log-transformed NP values and response log-transformed hospitalization durations was 0.25 (95% CI 0.22–0.28), meaning that a 1% increase in BNP is associated with an ~0.25% increase in hospitalization duration. Similarly, a 1% increase in NT-proBNP is associated with a 0.21% increase in hospitalization duration (95% CI 0.17–0.24). The results are sustained and even somewhat stronger when adjusting for age, with

Table 1 Primary discharge diagnoses for all patients registered with a natriuretic peptide level at admission (including patients who died during hospitalization) ($n = 3194$)

Primary discharge diagnoses	No.	% of total population
Arrhythmias	443	14
Heart failure and cardiomyopathy	376	12
Hypertension	201	6
Airways infection	194	6
Angina pectoris/ischaemic heart disease	193	6
Other	1787	56
Total	3194	100

estimated effects of 0.28 (0.25–0.32) and 0.23 (0.19–0.26) for BNP and NT-proBNP, respectively. As indicated by the R^2 and ΔR^2 values, which were approximately equal, BNP and NT-proBNP levels explain ~12% and 13% of the variation in duration. Age explains <1% of this variation.

The ROC curves in *Figure 3* show sensitivities and specificities with regard to discriminating between patients requiring long stays (>4 days) and patients with shorter stays. Of the patients registered with a BNP value, 63% had stays longer than 4 days (96 h). Of the patients registered with an NT-proBNP value, 68% required >4 days in hospital.

The ROC area under the curve (AUC) was 0.68 (95% CI 0.66–0.71) for BNP and 0.68 (95% CI 0.64–0.71) for NT-proBNP, indicating some discriminative power. The cut-off points that maximized the sum of sensitivity and specificity for identifying prolonged stays (>4 days) were 115 pmol/L for BNP [sensitivity 55%, specificity 74%, positive predictive value (PPV) 78%, negative predictive value (NPV) 49%] and 390 pmol/L for NT-proBNP (sensitivity 49%, specificity 78%, PPV 83%, NPV 42%); however, other cut-off points performed nearly equally well.

The primary discharge diagnoses were registered for all patients, and the five most frequent are listed in *Table 1*. A total of 14% of the patients were discharged with a primary diagnosis of arrhythmia, 12% with HF or cardiomyopathy, 6% with hypertension, 6% with an airway infection, and 6% with angina pectoris or ischaemic heart disease. The secondary diagnoses were unfortunately not captured in the hospital's EMR.

The primary objective of this analysis was to evaluate the association between NP values and the duration of hospitalization; however, mortality data over a median follow-up of 1.2 years for BNP and 5.2 years for NT-proBNP were available and it is appropriate to report the relationship of NP levels to survival. Kaplan–Meier survival curves for all-cause mortality within quartiles of NP values are depicted in *Figure 4*, showing poorer outcome associated with increasing NP values. Median survival times were 7.9 years for patients with NT-proBNP values within the first quartile; 5.8 years within the second quartile; 3.8 years within the third quartile; and 1.3 years within the fourth and highest quartile. Corresponding results for quartiles of BNP values are not presented due to shorter follow-up time.

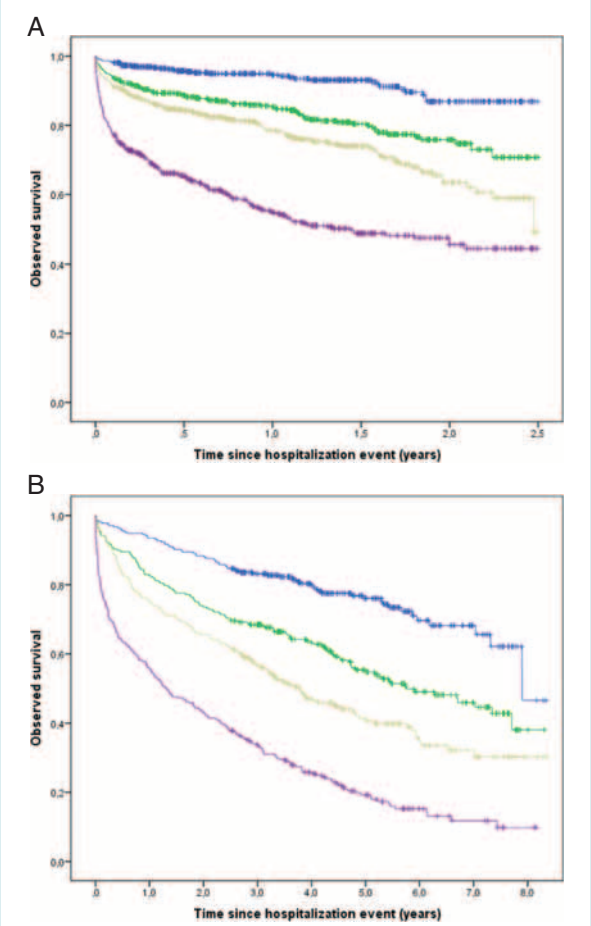

Figure 4 Observed survival within quartiles of (*A*) BNP values ($n = 2094$): Q1, range 2.3–34.4 (blue); Q2, range 34.6–101.9 (green); Q3, range 102.5–249.7 (yellow); Q4, range 250.6–3925.7 (purple); and (*B*) NT-proBNP values ($n = 1100$): Q1, range 1.0–84.0 (blue); Q2, range 85.0–286.0 (green); Q3, range 287.0–746.0 (yellow); Q4, range 748.0–7500 (purple). Censored observations are indicated by '+'.

For NT-proBNP, the hazard ratio for all-cause death for Q2 vs. Q1 was 2.0 (95% CI 1.5–2.7), for Q3 vs. Q1 it was 3.0 (2.2–3.9), and for Q4 vs. Q1 it was 5.9 (4.5–7.7). For BNP, the corresponding hazard ratio for Q2 vs. Q1 was 2.5 (95% CI 1.6–3.9), for Q3 vs. Q1 it was 4.0 (2.6–6.2), and for Q4 vs. Q1 it was 6.9 (4.6–10.5).

Discussion

This retrospective analysis of 2978 patients demonstrates a significant and convincing linear relationship between NP level and the length of hospital stay, and indicates that NP levels measured following unplanned admission to a cardiology department are a strong predictor for hospitalization duration. After adjusting for age, NP values remained significant predictors for the duration of hospitalization. Increased NP levels identify patients with a prolonged hospital stay as well as a poor long-term prognosis.

The European Society of Cardiology (ESC) 2012 HF guidelines recommend that NP levels are measured routinely in all patients with clinical signs and symptoms suggestive of HF, such as pulmonary rales and exertional dyspnoea.[6] Clinical practice and diagnostic algorithms vary according to local routines between hospitals, making rapidly available measurements of NPs useful diagnostic biomarkers in designing short- and long-term treatment strategies.

Elevated NP levels can be seen in several cardiac and non-cardiac conditions such as AF, pulmonary embolism, and renal failure; however, normal NP levels in an untreated patient exclude significant cardiac disease with an NPV of 98%, making it an excellent rule-out test.[6,13] In recent years, there has been an increased interest regarding the diagnostic and prognostic value of NPs, extending their use as a rule-out test for HF. Studies have proven NP levels to have a stronger prognostic value than LVEF, peak VO_2, and the Heart Failure Survival Score (HFSS),[14] and to correlate strongly with NYHA class.[15] Low NP levels have a strong NPV and have been associated with improved long-term prognosis. NP-guided therapy has been shown to assist in identifying patients who may be discharged with reasonable short-term outcomes.[10,16–21] Conversely, elevated levels of the biomarkers assist in the identification of patients with a risk of readmission or death. A number of demographic factors have also been shown to influence the serum concentration of NPs modestly. Age, female gender, renal dysfunction, hypertension, and diabetes have all been shown to elevate the NP level mildly, while obesity may reduce NP levels.[9]

A question of topical interest is whether BNP and NT-proBNP, having substantial differences, can be used interchangeably. The two NPs have been shown to be nearly equivalent predictors for death in patients with HF,[19] and to have similar diagnostic characteristics,[22,23] while some studies suggest that NT-proBNP may be a more discerning marker of HF than BNP.[24,25] In our analysis, the performance of the two peptides with regard to predicting the duration of hospitalization was remarkably similar.

There are several studies that investigated how NP testing influences the duration of hospitalization, and it has been suggested that the use of NPs reduces hospitalization rates and costs, primarily as a result of improved evaluation and treatment.[26–30]

Rutten *et al.*[27] showed that the introduction of NT-proBNP has led to decreased hospital-related costs, and Siebert *et al.*[28] suggested that hospital days could be reduced by 12% by optimal use of NT-proBNP. In contrast, in a randomized trial comparing BNP testing with no BNP testing in patients with stable chronic HF, Schneider *et al.*[26] showed no between-group differences in hospital admission rates, duration of admission, or management of patients in an emergency department setting.

Our findings in a large unselected population with long-term follow-up are consistent with the few smaller studies that assessed the value of NPs in predicting the duration of hospitalization. When evaluating patients with acute decompensated HF, Fonarow *et al.*[10] showed that patients in higher admission BNP quartiles had longer lengths of stay. Kucher *et al.*[31] reported that a low NT-proBNP value (<500 pg/mL) at admission is highly accurate in predicting an uneventful hospital course for patients presenting with pulmonary embolism ($n = 73$). They suggest that a low NP

value can help identify potential candidates for a short hospital stay or outpatient care.

Methodological limitations

In this analysis only patients with an unplanned admission to cardiology departments and a clinical suspicion of HF were included, and the applicability of the results should be restricted to such patients. Our results do not provide information on the performance of NP measurements in predicting the duration of hospitalization in other populations.

The results confirm that NP levels taken following unplanned admission to a cardiology department are predictive of the duration of hospitalization after adjustment for age. Other relevant data such as diagnosis, aetiology, co-morbidity, gender, body mass index, and estimated glomerular filtration rate were not available and have not been adjusted for in the analysis. The predictive value of NPs partially reflects their correlation with such factors, but is has been demonstrated that NPs provide information independent of these factors in multivariable analysis.[32] Adjusting for factors such as age, obesity, gender, or renal dysfunction might modestly influence the accuracy of the predictive value of NP levels, and clinicians should be aware of their potential impact. Management strategy cannot be based on NP level alone. However, in practice, the clinical utility of a routinely available NP level remains strongly independent of these demographics.

Patients who died during the index hospitalization were censored from the analysis, as it would have been inappropriate to estimate their duration of hospitalization. Only all-cause mortality is reported in this study, as cause-specific death was not registered in the hospital database. Of the NT-proBNP values, 34 were registered as a fictive number (>4000) as the samples had not been diluted; these values were changed to 4010 in this study. If diluted, the true values could possibly have been far higher than 4010, which would have given a higher mean NT-proBNP for the 10th decile than calculated in this study.

Only the primary discharge diagnoses were available for all patients, showing that only 38% were discharged with a primary cardiovascular diagnosis. However, HF is frequently registered as a secondary diagnosis, which was not captured in the EMR.

Clinical implications

This analysis demonstrates that measurement of NPs following an unplanned admission to a cardiology department in patients with a suspicion of HF are predictive of the length of hospital stay after age adjustment. This suggests that together with other clinical, demographic, and laboratory information available to the clinician, early sampling of NPs in such patients may represent a useful tool in the early identification and triage of patients in need of an aggressive management strategy. NP levels can inform the design of diagnostic and treatment strategies, and potentially assist in efficient allocation of hospital resources, reducing the cost of hospital stay. Hospitalization represents the major financial burden for healthcare systems, and NP sampling at admission, a relatively routine and rapidly available laboratory assay, could be cost-effective. This hypothesis deserves to be tested prospectively.

Conclusion

The results of this study demonstrate a strong and significant relationship between NP levels taken following an unplanned admission to a cardiology department and the duration of hospitalization. Our findings suggest that NP levels measured at hospital admission assist in identifying a population likely to require prolonged hospitalization. The latter group will presumably consume more healthcare resources and therefore would require a more aggressive diagnostic, treatment, and management strategy.

Conflict of interest: none declared.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013;**127**:e6–e245.
2. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? *Europace* 2011;**13** Suppl 2:ii13–ii17.
3. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014;**171**:368–376.
4. Butler J, Marti C, Pina I, DeFilippi C. Scope of heart failure hospitalization. *Congest Heart Fail* 2012;**18** Suppl 1:S1–S4.
5. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006;**92**:843–849.
6. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
7. Troughton R, Michael Felker G, Januzzi JL Jr. Natriuretic peptide-guided heart failure management. *Eur Heart J* 2014;**35**:16–24.
8. Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J, Pedersen F. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. *Heart* 2003;**89**:745–751.
9. Luchner A, Behrens G, Stritzke J, Markus M, Stark K, Peters A, Meisinger C, Leitzmann M, Hense HW, Schunkert H, Heid IM. Long-term pattern of brain natriuretic peptide and N-terminal pro brain natriuretic peptide and its determinants in the general population: contribution of age, gender, and cardiac and extra-cardiac factors. *Eur J Heart Fail* 2013;**15**:859–867.
10. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:1943–1950.
11. Davison BA, Metra M, Senger S, Edwards C, Milo O, Bloomfield DM, Cleland JG, Dittrich HC, Givertz MM, O'Connor CM, Massie BM, Ponikowski P, Teerlink JR, Voors AA, Cotter G. Patient journey after admission for acute heart failure: length of stay, 30-day readmission, and 90-day mortality. *Eur J Heart Fail* 2016; in press.

12. Khan H, Greene SJ, Fonarow GC, Kalogeropoulos AP, Ambrosy AP, Maggioni AP, Zannad F, Konstam MA, Swedberg K, Yancy CW, Gheorghiade M, Butler J; EVEREST Trial Investigators. Length of hospital stay and 30-day readmission following heart failure hospitalization: insights from the EVEREST trial. *Eur J Heart Fail* 2015;**17**:1022–1031.
13. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001;**37**:379–385.
14. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;**24**:1735–1743.
15. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, Luchner A, McDonagh T, Mair J, Nieminen M, Francis G. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;**24**:1710–1718.
16. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juillière Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol* 2007;**49**: 1733–1739.
17. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. *J Am Coll Cardiol* 2009;**53**:2343–2348.
18. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, Leosco D, Perrone-Filardi P. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. *PLoS One* 2013;**8**:e58287.
19. N Noveanu M, Breidthardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, Socrates T, Arenja N, Reiter M, Meissner J, Heinisch C, Stalder S, Mueller C. Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. *Crit Care* 2011;**15**:R1.
20. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. *Arch Intern Med* 2010;**170**:507–514.
21. Brunner-La Rocca HP, Eurlings L, Richards AM, Januzzi JL, Pfisterer ME, Dahlström U, Pinto YM, Karlström P, Erntell H, Berger R, Persson H, O'Connor CM, Moertl D, Gaggin HK, Frampton CM, Nicholls MG, Troughton RW. Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials. *Eur J Heart Fail* 2015;**17**:1252–1261.
22. Worster A, Balion CM, Hill SA, Santaguida P, Ismaila A, McKelvie R, Reichert SM, McQueen MJ, Booker L, Raina PS. Diagnostic accuracy of BNP and NT-proBNP in patients presenting to acute care settings with dyspnea: a systematic review. *Clin Biochem* 2008;**41**:250–259.
23. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. *Heart* 2005;**91**:606–612.
24. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. *Clin Chim Acta* 2004;**341**:41–48.
25. Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H, Takano T. Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure. *Eur J Heart Fail* 2004;**6**:295–300.
26. Schneider HG, Lam L, Lokuge A, Krum H, Naughton MT, De Villiers Smit P, Bystrzycki A, Eccleston D, Federman J, Flannery G, Cameron P. B-type natriuretic peptide testing, clinical outcomes, and health services use in emergency department patients with dyspnea: a randomized trial. *Ann Intern Med* 2009;**150**:365–371.
27. Rutten JH, Steyerberg EW, Boomsma F, van Saase JL, Deckers JW, Hoogsteden HC, Lindemans J, van den Meiracker AH. N-terminal pro-brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, costs, and outcome. *Am Heart J* 2008;**156**:71–77.
28. Siebert U, Januzzi JL Jr, Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. *Am J Cardiol* 2006;**98**:800–805.
29. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, Scholer A, Christ M, Perruchoud AP. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006;**166**:1081–1087.
30. Ledwidge MT, O'Connell E, Gallagher J, Tilson L, James S, Voon V, Bermingham M, Tallon E, Watson C, O'Hanlon R, Barry M, McDonald K. Cost-effectiveness of natriuretic peptide-based screening and collaborative care: a report from the STOP-HF (St Vincent's Screening TO Prevent Heart Failure) study. *Eur J Heart Fail* 2015;**17**:672–679.
31. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation* 2003;**107**:1576–1578.
32. van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, Paulus WJ, Voors AA, Hillege HL. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol* 2013;**61**:1498–1506.