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ORIGINAL RESEARCH ARTICLE

Plasma amino-terminal pro B-type natriuretic peptide as a predictor of late cardiovascular mortality in patients with acute lung disorders: a prospective, observational cohort study

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Abstract

Aims Pneumonia and acute exacerbations of obstructive lung diseases (AEOLD) are associated with a significant long-term mortality. Elevated level of amino-terminal pro B-type natriuretic peptide (NT-proBNP) is a predictor of late all-cause mortality in these disorders but the pathophysiological basis for this is unknown. The present study was conducted to define the predictive role of NT-proBNP on late cardiovascular mortality among patients with acute lung disorders.

Methods and results This prospective, observational cohort study included 269 hospitalized patients with pneumonia or AEOLD. Plasma level of NT-proBNP, age, sex, body mass index, arterial blood oxygen saturation, C-reactive protein, and urea were recorded. The survival and causes of death were recorded after a median of six years. NT-proBNP $>$ 666 ng/mL was related to cardiovascular mortality with an adjusted hazard ratio of 2.93 (1.19–7.18). This risk was of similar magnitude to that associated with diabetes and greater than that associated with arterial hypertension, hypercholesterolemia, and smoking. NT-proBNP was also related to all-cause mortality with adjusted hazard ratio of 2.39 (1.49–3.85) per 10 times increase in NT-proBNP concentration. However, the association between NT-proBNP and non-cardiovascular mortality did not reach statistical significance [adjusted hazard ratio 1.89 (0.93–3.85)].

Conclusion NT-proBNP concentration during pneumonia or AEOLD was strongly associated with late cardiovascular mortality but not with non-cardiovascular mortality. The results suggest that the increase in NT-proBNP during acute lung disorders may reveal occult cardiac diseases arousing a question whether patients with acute pulmonary disorders with elevated NT-proBNP levels should be subjected to further diagnostic or therapeutic cardiovascular interventions.

Keywords Pneumonia; Asthma; COPD; Heart failure; Mortality; Amino-terminal pro B-type natriuretic peptide

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Introduction

Pneumonia and acute exacerbation of obstructive lung diseases (AEOLD) are probably the most common acute pulmonary disorders that require hospitalization. In addition to acute in-hospital mortality, these disorders are also associated with an increased risk of death for several years after the initial episode. Given the high incidence of these disorders, their long-acting effect on mortality should be regarded as major public health threat.[1–3]

Several biomarkers have been evaluated to identify patients with an increased risk of late mortality after acute lung disorders. B-type natriuretic peptide (BNP) is one of the biomarkers used in this setting. Mechanical myocyte stretch in the heart, reflecting an increase in either the blood volume or pressure, results in the production of an intracellular precursor of BNP.

Its further processing results in the release of the biologically active BNP and an inert amino-terminal fragment [amino-terminal pro B-type natriuretic peptide (NT-proBNP)]. The plasma concentration of NT-proBNP is widely used to diagnose acute decompensated heart failure, and it is also increased in patients with asymptomatic left ventricular dysfunction.[4,5]

Several studies show that elevated NT-proBNP predicts late all-cause mortality in patients admitted to hospitals because of AEOLD and pneumonia.[6–13] However, the pathophysiological basis for this is unknown.[5] Apparently, it is usually assumed that the transient rise in NT-proBNP reveals an occult heart failure that is responsible for the increased risk of late all-cause death. However, there are also several non-cardiac factors that are associated with elevated NT-proBNP levels, including advanced age, female sex, low body weight, and impaired renal function.[4,14] Interestingly, recent studies have shown that hypoxia[15,16] and systemic inflammation[6,17] can also increase NT-proBNP levels. These two phenomena are common during the acute episodes of lung disorders and may associate with the late mortality.[3,18,19] Thus, it is possible that the association between NT-proBNP and late all-cause mortality after acute lung disorders may not relate to cardiac morbidity but to the lung disorder-associated hypoxia or systemic inflammation. Indeed, a recent study utilizing echocardiography reported that cardiac systolic or diastolic dysfunction is present in only a small proportion of patients with AEOLD with elevated plasma BNP levels.[5]

The primary purpose of the present study was to investigate whether NT-proBNP carries prognostic information on late cardiovascular and non-cardiovascular mortality among patients with acute lung disorder in a multivariate model including all confounders possibly affecting the NT-proBNP level. We hypothesized that if NT-proBNP level predicts the cardiovascular mortality better than non-cardiovascular mortality, the increased late mortality among patients with elevated NT-proBNP levels is predominantly because of occult cardiovascular morbidity.

Methods

Study design and the subjects

This prospective, observational cohort study was carried out in a single secondary centre. From November 2006 to May 2008, all adult patients admitted to the respiratory ward because of exacerbation of asthma, exacerbation of chronic obstructive pulmonary disease (COPD), or community-acquired pneumonia, were recruited. Of the 399 recruited patients, 129 were excluded from the study because of the following reasons: A need for treatment in intensive care unit, inability to give informed consent because of confusion, treatment of the acute lung disease had been started in other institution, refused to participate, and technical reasons. One patient with early (<30 days) death was also excluded from the analysis. Thus, a total of 269 patients remained in the final analysis. There were 87 patients with asthma exacerbation, 33 patients with COPD exacerbation, 119 with pneumonia, and 30 with both pneumonia and obstructive lung disease exacerbation (*Table 1*). Finally, there were 28 patients with a diagnosis of heart failure before the admission.

Measurements at admission

A detailed description of the baseline measurements have been described earlier.[20,21] The pre-hospitalization Karnofsky

Table 1. The basic characteristics of the 269 patients with acute lung disorder and association of the lung disorder type with mortality

Characteristic	Asthma exacerbation *N* = 87	COPD exacerbation *N* = 33	Pneumonia *N* = 119	Pneumonia and obstructive lung disease exacerbation *N* = 30	*P*-value	No. of missing values
Age, years	61 (58–65)	71 (68–73)	57 (54–60)	68 (65–72)	<0.001	0
Proportion of males	42%	79%	60%	53%	0.002	0
Body mass index, kg/m^2	31.5 (30.0–33.0)	25.8 (23.6–28.0)	27.7 (26.6–28.8)	28.3 (26.0–30.7)	<0.001	0
C-reactive protein, mg/L	28 (17–38)	56 (34–78)	166 (147–186)	162 (126–199)	<0.001	5
Urea, mmol/L	6.46 (5.76–7.17)	6.39 (5.35–7.43)	5.43 (4.77–6.08)	7.63 (5.62–9.63)	0.018	22
Arterial blood oxygen saturation, %	94.0 (93.3–94.8)	87.8 (85.2–90.4)	92.8 (92.0–93.7)	90.7 (88.5–93.0)	<0.001	16
NT-proBNP, pg/mL[a]	161 (118–218)	383 (270–544)	249 (186–334)	585 (351–975)	<0.001	0
Patients with NT-proBNP > 666 pg/mL	21%	33%	28%	47%	0.048	0
Patients with NT-proBNP over age-specific reference value for cardiac failure[24]	7%	12%	25%	30%	0.002	0
Association with late mortality, HR (95% CI)[b]	1.0	3.99 (2.20–7.24)	0.86 (0.48–1.54)	1.88 (0.92–3.82)	<0.001	0

The data are expressed as means (95% CIs) or as a percentage of a feature in the subgroup.
[a]Geometric mean and 95% CIs.
[b]Asthma as the reference group.

performance score was assessed. The patients' medical history and current medication were recorded from the patient files. The height, weight, waist circumference, oxygen saturation, blood pressure, temperature, and heart rate were measured. Plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration was measured utilizing a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). In addition, the following blood tests were performed: Glycosylated haemoglobin A1c, expressed as percentage of total haemoglobin (gHbA1c), C-reactive protein, haemoglobin, leukocytes, thrombocytes, albumin, urea, and arterial blood gas analysis.

Comorbidities were recorded if they were diagnosed by a physician before the hospitalization and verified from patient files. Hypercholesterolemia was recorded if it required medication. Screening diabetes was defined as presence of admission HbA1c $\geq$ 6.5% in a patient without a doctor's diagnosis of diabetes.[22]

Follow-up

In September 2013, the survival status was obtained in all patients from the National Statistical Service of Finland. The underlying causes of death, according to the International Classification of Diseases version 10, were obtained from death certificates. The median follow-up was 6 years.

Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki and was reviewed by Research Ethics Committee, Hospital District of Northern Savo (75//2006). All patients gave their written informed consent.

Statistical analysis

The distribution of NT-proBNP concentrations differed significantly from normal distribution ($P < 0.001$, Kologorov–Smirnov test) but was close to normal after 10 base logarithmic transformation. Therefore, logarithm transformed values were used for parametric statistical analysis.

At baseline, the associations of NT-proBNP levels with the following variables were analysed: The type of pulmonary disorder, age, sex, body mass index, arterial blood oxygen saturation, C-reactive protein, and serum urea. Unpaired *t*-tests, univariate analysis of variance, and Pearson's correlation coefficient were applied when appropriate.

Receiver operating characteristic curves were produced to define the best cut-off values for various variables to predict death during the follow-up. Comparative survival curves were constructed using Kaplan–Meier methodology. The assumption of proportional hazard was checked by graphically comparing the hazard curves. The linearity of the association of a variable with mortality was investigated by dividing the continuous variables to quartiles.

The unadjusted hazard ratios (HR) were assessed utilizing univariate Cox regression analysis. Adjusted HRs (aHR) were assessed using multivariate Cox regression analysis with backwards directed stepwise procedure. The outcome variables were cardiovascular, non-cardiovascular, and all-cause death during the follow-up. The predictor variable was the NT-proBNP level measured at admission. It was expressed as a continuous variable if the association with the outcome variable was linear or as a threshold value if the association was not linear. A confounder was a variable that showed an association with both the NT-proBNP concentration and all-cause mortality. Again, a continuous confounder was included as a continuous variable if the association with the outcome variable was linear or as a threshold value if the association was not linear.

Results

Table 1 shows the basic characteristics of the patients divided to subgroups according to the type of lung disorder. The NT-proBNP values differed significantly between the subgroups.

Table 2. Association of the baseline variables with admission NT-proBNP concentration and all-cause late mortality

Variable	Association with baseline NT-proBNP, Pearson correlation coefficient or unpaired t-test, *P*-value	Association with all-cause mortality, crude HR, *P*-value
Age, years	Rp = 0.56, $P < 0.001$	5.00 (3.12–8.02)[a], $P < 0.001$
Male sex	Yes: 284 (220–368) pg/mL, no: 213 (166–274) pg/mL, $P = 0.12$	1.98 (1.23–3.18), $P = 0.005$
Body mass index, kg/m^2	Rp = −0.14, $P = 0.017$	0.98 (0.95–1.02), $P = 0.27$
C-reactive protein, mg/L	Rp = 0.25, $P < 0.001$	0.99 (0.99–1.00), $P = 0.53$
Urea, mmol/L	Rp = 0.46, $P < 0.001$	1.14 (1.09–1.19), $P < 0.001$
Arterial blood oxygen saturation, %	Rp = −0.31, $P < 0.001$	2.91 (1.82–4.65)[b], $P < 0.001$
NT-proBNP, pg/mL		3.83 (2.63–5.57)[c], $P < 0.001$

Rp, Pearson's correlation coefficient; HR, hazard ratio, calculated per one unit of variable unless otherwise stated.
[a]HR for age more than 70 years.
[b]HR for saturation less than 93%.
[c]HR per every ten-fold increase in NT-proBNP concentration.

The highest values were seen among the patients with both pneumonia and obstructive lung disease exacerbation. The type of lung disorder was also related to late mortality with COPD showing the highest predictive power. Therefore, the type of lung disorder was included as a confounder in the multivariate models. Of the other baseline variables that could theoretically affect the NT-proBNP levels, the following were associated both with baseline NT-proBNP and mortality: age, urea, and oxygen saturation (*Table 2*). They were thus also included as confounders in the multivariate models. During the follow-up, there were 83 deaths with the following underlying causes: 27 cardiovascular (33% of all deaths), 28 respiratory (34%), 16 cancer (19%), and 12 other causes (14%).

NT-proBNP was related to the cardiovascular mortality in a non-linear manner with only the highest quartile being associated with increased mortality (*Figure 1*). Also, the relation of NT-proBNP to non-cardiovascular mortality was non-linear with a mortality increase in the two highest quartiles (*Figure 2*). Therefore, NT-proBNP was included as threshold values in the models investigating the cardiovascular and non-cardiovascular mortality. However, NT-proBNP level was related to all-cause mortality in a linear manner across the whole range of concentrations (*Figure 3*). Thus, the NT-proBNP concentration was included as a continuous variable in the models investigating the all-cause mortality.

According to the receiver operating characteristic analysis (data not shown), the best NT-proBNP cut-off value to predict cardiovascular mortality was 666 pg/mL, providing a sensitivity of 69% and a specificity of 76%. The best cut-off value to predict non-cardiovascular mortality was 307 pg/mL with 74% sensitivity and 60% specificity. The best cut-off value for

Figure 2 The association of NT-proBNP concentration and late non-cardiovascular mortality. NT-pro-BNP values were divided in quartiles. First quartile 0–92 ng/mL, second quartile 92–247 ng/mL, third quartile 247–737 ng/mL, and fourth quartile above 737 ng/mL.

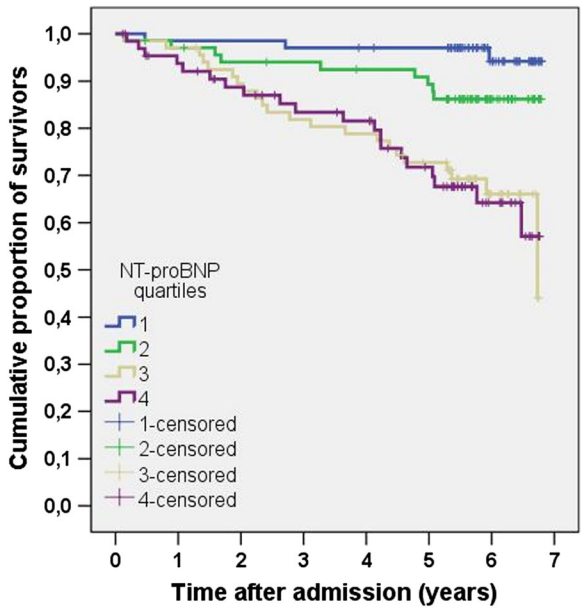

Figure 1 The association of NT-proBNP concentration and late cardiovascular mortality. NT-pro-BNP values were divided in quartiles. First quartile 0–92 ng/mL, second quartile 92–247 ng/mL, third quartile 247–737 ng/mL, and fourth quartile above 737 ng/mL.

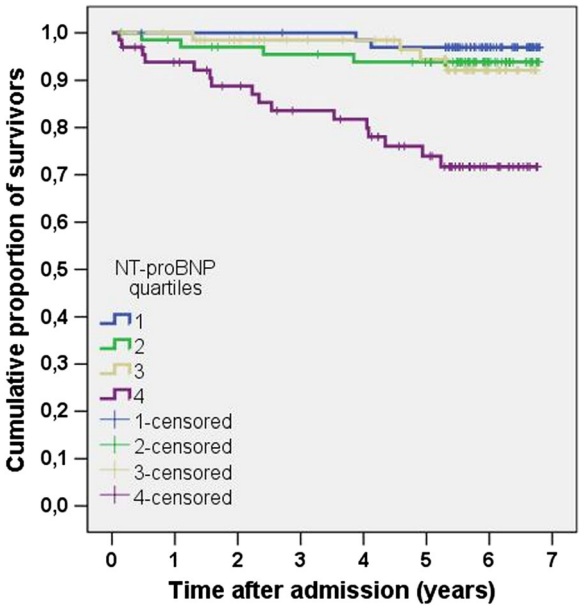

Figure 3 The association of NT-proBNP concentration and late all-cause mortality. NT-pro-BNP values were divided in quartiles. First quartile 0–92 ng/mL, second quartile 92–247 ng/mL, third quartile 247–737 ng/mL, and fourth quartile above 737 ng/mL.

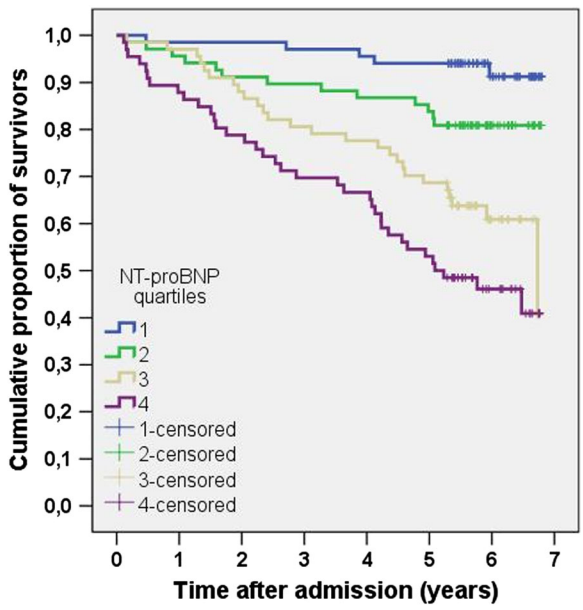

Table 3. Association of various risk factors with late mortality after acute lung disorder (Cox multivariate regression analysis with backwards directed stepwise procedure)

Risk factor	Cardiovascular mortality		Non-cardiovascular mortality		All-cause mortality	
	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
NT-proBNP	2.93 (1.19–7.18)[a]	0.019	1.89 (0.93–3.85)[b]	0.081	2.39 (1.49–3.85)[c]	<0.001
Diabetes	3.27 (1.40–7.66)	0.006	3.32 (1.59–6.95)	0.001	3.28 (1.84–5.84)	<0.001
Screening diabetes	0.42 (0.09–1.90)	0.26	0.46 (0.19–1.12)	0.085	0.46 (0.21–1.01)	0.052
Arterial hypertension	1.48 (0.65–3.38)	0.36	1.35 (0.72–2.53)	0.35	1.42 (0.85–2.36)	0.18
Hypercholesterolemia	2.55 (1.12–5.83)	0.026	1.12 (0.58–2.17)	0.74	1.43 (0.86–2.39)	0.17
Ever smoking	0.70 (0.30–1.66)	0.42	1.42 (0.64–3.16)	0.38	1.12 (0.62–2.02)	0.71

Every risk factor was confounded with the type of lung disorder, age, urea concentration, and arterial blood oxygen saturation to calculate the adjusted hazard ratios (aHR).
[a]aHR for NT-proBNP concentration > 666 pg/mL.
[b]aHR for NT-proBNP concentration > 307 pg/mL.
[c]aHR calculated per 10 times increase in the NT-proBNP concentration.

NT-proBNP to predict all-cause mortality was 307 pg/mL, providing a sensitivity of 75% and a specificity of 66%.

The multivariate Cox regression analysis revealed that NT-proBNP value > 666 pg/mL was an independent, statistically significant predictor of cardiovascular death with aHR of 2.93 (1.19–7.18). When both the pre-admission diagnosis of heart failure and NT-proBNP value > 666 pg/mL were included in the same model, both remained as significant predictors of cardiovascular mortality [aHR 4.78 (1.97–11.6) and aHR 2.68 (1.08–6.60)]. The association of NT-proBNP value > 307 pg/mL with non-cardiovascular death failed to reach statistical significance [aHR 1.89 (0.93–3.85)]. However, NT-proBNP was an independent predictor of late all-cause death with an aHR of 2.39 (1.49–3.85) per 10 times increase in the NT-proBNP concentration. Even after omitting the 28 patients with pre-admission diagnosis of heart failure, NT-proBNP remained as a significant predictor of all-cause mortality [aHR 2.21 (1.26–3.87) per 10 times increase in the NT-proBNP concentration].

To be able to compare the predictive power of elevated NT-proBNP levels with those of other known cardiovascular death risk factors, aHRs were also calculated for diabetes, screening diabetes, arterial hypertension, hypercholesterolemia, and ever smoking. Each risk factor was confounded similarly to NT-proBNP (type of lung disorder, age, urea, and oxygen saturation) (*Table 3*). Of these risk factors, diabetes and hypercholesterolemia showed statistically significant associations with cardiovascular death [aHR 3.27 (1.40–7.66) and 2.55 (1.12–5.83)], respectively.

Discussion

This is by far the longest follow-up study evaluating the impact of plasma NT-proBNP on long-term mortality in patients with acute lung disorders. The main finding was that plasma NT-proBNP concentration measured at admission because of pneumonia or AEOLD was more closely associated with cardiovascular mortality than with non-cardiovascular mortality. Furthermore, NT-proBNP was also associated with all-cause mortality.

Our study is in accordance with earlier studies reporting an association between NT-proBNP and late all-cause mortality in patients with acute lung disorders.[6–8,10–13] To the best of our knowledge, there is only one previous study investigating the association between NT-proBNP and late cardiovascular mortality after acute lung disorders.[9] However, that study by Medina *et al.* was smaller than the present one with only 14 cardiovascular deaths, and the follow-up time was shorter, 1 year. Furthermore, that study did not report non-cardiovascular mortality and did not take into account the level of hypoxia or systemic inflammation.

In the present study, all factors that might theoretically affect the admission NT-proBNP concentration could be taken into account, including age, sex, body weight, impaired renal function, hypoxia, and systemic inflammation.[4,6,14–17] Importantly, in the present study, NT-proBNP correlated statistically very significantly with low admission arterial oxygen saturation and high admission C-reactive protein. These findings support the previous studies, which suggest hypoxia and systemic inflammation as possible inducers of BNP production.[6,15–17] Both are often present during pneumonia and AEOLD. Even after careful adjustment of confounding factors in the present multivariate analysis, NT-proBNP remained as a strong predictor of cardiovascular mortality, whereas its association with non-cardiovascular mortality failed to reach statistical significance. Therefore, it seems that cardiac diseases are mainly responsible for the elevated risk of late death in patients with acute lung disorders with high concentrations of NT-proBNP. NT-proBNP was a predictor of death also among patients without a previous history of heart failure. An acute lung disorder might act as a 'stress test' revealing occult cardiac diseases, possibly via hypoxic pulmonary vasoconstriction.[6,23]

In our study, the best cut-off values for plasma NT-pro-BNP concentration were 307 pg/mL for all-cause mortality and 666 pg/mL for cardiovascular mortality. In the study of Medina *et al.*, the respective cut-off values were 588 and 782 pg/mL.[9] The subjects in our study were younger than

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those in the study of Medina *et al.*, which most plausibly explains our lower cut-off values. However, both studies point that the threshold value for cardiovascular mortality is higher than that of all-cause mortality. Furthermore, these studies show that the cut-off points for late mortality are lower than those applied to diagnose acute heart failure. In the present study with the majority of patients being 50–70 years old, the cut-off value for acute heart failure diagnosis would be around 900 pg/mL.[24] Therefore, the proportion of patients with abnormal NT-proBNP values is much larger when considering late mortality than when considering acute heart failure, as can be seen in *Table 1*. This phenomenon has also been described in a population-based study.[25]

The quartile analysis revealed that the NT-proBNP concentration was associated with late all-cause mortality across the whole range of the values. A similar linear association has also been described between late all-cause mortality after COPD exacerbation and the levels of natriuretic peptides.[8,12]

On the contrary, the associations between NT-proBNP concentration and non-cardiovascular and cardiovascular mortality were not linear. These findings are novel. The risk of non-cardiovascular death started to increase from relatively low concentrations, then stabilizing. The risk of cardiovascular death started to increase not until the concentration was within the highest quartile.

The present study shows that among 50- to 70-year-old patients with pneumonia or AEOLD, a NT-proBNP concentration exceeding 666 ng/mL is an independent risk factor for late cardiovascular death with an aHR of 2.93. Should it trigger further diagnostic tests, such as echocardiography, or therapeutic interventions? For comparison, the risk of cardiovascular death associated with elevated NT-proBNP was of similar magnitude to that associated with diabetes (aHR 3.27) and greater than that of arterial hypertension (aHR 1.48), hypercholesterolemia (aHR 2.55), and smoking (aHR 0.70). All are risk factors that are usually considered important enough for therapeutic interventions. Interestingly, screening diabetes, defined as a presence of admission HbA1c $\geq$ 6.5% in a patient without a history of diabetes, showed a suggestive association with decreased mortality risk. The association between HbA1c and cardiovascular disease risk is J-shaped, and it has been postulated that low plasma glucose levels are markers of ill health.[26] Perhaps a HbA1c level $\geq$ 6.5% without clinical diabetes should be considered as a sign of good health in a population with high prevalence of chronic lung diseases. The lack of association between smoking and cardiovascular death is probably because of the patients with lung disorders dying of pulmonary diseases before they experience smoking-associated cardiovascular complications. The present results highlight the importance of population-specific definitions of cardiovascular risk factors.

There is a recent study utilizing echocardiography, which reported that cardiac systolic or diastolic dysfunction is present in only a small proportion of patients with AEOLD with elevated plasma BNP levels.[5] However, the present study demonstrated that elevated NR-proBNP is a strong predictor of late cardiovascular death in acute lung disorders. These observations suggest that echocardiography may lack sensitivity to detect mild cardiac dysfunction during acute lung illnesses, which, however, may be of prognostic significance.

The major strengths of the present study are its prospective nature, the comprehensive adjustment of confounding factors in the multivariate analysis, and the long follow-up time. The throughout examination of the death certifications may also be regarded as a strength. The major limitation of this study is the exclusion of patients who were confused or needed treatment in intensive care unit. The present population thus consists of patients with mild to moderate acute lung diseases, and the results cannot be generalized to all hospitalized lung patients. One may also criticize our way to pool different lung disorders in one analysis. This problem was addressed by including the type of lung disorder in the multivariate analysis. Lack of echocardiography and other cardiologic investigations may also be considered as a weakness in the present study.

In conclusion, a plasma NT-proBNP concentration $>$ 666 ng/mL was strongly associated with late cardiovascular mortality in patients hospitalized because of acute lung disorders. Elevated NT-proBNP levels did not predict non-cardiovascular mortality. The results suggest that the increase in NT-proBNP during acute lung disorders may reveal occult cardiac diseases leading to increased risk of cardiovascular death during the subsequent years. The risk of cardiovascular death associated with elevated NT-proBNP was of similar magnitude to that associated with diabetes and greater than that of arterial hypertension, hypercholesterolemia, and smoking. Thus, a question rises whether patients with acute pulmonary disorders with elevated NT-proBNP levels should be subjected to further diagnostic or therapeutic cardiovascular interventions.

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Conflicts of Interest

None declared.

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