Comparison of prognostic value of N-terminal pro-brain natriuretic peptide in septic and non-septic intensive care patients

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Abstract

Introduction: The aim of this study is to compare the prognostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in septic and non-septic intensive care patients.

Material and methods: Fifty consecutive patients admitted to the intensive care unit (ICU) were enrolled in either the septic or non-septic group according to the criteria in the International Sepsis Definitions Conference in 2001. Demographic and clinical data, procalcitonin and lactate levels at admission, and death within 28 days were registered. Five blood samples were collected from all patients for NT-proBNP measurements.

Results: Septic patients had higher APACHE II (19 (16.00–24.25) vs. 16 (13.00–18.25)), and SOFA (8 (5–10) vs. 6 (4–7)) scores (p <0.05). Procalcitonin levels were also higher in septic patients (3.33 (1.06–10.96) vs. 0.46 (0.26–1.01) ng/ml) and more patients required vasopressors in this group (9 (36%) vs. 2 (8%)) (p < 0.05). In the septic group, the correlation between mortality and the level of NT-proBNP was significant for each measurement, starting from the admission. In the non-septic group the correlation between mortality and the level of NT-proBNP was significant only at the 120th h.

Conclusions: We concluded that the level of NT-proBNP at admission is well correlated with 28-day mortality in septic ICU patients. However, single measurement of NT-proBNP levels in non-septic patients does not correlate with the 28-day mortality. Repeated measurements and an increasing trend of the NT-proBNP levels may show a correlation with mortality in non-septic intensive care patients.

Key words: NT-proBNP, intensive care unit, patient outcome assessment, critically ill.

Introduction

Brain natriuretic peptide (BNP) is a prohormone synthesized by the cardiac myocytes in response to pressure or volume overload. This peptide promotes diuresis, natriuresis, and vasodilation and inhibits the renin angiotensin system and the sympathetic nervous system. It is finally excreted by the kidneys. Utility of the BNP in diagnosis and guiding the treatment of heart diseases has been well documented in the literature [1–9].

Brain natriuretic peptide levels are found to be increased in septic patients in most studies. Increased levels of proinflammatory cytokines (IL1b, TNF-α, IL-6) stimulate secretion of BNP. These cytokines also con-

tribute to the development of septic myocardial depression [10].

Recently, a number of studies have reported the predictive value of BNP in the critically ill intensive care population. Although these studies had various designs and patient groups, most of them reported that BNP was an alternative predictor of outcome in the intensive care unit (ICU). The major emphasis in most of these studies was the correlation between elevated levels of BNP and the ICU outcome [11–17]. In contrast to other studies, Park *et al.* [18] suggested that instead of considering absolute levels, the trend of BNP might provide better prognostic utility in ICU patients.

The aim of this study was to compare the prognostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in septic and non-septic ICU patients.

Material and methods

Patient selection

This prospective observational study was performed in a 12-bed ICU of Ankara Research and Training Hospital. The study protocol was approved by the institutional review board. Written informed consent was obtained from the patients' first degree relatives.

Fifty consecutive patients admitted to the ICU were enrolled either in septic (including sepsis, severe sepsis, and septic shock) or non-septic group (25 each) according to the criteria in the International Sepsis Definitions Conference of 2001. Exclusion criteria were age less than 18 years, evidence of any kind of current or previous heart disease, renal disease requiring renal replacement therapy, pregnancy, and acute cerebrovascular events. Patients who died before the fourth day of ICU admission were also excluded.

Study protocol

The same brand and model of ventilators (Galileo Gold, Hamilton Medical AG, Switzerland) were used for all patients who needed ventilatory support. Propofol and remifentanil infusions were used interchangeably for sedation as needed. All patients received low molecular weight heparin prophylaxis during the ICU stay. Vasopressor treatment included norepinephrine and dopamine infusions if needed.

Data collection

Demographic and clinical data including age, sex, presence of ventilatory support, presence of hemodynamic support, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores and RIFLE criteria at admission, and death within 28 days were registered. Five blood samples were collected from all patients at admission and the 24^{th}, 48^{th}, 72^{nd} and 120^{th} h for NT-proBNP measurements. In addition to NT-proBNP, procalcitonin and lactate levels were also measured at admission.

For the determination of NT-proBNP concentrations electrochemiluminescent immunoassay (ElecSys 2010, Roche Diagnostics, Mannheim, Germany) was used. The analytic range for this test was 30–35 000 pg/ml and the coefficient of variance was below 3%.

Statistical analysis

The area under the ROC curve quantifies the diagnostic accuracy of a test. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test [19]. An area of 0.75 represents a fair test of accuracy. For this study, the area under the ROC curve which is expected to be significant was 0.75. The value of the area under the curve for the null hypothesis was 0.5. Type I error was defined as $\alpha = 0.05$ and type II error $\beta = 0.10$. Hence, the sample size for each group was calculated as 25.

Metric continuous variables between groups were compared with Student's *t*-test or the Mann-Whitney *U* test after the Kolmogorov-Smirnov test was applied for normality and variables were presented as mean ± SD or median (25^{th}–75^{th} percentiles). Categorical variables between groups were compared with χ^2 or Fisher's exact test and variables were presented as percentages (%). For the trend analysis within groups, the repeated measures analysis of variance test or Friedman variance analysis test were used. Multiple pairwise comparisons were made with Bonferroni correction within groups. Receiver-operating characteristic (ROC) curves were plotted to define the prognostic performance and the cutoff value of NT-proBNP, SOFA score, lactate, and procalcitonin, which provides the best sensitivity and specificity in both non-septic and septic groups. Results are presented as area under the curve (AUC) and 95% confidence intervals. *P*-value < 0.05 was considered statistically significant for all tests. AUC for different parameters are compared with the Hanley and McNeil method.

Also a multivariate logistic regression model was fitted to detect the independent predictors of ICU mortality. Variables that were significant in the univariate model were tested further with multivariate logistic regression analysis for independent contribution to ICU mortality.

All statistical analyses were performed with MedCalc version 12.2.1.0 (MedCalc Software bvba, Mariakerke, Belgium).

Results

In total 50 patients were enrolled in this study. In the non-septic group, postoperative patients of abdominal and orthopedic surgery were in the majority. In the septic group, the patients were in sepsis mainly secondary to respiratory or urinary tract infection. Clinical characteristics of the patients at admission are shown in Table I. Age and gender of the patients, presence of ventilatory treatment and RIFLE criteria at admission were similar in groups. Septic patients had higher APACHE II (19 (16.00–24.25) vs. 16 (13.00–18.25)), and SOFA (8 (5–10) vs. 6 (4–7)) scores compared to non-septic patients ($p < 0.05$). Lactate levels were similar between groups. Procalcitonin levels were also higher in septic patients (3.33 (1.06–10.96) vs. 0.46 (0.26–1.01) ng/ml) and more patients required vasopressors in the septic group (9 vs. 2), ($p < 0.05$). Nine vs. fourteen patients died in non-septic and septic groups, respectively ($p = 0.26$) (Table I).

Receiver-operating characteristic curves of SOFA scores, procalcitonin and lactate levels were drawn for both groups to determine the prognostic accuracy. In the non-septic group, none of these parameters correlated significantly with mortality at admission. For the septic group, procalcitonin levels were significantly correlated with mortality at admission. Receiver-operating characteristic curve comparison for procalcitonin and NT-proBNP in the septic group was statistically insignificant (Table II, Figure 1 A and 2 A).

Table I. Clinical characteristics of patients

Parameter	Non-septic group (n = 25)	Septic group (n = 25)	P-value
Age [years]*	74 (64.50–79.25)	63 (34.75–76.50)	0.06
Gender (male) (%)	12 (48%)	15 (60%)	0.08
APACHE II*	16 (13.00–18.25)	19 (16.00–24.25)	0.03
SOFA*	6 (4–7)	8 (5–10)	0.01
RIFLE†	21/1/2/1/0/0	16/2/1/6/0/0	0.18
Mean arterial pressure [mm Hg]‡	102.60 ±13.42	91.53 ±16.88	0.013
Ventilator treatment (%)	16/25 (64%)	20/25 (80%)	0.34
Hemodynamic support (%)	2/25 (8%)	9/25 (36%)	0.04
28-day mortality (%)	9/25 (36%)	14/25 (56%)	0.26
Procalcitonin [ng/ml]*	0.46 (0.26–1.01)	3.33 (1.06–10.96)	< 0.001
Lactate [mEq/l]*	1.260 (0.927–1.597)	1.060 (0.942–1.477)	0.57
NT-proBNP [pg/ml]‡:			
Admission	2968.55 ±2558.39	9828.15 ±11272.61	0.006
24th h	3223.16 ±2691.93	9200.89 ±10849.39	0.11
48th h	3449.30 ±2954.54	9915.78 ±11262.94	0.06
72nd h	3635.25 ±3350.37	10768.24 ±11527.76	0.02
120th h	3820.42 ±3776.92	11133.06 ±11940.43	0.03

**Median (25th–75th percentile), †RIFLE – numbers represent normal, risk, injury, failure, loss and end stage for RIFLE criteria respectively, ‡mean ± SD.*

Table II. Areas under the ROC for NT-proBNP, SOFA, procalcitonin, lactate for groups at admission‡

Variable	Non-septic group (n = 25)		Septic group (n = 25)	
	AUC*	95% CI†	AUC*	95% CI†
NT-proBNP	0.556	0.345–0.752	0.740	0.528–0.893
SOFA	0.611	0.397–0.798	0.692	0.477–0.859
Procalcitonin	0.549	0.339–0.746	0.760	0.548–0.906
Lactate	0.694	0.480–0.861	0.659	0.444–0.835

*‡Pairwise comparison of ROC curves with Hanley & McNeil method revealed no statistically significant difference, *area under the curve, †confidence interval.*

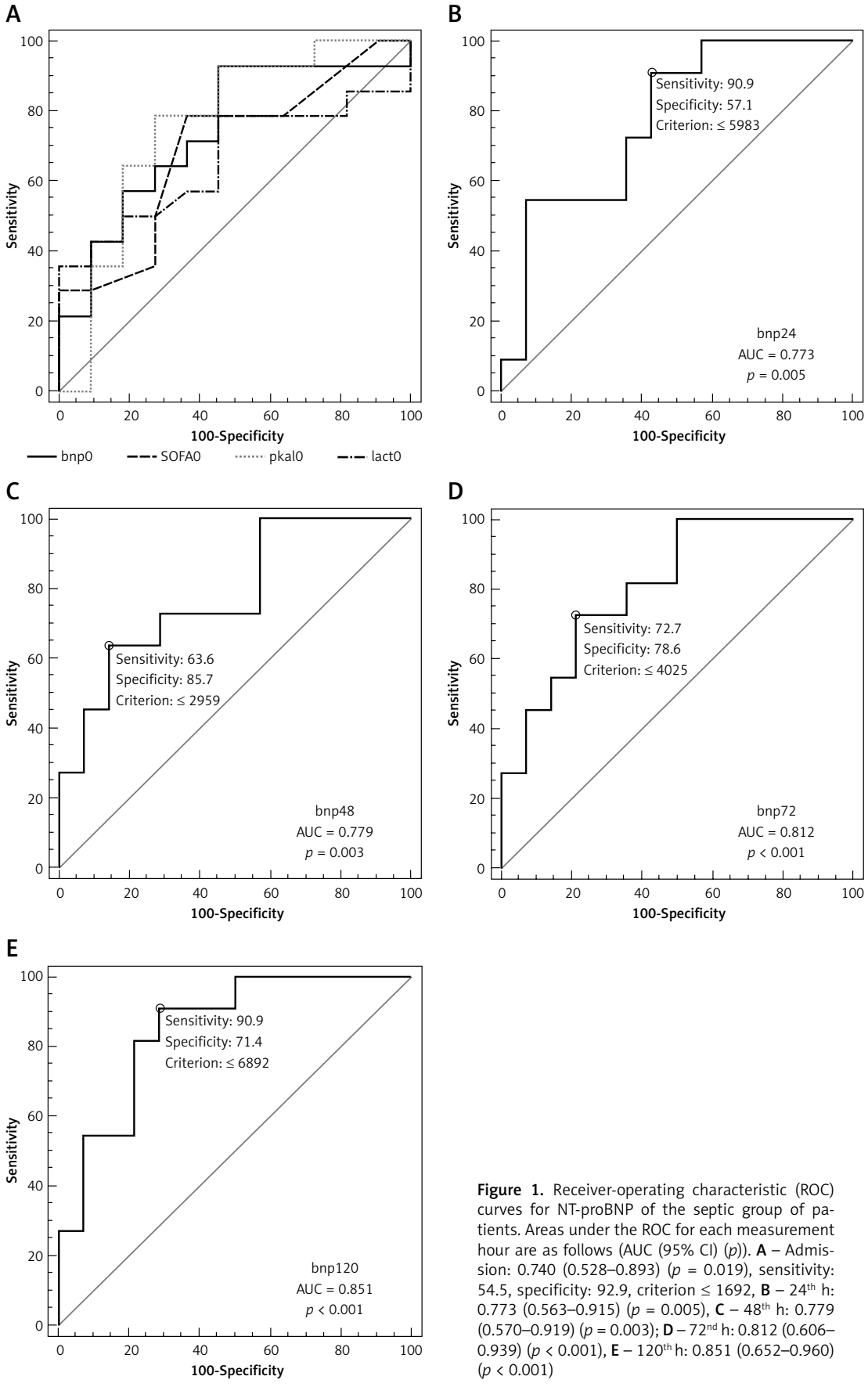

Figure 1. Receiver-operating characteristic (ROC) curves for NT-proBNP of the septic group of patients. Areas under the ROC for each measurement hour are as follows (AUC (95% CI) (*p*)). **A** – Admission: 0.740 (0.528–0.893) ($p = 0.019$), sensitivity: 54.5, specificity: 92.9, criterion ≤ 1692, **B** – 24th h: 0.773 (0.563–0.915) ($p = 0.005$), **C** – 48th h: 0.779 (0.570–0.919) ($p = 0.003$); **D** – 72nd h: 0.812 (0.606–0.939) ($p < 0.001$), **E** – 120th h: 0.851 (0.652–0.960) ($p < 0.001$)

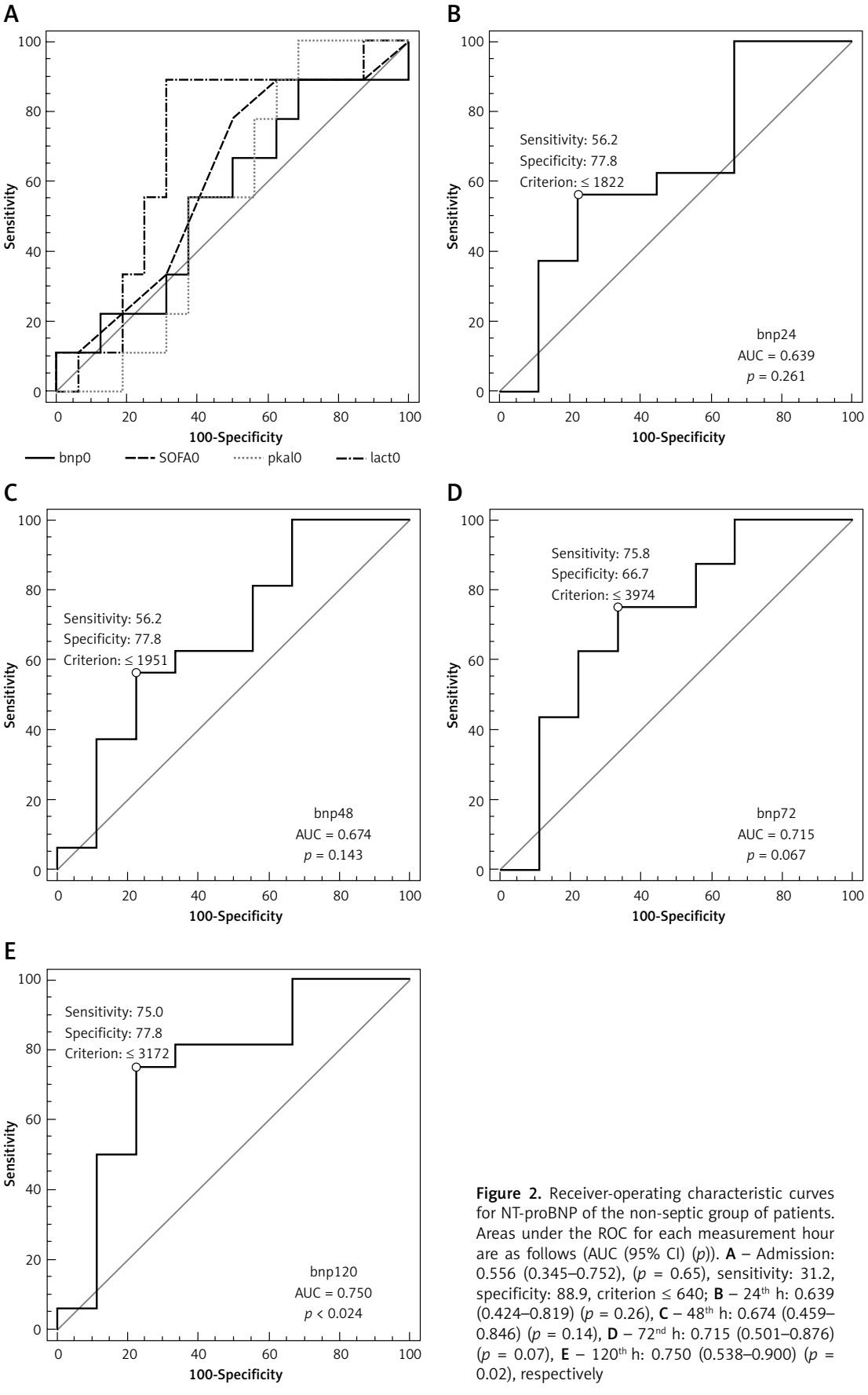

Figure 2. Receiver-operating characteristic curves for NT-proBNP of the non-septic group of patients. Areas under the ROC for each measurement hour are as follows (AUC (95% CI) (*p*)). **A** – Admission: 0.556 (0.345–0.752), (*p* = 0.65), sensitivity: 31.2, specificity: 88.9, criterion ≤ 640; **B** – 24th h: 0.639 (0.424–0.819) (*p* = 0.26), **C** – 48th h: 0.674 (0.459–0.846) (*p* = 0.14), **D** – 72nd h: 0.715 (0.501–0.876) (*p* = 0.07), **E** – 120th h: 0.750 (0.538–0.900) (*p* = 0.02), respectively

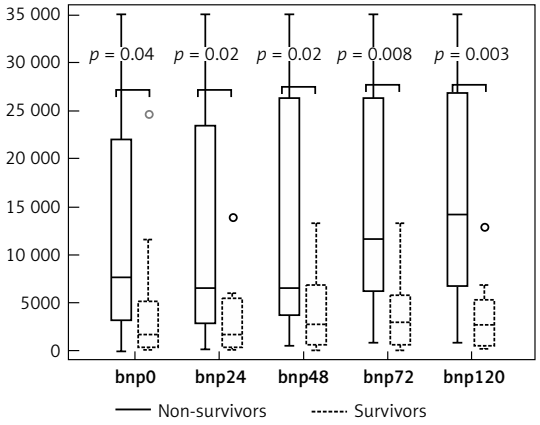

Figure 3. Comparison of NT-proBNP levels of survivors and non-survivors in septic group

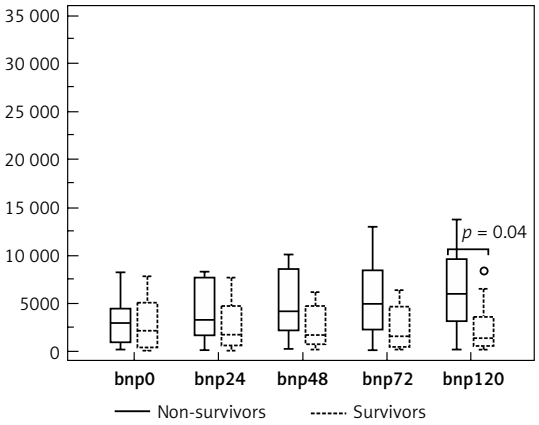

Figure 4. Comparison of NT-ProBNP levels of survivors and non-survivors in non-septic group

Receiver-operating characteristic curves for NT-proBNP were also drawn for every 24 h for the prediction of ICU mortality in each group. In the septic group, area under the ROC curve was significantly different from 0.5 on each day, indicating that the correlation between mortality and the level of the NT-proBNP in septic patients was significant at each measurement time starting from admission (Figure 1). In the non-septic group the AUC showed a significant correlation between mortality and the level of NT-proBNP only at the 120th h (Figure 2E).

In the septic group NT-proBNP levels of the nonsurvivors were significantly higher than the survivors in the entire cohort. In addition, in the septic group, NT-proBNP levels of the nonsurvivors increased significantly from admission to the 120th h ($p < 0.001$), while the NT-proBNP levels of the survivors did not change ($p = 0.40$) (Figure 3).

In the non-septic group, the NT-proBNP levels were similar between survivors and nonsurvivors except at the 120th h ($p = 0.04$). Similar to the septic group, nonsurvivors in this group displayed an increasing trend of NT-proBNP levels ($p < 0.001$), while the NT-proBNP levels did not increase throughout the study in survivors ($p = 0.25$) (Figure 4).

A logistic regression model for detection of independent ICU mortality predictors was established, but the sample size of a single group was insufficient. For the purpose of this analysis septic and non-septic groups are combined. Univariate analysis included admission NT-proBNP, procalcitonin and lactate levels, age, APACHE II, and SOFA scores. In univariate logistic regression analysis, significant predictors ($p < 0.05$) for ICU mortality were NT-proBNP, lactate levels and APACHE II score. They were entered into a multiple stepwise logistic-regression model (model significance $p = 0.0021$). The only independent predictor of ICU mortality was admission NT-proBNP levels (coefficient: 0.00011, $p = 0.045$).

Discussion

The present study shows that NT-proBNP is an independent predictor of mortality in the ICU and high levels measured at admission to the ICU are significantly correlated with mortality in septic patients. In non-septic patients repeated measurements and progressive increase in the NT-proBNP levels may correlate with mortality in the ICU.

NT-proBNP is synthesized in response to increased ventricular wall stress. Its level increases in patients with heart failure, pulmonary embolism, sepsis, shock and renal failure [20–25]. Sepsis-related cytokines lead to myocardial dysfunction and stimulate NT-proBNP excretion in patients with sepsis or septic shock [15]. NT-proBNP is excreted by the kidneys, and renal failure also increases the level of NT-proBNP [26]. Besides hypoxia, proinflammatory cytokines, lung injury, excessive fluid resuscitation, vasopressors and positive pressure ventilation also increase BNP levels [27–30]. It is a nonspecific prohormone and myocardial dysfunction due to any kind of severe illness which lead the patient to the ICU increase its level [10, 14, 21–23, 26, 29–31].

In most of the previous studies reporting the correlation between mortality and NT-proBNP levels, patients were septic, on vasopressors or required mechanical ventilation [6, 10, 12–16, 22, 23, 31]. Our patients in the septic group were consistent with the patients in these studies. APACHE II and SOFA scores and procalcitonin levels were significantly higher and more patients required vasopressor therapy in this group. In septic patients, the area under the ROC curve of 28-day mortality for NT-proBNP was 0.74 at admission and increased to 0.85 at the 120th h (Figure 1). However, no significant correlation was found between the level of NT-proBNP and mortality at admission to the ICU for non-septic patients. The fifth measurement at the 120th h showed a significant correla-

tion and the area under the ROC curve was 0.750 (Figure 2) in non-septic patients.

The prognostic power of NT-proBNP is controversial in an unselected, general ICU population. For instance, Cuthbertson *et al.* [12] stated that cardiac dysfunction is thought to be an important prognostic factor for poor outcome but B-type natriuretic peptide levels do not predict outcome accurately in all intensive care patients. Also Almog *et al.* [13] reported that NT-proBNP levels are highly variable among critically ill patients. High levels of NT-proBNP level at admission are an independent predictor of mortality. Many factors characterizing the patients may affect the level of NT-proBNP. This may explain the different cut-off values in different studies with different patient characteristics [10, 22, 31, 32]. Most of the studies in the literature are composed of septic patients. To our knowledge, this is the first study that compares the prognostic value of NT-proBNP levels in septic and non-septic ICU patients. APACHE II, SOFA scores and procalcitonin levels and vasopressor requirements were higher in the septic group. Analysis of levels of NT-proBNP in these septic and non-septic patients resulted in different AUCs and cut-off values. The only similarity between these groups was the significant increase in NT-proBNP levels in the nonsurvivors of both groups. Survivors in both groups showed a steady level of NT-proBNP level in the cohort. These findings are also consistent with those of Varpula *et al.* [10], Cuthbertson *et al.* [12] and Roch *et al.* [31].

In non-septic patients NT-proBNP levels were low at the beginning, and no significant correlation between mortality and NT-proBNP levels was observed. In nonsurvivors NT-proBNP levels increased and the correlation with mortality became significant on the fifth day. For the patients with low levels of NT-proBNP at admission, similarly as the non-septic group of this study, repeated measurements may be useful to catch the NT-proBNP increase during the ICU stay. Consistent with this observation, Park *et al.* [18] suggested repeated measurements to observe the percent change in NT-proBNP, which may provide prognostic accuracy in patients with septic shock.

This study had some limitations. The number of patients in each group was limited to 25. Bigger groups might provide more clear-cut results. Although we excluded patients with heart failure at admission, ventricular dysfunction due to severe illness (sepsis and systemic inflammation) also cannot be excluded. In addition, if we had measured levels of inflammatory cytokines, we might have detected a correlation between septic cardiomyopathy and NT-proBNP levels.

We conclude that NT-proBNP is an independent predictor of mortality in the ICU and the level at admission is well correlated with 28-day mortality in septic ICU patients. However, single measurement of NT-proBNP levels in non-septic patients does not correlate with the 28-day mortality. Repeated measurements and the increasing trend of the NT-proBNP levels may show a correlation with mortality in non-septic intensive care patients with low levels of NT-proBNP at admission.

Conflict of interest

The authors declare no conflict of interest.

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