DOI: 10.4149/BLL_2016_114

Bratisl Med J 2016; 117 (10)
587 – 594

CLINICAL STUDY

Can N-terminal pro B-type natriuretic peptide, neutrophil-to-lymphocyte ratio, C-reactive protein help to predict short and long term mortality?

Ozmen I[1], Karakurt Z[2], Salturk C[2], Kargin F[2], Takir HB[2], Aksoy E[2], Sari R[3], Celik E[3], Tuncay EA[2], Yildirim E[1], Mocin OY[2], Adiguzel N[2], Oztas S[1], Gungor S[2], Gungor G[2]

Süreyyapaşa Chest Diseases and Thoracic Surgery Teaching Hospital-Respiratory Intensive Care Unit, Istanbul. **ipekozmen2011@gmail.com**

ABSTRACT

BACKGROUND: There is limited data about ICU, short and long-term mortality prediction of severe CAP with neutrophil-to-lymphocyte ratio (NLR): N-terminal proB- type natriuretic peptide (NT-proBNP): C-reactive protein (CRP).

AIM: Besides the known severity indexes of ICU, can NLR, NT-proBNP, CRP predict ICU, short and long term mortality?

METHODS: A retrospective cohort study was carried out in a level III ICU of a tertiary training hospital for chest diseases and thoracic surgery.

RESULTS: Over the study period, a total of 143 patients were enrolled in the study. The APACHE II scoring showed a significantly higher predicting performance for ICU mortality ($p = 0.002$). The performance for predicting short term mortality NLR ($p = 0.039$) and long term mortality NTproBNP ($p = 0.002$) had a significantly higher performance. The survival analysis revealed that mortality was significantly higher in patients with CURB65 score ≥ 4 ($p = 0.047$).

CONCLUSION: NLR, NTproBNP > 2000pg/mL can be used to predict pneumonia severity in ICU alike CURB65 and PSI. Higher NLR, APACHE II and atrial fibrillation can cause an important mortality factor in long term. Consequently, clinicians should take an attention for good cardiac evaluation and cardiac follow-up of patients with CAP *(Tab. 4, Fig. 3, Ref. 36)*. Text in PDF *www.elis.sk.*

KEY WORDS: atrial fibrillation, C-reactive protein, intensive care unit, pneumonia severity, neutrophil lymphocyte ratio, NT-proBNP, respiratory failure.

Introduction

Pneumonia poses a risk for respiratory failure (ARF) (1, 2). Community acquired pneumonia (CAP): when requiring an intensive care unit (ICU): has an increased risk of mortality. In daily life, clinicians need predictors to gauge outcomes for these patients. Some biochemical parameters mediators [C-reactive-protein (CRP)] and pneumonia risk scores such as CURB-65 and pneumonia Severity Index (PSI)] are currently used to predict mortality (3–5). There is limited data about ICU, short and long-term mortality prediction of severe CAP with neutrophil lymphocyte ratio (NLR): **N**-terminal proB- type natriuretic peptide (NT-proBNP): C-reactive protein (CRP).

N-terminal proB- type natriuretic peptide (NT-proBNP) is released from cardiac ventricles in response to stress/stretch/hypoxia. However, it is also increased by noncardiac causes, such as sepsis, pulmonary embolism, pulmonary hypertension, cor pulmonale with chronic obstructive pulmonary disease (6– 8). Pneumonia with an acute respiratory failure (ARF) may similarly lead to an increase in NT-proBNP secretion. Studies are ongoing in an attempt to identify biochemical markers that can be used for clinical and prognostic assessment of pneumonia (9–11). NT-proBNP may offer potential advantages over clinical scores and biomarkers, as it is reliable and easy to measure (12). Recent studies mention NLR as a new inflammatory marker in exacerbation of chronic obstructive pulmonary diseases and in prognosis of lung cancer, colorectal cancer and acute coronary syndrome (13–17).

In literature, there are only few studies published on ICU-patients with pneumonia regarding the primary outcome of long-term-mortality (10, 12, 18).

The research question of this study is: can NLR, NT-proBNP and CRP predict ICU, short and long term mortality of patients with pneumonia?

Materials and methods

The study was designed as a retrospective cohort study in a level III ICU of a tertiary training hospital for chest diseases and thoracic surgery between January 2012 and May 2013. The study

[1]Sureyyapaşa Chest Diseases and Thoracic Surgery Teaching Hospital, Chest diseases, Istanbul, Turkey, [2]Sureyyapaşa Chest Diseases and Thoracic Surgery Teaching Hospital, Intensive Care Unit, Istanbul, Turkey, and [3]Haydarpasa Numune Research Hospital, Istanbul, Turkey

Address for correspondence: I. Ozmen, MD, Nishadalar sitesi. 51/10 Maletep, Istanbul, Turkey.
Phone: +90.5053869102

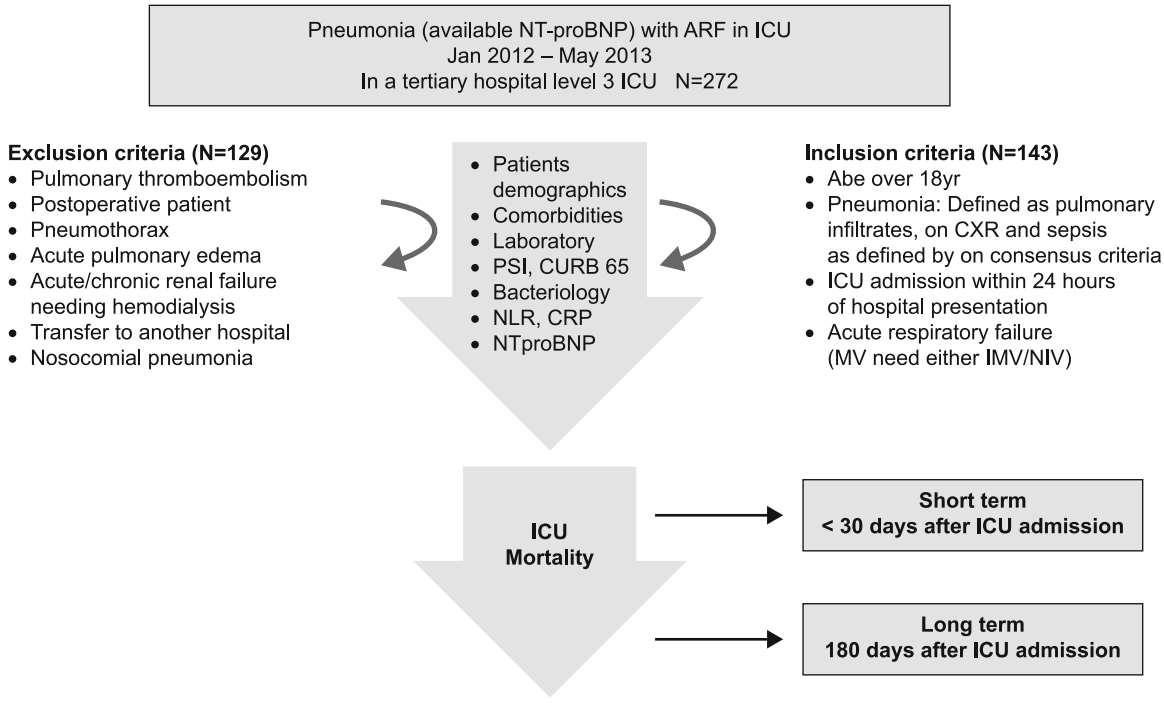

Fig. 1. Flow Chart of patients. NLR – neutrophil-to-lymphocyte ratio, ICU – intensive care unit, PSI – pneumonia Severity Index, ARF – acute respiratory failure, MV – mechanical ventilation, IMV – invasive mechanical ventilation, NIV – noninvasive mechanical ventilation.

was approved by the local ethics committee of Kartal Lutfi Kirdar Teaching and Research Hospital and ethical approval was in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study design, an informed consent was not obtained. The identities of the patients that were provided to be used, have been approved by the scientific committee of the hospital.

Patients

Pneumonia patients aged over 18 years, patients admitted to the ICU within 24 hours of hospital presentation and those with NT-proBNP measurements available were included in the study. Subject inclusion is summarized in a flow chart (Fig. 1.)

Definition

Pneumonia

Pneumonia was defined as the presentation of the acute onset of symptoms suggestive of lower respiratory tract infection and radiographical evidence of a new infiltrate (20, 21).

ARF

"Hypoxic ARF" was defined, when partial arterial oxygen pressure in an inspired fractionated oxygen (PaO_2/FiO_2) was < 300 and a partial arterial carbon dioxide pressure ($PaCO_2$) was < 45 mmHg. "Hypercapnic and hypoxemic ARF" was defined if $PaCO_2$ > 45 mmHg and PaO_2/FiO_2 < 300 and "hypercapnic ARF" was defined if $PaCO_2$ > 45 mmHg and PaO_2/ FiO_2 > 300 (22, 23).

Severity of pneumonia

Acute physiology and chronic health evaluation (APACHE II) scores were calculated for patients on admission to the ICU (22). Pneumonia Severity Index (PSI) and CURB 65 score were calculated. Pneumonia Severity Index (PSI) is a scoring system to estimate the short term mortality risk for pneumonia patients and there are a total of 20 variables (3, 24). CURB 65 is another scoring system for predicting pneumonia severity and has the following variables: confusion of new onset, blood urea nitrogen greater than 19 mg/dL, respiratory rate of 30 breaths per

Tab. 1. The baseline chacteristics and comorbidities of pneumonia patients.

Number of patients	143
Gender, male n (%)	83 (58)
Age, year, mean ± SD	70±12
BMI, mean ± SD	27±8
Smoke history, n (%)	85 (61)
Comorbidities n (%)	
COPD/Asthma	74 (52)
Hypertension	62 (43)
Congestive hearth failure	53 (37)
Coronary artery diseases	37 (26)
DM	34 (24)
AF	23 (16)
Neurogical diseases	15 (11)
Long term oxygen therapy, n (%)	51 (36)
Home non invasive ventilation, n (%)	23 (16)

BMI – Body mass index, COPD – Chronic obstructive lung diseases, DM – Diabetes mellitus, AF – Atrial fibrillation,SD – standard deviation

Tab. 2. The comparison of survivor and nonsurvivor of intensive care unite.

	Survivor n = 116	Nonsurvivor n = 27	p
Genger, male n (%)	67 (58)	16 (59)	0.88
Age, year, median (IQR)	72 (61–79)	74 (63–80)	0.31
BMI, median (IQR)	24 (21–28)	28 (24–35)	0.021
Smoke History, n (%)	70 (61)	15 (58)	0.72
Co-morbidies, n (%)			
COPD/Asthma	64 (55)	10 (37)	0.89
Hypertension	49 (42)	13 (48)	0.57
Congestive hearth failure	44 (38)	9 (33)	0.65
Coronary artery diseases	27 (23)	10 (37)	0.14
DM	25 (22)	9 (33)	0.19
AF	18 (16)	5 (19)	0.70
Neurogical diseases	11 (10)	4 (15)	0.42
Long term oxygen therapy, n (%)	46 (40)	5 (19)	0.039
Home non invasive ventilation, n (%)	22 (19)	1 (4)	0.052
ICU Data			
APACHE-II, median (IQR)	19 (16–23)	27 (20–33)	0.001
Mechanical ventilation, n (%)			
IMV	32 (28)	21 (79)	0.001
NIV	22 (19)	1 (4)	0.70
Arterial blood gases analysis on admission			
pH, median (IQR)	7.28 (7.23–7.39)	7.30 (7.19–7.45)	0.84
$PaCO_2$, mmHg, mean± SD	64±23	61±22	0.25
PaO_2/FiO_2	145 (106–200)	155 (98–270)	0.40
HCO_3, mmol	27 (24–33)	24 (20–37)	0.20
Total Blood Count			
Leukocyte count, 10^9L	12 (8–15)	13 (8–16)	0.64
Hematocrit , %	41±9	38±8	0.13
Platalet count, 10^9L	252 (199–304)	225 (162–359)	0.55
Biochemistry			
Glucose, mg/dl	153 (113–200)	147 (121–204)	0.81
BUN mg/dl	25 (18–34)	35 (20–48)	0.013
Serum creatinine, mg/dl	0.93 (073–1.3)	1.3 (0.86–1.8)	0.007
Serum Albumine, g/dl	3.1 (2.7–3.4)	2.7 (2.1–3.1)	0.006
Pneumonia severity Index			
Pneumonia Severity Index score	128 (110–157)	146 (114–184)	0.08
CURB 65 score	2 (1–3)	3 (2–4)	0.015
İnflammatorymarkers			
CRP, mg/dl	56 (24–127)	100 (31–149)	0.13
Neutrophil–to-lymphocyte ratio	7 (4–16)	10 (4–17)	0.59
NT-proBNP	2193 (667–5468)	3224 (1295–10182)	0.09
Length of ICU stay, day	7 (4–10)	10 (4–15)	0.07

BMI – Body mass index, COPD – Chronic obstructive lung diseases, DM – Diabetes mellitus, AF – Atrial fibrillation, BUN – Blood urea nitrogen, IMV – invasive mechanical ventilation, NIV – noninvasive mechanical ventilation, APACHE II – acute physiology and chronic health evaluation scores, IQR – interquartile range

minute or greater, systolic blood pressure less than 90 mmHg or diastolic blood pressure 60 mmHg or less and the age 65 years or more (5).

Measurements

Complete blood count

Total leukocyte, neutrophil, eosinophil, lymphocyte and platelet counts and MPV were determined using a Coulter LH 780 Haematology Analyser (Beckman Coulter, USA).

CRP

CRP was checked by the nephelometry method BN II System with a Siemens (Germany). The normal range of CRP is 0–5 mg/L.

NT-proBNP

Blood samples for NT-proBNP were collected at the time of the first 24 hours in admission to ICU. Plasma was collected with the standard sampling tubes containing heparin-Na or EDTA. NT-proBNP measurements were performed using PATHFAST assay based on chemiluminescent immunoassay (CLIA) and MIGRATION methodology.

Neutrophil-to- lymphocyte ratio

As a marker of systemic inflammation, NLR was defined as absolute neutrophil count divided by absolute lymphocyte count.

Microbiology

Bronchial secret of patients were collected by a deep tracheal

Tab. 3. The culture work up and microorganisms isolated from clinical culture specimens in ICU.

	Survivor (ICU) n=116	Nonsurvivor (ICU) n=27	p
Any culture work up n (%)	57 (49)	22 (82)	0.002
Urine	22 (22)	6 (25)	0.75
Blood	11 (10)	4 (15)	0.41
Bronchial lavage	10 (9)	7 (26)	0.013
Sputum	23 (41)	1 (5)	0.002
Culture results			
Acinetobacter Baumannii	3 (5)	6 (27)	0.006
Enterococcus	0	1 (5)	0.11
Pseudomonas Aeruginosa	2 (4)	3 (13)	0.097
Initial Antibiyotic treatment			
Single	61 (53)	14 (52)	0.95
Double	33 (29)	9 (33)	0.64
Triple	0	1 (4)	0.038
Antibiotics Upgrade	19 (17)	13 (48)	0.001
Antifungal treatment	3 (3)	2 (7)	0.23
Antiviral	2 (2)	0	0.49

Tab. 4. Cox regression analyses of short and long term mortality after ICU admission.

	Hazard ratio	95% CI: lower-upper limit	p
30 days mortality			
Atrial fibrillation	4.63	1.31–16.47	0.018
CURB65	2.14	0.99–4.62	0.53
Bilateral pneumonia	1.26	0.43–3.73	0.67
APACHE II ICU admission	1.05	0.97–1.13	0.27
NLR	1.04	0.99–1.01	0.80
BMI	1.04	0.98–1.10	0.18
NTproBNP	1.00	1.00–1.00	0.57
PSI	0.99	0.97–1.01	0.18
CRP	0.99	0.99–1.01	0.49
180 days mortality			
Atrial fibrillation	5.40	2.11–13.79	0.001
Bilateral pneumonia	1.49	0.71–3.12	0.29
CURB65	1.40	0.86–2.29	0.18
APACHE II ICU admission	1.08	1.02–1.15	0.012
NLR	1.04	1.01 –1.07	0.015
BMI	1.02	0.98–1.06	0.44
NTproBNP	1.00	1.00–1 00	0.28
CRP	1.00	0.99–1.01	0.83
PSI	0.99	0.98–1.01	0.19

CI – confidence interval; NLR – neutrophil lymphocyte ratio; BMI – Body mass index; ICU – intensive care unit

aspiration if the patient was intubated and sputum was collected into a petri dish, when patients were non-intubated. In the case of a very low temperature (< 35 °C) or high fever (> 38 °C): a venous blood sample was collected into an aerobic culture media. Empirical antibiotic treatment was initiated following a clinical diagnosis and immediately after obtaining results of culture (21).

Mechanical ventilation

The application of non-invasive mechanical ventilation (NIV) or invasive mechanical ventilation (IMV) in the ICU, the lengths of ICU stays (days): ICU mortality (mortality during the ICU stay) and mortality after discharge were recorded. NIV was the first choice of ventilatory support for hypercapnic and hypoxemic respiratory failure (ABG analysis pH 7.28–7.34, $PaCO_2$ = 45–90 mmHg, PaO_2/FiO_2 > 200 and a Glasgow coma scale > 13) if the patient was alert, able to protect the airway, had no risk of aspiration and no burn or wound on the face (25). IMV was applied with ICU ventilators (Puritan Bennett 760, Newport and Vela): if the patient had criteria for intubation, such as cardiac arrest, increased work of breathing, respiratory depression, shock and altered mental status. The Richmond agitation sedation scale was used to assess the daily need for sedation (25).

Data recording

Data of community acquired pneumonia (CAP) cases admitted to the intensive care unit with ARF and with NT-proBNP levels available were recorded from the patients' ICU files. The patients either required IMV or NIV were judged to be in an unstable condition requiring an intensive care.

Demographics, comorbidities including diabetes mellitus (DM): hypertension, COPD/asthma, congestive heart failure, coronary artery disease (CAD): malignancy and diffuse parenchymal lung disease, neurological diseases (Alzheimer's disease, cerebrovascular attack, Parkinson's disease): use of long-term oxygen therapy (LTOT) and long-term mechanical ventilation (MV) (NIV or invasive [IMV]): body mass index (BMI) and length of ICU stay were also recorded.

Complete blood count, CRP, biochemistry, radiology patterns and antibiotic therapy data were also recorded. Arterial blood gas (ABG) values at the time of ICU admission were recorded from the patients' files.

Outcomes

The primary outcome was long term mortality (180 days after ICU admission): and the secondary outcome was short term mortality (30 days after ICU admission)

Statistical analysis

The Mann-Whitney *U* test and the Student's *t* test were used for analysis of continuous variables with non-parametric and parametric values, respectively. The chi square test was applied for categorical variables (gender, comorbidity) of survivors and non-survivors. The median with interquartile range (IQR) was employed for non-parametric continuous variables, and the mean ± standard deviation (SD) was used for parametric continuous variables. Count and percentage were used when applicable. The p value < 0.05 was accepted as statistically significant. 30 and 80 days of survival analysis were done by the Kaplan Meier survival curve. ROC curve analysis was used for NT-proBNP, NLR, CRP, PSI score and APACHE score for mortality (ICU, short and long term).

Results

Totally, 143 patients were enrolled in the study. The mean age was 69 ± 12 years and 58 % of the patients were male. The baseline characteristics and comorbidities of pneumonia patients

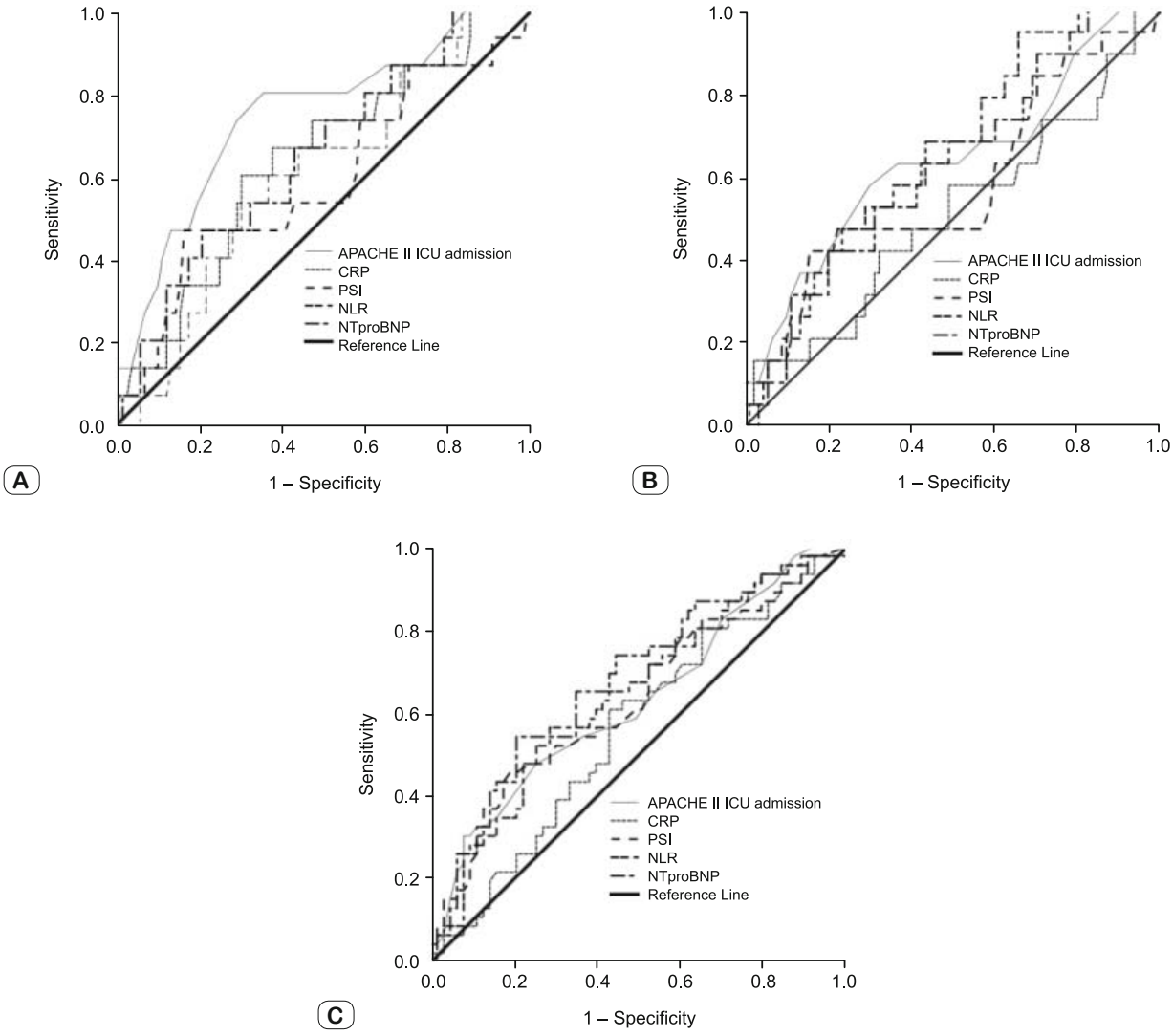

Fig. 2. Roc curves for predicting ICU, short termand long term mortality. A) ROC curves for NTproBNP and predictive rules including APACHE II, PSI, CRP, NLR for predicting ICU mortality. The area under the ROC curves are 0.74 (95 %CI, 0.61 to 0.89) for APACHE II (p = 0.002): 0.65 (95 %CI, 0.51 to 0.80) for NTproBNP (p = 0.06): 0.64 (95 %CI, 0.49 to 0.79) for CRP (p = 0.08): 0.60 (95 %CI, 0.46 to 0.75) for NLR (p = 0.20): 0.59 (95 %CI, 0.42 to 0.76) for PSI (p = 0.26). The performance of APACHE II predicting ICU mortality was significantly higher. B) ROC curves for NTproBNP and predictive rules including APACHE II, PSI, CRP, NLR for predicting short term mortality. The area under the ROC curves are 0.65 (95 %CI, 0.53 to 0.78) for NLR (p = 0.039): 0.64 (95 %CI, 0.49 to 0.79) for APACHE II (p = 0.06): 0.63 (95 %CI, 0.50 to 0.77) for NTproBNP (p = 0.07): 0.58 (95 %CI, 0.43 to 0.73) for PSI (p = 0.27): 0.51 (95 %CI, 0.36 to 0.66) for CRP (p = 0.87): The performance of NLR predicting short term mortality was significantly higher. C) ROC curves for NTproBNP and predictive rules including APACHE II, PSI, CRP, NLR for predicting long term mortality. The area under the ROC curves are 0.68 (95 %CI, 0.58 to 0.78) for NTproBNP (p = 0.002): 0.65 (95 %CI, 0.54 to 0.75) for NLR (p = 0.010): 0.63 (95 %CI, 0.52 to 0.74) for APACHE II (p = 0.023): 0.63 (95 %CI, 0.53 to 0.74) for PSI (p = 0.018) ,0.56 (95 %CI, 0.45 to 0.67) for CRP (p = 0.56). The performance of NTproBNP predicting long term mortality was significantly higher.

are summarized in the Table 1. The comorbidities were similar in survivors and nonsurvivors, chronic obstructive lung diseases (COPD) and hypertension were the most frequent comorbidities.

Table 2 shows the comparison of survivors and nonsurvivors of the intensive care unit. The nonsurvivors in ICU were more obese than survivors (p = 0.021). Hypertension was more common than the other comorbidities among nonsurvivors in ICU. Long term oxygen therapy use at home was significantly higher in nonsurvivors.

The culture work up and microorganisms isolated from clinical culture specimens in ICU are summarized in the Table 3. For 77 patients (54 %): diagnostic procedures such as bronchial lavage, bronchial lavage, blood, and urine cultures were performed to identify the microorganism causing sepsis. Agents were identified by culture positivity and Acinetobacter Baumannii was the major pathogen isolated (n = 9.6 %).

Cox regression analyses is summarized in the Table 4 for short and long term mortality after ICU admission. We included atrial

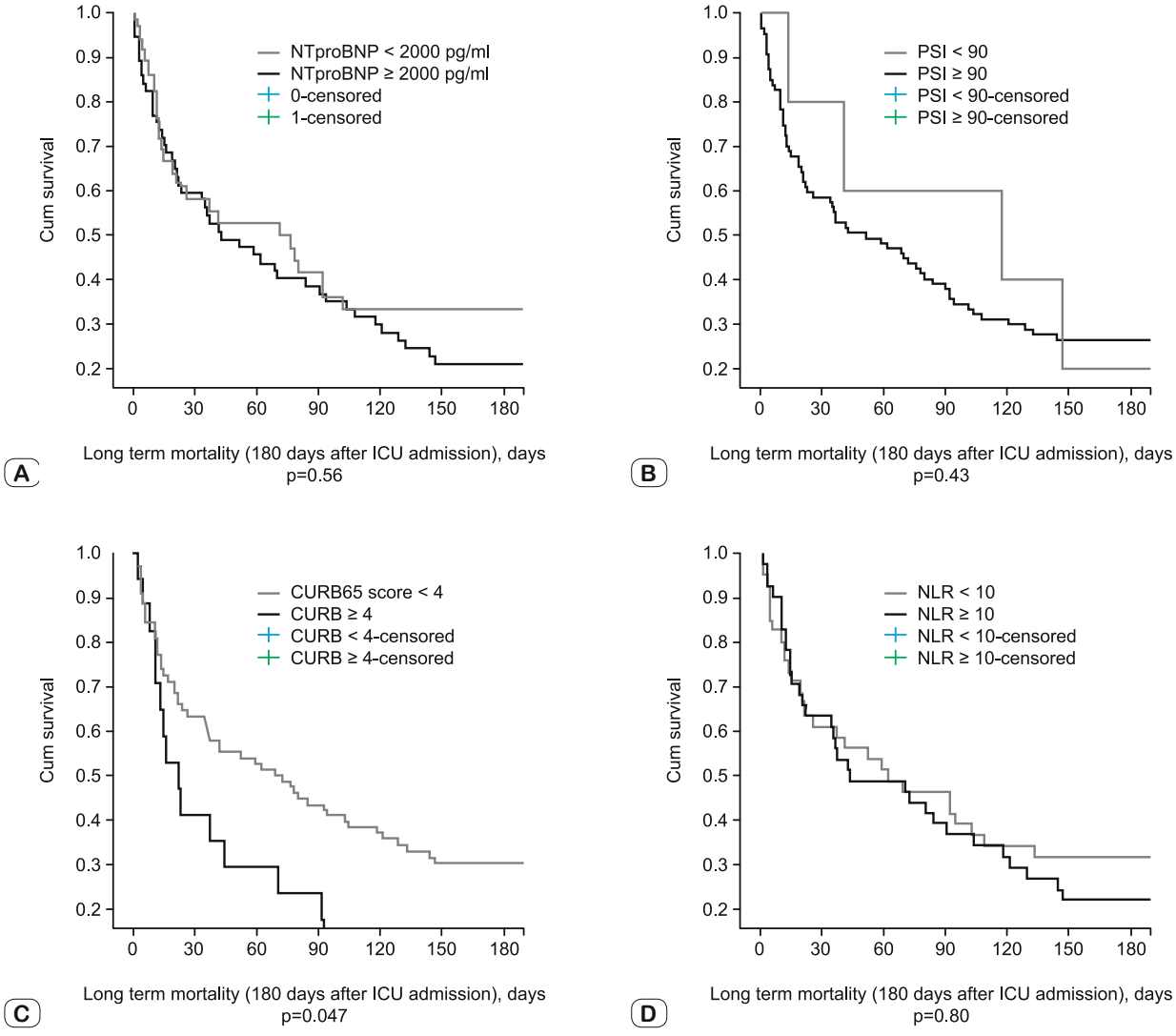

Fig. 3. Kaplan–Meier survival curves for A) NTproBNP values above and below 2000 pg/ml, B) PSI scores above and below 90, C) CURB-65score <4 and ≥ 4, D) NLR <10 and ≥ 10.

fibrillation, CURB65, bilateral pneumonia, APACHE II on ICU admission, NLR, BMI, NTproBNP, CRP and PSI parameters in the COX regression model, and the risk factors are summarized in the Table 4.

The comparison between the performance of NTproBNP, APACHE II, PSI, CRP and NLR is shown in Figure 2. The performance of APACHE II in predicting ICU mortality was significantly higher ($p = 0.002$). The performance of NLR ($p = 0.039$): predicting short term mortality and NTproBNP ($p = 0.002$) predicting long term mortality was significantly higher.

Figure 3 illustrates Kaplan – Meier survival functions. The survival analysis revealed that mortality was significantly higher in patients with CURB65 score ≥ 4 ($p = 0.047$).

Discussion

In the recent study, we showed that NLR, NTproBNP > 2000 pg/mL could be used to asses pneumonia severity as well as CURB65 and PSI. And higher NLR and higher APACHE II score on admission to ICU had a higher risk of long term mortality (180 days).

Pneumonia severity scores are predictors of short term mortality and may help to decide on hospitalization (9, 11). In reality, clinical practice scores are difficult to calculate and parameters in the scoring system may be missed. In the present study, the CURB-65 score was a predictor of short term mortality, whereas the PSI score showed no significant difference in assessment of short- term mortality (3, 26–28).

This study supports the theory that higher NT-proBNP levels are associated with cardiac dysfunction leading to long term mortality (29). Systemic inflammation, endothelial dysfunction, hypoxia, catecholamine release and systemic vasodilatation cause an increased myocardial oxygen demand and decreased myocardial contraction resulting in increased cardiac mortality (8). Krüger et al described mid-regional pro-atrial natriuretic peptide (MR-proANP) and C-terminal pro-atrial natriuretic peptide (CT-prANP) and CT-proAVP as better predictors of 28-day and 180-day morality than CRB 65 scores (8).

Acute coronary syndrome, arrhythmias, heart failure, and stroke are cardiovascular conditions reportedly associated with long-term mortality among CAP patients (30–35). In the present study, pneumonia patients with AF had a significantly higher mortality. Interestingly, AF seems to be another prognostic factor for mortality. Patients with AF need to be followed closely, even after discharge from ICU. Inflammation has also been reported as a risk factor for AF. Pneumonia can also have a negative effect on existing fibrillation by causing atrial fibrillation. The relationship of mortality and pneumonia associated with AF has not been reported. AF is also often observed in patients with COPD (32, 33).

Inflammation, hypoxia and electrolyte disturbance also play an important role in precipitating the onset of AF or increasing AF in malignancy and COPD (33). Long term cardiovascular mortality risk seems to be an increased sequela from CAP, compared to the healthy population (34–36). In the present study, malignancy was the most significant and common comorbidity in both short and long term mortality and was predictably much higher in patients with long term mortality.

There are some limitations of the present study; as this is a retrospective study, all required data may not be available. The study was carried out in a single centre and as such there can be limited generalization of the data. In addition, the mean age of the study population was above 65 years, thus there was a low amount of information on the younger population. The small sample size limits the ability to detect small, but potentially significant associations. The strength of this study lies in the data indicating the potential predictor for pneumonia severity of NLR and high NT-proBNP levels in pneumonia in ICU.

Conclusion

Higher NT-proBNP values (above 2000 pg/mL) and NLR can be used to predict pneumonia severity in ICU as well as CURB65 and PSI. These promising results of routinely used total blood count test has helpful information for pneumonia severity diseases. Higher NLR and APACHE II score together with the presence of atrial fibrillation can be an important sequelae leading to long term mortality in CAP. The clinician should focus on a thorough cardiac evaluation and even cardiac follow-up of patients with CAP. The results of this pilot study are hypothesis-generating and provide the direction for future prospective studies.

References

1. British Thoracic Society Research Committee and The Public Health Laboratory Service. The aetiology, management and outcome of severe community acquired pneumonia on the intensive care unit. Respir Med 1992; 86: 7–13.

2. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA et al. Prognosis and outcomes of patients with community-acquired pneumonia: a metaanalysis. JAMA 1996; 275 (2): 134–141.

3. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. New Engl J Med 1997; 336 (4): 243–250.

4. Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dremsizov TT, Coley C et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Amer J Resp Crit Ccare Med 2002; 166 (5): 717–723.

5. Lim WS, Van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58 (5): 377–382.

6. Balion C, Don-Wauchope A, Hill S, Santaguida PL, Booth R, Brown JA et al. Use of natriuretic peptide measurement in the management of heart failure. Rockville Compar Effect Rev 2013; (126).

7. Lee YJ, Lee J, Park YS, Lee SM, Yim JJ, Yoo CG et al. Predictors of Cardiogenic and Non-Cardiogenic Causes in Cases with Bilateral Chest Infiltrates. Tuber Resp Dis 2013; 74 (1): 15–22.

8. Krüger S, Ewig S, Giersdorf S, Hartmann O, Suttorp N, Welte T et al. Cardiovascular and inflammatory biomarkers to predict short-and long-term survival in community-acquired pneumonia: results from the German Competence Network, CAPNETZ. Amer J Resp Crit Care Med 2010; 182 (11): 1426–1434.

9. Lin SC, Tsai YJ, Huang CT, Kuo YW, Ruan SY, Chuang YCe t al. Prognostic value of plasma N-terminal pro B-type natriuretic peptide levels in pneumonia patients requiring intensive care unit admission. Respirology 2013; 18 (6): 933–941.

10. Nowak A, Breidthardt T, Christ-Crain M, Bingisser R, Meune C, Tanglay Y et al. Direct Comparison of Three Natriuretic Peptides for Prediction of Short-and Long-term Mortality in Patients With Community-Acquired PneumoniaNatriuretic Peptides for Risk Stratification. CHEST J 2012; 141 (4): 974–982

11. Menéndez R, Martinez R, Reyes S, Mensa J, Filella X, Marcos MA et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax 2009; 64 (7): 587–591.

12. Krüger S, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. Eur Resp J 2008; 31 (2): 349–355.

13. Duman D, Aksoy E, Agca MC, Kocak ND, Ozmen I, Akturk UA et al. The utility of inflammatory markers to predict readmissions and mortality in COPD cases with or without eosinophilia. Intern J Chron Obstr Pulm Dis 2015; (10): 2469.

14. De Jager CP, Wever PC, Gemen EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PLoS One 2012; 7 (10): e46561.

15. De Jager CP, Van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T et al. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care 2010; 14 (5): R192.

16. Günay E, Ulaşli SS, Akar O, Ahsen A, Günay S, Koyuncu T et al . Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014; 37 (2): 374–380.

17. Walsh SR, Cook EJ, Goulder F, Justin TA et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 2005; 91 (3): 181–184.

18. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA et al. Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. Ame J Resp Crit Caer Med 1999; 160 (5): 1585–1591.

19. Jeong KY, Kim K, Kim TY, Lee CC, Jo SO, Rhee JE et al. Prognostic value of N-terminal pro-brain natriuretic peptide in hospitalised patients with community-acquired pneumonia. Emerg Med J 2011; 28 (2): 122–127.

20. Ozlu T, Bulbul Y, Alataş F, Arseven O, Coskun AS, Cilli A et al. Turkish Thoracic Society concensus paper on the diagnosis and treatment of community acquired pneumonia. Turk Thor J 2009; 10 (S9): 3–16

21. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M et al. Guidelines for the management of adult lower respiratory tract infections-Full version. Clin Microbiol Infect 2011; 17 (s6): E1–E59.

22. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet 2009; 374: 250–259.

23. Ambrosino N, Vagheggini G. Noninvasive positive pressure ventilation in the acute care setting: where are we? Eur Respir J 2008; 31: 874–886

24. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13: 818–829

25. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166: 1338–1344.

26. Chalmers JD, Singanayagam A, Akram AR, Mandal P, Short PM, Choudhury G et al. Severity assessment tools for predicting mortality in hospitalised patients with communityacquired pneumonia. Systematic review and meta-analysis. Thorax 2010; thx–2009.

27. Kolditz M, Santiago E, Gert H. Management-based risk prediction in community-acquired pneumonia by scores and biomarkers. Eur Resp J 2013; 41 (4): 974–984.

28. Richards G, Levy H, Laterre PF, Feldman C, Woodward B, Bates BM et al. CURB-65, PSI, and APACHE II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS. J Intens Care Med 2011; 26 (1): 34–40.

29. Chang CL, Mills GD, Karalus NC et al. Biomarkers of cardiac dysfunction and mortality from community-acquired pneumonia in adults. PloS one 2013; 8: e62612.

30. Corrales-Medina VF, Suh KN, Rose G, Chiinos JA, Doucette S, Cameron DW et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med 2011; 8 (6): e1001048

31. Dong M, Liu T, Li G. Association between acute infections and risk of acute coronary syndrome: A meta-analysis. Int J Cardiol 2011; 147: 479–482.

32. Tükek T, Yildiz P, Akkaya V, Akif Karan M, Atilgan D, Yilmaz V et al. Factors Associated with the Development of Atrial Fibrillation in COPD Patients: The Role of P-Wave Dispersion. Ann Noninvas Electrocardiol 2002; 7 (3): 222–227.

33. Lainscak M, Dagres N, Filippatos GS, Anker SD, Kremastinos DT. Atrial fibrillation in chronic non-cardiac disease: where do we stand? Internat J Cardiol 2008; 128 (3): 311–315.

34. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 2002; 162 (9): 1059–1064.

35. Yende S, Angus DC, Ali IS, Somes G, Newman AB, Bauer D et al. Influence of Comorbid Conditions on Long Term Mortality After Pneumonia in Older People. J Amer Geriatr Soc 2007; 55 (4): 518–525.

36. Johnstone J, Eurich DT, Majumdar SR, Jin Y, Marrie TJ. Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. Medicine 2008; 87 (6): 329–334.

Received March 31, 2016.
Accepted June 14, 2016.