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 I1, Karakurt Z2, Salturk C2, Kargin F2, Takir HB2, Aksoy E2, Sari R3, Celik E3, Tuncay EA2, Yildirim E1, Mocin OY2, Adiguzel N2, Oztas S1, Gungor S2, Gungor G2

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
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 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 \(\text{PaO}_2/\text{FiO}_2\) was < 300 and a partial arterial carbon dioxide pressure \(\text{PaCO}_2\) was < 45 mmHg. “Hypercnic and hypoxemic ARF” was defined if \(\text{PaCO}_2 > 45\) mmHg and \(\text{PaO}_2/\text{FiO}_2 < 300\) and “hypercnic ARF” was defined if \(\text{PaCO}_2 > 45\) mmHg and \(\text{PaO}_2/\text{FiO}_2 > 300\) (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 minute.

**Tab. 1. The baseline characteristics and comorbidities of pneumonia patients.**

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

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

**Microbiology**

Bronchial secret of patients were collected by a deep tracheal
180 days mortality

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 Antibiotic treatment

Single 61 (53) 14 (52) 0.95
Double 33 (29) 9 (33) 0.64
Triple 0 1 (4) 0.038

Antifungal treatment 19 (17) 13 (48) 0.001
Antiviral treatment 3 (3) 2 (7) 0.23

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

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

<table>
<thead>
<tr>
<th>Culture results</th>
<th>Survivor (ICU) n=116</th>
<th>Nonsurvivor (ICU) n=27</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any culture work up n (%)</td>
<td>57 (49)</td>
<td>22 (82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Urine</td>
<td>22 (22)</td>
<td>6 (25)</td>
<td>0.75</td>
</tr>
<tr>
<td>Blood</td>
<td>11 (10)</td>
<td>4 (15)</td>
<td>0.41</td>
</tr>
<tr>
<td>Bronchial lavage</td>
<td>10 (9)</td>
<td>7 (26)</td>
<td>0.013</td>
</tr>
<tr>
<td>Sputum</td>
<td>23 (41)</td>
<td>1 (5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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

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

CI – confidence interval; NLR – neutrophil lymphocyte ratio; BMI – Body mass index; ICU – intensive care unit
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
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-proANP) and CT-proAVP as better predictors of 28-day and 180-day mortality 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 sequela 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


