Diagnostic value of urea, creatinine and blood parameters in patients with pneumonia diagnosed with chronic obstructive pulmonary disease [version 1; peer review: 2 approved with reservations]

Seha Akduman
Pulmonary Medicine, Yeditepe Üniversitesi Koşuyolu Hastanesi, Koşuyolu, İstanbul/Kadıköy/Istanbul, Turkey

Abstract

Background: This study aimed to investigate the diagnostic value of urea, creatinine and other blood parameters in patients with pneumonia diagnosed with chronic obstructive pulmonary disease (COPD) for the first time.

Methods: In this retrospective study, patients who had been diagnosed with COPD for the first time and were diagnosed with pneumonia were included. A total of 193 patients were divided into three groups as COPD + pneumonia (n=123), COPD (n=36) and pneumonia (n=34).

Results: In total, 59 women (48.0%) and 64 men (52.0%) from the COPD + pneumonia group, 13 women (36.1%) and 23 men (63.9%) from the COPD group, 21 women (61.8%) and 13 men (38.2%) from the pneumonia group were assessed. The mean age of the COPD + pneumonia group was 69.58±13.62, 66.28±12.55 for the COPD group and 53.97±19.72 for the pneumonia group. The highest values of C-reactive protein (CRP), urea, creatinine, white blood cells (WBC), neutrophils, eosinophils and hemoglobin were the highest in COPD + pneumonia group. CRP levels were significantly different between COPD + pneumonia group (p<0.05). The parameters urea, WBC and neutrophils were significantly different between COPD + pneumonia group and pneumonia group (p<0.05). There was a statistically significant difference between COPD and pneumonia groups in terms of neutrophils and eosinophils values (p<0.05). According to the results of receiver operating characteristic analysis, the diagnostic value of the urea parameter in determining the COPD + pneumonia group was not statistically significant (p>0.05). On the other hand, the diagnostic value of CRP, WBC and neutrophils values were statistically significant (p<0.05).

Conclusions: Elevation in WBC and neutrophil values in patients diagnosed with pneumonia have an important role in diagnosis of COPD.

Keywords
COPD, Pneumonia, urea, creatinine, blood count
Corresponding author: Seha Akduman (sehaakduman42@gmail.com)

Author roles: Akduman S. Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction
Pneumonia has been known since late 1800s, and has been recognized as a major cause of death\(^1\). Pneumonia is one of the most common causes of mortality in children under 5 years, and common in South Asia and sub-Saharan Africa; it is a form of acute respiratory tract infection\(^2\). The annual incidence of community-acquired pneumonia (CAP) ranges from 5 to 11 per 1000 persons in the United States. In the winter. There are several risk factors associated with CAP, such as neurologic and gastrointestinal abnormalities, male gender, multilobar involvement, high fever, etc.\(^3\). CAP is an infection of the pulmonary parenchyma by causative microorganisms\(^4\).

Streptococcus pneumonia is the leading cause of bacterial pneumonia, causing 30-50% of childhood pneumonia in developing countries\(^5\). In diagnosis of the disease, chest X-rays, complete blood count and electrolyte count tests are used\(^6\). In treatment of pneumonia, medication and antibiotic therapy are commonly used. A 6-month observation is recommended by the UK National Institute for Health and Care Excellence. In addition, it is important to examine environmental conditions as well as given medication or therapy\(^4\). It is reported that smoking, chronic lung diseases, heart disease and diabetes increase the prevalence of disease\(^2\).

Chronic obstructive pulmonary disease (COPD) is another common lung disease, characterized by a slow and debilitating progression\(^7\). It causes changes in the lungs with airflow restrictions and physical symptoms such as dyspnoea\(^7\). Obstructive bronchiolitis and emphysema may represent comorbidities of COPD\(^8\)\(^9\). There is evidence that inhaled corticosteroids, a treatment for COPD, and increase risk of pneumonia\(^10\). In addition, previous research has shown that exacerbation of COPD and pneumonia in COPD has different clinical and analytical properties, although mechanisms are similar\(^11\)\(^1\).

This study aimed to investigate the diagnostic value of urea, creatinine and some blood parameters in patients with pneumonia that had been diagnosed with COPD for the first time.

Methods
Study participants and eligibility
In this retrospective study, patients who had been diagnosed with COPD for the first time and were diagnosed with Pneumonia and who were admitted to Kadıköy Medicana Hospital, Istanbul, Turkey, between 12 October 2017 and 12 October 2018 were included in the study. A sample of convenience was used, with a voluntary patient consent form. The eligibility criteria were as follows:

- Previously diagnosed with pneumonia,
- First diagnosed with COPD,
- Without a history of clinical intervention in patient epicrisis,
- Without a malignant disorder
- Completed patient consent form

A total of 123 patients with pneumonia among 160 patients who met inclusion criteria were included in the study. A total of 193 patients were divided into three groups as COPD + pneumonia (n = 123), COPD (n = 36) and pneumonia (n = 34). In the second group of patients diagnosed with COPD, the patients who were not diagnosed with pneumonia were designated as the first control group, and patients diagnosed with pneumonia and patients who were not diagnosed with COPD was the second control group. Each patient provided written informed consent for their clinical details to be used when admitted; the hospital management granted approval for this study.

Variables assessed in this study
The variables assessed in this study were age, gender, CRP, Urea, Creatine, WBC, NEU, EOS and HGB, which were taken from patient records with approval.

Statistical analysis
The binary and ordinal data were described by frequency analysis and the other measurement parameters by mean and standard deviation values. Kolmogorov-Smirnov analysis was performed to assess normality distribution of the data before the difference analysis. Independent samples t-test was used for the difference of normal distribution between WBC and hemoglobin data. The Mann-Whitney U-test was used to analyze the difference between paired groups (COPD + pneumonia vs COPD only; COPD + pneumonia vs pneumonia only; COPD only vs pneumonia only) of CRP, urea, creatinine, neutrophils and eosinophils parameters which did not conform to normal distribution. Receiver operating characteristics (ROC) analysis was used for CRP, urea, WBC and NEU. All analyses were performed in SPSS 17.0 for Windows, and performed at 95% confidence interval.

Results
Demographic information and clinical values
The distribution of gender, age and some clinical parameters of the case groups included in the study are shown in Table 1.

In total, there were 59 women (48.0%) and 64 men (52.0%) in the COPD + pneumonia group, 13 women (36.1%) and 23 men (63.9%) in the COPD group, and 21 women (61.8%) and 13 men (38.2%) in the pneumonia group included in the study. The mean age of patients was 70±14 in the COPD + pneumonia group, 66±13 in the COPD group and 54±20 in the pneumonia group. The highest values of CRP, urea, creatinine, WBC, neutrophils, eosinophils and hemoglobin were observed in the COPD + pneumonia group. The results of the differential analysis of the clinical parameters in the study are presented in Table 2. Raw values are available on Open Science Framework\(^11\).

Data analysis
According to the results of the difference analysis, there was a statistically significant difference between CRP levels of the COPD + pneumonia and COPD groups (p<0.05). The parameters urea, WBC and neutrophils were significantly different between the COPD + pneumonia and pneumonia groups (p<0.05). There was a statistically significant difference between COPD and
pneumonia groups in terms of neutrophils and eosinophils values (p<0.05). The results of ROC analysis of CRP, urea, WBC and neutrophils variables were given as follows.

According to the results of the ROC analysis (Figure 1), the diagnostic value of the urea parameter in determining the COPD + pneumonia group was not statistically significant (p>0.05). On the other hand, the diagnostic value of CRP, WBC and neutrophils values were statistically significant (p<0.05). The distribution of areas under the curve according to ROC analysis is given in Table 3.

The area under the curve was the highest for the CRP value.

Discussion

Pneumonia15-17 and COPD18-20 are two diseases that are the focus of considerable research into respiratory complaints. In addition, there are studies reporting the distribution of these diseases in different demographic groups11-26. In our study, pneumonia was more common in women, whereas COPD was more common in men. In both groups, the gender distributions were similar, although males made up the majority. However, the mean age of patients was the highest in COPD + pneumonia patients.

In patients with COPD and pneumonia, the clinical condition of the patients is poorer than for patients with one or the other conditions, and it is suggested that two diseases trigger each other25-34. In our study, urea and creatinine levels were higher in patients with pneumonia who were diagnosed with COPD for the first time. WBC and neutrophil values were statistically higher among patients with COPD than in patients with only pneumonia. The difference in urea, WBC and neutrophil values was not significant between the COPD and COPD + pneumonia groups. It can be said that the increase in these three parameters may have diagnostic implications for COPD in patients with pneumonia.

Table 1. Demographic and clinical parameters of patient groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD + Pneumonia (n=123)</th>
<th>COPD (n=36)</th>
<th>Pneumonia (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>59 (48.0)</td>
<td>13 (36.1)</td>
<td>21 (61.8)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>64 (52.0)</td>
<td>23 (63.9)</td>
<td>13 (38.2)</td>
</tr>
<tr>
<td>Age, (mean ± SD)</td>
<td>69.58±13.62</td>
<td>66.28±12.55</td>
<td>53.97±19.72</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>1.98±3.40</td>
<td>0.59±1.15</td>
<td>1.84±2.98</td>
</tr>
<tr>
<td>Urea, mg/dl</td>
<td>47.13±30.62</td>
<td>42.50±30.45</td>
<td>34.52±18.32</td>
</tr>
<tr>
<td>Creatine, mg/dl</td>
<td>0.89±0.35</td>
<td>0.87±0.46</td>
<td>0.83±0.36</td>
</tr>
<tr>
<td>WBC, ×10^3/μl</td>
<td>8.92±3.55</td>
<td>7.71±2.23</td>
<td>7.37±3.01</td>
</tr>
<tr>
<td>NEU, ×10^3/μl</td>
<td>6.19±3.43</td>
<td>5.08±1.94</td>
<td>4.90±2.44</td>
</tr>
<tr>
<td>EOS, ×10^3/μl</td>
<td>0.20±0.22</td>
<td>0.19±0.14</td>
<td>0.13±0.11</td>
</tr>
<tr>
<td>HGB, g/dl</td>
<td>13.54±2.01</td>
<td>13.45±1.63</td>
<td>12.91±1.68</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; WBC, white blood cells; NEU, neutrophils; EOS, eosinophils; HGB, hemoglobin.

Table 2. Difference analysis results between paired groups (COPD + Pneumonia, COPD and Pneumonia) and p-values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 vs group 2</th>
<th>Group 1 vs group 3</th>
<th>Group 2 vs group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP*</td>
<td>0.006</td>
<td>0.536</td>
<td>0.117</td>
</tr>
<tr>
<td>Urea*</td>
<td>0.153</td>
<td>0.006</td>
<td>0.329</td>
</tr>
<tr>
<td>Creatine*</td>
<td>0.319</td>
<td>0.311</td>
<td>0.850</td>
</tr>
<tr>
<td>WBC*</td>
<td>0.056</td>
<td>0.022</td>
<td>0.592</td>
</tr>
<tr>
<td>NEU*</td>
<td>0.137</td>
<td>0.033</td>
<td>0.040</td>
</tr>
<tr>
<td>EOS*</td>
<td>0.438</td>
<td>0.238</td>
<td>0.005</td>
</tr>
<tr>
<td>HGB*</td>
<td>0.803</td>
<td>0.099</td>
<td>0.182</td>
</tr>
</tbody>
</table>

*Mann-Whitney U-test; independent samples t-test. Group 1, COPD+pneumonia; group 2, COPD only; group 3, pneumonia only. Figures in bold represent statistically significant differences. CRP, C-reactive protein; WBC, white blood cells; NEU, neutrophils; EOS, eosinophils; HGB, hemoglobin.
Conclusion

According to the results of this study, a history of pneumonia aggravates the clinical course of patients with COPD for the first time. On the other hand, the increase in CRP, WBC and neutrophil values in patients diagnosed with pneumonia but not COPD may give the first indication of a possible development of COPD.

According to the results of ROC analysis, CRP is among the most important determinants of patients with the first time diagnosed with COPD and diagnosed with pneumonia. On the other hand, WBC and neutrophil elevation in patients with previously diagnosed pneumonia may also be an important factor in the diagnosis of COPD.

Table 3. Receiver operating characteristic analysis results and areas under curves.

<table>
<thead>
<tr>
<th>Test result variable</th>
<th>Area</th>
<th>Standard error</th>
<th>p-value</th>
<th>Asymptotic 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>CRP</td>
<td>0.693</td>
<td>0.060</td>
<td>0.005</td>
<td>0.575</td>
</tr>
<tr>
<td>Urea</td>
<td>0.596</td>
<td>0.068</td>
<td>0.163</td>
<td>0.462</td>
</tr>
<tr>
<td>WBC</td>
<td>0.638</td>
<td>0.061</td>
<td>0.044</td>
<td>0.518</td>
</tr>
<tr>
<td>NEU</td>
<td>0.638</td>
<td>0.063</td>
<td>0.044</td>
<td>0.515</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; WBC, white blood cells; NEU, neutrophil.

Figure 1. Receiver operating characteristic analysis results for C-reactive protein (CRP), urea, white blood cells (WBC) and neutrophils (NEU).
Data availability


This project contains the demographic and clinical variables of patients measured in this study.

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Grant information

The author(s) declared that no grants were involved in funding supporting this work.

References


Open Peer Review

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Reviewer Report 09 December 2019

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Elena Titova
Department of Thoracic and Occupational Medicine, Trondheim University Hospital, Trondheim, Norway

This retrospective study is aimed “to investigate the diagnostic value of urea, creatinine and some blood parameters in patients with pneumonia that had been diagnosed with COPD for the first time”.

I would like to make following comments:

Introduction:
- Article starts with the sentence “Pneumonia has been known since late 1800s, and has been recognized as a major cause and death” with reference 1.
  I absolutely agree with the author that pneumonia remains a significant cause of mortality worldwide.

  But the original text (reference 1) was written as follows: “Long recognized as a major cause of death, pneumonia has been studied intensively since the late 1800s “

  Pneumonia was first described by Hippocrates (460-370 BC), pathological features were made 22 centuries later in 1819 by Laennec, while Rokitansky in 1842 was the first to differentiate lobar and bronchopneumonia (ref.: G. Mackenzie, Pneumonia (Nathan), 2016; 8:14 1).
  - The author mentioned that annual incidence of CAP in the United States ranges from 5 to 11 per 1000 persons.
    It should be natural to include a reference here because the numbers can vary depending on the source.

Could the data on patients with pneumonia taken from the Turkish Thoracic Society CAP database (TURCAP) be more interesting/relevant compared to the data from USA?
  - The author wrote that “Obstructive bronchiolitis and emphysema may be represent comorbidities of COPD”. Maybe the author can formulate this sentence in a different way.

  The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airway disease (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which vary from person to person (GOLD COPD, 2019)
  - I would like the author to clarify the choice of urea, creatinine, white blood cells, neutrophils, eosinophils and haemoglobin as the parameters are of interest in his research.
Methods:
- Patients in the study get diagnosis COPD for the first time. Spirometry is required to make the COPD diagnosis.
- Basic characteristic (FEV1, FEV1/FVC) in patients with COPD should be listed.
- It should be explained to readers what the criteria "without a history of clinical intervention in patient epicrisis" means.
- It would be nice to know when blood samples in the study were taken (at admission? after admission?)
- It is important to describe clinical status of patients with COPD patients. Did the patients have the COPD exacerbation or not; what symptoms did the patients have?

Results, conclusion and discussion:

I would like to propose that the Results, Conclusion and Discussion parts of this research should be rewritten with necessary details.

This article has a great potential for improvement and needs major revision.

References

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
1. The study population is enough but the control group is too small. Maybe a power is needed.

2. In the abstract section the authors wrote "According to the results of receiver operating characteristic analysis, the diagnostic value of the urea parameter in determining the COPD + pneumonia group was not statistically significant (p>0.05). ROC curves gives the sensitivity and specificity and cut off values not the difference between two variables. I think they mean the AUC value. So the article should be revised by an statistican specialist.

3. There is no information about the study population whether they are outpatients or hospitalized patients. All the patient are CAP?

4. Also in the eligibility criteria, I did not understand the meaning of:
   - Previously diagnosed with pneumonia, (did you mean: diagnosed with pneumonia?)
   - First diagnosed with COPD, (did you mean: new diagnosed COPD?)
   - Without a history of clinical intervention in patient epicrisis? The authors should explain what did they mean and clearly explain the including and excluding criteria.

5. Are the all COPD patients are stable or in acute exacerbation?

6. In table 1: authors give the descriptive values of study groups but the p values is absent. In the table 2 comparing the paired group there is no information about mean age, gender

7. In table 2 when compared the paired groups, interestingly there is no difference between COPD group and COPD with pneumonia and pneumonia without COPD. How can you explain these results?

8. The discussion section too small and it is similar with the result section. The authors should detail in the discussion section and discuss the results, not repeat the results

9. I am not a native speaker but the article should revised for language.

   As a result according to me: The article is not well written, well designed and well discussed. So it is not eligible for indexing without a major revision.

**Is the work clearly and accurately presented and does it cite the current literature?**

No
Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** copd, icu, infection

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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