

Medical University – Varna Prof Dr. Paraskev Stoyanov

Faculty of Medicine Department of Internal Medicine Scientific and Educational Sector of Pulmonary Disease and Allergology

# ROLE OF COMORBID DISEASES AND SOME BIOCHEMICAL MARKERS IN DETERMINATION OF SEVERITY AND PROGNOSIS OF COMMUNITY ACQUIRED PNEUMONIA

# Dr. Darina Nikolova Miteva – Mihaylova

# ABSTRACT

of dissertation paper for awarding the educational and scientific degree of **Doctor** 

# Supervisor:

Assoc. Prof. Yordan Radkov Dimitrov, MD, PhD

# **Official reviewers:**

Prof. Ognyan Georgiev, MD, PhD, DSc Assoc. Prof. KamenYankov, MD

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### Introduction

Community-acquired pneumonia (CAP) is a disease with a high incidence, hospitalization and still high mortality rate. Despite the success of antibiotic treatment, the mortality rate ranged between 5-15%, and in intensive care units it is up to 50%.

The presence of comorbid diseases affects the course and outcome of the disease. There is no single opinion regarding their significance as the concomitant diseases vary in their nature and severity and their impact in the course of pneumonia is difficult to define. In this paper we evaluate not only the significance of particular diseases to the course of pneumonia, but also evaluate the cumulative risk in polimorbid patients assessed through Charlson Comorbidity Index (CCI). Adding of CCI to the basic severity scales can improve the stratification of risk in patients with pneumonia. Some of the severity scales for CAP such as PSI and IDSA/ATS criteria include a relatively large number of indices and require time to complete them making them difficult to be used in routine practice. Therefore, the interest in markers that are quickly achievable, objective and reliable severity predictors is growing. Some biochemical markers meet these conditions. Their role in diagnosing pneumonia is expressed in several directions – establishing of diagnosis, referring to etiological agent, severity prediction, treatment failure and mortality from pneumonia, referring to an appropriate choice of antibiotic and determining the duration of treatment. Some of the biomarkers such as leucocytes and CRP are routinely used in clinical practice. Other, such as procalcitonin (PCT) and D-dimer are yet to enter in diagnosis and determination of prognosis in CAP. Adding biomarkers to pneumonia severity scales and even their individual use will improve the detection of high-risk patients and reduce the mortality from the disease. For that reasons the topic has not only great scientific but also practical application.

#### Aim of Dissertation:

The aim of this paper is to investigate the role of comorbid diseases and some biomarkers on the community-acquired pneumonia severity and outcome.

#### Tasks:

To achieve this aim, we set ourselves the following tasks:

- 1) To determine the frequency of comorbidities in patients hospitalized with CAP.
- 2) To establish the role of some more common socially significant diseases in the clinical course of CAP.
- 3) To determine the predictive value of comorbid diseases regarding in-hospital mortality rate.
- 4) To determine the cumulative effect of comorbid disease through using Charlson Comorbidity Index (CCI) on CAP severity rate and outcome.
- 5) To determine the predictive value of some biomarkers leucocytes, CRP, D-dimer and PCT for the severity and prognosis of the disease.
- 6) To perform a comprehensive analysis of in-hospital mortality in CAP.

7) To develop a profile of the patients at high risk of mortality.

8) To establish an algorithm to select the site of treatment and control of patients with CAP.

### **Material and Methods:**

**1292** CAP patients hospitalized in the Clinic of Pneumology and Phthisiatrics at "Saint Marina" University Hospital for the period from 2012 to 2015 were studied retrospectively and prospectively.

The following methods were used:

# A. Clinical examination

# **B.** Diagnostic imaging

# C. Laboratory tests

Complete blood count analysis was done with automated machines. The reference value of the leucocyte count was  $4-10 \times 10^9$ /L, and the platelets count–  $140-440 \times 10^9$ /L.

CRP was measured by latex-enhanced immunoturbidimetric method with reference value of <5mg/L. Both initial and control CRP on the 4-5 day were measured.

The initial PCT on the day of hospitalization was determined in 160 patients. The control PCT on the 4-5 day of hospitalization was determined in 80 of them. PCT was measured by standard ELISA method. The reference value was 0,05ng/ml.

D-dimer was studied in 144 patients on the day of their hospitalization. It was quantified based on latex-enhanced immunoturbidimetric method. The reference value was 0,232mg/L.

### **D.** Pneumonia severity assessment

To assess the severity of CAP internationally established scales were used– PSI, CURB-65, IDSA/ATS criteria.

# **E. Assessment of comorbid diseases** through CCI. CCI was determined for each patient. **F. Statistical methods**

Comparative analysis (evaluation of hypotheses, correlation analysis, analysis of variance (ANOVA), analysis of risk assessment (OR), regression analysis. P<0,05was accepted as statistically significant in all comparisons.Quantitative variables were reported as mean value and standard deviation (mean  $\pm$  SD), and qualitative variables were reported as a count and relative share (%).In various aspects of the study some of the patients served as auto-controls.

### **Results and discussion**

### 1. Socio-demographic characteristics of patients

The average age of patients was  $59,94\pm17,03$  y.o. as the minimum age was 18 y.o. and the maximum age was 98 y.o. Male were - 57,2%. More than three fourths of the patients (76,40%) had comorbidities and 55,80% developed complications. 24,1% of the patients developed multilobar infiltrates, and in the remaining patients there were unilobar infiltrates. 267 patients or 20,70% of the total sample were treated in the intensive care unit. The total number of diseased

patients was 148 (11,50 %), as there is a significant difference between diseased in ICU (45,70 %) and in the general unit (2,60 %) ( $\chi^2$ =385,1, p < 0,001). The average hospital stay was 8,2±4,5 days.

#### 2. Frequency of comorbid diseases in patients hospitalized with CAP

Comorbid disease analysis covers 1203 patients who stayed in the Clinic during 2012-2014. Patients with comorbid diseases were 76,40% of the sample, as the most common comorbidities were the cardiovascular diseases. Leading in their frequency were the hypertensive disease (61,7%) ,IHD (24,5%), diabetes mellitus (23,6%). Patients with CHF (23,5%)and cerebrovascular disease (17,2%) also were with high frequency.

The high percentage of patients with comorbid diseases is noteworthy. One possible reason is the age of the patients as the more their age increases the higher is the frequency of polimorbid patients. On the other hand, some low-frequency diseases such as dementia have significant impact on the outcome of pneumonia as it will be described later in this paper.

We examined the impact of certain common and socially significant diseases on the clinical course of CAP.

#### 3.Impact of comorbid diseases on CAP severity and prognosis

#### Cardiovascular diseases

These are the most common comorbidity among the study group. We paid particular attention to patients with chronic heart failure (CHF). 282 patients (23,50%) had CHF. Of CHF patients 97,2% had underlying hypertensive disease, 66,7% had IHD, 35,5% had atrial fibrillation, 12,8% had valvular heart disease and 3,5% - cardiomyopathy.

CHF patients were significantly older - 71,5y.o.± 10,8 y.o. compared to 56,4 y.o.± 17,1 y.o. in the group without CHF. They developed more often complications such as acute respiratory failure (49,7% vs. 29,8% in patients without CHF) and pleural effusion (35,1% vs. 21%). The frequency of cavitations was lower (1,8% compared to 5%). The presence of multilobar infiltrates in patients with CHF was more common (31,6% vs. 21,9%). The need of intensive care was also more common - 30% of the patients with CHF were treated in ICU vr. 17,6% of the patients without CHF. For them the average PSI score was significantly higher  $117,79 \pm 39,42$  versus  $83,47 \pm 36,87$ , which was indicator for greater severity of the pneumonia and increased risk of mortality. Patients with CHF fell in higher risk groups in the two main scales CURB-65 and PSI significantly more often. 31% of the patients with CHF fell in high risk groups of CURB -65  $\geq$ 3 compared to 14,6% of the patients without CHF. 72,3% of patients with CHF fell in the high-risk groups of PSI (IV and V- group) versus only 26,3% of these not suffering from CHF (p < 0.001). As a result of the greater severity of CAP in patients with accompanying CHF the in-hospital mortality was logically significantly higher- 20,2% versus 9,1% (p < 0.001). No significant difference was established in the length of the hospital stay - 8 days. We calculated OR for in-hospital mortality of patients with CHF - 2,54 (1,76-3,67), which is similar to the one determined by Fine in a meta-analysis of studies on CAP prognosis and outcome - 2,4 [92]. Kaplan and Thomsen reported lower risk -OR 1,82(95% CI 1,77-1,87)

[131] and OR 1,8 (MRR 1,8 95% CI 1,67-1,95) [277]. Our study determined the presence of IHD and atrial fibrillation as predictors of higher in-hospital mortality among patients with CHF while patients with cardiomyopathy and valvular heart disease showed no increase in mortality.

To conclude, we can say that patients with cardiovascular diseases are in a risk group and particular attention is to be paid to patients with IHD, atrial fibrillation and those with manifestation of CHF. The higher risk of complications and mortality requires close attention of the medical team.

#### **Diabetes mellitus**

Patients with DM were significantly older 65,8y.o. $\pm$  13,2y.o. compared to 58,2y.o. $\pm$  17,7 y.o. Diabetes mellitus significantly affects the course of CAP. CAP patients with accompanying DM more often developed complications of pneumonia such as ARF (44,9% versus 31,1% in patients without DM) and pleural effusion (28,3% versus 23,1%), but did not show greater frequency of cavitation. Multilobar infiltrates (31,8% versus 21,8%, p<0,001) were more frequently observed in these patients. Patients with diabetes mellitus are treated in ICU in 31,4% of cases compared to 17,1% in the group of patients without DM. The greater severity of CAP in patients with DM is also reflected in the significantly higher average PSI score (105,49  $\pm$  42,14 compared to 88,08  $\pm$  38,92, p< 0,001). Patients with diabetes mellitus significantly more often fell in the higher risk groups of both PSI and CURB-65 scales. Mortality rate in the group of patients with DM was significantly higher (19,4% vs. 9,3%, p<0,001).

The relation between diabetes mellitus control and the outcome of pneumonia is also of interest. We divided DM patients into 4 groups according to the level of blood sugar control–patients with blood sugar of  $\leq 6,1$ mmol/L; between 6,11 - 11 mmol/L; 11,01 - 13,9 mmol/L and  $\geq 14$  mmol/L. Mortality rate in the first three levels of control showed no significant difference, but in the group with blood sugar of $\geq 14$ mmol/L mortality significantly increased reaching 37,1%. We carried out univariet analysis of the risk for in-hospital mortality in patients with DM and established the presence of acute respiratory failure (OR 10,87; 4,89-24,13, p<0,001),bad blood sugar control $\geq 14$  mmol/L(OR 3,71; 1,98-6,92, p<0,001) and the presence of multilobar infiltrate (OR 3,36; 1,83-6,16, p<0,001) as the most powerful predictors. The cerebrovascular disease is the accompanying disease increasing at higher level the risk of mortality (OR 3,06; 1,64-5,71, p<0,001).

We can conclude that patients with diabetes mellitus are vulnerable and high-risk group for developing complications and death. Patients with poor control of diabetes and presence of other accompanying pathologies, such as cerebrovascular disease require special attention.

#### COPD

Lately the problem of "pneumonia– COPD" relation is especially relevant due to accumulated evidence of an increased risk of pneumonia in patients with COPD treated with inhaled corticosteroids. However, the question of the impact of COPD on the course of CAP is subject to discussion. In our group only 69 patients (5,80 %) had accompanying COPD. This rate is lower than the one cited in the literature, where COPD is determined as one of the most common comorbidities in CAP with frequency of about 19% [213].

Patients with COPD were older (67,7y.o.  $\pm$  10,6 y.o. compared to 59,5 r. $\pm$ 17,2y.o., p< 0,001) and were more often male ( 69,6% ). The frequency of other comorbidities, especially CVD and DM was higher.

There are controversial data in literature on the impact of COPD on the course of CAP. In our study we found higher frequency of some pulmonary complications such as ARF in patients with COPD (57,9% vs. 33,1% in patients without COPD). The higher frequency of ARF naturally leads to more frequent need on intensive treatment (31,9% vs. 20%, p<0,001)and application of non-invasive ventilation (9,2% compared vs. 3,3%, p<0,05) and invasive pulmonary ventilation (10,4% vs. 3,2%, p<0,01). However, there was no significant difference in the development of other lung complications such as pleural effusion or cavitation. Patients with COPD did not show higher frequency of multilobar infiltrates (26,1% vs. 24,3%, p>0,05). There is no difference in the distribution of the various groups of severity according to CURB-65 between patients with COPD and these not suffering of COPD, but there is such a difference in the distribution according to PSI – patients having COPD more often fell into higher risk groups of PSI. The average PSI score was significantly higher in patients with COPD compared to these without COPD (106,75±38,74 vs. 91,87±40,56; p<0,01). Despite the higher frequency of respiratory failure in patients with COPD and their more frequent need of intensive care, no significant difference was established in the mortality rate between the two groups. Mortality rate in the COPD group was slightly higher, but the difference was not significant (14,50 % vs. 11,7%, p>0,05). No difference was established in the average hospital stay as well -8 days.

In our study, 42% of the COPD patients were treated with inhaled corticosteroids and 58% were not. We did not find statistically significant difference between the two groups in developing of complications such as ARF. No significant difference in the need of intensive care and in the frequency of multilobar infiltrates was established. Also, there was no significant difference in the mortality rate between the two groups (13,8% in patients treated with ICS vs. 15% in patients without ICS, p>0,05). It could therefore be concluded that the use of inhaled corticosteroids do not significantly affects the course and outcome of CAP.

In conclusion we can say that although COPD modifies the course of CAP, it does not significantly increase the in-hospital mortality from CAP. The use of inhaled corticosteroids does not affect the course and outcome of CAP in patients with COPD.

# Predictive value of the cumulative effect of comorbid diseases assessed by CCI for the the severity and outcome of CAP

CCI is the most commonly used index to assess the impact of comorbid diseases on the mortality rate for the purposes of longitudinal studies. Its role in acute conditions such as pneumonia has been approbated.

The average value of CCI for the entire sample was  $1,58\pm1,84$ , as values ranged from 0 to 10. The mean CCI in non- survivors was significantly higher than in survivors (3,28 vs. 1,36; p<0,001). For patients treated in ICU, CCI was also higher compared to the patients in the general ward (2,65 ± 2,09 vs. 1,26 ± 1,63 t=11,65, p < 0,001). We determined three levels of

comorbidity: low level of comorbidity (CCI=0 points.), moderate lever (CCI=1-2p.) and high level of comorbidity (CCI  $\geq$ 3p.). The in-hospital mortality rate was significantly related to the level of CCI - in the low level of comorbidity the mortality rate was only 3,8%, and in the high level it reached 28,9% (p<0,001). By drawing ROC- curve we compared the predictive value of CCI for in-hospital mortality with this of the basic scales. The best predictors for in-hospital mortality were PSI and IDSA/ATS criteria, followed by CURB-65 and CCI. AUC for each one of the scales was respectively 0,859; 0,852; 0,849 and 0,769. The area under the curve (AUC) of CCI is close to that of the basic scales and its predictive value for in-hospital mortality is high (fig. 1).



Fig. 1.Predictive value of severity scales and CCI for in-hospital mortality

#### 4. Predictive value of some biomarkers for severity and prognosis of CAP

Biomarkers are quick and objective indicators that carry valuable information about the severity of the infection. In our study we analyzed the role of the WBC count, CRP, PCT and D-dimer as severity and mortality predictors in patients with CAP.

#### **C-reactive protein**

One of the key markers already widely used in everyday clinical practice is CRP. Its affordability and common application make the study of its informative value in CAP very interesting. We measured the initial CRP on admission, and its control value on the  $4^{th}$  -  $5^{th}$  day of treatment. The average initial value of CRP was 128,84±99,13mg/L, and its control value dropped to 47,66±55,03mg/L. We also determined the CRP value in patients with proven bacterial pneumonia and in patients with pneumonia caused by atypical intracellular microorganisms (Mycoplasma pneumoniae and Chlamydia pneumoniae). We found a significant difference between both etiological agents of pneumonia – in the proven bacterial infection the

CRP value was  $159,76\pm107,95$ mg/L, and in the proven atypical agents-  $77,61\pm70,1$ mg/L, t=4,22, p<0,001. The initial CRP value in the presence of at least one comorbidity was higher than that without the presence of comorbidity ( $138,29 \pm 98,44$ mg/L vs.  $109,21\pm97,70$ mg/L, p<0,001). CRP mean values in the presence of pulmonary complications such as pleural effusion, cavitation, ARF, and in the presence of multilobar infiltrates were significantly higher. CRP mean value in patients treated in ICU, was also higher  $176,11\pm93,85$ mg/L vs.  $116,71\pm96,77$ mg/L for patients treated in the general unit, p< 0,001. In non-survivors CRP was also significantly higher than in survivors ( $171,85\pm83,17$ mg/L vs.  $123,42\pm99,68$ mg/L, p< 0,001).

We distributed patients into four groups according to CRP initial value – first group with CRP<20mg/L (16,1% of the patients); second group with CRP $\geq$ 20 mg/L and <100mg/L( 28,5% of the patients ); third group with CRP $\geq$ 100 mg/L and <200mg/L( 31,3% of the patients) and fourth group with CRP  $\geq$ 200mg/L(24,1% of the patients). We analyzed the mortality rate in each group and found that it increased progressively with the increase of the CRP value –it was only 2% in the group with the lowest CRP value, and in CRP $\geq$ 200 mg/L group it reached 20,1% , p < 0,001. We also found a significant difference in the risk of developing complications according to different values of CRP. For example in CRP<200mg/L 49% of the patients developed complications, and in CRP $\geq$ 200mg/L complications were developed by 76,9% of the patients,  $\chi$ 2=70,14, p<0,001.

We also examined the initial CRP values in low and high-risk patients according to the three severity scales– PSI, CURB-65 and IDSA/ATS criteria.We found a significant increase of CRP in the severe groups of the three scales. For example, the lowest CRP value is observed in the first group according to PSI (74,82 mg/L), while the highest- in the fifth group (177,34mg/L), p < 0,001.

Significantly higher levels of CRP in bacterial pneumonia compared to pneumonia caused by atypical agent showed that CRP is able to direct to a bacterial cause of the infection, like the PCT. We also found higher initial levels of CRP in patients with complications, as this was observed for the three pulmonary complications - pleural effusion, cavitations and development of ARF. CRP was also significantly higher in more extensive involvement of the pulmonary parenchyma which was observed in multilobar infiltrates. We assume that these higher CRP values may be associated with the more severe inflammatory response in these patients. The starting CRP values in deceased patients were also higher compared to survivors. The proportion of deceased patients in the group with  $CRP \ge 200 mg/L$  (20,1%) is too high. Therefore we conclude that patients with CRP>200mg/L should be regarded as high-risk patients and are subject to more active monitoring. In addition to the initial CRP value its dynamics is also important. In our study we found that in about three fourths of the patients there was a 50% drop down of the values on the fourth – fifth day of the treatment. However, when there was no such a decline we observed significantly higher mortality rate, increased risk of complications and prolonged hospital stay. The lack of decline in CRP control value could serve as an indicator of a tightened course of the infection and requires re-evaluation of diagnostic and therapeutic decisions.

In conclusion we can say that CRP is a quick, affordable and relatively inexpensive marker that is very useful in the diagnosis and management of patients with CAP.

#### Procalcitonin

We measured the levels of the initial procalcitonin on admission in 160 patients, and 80 of them we also tested the control PCT on the fourth-fifth day of the hospitalization. The average pnitial value was  $1,16 \pm 1,43$ ng/ml, the minimum value was 0,036ng/ml, and the maximum value was 7,5ng/ml. We determined the average initial value of PCT in different etiologic agents. The initial PCT was higher in patients with proven bacterial agent compared with CAP, caused by atypical intracellular microorganisms ( $1,35\pm1,54$  ng/ml vs.  $0,36\pm0,63$  ng/ml, p<0,05). In patients with complications, the initial PCT was significantly higher ( $1,39\pm1,65$ ng/ml vs.  $0,77\pm0,8$ ng/ml, p<0,01). It was significantly higher in patients with ARF, but no difference was detected in patients with pleural effusion and cavitation. In the presence of multilobar infiltrate, PCTwas also significantly higher in deceased patients compared to survivors ( $3,03\pm2,37$ ng/ml vs.  $1,04\pm1,26$ ng/ml, p<0,001).

We divided the patients into four groups according to the level of PCT. In 9,4% we observed normal PCT values. In 23,1% PCT was within the range 0,05-0,5ng/ml, which indicated the presence of only local infection and lack of a significant systemic inflammatory response. In the remaining 67,5% there was a systemic inflammatory response– moderate in 50%( PCT=0,5-2ng/ml ) and severe in 17,5% (PCT $\geq$ 2ng/ml). In these 67,5% PCT values indicated the presence of sepsis. We examined the mortality rate in each of the groups and found that all patients with PCT<0,5ng/ml survived, there were no deceased among them. In PCT between 0,5-2ng/ml the mortality rate was 5%, and in PCT $\geq$ 2ng/ml it increased up to 21,4%.

We determined the PCT levels in different risk groups according to the three main severity scales. In all three scales PCT increased significantly with the increase of the severity of pneumonia. For example, in PSI the highest score was recorded in the highest risk fifth groups according to PSI (2,38ng/ml), and the lowest one was in the first group (0,48 ng/ml) (F=10,20; p < 0,001).

In managing of CAP, PCT is used in various fields. One of them is the determination of the etiological diagnosis. In patients with proven bacterial agent we established significantly higher PCT compared with the pneumonia caused by atypical intracellular pathogens (Mycoplasma pneumoniae and Chlamydia pneumoniae). Thus, PCT is able to direct to an etiological agent. Therefore it can assist in the selection of the correct empirical antibiotic treatment. At PCT values about 0,3ng/ml the likelihood of atypical infection is higher and antibiotic treatment directed to these agents (macrolide, fluoroquinolone) is to be considered. Of course, this value is to be interpreted within the context of the overall clinical picture. We also established significantly elevated values in the presence of complications in general, and from pulmonary complications – in the presence of ARF. We believe that on the one hand ARF is related to the extent of pneumonic infiltrate (in patients with multilobar infiltrate PCT was also

significantly higher), and in some of the cases it could be regarded as a manifestation of severe systemic inflammatory response with organ dysfunction (a condition in which PCT is particularly useful for determination of its severity). In the presence of severe systemic inflammatory response which corresponds to PCT $\geq$ 2ng/ml, the in-hospital mortality significantly increased. This puts patients with PCT $\geq$ 2ng/ml in a risk group which requires active monitoring and more aggressive treatment. A value of PCT $\geq$ 2ng/ml can serve as a quick guide to severity of infection. This was confirmed by the fact that the average PCT value in patients requiring intensive care, approached this value again (1,91±2,00ng/ml in ICU patients vs. 0,92±1,09ng/ml in the general ward, p<0,001). The persistence of elevated PCT values may serve as predictor of poor outcome. In our study we found that in patients with complications, the control value on the 4<sup>th</sup>-5<sup>th</sup> day stayed significantly higher compared to patients without complications. In patients where there was an increase of the control value, the frequency of complications is much higher. Therefore we believe that the control value on the 4<sup>th</sup>-5<sup>th</sup> day can be considered a good predictor of complications

In conclusion PCT is an innovative marker of great practical value in diagnosis and monitoring of patients with CAP.

#### **D-dimer**

Coagulation disturbances are one of the markers of systemic inflammation. D-dimer is the most commonly used in routine practice. As a marker for activated fibrinolysis it is not only used to diagnose venous thromboembolism but also in many other conditions. Recently data were found that its values are increased in the large proportion of patients with CAP. In our study, D-dimer was studied in 144 patients. Elevated levels of D-dimer were found in 86,70 % of the tested patients. The average value was  $1,38mg/L\pm1,56mg/L$ . We found significantly higher values of D-dimer in deceased patients compared to survivors  $(2,19\pm2,01mg/L \text{ vs. } 1,28\pm1,46$ mg/L, p<0,05). A significant difference was established in the examined pulmonary complications in the presence of pleural effusion and ARF, for example in ARF the average Ddimer value was  $1,817\pm1,829mg/L \text{ vs. } 1,068\pm1,258mg/L$  in patients without ARF, p<0,01. Despite its higher values in ICU patients, the difference did not reach significance.

D-dimer values in high-risk groups of PSI, CURB-65 and IDSA/ATS criteria are significantly higher, e.g. D-dimer showed significant difference in low and high-risk severity groups according to PSI. In I-III low-risk groups, the average D-dimer values ranged between 0,68-1,15mg/L, and in IV-V high-risk groups the average value ranged between 1,67- 2,04 mg/L (F=2,51; p<0,05).We found a significant increase in mortality rates in patient with D-dimer above 1mg/L( 26,1%), as with its increase above 2mg/L mortality rate did not grow (20,7%), p<0,05. We found OR of D-dimer >1mg/L for in-hospital mortality 4,25 (1,48-12,14; p<0,01). Therefore we assume that patients with D-dimer >1mg/L should be considered as having an increased risk of mortality. D-dimer can be considered as a reliable prognostic marker in CAP, identifying patients with an increased risk of developing complications and mortality.

#### Correlation of biomarkers with the basic severity scales

We identified correlation coefficients of the studied biomarkers with the basic severity scales. Compared with other biomarkers, PCT had the strongest correlation with the scales. Correlation coefficients are presented in table 1.

Biomarker	PSI	CURB-65	IDSA/ATS criteria
РСТ	r=0,454	r=0,430	r=0,402
CRP	r=0,209	r=0,232	r=0,260
D-dimer	r=0,249	r=0,228	r=0,217
Leuc	r=0,20	r=0,175	r=0,101

#### Table 1. Correlation coefficients of biomarkers with CAP severity scales

The analysis of the correlation coefficients of biomarkers showed that PCT has the best correlation coefficient with the severity scales. Therefore we consider it as the strongest predictor of CAP severity and mortality among the biomarkers included in the study.

#### **5. In-hospital mortality analysis**

One of the main tasks we set was to make a comprehensive analysis of in-hospital mortality. Revealing and analyzing the major risk factors for mortality we will be able to identify patients who fall in high-risk groups. Such patients require more intensive monitoring and more aggressive treatment to prevent the onset of complications and reduce in-hospital mortality.

Although the relative share of deceased males is slightly higher than that of females, no significant difference in the mortality rate between two sexes was proven (12,70 % for men and 10,40 % for women, p>0,05).

Patients' age is one of the major factors related both to the development of pneumonia and to the increased mortality rate. We found a significant difference in the proportion of deceased patients in individual age groups as there is a tendency the share of deceased patients to increase with the age. The lowest mortality rate we had in the group of 31-40y.o.(1,7%)., then gradual increase of mortality rate is observed and in the age over 80 y.o. it reached 20,9% (p < 0,001).

Comorbid diseases play a significant role on in-hospital mortality. The mortality rate in patients without comorbidities was only 2,9%, and in the presence of one comorbidity the mortality rose to 15,8%.

When performing univariate analysis of concomitant diseases by calculating the odds ratio (OR) of each disease in terms of in-hospital mortality, the highest OR showed the following diseases: dementia(OR 6,85; 95% CI 5,97-11,86), cancer with metastases (OR 4,33; 95% CI 1,4-13,1), cerebrovascular disease (OR 4,05; 95% CI 2,77-5,92) and chronic renal failure (OR 3,66;

95% CI 3,35-5,73). Among patients with cerebrovascular disease, those with severe residual changes – hemiplegia, had the highest risk of in-hospital mortality (OR 5,71; 95% CI 3,44-9,45). Chronic liver disease, CHF, diabetes mellitus and IHD also significantly increased in-hospital mortality (table 2).

Comorbid disease	OR (95% Cl)	p-value
Dementia	6,85 (5,97-11,86)	P<0,001
Cancer with metastases	4,33 (1,4-13,1)	P<0,05
Cerebrovascular disease	4,05 (2,77-5,92)	P<0,001
Chronic renal failure	3,66 (2,35-5,73)	P<0,001
Chronic liver disease	3,11 (1,70-5,71)	P<0,001
Chronic heart failure	2,54 (1,76-3,67)	P<0,001
Diabetes mellitus	2,36 (1,63-3,42)	P<0,001
Ishemic heart disease	2,22 (1,54-3,21)	P<0,001
Malignant hemopathy	1,77 (0,72-4,38)	p>0,05
		(NS)
Ulcer disease	1,61 (0,79-3,25)	p>0,05
		(NS)
Peripheral vascular	1,54 (0,66-3,53)	p>0,05
disease		(NS)
COPD	1,28 (0,64-2,57)	p>0,05
		(NS)
Connective tissue disease	1,23 (0,51-2,96)	p>0,05
		(NS)
Cancer without	0,98 (0,46-2,10)	p>0,05
metastases		(NS)
Bronchial asthma	0,54 (0,16-1,76)	p>0,05
		(NS)

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Although dementia is a relatively rare disease, it led to the highest risk for in-hospital mortality. Even the presence of cancer with metastases gave way to dementia as a risk factor for mortality and ranked second. Our study found that hematological malignancies, ulcer disease, peripheral vascular disease, connective tissue diseases, COPD, bronchial asthma and cancer without metastases did not significantly increase the in-hospital mortality.

We compared CRP and PCT predictive values for in-hospital mortality with the predictive value of the main scales. For this purpose we made ROC-curves, including these biomarkers and the main scales. The three main scales have a higher predictive value as for PSI, IDSA/ATS criteria and CURB-65 AUC was respectively 0,860; 0,856 and 0,849. AUC for CRP was 0,658. (Fig.2)



Fig. 2.Predictive value of severity scales and CRP for in-hospital mortality

We also made a ROC-curve comparing the PCT predictive value for in-hospital mortality with that of the main scales. Unlike CRP, AUC for PCT was comparable to that of the basic scales. In this case, the area under the curve for PSI, CURB-65 and IDSA/ATS criteria and for PCT was respectively: 0,878; 0,872; 0,842 and 0,824. These results showed the good predictive value of PCT for in-hospital mortality (fig.3).



Fig. 3.Predictive value of severity scales and PCT for in-hospital mortality

We conducted univariate analysis of all factors, which, according to our study, can serve as predictors of mortality. The results are shown in table 3 as the indicators are systematized according to the OR. Among the CAP severity scales IDSA/ATS criteria had the greatest predictive value. Despite the smaller number of indicators included, the predictive value of CURB-65 was close to that of PSI- OR 20,17 (13,28-30,65) compared to 22,53(12,81-39,65) respectively. This makes CURB-65 very suitable for routine clinical practice. Of the laboratory parameters tested, the highest predictive value of mortality had the acute respiratory failure, established by blood-gas analysis- OR 23,31 (13,45-40,37). This requires close monitoring of

such patients with examining the parameters in 4-6 hours. The spread of pneumonic infiltrate also affects the outcome of the disease, as the multilobar infiltrate showed OR 5,28 (3,69-7,54). The complex impact of comorbidities reflected in CCI $\geq$ 3, also had a high predictive value with OR 6,82 (4,74-9,80). Among the tested biomarkers PCT $\geq$ 2ng/ml had the highest OR 8,73 (2,27-13,45).

Risk factor	OR (95% CI)	p-value
IDSA/ATS criteria for severe CAP	41,59 (26,01-66,52)	P<0,001
ARF	23,31 (13,45-40,37)	P<0,001
PSI IV-V groups	22,53 (12,81-39,65)	P<0,001
CURB-65≥3	20,17 (13,28-30,65)	P<0,001
Confusion	19,43 (13,04-28,95)	P<0,001
Respiratory rate>30/min	10,36 (6,86-15,64)	P<0,001
PCT≥2ng/ml	8,73 (2,27-13,45)	P<0,01
Urea>7mmol/L	8,11 (4,96-13,25)	P<0,001
CCI≥3	6,82 (4,74-9,80)	P<0,001
Heart rate ≥125/min	6,67 (4,18-10,63)	P < 0,001
Hypotension< 90 mmHg (systolic) and 60mmHg	5,84 (4,05-8,4)	P<0,001
(diastolic)		
Multilobar infiltrate	5,28 (3,69-7,54)	P<0,001
D-dimer>1 mg/L	4,25 (1,48-12,14)	P<0,01
Tr<100x10 <sup>9</sup> /L	4,05 (2,04-8,04)	P<0,001
CRP≥200mg/L	2,74 (1,89-3,95)	P<0,001
Leuc<4x10 <sup>9</sup> /L	2,57 (1,64-4,04)	P<0,001
Age≥65r.	1,89 (1,34-2,67)	P<0,01
Uneffective initial AB therapy	1,84 (1,25-2,69)	P<0,01
Pleural effusion	1,56 (1,07-2,26)	P<0,05

# Tabl. 3. Risk factors for in-hospital mortality

In conclusion, risk factors for mortality in CAP include clinical, laboratory and radiological criteria. These factors should be evaluated quickly, at the time of admission, which will allow taking correct treatment decisions.

# 6. Algorithm for selecting a site of care and monitoring patients with CAP

Analyzing risk factors of in-hospital mortality allowed us to establish a risk profile of patients and to develop an algorithm for choosing a site of care and monitoring patients with CAP. Patients with increased risk of mortality are these, included in the risk groups of the main scales, as according to our study, the risk profile also includes the following risk factors (RF):

- ► CCI≥3
- > ARF
- Multilobar infiltrate

- ➢ PCT≥2ng/ml
- ➢ D-dimer>1mg/L
- ≻ CRP≥200mg/L
- >  $Tr < 100 x 10^9 / L$
- $\blacktriangleright$  Leuc<4 x10<sup>9</sup>/L

The algorithm is based on CURB-65 as the easiest and most affordable scale and includes the established risk factors (RF). In the presence of CURB-65=0-1 and no RF, outpatient treatment is advised. A follow-up examination in 2-3 days is required. If there is a clinical improvement, the outpatient treatment continues. If there is a clinical deterioration, the patient is to be referred to hospitalization. In CURB-65=0-1, and one RF or in presence of CURB-65=2, hospitalization in the internal ward is recommended. In CURB-65=0-1 and RF  $\geq$ 2 or CURB-65=2 and RF $\geq$ 1 or in CURB-65=3, we advise intensified monitoring in a specialized Pulmonology Clinic. Intensified monitoring includes control of heart rate, respiratory rate and blood gas analysis in 4-6 hours. In practice, it can be implemented in intensive care rooms to a pulmonary clinic/unit with opportunity to conduct oxygen treatment. If there is clinical improvement within 72 hours, intensified monitoring may be discontinued and the patient should continue treatment in a general unit. If there is clinical deterioration, patients should be referred to a specialized intensive care unit. Patients with CURB-65=3 in combination with RF  $\geq$ 1 or with CURB-65=4-5 should be immediately admitted to ICU. The prognosis of such severe cases is better if they are admitted directly to ICU compared to postponed admission (Fig. 4).



Fig. 4. Algorithm for selecting a site of care and monitoring patients with CAP

The algorithm includes 4 levels of care – outpatient, treatment in a general internal unit, intensified treatment and treatment in an ICU. Proper risk assessment of each particular patient will result in individualization of treatment and improvement of prognosis.

#### Conclusion

CAP is a common disease with heterogeneous clinical picture – from mild and well amenable outpatient treatment, to severe life-threatening infection. Comorbid diseases have significant impact on the course and prognosis of CAP. There cumulative burden can be well assessed through CCI, which must be incorporated in risk assessment models. It is also appropriate to add biomarkers to other factors included in the main scales in order to improve risk stratification in CAP patients. Proper risk assessment will help to identify high-risk patients who require active monitoring and more aggressive treatment to improve the prognosis of the disease.

#### Inferences

- 1. The most common comorbidities in CAP patients are hypertension, IHD, diabetes mellitus, CHF and cerebrovascular disease.
- 2. The presence of dementia, cancer with metastases, cerebrovascular disease and chronic renal failure increase the risk of in-hospital mortality to the highest degree.
- 3. The presence of CHF and diabetes mellitus is also related to greater severity of CAP, assessed through the main scales, more frequent development of complications and increased in-hospital mortality.
- 4. Despite the more frequent development of certain complications such as respiratory failure, the presence of COPD does not increase in-hospital mortality from CAP. Treatment with inhaled corticosteroids does not affect the severity and outcome of CAP.
- 5. Comorbidity level assessed through CCI is a good predictor for the development of complications, the need of intensive care and mortality, although CCI predictive value is lower than this of the main scales– PSI and CURB-65.
- 6. CRP and PCT are significantly higher in bacterial pneumonia compared to one caused by atypical intracellular pathogens.
- 7. Patients with CRP $\geq$ 200mg/L, PCT $\geq$ 2ng/ml, D-dimer>1mg/L and leucocytes  $<4x10^{9}/L$  should be regarded as having an increased risk of mortality.
- 8. Among biomarkers, PCT is the best severity predictor that correlates moderately with the main scales. CRP, D-dimer and leucocytes correlate mildly with CAP severity scales.
- 9. The profile of patients having increased mortality risk includes high level of comorbidity, increased levels of the examined biomarkers, presence of ARF and multilobar infiltrate.
- 10. According to our study risk factors define a four-level algorithm for selecting the site of treatment and monitoring of patients.

# Contributions of scientific, theoretical and applied nature

- 1. For the first time in Bulgaria a systematized analysis of the impact of the most common socially significant diseases on the course and prognosis of CAP was made.
- 2. The cumulative risk of comorbidities, assessed through CCI, for development of complications and mortality from CAP is the first one made in our country.
- 3. For the first time in Bulgaria we assessed the role of PCT in the diagnosis and prognosis of CAP.
- 4. We developed a profile of the patients with increased risk of mortality from CAP including comorbid diseases and biomarkers.
- 5. Based on CURB-65 an algorithm for selecting the site of treatment and monitoring of CAP patients was developed.