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BIOMARKERS FOR ASSESSING SEVERITY AND COMPLICATIONS IN COMMUNITY-ACQUIRED PNEUMONIA

Summary
Early prognostic assessment by the clinical scale with the biomarker panel is crucial for the optimized management of community-acquired pneumonia (CAP).
The **aim** was to evaluate the usefulness of several biomarkers (representing different pathophysiological pathways) and thyroid hormones in combination with the CURB-65 scale to understand how these biomarkers might be used in clinical practice for assessing CAP severity as well as the relationship between these biomarkers and adverse clinical outcomes.
Methods. A total of 62 in-patients with proven CAP of CURB-65 class 2-5 were enrolled into the study. We measured the values of C-reactive protein (CRP), procalcitonin (PCT), d-Dimer (d-D), copeptin (CP), adrenomedullin (ADM) and thyroid hormones such as free triiodothyronine (FT_3), tetraiodothyronine (FT_4) and thyroid stimulating hormone (TSH).
Results. Intensification of CAP severity and in-hospital mortality (IHM) cases were associated with increased values of infection and inflammation biomarkers (CRP, PCT), disorders of coagulation (d-D) and vascular tone (CP, ADM). Non-survivors had significantly higher values of CRP, PCT, d-D and CP vs. survivors. PCT, d-D showed significantly higher concentrations in patients requiring vasopressor support (VS) vs. those with stable haemodynamics (by 10 and 2.1 times respectively). On admission in intensive care unit (ICU) CRP, PCT and D-d values were significantly correlated with need for VS (r=0.39; 0.74 and 0.54) and IHM (r=0.38; 0.72 and 0.48). Both CP and ADM values were significantly associated with duration of ICU stay (r=0.43; 0.91) as well as CP with the need for VS (r=0.54). The levels of FT_3 and FT_4 were significantly lower in non-severe and severe CAP groups (by 12% and 23%) vs. the control group as well as in patients requiring invasive mechanical ventilation (IMV). There were a relevant correlations between FT_4 and CAP severity (r= –0.55), FT_3 and IHM (r= –0.44) as well as between FT_3, TSH and the need for IMV (r= –0.47; r=0.37 respectively). The development of non-thyroidal illness syndrome (NTIS) was detected in 42% of these CAP patients.
Conclusion. This biomarker panel and thyroid dysfunction can be used for adequately assessing the severity of CAP. We detected a close relationship between this biomarker panel and some adverse clinical outcomes.

Keywords
Community-acquired pneumonia, biomarkers, C-reactive protein, procalcitonin, d-Dimer, copeptin and thyroid hormones.

Community-acquired pneumonia (CAP) remains a common and serious illness in adults with an estimated incidence of approximately 6 cases/1.000 population per year [1]. The majority of cases are managed outside hospital, but 20% require hospital admission. Out of this group of immunocompetent patients, around 20% develop severe CAP (sCAP) with multiple pathophysiological pathways that requires immediately hospitalized in intensive care unit (ICU) often for invasive mechanical ventilation (IMV) or vasopressor support (VS) [1, 2]. More than one third of these patients will die in the first few days of hospitalization, despite significant advances in etiological investigation, early initiation of antimicrobial therapy and improvements in adequate supportive care. A standard of CAP management recommend the tactics of diagnosis and treatment based on the early evaluation of the CAP severity. Most of clinical factors obtained by history and physical examination (such as pathological chest auscultation) as well as routine tests (as leucocyte count — WBC) have limited the ability with surprisingly poor accurate predictors for the CAP severity and its complications. Thus, a clinical judgment is not reliable in the appropriate management of CAP. In support, some studies have shown a tendency for clinicians to either overestimate or underestimate CAP severity.

There are some different international prognostic scales that based on the approach with initial stratification of CAP (assess its severity and possible mortality) as well as the need to determine the amount of specific treatment and tactical matters during hospitalization (mainly in ICU). So, CURB-65 scale is a popular scale in Western Europe at the present time due to its simplicity and reliability in everyday practice [3]. This risk predic-

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tion tool perform well in identifying CAP patients with a low mortality risk, but are poor in predicting ICU-admission (as well as in requirement for IMV or VS) and other important adverse sCAP outcomes, including early deterioration and some serious complications [4-6].

The use of several biomarkers may represent a different branches of the CAP pathogenesis (as disease-related stress, physiological reserve and a response to a therapeutic intervention) and improve practices in emergency medicine [7-10]. Thus, biomarkers could significantly help management of CAP by improving the accuracy of clinical severity scores and outcomes [4, 11, 12]. The complex assessment of CAP include the diagnostic work-up (the clinical decision-making process), guiding antibiotic therapy (the choice and route of antimicrobial agents), evaluating the clinical response to therapy and recovery from sCAP, the development of organ dysfunction (heart, kidneys, liver or multiple organs dysfunction) as well as stratify sCAP patients based on predicted risks for IHM [3, 13, 14]. The biomarker's results are completely dependent on being performed with appropriate clinical suspicion and using sensitive and specific assays. It is highly likely, that no single biomarker in isolation will accurately provide all the information necessary for accurate clinical sCAP management, possible due to disease heterogeneity.

C-reactive protein (CRP) is the most widely used biomarker of infection in severe ill patients, but its specificity has been challenged [15-17]. CRP is an acute phase-protein synthesized only by the liver largely under control of IL-6, a cytokine released at sites of inflammation. CRP levels rise rapidly (within 4-6 h) in response to several inflammatory stimuli during acute and chronic inflammatory states (bacterial infection being one of the most potent). After the disappearance of or removal of the stimulus, the CRP concentration decreases rapidly with a half-life of 19 h. The rate of synthesis is the only significant determinant of its plasma level and, hence, CRP level is a useful objective index of acute phase response. It should be known, that CRP may be several elevated in the elderly as well as a low CRP level may reflect severity of hepatic synthetic function disorders rather than absence of infection. Although results are controversial, CRP may help the diagnosis, severity assessment and treatment follow-up of CAP [18]. For CRP, recent data suggest that steroids and prior antimicrobial therapy could a slightly decrease or did not influence CRP level on admission in patients with CAP [19].

CRP alone should not be used to diagnose CAP as well as absolute CRP values are less useful than their dynamics in predicting the prognosis and severity of CAP. Probably, it may have more utility in the combination with other clinical features and biomarkers. With regard to CAP severity and adverse clinical outcomes, several studies [16, 20] have demonstrated that high CRP levels on admission and the absence of CRP kinetics over the course of a hospitalization were associated with ICU admission and serious complications including a higher incidence of organs failure and IHM. The higher CRP levels on ICU discharge were also associated with higher ICU readmission and IHM. So, in patients with higher CRP levels, IHM was decreased up to 15% if CRP levels decreased after 48 h, whereas IHM was 60% in patients, whose CRP did not decrease [18]. Furthermore, there are discordant results with regard to the associations of CRP and CAP outcomes, suggesting that CRP may not be useful for determining the prognosis of this disease [21, 22].

It was shown the diagnostic utility of PCT for acute systemic bacterial infections [23-25] and now PCT is being increasingly used as a diagnostic, prognostic and therapeutic biomarker in CAP [21, 26]. Thus, evaluation of PCT complements and improves the complex assessment of CAP based on careful patient history, physical examination and appropriate cultures.

PCT is the prohormone of the hormone calcitonin which is normally produced in the thyroid gland. In the absence of infection, extra-thyroidal production of PCT is suppressed and in healthy individuals, the levels of PCT are low. PCT is not a marker of early infection. So, PCT values start to rise 4 h after the onset of systemic infection and reach its peak at between 8 and 24 h. In microbial infections and various forms of inflammation, PCT levels increase up to several-thousand-fold (however, this rise is negligible in viral infections). Its rising (especially in dynamics) was correlated with the CAP severity and IHM, while the PCT cut-off levels for diagnosing infection have not been clearly established.

PCT has superior diagnostic accuracy [22, 27] as compared with other markers in severe systemic bacterial infection which most frequent source is the lung. Both CRP and PCT levels have been shown to predict the severity of illness and 28-day mortality [28-29], but PCT was more strongly associated with the adverse outcomes than CRP [30-33], while the levels of CRP and WBC were not found to be predictive of mortality. Administration of steroids and antibiotics does not diminish the value of PCT [34]. Renal clearance is one of the PCT elimination pathways.

The presence of inflammatory conditions (with realizing the proinflammatory mediators — IL-1,6 and TNF-α) and microbial infection (e.g. microbial toxins) as well as multiple organ dysfunction induce increased production and release of PCT from all non-thyroidal parenchymal tissues and dif-

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ferentiated cell types (liver, adipose tissue, kidney, and muscle but not by leukocytes) [18]. However, as the surrogate marker, PCT can be elevated [7, 30, 35] in noninfectious conditions (for example, in: thyroid or lung cancer, liver metastasis, renal failure, severe trauma, pneumonitis, burns and paraneoplastic syndrome) and may remain low in some cases of bacterial infections (especially in localized infections — empyema or blocked abscess). PCT (in contrast to CRP) is inhibited through interferon γ, which is released in viral infections, thus exhibiting a strong specificity for bacterial infections [33]. Thus, PCT may give information on whether the patient is suffering from a bacterial infections, while this information cannot be assessed by using CRP.

PCT level was increased with rising the severity of sepsis and organ dysfunction [36]. Vice versa, it was detected, that low levels of PCT were associated with low short- and long-term mortality across CURB classes [23, 27]. The serial measurements of PCT over time in sCAP patients may more accurately describe CAP outcomes (serious complications and IHM) and may be more useful than single measurement [32], because PCT levels often show a gradual increase during follow-up, while a falling level of PCT suggests a favorable outcome. Unfortunately, PCT levels on the day of admission were often failed to predict CAP severity and its prognosis [36, 37].

The results of several studies [38, 39] have demonstrated that high initial levels of d-Dimer (d-D) as degradation product of fibrin formation and biomarker of coagulation disorders in patients with critical conditions was associated with high risk of IHM in sCAP. The significant disorders of hemostasis are often accompanied in sCAP. During acute or chronic of lung parenchyma damage developments activation of both vascular and extravascular coagulation is known to develop. This activation of the coagulation cascade leads to deposited of fibrin in interstitium and alveoli of the lung. The fibrin matrix is part of the acute inflammatory response and initiates the sequence of events leading to remodeling of the lung tissue [40]. The relationship between levels of d-D and the severity as well as the adverse outcomes of CAP is not sufficiently studied.

Arginine vasopressin (AVP) is a key hormone in the human body. AVP has vasoconstrictor (restoring vascular tone in vasodilatory hypotension) and antidiuretic properties (maintaining the fluid balance). AVP produced by hypothalamic neurons and released due to different stimuli such as infections, stress, hypotension, hypoxia, hyperosmolarity and acidosis. Measurement of AVP is difficult due to its short half-life and instability. Recently, provasopressin — copeptin (CP) was found to be a stable and sensitive surrogate marker for AVP release. So, the high CP level might be used as a biomarker of the stimulated neuroendocrine regulation as well as provide evidence that of AVP is also elevated in sepsis and septic shock or insufficient endogenous AV production in these conditions [41, 42]. ICU admission and IHM was more frequent in sCAP patients admitted with the high CP levels [42-44]. Thus, CP (like cortisol) reflects individual stress response and has hemodynamic and osmoregulatory effects.

However, accurate IHM prediction does not automatically lead to accurate identification of patients developing critical stage of disease and the need for ICU treatment. So, CP was better in predicting early clinical instability (within 72 h after admission) and mortality than other biomarkers, including WBC, CRP and PCT [42]. Thus, in patients who died, the CP levels on admission were significantly higher as compared with the levels in survivors. The role of neuroendocrine regulation as well as behavior of CP in sCAP is under investigation.

It is now known that adrenomedullin (ADM) is rather more than simply a vasodilator. It may be predictor development of septic shock as well as may have a remarkable range of actions (from regulating cellular growth and differentiation, through modulating hormone secretion, to antimicrobial effects). The levels of the ADM were related with CAP severity and its outcomes well as with sepsis [45-48].

A number of studies [49, 50] have demonstrated the presence of significant thyroid dysfunction («nonthyroidal illness syndrome» — NTIS) in ICU patients with acute respiratory distress syndrome (ARDS) and in critical conditions. NTIS in the patients with severe conditions was characterized by low levels of total and free triiodothyronine (FT_3) as well as tetraiodothyronine (FT_4) against the background of disproportionately high values of thyroid stimulating hormone (TSH). NTIS is predictor of adverse outcomes in critically ill patients and its presence leading to a marked mortality in these patients [51, 52]. Thyroid status in patients with different severity of CAP and its relationship to outcomes of sCAP are poorly understood.

The aim of our study was to evaluate the usefulness of some biomarkers (CRP, D-d, PCT, CP, ADM) and thyroid hormones with combination of the CURB-65 scale to understand how these biomarkers might be used in standard clinical practice for CAP severity assessment as well as the relationship between these biomarkers and some clinical parameters — IHM, length of in-hospital stay (LIHS) and ICU stay, need for IMV and VS.

Materials and methods

We enrolled consecutive 62 patients (18 years old or above) recruited from Minsk population

(Belarus) with a diagnosis of CAP based on the following inclusion criteria (most of them are unspecific): temperature >37.5 °C or hypothermia, acute respiratory relevant symptoms (at least two of the following symptoms): fever, cough with increased purulent sputum production, dyspnea, pleuritic chest pain, altered local breath sounds during auscultation, leukocytosis as well as presence of a new or increasing radiological pulmonary infiltrate. Chest radiograph images were recorded as lobar, localized and diffuse bilateral.

In the course of the study were recorded: sex and age of patient, presence of concomitant diseases, the amount of lung tissue damage and the parameters required for the account scale CURB-65 (levels of consciousness and urea, the frequency of breaths respiratory rate, blood pressure). ICU admission was considered in sCAP patients with the presence one of two major criteria (the need for IMV or VS) or two of three minor criteria (systolic blood pressure <90 mm Hg, multilobar disease, psO_2<90%) or more than two CURB points and no response or worsening mental status (confusion, coma) despite of adequate initial therapy.

Written informed consent was obtained from every patient prior to inclusion in the study. The study was approved by the ethical review board of Belarusian State Medical University.

Exclusion criteria from the study: hospital-acquired pneumonia, systemic immunosuppression (systemic steroid medication of ≥10 mg prednisolone equivalent per day for more than 14 days) and severe immunosuppression other than corticosteroids; ongoing chronic antibiotic administration; the presence of foci of active tuberculosis 4 weeks prior to hospitalization; patients with organic pathology of the thyroid gland or treated with thyroid hormones or iodine-containing drugs in the past 6 months; thromboembolism burdened by history and high probability of pulmonary embolism at present; the classes 3-4 of congestive heart failure according to NYHA; the presence of malignant tumors and leukemia; chronic moderate-to severe renal, hepatic and rheumatic diseases or vasculitis; 3 months before of injury and surgery; decompensated diabetes mellitus and the patients whose biomarkers were not available on the first day on admission. These exclusions were needed to make sure that the inflammatory reactions result from acute infectious disease and not from underlying diseases.

Initially (the first stage of our study), 36 patients with CAP were divided into the two groups (Table 1): 1st group was formed of 16 patients with non-severe CAP (2-3 class severity according to the CURB-65 scale) and the 2nd group — 20 patients with sCAP (4-5 class of the severity). The control group included 16 comparable healthy volunteers with no infectious inflammatory conditions from the medical staff of our clinic. Adequate empirical antibiotic therapy was carried out. The correction of latter (more often in sCAP patients) was performed based on the data of the microbiological examination and the antibiogram. Short-term prior antibiotic therapy (was revealed in 1/3 of the patients) before hospitalization did not affect eligibility. A causative microbial pathogen was detected in half of sCAP patients. Detailed baseline characteristics of the study population are presented in Table 1.

As seen in Table 1, the age of patients in the 2nd group was higher as compared with the 1st group ($p<0.05$) while the sex structure of these groups was comparable. The analysis structure of these groups according to a CURB-65 scale showed that the half of patients from the 1st group had 2 or 3 class, while 60% and 40% of the patients from the 2nd group had 4 and 5 classes respectively.

Additionally (the second stage of study), we have analyzed the patients who were treated in ICU. They were divided into survivors and non-survivors (during 20 days after the first hospital contact until death) patients (Table 2). There were no significant differences between the numbers of male patients and class of severity among these groups. The most of non-survivors men were smokers and abused alcohol. Of the analyzed pre-exiting comorbidities, non-survivors had higher rates of prior reported congestive heart failure, hypertension and coronary artery disease, indicating a definite contribution of these comorbidities to mortality. But, from our point of view, the death of these patients was prima facie influenced by the presence of severe respiratory failure, septic shock and organ failure against the background of high CURB severity scores rather than comorbidities.

The reasons of the deaths among these 6 patients during antibiotics treatment in ICU were the following: the two patients died during IMV (from severe respiratory failure) and VS (from septic shock

Table 1. The baseline characteristics of 36 patients according to CAP severity (Me-IQR)

Group	Age (years)	Sex	CURB-65 class
1st (n=16)	44.5 (32.0; 58.1)	women (25%), men (75%)	class 2-50%, class 3-50%
2nd (n=20)	63.5* (52.2; 77.6)	women (40%), men (60%)	class 4-60%, class 5-40%

*Me and IQR denote median and interquartile range; * — p<0.05 between these groups.*

Table 2. Comparison of age, sex and CURB-65 scale structure between survivors and non-survivors (Me-IQR)

Group	Age (years)	Sex	CURB-65 class
Survivors (n=20)	49.7 (36.2; 63.3)	women (20%), men (80%)	class 3-40%, class 4-60%
Non-survivors (n=6)	51.1 (42.4; 59.8)	men (100%)	class 4-67%, class 5-33%

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and refractory hypotension) as well as due to multiple organs failure. Some of these sCAP patients experienced more than one serious complications (e.g. severe hypoxemia, ARDS, pleural effusion, acute renal failure and cardiovascular dysfunction).

As seen in Table 3, only 1 patient from survivors have required VS and IMV at the first day on admission as compared with all the patients in non-survivors group. Duration of VS and IMV as well as ICU length stay was higher in non-survivors as compared with survivors.

WBC, serum CRP, d-D and PCT values were measured within the first 24 h after admission by the local hospital laboratories. CRP values were detected by immunoturbometry method («CRP Latex Beckman») and d-D levels by immunochemical method («d-Dimer; Hemosil»). PCT was determined by an immunnochromatographic method («Brams PCT-Q»). The levels of thyroid hormones were evaluated by RIA method («Roche diagnostics», Germany). CP and ADM were measured by a sandwich immunoluminometric assay (Kryptor, Thermo Scientic Biomarkers). Laboratory measurements were performed in a blinded fashion without knowledge of the clinical status of the patient.

Statistical analysis. The statistical analysis was performed using the developed software packages in STATISTICA for Windows 8.0 (2007, Statsoft Inc., USA). The preliminary analysis of the variables under consideration was a Shapiro-Wilk test of correspondence to normal distribution. The results of the analysis were shown as median and interquartile range (Me-IQR) because all the parameters differed from normal distribution. The comparison of non-parametric parameters in two independent groups was carried out using a Mann-Whitney test. Spearman's rank correlation coefficient (r) was used to describe the relationship between the two quantitative variables that differed from normal distribution. The level of statistical significance was set at $p<0.05$.

Results

WBC was significantly differed in patients with different classes of CAP severity as well as it was depended on the volume affection of lung tissue. As seen in Table 4, WBC in patients of the 2nd group was about 2 times higher than in the 1st group ($p<0.05$). WBC was correlated with the class severity of CAP according to CURB-65 scale ($r=0.54$; $p<0.05$). WBC in non-survivors did not differ from survivors patients. It was not revealed the correlation between WBC and IHM.

On admission CRP level was higher in patients of 2nd group as compared with the 1st group (by 21%; $p<0.05$) as well as in non-survivors vs. survivors (by 1.5 time; $p<0.05$). CRP showed a significantly higher concentration in patients requiring VS as compared with those with stable haemodynamics (2.2 vs. 1.9 mg/L). Additionally, CRP level was significantly correlated with the classes of CURB scale ($r=0.55$), need for VS ($r=0.39$) and IHM ($r=0.38$).

Table 3. Clinical parameters in survivors and non-survivors (Me-IOR)

Parameters	Survivors (n=20)		Non-survivors (n=6)	
	1st day	8th day	1st day	8th day
Need for VS (n)	1	-	6	5
VS duration (h)	-	12	46 (32;63)	91 (74; 105)
IMV (n)	1	-	6	5
IMV duration (h)		24	67 (38; 92)	175 (143; 192)
length of ICU stay (days)	-	8	-	16 (14; 17)

Table 4. Baseline levels of biomarkers in different CAP patient's groups (Me-IQR)

Group	WBC (10^9/L)	CRP (mg/L)	PCT (ng/ml)	d-D (mg/ml)	CP (pg/ml)
1st (n=16)	9.7 (6.1; 13.8)	1.9 (1.5; 2.0)	1.8 (0.4; 10.0)	0.8 (0.3; 1.2)	45.2 (24.5; 59.8)
2nd (n=20)	21* (15.0; 26.5)	2.3* (1.8; 2.6)	7.1* (1.6; 29.0)	1.7* (1.2; 2.0)	76.0* (55.0; 90.1)
survivors (n=20)	13.9 (11.1; 22.4)	1.9 (1.7; 2.3)	1.3 (0.4; 8.6)	1.2 (0.8; 1.4)	44.7 (36.3; 58.4)
non-survivors (n=6)	25.3 (21.3; 29.6)	2.8** (2.5; 2.9)	5.9** (4.7; 9.2)	1.6** (1.2; 2.0)	74.2** (54.9; 89.7)

** — p<0.05 between 1st and 2nd groups; ** — p<0.5 between survivors and non-survivors.*

The similar picture was observed concerning the PCT dynamics. Thus, PCT was increased as severity of CAP was raised too. We revealed a positive correlation between the PCT level and a classes of CURB scale ($r=0.74$; $p<0.05$). So, it was detected that PCT level was significantly higher in patients with 4th class severity as compared with 3rd class (by 3.5 times) as well as in the 2nd group vs. the 1st group (by 3.9 times).

Additionally, we noted the significant variations of PCT levels in the observed groups (Fig.). So, it was <0.5 ng/ml in 56% of the patients from 1st group and >0.5 but ≤10 ng/ml in other 44% of patients. The changes of PCT level in the 2nd group were noticeably differed from the same in the 1st group. Thus, PCT level was >0.5 ng/ml in all of patients and ≥10 ng/ml in 70% of these patients. We revealed that PCT with cut-off point ≥10 ng/ml may be a good guide for identifying sCAP patients for ICU admission.

Non-survivors had significantly higher values of biomarkers of infection and inflammation, and, as expected, showed the trend to higher values of the calculated CURB-65 scores describing severity of CAP on admission. Analysis showed, that PCT level was higher in non-survivors than in survivors (by 4.5 times; $p<0.05$) and its value was increased more pronounced as compared to WBC, CRP, body temperature and abnormal local chest auscultation changes. Additionally we detected that the patients

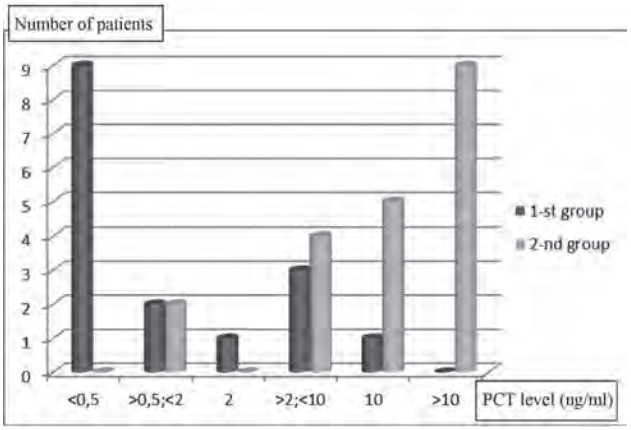

Fig. Distribution of PCT levels in different CAP groups

who required VS had a higher PCT level as compared with those with stable hemodynamics (by 10 times; p<0.05). Thus, a diagnostic accuracy of PCT for CAP severity was significantly higher as compared to CRP, WBC and the observed clinical symptoms. We revealed that PCT level was significantly correlated with IHM, need for VS and duration of ICU stay (r=0.74, r=0.72 and r=0.81 respectively). Usually, the observed patients with the typical bacterial etiologies of CAP showed the higher levels of PCT than the patients with viral etiologies.

We detected a significant difference of d-D level in patients with various classes of CAP severity. So, d-D level was significantly higher in the 2nd group vs. the 1st group, in non-survivors as compared with survivors as well as in patients requiring VS vs. those with stable hemodynamic (by 2, 1,3 and 2,1 times respectively). d-D concentration was also depended on the volume of lung tissue affection. So, the patients with bilateral or polysegmental disease affection had a higher d-D level too. The latter was correlated with intensification of the CAP severity (r=0.62; p<0.05). Additionally, we found the significant correlations of d-D levels with LIHS, need for VS as well as with IHM (r=0.50, r=0.54 and r=0.48 respectively).

On admission CP levels was significantly higher: in the 2nd group as compared with 1st group (by 68%), in the 4th class of CAP severity vs. the 3rd class (by 57%) and in non-survivors vs. survivors (by 66%) as well as in patients who required VS as compared with those with stable haemodynamics (by 57%; p<0.05). We noted, that intensification of CAP severity was also associated with increased CP value (r=0.53; p<0.05). The latter was significantly correlated with need for VS and duration of ICU stay (r=0.54 and r=0.43). Although ADM level did not correlated with CAP severity, but it was significantly associated with duration of ICU stay (r=0.91) and with the need for IMV (r=0.47).

The analysis showed that CAP patients had the significant differences in their baseline thyroid hormones status as compared with the control (Table 5). So, a level of TSH was significantly higher in 1st and 2nd groups (by 2 and 2.9 times respectively) as compared with the control. TSH levels did not correlate with CURB scale and with volume of lung parenchyma damage.

Table 5. The baseline levels of thyroid hormones in CAP patient's groups (Me-IQR)

Parameter	Control (n=12)	1st group (n=16)	2nd group (n=20)
TSH (mME/L)	1.1 (0.8; 1.4)	2.3 (1.4; 2.6)*	3.2 (2.3; 4.2)*,**
FT_3 (pmol/L)	5.5 (4.7; 5.7)	4.6 (4.0; 5.2)*	4.0 (3.6; 4.6)*
FT_4 (pmol/L)	19.2 (17.3; 20.2)	17.6 (16.6; 19.5)*	15.5 (14.6; 16.9)*,**

** — p<0.05 vs. the control; ** — p<0.05 between the CAP groups.*

As seen in Table 5, the levels of FT_3 and FT_4 were significantly lower in 1st and 2nd groups (by 12% and 23%) than in the control group. We did not find a significant difference of FT_3 levels in patients with different grades of CAP severity as well as with different volumes of lung tissue damage, but FT_3 level was significantly higher in survivors as compared with non-survivors (by 1.5 time). The FT_3 and FT_4 values were significantly lower (by 15% and 7%) in patients requiring IMV than in those being under spontaneous respiration. There were a significant correlations between FT_4 and CAP severity (r= –0.55) and between FT_3 and IHM (r= –0.44) as well as between FT_3, TSH and need for IMV (r= –0.47; r=0.37 respectively). It was detected the development of NTIS in 42% of these CAP patients. NTIS was revealed against the background of decreased the $FT_{3,4}$ levels and increased TSH value.

Discussion

Our results are generally in a line with previous observations. Several severity CAP assessment tools (as the CURB-65 scale) have been developed to guide the rapid and accurate initial evaluation of disease and prediction of adverse outcomes. This scoring system measure the physiological effect of the infection on the host, but not the microbial and inflammatory mechanisms of the injury response. What is why these scales are not ideal by itself. Thus, in some cases among of our patients the CURB-65 scale was not accurate. This drawback of the latter suggests that the factors other than those included in this scale may contribute to the CAP class severity.

The incorporation of a some biomarkers combination (integrate reflecting systemic inflammation, endothelial dysfunction, stress and other mechanisms of disease progression) in CAP patients have significantly improved the objective severity evaluation and individualized prognostic accuracy for prediction of short term CAP complications rate and to a lesser extent of sCAP mortality. As shown by our data, together with a careful clinical assessment and radiology,

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some biomarkers (first of all PCT) can significantly increase diagnostic accuracy for the evaluation of CAP severity and prognosis of some clinical complications development. So, we could show the different prognostic values of the abovementioned biomarkers in predicting the adverse clinical outcomes (such as IHM, ICU admission and the need for VS or IMV). In view of the complexity of the response in sCAP, it is unlikely that a single ideal biomarker will ever be found for accuracy diagnosis and prognostic assessment of sCAP. A combination of a several CAP biomarkers may be more effective, but this requires further evaluation. These biomarkers values should be considered in close connection with the patient's clinical presentation, history, imaging and other laboratory results.

CRP is considered to be markers of inflammation in general, which are elevated not only in patients with an infection, but also in other kinds of inflammation. Summarizing our results, both the biomarkers and the clinical CURB-65 score scale have acceptable prognostic value in patients with CAP (particularly who was treated in the ICU), but the clinical CURB scores seems to perform slightly worse as judged by the higher biomarkers (CRP, PCT, d-D and CP) values. It should be noted, that the rate and criteria for admission to ICU vary widely across units and different health-care systems as well as they are highly dependent on individual physician decisions.

We (as well as the most of clinicians) may consider that low CRP values may be associated with a less severe systemic inflammation response, which should reflect a better prognosis. Although CRP is a quite good marker of CAP clinical severity, but CRP has poor prognosis value, while PCT have improved severity assessment of CAP and have proved to be better predictors of complications and mortality [22, 26]. In addition, PCT seems to have an advantage over CRP because of its earlier increase when infection occurs. Thus, according to our data, PCT values were more correlated with need for VS and IHM than CRP. We can suggest that PCT is a diagnosis tool rather than a reliable prognosis marker. These results are similar to other data [30, 31].

An information about the CAP driven host-response mirrored by the markedly elevated circulating level of abovementioned biomarkers that may provide insights into the pathophysiology and prognosis of a sCAP process. We detected in most of cases, that the values of these biomarkers were significantly increased with rising the CURB-65 scores, that was in concordance with previous studies [3, 6]. Some factors in our CAP patients may be associating with a significantly variations of initial PCT and CRP values, for example: older age, antibiotic pretreatment or being male and chronic liver insufficiency (often due to alcohol abuse). We revealed, that if a patient shows an new infiltrate on chest radiograph (that was usually mandatory for the diagnosis of CAP) in the presence of acute respiratory symptoms but very low PCT value (≤0.5 ng/ml), clinicians should actively seek for an alternative diagnosis.

Our results confirmed findings from previous studies [10, 24, 30] showed that a high PCT level was a good predictor of CAP severity and ICU admission. So, in our study PCT value with a cut-off point of ≥10 ng/ml provided the best guide for identifying patients for ICU admission while the need for treatment in ICU was very unlikely if a PCT level was <5 ng/ml. From our point of view, PCT seems to be a more specific biomarker for bacterial infections and therefore has been proposed for guidance of antibiotic therapy in CAP, particularly in the ICU.

We also revealed that the raised PCT level was significantly related to increasing severity of CAP while CRP and WBC did not show the same systematic relationship that was in consistent with the results of other researchers [31, 32, 35, 37, 40]. The higher PCT concentrations were associated with the development of serious complications and death [32, 37], while a low PCT level has been associated with low mortality, even in patients at high risk according to their CURB-scale. The prognostic value of PCT can be markedly increased by serial measurement during hospital treatment. Unfortunately, we did not make the latter due to some objective reasons (the patient's death was the one of them).

Although ICU admission and IHM are the main outcomes in the majority of studies on sCAP, it seems that the additional presence of sepsis (with or without the need for VS) and/or the presence of acute respiratory failure (with or without the need for IMV) are simple and useful outcomes for identifying the most severe ill patients who require ICU admission. From a pathophysiological point of view, the presence of at least one of these two conditions (or other unstable comorbidities) during the evaluation of a sCAP patient in an emergency department of the hospital, can lead directly to ICU admission. For the latter, we believe that severity of CAP just on hospital admission should be assessed immediately, first of all by the simple parameters (such as respiratory rate, oxygen saturation and blood pressure) and subsequently by simple prediction rules (such as the CRB-65 scale). In our opinion, sophisticated biomarkers have no clear advantage over validated clinical prediction rules to assess the severity of CAP just at hospital admission.

The study was also limited by its small sample size and the lack of causative etiology in half of sCAP patients. The data on the diagnostic value of PCT (including comparisons with other biomarkers

such as CRP) in critically ill patients are rare and the reported results are inconsistent. sCAP status was associated with a remarkable release of pro-inflammatory cytokines (such as IL-6) and a defective T-cell response, both of which might affect PCT release and hence discriminatory performance of PCT in diagnosing this pathology. A significant variation of PCT results in our severe ill patients was most likely due to the small number of patients and substantial differences in populations studied. More powerful analyses are needed to address the role of potential confounders of the diagnostic accuracy of PCT (such as antibiotic pretreatment and underlying impairment of the immune system).

It was shown, that high d-D value was associated with 30-day mortality and major morbidity in patients with CAP [39]. Our data detected, that a patients with bilateral or polysegmental CAP affection as well as non-survivors had a higher levels of d-D that supported the role for disorders of coagulation in sCAP and it was in agreement with the data of other researchers [39, 40]. We revealed that the predictive ability of d-D level concerning the evaluation of CAP severity was comparable with PCT and was higher than WBC and CRP. The new biomarkers CP and ADM had association with IHM in CAP and should be studied further for their value in stratification of these patients in clinical trials.

CAP is a «friend» of elderly and multimorbid patients. Here mortality does not always reflect «dying from pneumonia» but rather «dying with pneumonia». In some cases mortality was predicted by concomitant diseases (for example, coronary artery disease) and high age. So, sCAP may cause release of inflammatory mediators and prothrombic factors resulting in instability the coronary plaques, increased biomechanical stress and load from high metabolic demand.

sCAP was predicted by higher PCT (first of all), CRP, d-D and CP levels which indicated a high systemic inflammation. Accordingly, although inflammatory markers (like CRP and PCT) were associated with IHM in CAP, but their predictive accuracy does not allow high risk prediction by themselves. The biomarkers like CP and d-D did not predict an adverse outcomes in our sCAP patients because they may have varying degree of liver or kidney dysfunction. Such pre-analytic factors could affect the initial biomarker levels and hence confound assay interpretation. For example, hepatocyte malfunction affects the main site of CRP synthesis or elderly patients might have a suppressed inflammatory response.

The majority of our patients with sCAP fulfilled the criteria for sepsis while different cytokines and toxins contribute to the extensive vasodilatation often seen in systemic infection. We detected that CP level was increased progressively with the severity of CAP and was significantly higher in non-survivors as compared with survivors that was consistent with findings reported about CP levels in septic patients [42-44]. Additionally, sCAP patients with the highest values of CP also presented and highest need for VS, IMV, duration of ICU and IHM. ADM levels have improved the evaluation of serious complications prediction. So, increased levels of CP and ADM (seen in sCAP) may affect the endothelial system and contribute in blood pressure homeostasis causing multiorgan failure and eventually short-term death.

Our findings concerning the dynamics of thyroid hormones are also consistent with earlier studies [53]. In CAP with NTIS (without clarifying the reason) a decrease of FT_3 level was a mild form of NTIS and the latter was not associated with increase of IHM. The more definite predictor of IHM in these patients was a low FT_4 level. This fact was consistence with the data of the other researchers [54], who indicated a similar prevalence of NTIS in ICU patients as well as in sCAP patients. Our data showed that $FT_{3,4}$ levels were more correlated with IMV than PCT value. This fact may be used for detection the patients with sCAP who need IMV.

Thus, our study have demonstrated that the suggested complex of biomarkers had a moderate prognostic utility as early risk predictor for adverse clinical outcomes in sCAP patients. Novel biomarkers offer great potential in aiding critical decisions for patients with sCAP. Validation of our findings in clinical practice is needed to determine whether the use of abovementioned panel of biomarkers improves outcomes for patients with CAP. Thus, identifying patients with a benefit from initial intensive management strategies in CAP remains an important task to be done.

Conclusions

- This multimarker's panel (with a high levels of CRP, PCT, d-D, CP) and low values of FT_3 can be used for adequately assessment the severity of CAP. PCT is more reliable biomarker with moderate diagnostic and prognostic utility compared to d-D, CRP and CP in predicting prognosis, adverse clinical outcomes and need for ICU admission in severe CAP patients.
- Adding this biomarker panel to CURB-65 scores improves the predictive power for evaluation of CAP severity and allows getting the consideration of the entire CAP clinical picture.
- We detected a close relationship between these biomarkers and in-hospital mortality, length of in-hospital stay, ICU admission and duration of stay, as well as need for invasive mechanical ventilation and vasopressor support.
- The presence of thyroid dysfunction (NTIS) on the background of high levels of these biomarkers may help to identify patients with adverse clinical outcomes.

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Надійшла до редакції 05.05.2016

БИОМАРКЕРЫ ДЛЯ ОЦЕНКИ СТЕПЕНИ ТЯЖЕСТИ И ОСЛОЖНЕНИЙ ВНЕГОСПИТАЛЬНОЙ ПНЕВМОНИИ

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Резюме

Ранняя прогностическая оценка с помощью клинической шкалы и панели биомаркеров имеет важное значение для оптимизации тактики ведения пациентов с внегоспитальной пневмонией (ВГП).

Цель исследования — оценить информативность нескольких биомаркеров (представляющих различные звенья патогенеза) и гормонов щитовидной железы в сочетании со шкалой CURB-65, чтобы выяснить возможность их использования в клинической практике для оценки степени тяжести ВГП, а также их взаимосвязь с неблагоприятными клиническими исходами.

Материалы и методы. В исследование включено 62 больных с верифицированной ВГП (класс тяжести 2-5 по шкале CURB-65), которым измерялись уровни С-реактивного протеина (СРП), прокальцитонина (ПКТ), D-димера (D-д), копептина (КП), адреномедуллина (АДМ) и гормонов щитовидной железы (свободного трийодтиронина ($свТ_3$), свободного тетрайодтиронина ($свТ_4$) и тиреотропного гормона (ТТГ)).

Результаты. Увеличение степени тяжести ВГП и количества случаев внутригоспитальной смертности (ВГС) были связаны с повышенными уровнями биомаркеров инфекционного воспаления (СРП, ПКТ), нарушения свертывания крови (D-д) и сосудистого тонуса (КП, АДМ). У умерших больных с ВГП регистрировались значительно более высокие значения СРП, КПТ, D-д и КП, чем у выживших. Статистически значимое повышение уровней ПКТ и D-д выявлено у пациентов, нуждающихся в вазопрессорной поддержке (ВЗП), по сравнению с больными со стабильной гемодинамикой (в 10 и 2,1 раза соответственно). При поступлении в отделение интенсивной терапии (ОИТ) у пациентов показатели СРП, ПКТ и D-д достоверно коррелировали с необходимостью ВЗП (r=0,39; 0,74 и 0,54) и ВГС (r=0,38; 0,72 и 0,48). Отмечена статистически значимая взаимосвязь между уровнями КП, АДМ и продолжительностью пребывания в ОИТ (r=0,43; 0,91), КП и необходимостью ВЗП (r=0,54). Уровни $свТ_3$ и $свТ_4$ были значительно ниже в группах пациентов с нетяжелой и тяжелой ВГП (на 12% и 23%) по сравнению с контрольной группой, а также у пациентов, нуждающихся в механической инвазивной вентиляции легких (МИВЛ). Выявлена достоверная связь между показателями $свТ_4$ и степенью тяжести ВГП (r= –0,55), $свТ_3$ и ВГС (r= –0,44), а также между $свТ_3$, ТТГ и потребностью в МИВЛ (r= –0,47; r=0,37 соответственно). Развитие синдрома псевдофункции щитовидной железы обнаружено у 42% этих пациентов с ВГП.

Выводы. Данная панель биомаркеров и наличие дисфункции щитовидной железы могут быть использованы для адекватной оценки тяжести ВГП. Мы обнаружили тесную взаимосвязь между этой панелью биомаркеров и некоторыми неблагоприятными клиническими исходами.

Ключевые слова: внебольничная пневмония, биомаркеры, С-реактивный белок, прокальцитонин, D-димер, копептин и гормоны щитовидной железы.

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