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COMMUNITY-AQUIRED PNEUMONIA ASSOCIATED WITH CORONAVIRUS DISEASE (COVID-19): DETERMINATION OF PATHOLOGICAL PROCESS PROGRESSION PREDICTORS BY CLINICAL AND HEMOCOAGULATION PARAMETERS

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Ключевые слова: *внебольничная пневмония, вирусная пневмония, коронавирусная болезнь, COVID-19, диагностика, предикторы прогрессирования, факторы риска утяжеления, D-димер, фибриноген, коагулограмма*

Abstract. Community-aquired pneumonia associated with coronavirus disease (COVID-19): determination of pathological process progression predictors by clinical and hemocoagulation parameters. Pertseva T.O., Bielosludtseva K.O., Konopkina L.I., Krykhtina M.A., Myronenko O.V., Botvinikova L.A., Moiseienko O.F. *The search for clinical and laboratory markers of COVID-19-associated CAP progression is an urgent problem of today. The aim of our study was to determine the risk factors for the burden of the pathological process by establishing the diagnostic and prognostic significance of clinical and hemocoagulation parameters in the hospital stage of management of patients with CAP on the background of coronavirus disease (COVID-19). The study included 53 individuals of the main group. All patients were examined twice: on the first day of hospitalization (visit 1) and in the dynamics (7-10 days after hospitalization (visit 2)). In 30 (83.3%) patients of subgroup 1, despite adequate treatment, there was an increase in breathing rate and a decrease in saturation to severe (less than 92%) or critical (less than 85%) levels (in 28 and 2 cases respectively). In subgroup 2, the progression of respiratory failure to a critical level was observed in 5 of 12 (41.7%) patients. Conclusions: at the stage of hospitalization of patients with COVID-19-associated CAP the most sensitive clinical predictor of aggravation of the patient's condition is tachypnea of 20 or more; laboratory – the level of D-dimer 200 ng/ml, which increases the risk of progression of the pathological process by 16 times.*

Реферат. Внебольничная пневмония, ассоциированная с коронавирусной болезнью (COVID-19): определение предикторов прогрессирования патологического процесса по клиническим и гемокоагуляционным показателям. Перцева Т.А., Белослудцева К.О., Конопкина Л.И., Крыхтина М.А., Мироненко Е.В., Ботвинникова Л.А., Мойсеенко Е.Ф. *Поиск клинических и лабораторных маркеров отягощения течения COVID-19-ассоциированной внебольничной пневмонии (ВП) является актуальной проблемой современности. Целью нашего исследования было определение факторов риска отягощения патологического процесса путем установления диагностической и прогностической значимости клинических и гемокоагуляционных показателей на госпитальном этапе ведения пациентов с ВП на фоне коронавирусной болезни (COVID-19). В наблюдение в рамках исследования вошло 53 человека основной группы. Все больные были обследованы дважды: в первый день госпитализации (визит 1) и в динамике (на 7–10 сутки после госпитализации (визит 2)). У 30 (83,3%) больных подгруппы 1, несмотря на адекватное лечение, наблюдалось увели-*

чение частоты дыхания (ЧД) и снижение сатурации до тяжелого (менее 92%) или критического (менее 85%) уровня (в 28 и 2 случаях соответственно). В подгруппе 2 прогрессирование ДН до критического уровня наблюдалось у 5 из 12 (41,7%) больных. Выводы: на этапе госпитализации больных COVID-19-ассоциированной ВП наиболее чувствительным клиническим предиктором утяжеления состояния пациента является тахипноэ 20 и более; лабораторным – уровень D-димера 200 нг/мл, что повышает риск прогрессирования патологического процесса в 16 раз.

Despite a whole year of diligent fight against the coronavirus disease (COVID-19), hundreds of thousands of patients in the world need to be hospitalized every day with community-acquired pneumonia (CAP) due to complications of the disease and, unfortunately, thousands of them die at the stage of inpatient treatment [8]. During the clinical observation of hospitalized patients with COVID-19-associated CAP, it turns out that in many of them there is a progressive worsening of the condition, which may be related to the viral load, features of the autoimmune response, and accompanying pathology [3 , 7, 14].

Today, scientists around the world are searching for clinical and laboratory markers of the severity of the course of COVID-19-associated CAP [4, 12]. Considering the fact that one of the most dangerous complications of this condition is thrombus formation, which is observed in approximately 20% of cases of COVID-19 [9], the search for clinical and hemocoagulation indicators that could be used to predict the further course of the disease is promising.

It has already been determined that when vessels or tissues are damaged by various endogenous and exogenous factors or antibodies, the process of intensification of blood coagulation in the body starts, which leads to the formation of blood clots [5, 10]. Such complications were described by us in severe bacterial community-acquired pneumonia [10], however, in pneumonia against the background of COVID-19 this issue requires further study.

Pulmonary endothrombosis can have a subclinical course, when the condition deteriorates slowly: shortness of breath progresses daily, saturation decreases, and oxygen therapy becomes ineffective. Diagnosis of non-massive thrombosis is extremely difficult. Most often, screening includes determining the levels of such coagulation indicators as international normalized ratio (INR), prothrombin according to Kwik, prothrombin time (PT), fibrinogen, D-dimer.

INR is a standard coagulation indicator for people taking oral anticoagulants for the prevention and treatment of deep vein thrombosis or thromboembolism [13].

Prothrombin according to Kwik is determined by the ratio of the temporary activity of the prothrombin protein to the control sample. It is expressed as a percentage, the norm is 80-120%, it characterizes prothrombin formation which reflects the first phase of plasma hemostasis [13].

PT characterizes the first (prothrombin formation) and second (thrombin formation) phases of plasma hemostasis and reflects the activity of the pro-thrombin complex (factors VII, V, X and prothrombin itself - factor II) [13].

Fibrinogen is a central protein of the blood coagulation system and a soluble precursor of polymeric fibrin, which forms the fibrin framework of a thrombus. When interacting with platelets, it promotes their aggregation, which is the first stage of thrombus formation. That is why determining the level of this marker is quite promising in terms of finding a prognostic indicator of the aggravated and complicated course of pneumonia against the background of COVID-19 [13].

D-dimer is formed due to the breakdown of fibrin fibers. In contrast to the final products of fibrinogen decay, which are presented in the form of separate fragments D and E, during the cleavage of fibrin fibers cross-linked by factor XIIIa, larger fragments are formed - D-dimers, D-E-D trimers, since plasmin is unable to cleave covalent connection between D-dimers. An increase in the level of D-dimer in the blood mostly occurs with thrombosis, thromboembolism of the pulmonary artery and disseminated intravascular coagulation (DIC) syndrome. Normally, D-dimers are absent in blood plasma, but appear mainly when the blood coagulation system is activated [13, 15]. According to the Order of the Ministry of Health of Ukraine dated 04/06/2021 No. 638, "On amendments to the protocol "Providing medical assistance for the treatment of coronavirus disease (COVID-19)", today it is not recommended to prescribe anticoagulant therapy according to the level of this indicator, because D-dimer is a protein fragment that is formed during lysis of an already existing blood clot and does not fully reflect the risk of thrombus formation [2].

Despite the wide use of the above indicators in clinical practice, the role of these markers in COVID-19-associated CAP has not yet been established.

Thus, the purpose of our study was to determine the risk factors of aggravating the pathological

process by establishing the diagnostic and prognostic significance of clinical and hemocoagulation indicators at the hospital stage of management of patients with PN against the background of coronavirus disease (COVID-19).

MATERIALS AND METHODS OF RESEARCH

We examined 60 patients who sought medical advice at the reception ward of the Communal nonprofit enterprise "City Clinical Hospital No. 6" of the Dnipro City Council from May to December 2020 in connection with suspected coronavirus disease (COVID-19) and the associated CAP. During the clinical examination of patients, an analysis of complaints, anamnesis data and objective status was carried out.

The criteria for including patients in the screening were:

1) complaints, anamnestic data and clinical signs of acute infection of the upper respiratory tract;

2) complaints and clinical signs of infection of the lower respiratory tract, which could indicate the development of CAP;

3) consent to testing for COVID-19;

4) age – over 18 years.

The criteria for excluding patients from screening were:

1) the presence of a confirmed alternative diagnosis (pulmonary tuberculosis, chronic thromboembolism of the pulmonary artery, etc.), in which clinical signs could mimic the manifestations of CAP;

2) presence of previously confirmed HIV infection;

3) decompensation of chronic concomitant diseases, which could affect the results of research;

4) presence of previously diagnosed oncological pathology.

Verification of the coronavirus disease (COVID-19) was carried out by PCR testing for the detection of RNA of the SARS-CoV-2 coronavirus when taking mucus from the respiratory tract or the detection of antibodies (immunoglobulin class M (IgM)) to the spike (S) protein of SARS-CoV-2. All patients underwent a general blood test, and imaging methods (X-ray or computed tomography (CT) of the chest organs) were used, HIV status was determined by rapid blood testing using the “CITO TEST HIV ½” ("Pharmasco", Ukraine).

At the end of the screening stage, 7 patients were excluded from the study: 1 – with a positive HIV test result, 1 – with suspected pulmonary tuberculosis, 1 – with suspected neoplasm, 2 – with no laboratory confirmation of COVID -19 (according to the results of a PCR test and a serological test for IgM), 2 – with no radiological confirmation of the presence of CAP (according to the data of both radiography and CT of the chest organs). Thus, 53 people, who made up the main group were included in the further observation within the framework of the study.

Formulation of clinical diagnoses of coronavirus disease and CAP against its background was carried out in accordance with national recommendations [1, 2].

To specify the degree of severity of the coronavirus disease, the criteria specified in the Protocol "Provision of medical assistance for the treatment of the coronavirus disease (COVID-19)" dated April 6, 2021 [2] were used. Severe disease was verified in the presence of one or more of the following criteria: 1) RR≥30 per minute; 2) SpO_2 ≤93% or PaO_2/FiO_2 ratio <300; 3) the area of infiltrative lung lesions of more than 50%. Critical illness was diagnosed with one or more of the following criteria: acute respiratory distress syndrome (ARDS), sepsis, altered consciousness, multiple organ failure. In the absence of any of the listed criteria, a disease of moderate severity was diagnosed.

Given the fact that in real clinical practice it is quite problematic to track the dynamics of infiltrative changes on CT of the chest organs, the distribution of patients into subgroups was carried out mostly according to clinical data, taking into account the RR and the SpO_2 level on admission to the hospital. Thus, according to the severity of the coronavirus disease at the time of hospitalization, all patients of the main group were divided into 3 subgroups: subgroup 1 included 36 people with moderate severity of COVID-19, in whom, at the time of hospitalization, the RR was lower than 30, the SpO_2 level was higher than 93%, and the clinical symptoms remained stable, which most likely indicated the absence of prolongation of the pathological process in the lungs; subgroup 2 – 12 people with severe COVID-19, in whom, at the time of hospitalization, the RR was also lower than 30, however, the SpO_2 level was 93% or less, which required auxiliary oxygen therapy (indications for artificial lung ventilation (ALV) not noted); subgroup 3-5 people with COVID-19 in a critical course, in whom, at the stage of hospitalization, signs of respiratory failure prevailed in the clinical symptoms (RR was above 23, and the SpO_2 level was 89 and below), and the desaturation was stable and was not corrected by auxiliary low-flow oxygen therapy), which indicated the development of ARDS and the need for mechanical ventilation.

The correctness of the distribution of patients by subgroups was confirmed by the difference between the average indicators of RR and SpO_2 in the subgroups. For example, the average level of RR in subgroup 1 was the lowest and amounted to 18 (16; 21), in subgroup 2 it was already significantly higher and amounted to 20 (20; 21), and the highest (24 (23; 27)) in subgroup 3 (p1-2=0.001, p1-3=0.001, p2-3=0.001). The level of SpO_2 also differed significantly between subgroups of patients and was 94.0 (93.0; 96.0) in subgroup 1, 90.0 (80.0; 91.0) in subgroup 2 and 79.0 (70.0; 88.0) – in subgroup 3 (p1-2=0.001, p1-3=0.001, p2-3=0.049).

All patients were examined twice: on the first day of hospitalization (visit 1) and in dynamics (7-10 days after hospitalization (visit 2)).

At visit 1, all patients of the main group underwent general clinical research methods and the levels of coagulation indicators (INR, prothrombin according to Kwik, PT, fibrinogen, D-dimer) were determined. Venous blood sampling was performed before prescribing anticoagulant drugs. The level of fibrinogen was determined according to Clawson, D-dimer – with the help of immunoturbodimetry [13, 15]. The results of the indicators were evaluated in comparison with reference laboratory values [13].

At visit 2, the clinical condition of the patient was assessed and the presence of clinical symptomatology progression was recorded (in case of increasing shortness of breath and an increase in RR by more than 5 movements and/or a decrease in SpO_2 by more than 4% compared to the initial data) or stabilization of the course of the disease with gradual improvement of the condition.

Patients were treated in accordance with national recommendations [1, 2]. Patients of subgroup 1 received anticoagulant therapy (subcutaneous administration of enoxaparin or analogues in prophylactic doses), anti-inflammatory (nonsteroidal drugs (aspirin, paracetamol, ibuprofen) and low doses of steroid drugs (dexamethason, methylprednisolone)), and antibacterial therapy with beta-lactams (protected penicillins (amoxicillin/clavulanate) or cephalosporins of the II or III generation (cefuroxime, ceftriaxone)). Patients of subgroup 2 received anticoagulant therapy (subcutaneous injection of enoxaparin or analogues in high prophylactic doses), anti-inflammatory (nonsteroidal drugs (aspirin, paracetamol, ibuprofen) and low or medium doses of steroid drugs (dexamethasone, methylprednisolone)), antibacterial therapy (combination of beta-lactam (protected penicillins (amoxicillin/clavulanate) or cephalosporins of the II or III generation (cefuroxime, ceftriaxone)) with a macrolide (azithromycin, clarithromycin), in case of ineffectiveness-respiratory fluoroquinolones (levoflox) sacin, moxifloxacin)), as well as oxygen therapy. Patients of subgroup 3 received anticoagulant therapy (subcutaneous administration of enoxaparin or analogues in high prophylactic doses, and in case of confirmed thrombosis – therapeutic), anti-inflammatory (nonsteroidal (aspirin, paracetamol, ibuprofen) and medium or high doses of steroids (dexamethazone, methylprednisolone) drugs), antibacterial therapy (beta-lactams or respiratory fluoroquinolones), in case of ineffectiveness, reserve drugs (linezolid or meropenem) were added, as well as oxygen therapy.

The study was conducted in accordance with the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles of Medical Research Involving Humans" and the "General Declaration on Bioethics and Human Rights (UNESCO)", also approved by the Commission on Biomedical Ethics of the Dnipro State Medical University. All patients gave informed consent for the necessary research methods.

Statistical processing of the obtained results was performed using biometric analysis methods implemented in the packages of the program "STATISTICA 6.0" (No. 31415926535897) and MedCalc [6, 11].

RESULTS AND DISCUSSION

The main demographic and clinical indicators of 53 people (average age – 59 (52; 65) years, men – 22 (41.5%)), hospitalized with the CAP against the background of laboratory-confirmed coronavirus disease COVID-19, who made up the main group, are presented in Table 1.

When analyzing the demographic indicators, attention was drawn to the fact that patients with a critical course of the disease were the youngest; according to the gender distribution, the subgroups were identical (Table 1). Most of the patients sought medical advice and, accordingly, were hospitalized on day 6-14 of the disease.

In the vast majority of patients, characteristic clinical signs during hospitalization were fever, shortness of breath, and a decrease in saturation (Table 1). Patients of subgroup 3 were more likely to be obese (BMI>30).

As for coagulation parameters, the levels of INR and prothrombin according to Kwik were the same in subgroups of patients and did not differ from the reference values (Table 2). However, it is known that in the case of thrombotic complications, hypercoagulation, massive influx of tissue thromboplastin into the bloodstream, the level of prothrombin according to Kwik decreases, in connection with which an individual analysis was

carried out. The latter showed that the level of prothrombin below the lower limit of the reference value was observed in 4 patients with a critical course of the disease (Table 2).

Table 1

Demographic parameters, anamnestic and clinical findings in the patients examined, Me (25%; 75%)

Parameter	Subgroups of patients			p
	1 (n=36)	2 (n=12)	3 (n=5)	
Average age, years	60 (52; 65)	63 (52; 68)	47 (45; 56)	p_{1-2}=0.453 p_{1-3}=0.008 p_{2-3}=0.102
Distribution by gender, abs. (% in subgroup):				
men	12 (33.3)	8 (66.7)	2 (40)	p_{1-2-3}=0.127
women	24 (66.7)	4 (33.3)	3 (60)	
Day of disease on hospitalization	8.0 (6; 10)	9.0 (3; 12)	10.0 (5; 14)	p_{1-2}=0.602 p_{1-3}=0.077 p_{2-3}=0.386
Body temperature, ºC	38.5 (38.0; 39.0)	39.0 (37.0; 39.0)	38.0 (37.5; 38.0)	p_{1-2}=0.951 p_{1-3}=0.582 p_{2-3}=0.744
Body mass index (BMI)	30.1 (26.3; 33.3)	27.8 (25.1; 35.9)	35.3 (33.0; 37.0)	p_{1-2}=0.933 p_{1-3}=0.018 p_{2-3}=0.493

An increase in prothrombin time was observed in four patients (2 with a critical course, 2 with a course of moderate severity).

The level of fibrinogen was higher than the reference values in more than half of the examined patients (29 (54.7%)). At the same time, the average indicator differed significantly between subgroups, and its maximum values were observed in patients with a critical course (in three of them (60%), the level of the indicator exceeded the diagnostic maximum (7.5 g/l)) (Table 2). The distribution of fibrinogen levels in patients with COVID-19-associated CAP depending on the severity of the course of the disease and the gradations chosen by us (according to the results of the analysis of histograms of relative frequencies of the studied sample) is presented in Figure 1.

Table 2

Levels of coagulation parameters in the patients examined on hospitalization, Me (25%; 75%)

Parameter	Subgroups of patients			Reference value	p
	1 (n=36)	2 (n=12)	3 (n=5)		
INR, sec	1.06 (0.95; 1.2)	1.05 (1.0; 1.1)	1.1 (1.01; 1.2)	0.8–1.2	p_{1-2}=0.910 p_{1-3}=0.480 p_{2-3}=0.386
Prothrombin according to Kwik, %	94.1 (80.9; 104.6)	94.5 (76.2; 103.1)	81.4 (72.0; 90.0)	80–120	p_{1-2}=0.900 p_{1-3}=0.197 p_{2-3}=0.102
Prothrombin time, sec	13.5 (12.2; 14.5)	13.6 (12.1; 14.1)	15.2 (13.1; 16.5)	11–15	p_{1-2}=0.830 p_{1-3}=0.183 p_{2-3}=0.342
Fibrinogen, g/l	3.7 (3.0; 4.7)	4.2 (3.7; 4.9)	7.0 (6.5; 7.5)	2–4	p_{1-2}=0.044 p_{1-3}=0.033 p_{2-3}=0.015
D-dimer, ng/ml	679.9 (118.1; 170.0)	1103.1 (188.9; 1803.5)	5720.0 (4800.0; 7500.0)	0–285	p_{1-2}=0.149 p_{1-3}=0.000 p_{2-3}=0.009

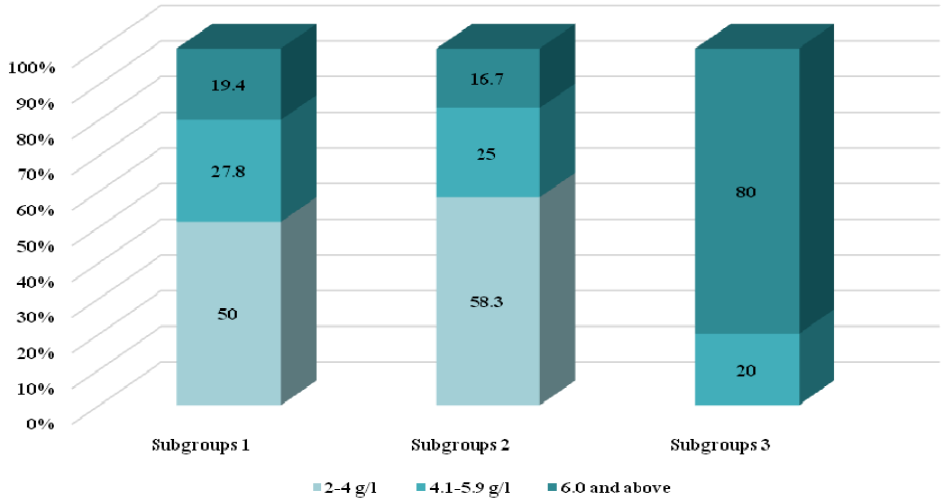

Fig. 1. Distribution of fibrinogen levels in subgroups

The level of D-dimer was significantly increased in the examined patients and correlated with the severity of the course of the disease. At the same time, in all patients of subgroup 3, it exceeded 2000 ng/ml, and in two people it was even higher than the diagnostic maximum (7500 ng/ml), in connection with which it was technically impossible to determine its true level. The distribution of D-dimer levels in patients with COVID-19-associated CAP depending on the severity of the course of the disease and the gradations chosen by us (based on the results of the analysis of histograms of relative frequencies of the studied sample) is presented in Figure 2.

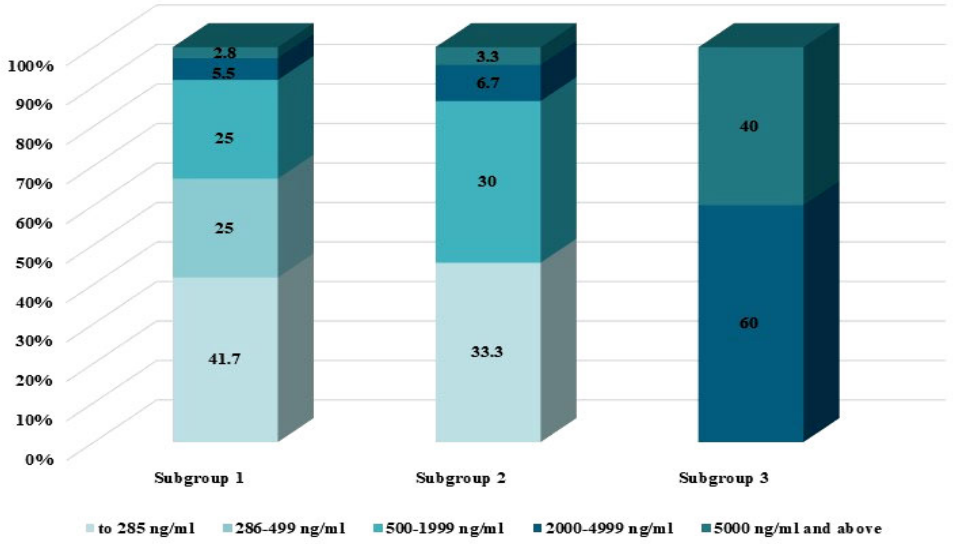

Fig. 2. Distribution of D-dimer levels in subgroups

At visit 2, despite the prescribed treatment according to the severity of the disease, a certain proportion of patients experienced a progressive worsening of their condition, which was mainly characterized by an increase in respiratory insufficiency (RI): increased shortness of breath, a decrease in the level of saturation, an increase in tachypnea. Thus, only 6 out of 36 (16.7%) patients of subgroup 1 did not experience worsening of clinical symptoms, while in 30 (83.3%) patients, despite adequate treatment, there was an increase in RR and a decrease in saturation to severe (less than 92%) or critical (less than 85%) level (in 28 and 2 cases, respectively). In subgroup 2, the progression

of RI to a critical level was observed in 5 out of 12 (41.7%) patients; 7 other people had a stable course with gradual improvement of the clinical condition. Thus, at visit 2, it was established that out of 48 patients with moderate and severe RI against the background of COVID-19, in 35 cases (72.9%) progression of the pathological process took place.

To determine the factors that could be recognized as risk markers for the progression of COVID-19-associated CAP, we conducted a ROC analysis. The clinical (levels of RR, SpO_2, BMI, body temperature) and laboratory (levels of INR, prothrombin according to Kwik, prothrombin time, D-dimer, fibrinogen) indicators on the admission of patients to the hospital were chosen as variables, and as classification grouping – the fact of the progression of the pathology. The analysis showed that of the clinical indicators selected by us, a sensitive and specific factor associated with the progression of the clinical course is only RR at the stage of hospitalization (Fig. 3A), and the cut-off criterion is the level of RR, which is 20 per 1 minute (Fig. 3B). The levels of coagulation indicators at the stage of hospitalization of patients turned out to be uninformative in terms of predicting the risk of progression of the pathological process (Fig. 4A). The level of D-dimer is recognized as a highly sensitive and highly specific factor, while the cut-off criterion was the level of the indicator, which is 200 ng/ml (Fig. 4B).

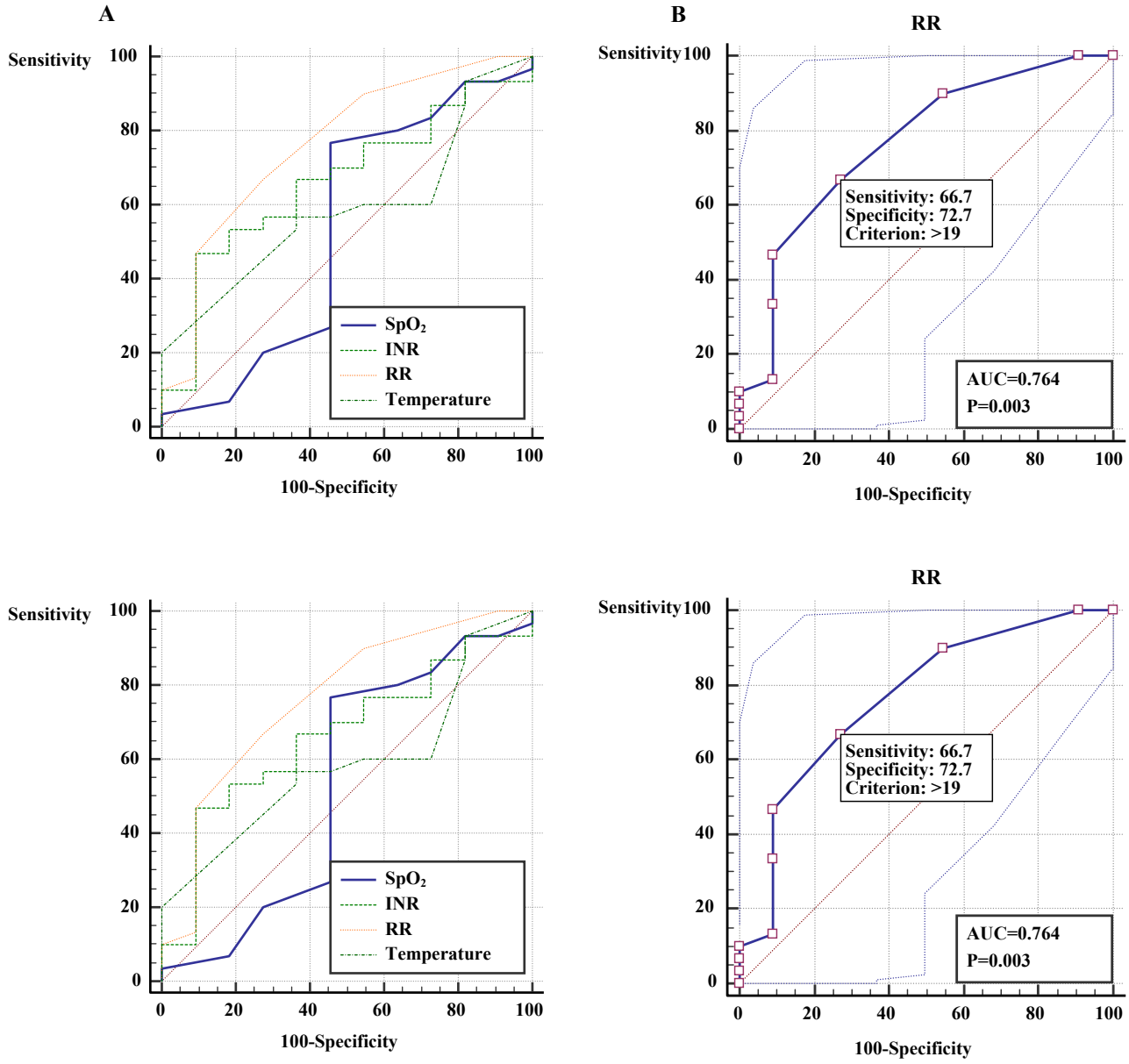

Fig. 3. ROC-curves of clinical parameters (A – RR, SpO_2, INR, temperature; B – RR) predicting the risk of progression of CAP, associated with COVID-19

The hypothesis regarding the fact that with a D-dimer level of more than 199 ng/ml during hospitalization of patients against the background of COVID-19, the risk of progression of the pathological process increases, required verification. It was determined that during the admission of patients with COVID-19-associated CAP, the level of D-dimer over 199 ng/ml was observed in 32 patients of subgroups 1 and 2, and progression of the pathological process occurred in 29 of them; the D-dimer level of 199 ng/ml and below was observed in 16 patients of subgroups 1 and 2, and progression of the pathological process occurred in 6 of them (Fig. 5). The obtained data were processed by medical testing with the search for the diagnostic odds ratio (OR). It was established that the diagnostic odds ratio exceeded 16 (OR=16.1), the confidence interval did not include units and was [3.38; 76.7], and the error – less than 0.05 (p=0.0005), meaning the reliability of the fact that in patients with CAP against the background of COVID-19, the level of D-dimer above 199 ng/ml at the stage of hospitalization increased the risk of progression of the pathological process by 16 times.

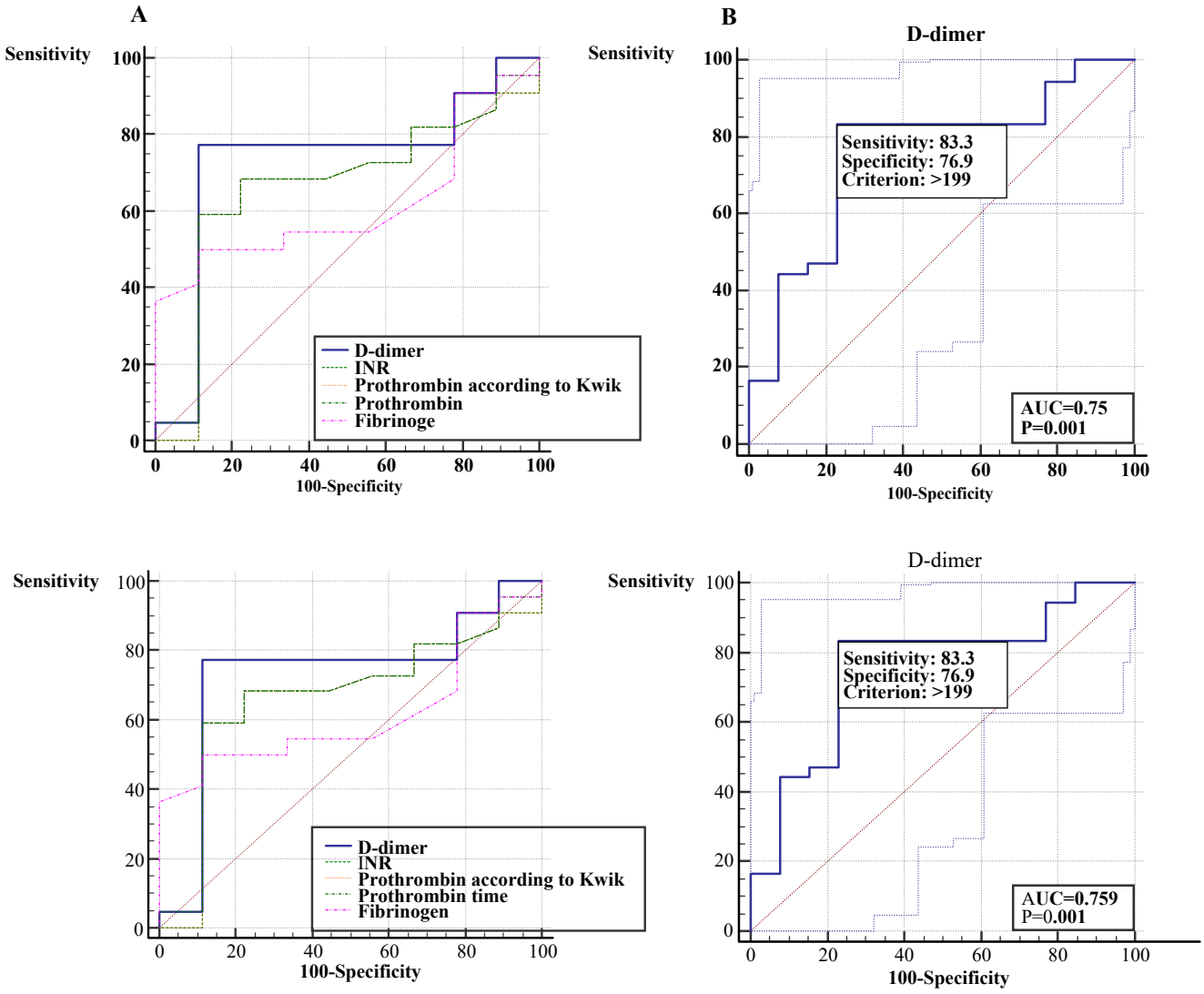

Fig. 4. ROC-curves of laboratory parameters (A – D-dimer, INR, prothrombin according to Kwik, prothrombin time, fibrinogen; B – D-dimer) predicting the risk of progression of CAP, associated with COVID-19

It should be noted that today the upper limit of D-dimer reference values in most laboratories of Ukraine reaches 250-285 ng/ml. The new data which we received indicate that the level of the indicator,

which is formally the norm but makes up 200 ng/ml and more, should be considered a reliable risk factor for the progression of the pathological process and the aggravation of the condition of a patient with CAP against the background of COVID-19.

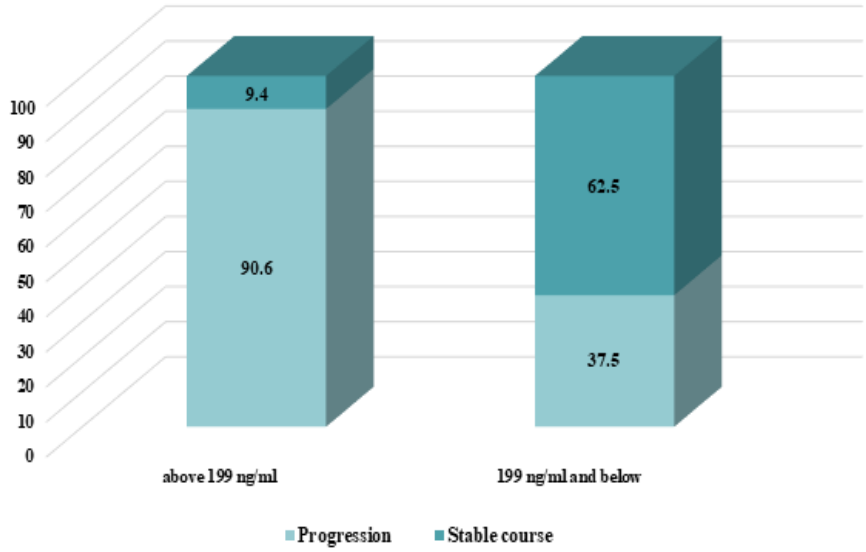

Fig. 5. Distribution of patients with CAP depending on D-dimer levels on admission to the hospital and progression of the pathological process during inpatient treatment

CONCLUSIONS

1. At the stage of hospitalization of patients with COVID-19-associated with community-acquired pneumonia, the most sensitive clinical predictor of the severity of the patient's condition is tachypnea of 20 or more.

2. At the stage of hospitalization of patients with COVID-19-associated community-acquired pneumonia, the most sensitive laboratory predictor of the severity of the patient's condition is a D-dimer level of 200 ng/ml, which increases the risk of progression of the pathological process by 16 times.

Contributors:

Pertseva T.O. – conceptualization, management, administration of the project;

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Konopkina L.I. – methodology, writing (reviewing and editing);

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