UDC 616.98:578.834-036-07-08:614.21 https://doi.org/10.26641/2307-0404.2021.4.248085

CLINICAL AND LABORATORY MARKERS OF THE NEW CORONAVIRUS DISEASE SARS-COV-2 COVID-19 IN HOSPITALIZED PATIENTS

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Цитування: Медичні перспективи. 2021. Т. 26, № 4. С. 48-55
Cited: Medicni perspektivi. 2021;26(4):48-55

Key words: *coronavirus disease, COVID-19, SARS-CoV-2, 2019-nCoV, pneumonia, antiviral therapy, invasive mechanical ventilation*
Ключові слова: *коронавірусна хвороба, COVID-19, SARS-CoV-2, 2019-nCoV, пневмонія, противірусна терапія, штучна вентиляція легенів*
Ключевые слова: *коронавирусная болезнь, COVID-19, SARS-CoV-2, 2019-nCoV, пневмония, противовирусная терапия, искусственная вентиляция легких*

Abstract. Clinical and laboratory markers of the new coronavirus disease SARS-CoV-2 COVID-19 in hospitalized patients. Shostakovych-Koretskaya L.R., Kireyeva T.V., Shevchenko-Makarenko O.P., Turchin M.O., Chumak V.I., Chortok V.O., Drobyshevska O.M. *The prognostic predictors of an unfavorable course of coronavirus disease (COVID-19) and its complications with manifestations of pneumonia and the need for oxygen support and connection to the invasive mechanical ventilation were studied. Clinical and laboratory associations in hospitalized patients with COVID-19 were evaluated, the possible predictors of connection to the invasive mechanical ventilator in 37 patients were identified. Patients were hospitalized on day 6.65±3.32 of the disease, blood oxygen saturation (SpO_2) depended on the severity of the disease and response to therapy. Positive significant correlations between the level of growth stimulating factor (ST2) and D-dimer, creatine phosphokinase MB fraction (CPK-MB) and D-dimmer, CPK-MB and ST2 were revealed, as well as of ferritin and D-dimer with ST2. There were no significant associations with troponin. C-reactive protein (CRP) probably correlated with CPK-MB and ferritin. The International Normalized Ratio (INR) indicator had significant correlations with D-dimmer, ST2 and CPK-MB. Cox regression analysis showed that the survival curve has a stepwised nature and the highest risk of deterioration, which requires mechanical ventilation, noted on day 6 of disease (95.0% CI = 0.9-1.0, with an average SpO_2 level =87.3%). ROC analysis showed the presence of a possible relationship between D-dimer, ST2 protein, CPK-MB and the risk of developing a critical condition requiring mechanical ventilation in patients. The study showed that COVID-19 disease has a phase nature, when after the first phase of the disease, the pulmonary phase and hypercytokinemia progress in some patients with the development of hypoxia, decrease in SpO_2. Therefore, the identification of markers of disease progression is essential for predicting the course and possible prevention of the development of acute respiratory distress syndrome with the use of invasive mechanical ventilation.*

Реферат. Клинико-лабораторные маркеры течения новой коронавирусной болезни SARS-CoV-2 COVID-19 у госпитализированных больных. Шостакович-Корецкая Л.Р., Киреева Т.В., Шевченко-Макаренко О.П., Турчин Н.О., Чумак В.И., Черток В.А., Дробишевская О.Н. *Изучены прогностические предикторы неблагоприятного течения коронавирусной болезни (COVID-19) и ее осложнений с проявлениями пневмонии и необходимостью кислородной поддержки и подключения к аппарату искусственной вентиляции легких (ИВЛ). Оценены клинико-лабораторные ассоциации у стационарных больных с COVID-19, выявлены возможные*

предикторы подключения к аппарату ИВЛ у 37 госпитализированных больных. Больные были госпитализированы на 6,65±3,32 день заболевания, сатурация кислородом крови (SpO_2) зависела от тяжести течения болезни и ответа на терапию. Выявлены положительные достоверные корреляционные отношения между уровнем белка стимулирующего фактора роста (ST2) и Д-димера, креатинфосфокиназы фракции МВ (КФК-МВ) и Д-димером, КФК-МВ и ST2, а также ферритина и Д-димера с ST2. Не выявлено достоверных связей с тропонином. С-реактивный белок вероятно коррелировал с КФК-МВ и ферритином. Показатель международного нормализованного отношения имел достоверные корреляции с Д-димером, ST2 и КФК-МВ. Регрессионный анализ Кокса показал, что кривая выживания имеет ступенчатый характер и наибольший риск ухудшения состояния, которое требует ИВЛ, отмечался на 6-й день заболевания (95,0% CI =0,9-1,0, при среднем уровне SpO_2=87,3%). ROC-анализ показал наличие возможной связи между показателями: Д-димером, белком ST2, КФК-МВ и риском развития критического состояния, требующего ИВЛ у больных. Проведенное исследование показало, что заболевание COVID-19 имеет фазный характер, когда после первой фазы заболевания у части больных прогрессирует легочная фаза и гиперцитокинемия с развитием гипоксии, снижением SpO_2. Поэтому выявление маркеров прогрессирования болезни имеет существенное значение для прогнозирования течения и возможного предотвращения развития острого респираторного дистресс-синдрома с применением инвазивной ИВЛ.

COVID-19 is an infectious disease caused by the last open virus of the coronavirus family. Prior to the outbreak of infection in Wuhan (China, Hubei Province) in December 2019, no new virus and disease caused by it was known. Today, the outbreak of COVID-19 has turned into a pandemic that has spread in many countries around the world [4, 5]. This is a new virus that is still poorly understood and differs significantly from other respiratory viruses, including the H1N1 influenza virus [6]. The behavior of COVID-19 is unpredictable, so epidemic predictions are often not confirmed and models do not work. To date, we do not know many epidemiological and pathophysiological features of COVID-19 [10, 12]. This coronavirus is a virus that can be contagious during the incubation period and can be transmitted by aerosol and aerogenous routes with clinical variation from complete absence of symptoms to severe multiorgan symptoms, and not only pulmonary, it can be isolated over a long period of time [9]. Since March 11, 2020, when the WHO announced the pandemic caused by the coronavirus SARS-CoV-2 (2019-nCoV), introducing the term "coronavirus disease 2019" (COVID-19), many studies have been conducted, thanks to which our ideas regarding the epidemiological, clinical and pathophysiological features of COVID-19 have expanded significantly [6]. It is now well known that the clinical picture of COVID-19 can vary, but is more often characterized by fever, dry cough, shortness of breath, muscle pain, possible diarrhea and skin rash, loss of smell and taste. Clinical variants of COVID-19 are classified as: mild, moderate (from minor symptoms to mild pneumonia) – 81%, severe (shortness of breath, hypoxia, pneumonia with 50% or more of lung damage) – 14%, critical (respiratory failure, septic shock or multiple organ failure) – 5% [2, 3, 6, 7].

But clinicians and scientists continue to face unresolved issues and challenges. This concerns the prediction of the course of infection and the development of complications in patients at the stage of hospital treatment. Polymorphism of clinical manifestations, as well as the peculiarities of the reaction of patients to hypoxia, which for a long time may not complain of respiratory problems, create some difficulties in predicting the adverse course of coronavirus infection and its complications with pneumonia manifestations and the need for oxygen support and connection to the device of artificial ventilation of lungs (AVL) [8].

The aim of the study was to determine clinical and laboratory associations in inpatients with COVID-19, to identify possible predictors of connection to the ventilator and death.

MATERIALS AND METHODS OF RESEARCH

We conducted research and analysis of clinical and laboratory parameters of 37 patients with coronavirus infection COVID-19 complicated by pneumonia admitted to the “City Clinical Hospital No. 21 named after prof. E.G. Popkova” DCC, Dnipro. Examination and treatment of patients was carried out in accordance with the clinical guidelines and protocols for the management of patients with COVID-19 (according to the Orders of the Ministry of Health of Ukraine No. 722 from 28.03.2020 and No. 762 from 02.04.2020 in the current version with changes, according to Order of the Ministry of Health of Ukraine dated 20.11.2020 No. 2693 and taking into account bioethical norms in accordance with the Declaration of Helsinki. In all patients diagnosis of coronavirus COVID-19 was confimed by investigation of nasal and pharyngeal smear by polymerase chain reaction (PCR) method for SARS-CoV-2 (COVID-19), pneumonia was diagnosed by computed tomography (CT) or X-ray. Laboratory examination included clinical analyses, biochemical blood tests (fibrinogen, creatinine, international normalized ration ((INR), etc.) and special blood

tests for markers of systemic inflammation and damage to the cardiovascular and pulmonary systems – the level of D-dimer (D-dimer, ng/m l), troponin (cardiac-specific troponin, ng/ml), ferritin (Ferritin, ng/ml), C-reactive protein (CRP), creatine phosphokinase fraction MB (CPK-MB, creatine phosphokinase, CPK-MB, U/l), protein ST2 (growth stimulating factor, IL1RL1 – a member of the family of interleukin-1 receptors (IL-1), ng/ml) – a biomarker of the risk of cardiovascular complications, cardiovascular failure. Statistical data processing was performed by parametric and non-parametric statistics using the software product Statistica v.6.1® (StatSoft, USA) (serial number AGAR909E415822FA) and SPSS package 23.0. (Free Trial Version access mode: https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-23). The diagnostic value of tests and their impact on disease outcome to optimize risk prediction and prognostic significance of indicators was determined using ROC-curves (English Receiver Operating Characteristic) with the calculation of operational characteristics of ROC-analysis [1]. The critical level of statistical significance was assumed to be <5% ($p<0.05$).

RESULTS AND DISCUSSION

Among the 37 hospitalized patients there were 20 women and 17 men. The average age of patients was 59±3 years (22-77 years). All patients were diagnosed with coronavirus disease complicated by bilateral polysegmental pneumonia on admission to the hospital. According to the degree of severity, 17 had a moderate degree of severity, and 20 had a severe one. Some patients had the following comorbid diseases (n): chronic pathology of the gastrointestinal tract (11), Cr Pancreas T2NxM1, st4 (1), Cr lung, chronic obstructive pulmonary disease (3), diffuse goiter, thyroiditis (4), systemic lupus erythematosus (1), chronic pyelonephritis (5), diabetes mellitus (9), coronary heart disease (9), varicose veins of the extremities (8). Other complications of the disease were as follows (n): arterial thrombosis (1), sepsis (2), septic shock (3), multiple organ failure (7).

In the treatment of patients, therapy was used in accordance with the protocol "Provision of medical care for the treatment of coronavirus disease (COVID-19)", approved by the order of the Ministry of Health of Ukraine from 02.04.2020 No. 762: dexamethasone (all patients), remdesivir (11), tocilizumab (7), oxygen therapy, antibiotics, symptomatic therapy. Seven patients were transferred to the intensive care unit due to disease progression, acute respiratory distress syndrome (ARDS), septic shock, and were connected to an invasive ventilator. One patient died.

Analysis of the time of admission to the hospital from the onset of symptoms showed that most patients were admitted to the hospital in the second week of the disease. Most patients were admitted to the hospital on day 6-7 of the disease (from day 2 to day 14) due to an increase in respiratory disorders and fever, which averaged 6.65±3.32 (M±SD) day of illness.

All patients needed oxygen support on admission to the hospital, in most of them the dynamics of blood oxygen saturation (SpO_2,%) depended on the severity of the disease and response to therapy (Fig. 1). Oxygen support was performed mainly through a face mask with a reservoir bag, the flow rate averaged 10-15 1/min.

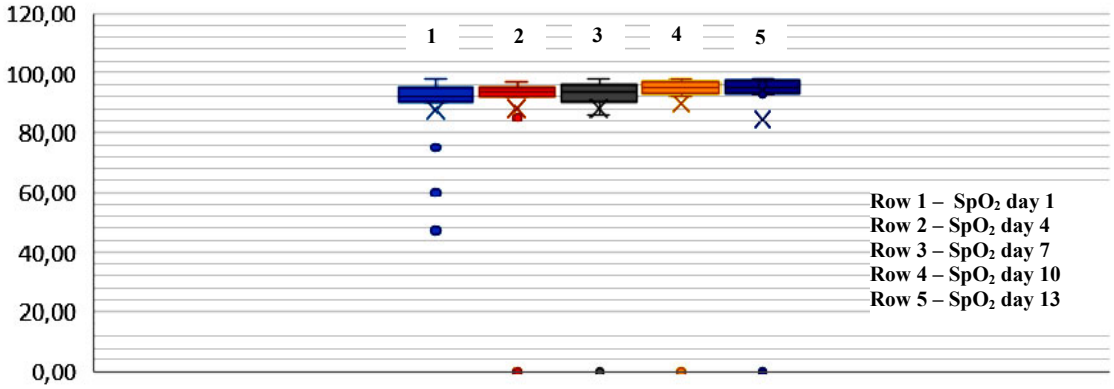


Fig. 1. Dynamics of SpO_2 (%) of hospitalized patients depending on the length of hospital stay: rows 1-5 on the abscissa – day 1, 4, 7, 10 and 13 of the disease, respectively, the ordinate axis - level of SpO_2,%

Figure 1 shows the overall positive dynamics of oxygen saturation on oxygen support from the first to the 13th day of hospital treatment, where the lowest level of SpO_2 in patients was on day 1 of hospital admission.

A comparison of the dynamics of oxygen saturation rates relative to day 1 of hospital admission and subsequent use (Yes) or non-use of invasive AVL (No) during treatment was performed (Fig. 2).

As can be seen in Figure 2, among those who subsequently required AVL (1), SpO_2 rates were lower, especially on day 1 of hospital admission.

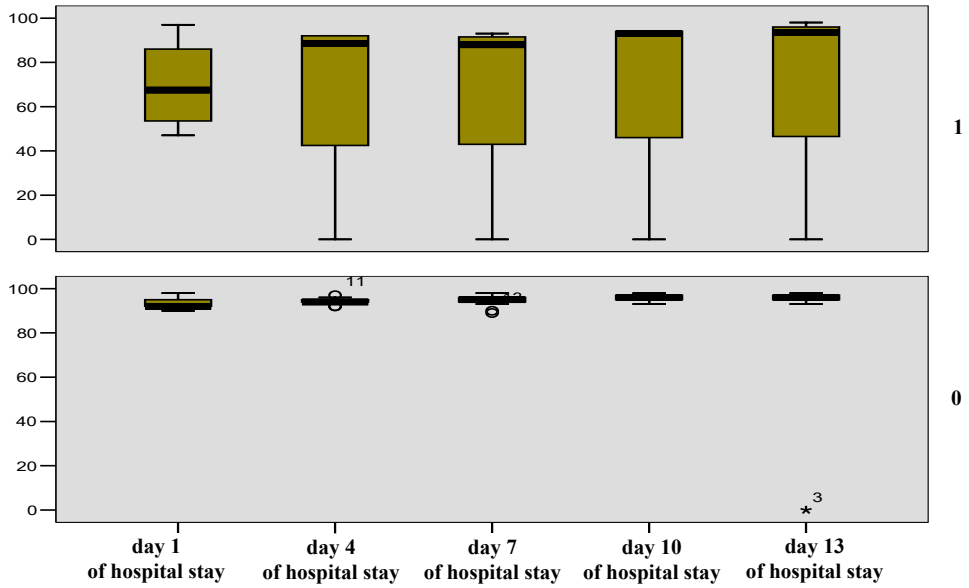


Fig. 2. Dynamics of SpO_2 in patients depending on AVL use on day 1, 4, 7, 10 and 13 of hospital stay, where 1 – AVL use; 0 – non-use of AVL, on the ordinate axis - SpO_2 (%), on the abscissa axis - the corresponding days of hospital stay

Also, the level of oxygen saturation depended to some extent on the day on which the patient was admitted to the hospital. A significant decrease in SpO_2 was observed in patients who arrived 4-6 days after the onset of the first symptoms of the disease.

A study of the correlation between biochemical markers of systemic lesions in inflammatory processes (Table 1) was performed and it showed the following probable coefficients: the highest relationship was found between the level of ST2 and D-dimer, CPK-MB – with D-dimer, CPK-MB and ST2, as well as ferritin and D-dimer with ST2. No probable association with troponin has been identified. CRP probably correlated with CPK-MB and ferritin. The INR index had probable correlations with D-dimer, ST2 and CPK-MB.

Table 1

Matrix of correlation coefficients between the main biochemical indicators of blood

Indicators / Correlation coefficient	D-dimer ng/ml	ST2, ng/ml	CPK-MB, U/l	Troponin, ng/ml	Ferritin, ng/ml	CRP, mg/l	INR, U
D-dimer, ng/ml	**1**						
ST2, ng/ml	**0.9***	**1**					
CPK-MB, U/l	**0.8***	**0.75***	**1**				
Troponin, ng/ml	**0.1**	**0.1**	**0.1**	**1**			
Ferritin, ng/ml	**0.5***	**0.54***	**0.3**	**0.04**	**1**		
CRP, mg/l	**0.38**	**0.4**	**0.7***	**0.5**	**0.5***	**1**	
INR, U	**0.7***	**0.8***	**0.5***	**0.1**	**0.4**	**0.2**	**1**

Notes: * – Spearman correlation coefficients (rs) with probability $p<0.05$; ST2 – growth stimulating factor; CPK-MB – creatine phosphokinase of the MB fraction; CRP – C-reactive protein; INR – international normalized ratio.

There was performed Cox regression analysis (Fig. 3) with the study of survival function, which showed that the survival curve is stepwise and the greatest risk of deterioration, which requires further mechanical ventilation was observed on day 6 of the disease (95.0% CI=0.9-1.0, at the average level of SpO_2 =87,3%).

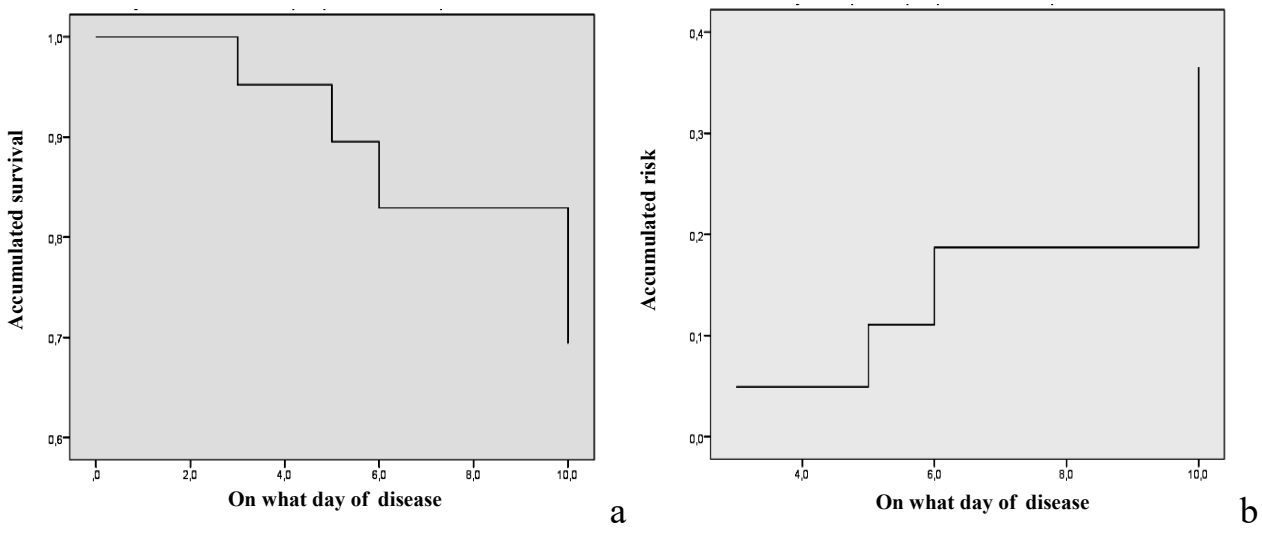


Fig. 3. Cox regression curves for the risk of disease progression and transfer to mechanical ventilation depending on the day of disease and SpO_2, where the abscissa is the corresponding day of disease:
a – survival function on average by covariants,
b – function of the risk of disease progression by SpO_2 on average by covariates

It was determined that the risk increased almost 2 times by day 6 of the disease in patients with new coronavirus disease complicated by pneumonia with a progressive decrease in SpO_2.

ROC analysis was performed to determine the relationship between the degree of reduction of SpO_2 on admission and some markers of inflammation (Fig. 4).

Figure 4 shows a plausible relationship between D-dimer levels >840.8 ng/ml and the risk of developing a critical condition requiring mechanical ventilation in patients with high sensitivity and specificity of the method, with an area limited by the ROC curve AUC=0.938±0.70 (95% CI=0.801-1.074), which shows the excellent (high) quality of this classifier.

Indicators such as ST2 and CPK-MB, which are sensitive and quite specific for predicting, were also found (Fig. 5). Namely, for ST2 at the level of >112.0 ng/ml ROC-curve shows excellent quality of the classifier with AUC area =0.923±0.074, for CPK-MB at the level of >40.0 U/l – very good quality of the classifier with AUC area =0.865±0.094. With regard to ferritin, ROC analysis showed insufficient sensitivity and specificity, which may be due to a small sample of patients.

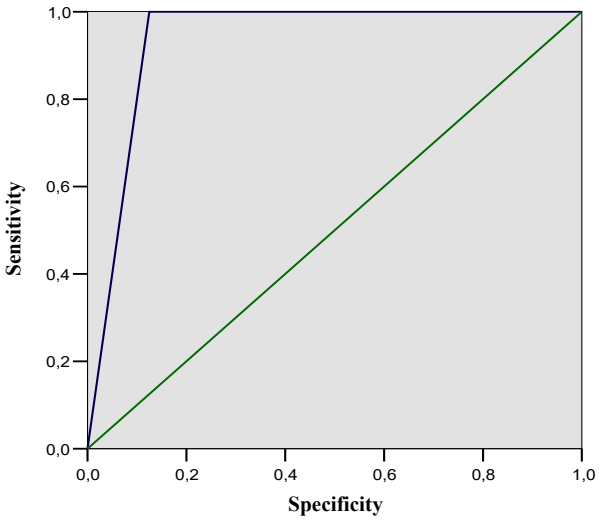
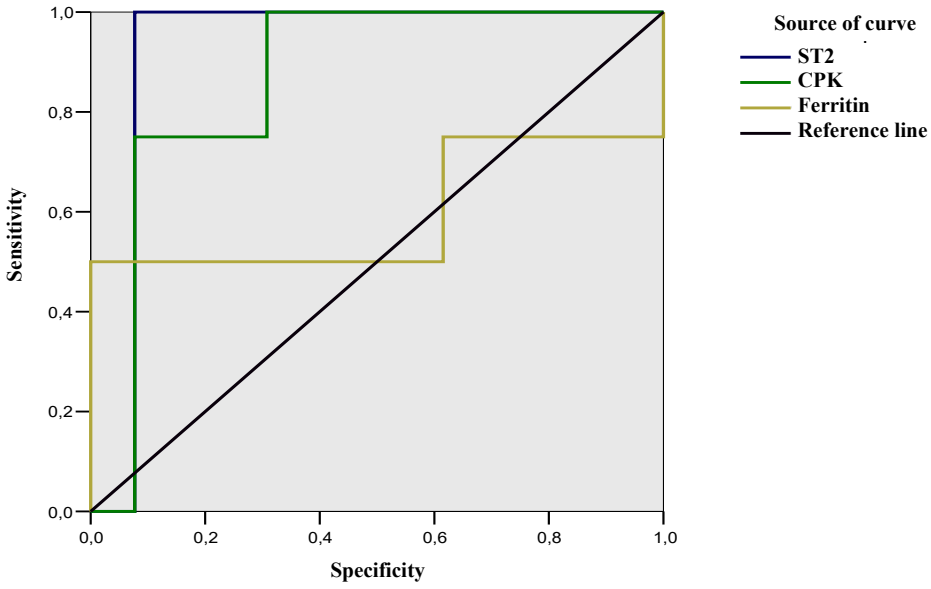


Fig. 4. ROC-curve for determining the optimal criterion for predicting the risk of transferring a patient to mechanical ventilation depending on the level of D-dimer (AUC =0.938)

ROC analysis was also used to assess the role of a comorbid condition such as diabetes mellitus for the risk of adverse coronavirus disease (Fig. 6).



Indicator	Area AUC	Standard error	Asymptotic value	95% confidential interval	
				IQR: Q1	IQR: Q4
ST2	0.923	0.074	0.013	0.778	1.068
CPK-MB	0.865	0.094	0.031	0.682	1.049
Ferritin	0.596	0.218	0.571	0.169	1.023

Рис. 5. Comparison of ROC-curves: prognostic significance of ST2, CPK-MB, ferritin indicators for prognosis of patient connection to ALV

The ROC curve with the area under the curve AUC=0.712±0.170 shows the presence of a high risk of mechanical ventilation in patients with diabetes mellitus with good quality of the model classifier for prognosis.

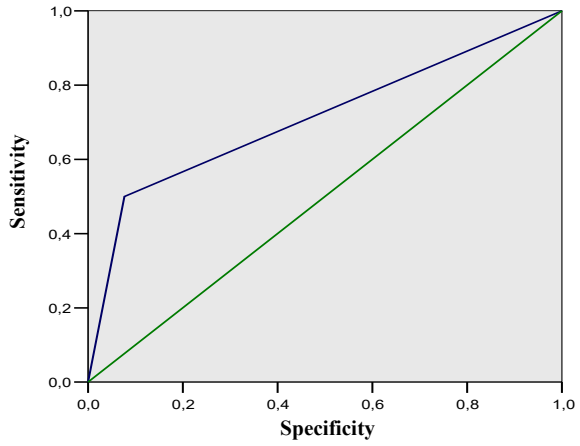


Fig. 6. ROC curve for predicting the risk of transferring a patient to mechanical ventilation on admission to a hospital if a patient has diabetes (AUC =0.712)

Already in the first months of the pandemic of the new coronavirus disease COVID-19 in Ukraine, doctors faced the problem of unpredictability of this infection, because in most patients at the onset of the disease within 4-5 days the clinical picture is similar to acute respiratory infection, although variable, without subjective signs of oxygen deficiency. But the further course of the disease is difficult to predict, in 80% it is favorable, in 15% it becomes severe with the development of bilateral poly-segmental interstitial pneumonia, and in 5% – critical [6]. It is believed that during the first 5-7 days there is a virological phase of the disease, which in the second week of the disease changes to the early pulmonary phase with the onset of an active immune response from cellular and humoral immunity, which either leads to virus elimination and recovery or disease progression, development of pneumonitis, ARDS, septic shock. The basis of these severe complications is the development of the so-called "cytokine storm", with hypercytokinemia, activation of macrophages and other inflammatory cells [4, 7]. In our study, we obtained evidence of the impact of the time of admission to the hospital, as well as the level of reduction of SpO_2 on

admission for further prognosis for the patient and the risks of invasive ventilation. The majority of patients (73%) had comorbid conditions that aggravated the course of coronavirus disease, but the most important is the presence of diabetes mellitus, which coincides with the observations of other authors [10]. The most informative markers for the prognosis of complicated course of COVID-19 were the following biochemical parameters: D-dimer, CRP-C-reactive protein, INR – international normalized ratio and markers of cardiovascular disease – ST2, CPK-MB.

CONCLUSIONS

1. A study of a small group of patients admitted during the first wave of the epidemic of the new coronavirus COVID-19 showed that the disease has a phase character, when after the first phase of the disease in some patients pulmonary phase and hypercytokinemia progress with a decrease in SpO_2 and the development of hypoxia.
2. Admission to the hospital after the 6th day of the disease with SpO_2<90% doubles the risk of disease progression and the need for further use of invasive ventilation.
3. The presence of diabetes mellitus in patients with coronavirus COVID-19 can be considered a specific and sensitive marker of unfavorable further course of the disease.
4. Detection of markers of disease progression is essential for predicting the course and possible prevention of the development of acute respiratory distress syndrome with the use of invasive artificial lung ventilation. There is a plausible association between D-dimer levels >840.8 ng/ml and the risk of developing a critical condition requiring pulmonary ventilation.
5. Such indicators as ST2 at the level >112.0 ng/ml, CPK-MB at the level >40.0 can be considered sensitive and quite specific for the prognosis. There is a probable correlation between these markers and the D-dimer level.

Conflict of interest. The authors declare no conflict of interest

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The article was received
2021.06.25