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Infectious and Parasitic Diseases

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PREDICTING THE RISK OF DEATH IN PATIENTS WITH COVID-19 INFECTION

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The article presents the associations of clinical, laboratory, and clinical and instrumental features of patients with COVID-19 with increased risks of death and survival. The final model for predicting the risks of developing a lethal outcome in COVID-19 was determined, which has high classification qualities (optimal threshold value of the calculated model is equal to -1.6149; sensitivity – 97.1%; and specificity – 82.6%. The purpose of our study was to determine the risks of developing fatal outcomes in patients with COVID-19 based on their clinical, laboratory and instrumental features. The study was performed at the Department of Infectious and Pediatric Infectious Diseases, Parasitology, Phthisiology and Pulmonology of the Kharkiv National Medical University in accordance with the current bioethical norms and rules. All patients signed informed consent. 179 patients with COVID-19 aged 20–88 years (average age was [58.75±13.82] years) were observed. Medical and statistical calculations were performed using the IBM SPSS 25.0 software package. The associations of indicators with the binomial dependent variable were calculated using multiple logistic regression analysis with the calculation of β coefficients. The significance of differences was determined using the Mann-Whitney U-test with a threshold of statistical significance p=0.05. Based on the results, the final prognostic model of the risk of developing a lethal outcome of COVID-19 indicates an increased risk of death in COVID-19 with increasing age (by 13.9%), leukocyte count (by 14.4%), D-dimers (by 0.001%) on day 5–7. According to the model, an increase in the probability of survival in COVID-19 was significantly proved with an increase in hemoglobin (by 6.1%) at the day of hospitalization, monocyte count (by 17.1%) on day 5–7 and the use of ceftriaxone (by 87.8%).

Keywords: *prognostication, thromboelastography, clinical and laboratory characteristics.*

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Introduction

Coronavirus disease (COVID-19), which emerged in late 2019, has become a global phenomenon in a short time with extreme levels of morbidity and mortality [1–9]. Mortality rates from COVID-19 are estima-

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ted to be at least 10.0% [4]. Although most patients with COVID-19 have a predominantly respiratory tract involvement, a certain cohort has a more severe course of the disease with the development of systemic involvement characterized by resistant fever, acute respiratory distress syndrome, shock, and subsequent multiorgan failure [2; 4; 10–13]. The combination of diffuse intravascular coagulation with the formation of large-caliber vascular thrombosis is also associated with the development of multiple organ failure [3].

It is difficult to determine the actual prevalence of thrombosis in patients with COVID-19. However, at least a quarter of patients with COVID-19 have coagulation disorders that are clinically manifested as venous thromboembolism [4; 6; 7; 14–16]. A significant proportion of them are pulmonary embolisms [6; 15]. It is particularly worth noting that thrombosis occurs in the setting of thromboprophylaxis [6; 15; 17]. It is emphasized that the definition of clinical and laboratory criteria for stratification of thrombotic risk should be the primary goal of research to optimize timely and appropriate thromboprophylaxis [15].

In recent years, ThromboElastoGraphy (TEG), which studies the viscoelastic properties of the thrombus, has been used quite successfully to determine the increased risk of developing blood coagulation disorders [18].

It is also important to identify risk factors for the severity of COVID-19 [12]. According to Coomes E.A. et al. [11], it is extremely promising to study the dysregulation of the humoral immune response in patients with COVID-19, which manifests itself as a cytokine response syndrome with a predominance of InterLeukin-6 (IL-6) production and activity and other acute-phase parameters, in order to optimize immunostabilizing therapeutic tactics, especially in patients with severe and extremely severe infection.

Thus, given the high mortality rate in COVID-19, the overwhelming severity of the course (due to the widespread cytokine response syndrome with the development of multiple organ failure), determining the risks of developing lethal outcomes in such patients based on clinical, laboratory and instrumental features is of great medical and social importance.

The aim of the study – determine the risks of developing lethal outcomes in patients with COVID-19 based on their clinical, laboratory, and instrumental features.

Materials and Methods

The study was performed at the Department of Infectious and Pediatric Infectious Diseases, Parasitology, Phthisiology and Pulmonology of Kharkiv National Medical University and at the Municipal Non-Profit Enterprise "Kharkiv Regional Infectious Diseases Hospital" of the Kharkiv Regional Council, in 2020–2024.

The study was conducted in accordance with international and national recommendations of bioethical norms and rules. All patients signed the informed consent on participation in the scientific research. 179 patients (53.63% female and 46.37% male) with COVID-19, aged 20–88 years were examined. The average age of patients was [58.75±13.82] years. 53.63% of women and 46.37% of men were elderly and senile (over 50 years old).

The diagnosis of COVID-19 was confirmed by Enzyme-Linked ImmunoSorbent Assay (ELISA) and Polymerase Chain Reaction (PCR). A laboratory examination was also carried out, which included:

- clinical blood test (determination of the quantitative composition of hemoglobin, erythrocytes, leukocytes, platelets, eosinophils, neutrophils (rod nuclear (r/n) and segmented), lymphocytes, monocytes, color index, hematocrit, Erythrocyte Coagulation Rate (ESR), etc);

- biochemical blood test (determination of glucose, IL-6, activation level of the

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blood coagulation system and the presence of intravascular coagulation (D-Dimer, procalcitonin and C-reactive protein values), coagulogram (international normalized ratio, Quick prothrombin, activated partial thromboplastin time, thrombin time, prothrombin index, fibrinogen).

Instrumental studies included:

- determination of the state of the respiratory system (respiratory rate and saturation);

- Computed Tomography (CT) scan and chest radiography (to confirm the presence and localization of pneumonia);

- TEG (determination of the levels of maximum thrombus formation rate, time to reach the maximum thrombus generation rate, total thrombus generation rate, maximum lysis rate, time to reach the maximum lysis rate, total lysis, reaction time, clot formation time, a-Angle, maximum amplitude, maximum amplitude time, maximum clot elasticity (G), clot density (immediately and after 30 and 60 minutes), coagulation index, degree of amplitude reduction after 30 and 60 minutes (LY60), degree of area reduction after 30 and 60 minutes, thrombus formation rate (TPI), etc.).

The medical and statistical calculation of the study results was performed using the SPSS 25.0 for Windows (IBM, USA).

The associations of the obtained indicators with the binomial dependent variable were determined using multiple logistic regression analysis with the calculation of standardized coefficients β (Odds Ratio (OR) and their 95.0% Confidence Intervals (CI)). The quality of the obtained models was checked by calculating the Nagelkerke R2 criterion. The model was fitted with a multiple binomial regression equation to calculate the probability of the desired event occurring as a percentage. The quality of the resulting model and the test for multicollinearity were evaluated using R and Durbin-Watson statistics.

The probability of differences in the obtained features was determined using the Mann-Whitney U-test. The threshold value of the statistical significance of the calculated traits was taken as 0.05 (p=0.05).

Results and Discussion

In the simultaneous analysis of the obtained associations of the above clinical, laboratory and clinical and instrumental characteristics of the examined patients with COVID-19 infection in relation to the increased risks of developing a lethal outcome associated with this disease, the most influential probable characteristics were identified, which formed the final model of death risks in COVID-19 (*Table*).

Table. The final model for predicting the risk of death in patients with COVID-19

Indices	β	OR	CI		p
			-95.0%	+95.0%	
Age, years	0.130	1.139	1.057	1.228	0.001
Hemoglobin (hospitalization), g/l	0.001	0.939	0.904	0.976	0.939
Leukocytes (hospitalization), x10^9/l	0.025	1.144	1.017	1.286	1.144
r/n (5–7 days),%	0.075	1.074	0.993	1.161	1.074
Monocytes (5–7 days),%	0.014	0.829	0.714	0.962	0.829
D-Dimer (hospitalization), FEU, ng/ml	0.026	1.000	1.000	1,001	1.000
Ceftriaxone	0.027	0.222	0.059	0.840	0.222
A-Angle, ^{0}	0.021	1.090	1.013	1.173	1.090
G, d/sc	0.001	1.509	1.186	1.920	1.509
LY60,%	0.060	1.036	0.999	1.075	1.036
TPI, sec	0.003	0.906	0.850	0.967	0.906
Constant	-8.305	–	0.037	–	

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At the same time, it was determined that there were direct associations of the analyzed characteristics that indicated increased chances of developing a lethal outcome of COVID-19 with increasing age of patients (β=0.130, OR=1.139 [95.0% CI 1.057–1.228], p=0.001), leukocyte count (β=0.025, OR=1.144 [95.0% CI 1.017–1.286], p==1.144) and D-Dimers (β=0.026, OR==1.000 [95.0% CI 1.000-1.001] at the time of hospitalization and neutrophil counts on days 5–7 after its onset (β=0.075, OR==1.074 [95.0% CI 0.993-1.161] p=1.074), p=1.000), higher A-Angle (β=0.021, OR==1.090 [95.0% CI 1.013-1.173], p=1.090), G (β=0.001, OR=1.509 [95.0% CI 1.186–1.920], p=1.509) and LY60 (β=0.060, OR==1.036 [95.0% CI 0.999-1.075], p=1.036) (*Table*).

Also, the existence of inverse associations of certain clinical laboratory and clinical and instrumental characteristics that increased the chances of survival in COVID-19 for higher hemoglobin levels at the time of hospitalization (β=0.001, OR==0.939 [95.0% CI 0.904–0.976], p=0.939), monocytes on days 5–7 after its onset (β==0.014, OR=0.829 [95.0% CI 0.714–0.962], p=0.829) and TPI values (β=0.003, OR==0.906 [95.0% CI 0.850–0.967], p=0.906) and the use of ceftriaxone in the treatment regimen (β=0.027, OR=0.222 [95.0% CI 0.059–0.840], p=0.222).

Based on the obtained associations, the final model for predicting the risk of developing a lethal outcome of COVID-19 was developed (*Fig. 1*), which has high classification qualities (optimal threshold value of the calculated model is equal to -1.6149; 97.1% sensitivity and 82.6% specificity (*Fig. 2*).

When assessing the previously obtained medical, anamnestic, clinical, laboratory and instrumental indicators in their totality to form the final prognostic model for determining the risks of developing a lethal outcome of COVID-19, it was determined that the probability of death in this disease increases with increasing age, quantitative levels of leukocytes at the time of hospitalization and neutrophil counts on days 5–7 from its onset, levels of D-Dimers at hospitalization and A-Angle, G and LY60 values at the time of hospitalization, by 13.9%; 14.4%, 7.4%, 0.001%, 9.0%, 50.9% and 3.6%, respectively (*Fig. 1*).

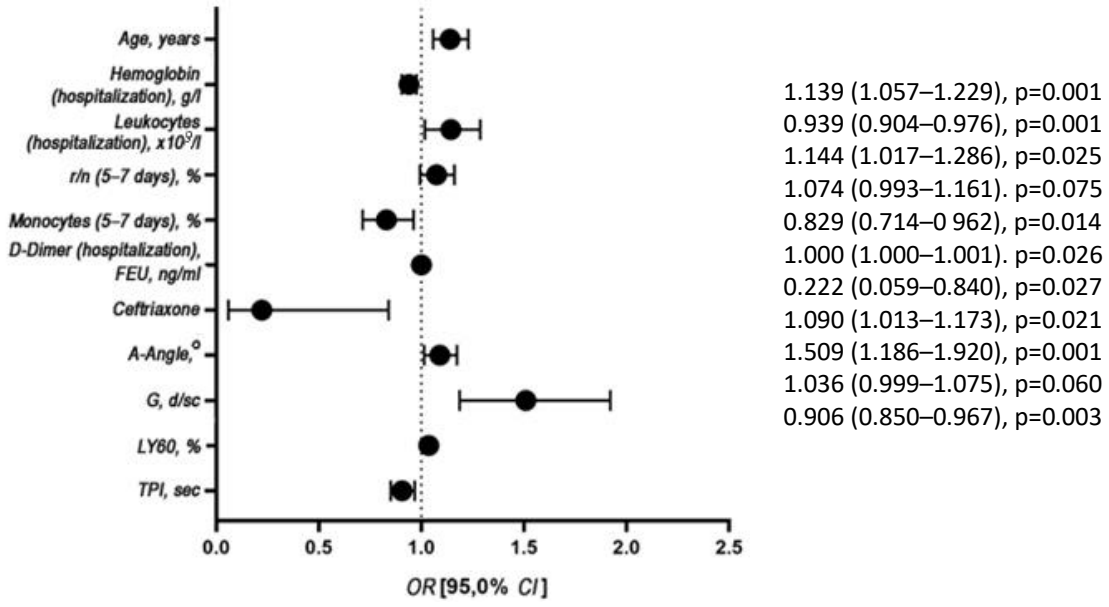


Fig. 1. Markers for predicting death in patients with COVID-19 (final prognostic model).

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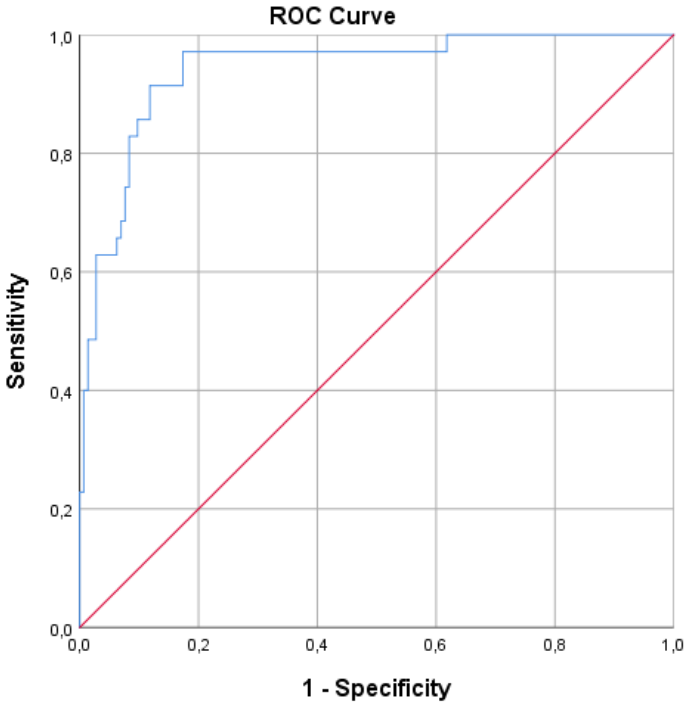


Fig. 2. ROC curve of the model for predicting the development of a lethal outcome in patients with COVID-19 (AUC=0.941 [95.0% CI 0.890–0.982], p<0.001).

It was found that an increase in the likelihood of survival in COVID-19 infection is associated with an increase in such indicators as hemoglobin level at the time of hospitalization, monocytes on day 5–7 after hospitalization, the use of ceftriaxone in the treatment regimen and the value of TRI TEG at hospitalization by 6.1%, 17.1%, 87.8% and 9.4%, respectively (*Fig. 1*).

Our findings are fully consistent with other studies that note high shifts in clinical laboratory and clinical and instrumental characteristics in COVID-19 and significant risks of mortality. For example, among the factors associated with mortality, an increase in D-Dimer levels above 1.0 ng/ml during hospitalization, an increase in prothrombin, IL-6, and troponin were identified [1]. This increase in D-Dimer (more than 1.0 mg/l) was significantly associated with an increased risk of mortality: OR= =18.42 [95.0% CI 2.64–128.55], p=0.003 [1; 2].

It has been shown that in deceased patients, the mean concentrations of D-Dimer were 2.12 (0.77–5.27) mg/l, compared with 0.61 (0.35–1.29) mg/l in survivors [2; 17]. Another study found that patients with D-Dimer levels >0.5 mg/l had a higher mortality rate than patients with levels <0.5 mg/l [1]. Another study involving 1099 patients with COVID-19 showed that an increase in D-Dimer levels above 0.5 mg/l was detected in 46% of cases [17]. A meta-analysis by McBane R.D. 2nd et al. [16] showed that coagulopathy in patients with COVID-19 differs significantly from disseminated intravascular coagulation in a number of ways, including increased fibrin levels, moderate thrombocytopenia, and a slightly prolonged prothrombin time.

Conclusions

The final prognostic model for the risk of developing a lethal outcome of COVID-19 has good parametric qualities: 97.1% sensitivity and 82.6% specificity and indi-

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cates an increased risk of death in COVID-19 with an increase in age (by 13.9%), white blood cell count (by 14.4%) and D-Dimers (by 0.001%), A-Angle (by 9.0%), G (by 50.9%) and LY60 (by 3.6%) at hospitalization, and neutrophil count (by 7.4%) on day 5–7. According to the model, an increase in the probability of survival in COVID-19 was significantly proved with an increase in hemoglobin (by 6.1%) and TPI (by 9.4%) at the time of hospitalization and monocyte count (by 17.1%) on day 5–7 and the use of ceftriaxone (by 87.8%).

Conflict of interest is absent.

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Андрусович І.В.

ПРОГНОЗУВАННЯ РИЗИКІВ ЛЕТАЛЬНОГО НАСЛІДКУ У ХВОРИХ ІЗ ІНФЕКЦІЄЮ COVID-19

В статті надано асоціації клініко-лабораторних та клініко-інструментальних особливостей хворих на COVID-19 із збільшеними ризиками летального наслідку захворювання та виживання. Визначено фінальну модель прогнозування ризиків розвитку летального наслідку при COVID-19, яка має високі класифікаційні якості (оптимальне граничне значення розрахованої моделі становить -1,6149; чутливість – 97,1 %; та специфічність – 82,6 %. Метою нашого дослідження було визначення ризиків розвитку летальних наслідків хворих із COVID-19 на основі клінічних, лабораторних та інструментальних їх особливостей. Проведене дослідження виконано на кафедрі інфекційних і дитячих інфекційних хвороб, паразитології, фтизіатрії та пульмонології Харківського національного медичного університету згідно з дотриманням діючих біоетичних норм та правил. Усі пацієнти приймали участь у дослідженні добровільно та підписали інформовану згоду. Було обстежено 179 хворих на COVID-19 віком 20–88 років (середнього віку [58,75±13,82] років), яких лікували у Харківській обласній інфекційній лікарні. Медико-статистичний розрахунки виконані у SPSS 25.0 (IBM, США). Обраховано асоціації показників із біноміальною залежною змінною за допомогою множинного логістичного регресійного аналізу із розрахунком коефіцієнтів β. Вірогідність відмінностей визначали за допомогою U-тесту Мана-Уітні з пороговою величиною статистичної значущості 0,05 (p=0,05). За результатами було вирахувано фінальну прогностичну модель ризиків розвитку летального наслідку COVID-19, яка вказує на збільшені ризики смерті при COVID-19 при збільшенні віку (на 13,9 %), кількості лейкоцитів (на 14,4 %) і Д-Дімерів (на 0,001 %) та ін. при госпіталізації, палочкоядерних нейтрофілів (на 7,4 %) на 5–7 добу. Згідно з моделлю достовірно доведено збільшення вірогідності виживання при COVID-19

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при підвищенні значень гемоглобіну (на 6,1 %) та швидкості утворення тромбу (на 9,4 %) на момент госпіталізації; кількості моноцитів (на 17,1 %) на 5–7 добу й застосування цефтріаксону (на 87,8 %).

Ключові слова: *модель ризику, тромбоеластографія, клініко-лабораторні характеристики.*

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