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IMPORTANCE OF IDENTIFYING MARKERS OF COAGULOPATHY IN COVID-19 PATIENTS

Niyozov G.E., Oblokulov A.R., Jalilova A.S.

Bukhara state medical Institute named after Abu Ali Ibn Sino

✓ ***Resume***

The value of D-dimer (DD), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FG) coagulation parameters in predicting the severity and prognosis of COVID-19 was studied. Violation of blood clotting function was found in almost all, more often in old patients.

Indicators of hemostatic homeostasis such as D-dimer, prothrombin time and fibrinogen can be used as indicators of the severity of the disease in patients.

Keywords: COVID-19, coagulation, prothrombin time, fibrin breakdown products, D-dimer, prognosis.

ЗНАЧЕНИЕ ОПРЕДЕЛЕНИЯ МАРКЕРОВ КОАГУЛОПАТИИ У ПАЦИЕНТОВ COVID-19

Ниёзов Г.Э., Облокулов А.Р., Джалилова А.С.

Бухарский государственный медицинский институт им. Абу Али ибн Сино

✓ ***Резюме***

Изучено значение показателей коагуляции D-димера (DD), протромбинового времени (ПВ), активированного частичного тромбопластинового времени (АЧТВ), тромбинового времени (ТВ) и фибриногена (Фг) в прогнозировании тяжести и прогноза COVID-19. Нарушение функции свертывания крови встречался почти у всех, чаще у тяжелых пациентов.

Показатели гемостатического гомеостаза, как D-димер, протромбиновое время и фибриноген могут быть использованы в качестве предикторами тяжести течения болезни у пациентов.

Ключевые слова: COVID-19, коагуляция, протромбиновое время, продукты распада фибрина, D- димер, прогноз.

COVID-19 БЕМОРЛАРИДА КОАГУЛОПАТИЯ МАРКЕРЛАРИНИ АНИҚЛАШНИНГ АҲАМИЯТИ

Ниёзов Г.Э., Облокулов А.Р., Жалилова А. С.

Абу Али ибн Сино номидаги Бухоро Давлат тиббиёт институти

✓ ***Резюме***

Коагуляциянинг D-димер (DD), протромбин вақти (ПВ), фаол қисмли трамбопластин вақти (АЧТВ), тромбин врақти (ТВ) и фибриноген (Фг) кўрсаткичлари COVID-19 олдиндан кечуви ва огирлик даражасини баҳолаш мақсадида ўрганиб чиқилди. Қон ивиш функциясининг бузилиши деярли барча беморларда учради, айниқса, ёши катта беморларда кўпроқ учради.

D-димер, протромбин вақти, фибриноген каби гемостатик гомеостазнинг кўрсаткичларидан беморларда касаллик кечиш огирлигининг предиктори сифатида фойдаланиш мумкин.

Калит сўзлар: COVID-19, коагуляция, протромбин вақти, фибрин парчаланиш моддалари, D-димер, прогноз.

Relevance

A new coronavirus infection (Corona VIrus Disease 2019 - COVID-19) is an infection caused by the SARS-CoV-2 coronavirus (Severe Acute Respiratory Syndrome-related CoronaVirus-2). According to the latest statistics from the World Health Organization (WHO), the disease has already covered all continents, with more than 171277079 diagnosed cases in 218 countries and almost 3561954 deaths were recorded as of May 31, 2021 [1]. The spectrum of clinical manifestations arising from COVID-19 includes fever, myalgia, cough and shortness of breath, less often headache, diarrhea, nausea and vomiting [2].

Coronavirus infection (COVID-19) is characterized by activation of the hemostasis system, which in the most severe cases can lead to the development of consumption coagulopathy. At present, it remains unclear whether COVID-19 is the direct cause of these disorders or they arise as the infectious process progresses [3].

Most patients with COVID-19 develop symptoms of respiratory infection, some of them worsen to a more severe systemic disease characterized by persistent fever, acute lung injury with acute respiratory distress syndrome, multiple organ failure, shock and high mortality [4, 5] . Careful observation of patients with COVID-19 showed that many of them had abnormalities in the results of laboratory tests of the blood coagulation system, reminiscent of other systemic coagulopathies, such as disseminated intravascular coagulation (DIC) and thrombotic microangiopathies [6]. In addition, it turned out that COVID-19-associated coagulopathy also has features that distinguish it from DIC and TMA [7].

Coagulation abnormalities have been reported in COVID-19 patients in several descriptive studies [8, 9, 10]. Increased levels of D-dimer and fibrin degradation products (FDP), shortened or increased prothrombin time (PT), abnormal platelet count, thrombosis or bleeding, and complications of disseminated intravascular coagulation have been observed in patients with COVID-19 at different clinical stages [11, 12 , 13]. These data show that blood clotting disorders play an important role in the clinical process of COVID-19. End-stage COVID-19 clotting disorder or after invasive treatment is common and reasonable, but with limited predictive value. In the early stages of hospitalization, more attention should be paid to coagulation function, which can help clinicians identify high-risk patients and guide clinical strategy.

Purpose of the work: To study the significance of coagulopathy markers in patients with COVID-

19 and their prognostic role in various clinical forms of the disease. Materials and methods

This study was a single-center retrospective cohort study. We included all patients with confirmed SARS-CoV-2 infection admitted to an infectious diseases hospital from March 21 to December 31, 2020 in Bukhara. Clinical data were obtained from electronic health records, including demographic data, exposure history, signs and symptoms, and laboratory data at admission.

Routine blood tests: white blood cell count (WBC), lymphocyte count (LYM), mononuclear cell count (MONO), neutrophil count (NEU), platelet count were performed on blood samples. Blood biochemistry parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose (GLU), urea, creatinine and C-reactive protein (CRP) were measured using an automatic biochemical analyzer MINDRAY BC-30 (Chitoi). Coagulation functions (prothrombin time (PTT), fibrinogen (FIB), activated partial thromboplastin time (APTT) were determined using a MINDRAY BA-88A analyzer (China). D-dimer concentration was determined by ELISA using reagent kits for enzyme-linked immunosorbent assay concentration of D-dimer in blood plasma D-dimer - ELISA-BEST. Moderate and severe patients used their first laboratory test at admission. All analyzes were performed by designated personnel in strict accordance with the instructions for use of the reagents.

Result and discussion

Upon admission to the inpatient emergency department, all patients were assessed using the NEWS scale. The average score was 5.6 ± 1.6. This made it possible to quickly sort out patients and send the most severe patients to the intensive care unit. All COVID-19 patients included in this study were diagnosed in accordance with the guidelines for the diagnosis and treatment of pneumonia caused by infection with the novel coronavirus. All patients had laboratory confirmed infection with SARS-CoV-2 (real-time RT-PCR specific for SARS-CoV-2 was positive).

Of the hospitalized patients from March 21 to December 31, 2020, 120 patients were randomly examined at the Bukhara Regional Infectious Diseases Hospital. The patients were divided into severe patients (n = 44) and patients with moderate forms (n = 76). Of these, 22 (28.9%) patients were admitted to the intensive care unit, 8 (6.6%) patients died.

The mean age was 53 years, of 120 patients 92 (76.7%) were men. The median time from symptom onset to hospitalization was 4-5 days, and the median time to diagnosis of severe illness was 6-7 days.

The most frequent chronic diseases were: hypertension, in 6 patients; cardiovascular disease, in 5; chronic obstructive pulmonary disease, in 8 patients.

The distribution of patients by severity can be represented by the degree of lung damage (Fig. 1). CT 0 was in 11 patients, CT 1 - in 18, CT 2 - in 58, CT 3 - in 33 patients. On admission, 65 (54.1%) patients had body temperature above 38 ° C, mean SpO2 = 91.5%.

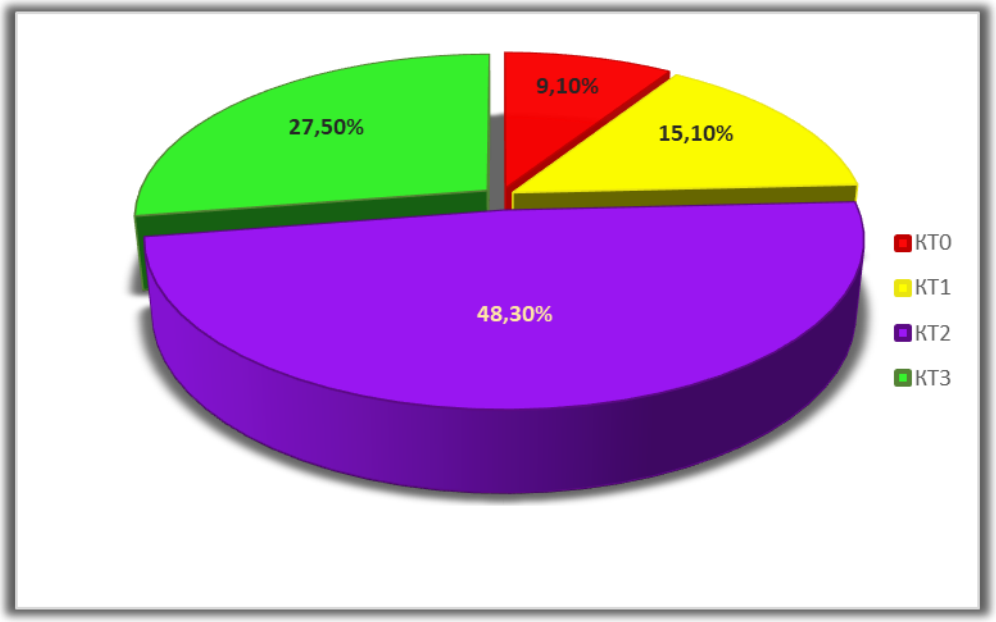

Figure 1. *Distribution of patients according to the degree of lung damage (%)*

According to the results of laboratory data, it was found that 41 patients had leukopenia, 20 patients had leukocytosis; 98 patients had lymphocytopenia, 4 patients had an increase in the number of lymphocytes, and 18 had a normal level of lymphocytes (Fig. 2).

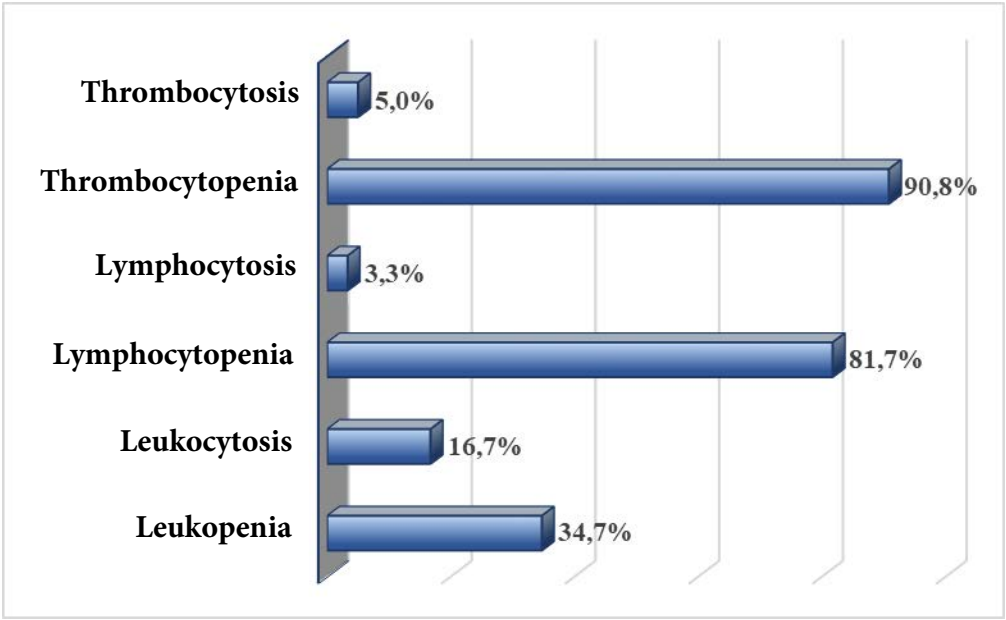

Figure 2. Comparative results of laboratory data in the examined patients

Platelet count and coagulation parameters were analyzed in this study. Of the 120 patients included in the study, thrombocytopenia less than 150 × 109 / L was found in 109 (90.8%), thrombocytosis - in 6 (5.0%).

Indicators of hemostatic homeostasis in patients with coronavirus infection on admission are shown in the table.

Table. Indicators of hemostatic homeostasis in patients with coronavirus infection upon admission (in abc and%)

Indicators	Normal reference values	Criteria	The severity of the flow	
			Medium severity (n=76)	Heavy (n=44)
D-dimer	<0,50 мг/л	<0,50	32 (42.1%)	11 (25%)
		0,50–1,10	36 (47.4%)	23 (52.3%)
		> 1,10	8 (10.5%)	10 (22.7%)
PTV	9.20-15 сек	<9,2	0 (0%)	0 (0%)
		9.20-15.0	18 (23.7%)	6 (13.6%)
		> 15	58 (76.3%)	38 (86.4%)
APTT	21.00-37.00 сек	<21.00	4 (5.3%)	2 (4.5%)
		21.00-37.00	52 (68.4%)	22 (50%)
		> 37,00	20 (26.3%)	20 (45.5%)
Fibrinogen	2,00-4,00 г/л	<2,00	4 (5.3%)	0 (0%)
		2,00–4,00	24 (31.6%)	11 (25%)
		> 4,00	48 (63.1%)	33 (75%)

From this table, it follows that the concentration of D-dimer is increased in 57.9% of patients with a moderate form, and in patients with a severe form, it is detected in 75%. A similar picture was found when studying the prothrombin time, the indicators were 89.5% and 79.5%, respectively. In 50% of patients with a moderate form, the concentration of fibrinogen is increased, and patients with a severe form are 75%. APTT was lengthened in 26.3% of patients with a moderate form of the disease, and 46.9% with a severe one.

The presented data demonstrate hyperfibrinogenemia as the most common marker of COVID-associated coagulopathy. Other researchers came to a similar conclusion. N. Tang et al. revealed a high level of fibrinogen in all patients hospitalized with COVID-19 [14]. H. Huan et al. noted a significantly higher plasma fibrinogen level in patients with COVID-19 compared with the control group: 5.02 ± 2.9 g / l, p <0.001. At the same time, severe patients had a higher value of the indicator: 5.59 ± 5.1 g / l in patients of moderate severity, p <0.01 [15]. An increased level of fibrinogen, along with D-dimer, is discussed as a marker of a poor prognosis of the disease [14]. In our study, hyperfibrinogenemia played the role of a predictor of unfavorable outcomes, but only when the norm was more than twofold. Hypofibrinogenemia proved to be a more significant prognostic sign. The revealed significant relationship between a decrease in the content of fibrinogen and thrombocytopenia is the basis for the inclusion of consumption coagulopathy in the list of discussed mechanisms. At the same time, thrombocytopenia in patients included in the study, and according to data from other studies of the hemostasiological profile in patients with COVID-19, in most cases does not go beyond 100 • 109 / L [14].

A frequent component of consumption coagulopathy is excessive fibrinolysis, which is one of the reasons for high D-dimer levels in these conditions. Results of the performed integral tests in patients

with hypofibrinogenemia showed no signs of excessive fibrinolysis in patients with neither high nor normal D-dimer levels. N. Tang et al. [14] showed that an increased concentration of D-dimer in the plasma of patients with COVID-19 is a predictor of death: in the deceased, the average concentration of D-dimer was 2.12 μg / ml (interquartile range - 0.77-5.27 μg / ml), while in survivors - 0.61 μg / ml (interquartile range - 0.35-1.29 μg / ml) (p <0.001) with normal values up to 0.50 μg / ml. In our study, the concentration of D-dimer was increased by 57.9% in moderately severe patients, and 75% in severe patients (p <0.001).

APTT changes little in COVID-19; however, an increase in APTT in patients with COVID-19, as mentioned above, may be caused by the presence of a lupus anticoagulant. In COVID-19, it did not differ significantly between patients transferred to the intensive care unit and those who did not need intensive care: 26.2 (22.5-33.9) vs 27.7 (24.8-34, 1) c, p = 0.57 [16]. In our study,> 37.0 sec was also determined in 26.3% of patients of moderate severity, in 45.5% of patients with a severe form.

COVID-19 is characterized by moderate thrombocytopenia at the onset of the disease. When examining 1,099 patients with COVID-19, the median blood platelet count was 168 × 109 / L. At the time of hospitalization, thrombocytopenia, defined as a platelet count of less than 150 × 109 / L, was observed in 36.2% [17]. Thrombocytopenia in pneumonia caused by SARS-CoV-2 is less pronounced than in pneumonia of other etiology [18]. In our study, thrombocytopenia less than 150 × 109 / L was found in 109 (90.8%), thrombocytosis - in 6 (5.0%).

Conclusions

Thus, such indicators of hemostatic homeostasis as D dimer, prothrombin time and fibrinogen are predictors of coagulopathy in patients with COVID-19 and indicate the severity of the course of the disease in patients.

LIST OF REFERENCES:

1. World Health Organization. Novel Coronavirus (2019-nCoV) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed: 31 may 2020.
2. Oblokulov A.R., Musaeva D.M., Elmuradova A.A. (2020) Clinical and epidemiological characteristics of the new coronavirus infection (COVID-19). // New Day in Medicine. №2 (30/2) p.110-115.
3. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. JACC. 2020. doi:10.1016/j.jacc.2020.04.031.
4. Cao Y., Liu X., Xiong L. et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. J. Med. Virol., 2020; doi: 10.1002/jmv.25 822.
5. Abdurashid Rahimovich Oblokulov, Zilola Zohirovna Husenova, Maksudjon Muzaffarovich Ergashev. (2021). Procalcitonin as an Indicator of Antibacterial Therapy in Covid-19. Annals of the Romanian Society for Cell Biology, Volume 25: Issue 3. 5220–5224.
6. Iba T., Levy J.H., Levi M. и соавт.: Coagulopathy of coronavirus disease 2019. Crit. Care Med., 2020; doi: 10.1097/CCM.0 000 000 000 004 458].
7. Levi M., Thachil J., Iba T., Levye J.H.: Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020; 7: e438–e440].
8. Wang D, Hu B, Hu C et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020.
9. Chen N, Zhou M, Dong X. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet.2020;395:507-513.
10. Han H, Yang L, Liu R et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med.2020;58:1116-1120.
11. Tao J, Song Z, Yang L. et al. Emergency management for preventing and controlling nosocomial infection of 2019 novel coronavirus: implications for the dermatology department. Br J Dermatol. 2020;182:1477-1478.
12. Wang L, He WB, Yu XM. et al. Prolonged prothrombin time at admission predicts poor clinical outcome in COVID-19 patients. World J Clin Cases 2020; 8(19): 4370-4379.
13. Oblokulov, A. R., Niyozov, G.E. (2020) Clinical and epidemiological characteristics of patients with COVID-19 International Journal of Pharmaceutical Research; 12(4):3749-3752.
14. Tang N., Li D., Wang X., Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18(4): 844–847.
15. Huan H., Lan Y., Liu R., et al. Prominent changes in blood coagulation of patients with SARS-Cov2 infection. Clin Chem Lab Med. 2020; 58(7): 1116–1120. DOI: 10/1515/cclm-2020-0188.
16. Huang C., Wang Y., Li X. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395 (10223): 497–506. DOI: 10.1016/S0140-6736(20)30183-5.
17. Guan W.J., Ni Z.Y., Hu Y. et al. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 2020; 382 (18): 1708–1720. DOI: 10.1056/NEJMoa2002032.
18. Yin S., Huang M., Li D., Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J. Thromb. Thrombolysis. [Preprint. Posted: 2020, Apr. 3].

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