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DYNAMICS OF D-DIMER LEVEL IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA ASSOCIATED WITH CORONAVIRUS INFECTION UNDER THE INFLUENCE OF TREATMENT

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Introduction. In December 2019, Chinese scientists first identified SARS-CoV-2 as the cause of COVID-19. Initially, COVID-19 was considered only a respiratory disease, with pneumonia being the most common and deadly complication. However, studies have shown that SARS-CoV-2 causes an excessive and uncontrolled immune response that leads to many complications. Therefore, it should be understood that COVID-19 is not only a respiratory disease, but also a multisystem disease (Kirtipal N., 2020; White-Dzuro G., 2021).

Understanding the course of COVID-19 is important for clinicians seeking to improve patient outcomes in this population. Studies since the beginning of the pandemic have estimated the overall hospital mortality rate from COVID-19 to be around 12.7% to 22.9%. This compares to an overall mortality rate of around 2.3% for COVID-19. The pathophysiology of COVID-19 pneumonia involves various pathways, such as immune-inflammatory activation, thrombogenic and direct viral lung injury (Goel S., 2020; Wu Z., 2020; Malik P., 2021).

Biomarkers that can detect thrombus formation in the early stages can be used to assess treatment response. Evidence shows that patients with severe COVID-19 often have clotting dysfunction and elevated levels of D-dimer. Abnormal clotting function further complicates the treatment of these patients and increases mortality. With the recent outbreak of the novel coronavirus infection worldwide, the risk of

thrombosis is a cause for concern. D-dimer is a breakdown product of fibrin, and its role as a potentially useful biomarker is currently being emphasised. However, the relationship between changes in D-dimer and the course of COVID-19-associated APE remains unclear (Tang N., 2020; Iba T., 2020).

Various markers are currently proposed to determine the treatment-responsive course of community-acquired pneumonia (CAP) associated with coronavirus infection. We decided to evaluate the levels of D-dimer and procalcitonin in patients with community-acquired pneumonia associated with coronavirus infection under the influence of treatment, which determined the aim of this study.

Objective. To evaluate the dynamics of D-dimer and procalcitonin levels in patients with community-acquired pneumonia associated with coronavirus infection under the influence of treatment.

Material and Methods: An open, prospective, observational study was conducted to achieve the aim and objectives. In the period from January 2021 to February 2022, patients with community-acquired pneumonia associated with SARS-CoV-2 aged 40 to 65 years were examined at the outpatient clinic of the Kherson City Clinical Hospital named after Afanasii and Olga Tropin of the Kherson City Council, 143 patients were admitted to the hospital. To participate in the study, patients signed the Voluntary Informed Consent to Participate in the Study form.

Study inclusion criteria: male and female patients aged 40 to 65 years; community-acquired pneumonia; informed consent to participate in the study.

Exclusion criteria for the study: Pregnant women; uncontrolled hypertension; stage III hypertension; decompensated diabetes mellitus; congenital and acquired haemodynamically significant heart defects; stage II B - III chronic heart failure; oncological diseases; lung damage of more than 75% according to CT scan; contraindications to the use of drugs and their components; alcohol dependence, drug addiction, mental disorders; patient refusal to participate in the study.

All patients were carefully examined for compliance with the inclusion/exclusion criteria. The diagnosis of community-acquired pneumonia was verified on the basis of the adapted evidence-based clinical practice guideline

Community-Acquired Pneumonia in Adults, 2019. COVID-19 was detected in accordance with Order No. 722 of the Ministry of Health of Ukraine dated 28.03.2020 as amended by Order No. 2122 of the Ministry of Health of Ukraine dated 17.09.2020.

Distribution of the examined persons into subgroups. After randomisation, 143 hospitalised patients with severe APE associated with COVID-19 were divided into subgroups depending on the anticoagulant included in the treatment regimen:

- The first subgroup consisted of 71 patients who were prescribed standard heparin infusions;

- the second subgroup included 72 patients receiving enoxaparin.

Definitions.

Plasma levels of D-dimer were measured using a Fiatest fluorescence immunoassay analyzer. The instructions for use of the Fiatest AFR-100 fluorescent immunoassay analyzer (Hangzhou AllTest Biotech Co., Ltd., China) were followed. The detection level of the Fiatest D-dimer assay was 0.1 - 10 mg/L. Reference level: < 0.5 mg/l.

The procalcitonin level was determined using a Fiatest cassette in blood plasma using a Fiatest AFR-100 fluorescent immunoassay analyzer (Hangzhou AllTest Biotech Co., Ltd., China). The linearity range of the Fiatest procalcitonin test is 0.1-50 ng/ml. Reference range: ＜0.1 ng/ml.

Drug treatment of patients. During inpatient treatment, all patients (n = 143) received oxygen support. Systemic corticosteroids were prescribed: dexamethasone (KRKA, Slovenia) at a dose of 6 mg once daily. Ibuprofen, a non-steroidal anti-inflammatory drug, was prescribed at a dose of 400 mg twice daily (Ibuprofen-Zdorovye, manufactured by Pharmaceutical Company Zdorovye, Ukraine). In the hospital, remdesivir (Corovir, Bruck Pharma PVT, LTD) was also prescribed on the first day in a single dose of 200 mg, and 100 mg per day intravenously on the following days. The course of treatment lasted 5 days.

After randomisation, 71 patients were additionally prescribed infusions of standard heparin (Heparin-Pharmex, Farmex Group LLC, Ukraine) at the rate of

1000 IU/h for 10 days, and 72 patients received enoxaparin (Flenox, Farmak JSC, Ukraine) at the rate of 100 IU anti-Xa/kg (1 mg/kg) twice daily for 10 days. The study parameters were assessed on day 3 and 14 after randomisation.

Statistical processing of the data obtained during the study began with descriptive statistics, including the calculation of the median and interquartile range (Me [Q25; Q75]). When testing statistical hypotheses, the null hypothesis was rejected at a level of $p < 0.05$.

Results and discussion. The first time the dynamics of D-dimer and procalcitonin levels was assessed after 72 hours of treatment. At screening, the levels of D-dimer were comparable between the first and second observation subgroups ($p > 0.05$). After 72 hours, there was a significant increase in this indicator by $\Delta 1\% = 19.23\%$ to 0.52 [0.28; 0.62] mg/l in the first subgroup and by $\Delta 2\% = 13.21\%$ to 0.50 [0.42; 0.56] mg/l in the second subgroup ($p < 0.05$). There were no statistically significant differences between the subgroups in the level of D-dimer after 72 hours of observation ($p > 0.05$).

Within 14 days, there were 10 deaths, and the number of patients in the observation subgroups decreased. The second time the dynamics of D-dimer and procalcitonin levels were assessed after 14 days of treatment.

Both treatment subgroups had comparable values at screening

D-dimer: 0.43 [0.21; 0.48] mg/l in the first subgroup and 0.45 [0.29; 0.48] pg/ml in the second subgroup ($p > 0.05$). After 14 days of treatment in the hospital, the level of this indicator significantly decreased, both in the first subgroup by $\Delta 1\% = -46.51\%$ to 0.18 [0.14; 0.24] pg/ml, ($p < 0.05$), and in the second subgroup by $\Delta 2\% = -32.84\%$ to 0.29 [0.18; 0.39] pg/ml, ($p < 0.05$). The value of D-dimer after 14 days significantly differed between the first and second subgroups - 0.18 [0.14; 0.24] mg/l versus 0.29 [0.18; 0.39] mg/l, respectively ($p < 0.05$).

D-dimer is a specific breakdown product formed during the hydrolysis of fibrin. It may reflect the effect of infection on coagulation in infectious diseases. A number of researchers confirm the importance of determining the dynamics of D-dimer, as this laboratory marker is associated with a higher risk of thrombotic

complications (Xu J., 2021; Long H., 2020). Our data support the idea that it is useful to determine the dynamics of D-dimer levels to assess the state of the haemostatic system during anticoagulant therapy. Heparin anticoagulation is apparently associated with favourable outcomes among moderately ill hospitalised patients with COVID-19 (Vuimo T. S., 2022). Thus, the results of our study showed that changes in D-dimer levels may be valuable in guiding an active surveillance strategy for the management of patients with COVID-19-associated APE. Although the study has limitations, as it includes a small number of patients and no patients with comorbidity, it is reasonable to recommend the use of heparin for patients at low risk of bleeding, while others use enoxaparin to prevent thrombotic complications. The open-label design of the trial represents a potential limitation, and further research in this area of knowledge is needed for routine clinical practice.

Conclusions.

1. In patients with community-acquired pneumonia associated with coronavirus infection, the level of D-dimer increases in the first days of the disease.

2. After 14 days of inpatient treatment, the level of D-dimer significantly decreased in both subgroups, but the median level of this indicator was lower in the use of heparin.

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