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COVID-19 PANDEMIC AND HEMATOLOGICAL DISEASES

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Annotation
COVID-19 is a systemic infection with significant effects on the hematopoietic system and hemostasis. Lymphopenia can be considered as a cardinal laboratory sign with prognostic potential. The neutrophil/lymphocyte ratio and the peak platelet/lymphocyte ratio may also be of prognostic value in determining severe cases. In addition, blood hypercoagulability is common among hospitalized patients with COVID-19. Elevated levels of D-dimer are consistently reported, while their gradual increase during the course of the disease is particularly associated with worsening of the disease. Thus, patients infected with COVID-19, both hospitalized and outpatients, have a high risk of exacerbation of hematological diseases, therefore, early rehabilitation and diagnosis of this pathology is strongly recommended.

Keywords: COVID-19, SARS-CoV-2, coagulopathy, hematological diseases, lymphopenia

COVID-19 ПАНДЕМИЯ И ГЕМАТОЛОГИЧЕСКИЕ ЗАБОЛЕВАНИЯ

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Аннотация
COVID-19 представляет собой системную инфекцию со значительным влиянием на систему кроветворения и гемостаз. Лимфопению можно рассматривать как кардинальный лабораторный признак с прогностическим потенциалом. Соотношение нейтрофилов/лимфоцитов и пиковое соотношение тромбоцитов/лимфоцитов также может иметь прогностическое значение при определении тяжелых случаев. Кроме того, гиперкоагуляция крови распространена среди госпитализированных пациентов с COVID-19. Постоянно сообщается о повышенных уровнях D-димера, тогда как их постепенное повышение в ходе болезни, в частности,

связано с ухудшением заболевания. Таким образом, пациенты, инфицированные COVID-19, как госпитализированные, так и амбулаторно, имеют высокий риск обострения гематологических заболевания, поэтому настоятельно рекомендуется ранняя реабилитация и диагностика данную патологию.
Ключевые слова: COVID-19, SARS-CoV-2, коагулопатия, гематологические заболевания, лимфопения

COVID-19 PANDEMIYASI VA GEMATOLOGIK KASALLIKLAR

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Annotatsiya
COVID-19 tizimli infeksiya bo'lib, gematopoetik tizim va gemostazga sezilarli ta'sir ko'rsatadi. Limfopeniya prognostik ahamiyatga ega kardinal laboratoriya belgisi sifatida ko'rib chiqilishi mumkin. Neytrofil/limfotsitlar nisbati va eng yuqori trombotsitlar/limfotsitlar nisbati og'ir holatlarni aniqlashda prognostik ahamiyatga ega bo'lishi mumkin. Bundan tashqari, qonning giperkoagulyatsiyasi COVID-19 bilan kasalxonaga yotqizilgan bemorlarda keng tarqalgan. D-dimerning yuqori darajalari doimiy ravishda qayd etilishi kasallik davrida ularning bosqichma-bosqich o'sishi, ayniqsa, kasallikning yomonlashuvi bilan bog'liq. Shunday qilib, COVID-19 bilan kasallangan bemorlar ham kasalxonada, ham ambulatoriyada gematologik kasalliklarning kuchayishi xavfi yuqori, shuning uchun ushbu patologiyani erta reabilitatsiya qilish va tashxis qo'yish qat'iy tavsiya etiladi.

Kalit so'zlar: COVID-19, SARS-CoV-2, koagulopatiya, gematologik kasalliklar, limfopeniya

Since the end of 2019, an epidemic pneumonia caused by a new coronavirus has emerged in Wuhan (Hubei Province), which quickly spread throughout China, developing into a global pandemic [1,2,20,22].
Initially named the 2019 novel coronavirus (2019-nCoV), the virus was later officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the WHO.

On January 30, 2020, WHO declared the SARS-CoV-2 epidemic an epidemic. A public health emergency of international concern.

Coronaviruses are a large family of viruses, some of which are better known as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). SARS-CoV-2 viruses are positive, single-stranded RNA viruses that can be asymptomatic or lead to coronavirus disease 2019 (Covid-19). Covid-19 has a very wide range of respiratory manifestations, but also other non-specific symptoms, including fever, headache, hemoptysis, nausea, vomiting and, in particular, diarrhea, also previously identified in other coronavirus infections [3,4,20,24]. Respiratory manifestations have a wide range of infectious signs from fever, dry cough and shortness of breath to pneumonia, pulmonary edema and acute respiratory distress syndrome (ARDS), requiring hospitalization in an intensive care unit (ICU). The clinical spectrum of COVID-19 ranges from asymptomatic to mild (more than 80% of all cases) to respiratory failure requiring mechanical ventilation and multiple organ dysfunction or failure syndromes. Patients requiring admission to an intensive care unit have a high mortality rate. In terms of pathogenesis, SARS-CoV-2 recognizes angiotensin by converting the enzyme receptor 2 (ACE2) to its spike protein. ACE2 is widely expressed in human tissues, including alveolar type 2 (AT2), capillary epithelium, heart, liver, kidney, and endothelial cells [5,17,24,26]. ACE2 is also expressed in hematopoietic stem and progenitor cells [6,14,19,25]. ACE2 stimulates the mobilization of progenitor cells from the bone marrow, migration to sites of vascular injury, and revascularization of ischemic areas in pathological conditions such as hypoxic stress [6–10].

SARS-CoV-2 is also likely to enter host cells via CD147 (also known as Basigin or EMMPRIN) [9]. This CD147 has also been identified as an erythrocyte receptor for the parasite Plasmodium Falciparum [10] and a vascular receptor for Neisseria meningitidis [11]. CD147 has been described as a marker of undifferentiated embryonic stem cells [12] and is also expressed on mesenchymal stem cells [13]. In addition, a research group from Germany showed that the cellular serine protease TMPRSS2 for priming the SARS-CoV-2 spike protein is also required for host cell entry and spread [14]. Currently, there is no specific treatment for Covid-19 and understanding the effects and mechanism of invasion and spread of SARS-CoV-2 will help find new targets.

Purpose: to analyze the results of the medical activities of the hematology department during the COVID-19 pandemic.

Research Materials

From October 20, 2020 to May 20, 2021, the Bukhara branch of the Research Center for Hematology and Transfusiology was hospitalized
512 patients. At the time of admission, 507 (98.5%) patients had a negative test result for the detection of SARS-CoV-2 causative agent RNA, 13 patients were hospitalized for vital reasons without a test result for discharge from the nasopharynx. The distribution by nosology was as follows: 135 (25.5%) patients with lymphomas, 82 (16.5%) with multiple myeloma, 75 (14.2%) with acute leukemia, 51 (9.3%) with hemophilia, 11 (4%) - anemia of unknown etiology, 5 (1.8%) - Waldenström macroglobulinemia, 7 (1.7%) - aplastic anemia, 92 (16.6%) - various diseases for surgical intervention, 81 (8.8%) - other hematological diseases.

Covid-19 is a respiratory infection with significant effects on the hematopoietic system and hemostasis. Currently, the hallmark of SARS-CoV-2 pathogenesis is a cytokine storm. Indeed, plasma concentrations of interleukin-6, interleukin-1β, TNF-α, as well as granulocyte colony stimulating factor (G-CSF) or protein inducible interferon gamma (IP10) seem to be very high in patients with Covid-19 and even higher in the intensive care unit (ICU) than in patients not in the intensive care unit [15]. This release of cytokines syndrome in patients with Covid-19 is associated with a decrease in the number of lymphocytes [15]. Lymphopenia occurs in more than 80% of patients with Covid-19 at admission and may predict the severity of Covid-19 disease [17]. This lymphopenia has been associated with a significant decrease in the number of T cells (particularly CD8 + T cells i) and this significant decrease in T-lymphocyte subset is positively correlated with in-hospital mortality and disease severity [18]. It is also suggested that B-lymphocytes are involved in Covid-19, since patients with agammaglobulinemia without B-lymphocytes had a mild clinical course, in contrast to patients with various immunodeficient Covid-19 patients with advanced disease [19]. Because human B-cell memory through the CD27dull and CD27bright epitope differs with age, B-lymphocytes may be responsible for differences in response between children and adults in the early stages of COVID-19. Indeed, B cells in children are better able to generate natural antibodies to new pathogens compared to B cells in adults [20]. Coagulopathy has been described in Covid-19 as soon as the first cases were described. In relation to inflammation storm, the association between coagulopathy and inflammation may be related to thromboinflammatory mechanisms. This thrombo-inflammation has been described in arterial and/or venous thrombosis, as well as cancer-related thrombosis, a complex interaction between blood clotting and inflammation. Covid-19 infection is associated with coagulopathies characterized by increased levels of procoagulant factors such as

fibrinogen, together with a strong increase in D-dimers, associated with higher mortality. D-dimer levels above 1000 ng/mL were an independent risk factor for hospital mortality [3].

Coagulopathy has also been found in fatal cases of Covid-19 patients, including a significantly higher proportion of patients with D-dimers above 500 ng/mL and prolonged prothrombin time (PT) in non-survivors [22]. This result was also found in another Chinese population where D-dimers were still associated with in-hospital mortality [23]. Dynamics of D-dimers can also reflect the severity, elevated levels were more pronounced in severe cases [3].

Guang et al. provided data on the clinical characteristics of 1099 laboratory-confirmed COVID-19 cases during the first 2 months of the epidemic in China [3]. On admission, the vast majority of patients had lymphocytopenia (79.3%), while 29.4% had thrombocytopenia and 30.6% had leukopenia. These hematological abnormalities were more prominent among severe and non-severe cases (94.3% versus 79.6% for lymphocytopenia, 54.3% versus 29.5% for thrombocytopenia, and 60.6% versus 27.9% for leukopenia). These results were in line with four other descriptive studies conducted during the same period in China, which included 41, 99,138, and 201 confirmed cases of COVID-19, respectively. association between lymphopenia and need for an intensive care unit, while Wu et al. 20 showed an association between lymphopenia and the development of acute respiratory distress syndrome (ARDS). In particular, Wu et al. retrospectively analyzed possible risk factors for ARDS and death among 201 patients with COVID-19 pneumonia in Wuhan, China. <0.001) in 2D Cox regression analysis. An increase in neutrophils (p=0.03) was associated with an increased risk of death.

512 patients with COVID -19 detected hematological pathologies 224 (43%) were patients with newly diagnosed diseases. In order to verify the diagnosis, the following were performed: 89 sternal punctures, 43 lumbar punctures, 95 central venous catheters were installed. Among 512 hospitalized patients, the distribution by nosology was as follows: 130 (25.5%) patients with lymphomas, 82 (16.5%) with multiple myeloma, 75 (14.2%) with acute leukemia (32 with acute myeloid leukemia (AML) ,35 - acute lymphoblastic leukemia (ALL), 8 - acute promyelocytic leukemia (APL)), 86 (9.3%) patients with hemophilia, 11 (4%) - anemia of unknown etiology, 5 (1.8%) - Waldenström macroglobulinemia , 7 (1.7%) - aplastic anemia, 78 (16.6%) - various diseases admitted for surgical intervention, 68 (8.8%) - other hematological diseases (9 - immune thrombocytopenia (ITP), 7 - myeloproliferative diseases, 4 - chronic lymphocytic leukemia (CLL), 5 - myelodysplastic syndromes (MDS), 7 - autoimmune hemolytic anemia (AIHA), 2 - acute porphyria, 3 - paroxysmal nocturnal

hemoglobinuria (PNH), 13 - chronic myeloid leukemia (CML), 3 - thrombotic thrombocytopenic purpura (TTP), 2 - microspherocytosis, 2 - beta-thalas family, 1 — hypereosinophilic syndrome) ($p < 0.05$).

Of the 512 patients admitted to the observational department, 79 (15%) were hospitalized in serious condition, 312 (71%) in moderate condition. In 87 (13.5%) patients, fever was noted at the time of admission. 419 patients underwent computed tomography (CT) of the chest, and in 73 (15%) of them fresh inflammatory changes in the lungs were found. 12 (2.6%) patients infected with SARS-CoV-2 were identified (in 20 patients, COVID-19 was identified by the polymerase chain reaction (PCR) method, in 4 patients, according to the CT scan of the chest organs.

In 10 patients, a positive result was detected during a routine examination or when fever was detected in a specialized department. Thus, a targeted examination for COVID-19 in the form of a double PCR study for SARS-CoV-2 and a CT scan of the chest organs made it possible to additionally identify 2.6% of patients with COVID-19, despite a negative test result before admission to the clinic.

Conclusion. Since the COVID pandemic in survivors of hematological patients, due to impaired hemostasis in patients with impaired primary hemostasis, the number of inpatients and their days of inpatient treatment has increased. It is necessary to carefully monitor patients before hospitalization and timely conduct hematological studies despite the negative result of PCR. Thus, there are four important aspects of the management of patients with COVID-19: early diagnosis and follow-up of DIC using blood parameters (platelet count, prothrombin time, fibrinogen, D-dimer monitoring), which can determine the prognosis. In conclusion, COVID-19 disease has prominent hematopoietic manifestations and is often associated with marked hypercoagulability of the blood.

Careful assessment of laboratory parameters at baseline and during the course of the disease can help clinicians develop an individual approach to treatment and timely provision of intensive care to those who need it most. Prophylactic thromboprophylaxis and early detection of potentially lethal complications, including DIC, for effective intervention will improve patient outcomes and likely reduce mortality overall and among infected patients without significant comorbidities.

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