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The possibility of predicting the COVID-19 severity by clinical-laboratory criteria taking into account the SARS-CoV-2 strain: An analytical review

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ABSTRACT

The survival of patients with severe COVID-19 depends on timely and adequate assessment of the risk of adverse disease outcomes. Currently, conflicting data on the prognostic value of various laboratory parameters in severe COVID-19 caused by different SARS-CoV-2 variants require analysis and systematization. The leading clinical and laboratory signs that determine the severity of COVID-19 include the syndrome of systemic inflammatory reaction and hemostasis disorders, which, in conditions of high viral load, hypoxia, and toxic exposure, contribute to the development of cytolytic syndrome, cytopenia, and multiple organ failure. Biological and immunological features of SARS-CoV-2 variants have an important influence on the severity of the infection. Based on literature sources, we have listed the most significant laboratory parameters, which, combined with clinical criteria, serve as an accurate guide for physicians both in monitoring patients and selecting therapy in Russia and abroad. Some SARS-CoV-2 variants exhibit reduced susceptibility to monoclonal antibodies and recombination plasma, which requires a revision of the therapy strategy. Detailed analysis of pathognomonic laboratory parameters and understanding of the immunological response to a particular SARS-CoV-2 variant will quickly and accurately identify the vulnerable patient groups, timely change in their therapy, and prevent complication development.

Keywords: severe COVID-19; laboratory predictors; SARS-CoV-2 strains; Wuhan strain; alpha variant; beta variant; gamma variant; delta variant; omicron variant; COVID-19 treatment.

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Возможность прогнозирования тяжести течения COVID-19 по клинико-лабораторным критериям с учётом штамма SARS-CoV-2: аналитический обзор

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АННОТАЦИЯ

Выживаемость пациентов с COVID-19 тяжёлого течения зависит от своевременной и адекватной оценки риска развития неблагоприятного исхода заболевания. Накопившееся в настоящее время большое количество противоречивых данных о прогностическом значении различных лабораторных показателей при тяжёлом течении COVID-19, вызываемого различными штаммами SARS-CoV-2, требует их анализа и систематизации. Показано, что ведущими клинико-лабораторными признаками, определяющими тяжесть течения COVID-19, являются синдром системной воспалительной реакции и нарушения гемостаза, которые в условиях высокой вирусной нагрузки, гипоксии и токсического воздействия способствуют развитию цитолитического синдрома, цитопении и полиорганной недостаточности. Немаловажное влияние на тяжесть течения инфекционного процесса оказывают биологические и иммунологические особенности различных штаммов SARS-CoV-2. На основании литературных источников перечислены общепринятые в нашей стране и за рубежом наиболее значимые лабораторные показатели, которые в сочетании с клиническими критериями служат точным ориентиром для врачей как при наблюдении за состоянием пациентов, так и для подбора терапии. Некоторые из штаммов возбудителя SARS-CoV-2 демонстрируют пониженную восприимчивость к моноклональным антителам и реконвалесцентной плазме, что требует пересмотра стратегии терапии. Детальный анализ патогномоничных лабораторных параметров и понимание иммунологического ответа на конкретный штамм возбудителя SARS-CoV-2 позволят быстро и точно выявить уязвимые группы пациентов, своевременно изменить у них проводимую терапию и предотвратить развитие осложнений.

Ключевые слова: тяжёлое течение COVID-19; лабораторные предикторы; штаммы SARS-CoV-2; уханьский штамм; альфа-вариант; бета-вариант; гамма-вариант; дельта-вариант; омикрон-вариант; лечение COVID-19.

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INTRODUCTION

Coronaviruses (Coronaviridae) are a family of RNA-containing viruses that can cause diseases in humans, with various manifestations, ranging from asymptomatic carriage and mild forms of acute respiratory viral infection to severe acute respiratory syndrome with multiorgan damage [1]. The clinical presentation of a novel coronavirus disease 2019 (COVID-19) is influenced by a multitude of factors, including the individual susceptibility of the host to the pathogen and the presence of diverse antigens that determine the spectrum of pathogenic targets in the human body, contingent on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain. The SARS-CoV-2 outbreak was first reported in December 2019 in Wuhan, People's Republic of China. By March 2020, it had spread to most countries worldwide and was recognized as a pandemic by the World Health Organization [2]. Pneumonia caused by SARS-CoV-2 was characterized by the involvement of a large volume of lung tissue and rapidly progressive respiratory failure [3].

The accepted clinical criteria for severe COVID-19 are as follows: body temperature of ⩾39°C, decreased consciousness, agitation, respiratory rate of ⩾30 breaths per min, oxygen saturation (SpO_2) of ⩽93%, and oxygenation index (PaO_2/FiO_2) of ⩽300 mm Hg. Furthermore, patients must present with one or more of the following: unstable hemodynamics (systolic blood pressure of <90 mmHg or diastolic blood pressure of <60 mmHg), diuresis of <20 mL/h, and arterial blood lactate level of >2 mmol/L. Typical lung lesions, as identified through computed tomography (CT), and organ failure, as indicated by the quick sequential organ failure assessment scale, are considered pathognomonic [1, 4]. Statistical data indicate a mortality rate of 85% [3, 5]. In light of this, prompt and accurate assessment of the risk of a poor outcome from COVID-19 and adjusting the current treatment plan accordingly are necessary. The concept of general laboratory diagnostics in conjunction with the results of clinical and instrumental methods of investigation is presented in the Temporary Methodological Recommendations of the Ministry of Health of the Russian Federation [1]. Conflicting data on the prognostic value of various laboratory parameters in severe COVID-19, caused by different SARS-CoV-2 strains, necessitate analysis and systematization to determine the most significant criteria to for the draw up a laboratory chart of patient examination and predict complications in early disease stages.

EVOLUTION OF IDEAS ABOUT LABORATORY PREDICTORS OF SEVERE COVID-19

At the outset of the pandemic, Chinese scientists observed that patients with an unfavorable COVID-19 course exhibited a more pronounced increase in the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin (IL)-6, ferritin, and D-dimer, accompanied by a notable reduction in lymphocyte, platelet, and leukocyte counts. These indicators are correlated with the increasing intensity of the inflammatory process, disease severity, and mortality [3, 5, 6]. IL-6 is the most significant laboratory marker for assessing the clinical picture of COVID-19 [7]. Furthermore, simultaneous elevation in IL-6 levels above 40–100 pg/mL and CRP levels >10 mg/L is associated with pronounced cytokine storm and severe complications [8, 9]. Furthermore, numerous researchers have demonstrated that sustained elevated levels of proinflammatory mediators, including granulocyte-colony stimulating factor, IP-10, IL-2, IL-7, IL-10, MCP-1, MIP1A, and tumor necrosis factor-α, exacerbate lung tissue injury and stimulate the coagulation cascade, thereby precipitating multiorgan failure and markedly worsening the prognosis [1, 10]. In light of the findings of recent studies, a hypothesis suggested that the deterioration of patients with COVID-19 is associated with the development of a hyperinflammatory response and the suppression of components of the anti-inflammatory profile, particularly IL-10 [11].

High procalcitonin levels are indicative of a secondary bacterial infection, which is a further indicator of advanced inflammation. This biomarker demonstrates greater sensitivity and specificity than CRP and IL-6 [1, 12]. Serum amyloid A, a nonspecific acute phase protein, is also a promising prognostic criterion for immunologic tissue damage in COVID-19 [13]. Some authors have demonstrated a correlation between the degree of systemic inflammation and ferritin level. This increase is caused by hemolysis of erythrocytes in pulmonary vessels. An increase in ferritin level >1,000 μg/L is a specific predictor of the development of acute severe respiratory distress syndrome [1, 8]. Ferritin levels >700 μg/L are pathognomonic indicators of increasing severity and mortality risk in patients with comorbid pathologies such as arterial hypertension, type 2 diabetes mellitus, and coronary heart disease [1, 12, 14].

The accessibility of the general clinical blood test is a significant factor that influences the level of interest in studying the prognostic value of its individual parameters. In the context of erythropenia, the relationship between the severity of the course and low hemoglobin levels is currently a subject of debate [15]. Several studies have indicated that one of the key indicators of a more severe COVID-19 is a significant reduction in lymphocyte count, with <1,000/μL of blood. This reduction is found to be significantly correlated with disease severity, with levels as low as 0.60 thousand per microliter of blood being observed in extremely severe cases [3, 5, 6, 16]. The lowest levels of these blood cells were observed on day 7 of the disease. Subsequently, in instances of recovery, the number of lymphocytes increased, whereas in patients with a fatal outcome, severe lymphocytopenia persisted [17]. The study of lymphocyte subpopulations in severe COVID-19 revealed a decrease in

the main immunologic parameters CD4+ and CD8+ T cells, B cells, and NK cells. The strong negative correlation between the levels of lymphocytes and CD8+ T-cells with ESR, CRP, and IL-6 indicates that these cells and their subpopulation may serve as potential predictors of disease severity and as important clinical efficacy indicators for therapy [1, 6]. CD4+ T-lymphocytes are vital components in the regulation of cellular and humoral immunity. A reduction in this subpopulation has been demonstrated to result in the inhibition of INF-γ production [6, 18].

Significant alterations in the leukocytic formula were observed in patients with severe COVID-19. Consequently, a high neutrophil-to-lymphocyte ratio (>7.75) was observed in patients with suppressed immune responses, which may serve as a predictor of adverse outcomes [19, 20]. In patients with an extremely severe disease, in addition to leukopenia, eosinopenia was observed, which is likely due to pronounced viral and toxic suppression of hematopoiesis. Eosinopenia in combination with high CRP levels may be a sensitive and specific marker for assessing COVID-19 severity [21]. Leukocytosis in the general blood count is indicative of the activation of a concomitant bacterial infection and/or superinfection [5]. Thrombocytopenia of $<150x10^9$/L and prolonged prothrombin time to >13 s are associated with a high risk of mortality, and thrombocytosis with an increased platelet-to-lymphocyte ratio may indirectly indicate a high risk of cytokine storm [22].

A syndrome as prognostically significant as hypercoagulability demands special attention [1, 17, 23]. Therefore, a high D-dimer level and hyperfibrinemia are of primary importance [19, 23]. An increase in D-dimer levels by 1.5 times is associated with a high risk of developing severe COVID-19 [19]. Values of this index exceeding two norms are correlated with high mortality [17]. D-dimer levels exceeding three norms have been proposed as a means of predicting the asymptomatic development of deep vein thrombosis of the lower extremities and the occurrence of venous thromboembolism [24]. The rising leves of plasmin and plasminogen, which are bioindicators of heightened susceptibility to SARS-CoV-2 [25], were observed earlier and clinically significant in the evaluation of criteria for COVID-19 severity. The development of thrombosis in the small pulmonary microcirculatory bed, which is a consequence of hypercoagulability, leads to the progression of pulmonary hypertension and respiratory failure in patients with COVID-19. This process largely determines the prognosis of this disease [23, 24, 26]. Furthermore, hyperfibrinogenemia correlates with the severity of the inflammatory response and the IL-6 level [26]. However, in extremely severe cases, fibrinogen levels markedly reduced, with a decrease of <1 g/L, which significantly elevates the risk of hemorrhagic complications. A disruption in the coagulation process at the terminal stage of COVID-19 is evidenced by profuse bleeding in various organs [8]. In this regard, several researchers have highlighted the need for regular monitoring of D-dimer levels, prothrombin time, fibrinogen, and platelet count to predict the disease course and risk of complications associated with COVID-19 [27].

Russian scientists have proposed a theory regarding the relationship between severe COVID-19 and one of the main components of the hemostasis system, von Willebrand factor. An increase in its concentration in the blood is indicative of the severity of vascular endothelial damage and dysfunction [28]. An increase in homocysteine concentration is presumed to lead to an increased risk of thromboembolism and the progression of hemostasis disorders [29].

Research has been dedicated to the examination of key blood biochemical parameters in COVID-19 cases. These studies have identified alterations in biochemical indices suggestive of myocardial, liver, and kidney damage [5, 10]. However, the relationship between these indices and disease severity remains inconclusive. Despite a tendency for these indices to increase in patients with severe disease, the precise role of these biochemical changes in the pathogenesis of disease severity remains to be elucidated. Notably, hyperglycemia has a deleterious effect on the prognosis of patients with COVID-19, with an incidence >90% in complicated cases [10, 19]. A sustained elevation in blood glucose levels results in an augmented inflammatory response and increased production of cytokines, which subsequently induce the destruction of the vascular wall endothelium and enhanced procoagulant activity [30]. The extent of hyperglycemia correlates with the severity of leukocytic dysfunction and is accompanied by reduced bactericidal activity of the blood. A strong positive correlation was identified between glycemia levels >17 mmol/L and high hospital mortality in patients admitted in intensive care units, as reported by Russian researchers [31].

The laboratory parameters of glial fibrillary acidic protein and serum neuron-specific enolase were indicative of a breach in blood–brain barrier permeability and central nervous system damage [32]. The combination of specific neuroinflammation and prolonged hypoxia can lead to the development of neurological disorders and significantly worsen the condition of patients [33]. Reduced levels of vitamin D, which helps regulate cytokine secretion, and the production of antimicrobial peptides and antioxidants may affect the hemostasis system and increase the thrombosis risk [34]. However, compelling and conclusive evidence to support this hypothesis is lacking. The critical values of the most significant laboratory parameters are presented in Table 1.

A systemic analysis of laboratory predictors of severe COVID-19 indicates that isolated laboratory parameters are inadequate for the timely identification of patients with an unfavorable prognosis of this disease. The monitoring of patients with COVID-19 and evaluation of the effectiveness of therapy should be performed according to both clinical and laboratory criteria, which should be multifactorial.

Table 1. Most significant laboratory predictors of COVID-19 severity

Laboratory values	Reference values	Severe COVID-19
Erythrocyte sedimentation rate, mm/h	2–20	⩾52.5 [35]
Leukocytes, $\times 10^9$/L	4.5–11.0	>11.0 [5]
Lymphocytes, thousand/μL	1.2–4.8	⩽1.0 [6, 16]
Neutrophil-lymphocyte ratio	0.78–3.53	>7.75 [19, 20]
Platelets, $\times 10^9$/L	180–320	<150 [22]
Prothrombin time, s	9.0–15.0	>13.0 [22]
D-dimer, ng/mL	<243	>850 [19]
Fibrinogen, g/L	2.0–4.0	>4.0 [19]
C-reactive protein, mg/L	0–5.0	⩾41.8 [9]
Ferritin, ng/mL	Men: 20–250 Women: 10–220	⩾464.5 [36]
Lactate dehydrogenase, U	90–180	⩾255.5 [36]
Interleukin-6, pg/mL	<7.0	⩾32.1 [9]
Procalcitonin, ng/mL	<0.05	>0.22 [19]
Glucose, mmol/L	4.1–6.0	>9.0 [19]
Lactate, mmol/L	0.5–2.2	>2.0 [19]
Vitamin D, ng/mL	>30.0	<9.9 [19]
CD4+ T-cells, c/mL	500–1500	<400 [6, 18]
CD8+ T-cells, c/mL	300–700	<200 [6, 18]

COMPARATIVE ANALYSIS OF CLINICAL AND LABORATORY FEATURES OF COVID-19 ACCORDING TO THE SARS-COV-2 STRAIN

Different SARS-CoV-2 strains play an important role in the severity of the infection and development of COVID-19. The first variant, isolated from samples of patients hospitalized in Wuhan in December 2019, is the reference genome for all subsequent sequences derived from sequencing [1]. Multiple mutations in the SARS-CoV-2 spike protein modify the biological and immunogenic properties of the virus, which is critical in shaping the clinical picture of the disease and determining the peculiarities of the response of the macroorganism. The lack of a sustained immune response in both immunized and vaccinated individuals is a significant factor in the continuous circulation of SARS-CoV-2 strains in the population [37]. Currently, >1000 genetic lines of SARS-CoV-2 have been registered worldwide, and most of them are not pathogenic for humans. More than 80 such strains have been detected in Russia [1]. Strain variants that can induce the development of a more severe form of COVID-19 are designated as variants of concern (VOCs) [4, 37].

The alpha strain (lineage B.1.1.7.), first reported in the UK in September 2020 and Russia and the USA 2 months later, has 17 mutations relative to the Wuhan strain. Eight of these mutations are in the spike protein, which increases the affinity of the virus to angiotensin-converting enzyme type 2 receptors, enhancing virus attachment and subsequent penetration into the tropic cells of the host [37, 38]. This variant was associated with higher infectivity, faster rate of spread, more severe course, and higher mortality rate. A comparative multivariate analysis of severe COVID-19 caused by the alpha variant and the Wuhan strain revealed that patients infected with B.1.1.7 were significantly younger and had fewer comorbidities, including arterial hypertension, diabetes mellitus, hyperlipidemia, lung disease, heart failure, myocardial infarction, chronic kidney disease, and immunodeficiency, than patients infected with the Wuhan strain (Table 2). In patients with B.1.1.7, CT revealed a higher percentage of lung tissue lesions, resulting in severe hypoxia (70.0% vs. 62.5%, p=0.029). This was reflected in the disease severity and increased mortality [36, 40, 41]. In patients with B.1.1.7, symptoms such as myalgia, encephalopathy, and anxiety–depressive disorders were significantly more frequently reported and persisted longer than in other groups, whereas dysgeusia and anosmia were quite rare. Another distinguishing feature in this group was the presence of pruritic exanthem on the hands and abdomen [38, 41, 43]. Regarding laboratory parameters, higher levels of CRP, ferritin, lactate dehydrogenase, and lymphopenia were diagnostically significant in the group infected with B.1.1.7. The dynamics of these parameters were considered when predicting the risk of worsening patients' condition and when making timely changes to therapy techniques for this strain [36, 40]. The neutralizing activity of both the plasma of recovering patients and sera of vaccinated persons for the

Table 2. Comparative analysis of clinical-laboratory COVID-19 features depending on the SARS-CoV-2 strain

Indicators	Alpha	Beta	Gamma	Delta	Omicron
Contagiousness	↑↑	↑	↑↑↑	↑↑	↑↑↑↑
Severity of course, degree of laboratory indexes change	↑↑	↑↑	↑↑	↑↑↑↑	↓↓
Neutralizing activity of monoclonal antibody preparations	↓ insignificantly	↓↓↓, only a combination of casirivimab and imdevimab	↓↓↓↓, complete resistance	↓↓, only etesevima	↓↓↓, only a combination of sotrovimab and tixagevimab + cilgavimab (Evushelda)
Virus isolation from the respiratory tract	13 days	14 days	15 days	18 days	↓↓↓ 8 days

Note. ↑↓ — compared to the original Wuhan strain.

alpha variant was slightly reduced, yet retained sensitivity in vitro to monoclonal antibodies against SARS-CoV-2 [38, 44].

The beta variant (lineage B.1.351) was initially identified in the Republic of South Africa in December 2020, which subsequently became a predominant strain. The presence of nine mutations in the beta variant resulted in increased infectivity and the ability to evade postvaccine and postinfection antibodies [4, 39, 45]. One year later, the beta variant ranked second in prevalence worldwide, having been reported in >90 countries [37, 39]. Studies have indicated that young people with comorbidities and more severe disease are more susceptible to the beta variant [46].

Scientists were particularly concerned about the gamma strain (lineage P.1, descendant of B.1.1.28), which also emerged in Brazil in December 2020 and exhibited 10 mutations in the spike protein. Notably, three of these mutations were observed in the receptor-binding domain, which are responsible for connecting the coronavirus to the angiotensin-converting enzyme type 2 in human cells. The high affinity of the virus for cell receptors increased its infectivity. The location of most mutations in the most immunogenic domains of the S-protein increases susceptibility to this strain in those who have previously been infected with the alpha and beta variants, reduces the efficacy of vaccines, and negatively affects therapy with monoclonal antibodies [47, 48]. The gamma strain is 2.5–10.0 times more transmissible than the original Wuhan line, more contagious than the alpha and beta variants, and can cause re-infection within a short period after the disease. This strain is associated with higher virulence and a high risk of blood clots in the blood vessels of the intestine and extremities. It is severe even in healthy young people and pregnant women and correlates with high mortality. In Russia, the beta and gamma variants were introduced in March and May 2021, respectively; however, they have not been widely disseminated [37, 38]. The overall trend of the main laboratory parameters in a cohort study of patients hospitalized with alpha, beta, and gamma strains was identical [49–51]. However, the beta and gamma strains exhibited resistance to the primary group of monoclonal antibodies authorized for emergency use, including bamlanivimab, etesevimab, and casirivimab. However, the combined use of casirivimab and imdevimab markedly reduced the activity of the beta strain, but did not affect the gamma variant [45, 52].

The delta coronavirus strain (lineage B.1.617.2) was first identified in November 2020 in Navapur, India. It rapidly became the dominant strain, spreading at a rate 60% faster than the alpha strain. The initial cases of the delta strain in Russia were documented in April 2021, and by the fall of that year, its prevalence had reached 98.4%. The virus exhibited 10 significant mutations in the spike protein and numerous additional spike mutations, which enhanced its capacity to evade immune response [37, 39, 53]. This variant is distinguished by a brief incubation period, high viral load, and longer duration of virus excretion [49]. This variant exhibited a rapid, acute disease onset and a higher frequency of complications. The most prevalent clinical symptoms were marked lung damage, as indicated by CT scans and a lower PaO_2/FiO_2 ratio [54]. Gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain were the most notable [4, 39]. The lethality of the delta strain has increased significantly. Laboratory parameters also demonstrated a more aggressive trend, exhibiting significantly high lymphopenia, high platelet distribution width, thrombocytopenia, and increased of CRP and lactate dehydrogenase (LDH) levels [49, 54]. The delta strain was associated with a high percentage of acute coronary syndrome occurrence. The following parameters could be used as laboratory predictors of patient deterioration: the ratio of CRP to D-dimer of ⩾51.6, the ratio of ferritin to lymphocytes of ⩾134.5, and the ratio of CRP to lymphocytes of ⩾19.3 [55]. This variant exhibited reduced sensitivity to monoclonal antibodies relative to the alpha strain and the original Wuhan strain [56]. Consequently, bamlanivimab was found to lack neutralizing activity, whereas etesevimab demonstrated favorable efficacy [53, 57].

The next VOC is the omicron strain (lineage B.1.1.529), which was first identified in November 2021 in South Africa and has since become a persistent global presence. It has numerous mutation subtypes, including cerberus BQ1, centaur, kraken, and stealth [37, 39, 58]. In total, 30 mutations have been identified in the spike protein, encompassing alterations in the envelope, nucleocapsid protein, matrix, spike fusion peptide, and its N-terminal and receptor-binding domains. The omicron variant demonstrated a 13-fold increase in viral infectivity, exhibiting a 2.8-fold higher infectiousness than the delta variant. It is the most prevalent and dominant strain in numerous countries [58, 59]. Patients infected with the omicron strain who require hospitalization tended to be older. In most cases, the disease is more easily tolerated, and pulmonary tissue is rarely affected, as confirmed by CT [50, 58]. The omicron variant was distinguished by the shortest period of virus excretion [60]. As with the alpha and delta strains, the omicron strain was associated with a significantly lower prevalence of olfactory dysfunction, yet a higher incidence of neurocognitive disorders, including confusion, anxiety–depressive disorders, and myalgia [58, 59, 61]. In addition to older patients, the risk group for a severe course with this strain includes children and people with chronic diseases. The risk of lethal outcomes is low [59]. Nearly all monoclonal antibody preparations demonstrated a lack of efficacy against the omicron variant, which was the reason for their rejection. However, sotrovimab and tixagevimab + cilgavimab retain some neutralizing activity against this strain [57, 59, 62].

In light of the above analysis of the clinical and laboratory features of SARS-CoV-2, the results imply tahat the high mutational activity of the virus results in a constant change in its transmissibility and human susceptibility. This, in turn, leads to modifications in the main pathogenetic processes, which causes large variabilities in the spectrum and severity of clinical syndromes.

CONCLUSIONS

Therefore, the primary clinical and laboratory indicators that determine the severity of a patient's course with COVID-19 are the syndrome of systemic inflammatory response and hemostasis disorders. In patients with high viral loads, hypoxia, and toxic effects, these disorders can lead cytolytic syndrome, cytopenia, and multiple-organ failure. A comprehensive analysis of laboratory predictors of severe COVID-19 indicates that isolated laboratory parameters are insufficient for timely identification of patients with an unfavorable prognosis. Universal pathognomonic markers in assessing disease severity include the number of lymphocytes, platelets, and leukocytes; levels of CRP, ferritin, and D-dimer; and the presence of specific SARS-CoV-2 strains. The latter demonstrates reduced susceptibility to treatment with monoclonal antibodies and plasma of convalescents, necessitating constant revision of therapy approaches.

ADDITIONAL INFORMATION

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