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An experience of using Laennec in patients at high risk of a cytokine storm with COVID-19 and hyperferritinemia

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Abstract

The probability of formation of the so-called "cytokine storm" accompanied by an avalanche-like growth of inflammatory markers – interleukins (IL)-1β, -6, interferon-γ, tumor necrosis factor-α, C-reactive protein (CRP), ferritin, etc. is high at a heavy current of COVID-19. In the absence of adequate treatment in the development of "cytokine storm" increases the risk of death, especially against the background of comorbid pathology. **Methods.** In April–May 2020, patients (n = 28: 12 men, 16 women; age 39 – 86 years) with long, chronic COVID-19 course were under observation, hospitalized on critical days of the disease. All patients reported anosmia, cough with poor sputum, signs of conjunctivitis. The patients had chronic diseases (n = 22: coronary heart disease, diabetes mellitus type 2, scleroderma). All patients were given standard therapy; half (n = 14) were additionally prescribed Laennec for 3 – 10 days (6 mL per 350 mL of 0.9% NaCl solution, intravenous infusion for the first 3 days, from day 4 – 6 mL per 250 mL of 0.9% NaCl solution) until stable remission is achieved. **Results.** The majority state (n = 25) stabilized; several patients died in the control group (n = 3; p = 0.067). In spite of the state stabilization, no reliable positive dynamics was noted in the control group for the tested parameters. Initially, liver dysfunction (level of alanine aminotransferase (ALT) – 113 ± 121, aspartate aminotransferase (AST) – 90.8 ± 87) was registered in 71% of patients, 8 U/L) and high risk of "cytokine storm" development (ferritin levels in men – 480 – 1,072 μg/L, in women – 274.7 – 493 μg/L, C-reactive protein – 5.0 – 52.6 mg/L, lymphocytes – < 25%). Positive clinical dynamics, a decrease in the level of ferritin (–282 μg/L – in men, –80 μg/L – in women; p = 0.039), an increase in blood oxygenation to normal values (p = 0.0029), a decrease in the area of lung injury according to CT data (on average – 10%); p = 0.0027), increase in relative lymphocyte content (+8%; p = 0.04), normalization of markers of liver dysfunction (AST, ALT), creatinine and systolic blood pressure (p < 0.05) were observed on prescription of Laennec. All patients who received Laennec recovered within 3 – 15 days from the start of the drug and were discharged with a negative test for SARS-CoV-2. **Conclusion.** Health condition is significantly improved, a wide range of hepatoprotective, immunomodulatory and regenerative effects are observed when the polypeptide Laennec is included in the complex therapy in patients with severe COVID-19. Laennec should be used primarily in patients with liver pathology, diabetes mellitus type 2, coronary heart disease, including high ferritin levels.

Key words: COVID-19 therapy, comorbid conditions, ferritinemia, Laennec, predictive modeling, intellectual data analysis.

Conflict of interests. The authors declare the absence of conflict of interests.

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Опыт применения препарата Лаеннек у пациентов с высоким риском развития «цитокинового шторма» на фоне COVID-19 и гиперферритинемии

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Резюме

При тяжелом течении COVID-19 высока вероятность формирования т. н. «цитокинового шторма», сопровождающегося лавинообразным нарастанием маркеров воспаления – интерлейкинов (IL)-1β, -6, интерферона-γ, фактора некроза опухоли-α, С-реактивного белка (СРБ), ферритина и др. В отсутствие адекватного лечения при развитии «цитокинового шторма» повышается риск летального исхода, особенно на фоне коморбидной патологии. **Материалы и методы.** В апреле–мае 2020 г. под наблюдением находились пациенты (n = 28: 12 мужчин, 16 женщин; возраст – 39 – 86 лет) с длительным, застойным течением COVID-19, госпитализированные в критические дни заболевания. У всех пациентов отмечены потеря обоняния, кашель со скудной мокротой, признаки конъюнктивита. У больных отмечались хронические заболевания (n = 22: ишемическая болезнь сердца, сахарный диабет 2-го типа, склеродермия). У всех пациентов проводилась стандартная терапия; половине (n = 14) дополнительно назначался препарат Лаеннек в течение 3–10 суток (6 мл на 350 мл 0,9 % раствора NaCl, внутривенно капельно в первые 3 дня, с 4-го дня – 6 мл на 250 мл 0,9 % раствора NaCl) до достижения устойчивой ремиссии. **Результаты.** Состояние большинства (n = 25) стабилизировалось; несколько в группе контроля скончались (n = 3; p = 0,067). Несмотря на стабилизацию состояния, в группе контроля достоверной положительной динамики по исследованным параметрам не отмечено. Исходно у 71 % пациентов отмечены дисфункция печени (уровень аланинаминотрансферазы (АЛТ) – 113 ± 121, аспартатаминотрансферазы (АСТ) – 90,8 ± 87,8 ед. / л) и высокий риск развития «цитокинового шторма» (уровень ферритина у мужчин – 480–1 072 мкг / л, у женщин – 274,7–493 мкг / л, С-реактивного белка – 5,0–52,6 мг / л, лимфоцитов – < 25 %). При назначении препарата Лаеннек наблюдалась положительная клиническая динамика, отмечено снижение уровня ферритина (–282 мкг / л – у мужчин, –80 мкг / л – у женщин; p = 0,039), увеличение оксигенации крови до нормальных значений (p = 0,0029), снижение площади повреждения легких по данным компьютерной томографии (в среднем –10 %; p = 0,0027), повышение относительного содержания лимфоцитов (+8 %; p = 0,04), нормализация маркеров дисфункции печени (АСТ, АЛТ), креатинина и систолического артериального давления (p < 0,05). Все пациенты, получавшие Лаеннек, выздоровели в течение 3–15 дней с начала применения препарата и были выписаны с отрицательным тестом на вирус SARS-CoV-2. **Заключение.** При включении полипептидного препарата Лаеннек в комплексную терапию у пациентов с тяжелым течением COVID-19 существенно облегчается состояние здоровья, наблюдается широкий спектр гепатопротективных, иммуномодуляторных и регенеративных эффектов. Лаеннек следует использовать в первую очередь у пациентов с патологией печени, сахарным диабетом 2-го типа, ишемической болезнью сердца, в т. ч. на фоне повышенного уровня ферритина.

Ключевые слова: терапия COVID-19, коморбидные состояния, ферритинемия, Лаеннек, предиктивное моделирование, интеллектуальный анализ данных.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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In 2019, the world was faced with COVID-19 – a previously unknown and highly contagious respiratory viral infection that implies risks of serious complications (primarily in patients with chronic diseases in presence of high levels of inflammation). Unlike other respiratory diseases, COVID-19 can be asymptomatic or relatively mild in most patients. However, COVID-19 causes severe pneumonitis and acute respiratory failure in a number of patients. The main goal of therapy is to prevent death. Various methods of treating the coronavirus infection are being currently tested.

Multiple organ pathology is inherent in the COVID-19 infection. In addition to damage to the lung tissue and the resulting respiratory dysfunctions, there are *dysfunctions of other organ systems*, including:

- impaired blood coagulation profile (including increased D-dimer levels) and disseminated intravascular coagulation [1];
- "cytokine storm", an avalanche-like increase in the levels of multiple inflammation markers in the blood (IL-1β, IL-6, CRP, TNF-α, IFN-γ, ferritin, etc.);
- liver dysfunction involving increased levels of AST and ALT markers, albumin and bilirubin [2] and gastrointestinal symptoms (nausea, vomiting, diarrhea);
- damage to the parenchima of the kidneys, heart and of the other organs [3, 4].

These multiple organ complications are associated with severe COVID-19 and a higher risk of death [5]. A faster treatment of these COVID-19 complications requires the use of certain pharmacological medications. Unfortunately, each of the above complications requires the use of separate drugs leading to inevitable polypharmacy that implies multiple and quite unwanted drug-drug interactions and an increase in the iatrogenic load on the hepatobiliary system.

Therefore, it is essential to make the right choice of a drug for the treatment of patients with COVID-19 in presence of multiple organ pathology, in order to tackle the main challenge of COVID-19 therapy, i.e. to decrease mortality. In our opinion, the polypeptide drug Laennec (ATX A05BA Drugs for the treatment of liver diseases, L03 Immunostimulants), developed by Russian and Japanese scientists, has a significant potential in the therapy of COVID-19.

Laennec is registered in Russia as a hepatoprotector and immunomodulator that increases the functional activity of phagocytes and T-cells, and prevents the death of hepatocytes and other parenchymal cells. Laennec is characterized by a high degree of pharmaceutical standardization and a multidirectional therapeutic effect. According to the nosological classification, Laennec (ICD-10) is indicated for patients *with liver diseases* (K76.9 Liver disease, unspecified, K70.0 Alcoholic fatty degeneration of the liver, K76.0 Fatty liver degeneration, not classified elsewhere), viral infections (B00.9 Herpesviral infection, unspecified) and diseases characterized by an *increased background of inflammation, including allergic* (L20 Atopic dermatitis) [6]. Accordingly, Laennec has the potential to

compensate for the multiple organ pathology associated with COVID-19.

The purpose of this study is to test the use of Laennec in middle-aged and elderly patients with a long and stagnant course of COVID-19 with liver dysfunction, hyperferretinemia and with a high risk of cytokine storm against the background of a high comorbid load (chronic diseases were in 22 (79%) of 28 patients). The patients were followed up in April and May, 2020.

Materials and methods

A group of patients with a moderate/severe course of COVID-19 (n = 28) had been treated at the COVID center deployed at the Russian Gerontological Research and Clinical Center (RGRCC). Patients aged 39 to 86 (12 men, 16 women) were observed; 12 patients suffered from ischemic heart disease (IHD), 8 had type 2 diabetes mellitus (T2DM), one patient had multiple sclerosis, and one patient had psoriasis. All patients received complex therapy in keeping with the 5th version of the Guidelines of the Ministry of Health of the Russian Federation as of April 08, 2020; full blood cell count and biochemical blood tests were performed using standard methods; ferritin was determined spectrophotometrically by enzyme immunoassay.

Patients had liver dysfunction (mean ALT values 113 ± 121 U/L, AST 90.8 ± 87.8 U/L) and a high risk of cytokine storm: CRP 5 – 52.6 mg/L, the relative lymphocyte count less than 25 in 71% of patients; ferritin (men) was 480 – 1,762 mcg/L, ferritin (women) was 274.7 – 493 mcg/L (given the references intervals of 20 – 250 mcg/L for men and 10 – 120 mcg/L for women). General and biochemical blood tests were performed using standard methods; ferritin was determined spectrophotometrically by enzyme immunoassay.

From the first day of the disease, all patients reported lack of appetite; increasing, overwhelming weakness that would not subside after sleep; sweating, and muscle pain. All patients showed loss of smell, cough with scanty sputum, and signs of conjunctivitis. On examination, dyspnea at rest was noted aggravated by exertion (walking, climbing stairs). The patients were underactive and quickly got tired. The patients had an increased temperature (37 – 39 degrees during 2 to 5 days), skin pallor, and rapid breathing. The semi-sitting position made breathing easier.

Upon admission to the RGRCC, the patients showed rapid breathing (28 – 30 per minute), decreased blood oxygenation (SpO_2 < 90%), decreased partial oxygen pressure (PaO_2 < 60 mm Hg), and decreased systolic blood pressure (SBP, less than 100 mm Hg). Six out of 28 patients required mechanical ventilation (ALV); the rest of the patients received high-flow nasal oxygenation. Before Laennec was used, there was no positive dynamics observed during 5 to 7 days.

The severity of COVID-19 in patients was assessed by computed tomography (CT). Bilateral changes were recorded in patients with a predominant lesion of the lower lobes (more than 3 foci of ground glass compaction with a maximum diameter of < 3 cm, in combination with foci of consolidation). According to the CT data, the total area of injuries (0 – 100%) and the degree of damage in points (0 – 5 points) were assessed. The degree of damage was calculated as the average for each of the five lobes of the lungs (1 point – < 5% tissue is involved, 2 points – 5 – 25%; 3 points – 26 – 49%; 4 points – 50 – 75%; 5 points – > 75%).

The patients were hospitalized between the 5th and 10th days from the onset of the disease that corresponds to the stage of progression (Days 5 to 8 of the disease) and the peak stage of COVID-19 (Days 10 to 13 of the disease). According to the CT, the stage of progression was characterized by an increase in the prevalence of ground glass symptoms, local reticular changes, and the appearance of consolidation foci. At the peak stage, the CT showed the formation of perilobular compaction.

14 patients were prescribed the polypeptide drug Laennec (Japan BioProducts Co. Ltd., registration certificate of the Healthcare Ministry of the Russian Federation No.013851/01), registered in Russia as a hepatoprotector and immunomodulator. Depending on the severity of a patient's condition, Laennec was used from 3 to 10 days (the first three days, 6 mL per 350 mL of 0.9% NaCl solution, intravenously, drip, from Day 4, 6 mL per 250 mL 0.9% NaCl solution daily). Patients were discharged after achieving a stable remission, with a comprehensive assessment of the general condition, taking into account the data of blood biochemistry, blood oxygenation, in the stage of pneumonitis resolution shown in the CT.

The standard processing of the research results included the use of methods of mathematical statistics, including the calculation of the numerical characteristics of random variables, testing statistical hypotheses using parametric and nonparametric criteria, and correlation analysis and ANOVA. The predicted and observed frequencies of occurrence of the studied features were compared using the χ^2 test, the Wilcoxon–Mann–Whitney test, and the Student's test. The application program Statistica 10.0 and Microsoft Excel spreadsheets were used.

In addition to standard statistical methods, modern data mining methods were applied in the study, including the method of analyzing metric condensations in the parameter space, the method of metric maps [7] and methods for predicting numerical target variables [8, 9]. The mathematical details of the methods used (including the comparison with other approaches and algorithms) are given in our series of works on topological data analysis [7–9]. The method of analysis of metric condensations is highly sensitive and enables the detection of clusters (condensations) of points, even if the differences in the point density do not exceed a few percent.

Results

The condition of 25 patients stabilized; three patients in the control group died (p = 0.067). Despite the stabilization of the state, there was no significant positive dynamics in the studied parameters in the control group. The use of Laennec resulted in positive clinical dynamics, a decrease in ferritin levels, an increase in blood oxygenation to the normal range, a decrease in the area of lung dam-

age according to the CT data, an increase in the percentage of lymphocytes, and the normalization of liver dysfunction markers (AST, ALT), creatinine and systolic blood pressure (all $p < 0.05$). All patients who received the medication achieved a stable remission within 3 to 15 days after the start of Laennec use and were discharged with a negative test for SARS-CoV-2 to be followed up by a physician at their place of residence to secure further rehabilitation.

The use of Laennec facilitated complex changes in the values of indicators of the patients' condition that are presented on the metric map (Figure 1). The metric map of a clinical trial is a visual diagram showing each of the studied indicators of the state (for example, the level of ferritin) in correspondence to two points on the plane: the values of the indicator before and after therapy ("ferritin, before" and "ferritin, after"). The distance between any two points of the metric map corresponds to the degree of the indicators' association. The condensations (clusters) of points correspond to indicators with the values closely interacting with each other.

The metric maps enable both the study of complex relationships between indicators of the patients' condition (see, for example, in studies [10, 11]) and a comprehensive assessment of the efficacy of therapy, as well as the choice of the most informative predictors for predicting the therapy efficacy and responders/non-responders (see below). With a low efficacy of therapy (considering all the studied parameters), the positions of the points hardly alter, and a single cluster of parameters is maintained. An effective therapy results in a significant rearrangement of the points corresponding to the studied parameters into separate clusters.

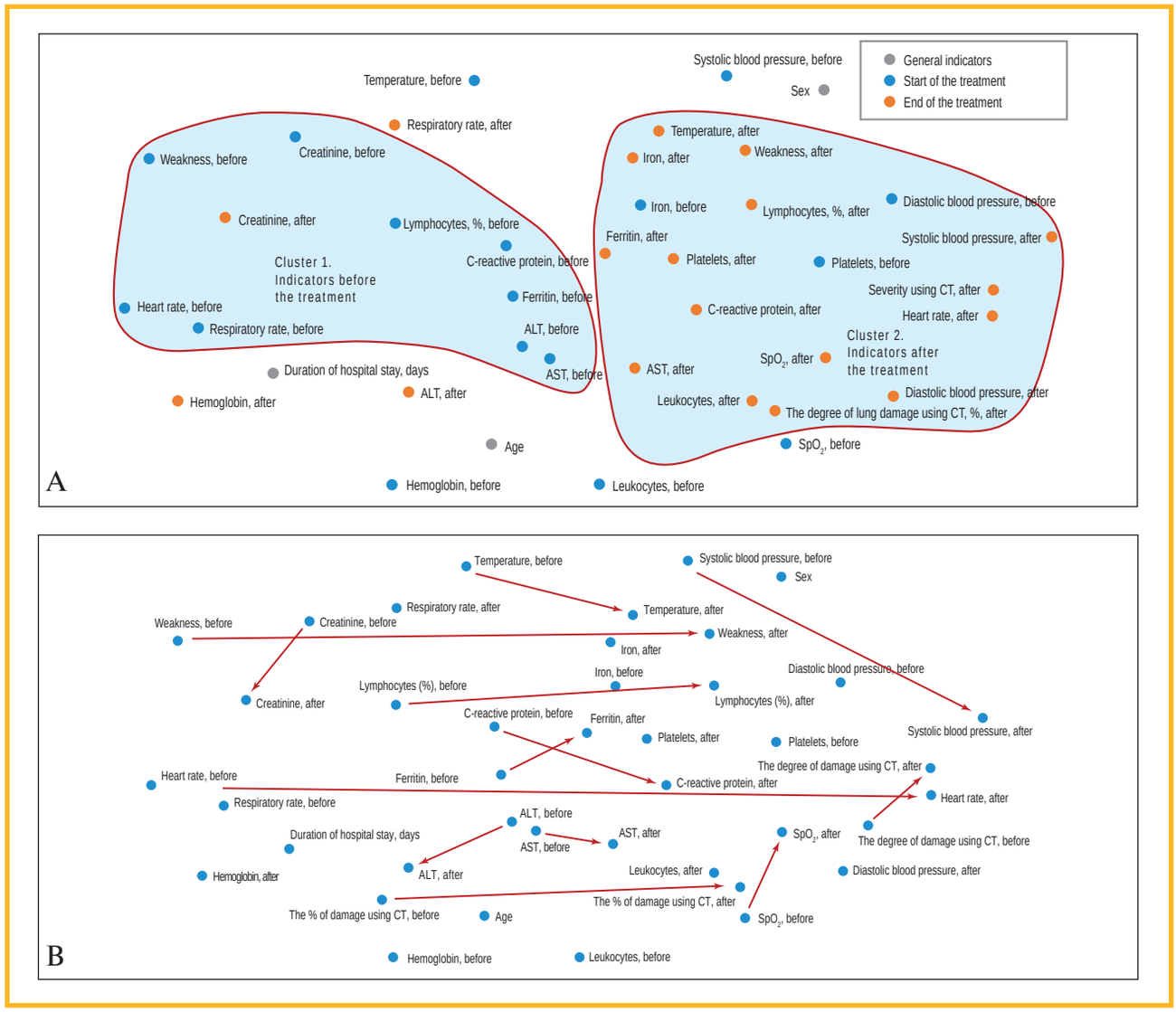

Figure 1. Metric card of the present study. The points on the metric map correspond to the indicators of the patient's condition. The distances between the points reflect the degree of interaction of indicators: the closer the points, the stronger the associations between the indicators: A, Metric condensations (clusters) of points on a metric map; B, Representation of the dynamics of treatment as a regrouping of points on a metric map.
Note: ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; SpO_2, blood oxygenation level.

Рис. 1. Метрическая карта настоящего исследования. Точки на метрической карте соответствуют показателям состояния пациентов. Расстояния между точками отражают степень взаимодействия показателей: чем ближе точки, тем сильнее ассоциации между показателями: А – метрические сгущения (кластеры) точек на метрической карте; В – представление динамики лечения как перегруппировки точек на метрической карте

In the present study it was found that the use of Laennec is associated with a clear division of the metric map into the cluster of parameter values before the start of therapy and into the cluster of parameter values after therapy (Figure 1A). No such division into clusters was observed in the control group. In other words, the use of Laennec in patients with a rather severe course of COVID-19 caused a coordinated complex change in many indicators of their condition corresponding to the movement of points "from left to right" on the metric diagram in Figure 1B. As the analysis of the individual parameters shows, this complex change corresponds to clear positive dynamics of the patient's condition: a decrease in inflammation, an improvement in the function, and a decrease in markers of liver and kidney dysfunction. In the control group, however, there was no clear positive dynamics in ferritin, CRP, AST and ALT ($p > 0.05$ according to Student's test and the rank criterion) and according to the CT data.

Laennec therapy in patients with COVID-19 primarily resulted in a *significant decrease in the levels of inflammatory markers (ferritin, CRP) and in an increase in the relative lymphocyte count compared to control* (Figure 2). Significant improvements in these parameters were observed both in the entire group of patients receiving Laennec, and in the male and female subgroups. On average, for the entire group, ferritin decreased from 603 ± 205 μg/L to 390 ± 124 μg/L ($p = 0.039$). At the same time, a significant decrease in ferritin was observed both in men (from 790 ± 249 to 462 ± 145 μg/L; $p = 0.033$) and in women (from 372 ± 86 μg/L to 244 ± 140 μg/L; $p = 0.034$).

The levels of C-reactive protein (a protein of the acute phase of inflammation), decreased from 23.1 ± 18.9 mg/L to 9.0 ± 6.8 mg/L ($p = 0.014$). Although after the end of therapy, CRP levels reached the upper range of normal (5 mg/L) in only 4 out of 14 patients; the median CRP (6 mg/mL) significantly approached the reference interval compared to the initial median value (14.2 mg/mL).

The relative content of lymphocytes (LYM%) indicating the state of antiviral immunity, significantly increased from 20.0 ± 10.9% to 27.8 ± 11.6% after treatment with Laennec ($p = 0.042$). Before treatment, LYM% values of more than 25% (the lower limit of the reference interval) were observed in only 3 of 14 patients, and after treatment, in 9 patients. This result corresponds to a significant reduction in the risk of LYM% values less than 25% according to the χ^2 test (OR, 0.15; 95% CI, 0.03 – 0.81; $p = 0.022$), that is, the activation of the antiviral system in the body.

The positive clinical dynamics corresponded to a decrease in inflammation markers during the use of Laennec (Figure 3): an increase in the degree of blood oxygenation according to pulse oximetry (SpO_2), a decrease in the degree and area of lung damage according to computed tomography, and a decrease in complaints of overwhelming weakness.

Laennec therapy resulted in an increase in the degree of blood oxygenation SpO_2 from 91.4 ± 4.6% to 96.2 ± 3.2% ($p = 0.0029$). SpO_2 values less than 95%, corresponding to respiratory failure, were observed in 11 patients before the start of therapy and only in 3 patients after therapy, which corresponds to a 13-fold decrease in the risk of respiratory failure (OR, 0.07; 95% CI, 0.01 – 0.45; $p = 0.0025$). It should be noted that already from Day 2 of Laennec therapy a significant decrease in respiratory rate

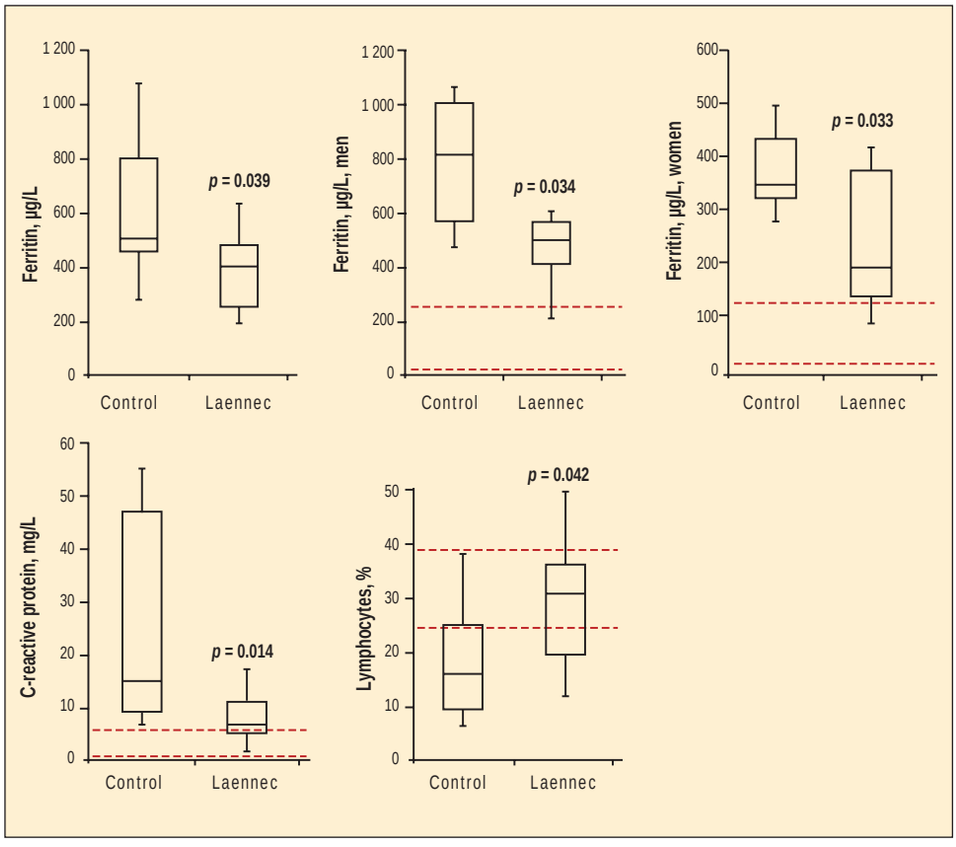

Figure 2. Dynamics of markers of inflammation/cytokine storm in patients with COVID-19 during treatment with Laennec. The rectangles represent the boundaries of 25 – 75% of the values, the lines within the rectangles are the median values of the parameters. Dash-dotted lines show the boundaries of the reference intervals
Note: CRP, C-reactive protein.

Рис. 2. Динамика маркеров воспаления / «цитокинового шторма» у пациентов с COVID-19 на фоне лечения препаратом Лаеннек. Прямоугольники обозначают границы 25–75%-ных значений, линии внутри прямоугольников – медианные значения параметров. Штрих-пунктирными линиями показаны границы референсных интервалов

was observed, from 18.9 ± 2.4 per minute to 17.5 ± 1.2 per minute ($p = 0.029$); the patients had improved sleep and improved mood.

The improvement in blood oxygenation was accompanied by a decrease in the degree of lung damage according to the CT data (a decrease in the score from 3.35 ± 0.50 to 2.71 ± 0.61; $p = 0.0027$) and a decrease in the area of lung damage according to the CT data from 73.4 ± 17.2% to 63.1 ± 13.9 % ($p = 0.047$). Along with the objective improvement in respiratory function, the patients complained less of the overwhelming weakness: before the start of therapy, 9 patients complained of general weakness, after therapy there were only two such patients (a 11-fold reduction in risk, OR, 0.09; 95% CI, 0.01 – 0.59; $p = 0.0068$).

The use of Laennec resulted in significant improvements in liver (ALT, AST levels; Figure 4) and kidney (creatinine levels) markers. The AST levels decreased from 121.3 ± 102.5 U/L to 45.7 ± 15.7 U/L ($p = 0.050$). Initially, there were elevated AST levels (more than 40 U/L) in 14 patients; after treatment, only in 7 (OR, 0.07; 95% CI, 0.007 – 0.70; $p = 0.0091$). The ALT levels decreased from 164 ± 155 U/L to 49 ± 28 U/L ($p = 0.049$). At the same time, abnormally high ALT levels (more than 41 U/L) were observed in 13 out of 14 patients at the start of therapy and in 8 patients after using Laennec (OR, 0.10; 95% CI, 0.01 – 1.00; $p = 0.029$). On average for the group, creatinine decreased from 105.3 ± 87.8 μmol/L to 20.5 ± 9.2 μmol/L ($p = 0.049$).

Discussion

Previous studies of the composition of Laennec did indicate considerable feasibility of using the drug in patients with COVID-19. In fact, peptides-inhibitors of the IKKB protein that were found in the composition of the drug do help to reduce systemic inflammation by inhibiting the NF-kB cascade. Further, a significant amount of the immunomodulatory element zinc necessary to activate innate antiviral defense systems in COVID-19 [3] and anti-inflammatory peptides-inhibitors of a number of kinases in human proteome were also found in Laennec. Earlier clinical experience with Laennec demonstrated normalized levels of pro-inflammatory cytokines (IL-6, TNF-α) and a significant decrease in the levels of AST and ALT enzymes in Laennec-treated patients [6]. Therefore, we hypothesized that the anti-inflammatory and anti-viral effects of Laennec could effectively inhibit the formation of a life-threatening cytokine storm in patients with severe COVID-19.

In this work, we considered ferritin, CRP, and the relative content of lymphocytes as biomarkers of a cytokine storm. It is known that patients with severe COVID-19

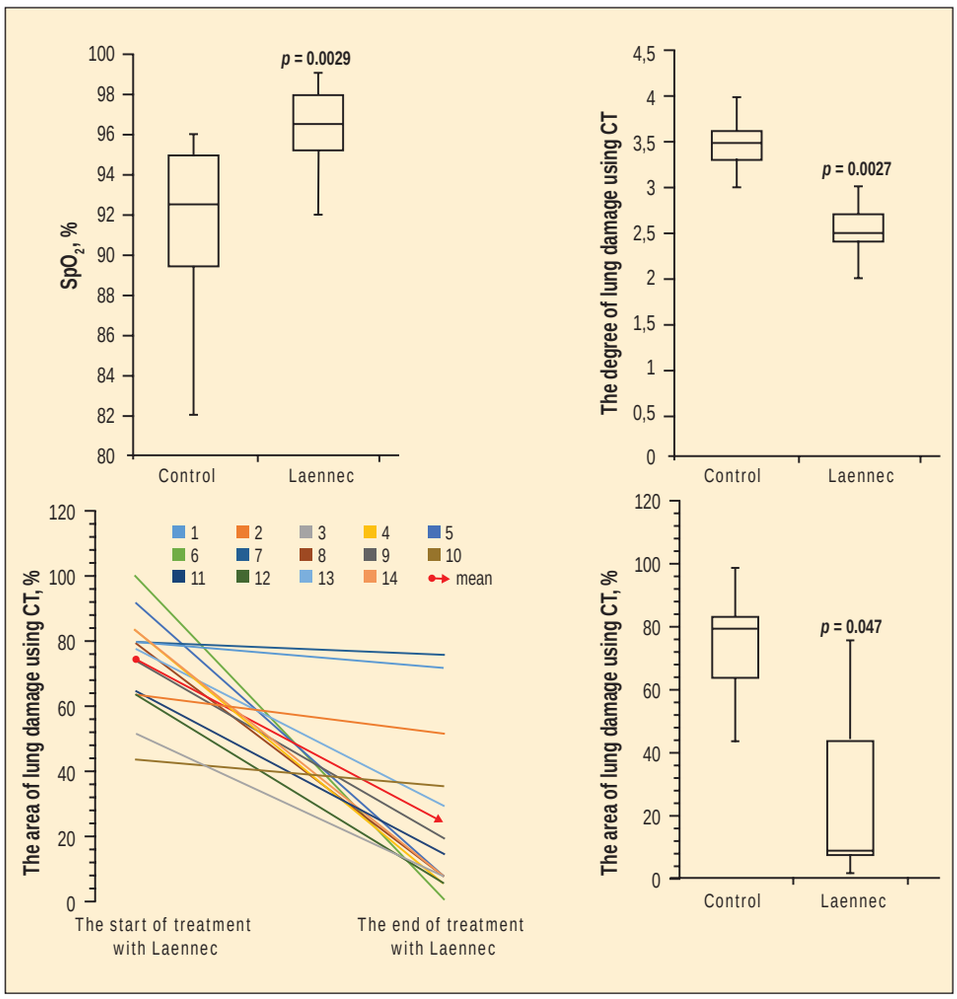

Figure 3. Improvement of respiratory function in the dynamics of Laennec therapy
Note: CT, computed tomography; SpO_2, blood oxygenation level.

Рис. 3. Улучшение дыхательной функции в динамике терапии препаратом Лаеннек

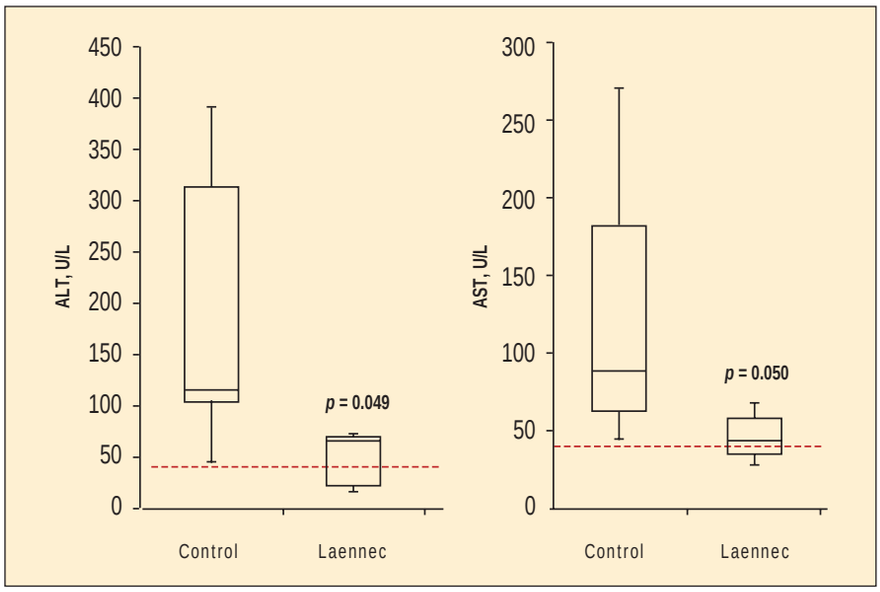

Figure 4. Levels of liver dysfunction markers in patients with COVID-19 in the dynamics of Laennec treatment. Dash-dotted lines show the boundaries of the reference intervals Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Рис. 4. Уровни маркеров дисфункции печени у пациентов с COVID-19 в динамике лечения препаратом Лаеннек. Штрих-пунктирными линиями показаны границы референсных интервалов

have increased ferritin levels associated with high mortality [5, 12]. Ferritin is an iron-carrying protein found in virtually all tissues. Normal levels of ferritin in the blood are 10–120 μg/L in women and 20 – 250 μg/L in men. Elevated serum ferritin levels are associated with disorders of iron accumulation in the body (hemochromatosis, etc.); they also indicate inflammation concomitant to severe ARVI, liver dysfunction, autoimmune or tumor diseases, etc.

In patients with COVID-19, ferritin levels dramatically increase both due to the acute phase of inflammation and through the mass death of red blood cells that enables the formation of the so-called "catabolic ferritin". When performing a biochemical blood test, it is impossible to distinguish "pro-inflammatory" ferritin from "catabolic" ferritin. Nevertheless, total ferritin is an effective marker of the severity of coronavirus infection: in patients with mild COVID-19, lower serum ferritin levels were observed (on average, by 282 μg/L; $p < 0.001$) [13, 14]. In the present study, a significant decrease in total ferritin was found in the dynamics of treatment (in men by 386 μg/L, in women by 80 μg/L).

The use of Laennec resulted in positive dynamics of C-reactive protein (another marker of the acute phase of inflammation that is produced in the liver). A meta-analysis that included 16 studies of COVID-19 patients (n = 3,962) confirmed that patients with less severe disease had lower levels of CRP (–41.8 mg/L; $p < 0.001$) and other markers of inflammation (IL-6, ESR, ferritin) [13].

In this study, the baseline CRP values in all the subjects were quite high (23.1 ± 18.9 mg/L while the reference interval is 0 – 5 mg/L; CRP levels >5 mg/L were found in 86% of patients). This indicated to us an extremely active inflammatory process that predisposes to the formation of microthrombi in the microvascular network of the lungs and in other tissues. Accordingly, a decrease in CRP during therapy to 9.0 ± 6.8 mg/L (p = 0.014) indicates both the extinction of the cytokine storm and a decrease in the risk of thrombotic complications of COVID-19.

Elevated CRP levels, leukocytopenia and lymphocytopenia are important features of the course of COVID-19 [15]. At the beginning of treatment, the relative content of lymphocytes (LYM%) was 20.0 ± 10.9% and the values within then reference interval of LYM% (25 – 40%) were found only in three patients. The course of COVID-19 with decreased contents of lymphocytes in the blood corresponds to an increased risk of a protracted disease and a decrease in the rate of rehabilitation. Therapy with Laennec led to a significant increase in LYM% up to 27.8 ± 11.6% (p = 0.042).

An increase in the content of lymphocytes in the blood corresponds to the activation of antiviral defense in the body. As noted earlier, a significant amount of zinc was found in Laennec that stimulates the body's interferon defense proteins against single-stranded RNA viruses (including SARS-CoV-2) [3]. Also, **14 peptides were found in the composition of the drug that produce antiviral effects at all stages of the life cycle of DNA/RNA viruses**. These 14 peptides of Laennec can inhibit the activation of viruses inside the cell (specific inhibition of the cellular HCFC1 protein), fusion of the viral envelope with the plasma membrane at the stage of infection with the host cell virus (inhibition of the cellular CD4 protein), viral replication (inhibition of the CTBP1 protein), maturation of the virion (inhibition of proteins CRM1, VPS4B, TPR, proline isomerase), and budding of viral particles from the cell membrane (inhibition of the NEDD4 protein) [16]. Therefore, an increase in the percentage of lymphocytes may be associated with the antiviral effect of peptides and zinc in Laennec.

Overcoming the cytokine storm and activated antiviral immunity are associated with improved respiratory function. SpO_2 blood oxygenation is a non-invasive but fairly objective method for assessing respiratory failure. The improved blood oxygenation in the dynamics of treatment with Laennec from 91.4 ± 4.6% to 96.2 ± 3.2% (p = 0.0029; SpO_2 levels > 95% were achieved in 11 of 14 patients) should be considered as the restored normal gas exchange between alveocytes and erythrocytes. The reduction in the

degree (–0.64 points; $p = 0.0027$) and the area of lung damage (–10.4%; $p = 0.047$), assessed using the CT data, correspond to a good rate of lung tissue regeneration as a result of treatment. This finding is supported by a significant reduction in patient complaints of overwhelming weakness (11-fold reduction in risk; $p = 0.0068$).

We should note that Laennec helps to increase the regenerative capabilities of the body and is used in the treatment of chronic fatigue syndrome (CFS). In particular, the positive effects of Laennec in CFS are associated with the modulation of mitochondrial function. **Laennec contains the peptides PGVSCR, HMVLLH, EALPGPL, LPGPLNP**, etc. that promote:

- inhibition of cell apoptosis under conditions of oxidative/toxic stress (via the activation of the antiapoptotic protein BcL-2);
- a decrease in hyperinsulinemia (activation of the PPARA receptor);
- an increase in the intensity of energy metabolism of mitochondria (inhibition of MAP kinases and kinases of pyruvate dehydrogenase) [6].

In addition, Laennec contains biologically active **peptides that stimulate the regeneration of damaged tissues** and improve the body's response to stress (fragments of proenkephalin A, peptides inhibiting CDK1, IKKB and mTOR kinases). An experimental study demonstrated geroprotective properties of Laennec: the addition of Laennec increased the lifespan of *Caenorhabditis elegans* under conditions of prolonged oxidative stress by 92% compared to the control [6].

The use of Laennec resulted in a significant improvement in liver (ALT, AST) and kidney (creatinine levels) markers. It should be emphasized that COVID-19 infection is associated with multiple organ pathology. First, chronic comorbid diseases aggravate the course of coronavirus infection. Second, infection with SARS-CoV-2 stimulates or worsens organ damage.

In COVID-19 patients is noted liver dysfunction (increased levels of AST, ALT markers, albumin, bilirubin) [2], renal dysfunction (proteinuria, hematuria) [17] and severe impairment of the blood coagulation profile (including an increase in D-dimer and fibrin degradation products) [1], which is associated with a higher risk of mortality from COVID-19. Liver dysfunction occurs in 24 to 37% of COVID-19 patients [18]; renal dysfunction occurs in 27 to 44% of patients [17].

In the present study, liver dysfunction was observed in all patients (AST and ALT levels were elevated). The use of Laennec resulted in a significant decrease in AST and ALT in all patients, and the AST/ALT ranges were achieved in half of the patients. This result is quite expected since Laennec is registered as a hepatoprotector (ATX A05BA). In experiment and in clinical practice, it has been shown that the drug eliminates hemosiderosis (chronic iron overload) of the liver, and reduces damage to hepatocytes and cells of other organs. The experiment demonstrated the cardioprotective effect of Laennec on the model of adrenaline damage to the heart and an increase in the antioxidant resource of the blood [6]. The molecular mechanisms of the regenerative action of Laennec on various tissues have been mentioned above.

Creatinine is a biomarker of the state of the renal filtration system; its elevated levels indicate impairment of renal filtration function [19]. Acute renal failure is an important risk factor for mortality in patients with COVID-19 [17]. At the start of treatment, creatinine levels in the patients examined were above the upper limits of the reference intervals (62 to 106 μmol/L in men, 44 to 80 μmol/L in women) in 5 out of 14 people in the therapy group. The use of Laennec promoted a significant decrease in creatinine from 105.3 ± 20.5 μmol/L to 87.8 ± 9.2 μmol/L ($p = 0.049$), i.e. towards the ranges of values corresponding to the reference intervals. Thus, Laennec has contributed to improved kidney function in COVID-19 patients.

We should also note that the analysis of the metric map (see Figure 1) reflecting the dynamics of the patients' condition during therapy, enables the design of effective algorithms for predictive modeling of various parameters at the time of the end of therapy. Such algorithms, based on the topological theory of pattern recognition [7–9, 20], facilitate the evaluation of the efficacy of COVID-19 therapy with Laennec based on the initial data in a particular patient. In particular, models were obtained and verified (in cross-validation) for predicting the duration of hospital stay (the correlation coefficient r (c) = 0.73), ferritin levels (r(c) = 0.49), CRP (r(c) = 0.50), ALT (r(c) = 0.62), creatinine (r(c) = 0.54), hemoglobin (r(c) = 0.84), platelets (r(c) = 0.57), the relative content of lymphocytes (r(c) = 0.65) and other important indicators of respiratory function such as Spo2 (r(c) = 0.88), respiratory rate (r(c) = 0.50), the degree of damage using CT (r(c) = 0.51) and lesions using CT (r(c) = 0.87). The developed algorithms for predictive modeling constitute the subject of a separate paper.

Here are two clinical cases that clearly illustrate the results of the treatment of COVID-19 using Laennec.

Case 1

Patient B., 63 years old, had diagnosis of T2DM (E11 MO ICD-10). The patient referred to the RGRCC with complaints of dry cough, fever up to 39 °C, air hunger, severe weakness, and sweating. Respiratory rate was 30 per minute and the patient had a positive PCR test for SARS-CoV-2 virus. According to the CT scan, the patient's lungs were affected by the 3rd degree, the lesion area was 52%. Baseline SpO_2 (on room air) was 94%. The temperature was high during 3 days, then it dropped to 37.6 °C.

Blood biochemistry: ferritin, 1,071.8 mcg/L (normal 20 – 250 mcg/L), ALT, 44 u/l (normal < 41 U/L), AST, 44 U/L (normal < 40 U/L), CRP, 52.6 mg/L (normal 0 – 5 mg/L), creatinine, 143 μmol/L (normal 80 – 115 μmol/L), hemoglobin, 153 g/L (normal 130 – 160 g/L), leukocytes, 6.1 × 10^9/L (normal 4 – 9 × 10^9/L), platelets, 169 × 10^9/L (normal 180 – 320 × 10^9/L), lymphocytes (LYM%), 26% (normal 25 – 40%).

In view of the fact that the patient had already been in a "cytokine storm" for a day (very high levels of ferritin, C-reactive protein, borderline lymphopenia), it was decided to prescribe Laennec i/v (6 mL in 350 mL of isotonic solution, 1 time per day, no. 10 daily).

The patient's clinical condition rapidly deteriorated and after the first use of Laennec by Day 3, the temperature increased to

38 °C, CRP, up to 64.7 mg/L, SpO_2 decreased to 89%, lymphocytes, to 7.4%. According to the CT data, there was lung lesion of the 4th degree, the lesion area was 80%. The use of Laennec continued. By Day 7 there was a decrease in ferritin to 408 μg/L, CRP, to 9.1 mg/L, and an increase in leukocytes up to 10.9%. On Day 11 there was a trend towards an increase in SpO_2 (91%), the state of the lungs according to CT improved to Grade 3, the lesion area decreased to 60%. The use of Laennec was stopped. The patient was followed up for another 5 days. 5 days after completing the course of Laennec, ferritin levels decreased almost to the normal range, 210 μg/L, and blood oxygenation SpO_2 increased to 97%. Respiration rate was 20 per minute. The patient was discharged in satisfactory condition.

Case 2

Patient A., 54 years old, was admitted to the RGRCC on emergency with complaints of paroxysmal cough with scanty sputum, hyperthermia up to 39 °C, severe weakness, and shortness of breath. She fell ill a week prior to being admitted to the RGRCC with the first symptoms of loss of smell and lack of appetite, after 3 days the temperature rose to 39 °C, and dry cough started. An RGRCC examination showed a positive PCR test for SARS-CoV-2.

The patient was in the RGRCC for three days on compulsory oxygen therapy. The temperature was high during three days, then dropped to 36.7 °C. Despite the hospital stay, the condition of the lungs worsened: the SpO_2 oxygenation in the air decreased to 82%, according to the CT data, there was 4th degree lung damage, the lesion area was 92%. There was a trend towards the formation of a cytokine storm, with ferritin 493.4 μg/L (normal 10 – 120 μg/L), a decrease in lymphocytes to 15.3% (normal 25 – 40%) with the developing liver dysfunction (ALT, 42 U/L, normal < 41 U/L, AST, 64 U/L, normal < 40 U/L). Blood pressure was 148/84 mm. Hg, heart rate was 91 per minute.

The patient was prescribed Laennec i/v (6 mL in 350 mL of isotonic solution, 1 time per day, no. 8 daily). Starting from the second day of using the drug, the patient's condition became significantly better: blood pressure returned to normal up to 110/80 mm. Hg, her heart rate decreased to 78 beats/min, blood oxygenation increased to 85%, and respiratory rate decreased from 20 to 18 per minute. There was a daily positive trend. On Day 7 SpO_2 increased to 97%, lymphocytes, up to 31.5% (normal 25 – 40%). According to the CT, the degree of lung damage decreased to the 3rd degree, the affected area was up to 80%, ferritin levels were up to 398 μg/L, weakness disappeared. The patient was discharged the next day in a satisfactory condition.

Conclusion

Various approaches to pharmacotherapy for COVID-19 are currently being tested. Decisions on the choice of pharmacotherapy should take into account all the important features of COVID-19 and, above all, the severe course of this coronavirus infection in presence of comorbid pathologies. It is well known that most of the drugs used in the treatment of viral diseases are highly toxic and cannot always be used in patients with liver dysfunction, coronary artery disease, T2DM and other chronic diseases. Therefore, in a severe course of COVID-19, especially against an unfavorable comorbid background, the requirements for the safety of the chosen pharmacotherapy are paramount.

The polypeptide drug Laennec has a good safety profile, a high degree of pharmaceutical standardization [21], and is characterized by reliable hepatoprotective, anti-inflammatory and immunomodulatory properties. The use of Laennec in the therapy of COVID-19 in patients with comorbid load (IHD, T2DM), liver dysfunction (increased AST, ALT by 2 – 3 times) and a high risk of a cytokine storm (increased CRP, ferritin, decreased lymphocyte count) have shown positive clinical dynamics and improvement in almost all studied laboratory parameters.

It is especially important to note the decreased ferritin levels ($p = 0.039$), an increase in blood oxygenation to the normal range ($p = 0.0029$) and a decreased area of lung damage according to the CT data ($p = 0.0027$). The sustained remission was achieved in all patients between 3 to 15 days after the start of Laennec; the patients were discharged with a negative test for the SARS-CoV-2 virus. The collected data allowed the development of algorithms for predictive modeling of the efficacy of COVID-19 therapy using Laennec.

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