# STUDYING THE FEATURES OF THE RISK OF DEVELOPING FATAL COMPLICATIONS IN ELDERLY PATIENTS, COVID-19 TREATMENTS

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**Introduction.** A new coronavirus infection can provoke acute myocardial injury and other new cardiac complications.
Since a number of drugs used in COVID-19 have cardiotoxic effects, constant monitoring of hemodynamic parameters. Viral infection can destabilize the state of the cardiovascular system, which significantly increases the risk of mortality in concomitant cardiovascular diseases (CVD).
Purpose of the study: to identify predictors of cardiovascular complications and mortality in patients with COVID-19 against the background of acute respiratory distress syndrome.

Materials and Methods: The study included patients with COVID-19 who assessed the onset of symptoms of the disease, health-related quality of life, a physical examination, laboratory tests, and in some patients an assessment of respiratory function and X-ray examination were performed.
Research results. Observation was carried out for 50 patients admitted to the COVID-19 covid hospital in Ferghana. Mean age 56.7±4.6, including 47 men (78.3%), 13 (21.6%) women. The duration of the disease (history from the onset of clinical symptoms to hospitalization) averaged 14.6±2.5 days, the duration of hospitalization ranged from 14 to 27 days (25.5±1.2). Of those included in the study, 57 (95%) had a history of cardiovascular diseases (IHD, AH, CHF, etc.), 46 (92%) had type 2 diabetes mellitus, 26 (52%) were overweight and / or obesity, 2 (4%) had newly diagnosed steroid diabetes.

Conclusions: An infectious disease caused by the SARS-CoV-2 virus (COVID-19) often occurs in patients with various cardiovascular risk factors that can affect the course of the infectious process with the development of acute cardiovascular failure, pulmonary embolism on against the background of acute respiratory distress syndrome due to total damage to the lung tissue with possible additional damage to the heart and blood vessels, contributing to the occurrence of cardiovascular complications and worsening of the prognosis in patients with COVID-19.
**Key words:** COVID-19, SARS-CoV-2, acute cardiovascular failure, pulmonary embolism, acute respiratory distress syndrome.

It is known that for almost three years now, the coronavirus infection caused by the SARS-CoV-2 virus—named COVID-19 and declared a pandemic by the World

Health Organization—has remained a pressing medical issue. Beginning with symptoms of acute respiratory involvement of the upper airways, the disease can present with varying degrees of severity. In severe cases, it progresses to viral pneumonia with widespread damage to the small pulmonary vessels, bronchioles, and alveoli. Research has shown that the main pathogenic trigger of COVID-19 is progressive systemic inflammation, accompanied by lymphopenia and neutrophilia. The pathological hyperreactivity of the immune system, manifested by the uncontrolled activation of immune cells by cytokines at the site of inflammation and the subsequent release of more cytokines and chemokines, is referred to as a "cytokine storm," a phenomenon supported by clinical and laboratory findings. It is important to note that the "cytokine storm" significantly increases the risk of acute respiratory distress syndrome and may lead to multiple organ failure, particularly in individuals with comorbid conditions \[1].

One of the most dangerous aspects of COVID-19 is the increased risk of thrombotic and thromboembolic complications, which directly contribute to multi-organ damage and inevitably worsen the prognosis. Numerous studies have demonstrated that COVID-19 can lead to a hypercoagulable state with suppressed fibrinolysis, resulting in microthrombosis in the vessels of the lungs, kidneys, and heart, and an elevated risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and arterial events such as stroke \[9, 10]. Furthermore, an elevated level of D-dimer, a fibrin degradation product used as a marker of thrombotic risk, has been identified as an independent predictor of poor outcomes in patients with COVID-19 \[9, 10, 11]. In light of these findings, it is important to emphasize that with the accumulation of knowledge and better understanding of the disease's pathogenesis, the timely and effective use of anticoagulant therapy has become increasingly recognized \[1, 2, 4, 11].

**Research Objective:** To identify predictors of cardiovascular complications and mortality in patients with COVID-19 against the background of acute respiratory distress syndrome (ARDS).

**Materials and Methods:** The study included patients diagnosed with COVID-19. Assessment included symptom onset, health-related quality of life, physical examination, and laboratory tests. In some patients, pulmonary function tests and radiological examinations were also performed.

**Study Results:** The observation covered 50 patients admitted to the COVID hospital in Fergana City, specifically to the intensive care and resuscitation unit (ICU), with a confirmed diagnosis of coronavirus pneumonia. The diagnosis in all cases was verified through PCR detection of SARS-CoV-2 RNA and characteristic lung changes on computed tomography (CT). The average age of patients was $67.8 \pm 4.6$ years, with 37 males (74%) and 13 females (26%). The average disease duration (from symptom onset to hospitalization) was $14.6 \pm 2.5$ days, and hospital stays ranged from 14 to 22 days. Among those enrolled, 57 (95%) had a history of cardiovascular disease (IHD, hypertension, CHF, etc.); 46 (92%) had type 2 diabetes mellitus; 26 (52%) had overweight and/or obesity; and 2 patients (4%) were newly diagnosed with steroid-induced diabetes. According to survey data, none of the

patients regularly received treatment for their underlying conditions.

Treatment was carried out in accordance with Protocol No. 8-9 for the management of COVID-19 patients, approved by the Ministry of Health of the Republic of Uzbekistan. Initially, standard therapy with hydroxychloroquine and azithromycin was administered, followed later by the addition of bronchodilators and spironolactone. Additionally, from the first day of hospitalization, all patients received anticoagulant therapy with low-molecular-weight heparins (LMWH), dosed according to body weight and monitored by coagulation parameters. In cases where the D-dimer level reached ≥5 μg/ml, patients were switched to therapeutic doses of LMWH.

When necessary, antibacterial therapy was adjusted, with patients in both groups receiving an average of 1.4 antibiotics. There were no differences in supportive therapy or in medications prescribed for comorbidities among the observed cohort. However, 33 patients (66%) experienced a critically severe course of the disease, marked by high persistent fever, reduced oxygen saturation, elevated C-reactive protein (CRP), and lack of improvement on CT. This required emergency anti-inflammatory therapy. Due to the unavailability of anti-interleukin drugs, pulse therapy with high doses of glucocorticosteroids (GCS) was administered—methylprednisolone 1000 mg intravenously for 3 days, followed by dexamethasone 8 mg twice daily for 3–7 days. One patient additionally received tocilizumab 400 mg.

Treatment Strategy: Seventeen patients with similar baseline characteristics, who were undergoing treatment at the same time and according to the same clinical protocols, served as the comparison group. These patients did not receive pulse therapy with glucocorticosteroids (GCS), but only moderate doses of 4 mg once daily for 3–7 days. No other specific anti-inflammatory therapy was administered in either group. The analysis of data in both the GCS therapy and control groups was conducted using double-blinded "concealed" endpoints at the data collection and statistical processing stages, fully eliminating subjective influence on outcomes.

Patients in the observed cohort did not differ significantly in the number or frequency of comorbidities (predominantly cardiovascular diseases, including arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and malignancies). Compared to patients receiving standard therapy, those treated with GCS pulse therapy exhibited statistically significantly higher fever (median difference $+0.9^0$C), and more pronounced, though not statistically significant, dyspnea (median respiratory rate 24 vs. 19 per minute), which was associated with lower oxygen saturation (median $SpO_2$ 85% vs. 94% on room air, and 92% vs. 96% with oxygen support). All patients received oxygen support; 26 (52%) of those receiving pulse therapy were on non-invasive ventilation, and 7 (14%) were on invasive mechanical ventilation.

Baseline systolic arterial pressure (SAP) did not differ significantly between the groups, though tachycardia was more common in the more severe group receiving GCS pulse therapy. Biochemical analysis revealed patterns typical for severe COVID-19 pneumonia, and most parameters showed no significant intergroup differences. The combined inflammation score (C-reactive protein, CRP) was

elevated 19-fold in the control group and 27-fold in the active therapy group (p=0.048). D-dimer levels were tripled, which, along with increased fibrinogen levels, indicated a heightened thrombotic tendency amid the inflammatory process (p=0.125). Both groups exhibited lymphopenia and elevated neutrophil counts, with values exceeding the normal range only in the active group. The neutrophil-to-lymphocyte ratio (N/L index) was 4.06 in the control group and 6.05 in the active therapy group (p=0.125). Platelet counts, glucose, creatinine levels, and estimated glomerular filtration rate (eGFR) remained within normal ranges and did not differ between groups.

CT imaging confirmed bilateral viral pneumonia in all 34 patients, typical of COVID-19. Based on staging, 58.8% of patients had stage 3–4 lung involvement. Computer analysis revealed total lung involvement volumes of 25.6% and 53.2% in the control and active therapy groups, respectively ($p<0.001$), including patterns of "ground-glass opacity," "crazy-paving," and areas of consolidation and fibrosis.

To assess the severity of patients with acute respiratory syndromes, and to guide timely and competent decisions regarding treatment location, COVID-19 therapy intensification, and risk stratification, clinical parameters were used: respiratory rate (RR), oxygen saturation, need for ventilation, level of consciousness, body temperature, heart rate (HR), and systolic blood pressure (SBP).

It is important to emphasize that the clinical status of COVID-19 patients depends on several key indicators—not only the degree of dyspnea, blood oxygen saturation, and need for ventilation. These metrics largely reflect the severity of lung injury and respiratory failure. Level of consciousness is closely correlated with ICU admission and especially with the need for invasive mechanical ventilation. One of the key indicators is the actual extent of lung tissue damage based on CT data, which does not always correspond with clinical symptoms such as breathlessness. The severity of inflammation—indicated primarily by the degree of fever and CRP level—is another crucial factor. Additionally, the risk of thrombotic and thromboembolic complications, reflected by D-dimer levels, is a major prognostic marker of adverse disease progression.

All collected data were statistically processed on a Pentium-IV personal computer using Microsoft Office Excel-2012, including its built-in statistical analysis functions. Both parametric and non-parametric methods of descriptive statistics were applied, with calculations of arithmetic mean (M), standard error of the mean (m), relative values (frequency, %), and statistical significance determined using Student's t-test with calculation of error probability (P).

**Study Results:** Among the 50 patients included in the study, all (100%) had a history of cardiovascular disease (including ischemic heart disease, hypertension, chronic heart failure, and others), 40 patients (80%) had type 2 diabetes mellitus, 46 (92%) had overweight and/or obesity, and 22 (44%) were newly diagnosed with steroid-induced diabetes. Survey data revealed that none of the patients in the observed cohort had been receiving regular treatment for their primary chronic conditions.

Biochemical blood tests revealed a 2.8-fold increase in coagulation hemostasis parameters (fibrinogen, INR, PTI, D-dimer), and a 3.2-fold increase in inflammatory markers such as C-reactive protein (CRP), ferritin, and procalcitonin, against a background of pancytopenia, typically observed on days 8–10 of hospitalization. Lung examinations revealed subtotal lung involvement (78±4.9%) with signs of bilateral interstitial pneumonia.

Treatment was administered in accordance with the national inpatient management guidelines (Protocol No. 8 for the treatment of COVID-19 patients). According to the study results, 5 patients (10%) showed recovery, though without complete restoration of respiratory function, while 11 patients (22%) had a fatal outcome.

The most significant changes in patients' condition were associated with improvements in oxygen saturation and reduction in dyspnea. Among patients who did not receive pulse therapy, oxygen saturation remained unchanged at 94.0% before and after treatment (p=0.51). In the GCS pulse therapy group, oxygen saturation showed a statistically insignificant increase from 85.0% to 90.0% (p=0.025). In 10 patients (30.3%) receiving GCS pulse therapy, there was a statistically significant reduction in body temperature to normal levels, a decrease in respiratory rate by 5 breaths per minute, and a reduction in heart rate by 13 beats/min.

The number of patients in the ICU decreased; one patient was transferred from invasive ventilation to non-invasive mechanical ventilation, and the number of patients in clear consciousness increased from 8 to 11. No significant changes occurred in the remaining patients, further characterizing COVID-19 pneumonia as a persistent and treatment-resistant condition in its advanced inflammatory phase.

In 11 patients (36.4%) who received GCS pulse therapy, CT analysis showed no change in lung involvement percentage: 53.2% before treatment and 53.9% afterward (p=0.67). Lung involvement staging also remained unchanged before and after pulse therapy (p=0.82). This supports the notion that improvements in dyspnea, oxygen saturation, and reduced need for oxygen support were associated more with qualitative rather than quantitative changes in lung tissue damage.

In 22 patients (66.6%) who received GCS pulse therapy, the median change in lung involvement on CT was +0.75 \[–10.95; 13.9]%, whereas in patients who did not receive pulse therapy it was +17.6 \[0.10; 23.6]%, with no statistically significant difference (p=0.062). Clinical monitoring during the transition from pulse therapy to maintenance therapy with moderate doses of GCS in 11 patients (22%) showed a slight positive trend in clinical parameters, including fever reduction. However, by days 4–5, a sharp deterioration occurred: persistent low-grade fever for three days (37.6°C), increased severe dyspnea (RR 28–36 per minute), oxygen saturation at 84%, CRP level 58.6 mg/dL, and D-dimer level 2.89 μg/mL. Despite appropriate therapy and transition to invasive ventilation, the condition critically worsened and resulted in death.

Clinical Case Example: We present the case of patient A., 62 years old, diagnosed with COVID-19 and with 68.2% lung involvement according to CT scan. The patient had prolonged inflammation, with CRP levels reaching 122 mg/dL, D-

dimer 1.33 μg/mL, and oxygen saturation at 89% without supplemental oxygen. Notably, the patient showed pronounced lymphopenia ($0.34\times10^9$/L), neutrophilia ($6.26\times10^9$/L), and a very high neutrophil-to-lymphocyte ratio (N/L index) of 18.4, indicating severe inflammation and high risk of venous thromboembolism (VTE). The patient was transferred to the ICU and placed on non-invasive mechanical ventilation. A decision was made to initiate high-dose GCS pulse therapy.

After 5 days, the patient's condition improved: body temperature normalized, CRP dropped to 46 mg/dL, oxygen saturation increased to 95%, and lung tissue involvement decreased to 38.2%. The patient was transferred to a general ward. However, lymphopenia persisted ($0.37\times10^9$/L), the N/L index increased to 20.6, and D-dimer rose to 2.74 μg/mL. The following day, the patient's condition deteriorated sharply—severe dyspnea and chest pain developed, and D-dimer rose to 13.52 μg/mL. This indicated possible pulmonary embolism (PE), despite ongoing therapeutic-dose LMWH. The LMWH dose was increased, but complications could not be reversed. On day 27 from symptom onset, the patient died. The primary cause of death was acute cardiovascular failure due to pulmonary embolism in the setting of acute respiratory distress syndrome (ARDS).

**Discussion:** COVID-19 progresses through several stages, each requiring specific treatment strategies. In the stage of developed viral pneumonia involving alveolar damage, the situation is worsened by the progression of systemic inflammation and the involvement of not only lung parenchyma, but also bronchioles, small vessels, and increased thrombosis. In such cases, immune system hyperreactivity triggers excessive cytokine release, activation of macrophages and epithelial cells, and a continuous increase in cytokine and chemokine output—commonly referred to as the "cytokine storm" \[2, 5, 14, 15, 18, 20].

The present study focuses specifically on the treatment of COVID-19 patients affected by such a cytokine storm. Current recommendations suggest the use of "preemptive anti-inflammatory therapy" to suppress the cytokine storm and manage severe inflammation \[2, 3]. Considering the central role of pro-inflammatory interleukins, agents such as the IL-6 inhibitor tocilizumab \[16], the IL-1β inhibitor canakinumab \[17], the IL-17 inhibitor secukinumab \[18], and the JAK-1/JAK-2 inhibitor ruxolitinib \[19] have been proposed.

Despite their potential efficacy, these therapies remain limited in accessibility and are often prohibitively expensive. Glucocorticosteroids (GCS)—the most widely used anti-inflammatory agents over the past 50 years—are not recommended by the WHO for routine use in COVID-19. However, versions 8–9 of the guidelines from the Ministry of Health of Uzbekistan permit the use of low-dose GCS (up to 1 mg/kg/day) \[6, 8, 9].

A meta-analysis of studies on corticosteroids in coronavirus pneumonia, including COVID-19, showed no significant benefit in prognosis and indicated delayed viral clearance \[20, 21]. However, early initiation of high-dose GCS pulse therapy in atypical pneumonia has demonstrated slower disease progression, better resolution of lung changes, and a low risk of side effects \[10, 14, 22, 23]. One limitation of GCS therapy is its prothrombotic effect, particularly in immune-

mediated inflammation such as the cytokine storm in COVID-19 \[24]. Some studies associate VTE risk with steroid dosing, with the highest risk observed at doses ranging from 1000 to 2000 mg/day \[25]. The most concerning issue is that thrombotic and thromboembolic events may occur shortly after GCS therapy initiation \[26].

Given the uncertainties and limited research on this issue, the objective of our study was to evaluate the risk-benefit balance of GCS pulse therapy (1000 mg methylprednisolone IV for 3 days followed by dexamethasone 4 mg for 3–5 days) in patients with severe COVID-19 pneumonia, compared to a group not receiving anti-inflammatory therapy.

The analysis showed systemic inflammation marked by extreme CRP elevation (19–27-fold increase), which serves as a marker of cytokine storm. Patients in the active therapy group also presented with fever, lymphopenia ($0.66\times10^9$/L), neutrophilia ($5.02\times10^9$/L), a high N/L index (6.05), a threefold increase in D-dimer, dyspnea (RR = 26/min), low oxygen saturation (85%), and tachycardia (HR = 97 bpm). Considering progressive cardiopulmonary failure, patients were transitioned to GCS pulse therapy.

Patients exhibited varying severity, which complicated comparisons between groups but also offered a broader perspective on treatment response. The study confirmed the potential effectiveness of GCS pulse therapy in COVID-19 pneumonia with cytokine storm. In the observed cohort, 39 patients (78%) showed significant clinical improvement: +9% increase in oxygen saturation, normalization of body temperature, and a substantial reduction in oxygen support requirements \[8, 11, 14]. This improvement was accompanied by a threefold decrease in CRP levels, indicating a rapid anti-inflammatory effect of high-dose GCS \[22, 27, 30].

However, in 11 (22%) of the observed cases, there was a progressive deterioration in patient condition. Ultimately, the extent of lung damage did not improve, and the progression of pneumonia with significant increase in lung involvement led to fatal outcomes \[32, 34, 40]. It is important to emphasize that the course of COVID-19 pneumonia is extremely persistent, and in the presence of elevated inflammatory markers, the pneumonia cannot be effectively managed without anti-inflammatory treatment \[35]. The results showed that GCS pulse therapy can interrupt the cytokine storm—particularly when administered early. However, studies on COVID-19 have not confirmed improved outcomes; on the contrary, pulse therapy was associated with worse prognosis \[27, 28]. These findings have led to recommendations favoring anti-cytokine agents over GCS, which may also delay viral clearance in COVID-19 patients \[29, 30]. The second aim of the study was to assess the safety of high-dose GCS pulse therapy in patients with COVID-19. Overall, no adverse effects on cardiovascular parameters were observed, including no significant elevation in blood pressure. There was also no statistically significant increase in average blood glucose levels in the GCS group, although a statistically significant decrease was noted in the control group. However, individual analysis revealed that 6 out of 17 patients (35.3%) in the GCS group experienced elevated glucose levels above 9 mmol/L, requiring initiation or intensification of

glucose-lowering therapy. The most concerning parameter was the dynamic change in D-dimer. In the control group, D-dimer levels remained stable, while in the GCS group, a statistically significant increase was observed (median up to 1.98 μg/mL). Previous studies have shown that when D-dimer exceeds 2.0 μg/mL, the risk of VTE in COVID-19 patients increases 51-fold \[31]. Other studies demonstrated that even D-dimer levels above 1.0 μg/mL increased the risk of thrombosis 18-fold \[32]. In our study, venous thrombosis occurred in 4 patients (including 2 cases of pulmonary embolism), all of whom had D-dimer levels exceeding 10 μg/mL. Given that thrombotic complications in COVID-19 are linked to autoimmune inflammation, we analyzed potential associations. It is well known that GCS can induce leukocytosis and neutrophilia \[33]. In our study, neutrophil counts increased by 73% with GCS therapy ($p<0.0001$), while no changes were seen in patients who did not receive GCS pulse therapy. Thus, although GCS therapy led to rapid reductions in CRP and acute inflammation and improved the clinical condition of COVID-19 patients, it also provoked an increase in neutrophilia, which statistically significantly raised the risk of thrombosis and thromboembolism, as evidenced by increased D-dimer levels. Therefore, when considering high-dose GCS pulse therapy as an anti-inflammatory response to cytokine storm in COVID-19 patients, it is essential to monitor available markers of chronic inflammation to predict the risk of severe disease progression and to determine optimal treatment timing. It is now evident that not only age but also comorbidities significantly worsen prognosis, with the highest risk found in patients over 80 years old, where the mortality risk is six times higher than in those aged 65 \[13]. These findings highlight the need to develop and implement clinical algorithms that use a minimal number of criteria to stepwise assess the severity and prognosis of the disease.

**Conclusion:** In assessing disease severity and the risk of complications in COVID-19, it is essential to consider not only the classic clinical indicators (respiratory rate, oxygen saturation, need for ventilation, level of consciousness, body temperature, heart rate, and systolic blood pressure), but also the duration of illness, the timing, method, and initiation of anti-inflammatory therapy. This alone, however, is insufficient—patient age and premorbid conditions must also be taken into account. Delays in initiating anti-inflammatory therapy, including GCS pulse therapy, may fail to produce the desired positive effect.

COVID-19, caused by the SARS-CoV-2 virus, frequently occurs in patients with various cardiovascular risk factors, which may influence the course of infection by contributing to acute cardiovascular failure, pulmonary embolism, and ARDS, due to diffuse pulmonary damage and probable secondary cardiac and vascular injury. These complications increase the risk of adverse cardiovascular outcomes and worsen prognosis in COVID-19 patients.

**Study Limitations:** The study included a small sample size, lacked randomization, and had imbalanced baseline severity between groups. Moreover, the retrospective design further limits the generalizability of findings.

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