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Research Article

# Common for COVID-19 cytokine storm in patients with SARS-CoV-2 infection and CLL (chronic lymphocytic leukemia)

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## Abstract

The cytokine storm has been identified as one of the leading causes of the severe course and, in some cases, the fatal outcome of COVID-19 infection. Other factors aggravating the course of the disease are accompanying disorders such as cardiovascular diseases, diabetes mellitus, diseases of the respiratory system, and oncological diseases. In this article, we present the course of the coronavirus infection in patients with an accompanying malignant disease, chronic lymphocytic leukemia (CLL), namely. The study included 8 patients with proven PCR-positive tests for SARS-CoV2 and confirmed chronic lymphocytic leukemia as a comorbidity. The course of the coronavirus infection in the CLL group was compared with that in the control group of 100 patients. In both groups, we compared subjective complaints such as tiredness, fatigue, and joint and muscle pain with objective criteria such as temperature, laboratory markers of inflammation, X-ray imaging, and frequency of necessary intubation.

Despite the expected poor prognosis in patients with concomitant oncological disease, in the case of chronic lymphocytic leukemia, our results showed a quite different milder coronavirus infection course. Obviously, patients with CLL cannot develop a pronounced cytokine storm, most probably due to certain immunosuppression related to the pathogenesis and drug treatment options for the comorbidity of CLL.

## Keywords

chronic lymphocytic leukemia, COVID-19, cytokine storm, immunity, immunomodulation, immunosuppression

## Introduction

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells from various toxins, toxic compounds, or radiation, and works by removing the causative agent and initiating the healing process (Medzhitov 2010; Chen et al. 2018).

The inflammatory response requires a balance between sufficient cytokine production to eliminate the pathogen while avoiding the development of a hyperinflammatory response. Cytokines play a key role in coordinating antimicrobial effector cells and providing regulatory signals that direct, amplify, and control the immune response. At elevated levels, however, they can cause serious damage to vital organs (Fajgenbaum and June 2020; Kany et al. 2020).

Cytokine storm has no precise definition. Generally speaking, this means a hyperactive immune response characterized by the release of interferons, interleukins, tumor necrosis factors, chemokines, and other mediators. These mediators are part of the well-implemented innate immune response responsible for the effective elimination of infectious agents. Most mediators involved in the cytokine storm demonstrate downstream pleotropic effects and are often interdependent in their biological activity. The interactions of these mediators and the pathways they initiate are neither linear nor uniform. Furthermore, although their quantified levels may correlate with the severity of cellular responses, they do not always explain the entire pathogenesis of the cytokine storm (Sinha et al. 2020).

Circulating cytokine levels can be difficult to measure because cytokines have a short half-life. Furthermore, they do not always reflect the exact tissue levels. It is not correct to set a specific threshold for elevation of cytokine levels above the normal range and specific cytokine panels (Fajgenbaum and June 2020).

The term cytokine storm was first used in 1993 to describe graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (Ferrara et al. 1993; Koyama and Hill 2019). The concept of cytokine storm has been widely used in infectious diseases since the outbreak of influenza infection. H5N1 in the early 2000s, when it was used to describe the excessive production of inflammatory cytokines after infection (Yuen and Wong 2005). It was then re-used to define the adverse syndromes secondary to the administration of immunostimulatory agents, such as anti-CD28 antibodies or bioengineered immune cells, i.e., CAR T-cell therapy. Currently, the concept of cytokine storm is better understood and demonstrated as part of the pathogenesis of many other conditions, such as sepsis, autoinflammatory disease, primary and secondary hemophagocytic lymphohistiocytosis, and multicentric Castleman disease (Morgan et al. 2010; Zanza et al. 2022).

Cytokines are small polypeptides (<40 kDa) that act as intercellular mediators. They are essential for the proper functioning of the immune system and are involved in many pathophysiological processes essential for survival – not only inflammation but also tissue repair, the development of fibrosis, and coagulation processes. However, when they are produced in excess due to dysfunction of the immune system, they can cause a state of systemic hyperinflammation, the so-called. cytokine storm (de Jesus et al. 2015; Shen 2021).

The clinical manifestation of a cytokine storm includes high fever and, in severe cases, a developed toxo-infectious syndrome. In addition, patients may have fatigue, anorexia, headache, rash, diarrhea, arthralgia, myalgia, and neuropsychiatric findings. These symptoms may be due directly to cytokine-induced tissue damage or physiological changes in the acute phase or may result from immune cell-mediated responses (Karki and Kanneganti 2021). In certain cases, the condition of patients progresses rapidly and worsens – disseminated intravascular coagulation (DIC) develops with vascular occlusion or catastrophic hemorrhage, dyspnea, hypoxemia, hypotension, hemostatic imbalance, vasodilator shock, and death. Respiratory symptoms are also seen, including cough and tachypnea, which may progress to acute respiratory distress syndrome (ARDS), with hypoxemia requiring mechanical ventilation. The combination of hyperinflammation, coagulopathy, and low platelet count places patients with cytokine storms at high risk for spontaneous hemorrhage (Savla et al. 2021).

The cytokine storm is a key aspect in the novel disease COVID-19, as affected patients have high levels of certain pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, TNF-α, IFN-γ, IP-10, GM-CSF, MCP-1, and IL-10, some of which correlate with disease severity. Therefore, since the beginning of the pandemic, many drugs have been tested in the context of mitigating the cytokine storm in patients with COVID-19. Some of them are effective in reducing mortality, especially in critically ill patients, and have gradually become the standard of care – glucocorticoids or some cytokine inhibitors (Zanza et al. 2022).

COVID-19 is a highly contagious viral disease caused by the SARS-CoV-2 virus. The coronavirus pandemic has had a catastrophic effect on the world, resulting in more than 6 million deaths. The first cases of this primarily respiratory viral disease were reported in Wuhan, Hubei Province, China, in late December 2019 (Cascella et al. 2023). SARS-CoV-2 primarily targets the respiratory system, but severe complications, including cardiovascular, neurological, and renal, also contribute to mortality. The clinical picture is significantly heterogeneous, varying from asymptomatic to mild, moderate, and severe forms of the disease (Kumar and Saxena 2021).

ARDS is one of the leading causes of death in patients with COVID-19 and is mainly caused by elevated levels of pro-inflammatory cytokines in the context of the developing cytokine storm. Interleukins, such as interleukin-6 (1L-6), interleukin-1 (IL-1), interleukin-17 (IL-17), and tumor necrosis factor-alpha (TNF-α), play a very important role in lung damage in patients with ARDS through damage to the respiratory epithelium. In a cytokine storm, pro-inflammatory markers are released uncontrollably, both locally and systemically (Montazersaheb et al. 2022).

The phrase "cytokine storm" is a descriptive term that encompasses a variety of events that can ultimately lead

to multiple organ failure and death (Ye et al. 2020; Ragab et al. 2020). Suppressing the cytokine storm is therefore critical to reducing mortality in severe COVID patients (Jiang et al. 2022).

The immune system is vital to the host in fighting viral infections. However, excessive immune responses can lead to the development of various pathological processes (Ye et al. 2020). Cells of the innate immune system are the first line of defense against pathogens. Neutrophils, monocytes, and macrophages, or killer (NK) cells, recognize pathogens, produce cytokines, and engulf pathogens and cells by phagocytosis. Innate immune cells use pattern recognition receptors that are not specific for any particular antigen to recognize and respond to a wide variety of microbial invaders by producing cytokines that activate cells of the adaptive immune system (Hashimoto et al. 2013).

The adaptive immune system consists of B cells and T cells. T cells differentiate into a number of subsets with different effector cell functions potentially involved in the unfolding of the cytokine storm. Type 1 helper T (Th1) cells and cytotoxic T lymphocytes (CTL) are responsible for host defense against viral infections. Th1 cells regulate macrophage functions, while type 2 helper T (Th2) cells are responsible for eosinophils and basophils, type 9 helper T (Th9) cells regulate mast cells, and type 17 helper T (Th17) cells are neutrophils (Sallusto 2016).

Viral invasion triggers a series of immune responses that can further lead to the development of a cytokine storm and even acute respiratory distress syndrome (ARDS) and death (Channappanavar and Perlman 2017).

A number of clinical studies have demonstrated higher plasma concentrations of pro-inflammatory cytokines in critically ill patients than in those with mild to moderate COVID-19 infection, suggesting that the cytokine storm is also directly related to the severity of COVID-19 disease (Huang et al. 2020).

The underlying mechanisms responsible for the unrestrained release of inflammatory factors are still unclear, but several hypotheses exist. The first is related to virus replication, which leads to pyroptosis, a highly inflammatory form of lytic-programmed cell death (apoptosis). In patients with COVID-19, pyroptosis triggers the release of proinflammatory cytokines and affects macrophage and lymphocyte functions, causing peripheral lymphopenia (McGonagle et al. 2020; Tavakolpour et al. 2020).

Increasing evidence points to an interferon (INF)-1-induced shift in innate immunity. INF-1 is a vital factor in viral replication and promotion of the adaptive immune response. Indeed, SARS-CoV2 affects the host's innate immune response and attenuates the function of INF-1 in response to infection (Huang et al. 2020). The IFN-response is an essential element in humoral antiviral defense. Current data point to a possible dysregulation of IFN type I and type III in SARS-CoV-2 infection. A number of studies have reported an impaired type I IFN response in severe or critical COVID-19 patients accompanied by high viral load and an uncontrolled inflammatory response generated by NF-kB. This type of immune response is associated with increased levels of tumor necrosis factor (TNF)- and interleukin (IL)-6. Recent analyses of results obtained from studies in animal models of SARS-CoV2 infection suggest that type I and III IFNs contribute to limiting local (type III) and systemic (type I) viral spread (Deng et al. 2020; Heymann et al. 2020).

IL-1, as part of humoral immunity, is another important cytokine associated with inflammatory responses in the human body. It is mainly secreted by activated mononuclear phagocytes and can induce other cytokines such as IL-6 and TNF. IL-1 activated by SARS-CoV2 stimulates the secretion of IL-6 and TNF in complex, which can trigger a cytokine storm with fatal pulmonary and systemic effects (Henry et al. 2020).

After a viral infection, macrophages, dendritic cells, and neutrophils launch the immune response as the body's first line of defense. Consistent with this notion, lung autopsies of patients who died of COVID-19 revealed a high infiltration of macrophages in the bronchial mucosa (Barton et al. 2020).

The second hypothesis is related to adaptive immunity and the production of neutralizing antibodies against the surface antigen of the virus. Several animal studies have demonstrated that immunoglobulin (Ig) Gs can bind to the S protein and trigger inflammatory cascades. This binding can accumulate proinflammatory macrophages and monocytes in the lungs by releasing IL-8 and monocyte chemoattractant protein (MCP)-1. The inflammatory response is mediated by the interaction of the Fc receptor (FcR) on the surface of monocytes/macrophages with the virus-anti-S-IgG complex. This notion is supported by the decreased level of pro-inflammatory cytokines following blockade of macrophage receptors (Lowe et al. 2019; Adhikari et al. 2020).

A multicenter retrospective study of 150 patients with COVID-19 in China evaluated predictors of mortality from COVID-19. The study analyzed data from 82 cases that recovered from COVID-19 and 68 cases that died from COVID-19 and reported significantly higher levels of IL-6 in death cases than in cured cases (Ruan et al. 2020).

Another study analyzing data from 21 patients in China reported increased levels of IL-10, IL-6, and TNF-α in severe cases (n = 11 patients) compared with moderate cases (n = 10 patients) (Chen et al. 2020).

A similar study by Gao et al. evaluated 43 patients in China and reported that IL-6 levels were significantly higher in severe cases (n = 15) than in mild cases (n = 28) (Gao et al. 2020).

Due to the large-scale impact of the novel coronavirus disease on the population due to the high contagiousness of SARS-CoV2, the work of scientists has mainly focused on the etiology, pathogenesis, prevention, prophylaxis, treatment, and recovery from this disease. Multiple studies have found that the course of the disease is directly influenced by the state of the immune system before infection with the SARS-CoV2 virus and the possibilities of immunomodulation during the disease itself. As unfavorable prognostic factors, a number of concomitant diseases

of the patients were indicated, such as cardiovascular diseases, diseases of the respiratory system, diabetes mellitus, and oncological diseases.

In this review, we will demonstrate the course of coronavirus disease in patients with an accompanying hemato-oncological disease, namely chronic lymphocytic leukemia.

Chronic lymphocytic leukemia (CLL) is a low-grade B-cell lymphoma with circulating cells, often presenting as hyperlymphocytosis. The 2022 updates of the classification of lymphoid neoplasms by the World Health Organization and the Clinical Advisory Committee for International Consensus Classification agree to define chronic lymphocytic leukemia (CLL) as a low-grade lymphoproliferative neoplasm with $\geq 5 \times 10^9$/L clonal B cells in the peripheral circulation, which express CD5, CD19, CD20 (dim), and CD23. All CLL cases were preceded by monoclonal B-cell lymphocytosis (MBL), a premalignant condition defined as $<5 \times 10^9$/L clonal B-cells in the absence of lymphadenopathy, organomegaly, and cytopenias (Alaggio et al. 2022).

CLL mainly affects the elderly. The average age of people when they are diagnosed is around 70 years old. It is rarely seen in people under the age of 40 and is extremely rare in children (Siegel et al. 2020). The American Cancer Society's projections for leukemia in the United States for 2023 are: about 59,610 new cases of leukemia and about 23,710 deaths from leukemia (all kinds). Of these, 18,740 new cases of chronic lymphocytic leukemia (CLL) and about 4,490 deaths from CLL. CLL accounts for about a quarter of new leukemia cases. The average lifetime risk of a person getting CLL is about 1 in 175 (0.57%). The risk is slightly higher in men than in women.

Representing the major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL), immunosuppression is a common feature of the disease. Effectors of the innate and adaptive immune response show marked dysfunction and bias toward generating a tolerant environment that favors disease propagation. Major dysregulations are found in T lymphocyte function, with inhibition of CD8+ cytotoxic and CD4+ activated effector T cells replaced by exhausted and more tolerogenic subsets. Likewise, monocyte differentiation to a suppressive M2-like phenotype is induced at the expense of proinflammatory subpopulations. Due to their B-regulatory phenotype, leukemic cells play a central role in promoting immunosuppression by progressively inhibiting immune responses (Arruga et al. 2020).

Immunosuppression and increased risk of infections may be due to factors related to the patient, therapy, and disease pathogenesis (Solomon et al. 2013; Teh et al. 2018). Quantitative and qualitative defects in the immune system are observed in almost all patients with CLL, such as alterations of the innate immune system. include defective function of neutrophils, natural killer (NK) cells, and reduced complement activity. On the adaptive immune response side, deficits in cell-mediated immunity with hypogammaglobulinemia, down-regulation of T-cell function, and defects in antibody-dependent cellular cytotoxicity have been reported (Forconi and Moss 2015).

Although the mechanisms remain unclear, new insights are emerging into the complex relationship between the CLL clone and its immune environment. T cells increase early in the disease and show progressive accumulation and exhaustion. The mechanisms that drive this expansion may involve auto-antigens involved in the initial clonal expansion. Attention is now focused largely on direct tumor immunosuppressive properties. Notably, CLL clones often have features of the recently described regulatory B cells producing immunosuppressive IL-10 (Forconi and Moss 2015).

A range of qualitative abnormalities in neutrophil function have been described, including impaired phagocytic killing of non-opsonized bacteria and a reduction in C5a-induced chemotaxis. Interestingly, the number of circulating monocytes is increased by >60% in CLL patients, but such cells carry a "non-classical" CD14+CD16++ phenotype and have a gene expression profile associated with immunosuppressive properties (Maffei et al. 2013). Deficiencies of β-glucuronidase, lysozyme, and myeloperoxidase are associated with a relatively "refractory" state with an impaired response to classical pathogen-induced inflammatory responses (Jurado-Camino et al. 2015).

Although not resistant to stimuli from normal B cells, monocytes can be directed to an immunosuppressive or "non-classical" M2 macrophage-like phenotype upon interaction with CLL-derived soluble stimuli. Natural killer (NK) cells are also increased in the circulation of CLL patients but appear to have several functional defects, including impaired cytotoxic activity, probably mainly due to defective expression of the NKG2D coreceptor (DiLillo et al. 2013; Burger and Gribben 2014; Audrito et al. 2015).

Only patients with active or symptomatic disease or with advanced Binet or Rai stages require therapy. They present with massive or progressive lymphadenopathy or hepatosplenomegaly, a low neutrophil count, anemia or thrombocytopenia, and/or symptoms of fever, profuse night sweats, and weight loss (symptom B). When treatment is indicated, several therapeutic options exist: a combination of the B-cell lymphoma 2 (BCL2) inhibitor venetoclax with obinutuzumab (an anti-CD20 monoclonal antibody), monotherapy with Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib and acalabrutinib, or chemoimmunotherapy. In case of relapse, the initial treatment may be repeated if the treatment-free interval exceeds 3 years. If the disease recurs earlier, therapy should be changed using an alternative regimen (Hampel and Parikh 2022; Shadman 2023).

Patients with del(17p) or TP53 mutations are usually resistant to chemotherapy and therefore should be treated with targeted agents. Targeted therapies have become the new standard of care in CLL, given their superior progression-free survival (and overall survival, in some cases) compared to chemoimmunotherapy, as well as their improved toxicity profiles. Targeted agents are FDA-approved for the treatment of CLL, including ibrutinib,

acalabrutinib, zanubrutinib, and venetoclax. Importantly, unlike traditional chemotherapy regimens, the benefits of these targeted therapies appear to be consistent regardless of high-risk mutational status (Burger 2021; Karr and Roeker 2023).

## Patients and methods

For the period from 01.04.2020 until 01.05.2022, through the COVID units of UMBALSM (University General Hospital for Active Care and Emergency Medicine), "N. I. Pirogov" passed 10,083 patients with a clinical picture of coronavirus infection and with a proven positive PCR test for SARS-CoV2.

Almost 2/3 of our patients had moderate-to-severe coronavirus disease. They were defined on the basis of clinical symptoms, the percentage of affected lung parenchyma determined by computed tomography examination, laboratory parameters, and accompanying diseases.

In the retrospective analysis performed, which may not be extremely accurate due to the emergency conditions in which the patients are admitted and the anamnesis taken, we found that the number of patients with proven concomitant oncological disease at the time of admission to the clinic was 216 (2, 14% of the total number of admitted patients). Patients with chronic lymphocytic leukemia are 3.7% (8 pc) of patients with a coronavirus infection and with an accompanying oncological disease.

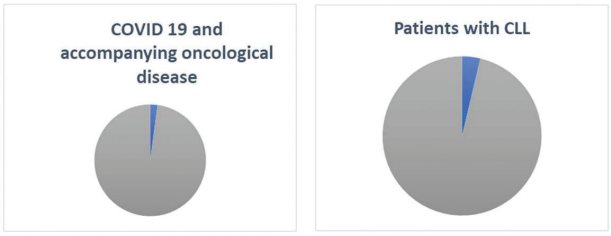


**Figure 1. A.** Cases with malignant tumors as percentage among coronavirus-infected patients in our department (hospital); **B.** Patients with CLL as a part of all infected oncological patients.

The course of the disease in the CLL patients was compared with a control group of 100 patients treated in the department for the same period of time, in the same age group corresponding to the average age of the patients with the oncological disease. The mean age of patients with CLL was 68.1 years; the mean age of the control group was 66.7 years.

Patients with a positive RT-PCR test for SARS-CoV2 and an accompanying diagnosis of chronic lymphocytic leukemia without CLL therapy before hospitalization were 6 (75%), and two on fludarabine and rituximab therapy (by anamnestic data).

For this purpose, we used subjective complaints such as tiredness, fatigue, and joint and muscle pain and objective criteria such as temperature, laboratory markers of inflammation, imaging, and intubation frequency.

## Results

No significant differences were found in the subjective complaints of patients with coronavirus infection with or without cancer. In all patients, the symptoms of general exhaustion, fatigue, and pain in the joints and muscles are present. Since these symptoms are also characteristic of the clinical picture of CLL, it cannot be specified whether they are the result of the coronavirus infection or are due to the accompanying disease.

Temperature as one of the characteristics of the inflammatory process was also the subject of the study. When comparing the mean value of the highest temperature measured within the first ten days of hospitalization, the following line diagram was obtained. In patients with CLL, the temperature values are not as high as in the control group.

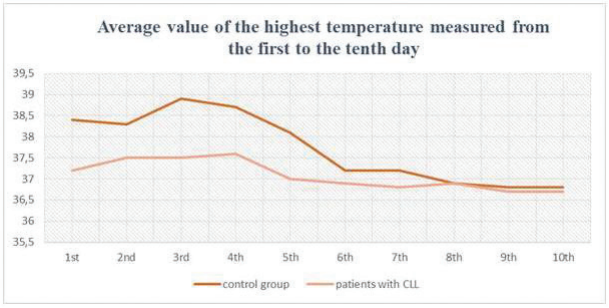


**Figure 2.** Average value of the highest measured temperature in the control group and in the CLL patients.

### Clinical laboratory

From the Table 1, it can be seen that the leukocyte count in patients with CLL is significantly higher. Platelet count was also lower in the CLL group. ERS (erythrocyte sedimentation rate) and CRP (C-reactive protein) were higher in the control group.

**Table 1.** Comparison of clinical laboratory results in controls and CLL patients.

| Test | Control group | CLL | Ref. borders | Unit |
|---|---|---|---|---|
| **WBC** | 8.76 | 55.4 | 4.1–11.0 | $\times 10^9$/L |
| **LY** | 0.38 | 32.1 | 0.6–4.1 | $\times 10^9$/L |
| **HGB** | 156 | 132 | 140–180 | g/L |
| **PLT** | 306 | 118 | 140–440 | $\times 10^9$/L |
| **ERS** | 42 | 23 | 0–20 | mm/h |
| **CRP** | 19.5 | 5.6 | 0.00–0.50 | mg/dL |
| **Fibrinogen** | 6.4 | 5.1 | 1.5–4.5 | g/L |
| **Ferritin** | 748.8 | 346 | 20–250 | ng/mL |

### Imaging diagnostics

Patients with a positive RT-PCR test for SARS-CoV2 and with atypical viral pneumonia, relative to the involved lung parenchyma, are divided into the following groups: with an involvement of less than 25%; 25–50%; 50–75%; and above 75%.

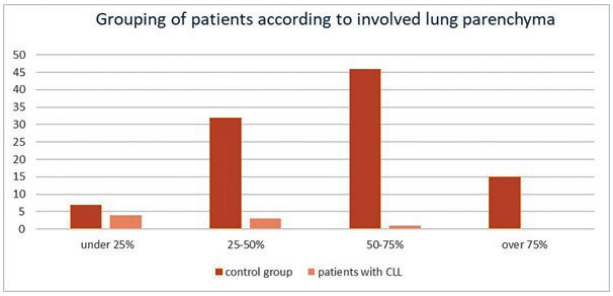


**Figure 3.** Distribution of COVID-19 patients into groups according to the percentage of parenchymal lung involvement. Lung parenchymal affection is clearly more extensive in the control group without CLL.

In the control group of patients, a trend of moderate and severe lung involvement with atypical viral pneumonia was noted, with patients with lung involvement 25–50% being 32 (32%), involvement 50–75% being 46 (46%), and over 75% being 15 (15%).

In the CLL patients, there was none with CT findings greater than 75% involvement and only one with involvement in the 50–75% group. Of course, these results are not sufficiently representative due to the insufficiently large number of patients included in the study. CLL patients with parenchymal involvement with atypical viral pneumonia under 25% are 4 (50%), 25–50% are 3 (37.5%).

Greater involvement of the lung parenchyma with atypical viral pneumonia is a prerequisite for a more severe course, a longer hospital stay, a greater likelihood of bacterial superinfection, a greater likelihood of intubation, and a fatal outcome of the coronavirus disease.

The average hospital stay of the patients with COVID-19 and CLL was 11.7 days; for the control group of patients, it was 18.4 days. Of the patients included in the study, six were intubated; all were from the control group.

## Discussion

Our retrospective analysis indicates that the small group of coronavirus-infected patients with CLL had a significantly milder course of COVID-19 as compared to the control group of patients without CLL. In patients with this hematologic malignancy, the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is significantly restricted, thus explaining the lower mortality rate of hospitalized for SARS-CoV-2 infection CLL in patients. Active immunization is an essential pillar to prevent SARS-CoV-2 infections, even in patients with hematologic malignancies. However, the immune response to SARS-CoV-2 vaccines may be significantly impaired, as only half of patients with hematologic malignancy develop a measurable antiviral antibody response. On the one hand, the subtype of hematologic malignancy and B cell-depleting treatments (e.g., Rituximab, Ofatumumab, and Obinutuzumab) are predictive for poor immune response to vaccination (Langerbeins and Hallek 2022). On the other hand, patients with hematological

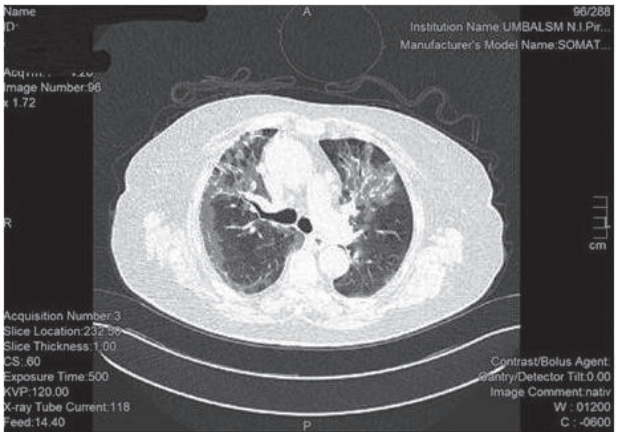


**Figure 4.** CT data for atypical pneumonia with viral genesis with moderately severe involvement 50–75% (patient with CLL).

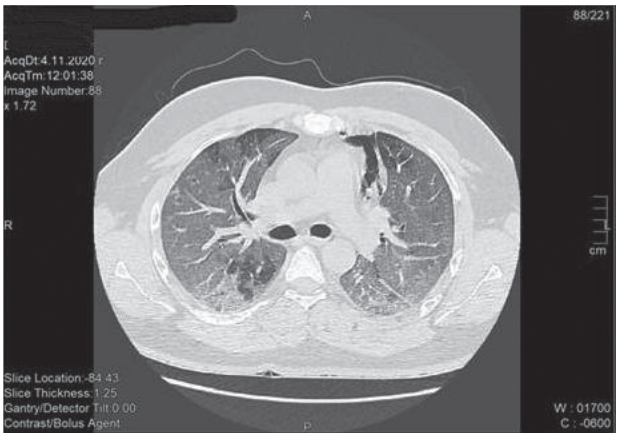


**Figure 5.** CT data for atypical pneumonia with viral genesis: very severe involvement over 75% (chest CT of a patient from the control group).

comorbidities require specific attention when managing the SARS-CoV-2 infection.

Acute respiratory distress syndrome (ARDS), in the pathogenesis of which elevated levels of pro-inflammatory cytokines and the development of the so-called "cytokine storm" play a major role, is recognized as the main cause for fatal outcomes in patients with COVID-19. Pro-inflammatory interleukins, such as interleukin-6 (1L-6), interleukin-1 (IL-1), interleukin-17 (IL-17), and tumor necrosis factor-alpha (TNF-α), play a key role in lung damage in ARDS patients through the impairments of the respiratory epithelium and pulmonary endothelium (Montazersaheb et al. 2022).

The more severe course of the coronavirus infection in the patients in our control group seems striking and unexpected in terms of higher and more prolonged fever, higher laboratory values of inflammatory markers, more extensive lung parenchymal involvement, and consequently longer hospitalization and more frequent intubation need. In contrast, the clinical manifestations in patients with a positive RCR test for SARS-CoV-2 and diagnosed accompanying chronic lymphocytic leukemia are relatively weaker and with a favorable outcome, followed by quicker recovery from COVID-19. Our explanation of the observed clinical findings is most probably related to some

typical CLL pathogenic alterations. Representing a major feature in the pathogenesis of CLL, immunosuppression in these 8 patients most likely "protected" them from the unfolding of the cytokine storm and ultimate development of ARDS, followed by multiple organ failure.

As already mentioned, the leukocyte count in patients with CLL is significantly higher. This, together with the lymphocyte count, directly reflects the accumulation of leukemic cells and the suppression of hematopoiesis and immunity. Lower hemoglobin values also support the above statement about alterations of the hematopoietic system during CLL progression. Platelet count was also lower in the CLL group. ERS and CRP were higher in the control group, and this reflects the unrestricted inflammatory processes, thus showing the capacities of the uncompromised immune system of these patients to react against the SARS-CoV-2 invasion. In addition, given the additional immunosuppression after CLL drug treatment, we cannot claim that CLL would be milder in actively treated CLL patients because 75% of our patient group had never received specific CLL therapy. Therefore, the only reason for the observed milder COVID-19 infection should be regarded as abundant to the CLL pathogenesis immunity modulation. A number of authors (Niemann et al. 2022) suggested that patients with CLL can limit their SARS-CoV-2 inflammatory reaction, thus avoiding severe manifestations (including death). Recent work has suggested that, in the general population, the risk of severe outcomes after SARS-CoV-2 infection is substantially lower for those infected with the omicron variant. The analysis by Niemann et al., for example, concentrates on immunocompromised patients and confirms that this reduction of the risk for severe outcomes also holds true for younger patients with CLL (Scarfò and Herishanu 2022).

The role of immunity in COVID-19 is highly complex. Briefly, the accepted paradigm is that infection by SARS-CoV-2 (affecting primarily T lymphocytes, particularly CD4+ helper and CD8+ cytotoxic effector T cells) is followed by rapid viral replication, unless it is controlled by a competent and efficient immune system. If the virus is not controlled at this point, further viral replication may lead to cytokine-induced inflammatory storms with severe pulmonary disease and disseminated thromboembolism. Patients with CLL do not have an efficient immune system. This results in a paradox: while a weakened immune system may not be capable of eliminating SARS-CoV-2, it might help to prevent a fatal immune and inflammatory overreaction (Scarfò and Herishanu 2020). It could be speculated that the CLL-related immunodeficiency, rather than exacerbating the effects of SARS-Cov-2, might prevent them (Baumann et al. 2020).

## Conclusion

Despite the expected poor prognosis in patients with concomitant oncological disease, in the case of chronic lymphocytic leukemia, our results show a different perspective. Due to the pathogenesis and clinical picture accompanying CLL, namely immunosuppression, patients with this disease cannot develop such a pronounced cytokine storm, which is the basis of the pathogenesis in patients with coronavirus infection who develop the most severe form of COVID-19. Clearly, our results are based on a very modest number of patients and are far away from common significance. The possibility of developing a secondary bacterial infection is higher in patients with CLL; this is taken into account, and therefore they are "protected" empirically with broad-spectrum antibiotic therapy. These peculiarities in the clinical course of both diseases demonstrate the need for thorough knowledge about comorbidities in COVID-19 hospitalized sick patients. In the specific case of our 8 CLL patients, the accompanying oncological disease does not impose a "severe sentence" on the patient, as was, in a certain sense, "speculated" at the beginning of the pandemic. On the other hand, however, it unequivocally emphasizes the absolutely necessary antibiotic prophylaxis as part of the complex treatment of the coronavirus infection. One of the goals of our study is to show the need for individual approach to the patient with COVID-19 even in the "emergency" conditions under which the patients were treated. A good therapeutic strategy requires detailed knowledge of the specifics of the accompanying diseases, thus matching the right therapeutic behavior according to the expected interplay between COVID-19 and the patient's comorbidities.

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