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Prognostic factors of COVID-19 pneumonia and the value of tocilizumab therapy

by Miklós Szabó MD

Supervisor: Zoltán Szekanecz MD, PhD, DSc

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By Miklós Szabó, MD

Supervisor: Prof. Zoltán Szekanecz, MD, DSc

Doctoral School of Clinical Medicine, University of Debrecen

Head of the **Defense Committee**:	Prof. Árpád Illés, MD, DSc
Reviewers:	Anna Kerpel-Fronius, MD, PhD Zoltán Griger, MD, PhD
Members of the Defense Committee:	Anna Kerpel-Fronius, MD, PhD Zoltán Griger, MD, PhD Prof. Ildikó Horváth, MD, DSc Prof. Lilla Tamási, MD, DSc

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1. Introduction

1.1. The impact of the COVID-19 pandemic on the healthcare system

The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported at the end of 2019 from the Chinese city of Wuhan. Due to its high infectivity, the virus caused a pandemic within a few months.

The multifaceted disease caused by the virus is called coronavirus disease 2019 (COVID-19). Although the majority of patients were asymptomatic or had mild symptoms, the average mortality in the first waves of the epidemic was 2-3%. In 5-10% of patients, the disease had a severe course, requiring hospitalization. In the vast majority of these patients, hospitalization was due to pneumonia developing as part of the multisystem inflammatory syndrome (MIS). The epidemic has led to a significant and rapid increase in hospital admissions worldwide, overburdening health care systems and pushing the limits of the capacities of intensive care units.

The number of SARS-CoV-2 infections, morbidity and mortality increased significantly in Hungary in the second and third waves as well. The fatality rate was 3.6% and 3.5%, respectively.

1.2. Pathogenesis, symptoms and stages of SARS-CoV-2 infection

The virus enters human cells via the angiotensin I converting enzyme 2 (ACE2) receptor, which is expressed in large quantities on the alveolar pneumocytes of the lung, so the lung is a prominent target organ for viral infection. In addition to many tissues, the virus can also infect immune cells, causing low white blood cell and lymphocyte counts in severe infections.

Virus particles released from infected cells are taken up by antigen-presenting cells, processed and then presented to T-lymphocytes. Activation of T- and B-lymphocytes leads to the release of cytokines and the production of antibodies. Under physiological conditions, the viral load decreases as a result of the immune response. At the same time, inflammatory processes are downregulated, which enables healing. However, in some cases, the immune

response becomes unregulated, which can lead to significant tissue damage, thereby worsening the patient's condition or even death.

Symptomatic patients mostly complained of disturbances in the sense of smell and taste, runny nose, sore throat, followed by fever or high temperature, weakness, muscle pain, headache, cough and gastrointestinal symptoms (vomiting, diarrhea and abdominal pain). Based on the data of hospitalized patients, dyspnea occurs 5-8 days after the onset of symptoms and indicates worsening of the disease.

Based on the pathogenesis, COVID-19 can be divided into several stages, which determine the therapeutic actions. Stage I is characterized by viral infection with general symptoms (fever, muscle pain, headache), impaired sense of smell and taste, cough, vomiting and diarrhea. The II. Stage is characterized by damage to the lungs and other organs, in which viraemia and an increasing inflammatory immune response are present at the same time. Based on the severity of lung involvement, the second stage is divided into stages IIA and IIB. Dyspnoea and hypoxia are already present in stage IIB, unlike stage IIA. The third stage is the multisystem inflammatory syndrome, which can be accompanied by a pronounced cytokine storm.

1.3. COVID-19 associated MIS/cytokine storm

The MIS/cytokine storm associated with COVID-19 is a clinical manifestation of excessive, pathological activation of the immune system. In many respects, the phenomenon is similar to other hyperinflammatory pathologies, such as macrophage activation syndrome, hemophagocytic lymphohistiocytosis, cytokine release syndrome (CRS) and macrophage activation-like syndrome associated with sepsis.

Through the activation of adaptive immunity and autoinflammation, many proinflammatory cytokines are produced to an increased extent, increasing vascular permeability, inducing endotheliitis and angiogenesis. The activation and immigration of white blood cells leads to further inflammation, tissue collagen deposition, and later fibrosis, while the activation of blood coagulation pathways leads to the formation of microthrombi. During the activation of adaptive immunity, immune cells (macrophages, neutrophil granulocytes and T-lymphocytes) secrete large amounts of IL-6, as well as IL-2, IL-4, IL-10, IL-18 cytokines, interferon γ (IFN- γ), they produce tumor necrosis factor α (TNFα), bradykinin, granulocyte

colony-stimulating factor (G-CSF) and chemokines. The MIS/cytokine storm associated with COVID-19 leads to damage in many organs (respiratory system, gastrointestinal system, heart, central nervous system, liver and kidney). Pronounced cytokine storm with high mortality manifests in nearly 2% of COVID-19 patients and in a tenth of severe patients.

The massive lung involvement characteristic for MIS can be verified and monitored with radiological imaging procedures (chest X-ray, chest CT). In addition to the clinical and radiological picture, MIS can be indicated by several laboratory parameters. In practice, elevated C-reactive protein (CRP), IL-6, ferritin, lactate dehydrogenase (LDH) and D-dimer values, leukocytosis, lymphopenia, the neutrophil-lymphocyte ratio and a decrease in the platelet count are mostly used to diagnose the condition.

1.4. Treatment of COVID-19

In the case of a symptomatic infection, the therapy must be adapted to the clinical stage. In the early stages of infection (stage I-IIA), antiviral drugs can help reduce the body's viral load. The use of corticosteroids is not recommended in this phase. This was also supported by the subgroup analysis of the RECOVERY study, in which dexamethasone treatment used in patients not requiring oxygen support even worsened survival. However, immunosuppressive therapies are recommended in stage IIB-III, which is already dominated by the body's excessive inflammatory response (MIS/cytokine storm). Corticosteroids are used in the first step, and then, if they are ineffective, anti-cytokine antibody therapies or Janus kinase (JAK) inhibitors can be used in addition to the corticosteroid treatment. It is extremely important to start the treatment of MIS/cytostorm with the appropriate indication and timing. The use of targeted therapies is generally not recommended earlier than 7 days after the appearance of the first symptoms and is considered ideal if less than 14 days have passed since the symptoms have worsened. In addition to clinically detectable fever, elevated levels of MIS biomarkers (CRP, ferritin, IL-6, LDH, D-dimer) are required for successful treatment.

1.5. Biological effects of interleukin 6, therapeutic options

IL-6 is one of the central molecules of the body's inflammatory processes, which is produced in large quantities at the beginning of inflammatory processes. By acting on neutrophils and macrophages, IL-6 increases tissue destruction and fibrosis via fibroblasts. It

inhibits Treg cells while stimulating the differentiation of B cells and Th17 cells. It enhances angiogenesis, increases the permeability of blood vessel walls, and the production of acute phase proteins in the liver. As an endogenous pyrogen, it plays a leading role in triggering fever. The physiological role of the rapid increase in IL-6 levels caused by infections and tissue injuries is the initiation of the body's immune defenses.

Excessive production of IL-6 or dysregulation of its signaling pathways can be seen in many inflammatory diseases. IL-6 receptor inhibitors have been successfully used in autoimmune inflammatory diseases such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis, and life-threatening cytokine release syndrome. One of the most widely used IL-6 receptor inhibitors is tocilizumab (TCZ), which is a humanized IgG1 monoclonal antibody.

1.6. The role of tocilizumab in the treatment of MIS associated with COVID-19

IL-6 also plays a central role in the pathomechanism of MIS associated with COVID-19, so the possibility of using the IL-6 receptor inhibitor TCZ was raised already within a few months of the outbreak of the epidemic. The first positive experiences came from a Chinese study, in which a reduction in fever, improved oxygenation, a decrease in CRP, cessation of lymphopenia and radiological regression were observed after the treatment.

Subsequently, the results of several clinical trials and meta-analyses (REMAP-CAP, CHIC, RECOVERY, WHO REACT consortium) also proved its effectiveness in stage IIB-III COVID-19 patients. In this group of patients, the drug improved the clinical condition, reduced the need for subsequent invasive mechanical ventilation and increased survival. Several studies have proven that TCZ combined with corticosteroids is more effective than TCZ monotherapy in terms of both survival and the subsequent need for ventilation.

However, TCZ did not provide a survival benefit in the phase III COVACTA study, which enrolled mild and moderate patients without the use of MIS biomarkers.

To predict the effectiveness of TCZ therapy, in addition to the clinical picture, we have biomarkers that confirm the existence of MIS. IL-6 serum level itself is a useful marker at the start of treatment. However, due to the mechanism of action of TCZ, the level of IL-6 increases temporarily after the treatment, so it is not suitable for monitoring the effectiveness of the therapy. In addition to the patient's clinical condition and radiological picture, laboratory

parameters such as CRP, ferritin, LDH, D-dimer and cardiac troponin (cTn) are suitable for assessing the therapeutic effect of TCZ.

In Hungary, on October 8, 2020, TCZ was authorized for off-label use in the treatment of the cytokine storm associated with COVID-19. It has been successfully used in several centers in Hungary in the treatment of severe COVID-19 patients, but a comparative study with a control group has not yet been published.

1.7. Factors determining the severity and prognosis of COVID-19 associated pneumonia

During the pandemic caused by SARS-CoV-2, the number of patients diagnosed with COVID-19 pneumonia reached an extremely high number, while the finiteness of healthcare resources became apparent. In order to guarantee patient safety and optimal use of healthcare capacities, it is essential to objectively determine the severity and prognosis of patients. Numerous demographic, medical history, symptomatic, physical examination, laboratory and imaging parameters have been described as prognostic factors in the literature. There are few reports on their studies on the Hungarian COVID-19 patient population.

1.8. The role of complex clinical scoring systems in determining the severity and prognosis of COVID-19 pneumonia

Complex scoring systems using a combination of several prognostic factors exceed the sensitivity, specificity and predictive value of individual markers, which is why they are used with preference in estimating the outcome of many diseases.

Several of the scoring systems used to assess the severity and prognosis of community-acquired pneumonia or other critical conditions have been suggested for use in COVID-19.

The calculation of some of the scoring systems is quite time-consuming, which is not necessarily proportional to their prognostic value.

The A-DROP scoring system is a modified version of the CURB65 (Confusion, Urea, Respiratory Rate, Blood Pressure, 65 years), which proved to be equivalent in determining the severity and risk of community-acquired pneumonia (CAP). The A-DROP scoring system for

CAP risk assessment was validated and approved by the Japan Respiratory Society. A-DROP gives equal weight (1-1 points) to age (≥70 years in men and ≥ 75 years in women), dehydration (blood urea level ≥7.5 mmol/l), respiratory failure (oxygen saturation [SaO_2]≤ 90% or partial arterial oxygen pressure [PaO_2]≤ 60 mmHg), disturbed consciousness and low blood pressure (systolic blood pressure ≤ 90 mm Hg). In addition to its simple applicability, one of the potential advantages of the A-DROP scoring system may be that, unlike CURB65, it uses arterial blood oxygenation, which can be measured in an exact way, in contrast to respiratory rate, the latter of which has been described as having a significant degree of variability. The prognostic value of A-DROP in COVID-19-associated pneumonia has only been investigated in very few cohorts. The aggregated risk can also be modified by ethnic, cultural and social factors, causing significant differences between individual countries and regions. We did not find any Hungarian study reports on the applicability of the available prognostic clinical scoring systems in COVID-19 pneumonia.

1.9. The role of chest CT in determining the severity and prognosis of COVID-19 pneumonia (radiological signs and patterns, chest CT severity scoring systems)

Imaging of the chest play a prominent role in the diagnosis of pneumonia that develops as a complication of a new type of coronavirus infection. Computed tomography (CT) examination of the chest is the most sensitive in evaluating the involvement of the chest organs. At the same time, it provides objective information about the presence, distribution, extent and quality of lung involvement.

The high-resolution (HRCT) examination also enables the objective assessment and monitoring of the pathological processes taking place in the lungs and the consequent morphological changes in patients with COVID-19 pneumonia.

During the course of the disease, ground-glass opacities, consolidation, reticular and crazy-paving patterns are most often described in the lungs, but in addition to these, air bronchogram, halo sign, inverted halo sign, mediastinal lymphadenopathy, pleural fluid, pericardial fluid, subpleural line, fibrosis are seen with varying frequency. In addition to their diagnostic role, radiological changes that can be traced back to pathological processes also have prognostic value. A worse prognosis was reported in the presence of lymphadenopathy, pleural fluid, air bronchogram, consolidation and increased pulmonary artery diameter. The dynamics of radiological progression can also be a prognostic factor.

The CT scan of the chest is suitable for assessing the extent of lung involvement, thereby determining the severity and prognosis of pneumonia. In order to quantify the degree of lung involvement in COVID-19 associated pneumonia, several semi-quantitative scoring systems have been developed, in which the radiologist determines and scores the extent of lung damage based on the image seen. The principle of these scoring systems is the same, they mostly differ only in how many volume units the lungs are divided into and on what scale the percentage of damage is classified.

Pan et al. proposed a chest CT severity score system (CTSS) ranging from 0 to 25, in which the percentage involvement of the lung lobes is scored individually from 0 to 5 and then summed. Using the scoring system proposed by Pan et al. (hereafter “CTSS-Pan”), Francone et al. found significantly higher scores in severe and critical patients than in milder cases. "CTSS-Pan" showed a significant correlation with D-dimer and CRP values. In their study, a "CTSS-Pan" value above 17 showed a significant correlation with a higher probability of death. Yang et al. divided the lung into 20 units and evaluated the percentage of involvement per unit on a scale of 0-2. In this study as well, a significantly higher score was calculated in severe patients than in mild cases. Considering the prognostic role of the CT pattern, some scoring systems quantify the degree of attenuation in addition to the extent of lung damage. Yuan et al.'s semiquantitative scoring system based on this principle indicated mortality with good sensitivity and specificity at a decision threshold of 24.5. There have been only a few studies comparing the prognostic value of semiquantitative scoring systems.

The application of CT severity scoring systems and radiological patterns and comparison with clinical and laboratory parameters can help to identify high-risk COVID-19 pneumonia patients in time and supporting therapeutic decisions.

2. Objectives

During the pandemic, our institution was designated for the care of COVID-19 patients. It was a serious challenge for our doctors to identify and treat serious cases with a poor prognosis among the large number of patients with COVID-19 pneumonia who came to our center. Due to the unexpected and rapid appearance of the pathogen and the epidemic, sufficiently tested prognostic scoring systems and therapies were not available. World literature data supported the use of prognostic scors and therapies used in other diseases. The applicability of the A-DROP scoring system developed for community-acquired pneumonia risk assessment in COVID-19 pneumonia has only been analyzed in a complex manner in a few studies. There are also few studies comparing the performance of available semiquantitative CTSS systems.

Several studies have confirmed the effectiveness of TCZ in the treatment of severe COVID pneumonia complicated by MIS, unresponsive to corticosteroid treatment. However, many questions remain unanswered regarding the optimal timing of TCZ treatment and the number of doses. We have successfully introduced the use of the drug in our COVID-19 center. Although, similar to our institution, TCZ has been used in several Hungarian centers, to our knowledge, a Hungarian study comparing the therapeutic efficacy of TCZ in patients with severe COVID-19 pneumonia with a suitable control group has not yet been published. We considered it a successful practice that when TCZ treatment is indicated, the attending physician consults a rheumatologist/immunologist expert in immunosuppressive treatments.

2.1. Study I: Determining the severity and prognosis of SARS-CoV-2 associated pneumonia: the value of clinical and laboratory biomarkers and the A-DROP scoring system

We wanted to retrospectively assess the following in patients hospitalized for pneumonia caused by SARS-CoV-2 in our COVID-19 care center:

- demographic data, symptoms, physical examination findings and laboratory parameters, on admission,

- the correlation of the patients' parameters with each other and the subsequent clinical outcome (respiration, need for intensive care unit placement, death),
- the value of the A-DROP scoring system in determining the severity and prognosis of patients
- the optimal threshold value of the A-DROP score recorded at admission to predict the subsequent adverse clinical outcome.

2.2. Study II: The value of chest CT severity scoring systems, radiological signs and patterns in risk estimation of COVID-19 pneumonia

We wanted to retrospectively assess the following in patients hospitalized in our center due to COVID-19 pneumonia confirmed by chest CT:

- assess the radiological signs and patterns seen on the admission chest CT image,
- calculate semiquantitative chest CT severity scores using several methods,
- to investigate the correlation of chest CT patterns and chest CT severity scores with clinical outcome (intensive care unit admission, ventilatory requirement, death) and other clinical parameters and
- to compare the prognostic value of each chest CT severity score system and to determine the optimal decision thresholds.

2.3. Study III: The place of tocilizumab added to corticosteroid therapy in the treatment of COVID-19 pneumonia

We wanted to retrospectively assess the following in patients with severe COVID-19 pneumonia treated in our COVID-19 center:

- the effect of TCZ on the clinical outcome compared to those not receiving the treatment,
- the effectiveness of TCZ treatment applied in the general and intensive care units in relation to the clinical outcome,
- to assess the optimal number of TCZ treatments (1 or 2) and
- the role of the consulting rheumatologist in the effect of TCZ treatment on the clinical outcome.

3. Patients and methods

3.1. Study I

3.1.1. Patients

This single-center, retrospective cohort study was conducted at the dedicated COVID-19 department of the Borsod Academic County Hospital, Miskolc, Hungary. Data from 233 patients hospitalized for COVID-19 pneumonia between October 1, 2020, and March 31, 2021 were retrospectively analyzed. Confirmation of SARS-CoV-2 infection was performed by RT-PCR method from throat-swab specimens. Pneumonia was confirmed by radiological imaging performing chest CT in 227 and plain X-ray in 6 cases. Most patients received favipiravir, corticosteroid (dexamethasone or methylprednisolone), enoxaparine treatment, as well as oxygen supplementation. In selected cases, remdesivir or tocilizumab was also introduced. The clinical criteria for hospital discharge included absence of fever for at least 3 days, cessation or significant improvement of respiratory symptoms, as well as clear improvement of the radiological picture.

The Ethics Committee of the Borsod Academic County Hospital approved this study (BORS 04/2021). We conducted this study according to the Declaration of Helsinki.

3.1.2. Data collection and clinical evaluation

We reviewed all clinical electronic medical records and laboratory reports, as well as chest CT and X-ray images. We collected data on age, sex, as well as history of smoking, chronic comorbidities including hypertension, coronary arterial disease (CAD), chronic obstructive pulmonary disease (COPD) or bronchial asthma, previous stroke, diabetes mellitus, current malignancy, chronic kidney disease (CKD), obesity, as well as the use of systemic immunosuppressive therapy within 1 month prior to the analysis. We also recorded the duration and type of symptoms (fever: axillary temperature $\geq 38^{\circ}$C, cough, dyspnea, confusion), vital signs (blood pressure, oxygen saturation [SaO_2] by pulse oximetry), laboratory values [white blood cell, absolute lymphocyte and platelet counts, serum CRP, ferritin, IL-6, LDH, D-dimer, procalcitonin (PCT), BUN, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer], partial arterial oxygen pressure (PaO_2) as determined by

blood gas analysis, as well as treatment (corticosteroids, antiviral, and antibacterial agents, targeted therapies) at hospital admission and during the time of hospitalization. A-DROP scores were calculated from the data obtained at the time of hospital admission. All data were evaluated by two physicians and a third researcher adjudicated any difference in interpretation between the two primary reviewers.

The primary outcome parameters were the need for intensive care, need for invasive (IV) vs. Non-invasive ventilation (NIV) and mortality. Mortality was calculated from mortality observed during hospitalization, and the disease-related mortality 30 days after discharge. The time of hospitalization was also recorded.

3.2. Study II

3.2.1. Patients

Among the 233 patients with COVID-19 pneumonia included in the first study, the 227 patients who underwent a chest CT examination at admission to pronounce the diagnosis or assess the severity were included in study II.

The Ethics Committee of the Borsod Academic County Hospital approved this study (BORS 04/2021). We conducted this study according to the Declaration of Helsinki.

3.2.2. Data collection and clinical evaluation

As described in study I, retrospective data collection of patients from the medical system was carried out, followed by data recording and data analysis. Three experienced radiologists performed the review, evaluation and scoring of the chest CT images according to the corresponding CTSS. The radiologists could only view the image material, they were blinded to the clinical data of the patients. Finally, the aggregated data were All data were evaluated by two physicians and a third researcher adjudicated any difference in interpretation between the two primary reviewers.

3.2.3. Chest CT scan protocol

Chest CT scans were performed using a single inspiratory phase in a 128 multi-detector CT scanner (SOMATOM Go Top, Siemens Healthineers, Germany). To minimize motion artifacts, patients were instructed on breath-holding; CT images were then acquired during a single breath-hold. For CT acquisition, the tube voltage was 90kVp with automatic tube current modulation. From the raw data, 1mm slices were reconstructed with a pulmonary Br 64 kernel and a mediastinal Br40 kernel (Siemens Healthineers, Germany) in all three planes. All thin-section CT images were reviewed at a window width and level of 400 and 40 HU and 1,200 and −600 HU respectively, for the mediastinum and lung parenchyma.

3.2.4. Qualitative and quantitative determination of lung involvement based on chest CT images

On the chest CT, the specific pathological features, such as ground-glass opacity (GGO), crazy-paving pattern, consolidation, fibrosis, subpleural lines, pleural effusion and lymphadenopathy were evaluated, based on the Fleischner Society Nomenclature recommendations and previous COVID-19 related radiology publications. For quantitative scoring (CTSS) we used the protocol first published by Pan et al. and adapted it to our patients. We will refer to this protocol as "CTSS-Pan." In this analysis, we used the chest CT images of 227 patients and calculated the Chest CT severity score based on 3 methods. CTSS was calculated according to Pan et al. for all 227 patients. In brief, the extent of anatomic involvement was calculated in each of the 5 lobes. In each lobe, the absence of lobar involvement (0%) yielded to a score of 0, while <5%, 5–25%, 26–50%, 51–75 and >75% involvement was scored as 1, 2, 3, 4 and 5, respectively. Thus, the individual scores of the five lobes resulted in a global score of 0 to 25.

In the case of 98 patients, two other validated scoring systems published by Yang et al. and by Yuan et al. were also used. We compared our results applying the CTSS-Pan protocol with these two other systems further referred to as "CTSS-Yang" and "CTSSYuan," respectively. In the CTSS-Yang protocol reported by Yang et al.,both lungs were divided into 10-10 regions. After that, we scored the involvement of each unit separately. 0 points were given for 0% involvement, 1 point for <50% and 2 points for ≥50% involvement. Thus CTSS-Yang may range from 0 to 40 points. In the CTSS-Yuan protocol published by Yuan et al., the extent of involvement of each abnormality was assessed independently for each of 3 zones:

upper (above the carina), middle (below the carina and above the inferior pulmonary vein), and lower (below the inferior pulmonary vein). The CT findings were graded on a 3-point scale (1: normal; 2: ground-glass attenuation; 3: consolidation). Each lung zone, with a total of six lung zones in each patient, was assigned a scale according to distribution of the affected lung parenchyma (0: normal; 1: <25%; 2: 25–50%; 3: 50–75%; 4:>75% abnormality).The four-point scale of the lung parenchyma distribution was then multiplied by the radiologic scale described above. Points from all zones were added for a final total cumulative score, with value ranging from 0 to 72.

We compared the prognostic value of "CTSS-Pan", "CTSS-Yang" and "CTSS-Yuan" in relation to ventilation, intensive care unit placement and death in 98 patients.

3.3. Study III

3.3.1. Patients

This single-centre, retrospective cohort study was conducted at the dedicated COVID-19 department of the Borsod Academic County Hospital, Miskolc, Hungary. Data from patients hospitalised for COVID-19 pneumonia between 16 October 2020, and 1 April 2021, were retrospectively analysed. The confirmation of COVID-19 pneumonia was done as described in study I. All patients received antiviral and intravenous corticosteroid treatment. Regarding other aspects of the treatment and hospital discharge, they proceeded as described in study I.

The Ethics Committee of the Borsod Academic County Hospital approved this study (BORS 04/2021). We conducted this study according to the Declaration of Helsinki.

3.3.2. Tocilizumab Dosing Regimen

In the TCZ-treated group, according to the recommended protocols, all patients received at least one dose of TCZ (8 mg/kg, max. 800 mg IV), which could be repeated once more within 24 h if required. TCZ was administered in one 60 min infusion to patients receiving systemic corticosteroid treatment, and those in need of oxygen therapy or ventilation. If, after the first dose, the clinical symptoms do not improve or worsen, a second dose of 8 mg/kg may be administered after a minimum of 8 h.

3.3.3. Clinical, laboratory, and imaging data collection

The data were collected as described in the first study. In TCZ-treated patients, in addition to the results of the admission laboratory test, we also collected the results of the laboratory test immediately before the treatment (within 24 hours) and after the treatment. Post-treatment laboratory tests were performed 3.52±1.43 days after the administration of the last dose of TCZ. We recorded the use of corticosteroids and antiviral drugs, as well as the number of TCZ treatments administered to the patients. We also observed where the patient received the first TCZ treatment: in the general ward or in the intensive care unit. As rheumatologists are experts in using TCZ in rheumatoid arthritis, we also assessed how a consultation between the managing physician and a rheumatologist would influence clinical outcomes. The CT procedures and analysis, as well as the "CTSS-Pan" calculation, were performed as described in the study II.

3.3.4. Clinical evaluation

The primary outcome parameters were the need for intensive care, need for ventilation (invasive or non-invasive), and death. The time of hospitalisation was also recorded. We also compared when TCZ was administered in a general ward vs. in the ICU and correlated this with all other parameters.

4. Statistical analysis

Statistical analysis was performed using the SPSS software (IBM, Armonk, NY, United States). We used version 26.0 for study I, version 28.0 for study II, and version 29.0 for study III. Data are expressed as mean±SD for continuous and case number plus percentages (n, %) for categorical variables. The distribution of continuous variables was determined by Kolmogorov–Smirnov test. Continuous variables (e.g., CTSS scores) were assessed by Mann–Whitney U-tests. Nominal variables were compared by $\chi 2$ or Fisher's exact test. Spearman's analysis was used to test for correlations.

Multiple comparisons were performed using the stepwise method. Multivariable regression analysis was performed in order to assess determinants of outcome parameters as dependent variables. Receiver Operating Characteristic (ROC) curves show the sensitivity and specificity for every possible cut-off for a test. The cut-off value was set where the sum of sensitivity and specificity was the highest. Area under the ROC curve is measure of the usefulness of a characteristic, where a greater area means a more useful test. Odds ratio (OR), negative (NPV) and positive predictive values (PPV) were calculated with respect to clinical outcomes. $p<0.05$ were considered significant in all tests mentioned above.

5. Results

5.1. Study I

5.1.1. Characterization of hospitalized COVID-19 pneumonia patients

Altogether 233 patients were included in this study. The patient cohort included 148 men and 85 women with a mean age of 56.8 ± 8.7 years (range: 40–76 years). Disease duration (time from the first symptom to hospital admission) was 8.5 ± 5.3 days (range: 1–35 days). Altogether 7.3% received immunosuppression, 19.1% were current smokers and 30.6% were obes. The medical history of the patients included hypertension (65.1%), CAD (22%), stroke (6%), CKD (5.6%), diabetes mellitus (27.2%), malignancies (4.3%), and COPD/asthma (22%). At the time of admission, about two-third of patients had fever, dyspnea and/or coughs, while 4.3% had confusion/dizziness. According to the mean laboratory values, most of these patients had elevated CRP, LDH, ferritin, D-dimer and IL6 levels indicating systemic inflammation (MIS). Out of the 233 hospitalized patients, 49 (21.2%) required admission to ICU. Altogether 46 patients (19.7%) needed ventilation, out of which 9 (3.9%) required NIV and 37 (15.9%) invasive ventilation. Forty patients (17.2%) died. The mean (±SD) duration of hospitalization was 12.1±6.8 days (range: 2–48 days).

5.1.2. Determinants of intensive care units admission, need for ventilation and death

In the binary analysis, admission to ICU was significantly more often associated with hypertension (p=0.002) or obesity (p=0.014) in the medical history, as well as with confusion at hospital admission (p=0.034). Among the laboratory parameters, ICU admission was associated with higher absolute leukocyte (p=0.045), higher neutrophil (p=0.034) and lower lymphocyte counts (p=0.007), CRP (p<0.001), PCT (p<0.001), LDH (p<0.001), ferritin (p=0.042), IL-6 (p=0.026), BUN (p = 0.015), creatinine (p=0.001), PaO_2 (p=0.001) and SaO_2 (p=0.001).

The need for ventilation was significantly associated with male sex (p=0.018), history of hypertension (p=0.010), obesity (p=0.031) or malignancy (p=0.021), as well as with confusion/dizziness upon admission (p=0.044). Among the laboratory parameters, the need for ventilation was associated with leukocytosis (p=0.012), neutrophilia (p=0.031) and

lymphopenia (p=0.011), as well as CRP (p<0.001), PCT (p<0.001), LDH (p<0.001), IL-6 (p=0.024), BUN (p=0.001), creatinine (p=0.001), PaO2 (p=0.001), and SaO2 (p<0.001).

Finally, death was associated with age (p=0.003), hypertension (p=0.011), CAD (p=0.029), diabetes mellitus (p=0.045) or obesity (p=0.043) in the medical history, as well as with confusion/dizziness at hospital admission (p=0.014). Poor survival was associated with higher absolute leukocyte (p=0.007) and neutrophil (p<0.001) but lower lymphocyte counts (p=0.003), as well as CRP (p<0.001), PCT (p<0.001), LDH (p<0.001), D-dimer (p=0.009), ferritin (p=0.041), IL6 (p=0.014), BUN (p<0.001), creatinine (p<0.001), PaO2 (p=0.004) and SaO2 (p=0.002).

Using multivariate regression analysis, obesity showed a significant correlation with both ventilation, the need for intensive care treatment, and death (p<0.05). Among the laboratory parameters, absolute neutrophil count, PCT and serum urea concentration showed a significant (p<0.05) correlation with death.

5.1.3. A-DROP is a suitable method to assess general state and risk in COVID-19-associated pneumonia

In the binary analysis, admission to ICU (p=0.002), the need for ventilation (p<0.001) and death (p<0.001) were significantly associated with higher A-DROP. In the ROC analysis, A-DROP>1.5 significantly predicted admission to ICU (p=0.026) and mortality (p<0.001). In the simple Spearman's correlation analysis, A-DROP significantly and positively correlated with absolute WBC and neutrophil counts, CRP, PCT, LDH, D-dimer, ferritin, IL-6, and creatinine. Using multivariate regression analysis, the A-DROP score showed a significant correlation with admission to the intensive care unit and need for ventilation (p<0.05).

5.2. Study II

5.2.1. Characteristics of patients hospitalized for COVID-19 pneumonia who underwent chest CT on admission

The 227 patients included 144 men and 83 women. Their mean age was 56.2±7.8years (range: 40–76years). Disease duration was 8.4±5.2days (range: 1–35days). Altogether 18.2% were current smokers, 7.1% received immunosuppressive drugs and 30.4% were obes. Among

the patients 65.6% had hypertension, 22.0% had CAD, 6.2% had stroke, 5.3% had CKD, 27.3% had diabetes mellitus, 4.4% had malignancies and 21.6% had COPD/asthma in their history. At the time of admission, about 63–71% of patients had fever, dyspnoea and/or coughs, while 4.0% had confusion/dizziness. With respect to lab results, at admission most of these patients had elevated CRP, ferritin, D-dimer, LDH and IL-6 levels. Out of the 227 included patients, 48 (21.1%) had to be admitted to ICU. Forty-five patients (19.8%) needed ventilation. Out of them, 9 (4.0%) required non-invasive (NIV) and 36 (15.6%) invasive ventilation (IV). Altogether 39 patients (17.2%) died. The duration of hospitalization was 12.2±6.9days (range: 2–48days). The mean A-DROP score within these 227 patients was 0.93±0.78.

5.2.2. „CTSS-Pan" and chest CT patterns may be useful tool to determine the severity and prognosis of pneumonia

The mean "CTSS-Pan" in the 227 COVID-19 patients was 14.6±6.7. In the binary analysis, the need for ICU admission ($p<0.001$) and death ($p<0.001$) were significantly associated with higher „CTSS-Pan". Ventilation also more commonly had to be administered to patients with higher „CTSS-Pan" ($p<0.001$). Using multivariate regression analysis, the correlation between "CTSS-Pan" and respiration was also significant ($p<0.05$).

With respect to chest CT patterns, GGO, crazy-paving pattern, consolidation, fibrosis, subpleural lines, pleural effusion, lymphadenopathy were observed in 68.3, 38.3, 34.4, 1.8, 14.5, 8.4 and 38.8% of the patients, respectively. Crazy-paving pattern was significantly associated with ICU admission ($p=0.023$). Consolidation correlated with death ($p=0.031$). Lymphadenopathy was significantly associated with ICU admission ($p=0.041$), ventilation ($p=0.044$) and death ($p=0.049$). In the presence of subpleural lines, the need for admission to the intensive care unit ($p=0.006$) and ventilation ($p=0.039$) was significantly lower, and death also showed a tendency in this direction ($p=0.089$). GGO, fibrosis and pleural effusion did not show any associations with any outcome measures, however, the number of patients with fibrosis and pleural effusion was small.

In the ROC analysis, „CTSS-Pan">18.5 significantly predicted admission to ICU ($p=0.026$) and „CTSS-Pan">19.5 was the cutoff for increased mortality ($p<0.001$). This cutoff has a sensitivity and specificity of about 60–70%.

In the simple Spearman's correlation analysis, „CTSS-Pan" significantly and positively correlated with age, absolute leukocyte and platelet counts, CRP, PCT, LDH, D-dimer, ferritin, IL-6, BUN and the A-DROP score. CTSS showed inverse correlation with total lymphocyte count, PaO_2 and SaO_2.

5.2.3. Comparison of the prognostic value of 3 chest CT severity scoring systems

We compared the performance of „CTSS-Pan" system to both „CTSS-Yang" and „CTSS-Yuan". When performing Spearman's correlation analysis between any two systems, „CTSS-Pan" correlated with „CTSS-Yang" ($R = 0.899$, $p < 0.001$), „CTSS-Pan" correlated with „CTSS-Yuan" ($R = 0.909$, $p < 0.001$) and „CTSS-Yang" correlated with „CTSS-Yuang" ($R = 0.928$, $p < 0.001$).

With respect to outcome, survival versus death and ICU admission versus non-ICU were also analyzed. According to the Mann–Whitney test, all three CTSS systems could significantly differentiate between patients who survived or died and between those who required ICU admission and those who did not. We performed ROC analysis for the comparison of the 3 systems with respect to survival versus death and ICU versus non-ICU. There were no differences between the performances of „CTSS-Pan", „CTSS-Yang" and „CTSS-Yuan". Using $\chi 2$ or Fisher's exact tests, we could determine cut-off values that were able to differentiate between favorable and non-favorable outcomes. With respect to „CTSS-Pan", „CTSS-Yang" and CTSS-Yuan, these cutoff values were 17, 23 and 28, respectively. The OR (95% CI) values of death versus survival were 5.9, 6.0 and 3.1, respectively, while these for ICU versus non-ICU were 7.8, 7.2 and 4.1, respectively. Among the 3 systems, „CTSS-Pan" had the highest PPV with respect to both death versus survival and ICU versus non-ICU. CTSS-Pan also performed well regarding NPV.

5.3. Study III

5.3.1. Characterization of patients

Altogether, 104 patients, 52 TCZ-treated and 52 TCZ-untreated (control group), were included in this study. The TCZ-treated and control groups were matched for patient numbers, age, sex, symptom duration, radiological extent of lung involvement (CTSS), antiviral therapy and corticosteroid use, as there were no significant differences in these parameters between the

two groups. The full patient cohort included 35 men and 17 women in both groups. In the TCZ-treated and control groups, the mean age was 60.2±9.6 years [range: 37–78 years] and 60.1±9.8 years [range: 40–76 years], respectively. Disease duration (time from the first symptom to hospital admission) was 9.75±3.66 days [range: 1–17 days] and 9.65±3.46 days [range: 1–15 days], "CTSS-Pan" was 19.9±4 and 20.2±4.2, respectively.

With respect to laboratory biomarkers, at baseline, the TCZ-treated patient group indeed had more pronounced COVID-19-related MIS compared to controls. In the TCZ treated group, baseline total WBC counts ($p<0.001$), absolute neutrophil counts ($p<0.001$), neutrophil-to-lymphocyte ratio ($p=0.005$), serum IL-6 ($p=0.003$), ferritin ($p=0.026$), and LDH levels ($p=0.020$) were higher compared to controls. The oxygenation of the patients was worse in the TCZ-treated group, but the difference did not reach the significant level.

Before determining the indication for TCZ therapy, consultation with a rheumatologist was performed in 31 cases (60%), while TCZ was initiated by the hospital/ICU personnel without consulting rheumatologist in 21 cases (40%). Such consultation was not performed in any of the 52 control cases. Out of the 52 TCZ-treated patients, 19 (37%) received one, while 33 (63%) received two 8 mg/kg IV doses. In addition, TCZ was administered to 28 patients (54%) already in the general ward, while TCZ treatment was carried out in the ICU in 24 cases (46%). In general, we did not find any differences in safety in the TCZ-treated versus nontreated group. No TCZ-related side effects were observed in patients receiving either one or two doses.

5.3.2. Effects of TCZ treatment on COVID-19 outcomes and MIS biomarkers

The need for ICU admission was 65% vs. 81% ($p=0.146$), the need for ventilation was 63% vs. 77% ($p=0.204$), the total duration of hospitalisation was 17.1 vs. 15.8 days ($p=0.515$), and death occurred in 44% vs. 63% ($p=0.040$), respectively.

We compared the values of biomarkers before and after TCZ treatment. After treatment, absolute lymphocyte count ($p=0.037$) and platelet count ($p=0.003$) were significantly higher, CRP ($p<0.001$) and ferritin value ($p=0.043$) were significantly lower than before treatment. No significant differences were found between the absolute white blood cell count, neutrophil count, neutrophil-lymphocyte ratio, LDH and D-dimer parameters in the pre-treatment and post-treatment laboratory tests. We also compared patients receiving TCZ in the general ward ($n=28$) to those treated with TCZ in the ICU ($n = 24$). The two groups were similar with respect

to age and symptom duration. However, the sex distribution among patients treated in the general ward was 50%-50%, while in the ICU, 21 patients (88%) were males (p=0.017). Consultation with a rheumatologist was performed in 79% vs. 38% of cases (p=0.005). Among patients treated in the general ward, only 36% required admission to the ICU, and also 36% needed ventilation later (p< 0.001). Only 7% of those receiving TCZ in the general ward died in comparison to 88%, who died in the ICU (p < 0.001). It should be noted that in the group of patients who started TCZ treatment in the intensive care unit, the baseline PaO_2 (p=0.046) and SaO_2 (p=0.019) values were significantly lower, and absolute white blood cell count (p<0.001), absolute neutrophil count (p=0.002), neutrophil-lymphocyte ratio (p=0.017), LDH (p=0.016) and D-dimer concentration (p<0.001) were significantly higher. Platelet count became significantly higher after TCZ treatment in the general ward (p=0.039), while ferritin (p=0.039), LDH (p=0.019) and D-dimer (p=0.008) showed significantly lower values in compared to intensive care TCZ treatment.

5.3.3 Correlations between clinical, laboratory, and imaging parameters before and after TCZ treatment

In the TCZ-treated group and the control group, we analyzed the correlations of clinical parameters, laboratory values and imaging data using Spearman's rank correlation test. We observed a significantly better (p<0.05) clinical outcome in terms of ventilation, intensive care unit placement and death in TCZ-treated patients who received a pre-treatment consultation with a rheumatologist and two doses of TCZ compared to those who were not consulted and received only one dose of TCZ. The absolute white blood cell count, absolute neutrophil count, neutrophil-to-lymphocyte ratio, elevated levels of IL-6, CRP, PCT, LDH, D-dimer, as well as the decreased platelet and lymphocyte counts, considered as biomarkers of MIS, showed a significant (p< 0.05) correlation with worse clinical outcome, lower baseline PaO2 and SaO2 values, and higher "CTSS-Pan" values. "CTSS-Pan" correlated (p<0.05) with the degree of hypoxia and baseline IL-6 and D-dimer values. Low SaO_2 was associated (p=0.025) with mortality. TCZ treatment in the intensive care unit (against the general ward) showed a positive correlation (p<0.001) with the need for ventilation and death. Consultation with a rheumatologist showed an inverse correlation with the need for treatment in the intensive care unit (p=0.004).

6. Discussion

6.1. Study I

In order to guarantee patient safety and optimal use of healthcare capacities, it is essential to objectively determine the severity and prognosis of COVID-19 pneumonia patients. The use of risk factors and complex risk estimation scoring systems can be of great help to clinicians in the early identification of high-risk patients. In this single-center study of 233 COVID-19 patients admitted to hospital, we assessed elements of medical history, as well as numerous clinical and laboratory parameters in association with the need for admission to ICU, need for ventilation and death. We also focused on the value of the A-DROP scoring system in the assessment of general health and prediction of outcome in hospitalized COVID-19 patients.

At the time of admission, among laboratory biomarkers, patients had elevated CRP, LDH, D-dimer, ferritin, and IL-6 levels. All these parameters, as well as higher absolute WBC and neutrophil and lower absolute lymphocyte counts, PCT, BUN, creatinine, PaO_2, and SaO_2 were associated with ICU admission, need for ventilation and death. Among clinical and other factors, age was associated with death and male sex with the need for ventilation. Our results are supported by the fact that the elevated CRP value, IL-6, ferritin, LDH, D-dimer, neutrophil/lymphocyte and urea/creatinine ratio have also been described in other studies as indicators of the severity and prognosis of MIS associated with COVID-19 as biomarkers. D-dimer and CRP values were higher in patients who were admitted to the intensive care unit than in those who were not. In the study published by Sciascia et al., a D-dimer value above the threshold of 3500 ng/ml was associated with worse survival.

In our study, hypertension, obesity, and confusion on admission were associated with the need for ventilation, the need for intensive care and death, while CAD and diabetes were associated with death. Based on reports, obesity increases the risk of COVID-19 patients requiring hospitalization, ventilation and intensive care, and there was also a trend towards higher mortality. Confusion has also been identified as a marker of adverse clinical outcomes in COVID-19. In other studies, higher age, male gender and several comorbidities (diabetes, liver, kidney, hematological, cardiopulmonary, oncological and immunological diseases) have been shown to be associated with an unfavorable outcome of COVID-19.

Based on our multivariate regression analysis, obesity is an independent influencing factor of the need for intensive care, the need for ventilation and death.

The A-DROP score showed a significant correlation with the need for intensive care and ventilation, while the "CTSS-Pan" showed a significant correlation with ventilation. Among the parameters analyzed, the absolute neutrophil count, PCT and serum urea concentration proved to be independent influencing factors of mortality.

In addition to several well-known and applied scoring systems, the A-DROP scoring system was also validated by the Japanese Society of Pulmonology and proved to be effective in determining the severity and risk of CAP. Due to its simplicity and objective determinability, we proposed its use in patients with COVID-19 pneumonia. In our own study, the average A-DROP scores of our patients determined at hospital admission was 0.94. A score of 2 or higher was significantly associated with all three adverse clinical outcomes (intensive care unit admission, ventilation, death).

Our results agree with the data of previously published studies regarding CAP, which supported the increased risk of death in patients with an A-DROP score of 2 and above. In our study the A-DROP score also showed a significant correlation with a number of laboratory parameters (white blood cell and neutrophil count, CRP, PCT, LDH, D-dimer, ferritin, IL-6, urea and creatinine), most of which are reported as a biomarkers of severe COVID-19, MIS and cytokine storm in the literature.

Our study I presented above has strengths and certain limitations. The main value of the study is that it was the first study with a larger number of patients, which comprehensively examined the prognostic value of A-DROP in SARS-CoV-2 associated pneumonia in relation to ventilation, intensive care unit admission and death, in connection with several clinical and laboratory markers. Limitations of the study may be the single-center execution and the resulting possibility of bias at the population level, as well as the lack of validation against other cohort studies.

6.2. Study II

Chest CT is an objective tool for monitoring pathological processes in the lungs. Describing chest CT patterns and quantifying the extent of lung involvement can provide very useful, objective help to clinicians in determining the severity of COVID-19-associated

pneumonia. In our single-center, retrospective study, we analyzed the chest CT scans of 227 patients admitted to the hospital due to COVID-19 pneumonia.

We assessed the radiological patterns and changes depicted on the chest CT at the time of admission, and calculated chest CT severity scores according to three semiquantitative methods ("CTSS-Pan", "CTSS-Yang" and "CTSS-Yuan"). We compared the data obtained during the analysis of the CT scans with the clinical outcome, such as admission to the intensive care unit, ventilation, death, and the length of hospitalization. A further extensive comparison was made with the clinical and laboratory parameters recorded at the time of admission and with the A-DROP score calculated by us. Based on our results, chest CT severity score systems may be suitable for identifying high-risk COVID-19 pneumonia patients. Among the three score systems examined, the "CTSS-Pan" proved to be the most useful for determining the expected clinical outcome.

The average "CTSS-Pan" calculated for all 227 patients was 14.6. In 98 patients selected randomly from these patients, the average "CTSS-Yang" was 20.67±9.28 points. Based on the CTSS they used, Yang et al. and Francone et al. obtained higher scores in their studies in severe COVID-19 cases than in mild ones. In their study by Yang et al., the lower threshold for separating severe cases was set at 19.5. Using the CTSS-Pan, Francone et al. measured an average score of 17.4±3.1 in their severe COVID-19 patients. Based on the literature data, the severity status of the majority of our patients included in our study can be classified as moderate-severe or severe COVID-19 pneumonia, which is also in line with the clinical parameters. In the study reported by Francone et al., a "CTSS-Pan" of 18 and above showed a significant association with mortality. In our own study, "CTSS-Pan" showed a significant correlation with intensive care unit admission, ventilation and death. Based on the ROC analysis, the optimal threshold value for admission to the intensive care unit was 18.5, and 19.5 for death, with a sensitivity and specificity of around 60-70%, which is in line with the data reported by Francone et al. In our study, the "CTSS-Pan" score showed a positive correlation with age, the A-DROP score, as well as absolute white blood cell count, platelet count, PCT, CRP, IL-6, ferritin, LDH, D-dimer and with urea lab parameters. At the same time, it showed a negative correlation with lymphocyte count, PaO_2 and SaO_2 values. This is consistent with the role of these biomarkers in COVID-19. In the more advanced stages of COVID-19, excessive systemic inflammation predominates, leading to further tissue damage and impaired blood coagulation. In the IIB-III stage of COVID-19, inflammatory markers (IL-6, CRP, PCT, ferritin) are produced in large quantities and the level of LDH, indicating lung tissue damage,

and D-dimer, indicating a blood coagulation disorder, increases. In cases of severe COVID-19, leukocytosis and lymphopenia are characteristic laboratory abnormalities. An increase in the degree of lung damage naturally correlates with a decrease in PaO_2 and SaO_2. In addition to the correlation with age, Francone et al. also reported the correlation of "CTSS-Pan" with CRP and D-dimer parameters.

When comparing the chest CT patterns and the clinical outcome, the crazy paving pattern was associated with admission to the intensive care unit, consolidation with death, while lymphadenopathy was associated with admission to the intensive care unit, ventilation and death. According to Francone et al., crazy paving, consolidation and fibrosis are typical in the late stage (>7 days). However, the authors did not analyze the correlation between CT patterns and clinical outcome. Based on the opinion of Martinez Chamorro et al., crazy paving and consolidation are signs of disease progression. In our study, the presence of subpleural lines showed an inverse relationship with the need for intensive care unit treatment and ventilation, so it may predict a better prognosis. Since the subpleural lines appear in the phase of resolution, it can be assumed that these patients have already passed the critical period, so further deterioration is less likely. Based on our results, crazy paving, consolidation, lymphadenopathy and subpleural lines, visible on the chest HRCT during decision-making may have a useful prognostic value for clinicians regarding the clinical outcome of COVID-19. Yanamandra et al also confirmed in their study that CTSS systems are also suitable for determining the prognosis of severe COVID-19 patients requiring hospitalization.

As part of our study, we compared the "CTSS-Pan", "CTSS-Yang" and "CTSS-Yuan" scoring systems in 98 patients. Based on the paired correlation and ROC curve analysis, the prognostic performance of the 3 point systems proved to be similar. All three showed a significant correlation with the length of hospital stay and proved to be useful in prognosticating the need for intensive care unit treatment and death, for which optimal threshold values were set. We calculated the odds ratios and the positive predictive values for the 3 tests. "CTSS-Pan" moderately outperformed "CTSS-Yang" and clearly outperformed "CTSS-Yuan". In terms of negative predictive value, all three methods performed exceptionally well.

Only a few studies comparing CTSS systems have been published in the literature. In their study, Elmokadem et al. compared the prognostic performance of five different chest CT severity scoring systems in 85 patients with COVID pneumonia. The scoring systems compared were “CTSS-Yang”, “CTSS-Pan”, “mTSS”, “TSS” and “3L-CTSS”. Based on the

authors' opinion, each scoring system is suitable for assessing the severity of COVID-19-associated pneumonia. Based on their results, "CTSS-Yang" and "TSS", which is very similar to "CTSS-Pan", showed the highest specificity and "TSS" was the fastest calculated score. However, it should be noted that in their study non-serious cases made up the vast majority of the patient population. Based on our own results and the study of Elmokadem et al., it seems that the examined complex scoring systems, which also take into account the type of lung involvement, do not provide a prognostic advantage over systems that only score the extent of the disease, despite their time-consuming nature. This may be because it is difficult to semiquantitatively score the many variations and degrees of radiological patterns. Automated, quantitative, artificial intelligence-based systems can help us in this, but they are currently not widely available. The sensitivity and specificity of CTSS, which describes the static state, can be further increased if we create point systems supplemented with clinical information.

Our study II also has strengths and certain limitations. The main value of the study is that it is one of the first studies carried out with a relatively high number of patients, in which the relationship between semiquantitative chest CT severity scores and chest CT patterns was investigated in a complex manner in patients with moderate, severe and critical COVID-19 pneumonia in a number of clinical and with laboratory parameters, a complex clinical scoring system, and the clinical outcome. There have also been few studies comparing the prognostic performance of different types of chest CT severity score systems among patients with moderate and severe COVID-19 pneumonia. A limitation of the study may be the possibility of bias at the population level resulting from the single-center and retrospective design. Another limitation may be the lack of validation against other cohort studies.

6.3. Study III

In our retrospective, single-center study, we compared the clinical outcome parameters of patients who received one or two doses of TCZ in addition to corticosteroids (n= 52) with the data of patients who received only corticosteroid therapy (n=52).

In both patient groups, the "CTSS-Pan" showed an average value of around 20 points. Based on the results of our II study and the data of other authors, patients in both groups had severe COVID-19 pneumonia with an increased expected mortality. This was consistent with other clinical parameters of patients.

The levels of several markers indicating the presence of MIS (absolute white blood cell count, absolute neutrophil cell count, neutrophil-to-lymphocyte ratio, IL-6, ferritin and LDH) were significantly higher in the admission laboratory values of the TCZ-treated patients compared to the control group. The literature has associated decreased lymphocyte and platelet counts, as well as elevated white blood cell counts, absolute neutrophil cell counts, neutrophil-to-lymphocyte ratios, and elevated CRP, IL-6, ferritin, and D-dimer concentrations with MIS and a worse course of COVID-19. Despite the expected worse prognosis, we observed a significantly lower mortality in the TCZ-treated group compared to the control group, and there was also a tendency towards reduced admission to the intensive care unit and a lower need for ventilation. Our results are consistent with the findings of studies in which mortality was reduced when TCZ was added to corticosteroids in severe, significant MIS-associated COVID-19 patients. However, studies have also been reported in which TCZ treatment did not reduce mortality compared to placebo.

Fifty-four percent of the 52 patients received TCZ treatment in the general ward, while 46% in the intensive care unit. In the group of patients who received TCZ treatment already in the general ward, mortality was significantly lower (7%) compared to the mortality of those treated in the intensive care unit (88%), and only 36% of them were later admitted to the intensive care unit or required ventilation. Prior to TCZ treatment, patients treated in the general department had a consultation with a rheumatologist experienced in TCZ treatment significantly more often ($p=0.005$) (79%) than in the intensive care unit (38%).

TCZ treatment also had a beneficial effect on MIS biomarkers. Based on the results of the post-treatment laboratory test (3.52±1.43 days), platelet and absolute lymphocyte counts increased, while CRP and ferritin concentrations decreased significantly compared to the pre-treatment values. However, the absolute white blood cell count, absolute neutrophil count, neutrophil-lymphocyte ratio, LDH and D-dimer values did not change significantly as a result of the treatment. LDH is a marker of tissue damage, while D-dimer is a marker of thrombotic events arising as a result of blood coagulation disorder, which phenomena presumably do not change rapidly as a result of IL-6 receptor blockade. However, the extent of tissue damage gradually decreases over time. Lakatos et al. reported a decrease in LDH values in addition to ferritin and CRP on the 7th day after TCZ treatment.

In our study, we compared the correlation of clinical outcome, laboratory values and "CTSS-Pan" in the TCZ-treated and control groups. Our results suggest that the clinical

outcome of patients with severe COVID-pneumonia can be improved if a specialist experienced in the treatment is involved in the indication of TCZ therapy. Our data confirmed a better clinical outcome with two doses of TCZ compared to one dose. Our results can be supported by the observation of Vu et al., who reported a repeated increase in CRP with a lower dose of TCZ (400 mg for 30-100 kg body weight, 600 mg for body weight over 100 kg). However, there are also reports that raise safety concerns regarding multiple TCZ treatments compared to a single treatment. In the patients we examined, a survival advantage was shown and no TCZ complications were detected either after the administration of one or two doses. In our opinion, appropriate patient selection is of prime importance both in terms of effectiveness and the avoidance of complications.

Similar to other studies, our results show that leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, elevated IL-6, CRP, ferritin, PCT, LDH and D-dimer values, as well as the patient's low oxygenation are useful biomarkers of MIS, which may be associated with a worse clinical outcome. The CTSS is a useful tool in determining the severity of lung involvement and the patient's prognosis, which we, like other authors, confirmed in our study II. "CTSS-Pan" together with the aforementioned biomarkers may be suitable for the selection of severe patients requiring TCZ therapy. In our study, COVID-19 pneumonia in the TCZ-treated group was associated with more pronounced MIS than in the control group. Our results confirm that TCZ therapy is recommended for use in severe stages of COVID-19 with increased inflammation.

The strength of our study III is that it was the first published Hungarian study that evaluates the place and value of TCZ treatment in patients with severe COVID-19 pneumonia against a control group using several laboratory, imaging and clinical biomarkers. It is also important to note that patient survival can be improved if the treating physician of COVID-19 patients involves a specialist experienced in the use of immunosuppressive therapies in the indication of TCZ. A limitation of the study may be the single-center and retrospective design and the resulting possibility of population bias, as well as the relatively small number of patients. CT follow-up of the patients was not routinely performed, so only the baseline CTSS was determined.

7. New findings

Due to the nature of the patient population included, the findings apply to patients admitted to hospital due to moderate and severe COVID-19 pneumonia.

1. The A-DROP scoring system also has a good prognostic value for COVID-19 pneumonia and shows a correlation with several laboratory and imaging parameters typical of severe COVID-19.
2. A-DROP ≥2 established at hospital admission indicated the need for subsequent admission to the intensive care unit, the need for ventilation, and death.
3. The CTSS determined at hospital admission of COVID-19 patients proved to be prognostic in terms of the subsequent need for intensive care unit placement, the need for ventilation, and the death.
4. CTSS-Pan correlates with many other validated prognostic biomarkers and the A-DROP score.
5. The presence of subpleural lines on chest CT may indicate a better prognosis.
6. The use of TCZ therapy in addition to corticosteroid treatment has been shown to be safe and provides a survival advantage for patients with severe COVID-19 pneumonia complicated by proven MIS.
7. TCZ used in the pre-intensive phase may be more effective than treatment in the intensive care unit.
8. Clinical outcome can be improved if a specialist experienced in the use of immunosuppressive therapy is consulted before starting TCZ.
9. Based on our data, in cases of severe COVID-19 associated with pronounced MIS, the use of two doses of TCZ may be more beneficial than a single treatment.

8. Summary

During COVID-19 pandemic, the high number of patients with pneumonia and the variable course of the disease posed a serious challenge to health care systems worldwide. Reliable risk assessment tools are also needed in SARS-CoV-2 associated pneumonia, in order to ensure patient safety and optimal use of healthcare resources. During our retrospective analysis of our hospitalized COVID-19 pneumonia patients, we were also able to confirm the prognostic role of several factors described in the literature. Complex scoring systems are more suitable for predicting the clinical outcome of pneumonia than individual factors. Based on the results of our study, the A-DROP scoring system validated for the risk assessment of community-acquired pneumonia may be suitable for the risk assessment of patients with COVID-19 pneumonia. Its application is supported by its simplicity, and its good prognostic performance compared to other scoring systems.

Chest CT in COVID-19 patients simultaneously provides objective information about the presence of lung involvement, its distribution within the organ, its extent, its quality and possible complications. Both the degree of extension and the radiological pattern have prognostic significance. Our results also confirm that chest CT severity scores quantifying lung involvement are suitable tools for determining severity and prognosis in patients with COVID-19 pneumonia, therefore the CTSS scoring should be done as part of the finding. Among the examined scoring systems, we recommend "CTSS-Pan" due to its good prognostic performance and simplicity. Combining and supplementing the scoring systems we have examined with the identified prognostic factors can help clinicians to make appropriate therapeutic decisions early. To develop an optimized scoring system, prospective studies with a larger number of patients are required.

In severe cases of COVID-19 pneumonia, TCZ was also introduced in Hungary. Among our patients, the use of TCZ proved to be safe. TCZ added to corticosteroid therapy improved the survival of patients hospitalized for severe COVID-19 pneumonia with MIS and had a beneficial effect on MIS biomarkers. We found that the clinical outcome of patients who received TCZ treatment in the general ward was better compared to those who wastreated in the intensive care unit. It is recommended to consult with a specialist experienced in the use of immunosuppressive therapies before treating severe COVID-19 patients with TCZ, because it may favorably influence the clinical outcome of the patients.

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10. List of publications related to the dissertation

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Candidate: Miklós Szabó
Doctoral School: Doctoral School of Clinical Medicine
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List of publications related to the dissertation

1. **Szabó, M.**, Kardos, Z., Kostyál, L., Tamáska, P., Oláh, C., Csánky, E., Szekanecz, Z.: The importance of chest CT severity score and lung CT patterns in risk assessment in COVID-19-associated pneumonia: a comparative study.
   Front. Med. 10, 1-9, 2023.
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