COVID-19 and rheumatologic disease in Dalmatia in comparison to diabetes mellitus

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COVID-19 AND RHEUMATOLOGIC DISEASE IN DALMATIA IN COMPARISON TO DIABETES MELLITUS

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LIST OF ABBREVIATIONS

ACE-2 - Angiotensin-converting enzyme 2

ARDS - acute respiratory distress syndrome

COVID-19 – Coronavirus disease 19

CRP – C-reactive protein

CROUP – laryngotracheobronichitis

DM – Diabetes mellitus

IG – immunoglobulin

IL – Interleukin

MERS – Middle East respiratory syndrome

NSAID – Nonsteroidal anti-inflammatory drugs

PCR - Polymerase chain reaction

RA – Rheumatoid arthritis

RF – Rheumatic factor

RAD – Rheumatic autoimmune disease

RAAS – Renin Angiotensin Aldosterone System

SARS-CoV-2 - acute respiratory syndrome coronavirus type 2

SLE – Systemic Lupus Erythematosus

WHO – World Health Organization

1.INTRODUCTION

1.1 COVID-19

Coronavirus disease, also known as COVID-19 is an acute, infectious respiratory disease caused by the newly discovered Coronavirus. The virus spread extensively worldwide since it first has been reported in 2019 in Wuhan, China. Epidemiologists suggest that the virus initially spread from animals to humans at a live animal market in Wuhan. Close person-to-person contact with an infected individual spreads the virus through respiratory droplets. These droplets usually circulate within six feet of an infected person but can also be dispersed 20 feet via small particle aerosols that can stay in the air for several hours. Another way of spreading the disease occurs through contact with contaminated surfaces by droplets. Symptomatic, asymptomatic, and pre-symptomatic individuals can transmit the virus, which is most contagious several days before and after the first onset of symptoms. The viral load is the greatest in respiratory secretions during this time (1). In general, most infected people will have mild to moderate symptoms and recover quickly without specific treatment or hospitalization. Underlying medical problems and comorbidities like hypertension, chronic respiratory disease, and cancer increase the risk to develop a more serious illness with worse outcomes (2).

Coronaviruses and the newly discovered COVID-19 virus are part of the family Coronaviridae, which cause mild respiratory infections. The First human isolation of the virus was done in 1965, revealing a single-stranded, enveloped RNA virus. Previous outbreaks have been caused by three coronaviruses. The first one in 2002 was causing a severe respiratory infection due to the SARS-CoV-2 (acute respiratory syndrome coronavirus type 2), followed by the Middle East respiratory syndrome in 2012, also known as MERS-COV. The current acute respiratory syndrome coronavirus was first reported in December 2019. The Huanan seafood market in the Hubei province was linked to most cases at this time. Next-generation sequencing discovered the unknown beta coronavirus through airway epithelial cells from lower respiratory tracts of infected patients. The new virus was named 2019-novel Coronavirus. The novel virus showed approximately 88% similarity to two bad derived coronaviruses and 79% similarity to coronavirus strains extracted from humans. The study group of the International Committee on Taxonomy of Viruses named on the 11th of February 2020 the virus SARS-CoV-2, and the WHO (world health organization) called the disease COVID-19 or Coronavirus disease. COVID-19 was announced as a pandemic on the 11th of March 2020 by the WHO, after evaluating the situation all over the globe (3).

One hundred fifty million cases of the coronavirus disease have been globally reported since the first outbreak in the central city of the Hubei Province of China. As only part of acute infections have been reported and diagnosed, these numbers of reported cases underrate the overall burden of the Coronavirus. It is suggested, after being reflected by seropositivity, the rate of prior exposure to SARS-Cov2 is exceeded by the reported cases 10-fold (4). Its high infectiousness is making this pandemic especially difficult to manage.

As already mentioned, the primary route of SARS-Cov2 infection is a direct person-to-person respiratory transmission. Recent studies show that the virus spreads mainly via close-range contact through the release of respiratory particles, primarily via coughing, sneezing, or talking. These particles tend to remain in the air over time, highlighting the potential for a longer airborne transmission by inhaling these respiratory droplets. Scattered reports of outbreaks, especially in buses, cafes, or restaurants, prove the long-distance transmission in poorly ventilated spaces. RNA of the SARS-CoV2 is also detected in non-respiratory specimens, but the role of this type of transmission is uncertain. Despite the high infectiousness of the SARS-CoV2, many individuals do not transmit the virus. The most significant period of infectiousness is early in the illness; the precise interval of transmitting the infection is uncertain. Experts believe that the potential to transmit the COVID-19 virus begins before the development of symptoms, and the risk of transmission decreases with time. For immunocompetent patients with non-severe infection, transmission after 7 to 10 days off illness is unlikely. The risk of transmission increases with the duration and closeness of contact with an infected person, especially in indoor settings with poor ventilation (5).

Until today Croatia had 360.000 confirmed cases of SARS-CoV2, 45.000 affecting the Split-Dalmatian County (6). Figure 1 demonstrates new cases of COVID-19 in Croatia according to dates.

Figure 1. New cases COVID-19 in Croatia

Adapted from the official government website for accurate and verified information on Coronavirus (koronavirus.hr)

1.1.1 Pathophysiology COVID-19

The single-stranded, enveloped RNA virus infects a wide range of host species. Based on the genomic structure, coronaviruses divide into four genera: α, β, γ, and δ. The subgroup α is known to cause croup or the common cold and belongs with the β variation to the coronaviruses that can infect only mammals. In contrast to the common cold and croup, SARS-CoV, the Middle East respiratory syndrome coronavirus, and SARS-CoV2 belong to the β genera. Attachment, penetration, biosynthesis, maturation, and release are the five steps of the virus's life cycle within the host. SARS-CoV2 attaches to the host receptors and, through membrane fusion, penetrates the host cells. Replication takes place inside the nucleus once the viral RNA enters.

Viral mRNA is necessary for the biosynthesis of viral proteins, so new particles maturate and are released. Four structural proteins make up Coronaviruses, namely: The Membrane (M), Spike (S), Envelop (E), and Nucleocapsid (N) (7). Two functional subunits make up the S protein, S1, and S2. S1 binds to the host cell receptor, and S2 takes part in the fusion of the viral and host cellular membranes, making it an essential protein for host attachment and penetration. ACE-2 (Angiotensin-converting enzyme 2), highly abundant on pulmonary epithelial cells, is identified as a functional receptor for SARS-CoV2.

By binding to the ACE-2 receptor, the S protein activates and initiates several biochemical steps causing conformational changes and leading to host and viral cell membrane fusion. Viral contents are released inside the epithelial cells of the host after post-membrane fusion takes place. Once inside the alveolar epithelial cells and the contents have been released, SARS-CoV2 undergoes replication and forms a new strand of RNA through the biochemical process known as transcription, making an RNA copy of a gene sequence. The newly formed negative RNA strands serve to produce positive RNA strands, which get translated. Translation happens inside the cell cytoplasm, synthesizing new proteins using positive RNA strands. The new genomic RNA is bound by the viral N protein and integrated into the cellular endoplasmic reticulum through the M protein, which facilitates this process. New Nucleocapsids are transported to the lumen, then via Golgi vesicles to the cell membrane, and finally, through the process of exocytosis, transported to the extracellular space. The newly formed viral particles

invade adjacent epithelial cells and cause community transmission by providing fresh infective material through respiratory droplets (8). The region of the lung affected determines the course of the COVID-19 disease. Mild to moderate disease is limited to the conducting airways, where the gas exchanging portion of the lung causes severe disease. 80% of infected individuals will experience a mild course of disease involving the upper airways. Unluckily, 20% of patients will develop pulmonary infiltrates and severe disease. SARS-CoV2 and the influenza virus tend to invade type II cells, preferably in comparison to type I cells. By invading the alveolar type II cells, which keep the alveolar space free from fluid and play an essential role in tissue repair and immune response, SARS-CoV2 causes severe respiratory damage. The affected alveolar cells undergo apoptosis and die once infected. Diffuse alveolar damage is the result of the SARS-CoV2.

Anomalous wound healing can cause extended scarring and fibrosis, further reducing lung function (9). Edema, degeneration, and necrotic changes result from the invasion of the virus into the lung cells, endothelial cells, and myocytes of the vascular system. Invading SARS-CoV2 activates various pro-inflammatory cytokines, including tumor necrosis factors, interleukins, and immunoglobulins, contributing to lung injury pathogenesis. Hypoxemia is another manifestation seen with the SARS-CoV2 infection, leading to changes in pH, accumulation of lactic acid and oxygen free radicals, changes in the electrolyte balance, further contributing to cell damage (10).

1.1.2 Clinical picture

80% of SARS-CoV2 infections are usually manageable by outpatient care and manifest as mild to moderate illness. Up to 98% of patients experience fever, 80% cough, 44% fatigue, 55% shortness of breath, and up to 44% report muscle soreness. Chest tightness, sore throat, rhinorrhea, vomiting, diarrhea, and headaches are additional symptoms. Some people tend to have no symptoms or experience only a mild fever. Approximately 15% of COVID-19 cases develop moderate to severe pneumonia and need inpatient care. Five days is the median time to the development of dyspnea and time to be hospitalized. One of the most common manifestations in infected patients is lower or average white blood cell counts, elevated C-reactive protein, thrombocytopenia, or lymphopenia. High suspicion of COVID-19 manifests with symptoms of the upper respiratory tract, fever, leuko-, or lymphopenia, as well as a traveling history in endemic areas (11). On physical examination, patients might show a raised body temperature, decreased oxygen saturation, and an increased respiratory rate. Lung

auscultations might show normal lung sounds or crackles and signs of heart failure (10). Although the pulmonary system is the primary affected system, COVID-19 can lead to many extra-pulmonary manifestations.

In 36% of cases, neurological symptoms are present in severe cases. Headache, dizziness, fatigue, anosmia, myalgia, and anorexia were mild neurological symptoms. Strokes, impaired consciousness, acute necrotizing encephalopathy, and demyelinating polyneuropathy were reports in more severe manifestations. Another extra-pulmonary manifestation of COVID-19 is thromboembolic manifestations, especially the occurrence of thrombosis and myocardial infarctions. SARS-CoV2 can cause indirect and direct cardiovascular injury, including cardiomyopathy, arrhythmias, cardiogenic shock, and cor pulmonale. Kidney damage may present as hematuria, proteinuria, and acute kidney failure. Anorexia, diarrhea, nausea, vomiting, abdominal pain are manifestations of the gastrointestinal system. COVID-19 can also lead to increased bilirubin values and, therefore, an impaired liver function. Dermatologic symptoms can vary from nonspecific urticaria vesicles to livedo reticularis and an erythematous rash (11).

1.1.3 Complications

Several complications with SARS-CoV2 have been reported. Coagulopathies, mainly disseminated intravascular coagulation, venous thromboembolism, and a prolonged prothrombin time, are associated with COVID-19. Laryngeal edema and necrotizing pneumonia caused by Staphylococcus aureus in severely ill patients can lead to a superinfection that can be fatal. Acute pericarditis, new or worsening arrhythmias, left ventricular dysfunction and acute myocardial injury are cardiovascular complications that are known to be associated with the virus. In approximately 5% of SARS-CoV2 infections, patients develop acute respiratory failure and need to be admitted to the ICU or develop sepsis, shock, multiple organ failure, and pulmonary embolisms. Up to 30% of hospitalized patients require intensive mechanical ventilation and have a higher risk of developing ventilation-associated pneumonia. A higher risk of death is noted in patients, particularly males, with the presence of severe cardiac complications like heart injuries, hyperglycemia, or are receiving high doses of corticosteroids (10).

1.1.4 Diagnosis

The most important step to treat SARS-CoV2 is an early diagnosis. Several different methods exist to diagnose COVID-19. Viral culture, serology, and molecular methods are the primary tools used to diagnose the disease. Hospitalized patients undergo laboratory investigations, including coagulation testing, complete blood count, serum biochemical tests, especially lactate dehydrogenase, creatine kinase, electrolytes, and procalcitonin. It appears that SARS-CoV2 targets especially T Lymphocytes, decreasing the total number of lymphocytes of most patients.

Real-time PCR (Polymerase chain reaction) and reverse-transcription polymerase for blood or respiratory specimens are the method of choice to confirm SARS-CoV2 (12). To perform the RT-PCR test, swabs are usually taken from lower tract aspirates or oropharyngeal, nasopharyngeal, and nasal sputum. SARS-CoV2 RNA is present with a positive test, which, together with the clinical picture, confirms COVID-19. A negative test result does not exclude a SARS-CoV2 infection.

Additionally, to the RT-PCR, Rapid antigen testing is performed. The test identifies monoclonal antibodies against the SARS-CoV2 nucleocapsid protein or protein N. The nucleocapsid protein is extensively expressed in infected cells, making it possible to detect SARS-CoV2. Rapid antigen testing shows specificity of 98.5% and a reported sensitivity of 84.1% (10).

1.1.5 Treatment

The treatment depends on the severity of the disease. Managing the patients should be based on physical exam, vital signs, availability of health care resources, and the risk factors for disease progression. Non-hospitalized individuals with an acute SARS-CoV2 infection should receive supportive care and be isolated to reduce the risk of transmission. Over-the-counter drugs like analgesics, antitussives, or antipyretics may be used as a symptomatic treatment to reduce fever, myalgias, coughs, and headaches (13). Patients with an increased risk of disease progression and hospitalization should be treated with SARS-CoV2 spike protein binding monoclonal antibodies like Casirivimab and Bamalanivimab. With their mechanism of action, these drugs block the entry of SARS-CoV2 into the host cell. Hospitalized patients who require supplemental oxygen should receive treatment according to the Panel recommendation guidelines on COVID-19 treatments with Remdesivir. The nucleotide analog inhibits viral

RNA production by inhibiting the RNA polymerase. It is proven to decrease recovery time by approximately four days. Corticosteroids and anticoagulation therapy are also used in the treatment of COVID-19, reducing the cytokine storm and decreasing the risk of venous thrombosis (14).

1.1.6 Mortality

Depending on the patients' age and underlying medical condition, the mortality rate varies between 0.5 and 3%. It increases significantly with age, the most lethal rage for people older than 80 years, where the mortality goes up to 15%. Patients with the following co-morbidities are at high risk for severe disease: renal failure, severe cardiovascular conditions, chronic lung disease, liver disease, severe obesity, and immunosuppression (13).

1.2. Autoimmunity

The immune response against self describes the term ‚Autoimmunity'. In the 20th century, the immunologist Paul Ehrlich called it a specter of ‚horror autotoxicus', describing the enormous consequences of this condition (15). Disorders of the immune system result from a breakdown of immunologic tolerance, which ultimately causes a response against self-molecules. The events initiating this process are unknown, but several studies show a correlation between genetic factors, infections, environmental factors, and autoimmune diseases. More than 75% of patients suffering from an autoimmune illness are women, the predominant risk group developing a rheumatic disease. Postpubescent, young women, are ten times more prone to autoimmune disease than men. Animal studies have proven the role of estrogen in the pathophysiology of autoimmune disease, showing that estrogen administration in mice greatly enhances mortality in both males and females.

A complex set of cells and proteins are designed to protect the body from environmental substances and make up the complex set of the immune system. *Antigens* are self-molecules that stimulate specific immune responses. Immunological cells are located either in organs like the thymus and sleep or diffuse in body tissues like lymphoid nodes, the skin, and the gut. Cell products and immune cells need to interact with each other to create an optimal function of the immune system. B and T lymphocytes express recognition molecules essential for the complex self and non-self-recognition mechanism. The first-line defense against pathogens includes a nonspecific effector mechanism that amplifies the lymphocyte responses and includes

cytokines, complement, and leukocytes like natural killer cells and macrophages. Aberrations in cytokine production show the role of these mediators in the development of autoimmune disease. Immune cells are divided further according to their functional properties. T-lymphocytes include cells that destroy infected cells (cytotoxic T-cells), down-regulate responses of the immune system (T-suppressor cells), or amplify immune responses (T-helper cells). These T-helper cells can produce cytokines that stimulate antibody responses called Th2 cells or assist other T-cells, referred to as Th1 cells. The role of B lymphocytes, on the other hand, is primary to produce antibodies. Autoimmune disorders develop through the interaction of T-cells and antibodies to self-antigens, which are on specific tissues. Th1 cytokines predominate in this process, triggering immune responses that induce killing by cytotoxic T-cells or via IgM (Immunoglobulin M) and IgG (Immunoglobulin G) antibodies, especially in organ-specific diseases. Elevated Th2 cytokines are characteristic in systemic autoimmune disorders.

The most common targets of organ-specific autoimmune disease are the pancreas, thyroid gland, stomach, and adrenal glands, as demonstrated in Table 1. The joints and muscle tissue tend to be predominantly affected in systemic illness.

Table 1. Spectrum of autoimmune diseases and putative autoantigens.

	Disease	Autoantigen
Organ specific	Hashimoto thyroiditis	Thyroglobulin
↑	Thyrotoxicosis	Thyroid-stimulating hormone
↑	Pernicious anemia	H^+/K^+ -ATPase
↑	Autoimmune atropic gastritis	Intrinsic factor
↑	Addison disease	21-Hydroxylase
↑	Insulin-dependent diabetes mellitus	Glutamic acid decarboxylase 65
↑	Goodpasture syndrome	Type IV collagen
↑	Myasthenia gravis	Acetylcholine receptor
↑	Male infertility (few cases)	Epididymal glycoprotein FA-1
↑	Sympathetic opthalmia	Interphotoreceptor retinol binding protein
↑	Multiple sclerosis	Myelin basic protein
↑	Autoimmune hemolytic anemia	X antigen, glycophorin
↑	Ulcerative colitis	Catalase, α-enolase
↑	Rheumatoid arthritis	Rheumatoid factor
↑	Scleroderma	Topoisomerase 1, laminins
Non-organ specific	Systemic lupus erythematosus	DNA nucleotides and histones, Sm-RNP

Table 1. Spectrum of autoimmune diseases ranging from organ specific to systemic
Adapted from: Dorinda A.Smithand, Dori R.Germolec: Introduction to Immunology and Autoimmunity

Auto-reactive T and B cells make up a small number that constitutes part of the immune cells, as observed in healthy normal individuals. Regulatory mechanisms maintain tolerance, which under certain conditions can be disturbed, and an autoimmune disorder can result. Genetic backgrounds can be triggered by certain bacterial, viral, or chemical factors (16).

1.3 Rheumatologic autoimmune disease

Rheumatology is derived from the Greek word *rheuma*, which translates as a river or stream. The British Society of Rheumatology defines *rheumatology* as following: ‚A multidisciplinary branch of medicine that deals with the investigation, diagnosis, and management of patients with arthritis and other musculoskeletal conditions (17). 3-9% of the general population suffer from autoimmune disorders, representing a significant health burden. According to their clinicopathology, autoimmune diseases classify as organ-specific and systemic. The systemic autoimmune disease includes end-organ injury through autoantibodies that target self-antigens, to a lesser extent by T cells. Organ-specific disease, in contrast, typically is mediated by self-antigens expressed on cells or tissues, and damage is mediated by antibodies and, notably, T-cells (15).
Typical examples of systemic autoimmune diseases are RA and SLE. It is also the two most common inflammatory rheumatic diseases.

1.3.1 Systemic Lupus Erythematosus

One of the multi-system disorders is the connective tissue disease Systemic Lupus Erythematous (SLE). Systemic illness can affect any organ; therefore, patients present with a variety of symptoms. A variation of specialties besides rheumatology is involved, especially nephrology, hematology, internal medicine, pulmonology, and neurology. Relapses and remissions dominate the disease course. Individual management is the key to treating these patients, adapting the drug treatment to specific organ involvement rather than the initial diagnosis. Part of the pharmacological treatment are corticosteroids, antimalarials, and non-steroidal anti-inflammatory drugs (NSAIDs) (18).

The American College of Rheumatology developed criteria for SLE classification in 1971, where four out of 11 criteria ensure the diagnosis (Table 2). These criteria do not have to manifest simultaneously, somewhat over weeks or years, to improve the classification; the

criteria divide into “immunologic” and “clinical” categories (19). The clinical and immunological criteria for SLE are demonstrated in Table 2.

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria >0.5g/ 24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipi IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Complement protenis domain	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodied domain	
Anti-dsDNA antibody	6
Anti-Smith antibody	6

Table 2. Clinical and immunological criteria SLE

Adapted from: Firestein and Kelley’s Textbook of Rheumatology

Predominant features in patients with SLE are fatigue, fever, and weight loss. 90% of patients will describe arthritis and arthralgias, which resembles inflammatory arthritis. SLE can affect the skin in three types: Chronic cutaneous lupus erythematosus, acute cutaneous lupus erythematosus, and subacute cutaneous lupus erythematosus. Involved Serosa manifests as pericardial or pleural effusions. Lymphadenopathy, pulmonary hypertension, and interstitial lung disease may present in some patients as well. It is essential to mention that renal involvement and cytopenia’s are joint in patients with SLE. Since it is a multi-system disease, SLE might also present as a neuropsychiatric symptom (18).

1.3.2 Rheumatoid Arthritis

RA is an inflammatory polyarthritis of unknown etiology and insidious onset. The autoimmune disease affects 1% of the population, predominately women. Its characteristics are morning stiffness, malaise, and fatigue, with affected joints being swollen and tender. RA

usually spares the cervical spine and the axial skeleton. Any joint can be affected with rheumatoid arthritis, but common areas being metacarpophalangeal joints, proximal-interphalangeal joints of the fingers, and interphalangeal joints of the thumb, knees, and wrist (18). Despite being a primary disease of the joints, RA has features of systemic disease. Extra-articular manifestations such as nodules, vasculitis, and atherosclerosis show abnormal systemic immune responses and the involvement of many organ systems. Autoantibody production and immune complexes contribute to these extra-articular manifestations.

The exact etiology of RA is not known, but environmental and genetic influences are apparent factors. Several studies have shown that autoimmunity precedes the onset of RA by many years. The role of cytokines, growth factors, adhesion molecules, and autoantibodies have a clear role. Investigations showed an increase in acute phase reactants. Rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) are serological abnormalities in RA (18). Soon after the onset of RA, patients develop irreversible loss of bone and cartilage, making early interventions crucial to improve long-term outcomes. On radiographic imaging, hands and feet show bony erosions and joint space narrowing. Magnetic resonance imaging and ultrasound are helpful in the detection of early changes (18). The suppression of systemic and especially synovial inflammation is treated aggressively to reduce mortality (19).

1.4 COVID-19 and rheumatologic autoimmune disease

Recent studies have shown that autoimmune diseases and COVID-19 show some similarities. Immune-mediated injuries due to the loss of regulation and immune tolerance and the existence of autoantibodies are also characteristic of SARS-CoV2. Several immune reactions are induced with a SARS-CoV2 infection, T-cells playing an important role. Lymphopenia and neutrophilia might be associated with severe illness and could be a prognostic factor (20). The way the SARS-coV2 virus acts on patients with the autoimmune rheumatic disease remains unclear. A respective number of new studies reveal that risk factors like older age, pre-existing comorbidities, male sex, and chronic respiratory disease are associated with severe COVID-19 outcomes, especially in patients with diabetes, hypertension, obesity, and cardiovascular disease (18). There is no evidence that people suffering from an autoimmune disease are more susceptible to COVID-19 and have worse outcomes than the rest of the population. The global rheumatology alliance looked at 600 cases of COVID-19 and published the data, revealing that most patients with the autoimmune disease recover from COVID-19. Older age, high doses of corticosteroids (>10 mg/day of prednisolone), and

comorbidities were associated with more hospitalizations in patients with rheumatologic disease. In addition to focusing on the prevalence of COVID-19 in rheumatologic disease, several population-based studies focused on the protective role of some immunomodulatory drugs used in treating autoimmune disease. An example drug was hydroxychloroquine, which is often used in autoimmune disease. Metanalysis studies noticed a difference in the prevalence of the disease between the rheumatologic conditions, especially in patients with connective tissue disease showing a higher prevalence of COVID-19 than patients with arthritis. The risk factors of COVID-19 are complex in patients with autoimmune rheumatic disease, advising these patients to update the vaccination status and continue with the treatment (20).

1.5 Diabetes Mellitus

Type one and type two diabetes mellitus are the two most common forms of diabetes and describe a group of metabolic diseases. Type one results in an absolute insulin deficiency by destroying the insulin-producing beta cells in the pancreas, caused by an autoimmune reaction. The more common type two is associated with genetic components, obesity, and an unhealthy lifestyle, characterized by pancreatic beta-cell dysfunction and insulin resistance, causing a relative insulin deficiency. Type two diabetes mellitus is defined by an abnormal metabolism resulting in impaired glucose tolerance, causing hyperglycemia, microvascular and macrovascular changes that lead to renal, retinal, cardiovascular, and neurological manifestations. Due to the abundance of symptoms caused by type II diabetes, this form usually remains undiagnosed for several years. Most signs include obesity, hypertension, and dyslipidemia, increasing the risk of cardiovascular disease. The management of risk factors and the normalization of glucose intolerance are the primary target of diabetes mellitus control, preventing complications such as renal insufficiency.

For type two diabetes, the treatment generally includes weight normalization, physical activity, and a healthy diet which is sufficient to prevent the progression of the disease. Patients who cannot adjust their lifestyles to the condition require oral and diabetic therapy with drugs or insulin. Type one diabetes is dependent on insulin replacement therapy and is essential for survival. Patients with type one diabetes need to learn how to coordinate insulin therapy and manage the diet. Both types require lifelong self-management training to improve glycemic values and reduce the risk of life-threatening complications such as hypoglycemia and hypoglycemia (22).

1.5.1 COVID-19 and Diabetes Mellitus

Cardiovascular disease and diabetes are among the most significant risk factors for coronavirus disease, with worse outcomes and higher mortality. This increasing incident might be a link between diabetes and COVID-19 concerning effects on glucose homeostasis, altered immune response, inflammation, and activation of the RAAS-System. Recent studies imply that the severity and increase mortality of SARS-CoV2 is associated with each patient's degree of hyperglycemia and the presence of comorbidities or complications of diabetes mellitus. Human monocytes are suspected of playing a crucial role in replicating SARS-CoV2, causing an immediate increase with elevated glucose levels, therefore, supporting viral proliferation. History of diabetes type one, type two, or hyperglycemia independently predicts higher mortality in patients infected with SARS-Cov2. There is a correlation between SARS-Cov2 infection severity and diabetes mellitus, anticipating that poor glycemic increases hospitalization, mortality, and the need for extensive treatment (23).

2. OBJECTIVES

This study aims to evaluate the clinical manifestations, course, and outcomes of COVID-19 amongst two groups of patients. One group of patients having rheumatologic autoimmune disease, while the other group being diagnosed with diabetes mellitus. Furthermore, the goal is to compare these two groups concerning SARS-CoV2 infection.

Hypothesis:

1. Patients with rheumatologic disease have a sever disease course and outcome compared to the general population

2. The course of the disease differs in different autoimmune diseases

3. There is a worse disease course and outcome in patients with diabetes mellitus

3. MATERIALS AND METHODS

3.1. Study Design

This cross-sectional study was carried out in the Department of Rheumatology and Clinical Immunology and Clinic of Infectiology medicine of the University Hospital Split (KBC Split) of the University of Split, School of Medicine and data were collected from the period of March 2021 to August 2021.

3.2. Study Population

In the study 200 patients positive for COVID-19 were considered, 52 had both diagnoses and were excluded to avoid confounding factors. From the 148 patients selected, 74 were diagnosed with a rheumatologic disease and 74 were diagnosed with diabetes mellitus. Eligible patients were identified using the Department of Rheumatology and Clinical Immunology database and the Clinic of Infectiology medicine of the University Hospital Split (KBC Split).

3.3. Materials

Medical data of eligible patients were categorized by the EULAR (European League Against Rheumatism)-COVID-19 Survey Checklist. Following data were collected for each patient, if available:

1. Age
2. Sex
3. Date of diagnosis COVID-19
4. Location of test
5. Test Method (PCR/Antigen)
6. Symptoms of COVID-19
7. Medications used to treat COVID-19
8. Outcome of COVID-19
9. Underlying disease
10. Complications COVID-19
11. Comorbidities
12. Lab value (CRP)

The EULAR-COVID-19 survey is demonstrated in Figure 2.

EULAR-COVID-19 Survey Checklist

Which information do you have to know about your patient when entering data into the platform?

- Patient's age and sex
- Date of COVID-19 diagnosis
- Place (location) at which the COVID-19 diagnosis was made (e.g. home/outpatient/inpatient/..)
- Test/Method with which COVID-19 diagnosis was made (e.g. clinical symptoms/PCR/..)
- Has the patient had symptoms of COVID-19 infection? YES/NO/UNKNOWN
  - in case of yes, you will get an extensive list with all kind of symptoms that can be chosen
- Which medication/procedures were given/performed to treat COVID-19?
- Outcome of COVID-19? Deceased/not deceased/vital status not known at this time
- COVID-19 complications
- Where was the infection (possibly) acquired? (e.g. nursing home/travel/...)
- Rheumatic/autoimmune diagnosis
- Disease activity of the rheumatic/autoimmune disease at the time of first COVID-19 symptoms (remission/low/moderate/high/unknown)
- Treatments for the underlying rheumatic/autoimmune disease:
  - glucocorticoids
  - immune modulating medication prior to the time of COVID-19
    → was this treatment stopped/continued/continued with lower dose/unknown?
- Information on other treatments:
  - ACE inhibitors, Angiotensin receptor blocker, non-selective NSAIDs, selective NSAIDS, PD5 inhibitor
- Comorbidity and pregnancy (e.g. ILD/COPD/Asthma/Diabetes/Renal insufficiency/Cardiovascular ...)
- Had the patient had his seasonal flu vaccination?
- Race/ethnic origin of patient
- Smoking status
- Use of e-cigarettes or vape
- Laboratory test results (if available; regular lab and/or microbiology/virology lab tests)

Figure 2. EULAR-COVID-19 Survey checklist

Adapted from: The European alliance of associations for rheumatology, eular.org

This study was approved by the committee of ethics of the university hospital of split by following number: 500-03/21-01/126

3.4. Statistical Evaluation

All data analyses were performed using MedCalc Statistical Software version 19.1.2 (MedCalc Software bv Ostend, Belgium, https://www.medcalc.org; 2019). The significance of differences between categorical variables of patient groups was determined using Fisher's exact test and, in cases where Fisher's test was not applicable, the Chi-squared test. The normality of the distribution of numerical data was determined using the D'Agostino-Pearson omnibus test. The Independent sample t-test and one-way ANOVA with Scheffé post-hoc test was used to assess the differences in the age of patients of different groups, while the Mann-Whitney U test and Kruskal-Wallis with Conover post-hoc test were used for assessing differences in CRP

values of patient groups. $P<0.05$ was considered to indicate a statistically significant difference and all confidence intervals (CI) are stated at the 95% level.

4. RESULTS

In this study of 148 patients, 74 patients were diagnosed with an autoimmune rheumatic disease (RAD) and the other 74 patients were diagnosed with diabetes mellitus (DM). 73 (49.32%) of those patients were male and 76 (51.35%) were female. The median age in group RAD was 55 years, while the median age in group DM was 70 years. There was a statistically significant difference in age between the studied groups (P<0.01), however when we look at each group individually there was no statistically significant difference in age or sex.

The 74 patients diagnosed with diabetes mellitus were more frequently inpatients than outpatients. However, the group of 74 patients with an autoimmune disease was significantly higher outpatient. There was a statistically significant difference between the two groups (P<0.01) and between male and female patients. The difference between male and female patients can be attributed to the fact that the group of patients with diabetes mellitus had a significantly higher proportion of men (P<0.01), while the group with autoimmune diseases had a higher proportion of women.

There was a statistically significant difference between the studied groups regarding the test methods used (P<0.01). The group of patients with diabetes mellitus was diagnosed with COVID-19 using the rapid antigen test more frequently than with the PCR method, while the opposite was found for the other tested group. There was no statistically significant difference in test methods when comparing the sexes.

The Chi-squared test showed that there was a statistically significant difference in the COVID-19 treatment between the studied groups (P<0.01). Rheumatologic patients were treated to a lesser extent for COVID-19 than diabetics, where a combination of treatments was used the most. In the two groups the Chi-squared test showed no differences between the sexes (P=0.07). Descriptive information for studied COVID-19 treatments in both groups are presented in Table 3.

Table 3. COVID-19 treatments observed in rheumatologic patients and diabetic patients

n(%)	RAD*	DM*
None	46 (31.1%)	5 (3.4%)
Antibiotics	9 (6.1%)	6 (4.1%)
NSAIDs*	6 (4.1%)	0 (0.0%)
Corticosteroids	2 (1.4%)	7 (4.7%)
Anticoagulation	2 (1.4%)	1 (0.7%)
Oxygen	0 (0.0%)	1 (0.7%)
Combination	9 (6.1%)	54 (36.5%)

*RAD = Rheumatic autoimmune disease
*DM= Diabetes Mellitus
*NSAIDs=Nonsteroidal anti-inflammatory drugs

Rheumatologic patients had statistically fewer respiratory COVID-19 complications than patients with diabetes mellitus (P<0.01). There was no statistically significant difference between the sexes (P=0.07). Descriptive information for studied COVID-19 complications in both groups are presented in Table 4.

Table 4. Observed COVID-19 complications in rheumatic patients and diabetes patients

n(%)	RAD*	DM*
None	35 (23.6%)	8 (5.4%)
Respiratory insufficiency	3 (4.1%)	27 (18.2%)
Dyspnea	5 (3.4%)	0 (0.0%)
Pneumonia	11 (7.4%)	39 (26.4%)
Fever	11 (7.4%)	0 (0.0%)
Hypertension	2 (2.7%)	0 (0.0%)
Loss of smell	7 (4.7%)	0 (0.0%)

*RAD = Rheumatic autoimmune disease *DM= Diabetes Mellitus

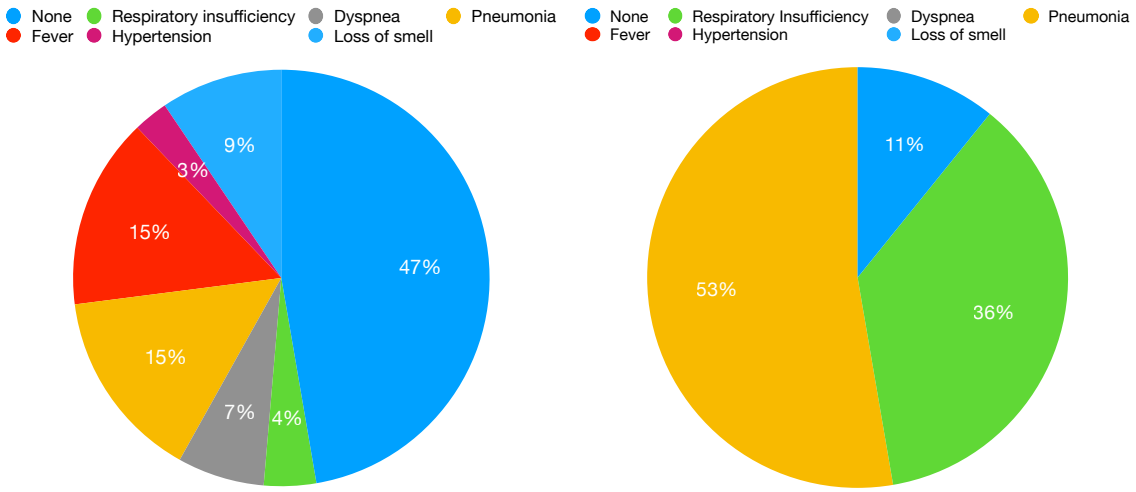

Figure 2. COVID-19 complications in RAD (left) and complications in DM (right)

The most common complications in group RAD were pneumonia, fever and loss of smell, while pneumonia to a much bigger amount and respiratory insufficiency were the most common complication amongst group DM.

The group of 74 patients with an autoimmune rheumatologic disease had fewer comorbidities, especially cardiovascular and nephrological related comorbidities, which was statistically significant (P=0.01). There was no difference between the sexes (P=0.06). However, there was a statistically significant difference in age between groups of patients separated by their comorbidities (P<0.01), with the group of patients with cardiovascular comorbidities being the oldest, which is presented in Figure 3.

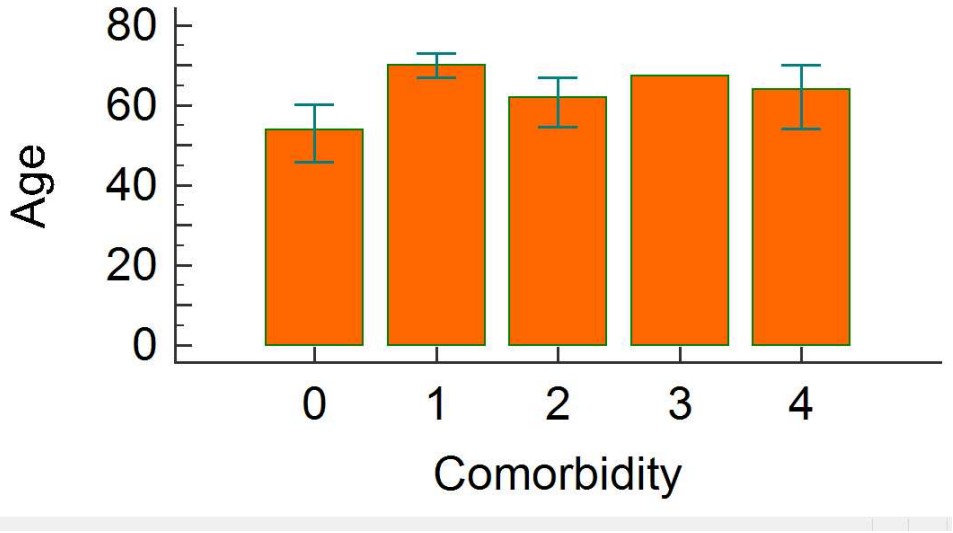

Figure 3. Comorbidities related to Age (0=No comorbidities, 1=Cardiovascular, 2=Pulmonary, 3=Nephrological, 4=others)

There was a statistically significant difference in the disease outcome of COVID-19 between the two studied groups. Patients with diabetes mellitus had a worse disease outcome than patients with a rheumatologic disease, which was statistically significant (P<0.01). The number of patients that survived or didn't survive COVID-19 measured the outcomes of each studied group. There was a statistically significant higher number of patients who deceased in group DM (P<0.1). There was no difference between the sexes (P=0.07). In both groups patients experienced symptoms in equal frequencies (P=1).

The blood values of the C-reactive protein during a COVID-19 infection were compared between the RAD and DM groups, which showed a statistically significant difference (P<0.01). The 74 patients from the RAD group had lower CRP values that averaged 3.60 with a 95% CI of 1.93 to 5.02. In contrast, the 74 patients from the DM group had higher CRP values with a median of 83.1 and a 95% CI of 44.78 to 125.73. The CRP values in both groups are shown in Figure 4.

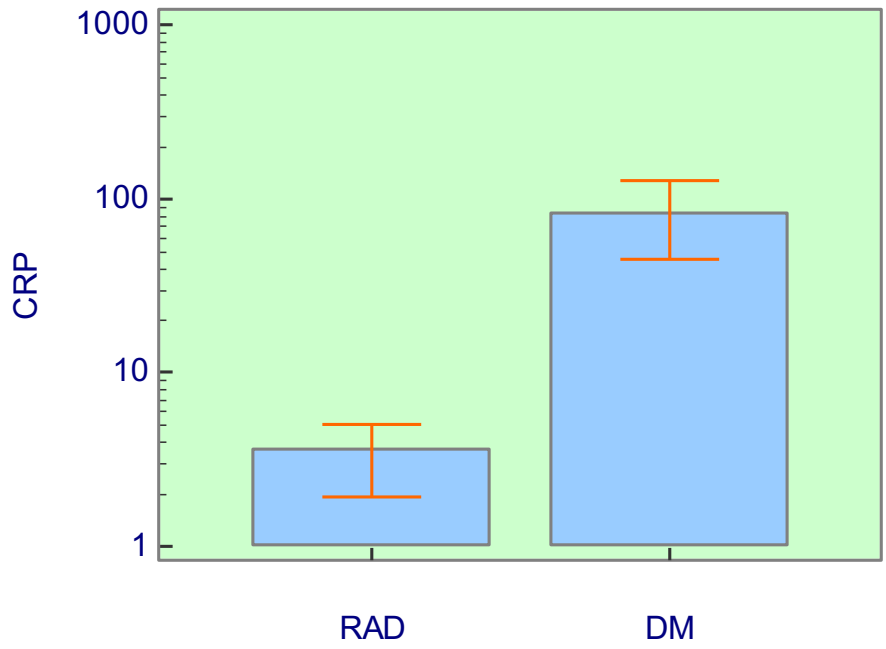

Figure 4. Bar graph showing medians with 95% confidence intervals of CRP values in the group of rheumatic autoimmune diseases and diabetes mellitus patients. Log. scale.

There was no statistically significant difference within the RAD group regarding the disease activity and treatment of the underlying disease (*P*=0.8). There was no significant correlation between CRP values and age (*P*=0.3). The disease outcome was not different between groups of patients with different rheumatological diseases (*P*=0.6). When looking at each group, patients with diabetes mellitus had no statistically significant difference in CRP values between the types of DM. There was also no difference between the sexes in DM group (*P*=0.2.)

5. DISCUSSION

According to the results obtained from this study, patients with diabetes mellitus had a worse disease outcome and more complications, which agrees with the data published so far. (24). Our study showed that patients with a rheumatic disease had fewer complications and needed milder treatment for COVID-19. This data correlates with other recent studies stating that there is no evidence that people suffering from an autoimmune disease are more susceptible to COVID-19 and have worse outcomes than the rest of the population (20). The results of a study conducted in northeast Italy indicated that autoimmune disease patients had a similar rate of infection of SARS-CoV-2 compared with the general population (35). Another Italian research performed in Milan confirmed that autoimmune disease is not a risk factor of being positive for COVID-19 (36). On the contrary, some Chinese studies have found that patients with autoimmune diseases are more susceptible to COVID-19 infection than controls (37). Thus, although we hypothesized that patients with autoimmune diseases would be more prone to COVID-19 infection, most studies did not confirm this thesis (20, 35,36). However, compared to patients with diabetes mellitus, the assumption was that rheumatic patients tend to have better results, more minor complications, and less need of treatment for COVID-19. We also implied that there might be a difference in disease outcome between the different autoimmune diseases and types of diabetes. The presumption was that COVID-19 had different results among the two studied groups, emphasizing the difference in the disease course and outcome in two similar immunocompromised groups of patients.

Patients with diabetes mellitus were more frequently hospitalized than patients with rheumatic disease, which could be explained by inadequate blood glucose control contributing to a severe disease outcome, as stated in recent studies. Evidence suggests that an increase in glucose levels directly supports viral proliferation (23). Furthermore, these results correspond with a current retrospective study published by Swedish groups of authors, which observed severe COVID-19 in patients with DM type one and type two, emphasizing the association between glycated hemoglobin and higher risk for outcomes, admission to intensive care, and death. Contrary to our study, these data showed a difference in disease outcome between the two types of diabetes mellitus (24).

Rheumatologic patients were more frequently outpatient, which is consistent with the already mentioned Italian studies (20, 35, 36). However, there is not much information on the hospitalization rates for patients with an autoimmune rheumatic disease, which emphasizes the need for more research. Comparing the two studied groups, our results also show a statistically

significant difference between male and female patients, which can be attributed to the fact that patients with diabetes mellitus had a significantly higher proportion of men. In comparison, the group with autoimmune diseases had a higher proportion of women. This finding is conceptually in line with published studies stating that men have a statistically significant risk of diabetes mellitus. On the contrary, females have a higher risk for autoimmune diseases (26, 27, 28). In addition, our data present a difference between the two studied groups concerning the test methods used. Patients with diabetes mellitus were more frequently tested with a rapid antigen test, while rheumatic patients were tested with the PCR method. The fact could explain that hospitalized patients with a more severe clinical picture are more extensively tested with rapid antigen tests, implying the need for faster results to minimize contaminations and infections of other patients.

The data in our study illustrate the difference in complications associated with COVID-19 between the two groups of patients. At the same time, patients with rheumatic diseases had minor symptoms and less severe complications like pneumonia than those with diabetes. Patients with diabetes had more severe complications, primarily pneumonia and respiratory insufficiency. As discussed beforehand, hyperglycemia contributes directly to the severity of COVID-19 and a dysregulated immune response, leading to extensive lung injury as seen in our results and are thematized in ongoing trials (23). Moreover, similar studies imply that due to an excess of glucose, these patients have increased pro-inflammatory mediators like cytokines IL-6 (interleukin) and IL-1, which could contribute to a cytokine storm reported in some patients (29). A recently published study observed severe COVID-19 in patients with DM and state that patients with diabetes had an increased outcome of mortality and intubation comparing to patients without DM (33). Contrary, a Turkish study on the clinical effects of COVID-19 in rheumatic disease shows that was no increased risk of severe COVID-19 among this group of patients (34). These findings correlate with our data, indicating that DM patients had a worse disease outcome than patients with ARD.

In addition, the data obtained from our study show that there was a statistically significant difference in the COVID-19 treatment between the studied groups, emphasizing the different course and outcome of COVID-19. While patients with diabetes mellitus received a combination of antibiotics, corticosteroids, oxygen, and anticoagulation, most patients with a rheumatic autoimmune disease didn't receive any treatment. These findings may reflect the role of constant corticosteroid therapy in patients with an autoimmune rheumatic disease and their effect on the pathogenesis of COVID-19. As discussed in recent studies, corticosteroids may decrease the development of respiratory failure and reduce mortality. Especially

dexamethasone has been shown to reduce the duration of mechanical ventilation. Long-term use of glucocorticoid therapy has been shown to improve alveolar-capillary membrane permeability and enhance tissue repair (20, 30). As stated in the ongoing trial RECOVERY (Randomized Evaluation of COVID-19 Therapy), patients with moderate COVID-19 pneumonia are likely to benefit from corticosteroid therapy, reducing the risk for mechanical ventilation by 36% (31). Furthermore, corticosteroids have been shown to reduce CRP blood values within 72 hours of therapy in patients with COVID-19 (33). This result reflects our findings, which show that patients with rheumatic autoimmune disease have significantly lower CRP values than diabetes mellitus. Recent studies illustrate the importance of inflammatory parameters like CRP in COVID-19. Due to ARDS (acute respiratory distress syndrome) development, severe edema of the alveolar wall and parenchyma develops, increasing the CRP values (20).

We also implied that there might be a difference in disease outcome between the different autoimmune diseases and types of diabetes. But our results didn't show a difference in disease outcome between the different types of autoimmune rheumatic disease or diabetes mellitus. A Spanish cohort study that included 228 rheumatic patients showed that among hospital patients with chronic inflammatory rheumatic diseases, having a systemic autoimmune disease but not inflammatory arthritis is an independent risk factor for poor COVID-19 outcomes (38). These data differ from ours, which is probably due to the smaller number of patients.

Some limitations of our study need to be considered. Since the beginning of COVID-19, we could only collect a specific number of eligible patients for this study, giving us a relatively small pool of patients, which were difficult to compare, especially regarding age and sex. Unfortunately, the number of patients was too low to draw specific conclusions comparing COVID-19 disease severity and outcome between patients with rheumatic autoimmune disease and diabetes mellitus. In addition, it is an observational study of one center, which can further reduce the value of the results.

Ultimately, more patients need to be collected to increase the sample size. Further prospective research is necessary to evaluate the number and causes of hospitalizations in rheumatic patients. Finally, the role of certain types of antidiabetic drugs and immunotherapy on the pathogenesis of COVID-19 should be a topic of further research which could yield new information on the outcome and severity in these groups of immunocompromised patients.

6. CONCLUSION

1. Patients with diabetes mellitus were more frequently hospitalized than patients with an autoimmune rheumatic disease. One of the reasons for that can be the role of hyperglycemia on viral proliferation and, therefore, disease severity and outcomes.

2. Rheumatologic patients were treated to a lesser extent for COVID-19 and had statistically fewer respiratory complications than patients with diabetes mellitus, pointing out the protective effects of corticosteroid treatment. Since hyperglycemia contributes directly to the severity of COVID-19 and a dysregulated immune response, patients with diabetes mellitus are more prone to extensive lung injury.

3. Patients with diabetes mellitus had a worse outcome than patients with an autoimmune rheumatic disease, which was statistically significant.

4. Patients with a rheumatic disease had statistically significantly lower CRP values, which is most likely the results of corticosteroid treatment and its effects on CRP.

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8.SUMMARY

Objectives: To evaluate the clinical manifestations, course, and outcomes of COVID-19 amongst patients with RAD and DM and compare these two groups concerning SARS-CoV2 infection.

Materials and methods: A cross-sectional study was done in the Department of Rheumatology and Clinical Immunology and Clinic of Infectiology medicine of the University Hospital Split (KBC Split) of the University of Split. Of the 148 patients selected, 74 were diagnosed with rheumatologic disease, and 74 were diagnosed with diabetes mellitus. The EULAR-COVID-19 Survey Checklist categorized the medical data of eligible patients. The following variables were included: Age, sex, diagnosis, symptoms, treatment, complications, outcome, laboratory parameters (CRP).

Results: Patients with DM were statistically significantly more inpatients comparing to patients with RAD ($P<0.01$). There was a statistically significant difference between the studied groups regarding the test methods used ($P<0.01$). Rheumatologic patients were treated to a lesser extent for COVID-19 than patients with diabetes, where a combination of treatments was used the most ($P<0.01$). Rheumatologic patients had statistically fewer respiratory COVID-19 complications than patients with diabetes mellitus ($P<0.01$). There was a statistically significant difference in the disease outcome of COVID-19 between the two studied groups. Patients with diabetes mellitus had a worse outcome than patients with rheumatologic disease, which was statistically significant ($P<0.01$). The patients from the RAD group had lower CRP values that averaged 3.60 with a 95% CI of 1.93 to 5.02. In contrast, the patients from the DM group had higher CRP values with a median of 83.1 and a 95% CI of 44.78 to 125. 73.

Conclusion: Our results showed that patients with rheumatic autoimmune disease tend to have a better disease outcome than patients with diabetes mellitus. Patients with diabetes mellitus had more complications, mainly respiratory, and needed more extensive treatment than the compared RAD group.

Key words: COVID-19, RAD, DM, clinical manifestation, outcomes

9. CROATIAN SUMMARY

COVID-19 i reumatske bolesti u Dalmaciji u usporedbi s Diabetes Mellitus

Cilj: Procijeniti kliničke manifestacije, tijek i ishode COVID-19 infekcije u bolesnika sa sistemskim upalnim bolestima te usporediti s kliničkim manifestacijama, tijekom i ishodom u bolesnika s šećernom bolešću.

Materijali i metode: Presječna studija provedena je na Zavodu za reumatologiju i kliničku imunologiju i Klinici za infektivne bolesti KBC-a Split i Sveučilišta u Splitu. U istraživanje je uključeno 148 bolesnika od kojih je 74 s upalnim reumatskim bolestima, a 74 sa šećernom bolesti. Za dobivanje podataka je korišten EULAR-COVID-19 upitnik. Uključene su sljedeće varijable: dob, spol, dijagnoza, simptomi, liječenje, komplikacije, ishod, laboratorijski parametri (CRP).

Rezultati: Bolesnici s šećernom bolešću su bili značajno češće hospitalizirani te im je češće rađen brzi antigenski test za dokazivanje COVID-19 infekcije u odnosu na bolesnike s upalnim reumatskim bolestima (P <0.01). Reumatološki bolesnici su liječeni blažim terapijskim mjerama zbog COVID-19 infekcije nego bolesnici sa šećernom bolešću u kojih se najčešće primjenjivalo kombinirano liječenje (P <0.01). Reumatološki bolesnici imali su značajno manje respiratornih komplikacija COVID-19 infekcije u odnosu na bolesnike s šećernom bolešću (P <0.01). Utvrđena je statistički značajna razlika u ishodu bolesti COVID-19 između dvije ispitivane skupine. Bolesnici sa šećernom bolešću imali su lošiji ishod od bolesnika s upalnom reumatološkom bolešću, (P <0.01). Bolesnici s upalnom reumatskom bolešću su imala niže vrijednosti CRP -a koje su u prosjeku bile 3.60 s 95% CI od 1.93 do 5.02 , dok su bolesnici sa šećernom bolešću imali veće vrijednosti CRP -a s medijanom od 83.1 i 95% CI od 44.78 do 125. 73.

Zaključak: Naši su rezultati pokazali da bolesnici s reumatskom upalnom bolešću imaju bolji ishod bolesti od bolesnika sa šećernom bolešću. Ovi bolesnici su imali učestalije komplikacije, uglavnom respiratorne, i trebali su intenzivnije liječenje u odnosu na bolesnike s upalnim reumatskim bolestima.

Ključne riječi: COVID-19, upalne reumatske bolesti, šećerna bolest, kliničke manifestacije, ishod

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