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# A CORRELATION BETWEEN RHEUMATOID ARTHRITIS AND COVID-19

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**Abstract:**

*An autoimmune disease called rheumatoid arthritis affects 0.5% to 1 of the general population. Due to hormonal factors, women are more likely to experience it. Pain and swelling are the main symptoms brought on by synovial inflammation, despite the fact that the specific etiopathology is unknown. Even while analgesics and biological treatments can put rheumatoid arthritis into remission, the condition is generally thought to be incurable. The 2019 coronavirus infection outbreak that it created had a devastating impact on the entire world. COVID-19 disease affected or killed people who had autoimmune conditions, compromised immune systems, or elderly people. Although there is a substantial danger of transmission, it seldom causes death. Organ failure and cytokine storm are two of the disease's main clinical signs and symptoms. A patient would find it extremely difficult to live with such a clinical picture, which necessitates serious medical treatment.*

**Key words**: *Rheumatoid arthritis, Covid-19, Cytokine storm, Immunoglobulins, Interleukins.*

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## INTRODUCTION:

Rheumatoid Arthritis (RA) is a multidisciplinary autoimmune disease that affects 1% of the general population[1]. The cause of this disease, which causes joint destruction, is unknown, is characterised by chronic inflammation, progresses cumulatively, has a negative impact on many body systems, and affects women three times more than men[2]. Genetic, environmental, age, and gender factors all play a role in its progression[3]. The disease can be distinguished from other types of arthritis by increasing inflammatory biomarkers in the inflamed synovium[4]. With the devastating COVID-19 outbreak that began in Wuhan, China in December 2019, some RA biomarkers have become critical[4,5]. Interleukin-6, ACPA, and anti-CCP are the most common markers (IL-6) that shed light on the progression and pathology of the disease. Inflammation is significantly increased in rheumatoid arthritis[4].

**Aetiology and Pathology of Rheumatoid Arthritis:**

Although the exact cause of RA is unknown, it manifests itself in a variety of clinical manifestations that are thought to be caused by infection, genetic, environmental, and endocrine dysregulation[3]. Synovium inflammation is a pathological event that destroys articular cartilage and bone. The most important feature distinguishing it from other articular pathologies is joint destruction[6]. Rheumatoid arthritis severity and progression are clearly influenced by genetic factors. The prevalence of RA, which is 1% in the general population, ranges from 12-15% in monozygotic (identical) twins to 2-5% in dizygotic twins or first-degree relatives[7]. Environmental factors, in addition to genetic factors (50%) play a role in the pathogenesis of RA. Infections are a major environmental factor. Many pathogens have been involved in the pathogenesis of RA. Although Mycobacterium tuberculosis, Proteus mirabilis, Escherichia coli, Epstein-Barr virus, Parvovirus 19, and some retroviruses have been blamed, no organism can be held responsible[8].

Women experience rheumatoid arthritis three times more frequently than males. The higher frequency of RA in women may be due to hormones, notwithstanding the inability to fully pinpoint the cause of the gender disparity[2]. They must pass through the synovial tissue layer, which is extremely thin in healthy joints but has a thick lining layer of macrophages and fibroblastoid synovial cells in rheumatoid joints, in order to enter the joint space. Lymphoid cells containing dendritic cells, such as lymphatic nodules, accumulate in the deeper regions of synovial tissue. Stromal fibroblasts change from having a long, stretched appearance to small, round cells, multiply, and accumulate in deeper regions of the synovial tissue alongside dendritic cells like nodules. These pathologies are classified according to their chronicity and severity. Within the same joint, these pathologies are not uniform. B and T cells are not only found in greater numbers in the stroma, but they are also commonly found near blood vessels and are accompanied by dendritic cells[9].

**Clinical characteristics of Rheumatoid Arthritis:**

Rheumatoid arthritis is a serious disease with numerous extra-articular manifestations. Extra-articular involvement may occur in 40% of patients during the disease's onset and progression. Extra-articular involvement is linked to an increased risk of death in RA. Patients with RA who do not have extra-articular manifestations have the same life expectancy as the general population[10]. Rheumatoid arthritis patients frequently have pulmonary involvement. As a result of pulmonary involvement, mortality rates are high. Despite the fact that it is asymptomatic, the prognosis of pleural disease is common in people with rheumatoid arthritis[11]. Rheumatoid nodules in the lung are most common in seropositive male synovitis patients. Diagnose in the clinic is extremely rare. In radiographic imaging, It can be seen alone or as a cluster of grapes[10]. Interstitial lung disease is the most crucial pulmonary involvement in rheumatoid arthritis[12]. The prevalence of the involvement of the cardiovascular system is high in rheumatoid arthritis. The patient's life expectancy is typically reduced by 5 to 15 years by cardiovascular illness, which typically affects individuals with early RA and has a death rate of 42%.

The most common heart condition is pericarditis. Many patients with early RA may have or develop pericarditis before developing RA. Although clinical symptoms were present in less than 15% of RA patients. According to the ECG, 20%-50% of patients had pericardial involvement manifesting as chest pain or shortness of breath. Heart failure is the leading cause of death in RA patients. Arrhythmia is another common cardiac complication in RA patients that may occur secondary to conduction abnormalities due to local ischemia, rheumatoid nodules, amyloidosis, or heart failure. The main cause of cardiovascular disease contributing to cardiac dysfunction remains unclear. Therefore, early diagnosis and prevention of cardiac dysfunction are crucial [13]. Anemia is one of the most common extra-articular symptoms of RA. There are

numerous contributing factors to anemia in RA. These include gastrointestinal bleeding, bone marrow suppression, and malnutrition brought on by medication. as well as inefficient erythropoiesis. The prevalence of actively inflamed joints and thrombocytosis are both common findings in RA patients. When RA is active, lymphadenopathy is occasionally noted; on biopsy, it is typically diagnosed as benign follicular hyperplasia.

**Laboratory findings in Rheumatoid arthritis:**
CRP has a very short half-life, and its concentration rises within a few hours with inflammation and peaks in 2 to 3 days. After the inflammation subsides, its concentration quickly returns to normal.

The CRP level in healthy individuals is less than 0.2 mg/dL, however depending on microtraumas, this level may increase to 1 mg/dL. Additionally, it can be utilised to assess the prognosis and track the progression of RA disease[16]. Analysis and secretion of α 1-acid glycoproteins rise in response to cytokines like IL-1 and TNFα. It was discovered that CRP and α 1-acid glycoprotein were the most helpful markers for RA disease activity. High CRP levels are linked to death and also the requirement for intubation. Numerous factors can cause an increase in CRP[16,17]. It was first identified in 1940 that rheumatoid arthritis (RA) patients serum contained a substance that caused red blood cells sensitized by immunoglobulin G (Ig G) antibodies to clump together. The rheumatoid factor was later given to this factor (RF). Rheumatoid factors (RFs) are antibodies that target the human IgG molecules crystallizable Fc region. These are the distinctive autoantibodies of the extravascular immune complex disease rheumatoid arthritis (RA)[18]. Rheumatoid factor measurement is the most often utilized test serum in the diagnosis of rheumatoid arthritis (RF). Its specificity can reach 85%, and its sensitivity ranges from 60% to 90%[19]. The presence or absence of antibodies to citrullinated peptides/protiens is an important parameter that assist a clinician in making a diagnosis of early RA and, consequently, initiating treatment. When compared to RF, IgG autoantibodies that recognize citrullinated peptides, known as anti-cyclic citrullinated peptides (anti-CCP), have improved specificity in the early diagnosis of RA. ELISA assays have traditionally been used for Anti-CCP testing[20]. In the enzyme-linked immunosorbent test (ELISA), administration of the citrulline-containing peptide (CCP) demonstrated the presence of anti-CCP autoantibodies in 76% of rheumatoid arthritis sera with 95%-100% specificity[21].

**Treatment of rheumatoid arthritis:**
Disease-modifying medications, glucocorticoids, non-steroidal anti-inflammatory medicines, and biological agents are utilised to treat rheumatoid arthritis. The first medication of choice for those with severe RA is methotrexate (MTX), an immunosuppressive medication that can disrupt DNA synthesis by impairing the metabolism of folic acid (vitamin B9) [22]. It raises adenosine and anti-inflammatory cytokine levels while lowering proinflammatory cytokines including IL-6 and IL-1 β, according to in vivo and ex vivo testing. These characteristics are also linked to the cause of the disease aggravation once drug use is stopped[23]. Leflunomide is a prodrug that was approved in 1998 and was first used to treat active RA illness. It turns into its active metabolite in the liver, stops the growth of lymphocytes, and inhibits T cell proliferation as pyrimidine synthesis inhibition[24].

**Aetiology and Pathology of SARS-CoV-2:**
The envelope encasing SARS-CoV-2 contains the viral nucleocapsid. It is a peculiar positive polarity, single-stranded RNA virus with virion sizes between 60 and 140 nm and surges between 9 and 12 nm. The nucleocapsid protein (N), spike glycoprotein (S), envelope glycoprotein (E), and membrane protein are the four main structural proteins of this virus (M) [25]. In order to facilitate viral entrance into the host cell, spike glycoprotein (S) mediates viral attachment to host cell surface receptors and subsequent membrane fusion [26]. Between 8 and 12 kDa in size, the envelope glycoprotein (E) is the smallest and least abundant of the major structural proteins and has the lowest copy in the lipid envelope of mature virus particles[27]. The most prevalent protein in virus-infected cells is the nucleocapsid protein (N). The N protein, which is the protein component of the helical nucleocapsid and has a molecular mass of 43–50 kDa, is hypothesized to bind the genomic RNA like beads on a string. The most prevalent part of coronaviruses, membrane protein (M), determines the shape of the viral envelope. The pre-glycosylated M polypeptide has an amino acid count of 221-262 and measures 25–30 kDa[28].

Pneumonia is brought on when SARS-CoV-2 affects the lower respiratory system. Dysfunction in the respiratory system and excessive inflammation are the main causes of death[29]. The S protein is ACE-2 mediated cell entrance receptor for coronaviruses and offers a specific S protein binding site[30]. The N-terminal peptidase (NTD) and C-terminal peptidase

(CTD) domains are both present in the ACE-2 protein. The S1 protein found in SARS-CoV-2 is responsible for cellular membrane adhesion. Membrane fusion is accomplished by the S2 protein[22]. As a result of membrane fusion, the virus enters the cell via endocytosis[31]. The type 2 transmembrane serine protease (TMPRSS2) activates the S protein and promotes the entrance of the ACE-2 receptor into the cell[30]. Analyzing the receptor-binding domain (RBD) of the S protein in interaction with ACE-2 is crucial to comprehend the infection potential of SARS-CoV-2 in humans. It was demonstrated in a study that, SARS-CoV-2-CTD had a stronger affinity than SARS-CoV-2-RBD[22].

**Clinical course of covid19:**

The COVID-19 outbreak, which began in December 2019, has been proven to be contagious up to a distance of 7 to 8 metres through tiny droplets released during sneezing[32]. After an incubation period of about 5.2 days, COVID-19 infection symptoms start to show up[33]. Fever, exhaustion, a dry cough, myalgia, and shortness of breath are the most prevalent signs of infection; headache, vertigo, nausea, vomiting, anorexia, and conjunctivitis are less frequent signs[22,34]. When considering how the COVID-19 disease progresses on the respiratory system, dyspnea typically appears 5-7 days after lung functions start to decline. This time frame could be shortened if the patient has a history of a concomitant condition. Young people with solid medical histories may have this period lasting longer. As a result of the disruption of gas exchange brought on by pulmonary inflammation, hypoxemia subsequently develops. The first line of treatment for hypoxemia should be oxygen supplementation if the oxygen saturation (SpO2) is below 93 at the time that symptoms first appear[22,35].

The life-threatening systemic inflammatory syndrome known as cytokine release syndrome can be brought on by a variety of therapies, pathogens, cancers, autoimmune diseases, and monogenic disorders. It is characterised by elevated levels of circulating cytokines and immune-cell hyperactivation. From a historical perspective, cytokine storm was formerly referred to as an influenza-like condition that happened following systemic infections like sepsis and following immunotherapies like sepsis. The Black Death, or plague (Yersinia pestis infection), has caused significant pandemics and causes alveolar macrophages to overproduce cytokines, resulting in cytokine storm[36]. The term "cytokine storm" refers to a group of immune dysregulation illnesses marked by systemic inflammation, multiorgan dysfunction, and constitutional symptoms that, if left untreated, can result in multiorgan failure. High fever, exhaustion, anorexia, headache, rash, diarrhoea, myalgia, and neuropsychiatric symptoms may be present in patients who develop cytokine storm. These signs and symptoms could be the direct result of cytokine-induced tissue damage, acute physiological changes, or immune cell-mediated reactions[37].

**COVID-19 Laboratory, Radiological Findings and Tests:**

The COVID-19 diagnosis and treatment recommendations state that nucleic acid testing should be used initially in clinically suspected cases to confirm the illness. Nucleic acid amplification test (NAAT) and gene sequencing are the two basic techniques for detecting SARS-CoV-2 nucleic acids[38]. Biomarkers for hematopathology In 80% of cases, the white blood cell (WBC) count falls, and in 72.3% of cases, lymphocytopenia also sets in. Patients with severe COVID-19 have a significantly decreased lymphocyte count compared to those with moderate instances[39]. Particularly in severe cases, emphasis was drawn to the biomarker lactate dehydrogenase (LDH). Along with it, it is followed by creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine[40]. Progressive cases may result in hypoalbuminemia developing, increasing LDH, troponin I, creatinine, and causing death[41].

In order to detect thoracic involvement early in suspected COVID-19 patients, radiological evaluation is necessary, especially in emergency rooms, while waiting for a real-time reverse transcription-polymerase chain reaction (RT-PCR) diagnosis of SARS-CoV-2, which has a gold standard sensitivity of 60% to 70% for diagnosis[42-44]. The most frequent site of organ involvement in COVID-19 is the chest, most specifically the lungs. Computed tomography (CT), particularly high-resolution CT (HRCT), and the patient's symptoms are the two main methods Chinese radiologists employ to diagnose and stage the severity of pulmonary involvement of COVID-19. 3.9% of COVID-19 diagnoses by CT are missed[45]. In imaging diagnosis, it is critical to differentiate COVID-19 from bacterial pneumonia and Chlamydia pneumonia. Bronchitis, also known as lobar pneumonia, is the most prevalent kind of bacterial pneumonia in the lung parenchyma. While ground-glass opacity is unusual for bacterial infection, the findings of CT imaging are characterised by uneven consolidation of the lung segment or subsegment[45].

**Treatment of COVID 19:**

COVID-19 is treated with glucocorticoids, antimalarial medications, antiviral medications, and biological agents. A powerful, long-acting, broad-spectrum glucocorticoid drug is dexamethasone that mimics the effects of the hormone cortisol in a synthetic form[46,47]. The antimalarial and anti-autoimmune drugs hydroxychloroquine and chloroquine can also prevent virus infection by raising the endosomal pH necessary for membrane fusion between the virus and the host cell[48]. Treatment also includes the use of favipiravir, an RNA-dependent RNA polymerase inhibitor that was developed in 2002. It has a potent and targeted inhibitory effect against influenza viruses and was studied as a potential agent against RNA viruses in 2018[49,50]. Antiretroviral therapy is used in conjunction with lopinavir-ritonavir to treat HIV-positive patients. Lopinavir inhibits HIV protease, a necessary enzyme for fresh viral assemblage. In response to lopinavir's limited oral bioavailability and significant biotransformation, ritonavir is co-administered with it to prolong levels and boost exposure in the human body[48]. Remdesivir, a broad-spectrum antiviral drug created in 2016 to treat the Ebola virus, can halt viral genome replication in COVID-19 disease by acting as an RNA-dependent RNA polymerase inhibitor[48].

## DISCUSSION AND CONCLUSION:

The COVID-19 outbreak, which had a global impact, raised the question of whether or not the autoimmune condition rheumatoid arthritis will worsen as a result[51]. Infectious diseases have a complicated association with RA. RA sufferers are at a higher risk of infection than the general population[52]. Concerns regarding the potential effects of SARS-CoV-2 infection in RA patients first surfaced at the beginning of the COVID-19 outbreak. There have been worries that infection will be linked to increased COVID-19 severity and high mortality in rheumatoid arthritis patients because of the potential negative impact of immunosuppressive medications on viral clearance. The challenge in evaluating the incidence of COVID-19 in RA patients is to review a large number of patients and diagnose COVID-19 in light of the limits of clinical testing[53]. We can infer that persons with a genetic predisposition to rheumatoid arthritis are more likely to develop the disease following infection with COVID-19 and that the clinical course of COVID-19 may be more severe in those with RA than in healthy individuals.

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