Section A-Research paper

SARS COVID-19'S CLINICAL IMPACT ON RHEUMATOID ARTHRITIS PATIENTS DURING THE THIRD WAVE IN DEHRADUN

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Abstract

The main pathogenic trait of the corona virus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), is an immune response that is overly activated and results in an excessive release of pro-inflammatory mediators in the alveoli and lung structures.The cytokine hyper activation in COVID-19 appears to be comparable to that seen in the autoimmune condition mainly rheumatoid arthritis (RA). RA patients now understand

to an extent the gravity and danger of COVID-19 because to new information. The findings of musculoskeletal symptoms involving immune-inflammation-dependent mechanisms and cases of arthralgia and/or myalgia in COVID-19 are commonly discussed in the context of crosstalk between COVID-19 and RA.By using multiple Serological and Molecular profiling, we attempted to identify a clinical association between RA and COVID-19. The severity of both was compared between the sexes. Additionally,the relationship was alsoestablished between COVID -19 and RA cases in rural and urban locations. The majority of positive cases in Dehradun occurred in urban areas (n=578), followed by rural regions (n=141), and mixed areas (n=75), albeit the number of positive cases was considerably lower compared to the first and second waves. After the normality had been examined, The CT values looked to have come from a population that was regularly distributed even though they showed no specific pattern. Since random individuals were selected, the population was not under control. The P value for Highly Positive CT findings was ($p = 0.03370$), Mean ± SD 17.896 ± 2.081 and n=22. for Mid Positive cases,($p = 0.22830$), Mean ± SD 33.280 ± 1.480 and n=35.Even in Low Positive where ($p < 10-4$), Mean ± SD 27.309 ± 2.733, the distribution of CT values did not always appear to have come from a population with a normally distributed distribution. The average age of the Covid-19-positive females was 48 years, but the average age of the Covid-negative males was 42 years, showing that females with Covid infection have a higher risk of developing RA, and vice versa. Autoimmune diseases are strongly related to immune system decline, which can surely attract many pathogens. There is still much that has to be developed in order to safeguard people's health.

1. Introduction

The beta corona virus known as SARS-CoV-2 infected the whole population of India. In the general community, older age and co morbidities are risk factors for severe COVID-19 outcomes in RA patients[1]. In contrast to other kinds of disease modifyinganti rheumatic medications (DMARDs), glucocorticoids appear to be linked to a higher risk. Research evidence suggests that people with Rheumatoid Arthritis (RA) are more likely than average to develop severe COVID-19.Many people with RA also have obesity and health conditions such as high blood pressure and heart disease, which raise risk of severe COVID-19 [2,3,4]. A few of the medications used to treat RA pose additional risks.SARS-CoV-2 is the cause of COVID-19, an illness of the

respiratory tract that resembles viral pneumonia. Patients with long-standing RA are more likely to experience relapses, and as people age and lose their immune systems, they develop new infections. Relapses of RA are also brought on by co-morbid conditions such Type 2 diabetes mellitus (T2DM), interstitial lung disease (ILD), and osteoporosis [5,6,14]. Due to the complexity of both conditions, there are yet no accurate diagnostic results. As COVID-19 is a viral infection, there is a great likelihood that it will mutate, and the cause of RA is yet unknown [15].The precise cause of the beginning of RA has not yet been determined. Several inflammatory markers are currently used to diagnose RA as well as Covid-19 [15].As is well-known, autoimmune tolerance plays a crucial role in maintaining immunological homeostasis, which can be upset for a variety of causes, including infections from pathogens. Multiple autoantibody production is a significant indicator of autoimmune tolerance failure, one of the risk factors for autoimmune disorders. According to research by Kerr JR, parvovirus B19 infection can result in the creation of a number of autoantibodies, including those that are anti-nuclear and anti-dsDNA. It can also serve as a catalyst for the onset of a wide range of autoimmune illnesses.

2. Materials and Method

The present study aims to investigate the Dehradun district area wise effect of COVID-19 on patients with Rheumatoid Arthritis. The study has been done in DNA Labs- A center for Applied Sciences (DLCAS Dehradun, Uttarakhand. during 3rd wave between 25th December 2021 to 31st January 2022. The present study also examines the association between urban and rural areas which represent the population density and life style of people, which is the big, factorcausing Covid-19 in people with autoimmune disorders.

To carry out the study 578 patients having complaints of COVID-19 symptoms were included, of them 63 were males and 63 females. RNA Extraction of suspected covid-19 specimen were done by GB SARS Lab Prep Viral RNA/DNA isolation Kit (Cat. number 4SDO0023).CoviPathCOVID-19 RT-PCR Kit (Cat. No. A52000) was used for RT PCR Amplification and amplification protocol, was followed as provided with the manufacturer's protocol.The Spike protein (S),Nucleocapsid Gene(N), Open Reading Frame(ORF) were the target genes and RNaseP was used as internal control (IC).Amplification was done by utilizing Rotor gene-Q Qiagen, Real time PCR machine. Serological parameters for Covid-19 and

Rheumatoid Arthritis (RA), were C-reactive protein(CRP), Erythrocyte Sedimentation Rate (ESR), RA Factor, and Qualisa anti cittrulatedProtein(ACP)Antibodies and were analyzed by Enzyme Linked Immunosorbent Assay (ELISA) method. Biochemistry Analyzermind ray/BA-88A semi automation was used for the whole study.For CRP quantitative coral clinical system and qualitative anmol laboratories Pvt. Ltd kit was utilized,RA Factor was analyzed by Beacon Diagnostics Pvt. Ltd.Cyclic Threshold (CT value) and clinical outcomes of serological tests were used to determine the severity of Covid infections and RA. Uni-variate analysis was performed between age and gender.

The Mann-Whitney test was used to compare the age median according to Gender. Alpha risk was set to 5% (α= 0.05).A multivariate linear regression was performed to assess the relation between Age and the explanatory variables: Gender. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. Heteroskedasticity and normality of residuals were assessed respectively by the Breusch-Pagan test and the Shapiro-Wilk test. A p-value 0.05 was considered statistically significant. Whole Statistical analysis was performed with the online application Easy MedStat. Analysis of Relevance of CT Values, Viral Load in RA Patients by High positive, mid positive and Low positive CT Values.Normality of*CT Value(Highly Positive)*was assessed with the Shapiro-Wilk test.

3. Results

A univariate analysis was performed with average age and gender of COVID infected and RA positive patients. From data analysis, there are 63 males and 63 females with average age of 42 years and 48 years respectively. From table I and figure I, it is evident that irrespective of the average age between both the genders, females infected with COVID-19 was more susceptible towards RA than compared to males.

The current study also reports the correlation of spreading of SARS CoV-2, area wise in densely populated areas with Rheumatoid Arthritis. The majority of suspected cases tested, was in Urban areas of Dehradun (n=578) in comparison to Rural Areas (n = 141) while least were in mixed areas (n = 75). The total population of COVID positive cases and RA is 126 in urban, rural and mixed areas where 63 were males and 63 were female. Here we focus on the co-infection of RA and COVID 19. The data suggests that, among the total, 126 cases of co-infection, 59.52% had

high CRP values, followed by 46.03% population having high AntiCCP values and 30.95% had elevated RA Factor.

The infectivity showed that urban population was more affected in comparison to rural areas (Figure II). It is observed from the data, that patients with COVID infections are at an increased risk of developing RA in urban areas than compared to rural areas. In the third wave, a large number of new infections were from urban areas up to 90 percent confirmed positive cases was asymptomatic with active RA.Areas from Vishnu Puram to Bhagat Singh colony had 117 tested cases of covid-19 with 47 positive and 70 negative cases. 21 had active RA affected with Covid-19 and 9 were found to be negative for Covid-19 with Active RA (figure IIIA).Different Areas from Doiwala to kaulagarh, there were total 500 cases out of which 198 cases were positive and 302 cases were negative. Cases with Covid-19 along with RA was 79 and with Covid negative and RA Positive cases were 20 comparably lower than cases with Covid-19 along with RA (figure IIIB)..Areas of Vasant Vihar, Araghar, Adarsh vihar upto Tapkeshwar had total 211 cases tested where78 cases were positive for covid-19, 133 negative, 27 cases were having RA along with positive covid-19 and 8 were Positive for RA (FigureI III)out of negative cases for covid-19 .

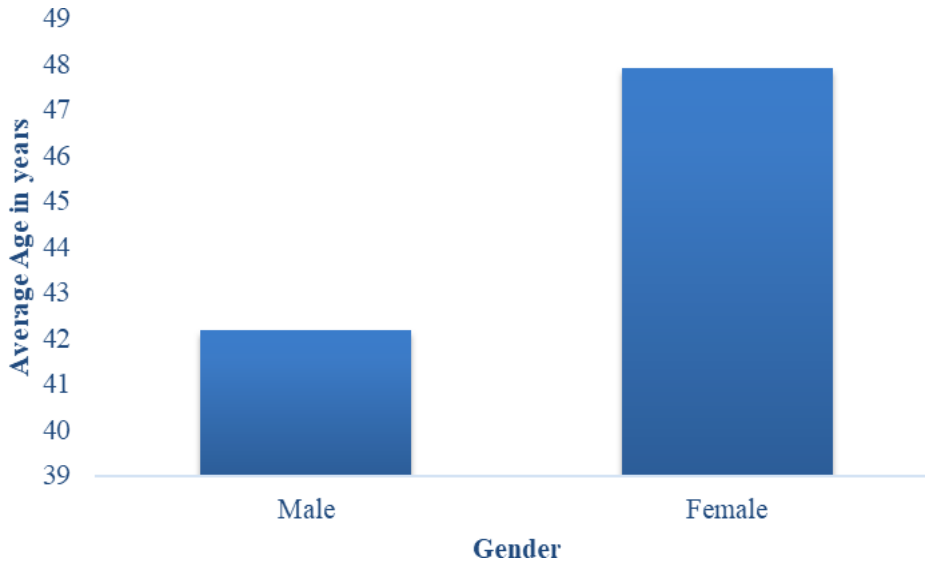

Figure I: Graph representing association of Gender with Age For Covid-19 and RA Positive patients

Table I: Univariate tablefor Association of Gender with Age For Covid-19 and RA Positive patients

Statistics(Age) ↓ Gender →	Men	Women
N	**63**	**63**
Mean ± SD	**42 ± 17.01**	**47.9 ± 19.21**
Min ; Max	**7 ; 89.0**	**12 ; 89.0**
Median	**41**	**47.0**
Q1 ; Q3 (IQR)	**32.5 ; 52.5 (20.5)**	**32.0 ; 65.5 (33.5)**

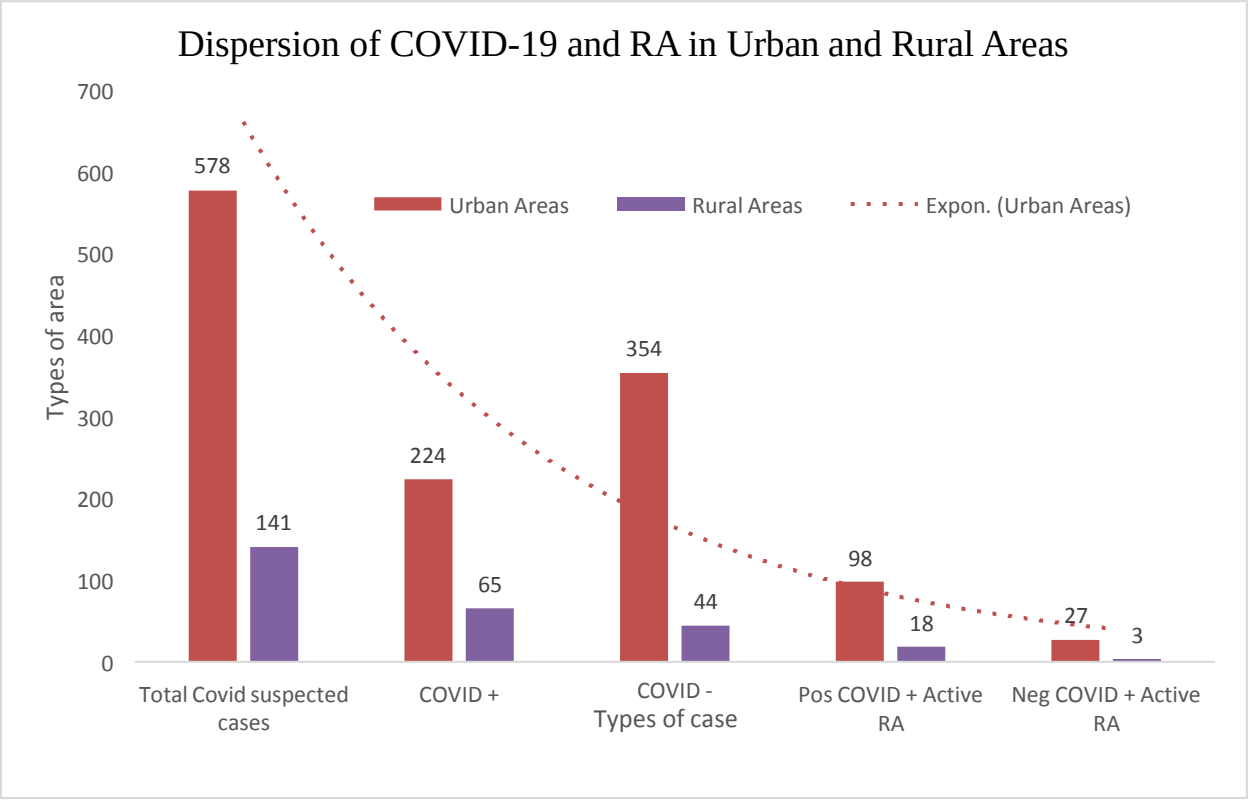

Figure II: Graph showing the correlation between COVID-19 and RA cases between rural and urbanareas.

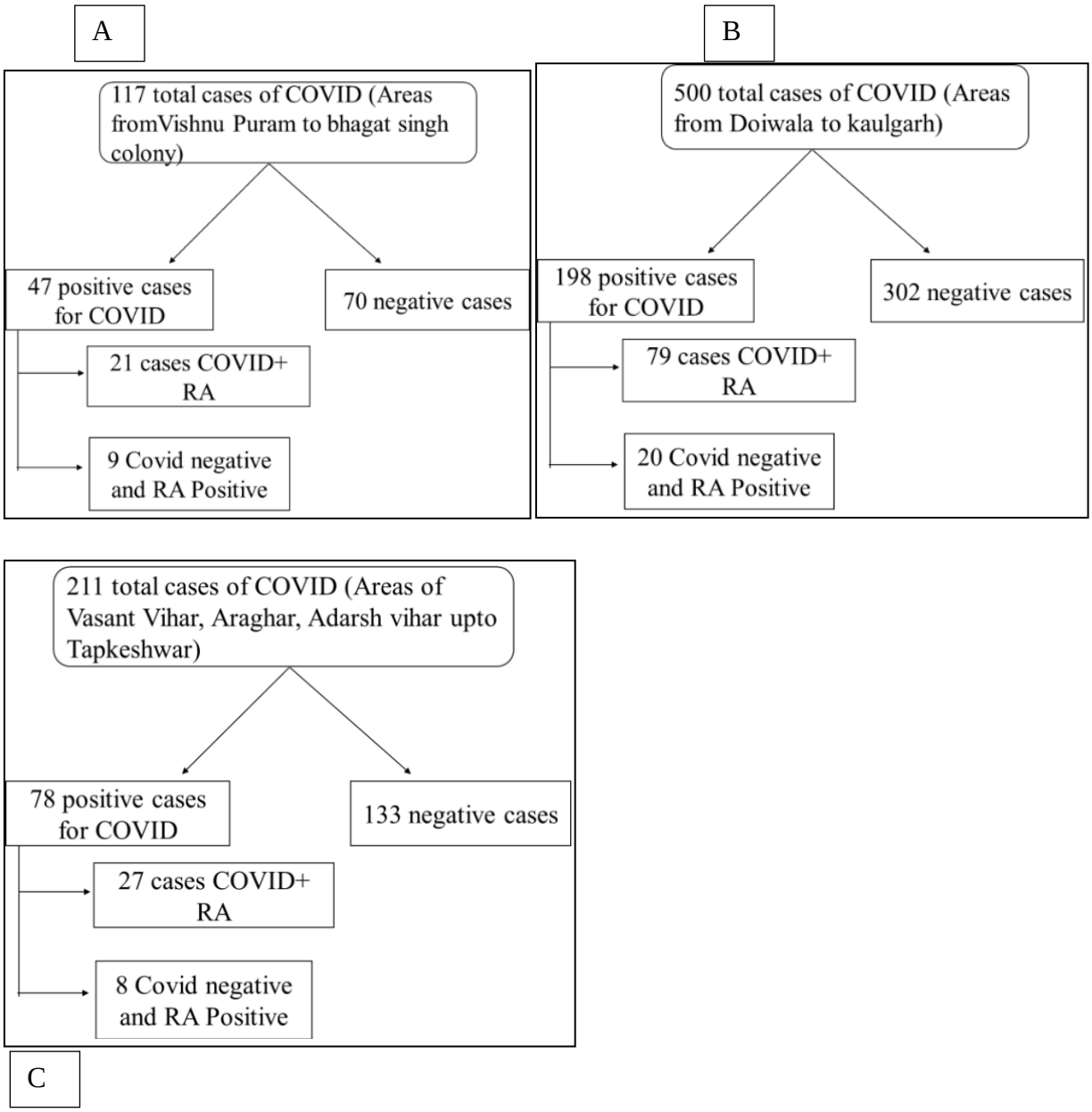

Figure III: Areawise division of Covid-19 cases.

In 126 cases with Covid-19 Positive CT Values along with RA as Autoimmune disorder, The CT Values was segregated on the basis of Highly Positive, Mid Positive and Low positive cases and Normality was assessed for each.(Figure IV)The Distribution of*CT Values*did not seem issued from a normally distributed population where*Highly Positive*(p = 0.03370),.Mean ± SD 17.896 ± 2.081 andn=22.

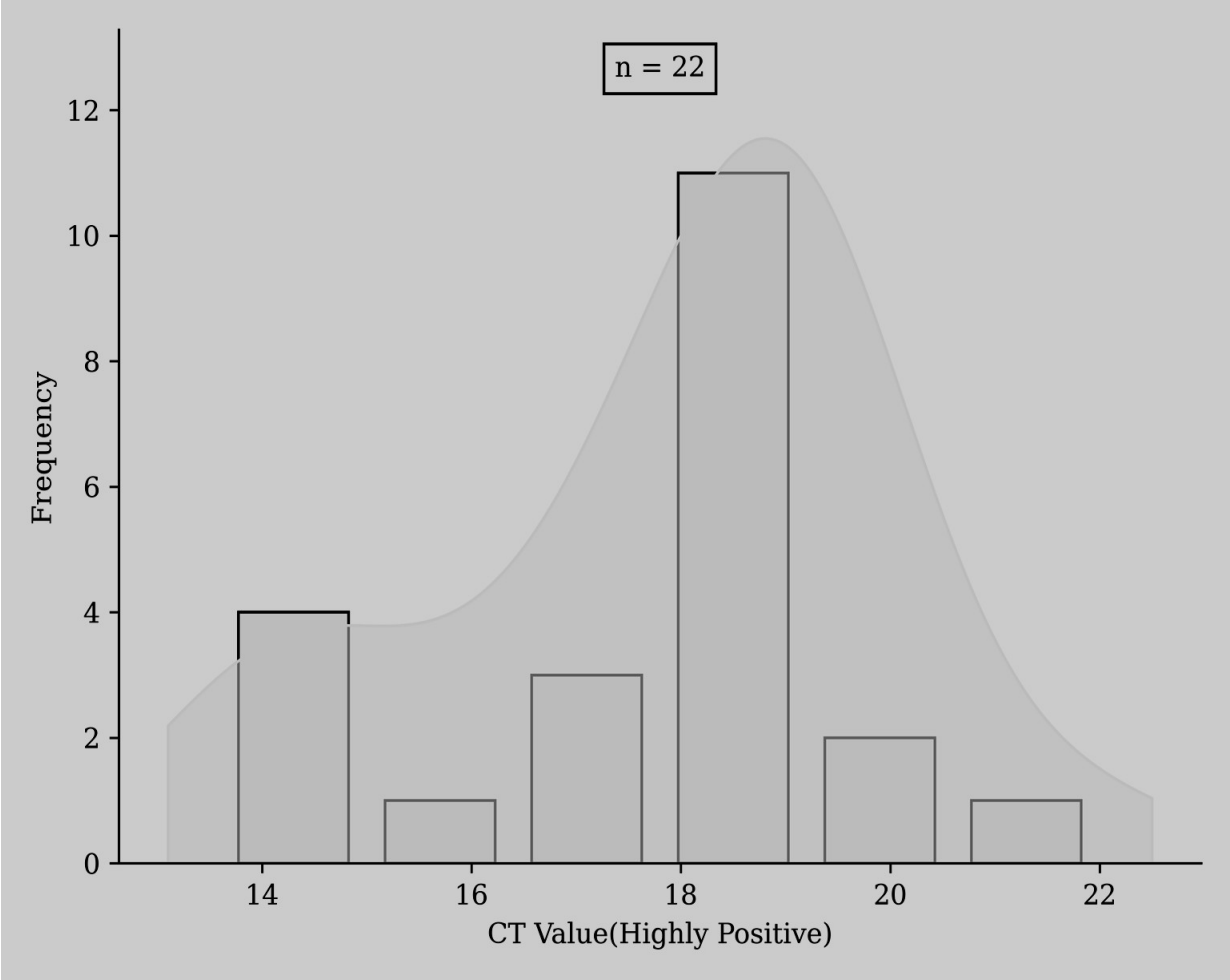

Figure VI: Graph representing Highly positive CT values of Covid-19 patients.

The Distribution of*CT Values*did not seem issued from a normally distributed population(Figure VI)where*Mid Positive*($p = 0.22830$), Mean ± SD 33.280 ± 1.480 and n=35. The Distribution of*CT Values*did not seem issued from a normally distributed population(Figure V) where*Low Positive*($p < 10^{-4}$).Mean ± SD 27.309 ± 2.733 and n=69.

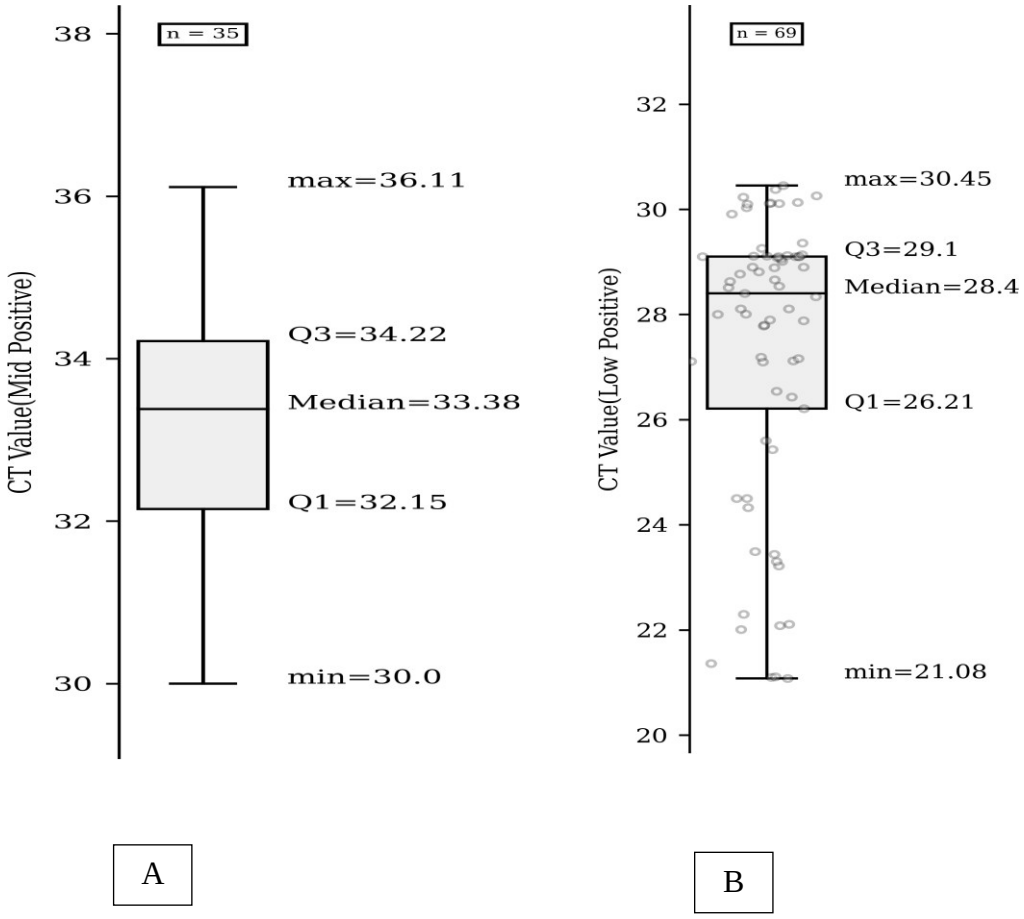

Figure V:**Graph representing Mid positive (A) CT values of Covid-19 patientsandLow Positive CT values (B) of Covid-19 patients**

4. Discussion

In this study, we examined the scientific data supporting any potential links between RA and SARS-CoV-2 infection. Due to the iatrogenic side effects of RA-related pharmacological therapy, we therefore think that patients who are predisposed to RA have a higher infection risk than the general population. Hence, the COVID-19 pandemic may increase the likelihood of a health emergency in complex conditions like RA.Intriguingly, inflammatory mediators show a complex connection between COVID-19 and RA. Therefore, we looked for possible causes of COVID-19 and RA co-existence as well as effects of the COVID-19 pandemic in RA Patients in various geographical areas of Dehradun.

When we compare the 3rd wave with first and second wave in Dehradun the ratio and patterns of positive case and admitted to hospital for covid-19 in 3rd wave in Dehradun were completely different. Since there was no lockdown during the 3rd wave, people were freely travelling from one place to another creating the mass movement by which SARS CoV-2 was spreading at market area and cities,but also positive cases was very less in comparison to the 1st and 2ndwave.The severe infection, hospitalization and death were very low. Previous studies have shown that patients with RA are most often either seronegative or triple-positive for rheumatoid factor, ACPA and anti-carbamylated protein antibodies.[3] .In this investigation, we discovered that Anti-CP, CRP, and RA Factor, three crucial clinical inflammatory biomarkers related to both Covid-19 and RA, were higher in Covid-19 positive cases, Covid positive cases with RA, and Active RA cases with negative Covid cases. It was also discovered in a few investigations that the incidence of severe and fatal COVID-19 was comparable in patients with and without RA. These studies included controls for sex, body mass, and comorbid medical disorders. Nevertheless, sepsis and blood clots in deep veins were among the problems that were more common in RA patients [5,6,7]. According to the most relevant genetic factors for disease vulnerability, HLA-DRB1 is the most closely connected allele responsible for RA at the molecular level according to the classification of RA as an HLA II (MHC II) linked disease [8,9,10]. The antigen presentation of MERS-CoV infections is significantly influenced by MHC II molecules, whereas MHC I and MHC II molecules are both implicated in SARS-CoV infections in Covid-[11]. There were 323 positive cases and 505 negative cases out of a total of 828 patients. The number of patients impacted by covid-19 was higher (127) than the number of patients with RA and negative covid-19, despite the fact that negative cases were more common than positive ones. Due to the lack of knowledge regarding the SARS-CoV-2 antigen presentation route, we can infer a hereditary predisposition to COVID-19 in RA.The COVID-19 sequel or recurrence is primarily seen in elderly people and is brought on by a number of factors. After recovery, the patient's physical health, resistance, and bodily functioning are seriously damaged [11]. Inadequate immune function after the period of treatment also increases the risk of re-infection. The treatment approach includes the use of glucocorticoids, which weaken the body's defences and increase the risk of subsequent infections [12].There are numerous articles on this subject that examine the impact of the SARS-CoV 2 spike on immune cells and endothelial cells both in vivo and in vitro. Spike can cause harm to

cardiac pericytes and cardiomyocytes [13,14,21,22] as well as interfere with pathways that contr ol the progression of cancer . Moreover, spike directly contributes to cardiovascular disease. If th e genic information for Spike is delivered to a particular bodily region, Spike expression in undes irable tissues (for example, important organs like the liver or the heart) and Spike epitope present ation to Tcells are encouraged, leading to an autoimmune-like attack. T-cells may assault the organ in an autoimmune-like attack, as if the organ were being attacked by a virus, as a result of the mechanism of action of these vaccinations [15,16,20].In a study on urban patients, it was discovered that urban residents had a much higher risk of contracting COVID-19 than rural residents (p 0.0001) .The urban population in our current study was likewise found to be significantly more favorable than the populace from rural areas. Men had more co-morbidities and a higher risk of COVID-19-related outcomes than women, according to a retrospective study that looked at gender differences in patientswithCOVIDandrheumatoidarthritis.When it came to SARS patients, the died group's perc entage of men was larger than the survivors' [17,18].However, in our inquiry, when Gender = M (=2.56, [8.89 ; 3.77], p= 0.4251) were not related with the value of AGE, we were unable to disc over any age and gender significance for covid19 infection and RA. Few studies have demonstrat ed that men with Covid19 are more at risk for poor outcomes and death, regardless of age, even t hough men and women had the same prevalence.The patient's co-morbidities are a substantial additional risk factor for the recurrence of Covid-19. The recurrence of COVID-19 is equivalent to the relapse of RA in terms of age, physical health state, and physical function. Compared to cities, there is less transit of people in villages. As a result, metropolitan areas naturally have a greater infection rate than rural ones. Our study from the third wave was based on a small data set of about 900 patients, but it was able to predict future symptoms and provide light on the relationships between RA and Covid-19. Since comprehensive patient data was not included in the public data set, only patients with SARS-CoV-2 requisitions and clinical histories of rheumatoid arthritis were included. High positive CT values (p = 0.03370), midpositive CT values (p = 0.22830), and low positive CT values (p = 104) did not follow any particular pattern appear to come from a population that was normally distributed. The population was not under control since random numbers were chosen for the study between December 2021 and January 2022. There was no analysis of mortality. The data set's normality, even distribution, and potential for bias results may have been influenced by these variables. People with RA were

more likely to experience severe Covid-19, hospitalization, complications such stroke, blood clots in deep veins, and sepsis, a kind of tissue damage. Plans for both prevention and rehabilitation can benefit from this study. New research in this area may help to clarify the connection between Covid-19, respiratory infections, and some autoimmune diseases including RA. Additional clinical and basic research with improved prediction criteria is required for tailored diagnosis and treatment.

5. Conclusion

Molecular mimicry, epitope dispersion, bystander activation, release of host antigens that have been encoded in tissues, and activation of superantigens are just a few of the potential autoimmune reactions that SARSCoV2 can trigger Even though this is the first analysis based on a case of active rheumatoid arthritis, an autoimmune disease in Covid19 positive individuals, the third wave of the Covid19 pandemic has varied effects depending on age, gender, and locale. In 2020, Sinha N. et al[14] found out that due to the lack of a lockdown, SARS-CoV-2 positive cases increased during this wave.Covid-19 Vaccines held the key to preventing infection and reducing transmission, which helped to limit the third wave of SARS-CoV-2 transmissionbut du e to the overconfidence in vaccines, the majority of patients avoided a COVID-19 treatment.Social distancing should be kept in place in densely populated urban areas where host-to-host communication is more likely to occur. To limit the impact of omicron and other varients, virulence factors, those who have received the Covid 19 vaccine must maintain their social isolation and wear masks in public places.Our study has certain limitations because Covid-19 and Rheumatoid arthritis, antigen presentation, and therapy strategy based on clinical inflammatory indicators show a considerable risk of respiratory infection, like Covid-19, in RA and other autoimmune disorders[19,23].Immune system deterioration, which can undoubtedly attract several infections, is closely associated to autoimmune illnesses. To protect people's health, there is still much that has to be developed.

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