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ORIGINAL ARTICLE

Clinical Impact of COVID-19 Infection on Rheumatoid Arthritis Patients

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ABSTRACT

Keywords: Rheumatoid arthritis, COVID-19, clinical impact

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Background: Rheumatoid arthritis is a chronic autoimmune inflammatory disease that manifests as stiffness, swelling, and pain in the joints, typical of symmetrical polyarthritis. **Aim:** To study the clinical impact of COVID-19 infection on rheumatoid arthritis patients in Aswan university hospital. **Materials and methods:** a Retrospective study was carried out in Aswan Governorate including patients attending the rheumatology outpatient clinic in Aswan university hospital. 250 RA patients diagnosed according to the 2010 ACR/EULAR classification criteria, Diagnosis of COVID-19 will be made in the patients with clinical manifestations consistent with COVID-19 and meeting one of the following criteria: Positive PCR or Chest CT scans findings of COVID-19 pneumonia. **Results :** COVID-19 positivity was higher in RA patients who had DM, and also showed a statistically significant increase in DAS 28, Arthralgia, Arthritis, Nervous system and GIT affection and Chest symptoms among the infected group as p-Value <0.05. However, there were no statistical significant difference between the two groups regarding sociodemografic data, lab investigations, radiological investigations and treatment as p-Value <0.05. **Conclusion:** DM increases the risk of Covid-19 infection in patients with rheumatoid arthritis. It caused reduced juxta-articular osteopenia and greater arthralgia, arthritis, nervous system, GIT, CVS, and chest symptoms with elevated platelet counts. Also, Covid-19 infection results in significant increase in disease activity (DAS 28) in RA patients.

INTRODUCTION

Rheumatoid arthritis can affect men, women, and children at any age; however, it is 2- 3 times more common in women and becomes more prevalent as age increases, with the start typically occurring between 60 and 70 years of age **(Slobodin and Shoenfeld, 2020).**

The COVID-19 pandemic is undoubtedly influencing the management of a complicated illness like rheumatoid arthritis (RA), which has a higher infectious risk than the general population due to immune system impairment common to autoimmune diseases as well as iatrogenic effects from corticosteroids and immunosuppressive Introduction 2 medications. But as our understanding of the pathophysiology of SARSCoV-2 infection grows, various anti-rheumatic medications are being considered as viable COVID-19 therapeutic options **(Favalli et al., 2020b)**

PATIENTS AND METHODS :

This study was carried out in rheumatology outpatient clinics, Aswan University Hospital, Aswan, Upper Egypt

Ethical Consideration

Approval of the ethical committee board will be obtained. Each participant will have written informed consent before study enrollment and will be told about all steps of the study. The confidentiality of all included participants will be considered. All participants have the right to leave at any stage of the study if they want .

Study population:

This study was conducted on 250 patients attending rheumatology outpatient clinics Aswan University hospital aged (< 18 years) All of the 250 RA patients diagnosed according to the 2010 American College of Rheumatology /European League Against Rheumatism (ACR/EULAR) classification criteria **(Aletaha et al., 2010),.** Diagnosis of COVID-19 was made in the patients with clinical manifestations consistent with COVID-19 and meeting one of the following criteria: (1) Positive PCR or (2) Chest CT scans findings of COVID-19 pneumonia. The study was conducted through a patient-reported questionnaire. Areas Patients and Methods 46 covered by the questionnaire will include COVID-19 symptoms, new onset symptoms of RA, any changes in the laboratory or radiological investigations of the patients, and complete medical history. All patients were subjected to complete history taking, complete general examination, and detailed rheumatological examination.

Laboratory assessment:

Patients will do the following investigations: 1. Complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anticitrullinated cyclic peptides antibodies (Anti-CCP). 2. PCR for COVID-19 infection.

Imaging:

Patients will do: 1. X-ray on: - Both hands, hard and soft films, (P-A) view. - Chest, (P-A) and lateral views. 2. High Resolution CT chest (HR-CT).

Results

Table (1): Sociodemographic data between two study groups.

		COVID-19 infection		Test of significance	
		No (N= 147)	Yes (N= 103)		
		Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)	p-Value	Sig.
Age		47.77 ± 11.73	47.94 ± 13.3	0.914(T)	NS
Sex	Female	133 (90.48%)	94 (91.26%)	0.832(C)	NS
	Male	14 (9.52%)	9 (8.74%)		

Disease duration (years)		6 (3 - 10)	7 (3 - 11)	0.535[(M)]	NS
Marital	Single	11 (7.48%)	10 (9.71%)	0.234[(F)]	NS
	Married	127 (86.39%)	92 (89.32%)		
	Divorced	2 (1.36%)	0 (0%)		
	Widow	7 (4.76%)	1 (0.97%)		

(T) Student t-test of significance.

(C) Chi-Square test of significance.

(M) Mann-Whitney test of significance.

(F) Fisher's Exact test of significance.

Table (1) shows relation between sociodemographic data and two study groups, there were ***no statistical significant*** difference between two groups as p-Value >0.05.

Table (2): Comorbidities and clinical manifestations between two study groups.

	COVID-19 infection		**Test of significance**	
	No (N= 147)	**Yes (N= 103)**		
	N (%)	**N (%)**	**p-Value**	**Sig.**
Diabetes	10 (6.8%)	22 (21.36%)	0.001[(C)]	S
HTN	23 (15.65%)	24 (23.3%)	0.127[(C)]	NS
Other comorbidities	31 (21.09%)	29 (28.16%)	0.198[(C)]	NS
Skin	2 (1.36%)	4 (3.88%)	0.233[(F)]	NS
Arthralgia	8 (5.44%)	14 (13.59%)	0.025[(C)]	S
Arthritis	6 (4.08%)	12 (11.65%)	0.023[(C)]	S
Eye	7 (4.76%)	7 (6.8%)	0.491[(C)]	NS
Nervous system	4 (2.72%)	9 (8.74%)	0.035[(C)]	S
GIT	1 (0.68%)	7 (6.8%)	0.009[(F)]	S
CVS	10 (6.8%)	10 (9.71%)	0.404[(C)]	NS
Chest	4 (2.72%)	12 (11.65%)	0.005[(C)]	S
Renal	5 (3.4%)	2 (1.94%)	0.703[(F)]	NS

(C) Chi-Square test of significance.

(F) Fisher's Exact test of significance.

Table (2) regarding the relation between comorbidities and two study groups, there was ***statistical significant increase*** in number of patients who had DM among infected group as p-Value <0.05, while there were no statistical difference between two groups in other comorbidities.

According clinical manifestations, there were ***statistical significant increase*** in number of patients who had Arthralgia, Arthritis, Nervous system, GIT and Chest among infected group as p-Value <0.05.

Table (3): Disease activity assessment between two study groups.

	COVID-19 infection		Student t-test	
	No (N= 147)	Yes (N= 103)		
	Mean ± SD	Mean ± SD	p-Value	Sig.
Disease Activity - (RA=DAS28)	3.79 ± 1.19	4.82 ± 0.97	<0.001	S

Table (3) regarding the relation between DAS 28 and two study groups, there was ***statistically significant increase*** in DAS 28 among the group of patients who infected with COVID-19 as p-Value <0.05.

Table (4): Treatment between two study groups.

	COVID-19 infection		Test of significance	
	No (N= 147)	Yes (N= 103)		
	N (%)	N (%)	p-Value	Sig.
Steroids	40 (27.21%)	26 (25.24%)	0.728(C)	NS
NSAIDS	66 (44.9%)	57 (55.34%)	0.104(C)	NS
Sulfasalazine	1 (0.68%)	1 (0.97%)	1.00(F)	NS
HCQ	119 (80.95%)	92 (89.32%)	0.073(C)	NS
AZA	0 (0%)	1 (0.97%)	0.412(F)	NS
MTX	75 (51.02%)	51 (49.51%)	0.815(C)	NS
LFN	69 (46.94%)	33 (32.04%)	0.018(C)	S
Biologic	11 (7.48%)	6 (5.83%)	0.608(C)	NS

(C) Chi-Square test of significance.

(F) Fisher's Exact test of significance.

Table (4) according the relation between treatment received and two study groups, there was ***no statistical significant difference*** between two groups as p-Value >0.05 ***except*** in LNF, as the

group of patients who did not catch the infection with COVID-19 had higher patients on LFN as p-Value <0.05.

Table (5): Lab investigations between two study groups.

	COVID-19 infection		Test of significance	
	No (N= 147)	Yes (N= 103)		
	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	p-Value	Sig.
Hb	11.43 ± 1.31	11.34 ± 1.19	0.588(T)	NS
TLC	7.25 ± 3.08	6.77 ± 2.41	0.184(T)	NS
PLT	288.94 ± 84.07	265.94 ± 76.23	0.028(T)	S
ESR	37 (25 - 60)	38 (20 - 55)	0.532(M)	NS
CRP	12 (6 - 24.5)	15.3 (6.5 - 25)	0.079(M)	NS
RF	36.7 (12.5 - 64.5)	44.2 (16 - 71.8)	0.349(M)	NS
Anti-CCP	47 (7 - 113.3)	39.3 (7 - 108)	0.289(M)	NS

(T) Student t-test of significance.

(M) Mann-Whitney test of significance.

Table (5) according the relation between lab investigations done and two study groups, there was ***no statistical significant difference*** between two groups as p-Value >0.05 ***except*** in PLT count, as the group of patients who did not catch the infection with COVID-19 had higher PLT count as p-Value <0.05.

Table (6): Radiological Investigations (X-RAY both hands) findings between two study groups.

	COVID-19 infection		Chi-Square test	
	No (N= 147)	Yes (N= 103)		
	N (%)	N (%)	p-Value	Sig.
Joint narrowing	120 (81.63%)	83 (80.58%)	0.834	NS
Juxta-articular osteopenia	120 (81.63%)	67 (65.05%)	0.003	S
Marginal erosions	109 (74.15%)	77 (74.76%)	0.914	NS
Cysts	43 (29.25%)	34 (33.01%)	0.526	NS

Table (6) according the relation between Radiological Investigations (X-RAY both hands) findings and two study groups, there was ***no statistical significant difference*** between two groups as p-Value >0.05 ***except*** in Juxta-articular osteopenia, as the group of patients who did not catch the infection with COVID-19 had higher number of patients as p-Value <0.05.

DISCUSSION

SARS-CoV-2, the virus that causes COVID-19, is extremely infectious. Over 6 million people have died as a result of COVID-19, which has had a disastrous impact on the world. SARS-CoV-2 spread quickly throughout the world after the first instances of this primarily respiratory viral disease were recorded in Wuhan, Hubei Province, China, towards the end of December 2019. Because of this, on March 11, 2020, the World Health Organization (WHO) declared it to be a global pandemic **(Sharma et al., 2021).** Rheumatoid arthritis (RA) is a chronic autoimmune disease that progresses over time and causes extra-articular symptoms. It can cause permanent impairment and has a death rate greater than the general population. The most common rheumatic inflammatory musculoskeletal disease among the rheumatic autoimmune disorders is RA **(Finckh et al., 2022).** Determining the exact association between COVID-19 and the population of vulnerable patients with immune-rheumatological disorders is vital in light of the expanding health emergency. Rheumatoid arthritis patients are inherently more susceptible to infection because of the illness itself and the iatrogenic effects of immunosuppressive medications like corticosteroids and synthetic or biological disease-modifying drugs. On the one hand, this rapid and uncontrolled spread of the epidemic may cause even greater concerns for these patients **(Favalli et al., 2014).**

250 RA patients participated in this retrospective analysis; their mean age was 47.84 ± 12.38 years and their mean disease duration was 8.21 ± 6.64 years. The mean age of Egyptian RA patients included in Gamal and colleagues study was 46.4 ± 11.7 years **(Gamal et al., 2016).** In Mir et al. study, The average age of RA patients was found to be 49.97 ± 18.34 years old **(Mir et al., 2022),** that also supports the widely accepted view that middle-aged and older adults are the primary populations affected by RA **(Safiri et al., 2019).** The average age in this research was marginally lower than in other earlier works; for example, Katchamart et al.'s study had an average age of 59.15 ± 11.43 years **(Katchamart et al., 2019**). According to Myasoedova et al., the average age of RA patients was also 55.4 years **(Myasoedova et al., 2020)**

Among RA patients included in this study 90.8% were females and 9.2% were males

The current study findings are supported by a prior study that found that the prevalence rates of RA in women were around twice as high (69%) as those in men **(Myasoedova et al., 2010).** According to a study by Hunter and colleagues, the prevalence of RA in women was nearly three times higher than that of men (74.26%) **(Hunter et al., 2017).**

The predominance of women can be explained by the findings of multiple studies, which suggest that factors associated with high oestrogen exposure may be protective against the development of RA and that a sudden decline in oestrogenic function (seen during menopause or with the use of anti-oestrogenic therapies) may be a risk factor **(Chen and Ballou, 2015; Bengtsson et al., 2017)**

most frequent marital status was married patients by 87.6% and the least frequent was divorced patients by only 0.8%. Agreeing with the current study, In a study conducted by Dargham and colleagues on 895 rheumatoid arthritis patients from five Arab nations, 87.5% had ever been married **(Dargham et al., 2018).** In the Mahran et al. study, 71.2% of the RA patients were married **(Mahran et al., 2020).** Discussion 66 Among RA patients included in this study, 41.2% had COVID infection, while 58.8% did not caught the infection. This is reinforced by a retrospective study that was carried out in seven hospitals in Spain and found that the prevalence of hospital PCRconfirmed COVID-19 was similar in RA patients and non-rheumatic illness patients (Pablos et al., 2020). A Spanish investigation also revealed a similar finding of a comparable COVID-19 incidence rate between rheumatologic patients and the general population (0.48% and 0.58%, respectively) **(Michelena et al., 2020).** According to Wang et al., there were 14,234 cases of suspected and confirmed

COVID-19 among 1,616,600 general population participants (9% person-months) and 17,268 RA patients (1.4% personmonths) **(Wang et al., 2022).**

However, the odds of COVID-19 among individuals with rheumatic diseases were 60% greater than those without rheumatic diseases, according to a meta-analysis of six case-control studies **(Akiyama et al., 2021).**

RA is frequently treated Discussion 67 with glucocorticoids, and there is evidence that these drugs raise the risk of serious infections in a dose-dependent way **(Dixon et al., 2011).** Furthermore, the use of biologics and non-biologic DMARDs, two other long-term immunosuppressive drugs frequently used to treat RA, may raise the risk of respiratory infections **(Bongartz et al., 2006),** increasing COVID-19 susceptibility in RA patients. As regards the detected comorbidities among this study participants; patients who had DM were 12.8%, while 24% of patients had other comorbidities. According to Albrecht et al., 498 (20%) of the 2535 RA patients had diabetes, which is consistent with the findings of this study (**Albrecht et al., 2018**). Rehling and colleagues agreed with this study, noting that among study participants with and without diabetes, rheumatoid arthritis was reported by 15.1% and 7.6%, respectively **(Rehling et al., 2019).** According to a prior study, women with type 2 diabetes had a higher chance of developing rheumatoid arthritis **(Lu et al., 2014**). The reason for the correlation between DM and RA is that if rheumatoid arthritis develops before diabetes, the discomfort from the RA may heighten the likelihood of physical inactivity, which is a risk factor for type 2 diabetes. Furthermore, it is important to remember that longterm steroid treatment for rheumatoid arthritis may raise the risk of type 2 diabetes, a process that may be sped up by inactivity **(Rehling et al., 2019**). HTN, a modifiable CV disease risk factor, is common in RA patients as reported in this study (18.8% of patients). A collection of 115,867 insurance claims from RA patients in the United States revealed that 76% of them had a diagnosis of HTN. By Discussion 68 contrast, just 44 percent of the matched controls had received a HTN diagnosis **(Chen et al., 2018).** These findings align with research from Canada and Europe, which revealed that RA patients had a greater prevelance of HTN than healthy controls **(Hitchon et al., 2016; Ramos et al., 2019**). Additionally, RA patients experience incident HTN far more frequently than the general population. The incidence rate of HTN development was 336/10,000 person-years based on the medical records of over fifty thousand RA patients residing in the United Kingdom. In contrast, the control population had an incidence rate of 211/10,000 person-years **(Jafri et al., 2017).** In terms of the study group's clinical manifestations of RA, 8.8% of patients had arthralgia and 7.2% had arthritis; the most impacted system was the cardiovascular system (8%), with only 2.4% of patients having affected skin. According to Mir and colleagues, the most common clinical complaints among RA patients in the Madinah region of Saudi Arabia were swollen joints (51.7%) and painful joints (69%) in line with the current study. In addition to arthritis (51.7%), RA patients also reported fatigue (46.6%), weight loss (44.8%), and appetite loss (41.4%) **(Mir et al., 2022).** The most common COVID-19 symptom among those infected with the virus was fever (55.3%), followed by anosmia/Dysgeusia (48.5%), while the least common symptom was rhinorrhea (13.6%), headache, and diarrhea (10.7%) for each. Ye et al. report that among rheumatic patients with COVID-19 infection, symptoms of fever, exhaustion, and diarrhea were observed in 76%, 43%, and 23% of patients, respectively **(Ye et al., 2020).** Discussion 69 When Di Iorio et al. looked at COVID-19 survivors who had systemic autoimmune rheumatic disorders (SARDs), they found that 72% of them had fatigue or malaise, 60% had fever, 60% had headaches, and 56% had myalgias **(Di Iorio et al., 2022**

Lab investigations done for patients, regarding complete blood count mean of Hb 11.39 ± 1.26, TLC 7.05 ± 2.83 and PLT 279.46 ± 81.56, while inflammatory markers mean of ESR after 1st hour 41.53 ± 23.15 and CRP 18.5 ± 17.2. Mean of RF was 58.56 ± 63.62 and AntiCCP was 88.07 ± 120.66. The study conducted by Yazici et al. revealed that the average hemoglobin level among RA patients was 12.1 ± 1.6 g/dl, the average platelet count was 307 ± 99 109/L, the average ESR was 52 ± 27 mm/h,

and the average CRP was 13.9 ± 26.3 mg/dl (Yazici et al., 2010). After two years of treatment (the inactive period), Milovanovic et al. found that all subjects in a trial involving sixteen patients with active RA had reduced platelet counts **(Milovanovic et al., 2004).** Adelowo et al.'s study found that 82.5% of the participants had an ESR above 20, and 20% of the cases had an ESR above 100 **(Adelowo et al., 2010).** The inconsistent findings regarding hematological parameters in patients with RA may be largely attributed to various patient selection Discussion 70 factors (e.g., age, sample size, inclusion of patients with comorbidities), as well as disparate diagnostic criteria. Disease activity assessment for the study group, mean of DAS 28 was 3.99 ± 1.13 and ranged from 1.6 to 7.25. Gökmen et al. found that 69% of RA patients had a DAS-28 score more than 3.2, which gives support to this result **(Gökmen et al., 2016).** According to Atwa and colleagues, the mean DAS28 among RA patients was 3.35, which is consistent with the current study **(Atwa et al., 2022).** The treatment received by the study group, the most frequent treatment used was HCQ by 84.4% followed by MTX 50.4%, NSAIDS (49.2%), while the least frequent treatments were Sulfasalazine and AZA by 0.8% and 0.4% respectively. According to Assar et al., 78.4% of COVID-19 infected RA patients were on steroids, and 50.5% of them also took NSAIDs **(Assar et al., 2022).** X-RAY both hands of this study participants showed that Joint narrowing was found in 81.2%, Juxta-articular osteopenia in 74.8%, Marginal erosions in 74.4% and cysts in 30.8%. Adelowo et al. found that among RA patients, 29.2% had erosions, 10.4% had carpal bone fusion and joint deformities, 38.7% had soft tissue edema and periarticular osteopenia, and 21.7% had joint space narrowing and periarticular osteopenia **(Adelowo et al., 2010).** According to Ohagwu and colleagues, 15.6% of RA patients exhibited osteopenia and 25% had erosion **(Ohagwu et al., 2017**). Participants in this study were split into two groups based on the occurrence of COVID-19 infection; both groups displayed negligible Discussion 71 differences in terms of age, sex, marital status, and the duration of RA illness; this study's strength is that it allows for accurate comparisons between groups. This is consistent with research by Rabia et al. that found no discernible differences in age, sex, marital status, or duration of illness between Egyptian RA patients who were infected with COVID-19 and those who were not **(Rabia et al., 2022)**

DM was shown to be substantially more common in COVID-19 infected RA patients in the current study as compared to the non-infected group. Otherwise, there isn't a statistically significant difference in comorbidities across the groups. This is in line with the results of Malek Mahdavi et al., who discovered that patients with diabetes mellitus and rheumatoid arthritis were more likely to become infected (OR: 1.77; 95% CI: 1.01–3.12; p = 0.050). **(Malek Mahdavi et al., 2021)**

When the clinical symptoms of the two groups were evaluated, the COVID-infected group had statistically significant higher levels of arthritis, arthralgia, nervous system, GIT, and chest symptoms than the non-infected patients. Rabia et al. research confirms the findings of the present study. It was discovered that COVID-19 infection causes a notable worsening of RA symptoms; in comparison to the RA non-infected group, the COVID19 RA group experienced a greater degree of fatigue, sore throat, fever, headaches, and skin rash **(Rabia et al., 2022**). The COVID-19 infected patient group in this study showed greater DAS 28 than the non-infected group, and the difference was statistically significant (p-Value

With regard to the relationship between the two study groups' treatments, there was no statistically significant difference between them other than LNF because there were more LFN patients in the non-infected patient group. Malek Mahdavi et al., on the contrary, found that RA patients with COVID-19 were treated with NSAIDs, TNFis, Prednisolone, Discussion 73 Sulfasalazine, and Azathioprine more often than RA controls. Regarding LFN use, there was no statistically significant difference between the two groups (**Malek Mahdavi et al., 2021).** In comparison to patients without COVID infection, RA patients with COVID infection had noticeably decreased mean platelet levels, according to lab tests performed in the two research groups. Regarding the mean hemoglobin, TLC, ESR, CRP, RF, and anti-CCP, there was no statistically significant difference between the two

groups. This is in line with a study by Stahl and colleagues that found no correlation between RA patients' recent COVID-19 diagnosis and their Disease Activity Score, which was calculated using serum CRP levels and the C-reactive protein level (DAS-CRP) **(Stahl et al., 2023)).** When x-ray scans of both hands were compared between RA patients with COVID infection and those without, it was revealed that 81.6% of the non-infected group exhibited juxta-articular osteopenia, compared to 65% of COVID patients. This difference was statistically significant. Other than that, there was no statistically significant difference in cysts, marginal erosions, or joint narrowing between the two groups

CONCLUSION:

DM increases the risk of Covid-19 infection in patients with rheumatoid arthritis. It caused reduced juxta-articular osteopenia and greater arthralgia, arthritis, nervous system, GIT, CVS, and chest symptoms with elevated platelet counts. Also, Covid-19 infection results in significant increase in disease activity (DAS 28) in RA patients.

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