RESEARCH ARTICLE

Effect of disease activity on the clinical outcome of SARS CoV-2 in patients with underlying rheumatic diseases; data from global rheumatology alliance

Shahida Perveen[1], Saba Samreen[2], Haris Gul[3], Babur Salim[4], Amjad Nasim[5]

Abstract

Objective: To determine the effect of disease activity on clinical outcomes of coronavirus disease-2019 in patients with rheumatic diseases.

Method: The prospective, cohort study was conducted from January 1st to June 30th, 2021, at Rheumatology department, Fauji Foundation Hospital, Rawalpindi. It comprised patients of rheumatic disorders who were affected by coronavirus disease-2019. The patients were categorised according to rheumatic disease activity into remission group I, low disease activity group II, moderate group III and high–activity group IV. Coronavirus disease-2019 outcomes compared included recovered vs death, hospitalisation yes vs no, mechanical ventilation yes vs no. The association of disease activity status with coronavirus disease-2019 outcomes was explored. Data was analysed using SPSS 23.

Results: Of the 100 patients, 78(78%) were females and 22(22%) were males. The overall mean age was 45.60±13.7 years. There were 23(23%) patients in group I, 42(42%) patients in group II, 21(21%) patients in group III and 14(14%) patients in group IV. Overall,17(17%) patients died and 83(83%) patients survived. In group III, 7(33.3%) patients died, followed by 6(42.9%) in group IV ($p<0.05$). In total, 7(7%) patients needed mechanical ventilation, with 3(21.4%) being in group IV ($p<0.05$). Hospitalisation was needed in 33(33%) cases, and intergroup comparison was non-significant ($p>0.05$).

Conclusion: Patients with severe rheumatic autoimmune disease affected by coronavirus disease-2019 were more likely to die and require invasive ventilation.

Keywords: Arthritis, Connective tissue diseases, Rheumatoid arthritis, Ankylosing spondylitis, Scleroderma, Vasculitis.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused a pandemic disease in 2019 called the coronavirus disease-2019 (COVID-19), which was considered a global pandemic causing health problems worldwide.[1] Patients with rheumatic disease were at a high risk of poor outcomes due to the underlying inflammatory condition, immunosuppression and comorbidities as soon as the pandemic started in 2019.[2] Early on during the pandemic, some reports suggested that autoimmune rheumatic disease (ARD) patients could be at a higher risk of respiratory failure and death from COVID-19.[3,4] However, there was accumulating evidence suggesting otherwise.[5,6] There are certain factors that may influence the risk of infection and disease outcome, including rheumatic disease type, level of disease activity, and the use of a specific disease-modifying anti-rheumatic drug (DMARD).

A large French study evaluating the risk of severe COVID-19 in ARD[5] showed the risk factors for COVID-19-related death included a diagnosis of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or psoriasis in addition to old age, male gender, increased weight, non-white race and diabetes.[5] It was reported in studies from Wuhan in China and Boston in the United States that higher risk of respiratory failure requiring mechanical ventilation (MV) was observed in COVID-19 patients who had rheumatic diseases.[3,4] However some case series reported generally mild COVID-19 clinical courses in rheumatic disease patients, and observational studies reported similar incidence of COVID-19 infection amongst patients with rheumatic disease and the general population.[6]

The study in Boston initially reported higher odds of MV in patients with rheumatic disease than those without rheumatic disease.[7] Later, an extension of the study was done 6 months into the pandemic, which included 143 patients with rheumatic disease, and showed that the MV risk in patients with rheumatic disease versus those without rheumatic disease had reduced, and it was found that there

[1,2]Department of Rheumatology, Foundation University Medical College, Foundation University, Islamabad, Pakistan; [3]Department of Rheumatology, Rheumatology Foundation University Medical College, Fauji Foundation Hospital, Rawalpindi, Pakistan; [4,5]Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi, Pakistan.

Correspondence: Shahida Perveen. e-mail: shahida.perveen@fui.edu.pk

ORCID ID. 0000-0002-8492-458X

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was a trend towards improvement in the MV risk over time.[8] A study suggested that those with moderate disease activity (MDA) or high disease activity (HDA) had poorer outcomes[9] whereas some studies did not find any such relationship.[10]

A Danish study observed that the risk of hospitalisation with COVID-19 was 46% higher for people with rheumatic disease than for the general population, but after adjustment for age, gender and comorbidities, only people with RA still had an increased risk of a poor outcome.[11]

The current study was planned to conduct a multi-centre study in Pakistan to see the effect of disease activity state of various rheumatic diseases on COVID-19-related outcomes.

Patients and Methods

The prospective, cohort study was conducted from January 1st to June 30th, 2021 at department of Rheumatology, fauji Foundation Hospital, Rawalpindi. After approval from the institutional ethics review committee of Fauji Foundation Hospital, Rawalpindi, Pakistan (letter No. 558/RC/FFH/RWP, dated: 1st Jan, 2021), the sample size was calculated using OpenEpi 3 open source calculator[12] using odds ratio (OR) 4.5,[13] 95% confidence interval (CI), 80% power and significance level (1-alpha) of 95. The calculated sample size was extended to cover any missing data. The sample was raised using purposive sampling technique from among adult patients with pre-existing rheumatic diseases who developed COVID-19.

After taking verbal informed consent from either the patient or the guardian, data was collected using a pre-designed proforma developed by the Global Rheumatology Alliance (GRA).[14] Given the specific objectives and requirements of the research, modifications were made to tailor the proforma to the study's context. New variables were incorporated to align with the study's objectives. The form was distributed to the rheumatologists and physicians involved in the care of these patients across the country through the platform of the Pakistan Society for Rheumatology. These physicians were trained about the study protocols. They recruited the patients after checking the inclusion and exclusion criteria, followed the patients through the course of COVID-19, and then entered the data in a common online platform. The data was subsequently entered into the GRA provider registry as per the requirement.

Data included patients' demographic details, underlying rheumatic disease, its duration, treatment, disease activity and co-morbid conditions. Data about COVID-19 included clinical, laboratory and radiological information. Outcomes were recorded in terms of mortality, hospitalisation status and need for MV (Mechanical Ventilation) support. Before analysing, the data was checked for missing values, and cases with insufficient information were excluded.

Those included were patients with confirmed or probable COVID-19 aged ≥12 years who were diagnosed with an ARD for at least 6 months[15] and were on treatment for at least ≥3 months. Patients not fulfilling the inclusion criteria, pregnant women, those with infections other than COVID-19 and those not willing to participate were excluded.

Cases of COVID-19 were defined as probable or confirmed, according to the definitions of World Health Organisation (WHO).[16] Probable case was defined as the patient having acute respiratory illness (fever plus one other sign/symptom suggestive of COVID-19) with history of travel / residence in an area with COVID-19 transmission, or contact with confirmed COVID-19 case within the preceding 14 days in whom the testing for COVID-19 was inconclusive or could not be performed due to any reason. Confirmed COVID-19 case was defined as laboratory-confirmed COVID-19, including polymerase chain reaction (PCR) or immunoglobulin M (IgM), IgG antibodies, irrespective of signs and symptoms.

The status of ARD activity in the month preceding the diagnosis of COVID-19 was obtained from the treatment records or treating physicians. Validated disease activity scores for particular disorders were used to assess the activity, like Disease Activity Score in 28 joints (DAS-28)[17] for RA, SLE disease activity index (SLEDAI)[18] ankylosing spondylitis disease activity score (ASDAS)[19] etc., for other disorders. The patients were categorised according to disease activity into remission group I, low disease activity (LDA) group II, moderate disease activity (MDA) group III and high disease activity (HDA) group IV. In cases of overlap syndromes, the activity of the predominant disease was reported.

Primary endpoints of the study were COVID-19-related mortality in patients with ARD and its association with disease activity. Secondary outcomes were the association of disease activity with other markers of COVID-19 severity, including hospitalisation and MV support.

Data was analysed using SPSS 23. Categorical variables were expressed as frequencies and percentages, while quantitative variables were reported as mean ± standard deviation (SD). Patients outcomes compared included recovered vs death, hospitalisation yes vs no, MV support yes vs no. These groups were compared using one-way analysis of variance (ANOVA) and chi-square test or its suitable alternatives, like the likelihood ratio (LR) or

Fischer's exact test, as applicable. P<0.05 was regarded as significant.

The association of disease activity with each COVID-19 outcome was tested by binary logistic regression analysis for which the disease activity status was dummy coded into remission, LDA, MDA and HDA. For each of these variables, the pertinent disease activity class was coded as 1 against all other categories coded as 0. Regression analysis was performed using one COVID-19 outcome at a time as dependent factor and one dummy-coded variable as independent factor using value 0 as the reference category. The association analysis of each COVID-19 outcome with disease activity status was adjusted for confounding factors that were age (≤50 vs >50 years), gender (male vs female), and smoking status (yes vs no).

Results

Of the 131 patients, 31(23.7%) were excluded owing to incomplete data, and the final sample comprised 100(76.3%) patients; 78(78%) females and 22(22%) males. The overall mean age was 45.60±13.7 years. There were 23(23%) patients in group I, 42(42%) patients in group II, 21(21%) patients in group III and 14(14%) patients in group IV. Baseline clinical and demographic characteristics of different ARD severity groups were compared (Table 1).

Mean duration of COVID-19 symptoms was 16±12.7 days. Infection was diagnosed on the basis of PCR, clinical features, serology, and high resolution computed tomography (HRCT) of chest in 83(83%), 14(14%), 2(2%) and 1(1%) patients, respectively.

The most common rheumatic disorders were RA, SLE and ankylosing spondylitis (AS) in 52(52%), 20(20%) and 8(8%) cases, respectively. The mean duration of rheumatic disorders was 7.54±7.66 years. In RA patients, mean DAS-28 erythrocyte sedimentation rate (ESR) was 3.2±1.23, SLEDAI in SLE was 8.49±7.14, and ASDAS in AS was 2.19±0.83.

Overall, 17(17%) patients died and 83(83%) patients survived. Among the RA patients, 5(9.6%) died, and the corresponding values for SLE and AS patients were 7(35%) and 1(12.5%), respectively. In group III, 7(33.3%) patients died, followed by 6(42.9%) in group IV (Table 2).

Hospitalisation was needed in 33(33%) cases and 21(21%) needed intensive care unit (ICU) care. Mean duration of hospital stay was 10.69±11.6 days. Among RA patients, 16(30.8%) were hospitalised, and the corresponding values for SLE and AS patients were 9(45%) and 1(12.5%), respectively.

Table-1: Demographic and baseline characteristics.

Variables	Remission (n=23)	LDA (n=42)	MDA (n=21)	HDA (n=14)	LR (*p*-value)
Mean Age (years)	48.96±12.37	47.43±12.51	43.86±14.95	37.21±15.47	*2.67(0.05)
Gender					
Male	7(30.4)	8(19)	2(9.5)	5(35.7)	4.75(0.19)
Female	16(69.6)	34(81)	19(90.5)	9(64.3)	
Education					
Uneducated	1(4.3)	3(7.1)	2(9.5)	1(7.1)	15.39(0.02)
<10 grade	0(0)	8(19)	7(33.3)	5(35.7)	
>10 grade	22(95.7)	31(73.8)	12(57.1)	8(57.1)	
Smoking status					
Never	22(95.7)	41(97.6)	19(90.5)	12(85.7)	
Current	0(0)	1(2.4)	0(0)	1(7.1)	7.89(0.25)
Former	1(4.3)	0(0)	2(9.5)	1(7.1)	
Rheumatic disorders					
RA	11(47.8)	28(66.7)	8(38.1)	5(35.7)	
SLE	4(17.4)	3(7.1)	8(38.1)	5(35.7)	
AS	0(0)	5(11.9)	0(0)	3(21.4)	
Scleroderma	2(8.7)	0(0)	0(0)	0(0)	
PsA	2(8.7)	2(4.8)	1(4.8)	0(0)	
Vasculitis	3(13)	1(2.4)	0(0)	0(0)	
Others	1(4.3)	3(7.1)	4(19.04)	1(7.4)	
ARD duration	9.19±6.08	7.2±9.22	7.21±7.68	6.39±4.67	*0.47(0.7)
Mean Hospital stay (days)	18.17±25.58	10.25±4.09	8.22±5.36	9.25±8.50	*0.91(0.45)
Mean Symptom duration (days)	21.96±20.52	13.39±7.09	16.3±11.97	16±12.74	*2.56(0.06)

*Results of ANOVA; LDA: Low disease activity, MDA: Moderate disease activity, HDA: High disease activity, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematous, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis, ARD: Autoimmune rheumatic disease, ICU: Intensive care unit, NIV: Non-invasive ventilation.

Table-2: COVID-19 outcomes according to rheumatic disease activity.

COVID-19 Outcomes	Remission (n=23)	LDA (n=42)	MDA (n=21)	HDA (n=14)	LR (*p*-value)
1)Hospitalisation					
None	17(73.9)	30(71.4)	12(57.1)	8(57.1)	3.82(0.7)
Hospital ward	3(13)	3(7.1)	4(19)	2(14.3)	
ICU	3(13)	9(21.4)	5(23.8)	4(28.6)	
2)Respiratory support					
None	17(73.9)	31(73.8)	16(76.2)	10(71.4)	14.50(0.1)
Supplemental Oxygen	4(17.4)	7(16.7)	2(9.5)	1(7.1)	
NIV	2(8.7)	3(7.1)	0(0)	0(0)	
Mechanical ventilation	0(0)	1(2.4)	3(14.3)	3(21.4)	
3)Mortality					
Recovered	22(95.7)	39(92.9)	14(66.7)	8(57.1)	15.48(0.001)
Death	1(4.3)	3(7.1)	7(33.3)	6(42.9)	

COVID-19: Coronavirus disease-2019, LDA: Low disease activity, MDA: Moderate disease activity, HDA: High disease activity.

In total, 7(7%) patients needed MV, with 3(21.4%) being in group IV. Mechanical ventilation was needed in 7(7%) patients. Among RA patients, 3(5.8%) and among SLE patients 3(15%) needed MV support. None of the AS patients was put on MV (Table 3).

The association of disease activity with COVID-19 outcomes after stratification for the confounding factors showed that mortality was higher in older age group and smokers in all disease activity groups other than remission group I. Older age and female gender were associated with higher MV requirements in group IV only. There was no effect of the confounders on the association of disease activity with hospitalisation (Table 4).

Discussion

There has been divergent data about the outcomes of COVID-19 in patients with systemic autoimmune disorders. Rheumatic disease patients were thought by some to be at higher risk of contracting COVID-19 and having worse outcomes, once infected[9] whereas others denied it.[10] Albeit true for some rheumatic diseases, in most of these syndromes poor outcomes may be pertinent to the severity of disease and other disease-specific or general factors rather than the diagnosis itself. The current study explored the influence of rheumatic disease activity on COVID-19 outcomes.

There was no difference in the demographic features except education status of patients in different categories of disease severity. Patients with remission or LDA had higher education. Overall mortality in the cohort was 17%, which is in agreement with a general range of 0-22% reported in literature.[20] However, it was higher than the 10% reported in one study.[21] The divergence can be explained by differences in racial profile socioeconomic background of the patients, as higher risk of poor outcomes was reported among Asians.[22] Majority of the current patients had fairly controlled disease (65%), whereas 21% had moderate and 14% had high disease activity. Nevertheless, the proportion of active disease was higher than the vaue reported in literature (20% patients with moderate-high disease).[21] Mean duration of rheumatic disease was 7.54±7.66 years and it didn't vary significantly across disease activity classes.

The current study found that ARD patients with higher disease activity had higher chances of death from COVID-19. Around 40% of HDA patients and one-third of MDA patients died. The remission group had the

Table-3: Association between the rheumatic disease activity and COVID-19 outcomes.

		Mortality			
Disease activity status	**Recovered** (n=83)	**Death**(n=17)	**OR**	**95% CI**	***p*-value**
Remission (n=23)	22(95.7)	1(4.3)	0.17	0.02-1.38	0.09
LDA (n=42)	39(92.9)	3(7.1)	0.24	0.06-0.90	0.03
MDA (n=21)	14(66.7)	7(33.3)	3.45	1.12-10.61	0.03
HDA (n=14)	8(57.1)	6(42.9)	5.11	1.49-17.55	0.009
Hospitalisation	**Yes** (n=31)	**No** (n=69)	**OR**	**95% CI**	***p*-value**
Remission (n=23)	6(26.1)	17(73.9)	0.73	0.26-2.09	0.56
LDA (n=42)	12(28.6)	30(71.4)	0.82	0.6-1.95	0.66
MDA (n=21)	9(42.9)	12(57.1)	1.94	0.72-5.25	0.19
HDA (n=14)	4(28.6)	10(71.4)	0.87	0.25-3.03	0.83
Mechanical ventilation	**Yes** (n=7)	**No** (n=93)	**OR**	**95% CI**	***p*-value**
Remission (n=23)	0(0)	23(100)	-	-	-
LDA (n=42)	1(2.4)	41(97.6)	0.21	0.02-1.83	0.15
MDA (n=21)	3(14.3)	18(85.7)	3.12	0.64-15.22	0.15
HDA (n=14)	3(21.4)	11(78.6)	5.59	1.10-28.36	0.03

COVID-19: Coronavirus disease-2019, LDA: Low disease activity, MDA: Moderate disease activity, HDA: High disease activity, OR: Odds ratio, CI: Confidence interval.

Table-4: Effect of rheumatic disease activity on COVID-19 outcomes stratified/ adjusted for confounding factors.

COVID-19 outcome		**Mortality**			**Hospitalisation**			**Ventilation**		
confounding factor	**Disease activity**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age group (≤50 years)	Remission	0.18	0.02-1.47	0.11	0.65	022-1.93	0.44	-	-	-
	LDA	0.25	0.07-0.94	0.04	0.75	0.31-1.83	0.53	4.79	0.55-41.60	0.16
	MDA	3.47	1.11-10.92	0.03	2.11	0.75-5.94	0.16	3.14	0.64-15.32	0.16
	HDA	4.48	1.28-15.70	0.019	1.12	0.31-4.10	0.86	6.24	1.15-33.97	0.03
Gender (male)	Remission	0.15	0.018-1.20	0.14	0.70	0.25-2.03	0.52	-	-	-
	LDA	0.46	0.14-1.47	0.19	0.83	0.35-1.99	0.68	0.22	0.03-1.86	0.16
	MDA	4.59	1.36-15.42	0.01	2.09	0.76-5.79	0.15	3.55	0.69-18.39	0.13
	HDA	4.69	1.34-16.42	0.01	0.83	0.23-2.92	0.77	5.48	1.06-28.53	0.04
Smoking (non- smoker)	Remission	0.18	0.02-1.41	0.32	0.75	0.26-2.14	0.59	-	-	-
	LDA	0.253	0.07-0.96	0.04	0.87	0.36-2.09	0.75	0.23	0.03-1.97	0.18
	MDA	3.34	0.36-14.89	0.03	1.89	0.69-5.13	0.22	2.98	0.60-14.71	0.18
	HDA	4.82	1.38-16.81	0.01	0.79	0.22-2.84	0.72	5.2	0.99-27.12	0.05

COVID-19: Coronavirus disease-2019, LDA: Low disease activity, MDA: Moderate disease activity, HDA: High disease activity, OR: Odds ratio, CI: Confidence interval.

lowest mortality of <5%. The finding was comparable to those reported by Santos et al. (25% in remission/LDA and 60% in MDA/HDA; OR: 41.4, 95 CI: 4.23-405.23, *p*=0.04.[9] The impact was significant after adjustment for age, gender, presence of comorbidities and smoking status. Additionally, smokers had higher mortality in LDA group as well. Strangfeld et al. also reported that moderate to high disease activity posed a greater risk of death in such patients (OR: 1.87, 95% CI: 1.27-2.77).[21] Smoking was an independent risk factor for death in RA patients having COVID-19 infection.[18] In striking contrast to the current findings, a study did not find any relation of disease activity with COVID-19 severity (OR: 1.79, 95% CI: 0.45-7.19, *p*=0.4).[10]

One-third of the current subjects required hospital admission. Mean hospital stay was 11.06±11.97 days, and it was comparable across the disease activity groups. Also, 42% of the admitted patients had MDA/HDA. No relation of hospitalisation was found with the preceding ARD activity. Hasseli et al. also determined moderate-high activity as a risk factor for COVID-19-associated hospitalisation (OR: 1.96, 95% CI: 1.02-3.76, *p*=0.04).[23] Two other studies also substantiated similar impact of disease activity on COVID-19 severity.[21,22] Ugarte et al. found older age and male gender to be associated with COVID-19 severity.[21] The current study did not find any influence of disease activity on hospitalisation even after adjustments for these factors as well as for smoking status, which was in line with other studies.[23,24]

In the current study, 21.4% HDA patients needed MV. This relation was statistically significant (OR: 5.59, 95% CI: 1.1-28.36, *p*=0.03). None of the current patients in remission required MV. A study reported that MDA/HDA predicted a composite of poor COVID-19 outcome, including mortality and MV, in antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis.[26] In patients with HDA, the association was significant after adjustment for gender and older age. Contrary to the trends in the general population and other studies of ARD patients, where male gender predicated severe infection[24] the current study found that females with HDA were at higher risk of MV (OR: 5.48, 95% CI: 1.06-28.53, *p*=0.04). A French study also recorded female gender as a risk for poor outcome.[27]

Despite the fact that Pakistan is a resource-poor country, the outcomes of rheumatic disease patients with COVID-19 was comparable to international statistics cited above. The current study may be biased towards patients on the severe side of COVID-19 disease spectrum, as it included patients who reported to healthcare professionals. Furthermore, rheumatic diseases are heterogeneous in various aspects, hence, the findings may not be applicable to an individual rheumatic disorder, and should be cautiously interpreted in such cases. Further large-scale studies analysing individual rheumatic disorders are recommended.

Conclusion

The severity of the underlying disease preceding the COVID-19 infection had a significant impact on mortality. Irrespective of the underlying diagnosis, these patients were more prone to severe complications of the infection, like invasive ventilation and mortality.

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Author Contribution:

SP: Concept, design, data acquisition, analysis and interpretation, drafting, revision, final approval, agreement to be accountable for all aspects of the work.

SS: Study design, data analysis and interpretation, drafting, revision, final approval, agreement to be accountable for all aspects of the work.

HG: Concept, design, drafting, revision, final approval, agreement to be accountable for all aspects of the work.

BS: Concept, data interpretation, revision, final approval, agreement to be accountable for all aspects of the work.

AN: Concept, design, critical revision, proof reading, final approval, agreement to be accountable for all aspects of the work.