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Original Article

Clinical Features and Outcome of SARS-CoV 2 Virus Infection in Patients with Autoimmune Diseases

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ABSTRACT

Objectives: To evaluate the clinical features, outcome and poor prognostic factors of COVID-19 in rheumatic disease patients.
Study Design: Cross-sectional study.
Place and duration of Study: Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi, from Mar to Sep 2020.
Methodology: The study included rheumatic disease patients with COVID-19. Patients' age, gender, smoking status; details of rheumatic disorder; method of COVID-19 diagnosis, treatment and outcomes were recorded.
Results: The study included 46 patients. Overall mortality rate was 23.8%. The most common symptoms were fever (35, 83.3%), cough (26, 61.9%) and myalgia (23, 54.8%). Dyspnea was associated with mortality (p=0.013), ICU admission (p<0.001), ventilation (p=0.02) and hospitalization (p<0.001). NSAIDs increased the risk of ventilatory support (p= 0.02). Long term steroids predicted mortality (p=0.02), hospitalization (p=0.014) and intensive care admission (p=0.004). Steroid and Hydroxychloroquine treatment for COVID-19 was associated with intensive care admission (p= 0.001 and 0.006, respectively) and ventilation (p=0 .007 and 0.03, respectively). Mycophenolate Mofetil was related to intensive care admission, ventilation and hospitalization (p=0.03, 0.03 and 0.02, respectively), whereas Cyclophosphamide was related to hospitalization (p= 0.03). Systemic lupus erythematosus was associated with all poor outcomes except ventilation (p<0.05)
Conclusion: Systemic lupus erythematosus, long-term steroids, Mycophenolate Mofetil, Cyclophosphamide and Dyspnea are associated with severe COVID-19.

Keywords: Autoimmune, Coronavirus, Prognosis, Rheumatoid arthritis, Systemic lupus erythematosus.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)is an exponentially spreading pandemic, affecting around 30 million people since its emergence in December 2019. Mostly a mild self-resolving disease, it can be lethal with a case fatality rate approaching 4%.[1] Pakistan has almost 1.1 a million cases with a mortality of 2.2%.[2] People with comorbidities and extremes of age are particularly susceptible.[3] Patients with immune-inflammatory diseases are thought to have a high risk of this infection by virtue of the underlying disease and immunosuppressive treatments. This population is deemed more prone to severe infec-tion and complications if affected. While data about the interaction between these two disorders is still evolving, huge knowledge gaps exist.

Immune dysregulation is common in the pathogenesis of both disorders. Both innate and acquired immunity are involved in COVID-19 pathogenesis. Recent works have suggested the role of increased cytokines, their receptors (IL-6 and IL-12 receptors), interferons and T-cells in COVID-19-induced lung injury.[4,5] IL-2, 7, 10, Monocyte chemoattractant protein and interferon-induced protein-10 were particularly high in critically ill SARS-CoV-2 patients and were reported as markers of severity and progression.[5] B-lymphocyte contribution to this inflammation is suggested by the mild disease in patients with agammaglobulinemia compared to those with combined variable immunodeficiency.[6] These findings led to considering immunomodulators and interleukin inhibitors as therapeutic options for this infection.[7]

There are mixed results on whether this excessive inflammation contributes to COVID susceptibility and poor outcomes in patients with immune diseases. Unfortunately, there is scarce data from Pakistan on this subject. This study describes the clinical features of autoimmune disease patients infected with SARS CoV-2, the outcome of these patients and factors associated with the severity of COVID-19 infection.

METHODOLOGY

This cross-sectional study was carried out at the Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi Pakistan, from March to September 2020. The sample size of 46 was calculated by the

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OpenEpi sample size calculator, version 3.01. The anticipated mortality rate of 5% was used,[8] with a 5% margin of error and 95% confidence level. Data collection was started after receiving approval from the Institutional Ethical Review Board (Reference Letter No. FF-R/23-20). Using consecutive non-probability sampling techniques.

Inclusion Criteria: Rheumatic disease patients between 18 to 80 years of age who were diagnosed with COVID-19 were include in the study.

Exclusion Criteria: Pregnant females, patients with rheumatic disease duration of fewer than six months or treatment duration of fewer than three months were excluded.

Data were collected by an online form and disseminated to the healthcare providers managing these patients. After taking informed written consent from the patient or the guardian (if the patient was not fit enough), data was collected regarding the patient's age, gender, smoking status and comorbidities. Details of the underlying rheumatic disease, its activity and treatment were recorded at the time of COVID diagnosis. We also recorded methods for diagnosing COVID, symptoms, treatment, duration of hospital stay, complications and outcome measures.

COVID-19 cases were defined according to the definitions of centres for disease control and prevention (CDC).[9] Disease activity was assessed by standard scoring systems for individual rheumatic disease by the caring physicians and categorized as remission, low, moderate and high disease activity. The outcome was assessed by mortality, hospitalization, ventilation and ICU admission. Steroid treatment for the rheumatic disease was specified as prednisone at ≥5 mg/day or equivalent.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were described as mean and standard deviation. Patients were grouped according to mortality outcome and level of care. These groups were compared using Chi-square ($\chi 2$). The independent sample t-test was used to compare continuous variables. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

The study included 46 patients, 4 patients had incomplete data and were excluded from the analysis. The mortality rate in our study was 10(23.8%). Table-I showed the demographic features of the study population.

Table-I: Demographic Profile of Study Population (n=42)

Characteristic	(%)	Characteristic	(%)
Gender		**Level of Care**	
		Hospitalization	14(33.3)
Male	13(31.00)	Intensive care	10(23.8)
Female	29(69.00)	Supplemental oxygen	4(9.50)
		Invasive ventilation	6(14.30)
Smoking		**Outcome**	
Smoker	4(9.52)	Death	10(23.80)
Non smoker	36(85.71)	Recovery	21(50.00)
Unknown	2(4.76)	Still under treatment	11(26.20)
Diagnosis		**Complications**	
Polymerase chain reaction	33(78.6)	Yes	11(26.2)
Symptoms	8(19.0)	No	29(69.0)
Serology	1(2.4)	Unknown	2(4.8)
Symptoms		**Age in years**	
Present	39(92.9)	(Mean± SD)	40.86±13.41
Absent	3(7.1)		
Contact History			
Positive	15(35.7)	Rheumatic disease duration (days, Mean± SD)	9.59±11.06
Negative	27(64.3)		
COVID Treatment			
Supportive	11(26.2)	Hospital stay (days, Mean±SD)	8.37±5.38
Medications	31(73.8)		
HRCT			
Yes	8(19.0)	Duration of COVID symptoms (days, Mean±SD)	10.00±4.60
No	34(81.0)		

Rheumatoid arthritis (RA) and Systemic lupus erythematosus (SLE) were the most common rheumatic diseases (RD), affecting 16(38.8%) and 12(28.6%) patients respectively. 3(31.7%) patients were in remission, whereas 9(21.4%) had low activity, 10(23.8%) had moderate activity and 7(17.07%) patients had high disease activity.

HCQ was the most frequently used medication for RD, being used by 24(57.1%), followed by steroids 22(52.4%) and Non-steroidal anti-inflammatory drugs (NSAIDs) 17(40.5%). Fever, cough, myalgia and dyspnea were the commonestCOVID-19 symptoms, present in 35(83.3%), 26(61.9%) 23(54.8%) and 17 (40.5%) respectively.

Eleven (26.2%) patients were still in the course of the disease at the time of data collection. We excluded these patients and analyzed the remaining 31 for mortality outcome. The death rate was 16%(4) in patients not requiring versus 100% (6 patients) in those needing invasive ventilation. Amongst the ICU patients, fatality was 7(70%). Non-survivors had a shorter hospital stay (7.00±5.12 versus 10.34±6.38 days) and RD duration (6.17±5 versus 12.46±14.47 years) than survivors. Higher disease activity was associated with mortality. Long-term steroid use was associated with increased risk of death. Among the patients who expired, 8(80%) were using glucocorticoids. Table-II showed the mortality predictors of the study population.

Factors associated with hospitalization risk were analyzed. Higher baseline rheumatic disease activity, mycophenolate mofetil (MMF) and cyclophosphamideresulted in higher hospitalization rate. Steroids were associated with hospitalization whether used for long-term rheumatic disease treatment or used during COVID management. Dyspnea and myalgia both predicted hospitalization. The results of the analysis were shown in Table III.

NSAIDs and MMF were related to the risk of ventilation. COVID-19 treatment with steroids and HCQ was related to a higher need for ventilation. These findings were shown in Table-IV.

We analyzed the association of COVID outcome with the two most prevalent autoimmune disorders in our study i.e. SLE and RA. SLE was associated with mortality (p=0.02) and hospitalization (p=0.004). Eleven (91.7%) SLE patients were receiving HCQ, 10(83.3%) were using steroids and 5(41.7%) received NSAIDs. Mortality and hospitalization rate was 50% and 66.7% respectively.

Table-II: Factors Predicting the COVID-19 Mortality in Patients with Rheumatic Disorders

Demographic Features	Mortality (n=31)		
	Recovery n(%)	Death n(%)	*p*-value
Gender			
Male	7(33.3)	2(20.0)	0.44
Female	14(66.7)	8(80.0)	
Smoking	1(4.8)	1(10.0)	0.59
Disease Activity			
Remission	9(42.9)	0(0)	0.009
Low	5(23.6)	2(20.0)	
Moderate	2(9.5)	4(40.0)	
High	2(9.5)	4(40.0)	
Hospitalization	6(28.6)	6(60.0)	0.09
Intensive care unit admission	3(14.3)	7(70.0)	0.002
Ventilatory support			
None	19(90.5)	3(30.0)	<.001
Supplemental Oxygen	2(9.5)	1(10.0)	
Invasive ventilation	0(0)	6(60.0)	
Rheumatic Disease Treatment			
Non steroidalanti-inflammatory drugs	7(33.3)	7(70.0)	0.05
Steroids	8(38.1)	8(80.0)	0.03
Hydroxychloroquine	13(61.9)	8(80.0)	0.3
Disease Modifying Drugs			
Methotrexate	7(33.3)	3(30.0)	0.85
Leflunomide	2(9.5)	10(100.0)	0.2
Mycophenolate mofetil	3(14.3)	3(30.0)	0.31
Azathioprine	1(4.8)	10(100.0)	0.37
Sulfasalazine	2(9.5)	10(100.0)	0.2
Cyclophosphamide	1(4.8)	1(10.0)	0.59
Biologics	4(19.0)	3(30.0)	0.5
COVID-19 Symptoms			
Fever	18(85.7)	9(90.0)	0.7
Cough	15(71.5)	7(70.0)	0.9
Sore throat	11(52.4)	2(20.0)	0.07
Dyspnea	7(33)	8(80.0)	0.01
Myalgia	12(57.1)	4(40.0)	0.31
Arthralgia	5(23.8)	0(0)	0.03
Diarrhea	2(9.5)	0(0)	0.2
Anosmia	2(9.5)	0(0)	0.2
COVID-19 Treatment			
Steroids	8(38.1)	7(70.0)	0.09
Hhdroxychloroquine	7(33.3)	7(70.0)	0.05
Azithromycin	5(23.8)	2(20.0)	0.81
Anticoagulants	1(4.8)	0(0)	0.37
Age (Years)	42.10±12.63	34.7±15.61	0.17
Disease duration (Years)	12.46±14.47	6.17±5.01	0.48

DISCUSSION

Patients with autoimmune disorders may have particular susceptibilities and responses to different conditions. Therefore, our study assessed the characteristics of SARS-CoV-2 infection in these patients.

Table-III: Predictors of Hospitalization in Rheumatic Disease Patients with SARS CoV-2 Infection

Demographic Features	Hospitalization(n=42)		
	Yes n(%)	No n(%)	*p*-value
Gender			
Male	3(21.4)	10(35.7)	0.33
Female	11(78.6)	18(64.3)	
Smoking	2(14.3)	2(7.1)	0.86
Disease Activity			
Remission	2(14.3)	11(39.3)	0.03
Low	1(7.5)	8(28.6)	
Moderate	5(35.7)	5(17.9)	
High	4(28.6)	3(10.7)	
Rheumatic Disease Treatment			
Non steroidalanti-inflammatory drugs	7(50)	10(35.7)	0.38
Steroids	11(78.6)	11(39.3)	0.01
Hydroxychloroquine	9(64.3)	15(53.6)	0.51
Disease Modifying Drugs			
Methotrexate	5(35.7)	9(32.1)	0.82
Leflunomide	0(0)	3(10.7)	0.11
Mycophenolate	5(35.7)	2(7.1)	0.02
mofetil	1(7.1)	1(3.6)	0.62
Azathioprine	0(0)	2(7.1)	0.2
Sulfasalazine	2(14.3)	0(0)	0.03
Cyclophosphamide	5(35.7)	4(14.3)	0.12
Biologics			
COVID-19 symptoms			
Fever	12(85.7)	23(82.1)	0.7
Cough	9(64.3)	17(60.7)	0.8
Sore throat	3(21.4)	12(42.9)	0.1
Dyspnea	11(78.6)	6(21.4)	<.001
Myalgia	4(28.6)	19(67.9)	0.01
Arthralgia	1(7.1)	7(25.0)	0.13
Diarrhea	2(14.3)	1(3.6)	0.22
Anosmia	0(0)	3(10.7)	0.11
COVID-19 Treatment			
Steroids	10(71.4)	11(39.3)	0.04
Hhdroxychloroquine	9(64.3)	10(35.7)	0.07
Azithromycin	3(21.4)	7(25.0)	0.7
Anticoagulants	2(14.3)	1(3.6)	0.22
Age (Years)	40.07±14.95	41.25±12.85	0.79
Disease duration (Years)	13.31±8.34	8.03±11.88	0.27

Our patients were younger than reported in the general population.[10] Females comprised more than 2/3rd of the patients. This is compatible with the gender prevalence of rheumatic diseases but is distinct from the general population, where males are affected more frequently. Overall mortality (23.8%) was comparable to that in the general population, as noted by Weiss *et al*.[10] In contrast to previous works, patients who died were younger than survivors, although the difference was insignificant. The fatality rate was exceedingly high in patients needing invasive ventilation. A recent study by Wang *et al.* noted that patients requiring ICU care were older and had numerous comorbid conditions compared to those not requiring ICU.[11] We also had similar results. Dyspnea and arthralgia were related to mortality and severity, as also found by Shi *et al*.[12]

Table-IV: Factors Associated with Invasive Ventilation in Rheumatic Disease Patients with COVID-19

Demographic Characteristics	Ventilation (n=42)		
	Yes n(%) (n=6)	No n(%) (n=36)	*p*-value
Gender			
Male	2(33.3)	11(30.6)	0.89
Female	4(66.7)	25(69.4)	
Smoking	1(16.7)	3(8.4)	0.45
Disease Activity			
Remission	None	13(36.1)	0.13
Low	1(16.7)	8(22.2)	
Moderate	2(33.3)	8(22.2)	
High	3(50)	4(11.1)	
Hospitalization	4(66.7)	10(27.8)	0.07
Intensive care unit admission	6(100.0)	4(11.1)	<.001
Rheumatic disease treatment			
Non steroidalanti inflammatory drugs	4(80.0)	11(33.3)	0.02
Steroids	4(80.0)	14(42.4)	0.09
Hydroxychloroquine	4(80.0)	17(51.5)	0.60
Disease Modifying Drugs			
Methotrexate	1(20.0)	11(33.3)	1.00
Leflunomide	0(0)	3(9.1)	0.32
Mycophenolate mofetil	3(60.0)	3(9.1)	0.03
Azathioprine	0(0)	2(6.1)	0.43
Sulfasalazine	0(0)	2(6.1)	0.05
Cyclophosphamide	0(0)	2(6.1)	0.43
Biologics	2(40)	5(15.2)	0.09
COVID-19 Symptoms			
Fever	5(83.3)	30(83.3)	1.00
Cough	4(66.7)	22(61.1)	0.70
Sore throat	1(16.7)	14(38.9)	0.27
Dyspnea	5(83.3)	12(33.3)	0.02
Myalgia	3(50)	20(55.6)	0.80
Arthralgia	0(0)	8(22.2)	0.09
Diarrhea	0(0)	3(8.3)	0.32
Anosmia	0(0)	3(8.3)	0.32
COVID-19 Treatment			
Steroids	6(100)	15(41.7)	0.002
Hhdroxychloroquine	5(83.3)	14(38.9)	0.04
Azithromycin	1(16.7)	9(25)	0.60
Anticoagulants	None	3(8.3)	0.32
Age (Years)	41.50±17.16	40.75±12.99	0.90
Disease duration (Years)	9.00±1.41	9.60±11.51	0.90

Lungs are the main target of COVID-related inflammation, so that dyspnea may serve as a sign of impending respiratory insufficiency. Myalgia may manifest muscle inflammation as a part of systemic inflammatory response.[13] In our study, myalgia was

associated with hospitalization. Lippi *et al*.[14] found no association between myalgia and COVID-19 severity. More than half of our patients had comorbidities. Hypertension, lung involvement and kidney disease were the most common comorbid. All these findings are similar to Gianfrancesco *et al*.[8] Proportion of smokers (10%) is lower compared to 34% reported recently. It may be due to the low percentage of males in our study, as smoking is more prevalent in males in our setup. RA was the most frequent diagnosis followed by SLE, similar to that of Michaud *et al*.[15]

We had a much higher prevalence of SLE than the previous reports.[8] In our study, the death rate in SLE was also strikingly higher than reported in another study (50% vs 9%).[16] Most of these patients were using HCQ, favouring the notion that HCQ does not protect from COVID-19. This is corroborated by the findings of Mathian *et al*.[17] Steroids have anti-inflammatory and immune-suppressing effects. Although beneficial, this also wea-kens the body's response to infections. In our study, long-term steroids predicted mortality and escalated care, whereas Gianfrancesco *et al*.[16] found their association with hospitalization only. As steroids are indicated for both active rheumatic disease and severe COVID-19, these factors may contribute to higher mortality with steroids. Zha *et al*. reported that steroid use did not affect the COVID severity, hospital stay, or time for viral clearance.[18] Whereas Wu et al. showed that steroids only benefited patients with ARDS.[19] Our findings contrast with Fadel *et al.* conclusion that early steroids prevented the escalation of care in severe COVID-19.[20] A previous study on pigs reported that one or two steroid doses steroids are beneficial in SARS viral infections, but longer treatment increases viral replication.[21] Initially, it was proposed that HCQ can effectively prevent the SARS CoV-2 infection and its progression to severe disease.[22] We found that long-term MMF, Cyclophosphamide, and HCQ use during COVID were associated with severe infection. Previously, one study, which was later retracted, reported poor outcomes with HCQ in patients with COVID.[23] Monti *et al*. con-cluded that the drugs used for inflammatory arthritis, including steroids, antimalarials and DMARDs, did not affect COVID outcome.[24] Michelena *et al*. reported that patients using targeted synthetics and biologics are not at risk of poor COVID outcomes.[25]

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LIMITATIONS OF STUDY

Although this study provides valuable knowledge, it is limited by its small size. As data contains only patients self-reporting to health professionals, it may represent patients with severe infection. Furthermore, it was not a controlled protocol. The choice and dosages of drugs were left to the judgment of attending doctors. We had not recorded the dosages of the drugs, which may have an impact on outcomes.

CONCLUSIONS

The mortality of SARS-CoV-2 in patients with rheumatic diseases is similar to that in the general population. SLE and long-term steroids are associated with mortality. Dyspnea, arthralgia, steroid and HCQ use during the infection is related to the severity of the condition. Among DMARDs, MMF and cyclophosphamide are associated with severe infection.

Conflict of Interest: None.

Author Contribution

Following authors have made substantial contributions to the manuscript as under:

SP: Conception, data acquisition, data analysis, data interpretation, drafting the manuscript, approval of the final version to be published.

BS: Critical review, drafting the manuscript, approval of the final version to be published.

MJF: Drafting the manuscript, data interpretation, approval of the final version to be published.

SS: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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