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Impact of the COVID-19 Pandemic on the Management Course of Paediatric Rheumatic Diseases in a Tertiary Care Hospital of Bangladesh

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Abstract

Background: The COVID-19 pandemic had a significant impact on every aspect of life. Like other chronic diseases, pediatric rheumatic diseases (PRDs) also faced unique challenges during the pandemic, including limited access to care, concerns regarding infection risk, drug shortages and social isolation. **Objective:** The objective of the study was to identify the impact of the COVID-19 pandemic on the management course of children with rheumatic diseases. **Methods:** This cross-sectional study was conducted in the department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from April 2021 to March 2022. Two hundred and twenty patients were enrolled. A predesigned questionnaire was completed which included socio-demographic, clinical and laboratory parameters. Disease activity was assessed clinically and from laboratory profile. Data were calculated manually and by using SPSS version 22. Z-proportion test and chi square test were done when applicable. **Results:** Among the enrolled PRD cases 87.7% were Juvenile Idiopathic Arthritis (JIA), 7.7% were Systemic Lupus Erythematosus (SLE) and 4.6% were other cases. Irregular follow-ups were found in 69.9% JIA cases, 82.4% SLE cases and 60% other PRD cases. Poor drug compliance was present in 18.2% of cases. A significant number of patients had higher disease activity or flare during the COVID-19 pandemic. **Conclusion:** During COVID-19 pandemic most (70.5%) of the PRD patients were irregular in their follow-ups. Poor drug compliance was also more than in the pre-COVID period. Disease activity status significantly worsened during this period.

1. Introduction

Epidemic/Pandemic outbreaks have devastating impacts on human wellbeing including widespread significant morbidity and mortality, food insufficiency, social, psychological, economic, political impacts, education and human health [1] [2] [3]. Pandemics are occurring more frequently nowadays. Perhaps due to globalization, open economy, increased animal-to-human contact, antimicrobial resistance and the transmission of zoonotic infections influencing the vectors due to climate changes [2] [3] [4].

Several epidemics/pandemics have had emerged globally over the past two decades, including severe acute respiratory syndrome (SARS) in 2002-2004, Influenza A virus subtype H1N1 in 2009, Middle East respiratory syndrome coronavirus (MERS-COV) in 2012, Ebola Virus Disease (EVD) in 2014, and finally the COVID-19 pandemic in December 2019 [1] [4] [5].

The COVID-19 is an ongoing pandemic of coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a very contagious disease which spreads from close contacts of an infected person through the air; primarily via small respiratory droplets while breathing, coughing and sneezing [6]. Several strategies were enacted to limit its spread such as social distancing, shutdown or lockdown, isolation and quarantine. As a result, there was abrupt closure of schools, community programs, and workplaces [7]. There was also partial or complete closure of the outpatient services in many countries as part of lockdown [8]. The COVID-19 pandemic had a sudden, profound and long-term impact on nations globally including health care systems [7]. These in turn had significant impacts on various aspects of life including human health [9].

Although social distancing and lockdown helped limit the spread of the virus to some extent, patients with chronic illnesses were unable to access healthcare facilities for their routine care. They had difficulties in revisits, follow-ups, check-ups and prescription refills [10].

In the field of rheumatology, many patients had to delay, postpone, and even cancel their follow-up visits during this pandemic. There were many reasons for this discontinuity of follow-up including individual (fear and reluctance, home isolation), and also collective (shortages of medical staff, weakening of PHC, and suspension of outpatient care) [11]. Studies showed that, during COVID-19 pandemic some rheumatic patients frequently avoided follow-ups, laboratory tests and there were also interruptions in their medications [12].

Rheumatologic conditions most often follow a course marked by flares and periods of remission, although some children have unremitting disease [13]. The

treatment of rheumatic diseases in children is complex, challenging and needs regular follow-ups and good compliance. During the initial phase of COVID-19 pandemic, the outpatient department (OPD) of BSMMU was almost closed for about two months. Also, there was lockdown and a life-threatening fear of COVID-19 infection. So, a gap could have remained in the regular follow-ups, though most of them took online advice. The aim of this study was to identify the impact of the COVID-19 pandemic on the management course of paediatric rheumatic diseases.

2. Materials and Methods

This was a cross sectional descriptive observational study conducted in the paediatric rheumatology outpatient department, Bangabandhu Sheikh Mujib Medical University (BSMMU), and also in the in-patient department of paediatrics, BSMMU, Dhaka, Bangladesh from April 2021 to March 2022.

A semi structured questionnaire was prepared for this study by the research team and feedback on the questionnaire was taken from 4 senior paediatricians, who have interest in paediatric rheumatology and psychometricians in the country and then the questionnaire was finalized. Pre-testing was done on 10 cases to test the reliability of it. The questionnaire was initially prepared in Bangla and later it was translated in English by one medical and one non-medical person. These 2 questionnaires were compiled and edited into one by another medical person who has better expertise in English.

BSMMU has a paediatric rheumatology outpatient clinic (OPD) and a paediatric rheumatology unit in the in-patient department of paediatrics. The study subjects were enrolled from OPD clinic. Children diagnosed with any type of paediatric rheumatic diseases before the COVID-19 pandemic and had a scheduled follow-up visit during the COVID-19 pandemic from March 2020 to March 2021, were included in the study. Sample size was calculated using the formula:

$$n = \frac{Z^2 pq}{d^2}$$

Expected proportion (*p*) was 12% [14]. Accordingly, the total sample size was 162. A total of 220 available PRD cases (36% increased from calculated sample size) were enrolled in the study through convenient sampling.

The paediatric rheumatology clinic in the OPD, BSMMU provides services in its follow-up clinic three days per week. All the medical records of each patient are documented in a registry book (hard copy) including patient identification number (PIN), history, examination findings, lab findings, diagnosis, ongoing treatment, current disease activity, disease course and next follow-up schedule. Additionally, all these records are kept in the online database of paediatric rheumatology division (http://www.pedrhum.com/), and updated regularly. Study cases were identified from the registry book records and online records.

Though, paediatric rheumatology clinic runs 3 days a week, principal investi-

gator of this study was allowed to attend only 1 day a week. So, Data was collected by purposive sampling on that particular day of the week.

Ethical clearance was taken from the Institutional Review Board (IRB) of BSMMU (BSMMU/2021/3364; 08.03.2021). Informed written consent was taken from the parents or patients. Data were collected manually and recorded in the questionnaire. Current disease activity status was assessed clinically and from laboratory profile accordingly (Using JADAS-27 and Wallace criteria for JIA) [15] [16], SLE-DAI for SLE [17], CMAS for JDM [18] and Sclero-ID [19] for assessing systemic sclerosis disease activity. Disease activity status before the COVID-19 pandemic was recorded from the registry book and paediatric rheumatology and immunology clinic (PRIC) file, which contains patient identification number (PIN), history, examination findings, lab findings, diagnosis, ongoing treatment, disease activity status, disease course and next follow-up schedule. Additionally, data were checked and verified from the online database of paediatric rheumatology division (http://www.pedrhum.com/).

All the data were checked, verified & analyzed manually using Microsoft office word and also by SPSS version 22 software. Data were presented as Tables & Figures. The normality in distribution of numeric variables was determined by using Shapiro-Wilk test. Numerical data were expressed as mean ± standard deviation and median when appropriate. Qualitative data were expressed as frequency and percentage. Z proportion test and Chi square test were calculated when applicable. A p value less than 0.05 was considered as significant.

Operational definitions:

Regular follow-up: Patients who attended the outpatient department on the scheduled date or within 30 days of the scheduled follow-up date [14]. **Irregular follow-up:** Those who did not attend the outpatient department within 30 days of the scheduled follow-up date [14]. **Good compliance:** Patients who took all the drugs at the recommended dose and duration [14]. **Poor compliance:** Patients who did not take all drugs or took 50% or less of the recommended dose and duration [14]. **Disease Activity Status for JIA: Were a**ssessed by using JADAS-27 [15] and Wallace criteria 2004 [16].

3. Result

Demographic profile in Table 1 show that age range of the cases was highest in 6 - 10 years group (45%), followed by 11 - 18 years group (28.6%). Male cases were more (54.5%) and majority of the cases (77.7%) attended the follow-up clinic from outside the capital city Dhaka. Among all the PRD cases, JIA was the most common (n = 193, 87.7%) followed by SLE (n = 17, 7.7%). Other PRDs (n = 10, 4.6%) included: polyarteritis nodosa (n = 4. 1.8%), juvenile dermatomyositis (n = 2, 0.9%), mixed connective tissue disorders (n = 2, 0.9%), scleroderma (n = 1, 0.45% and primary immune deficiency disorders (n = 1, 0.45%).

A highly significant number of PRD cases (70.5%) had irregular follow-ups during the COVID-19 pandemic, (p value < 0.0001). Among the JIA cases 69.9%

were irregular in their follow-up and it was 82.4% and 60% for SLE and other PRD cases respectively (Figure 1).

Most of the PRD cases were irregular in follow-up for more than 6 months.

Among the total 220 cases, 40 (18.2%) had poor drug compliance and it was 17.1% for JIA cases, 23.5% for SLE cases and 30% for other PRD cases (Figure 2).

Among the poor compliant cases, majority discontinued their medication for more than 6 months.

Reasons for irregular follow-up during the COVID-19 pandemic period included: fear of COVID-19 infection (57%), lockdown effect (54.5%) and financial crisis 24.4% (Table 2). The most common cause for poor drug compliance was financial crisis (42.5%), followed by poly-pharmacy (need multiple medicines), fear of injection, side effects of medicines (42%) and non-availability of medicine in 27.5% (Table 2).

Most of the irregularly followed up cases also had poor drug compliance. Among the irregularly followed up PRDs, 25.2% also had poor drug compliance while only 1.5% of regularly followed up cases had poor drug compliance (Table 3).

Before COVID-19 pandemic, 20.7% of JIA cases had active disease (DA), But DA cases significantly increased to 51.3% during the COVID-19 pandemic. The number of inactive disease (DI) or stable cases also significantly decreased from 32.6% to 10.4% during the COVID-19 pandemic. No significant differences were seen before or during COVID-19 pandemic among clinical remission on medication (CRM) or clinical remission off medication (CR) cases (Table 4).

Disease activity status of SLE and other PRD cases also significantly increased during the COVID-19 pandemic (Table 5).

Table 1. Demographic characteristics of the cases (n = 220).

Demographic Characteristics	Frequency (n)	Percentage (%)
Age at onset		
0 - 5 years	58	26.4
6 - 10 years	99	45
11 - 18 years	63	28.6
Mean age of onset ± SD (years)	8.01 ± 3.6	
Gender		
Male	120	54.5
Female	100	45.5
M:F		1.2:1
Residence		
Dhaka	49	22.3
Outside Dhaka	171	77.7

Data were expressed as frequency, percentage and mean ± SD.

Follow Up Status of Different Paediatric Rheumatic Diseases Patients in percentage (%) during COVID 19 Pandemic
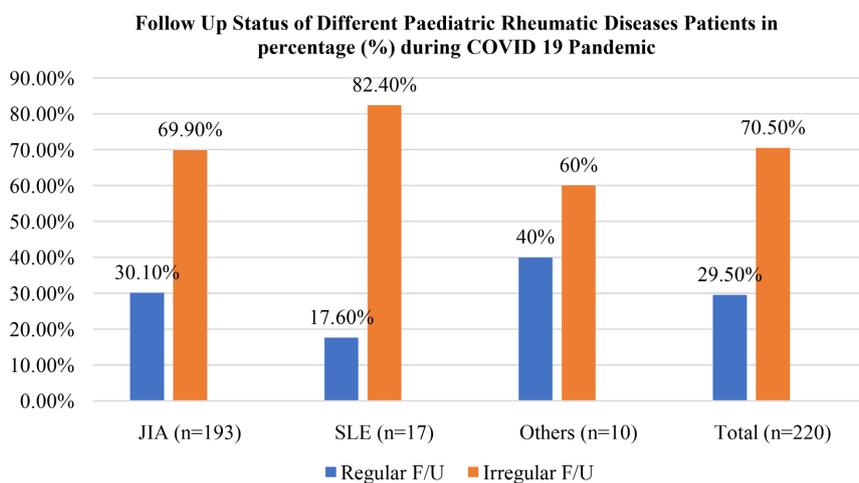
Figure 1. Follow-up status of different types of the Paediatric rheumatic diseases (n = 220). p value < 0.0001; Z proportion test. JIA = Juvenile idiopathic arthritis, SLE = Systemic lupus erythematosus.

Table 2. Reasons for irregular follow-up and poor drug compliance of pediatric rheumatic disease patients during COVID-19 pandemic.

Reasons	Number (n)	Percentage (%)
Irregular Follow-up (n = 155)		
Fear of COVID-19 infection	89	57
Lockdown effect	85	54.5
Financial crisis	38	24.4
Lack of transport	27	17.3
No attending person	16	10.26
Feeling well	15	9.6
Others (Birth of new sibling, no residence at Dhaka, going abroad, # of leg, school exam)	9	5.8
Remote area	3	1.9
Poor Drug Compliance (n = 40)		
Financial crisis	17	42.5
Polypharmacy, injection, side effects	16	42
Non-availability of medicine	11	27.5
Feeling well	5	12.5
Others (Fear of COVID-19 infection, chronicity of disease, difficulty in communication, father not at home, another doctor consultation)	5	12.5

Data were expressed as frequency and percentage. COVID-19 = Corona Virus Disease 2019.

Table 3. Association of follow-up status and drug compliance among the pediatric rheumatic disease patients (n = 220).

Follow-up Status	Drug Compliance		p-Value
	Good, n (%)	Poor, n (%)	
Regular (n = 65)	64 (98.5)	1 (1.5)	<0.0001*
Irregular (n = 155)	116 (70.5)	39 (25.2)	

Data were expressed as frequency and percentage. * Chi-square test.

Table 4. Disease activity status of the juvenile idiopathic arthritis cases before and during the COVID-19 pandemic (n = 193).

Disease status	Before COVID-19 Pandemic, n (%)	During COVID-19 Pandemic, n (%)	p-Value*
Disease Active (DA)/Flare	40 (20.7)	99 (51.3)	<0.001
Disease Inactive (DI)/Stable	63 (32.6)	20 (10.4)	<0.001
Clinical Remission on Medication (CRM)	81 (42)	67 (34.7)	0.142
Clinical Remission off Medication (CR)	9 (4.7)	7 (3.6)	0.609

Data were expressed as frequency and percentage. *Chi square test.

Table 5. Disease activity status of pediatric rheumatic disease cases other than juvenile idiopathic arthritis before and during the COVID-19 pandemic (n = 27).

PRDs (n)	Disease Activity Status	Before COVID-19 (n)	During COVID-19 (n)	P-value*
SLE (17)	Mild	10	4	0.008
	Moderate	7	6	
	Severe	0	7	
Others (10) PAN (4) + JDM (2) + MCTD (2) + Scleroderma (1) + PID (1)	Mild	8	4	0.075
	Moderate	2	6	
	Severe	0	0	

Data were expressed as frequency. *Chi square test. PRDs = Pediatric rheumatic diseases, SLE = Systemic lupus erythematosus, PAN = Polyarteritis nodosa, JDM = Juvenile dermatomyositis, MCTD = Mixed connective tissue disease, PID = Primary immunodeficiency disorder.

Distribution of Paediatric Rheumatic Diseases by regularity of Medication Intake in percentage (%)
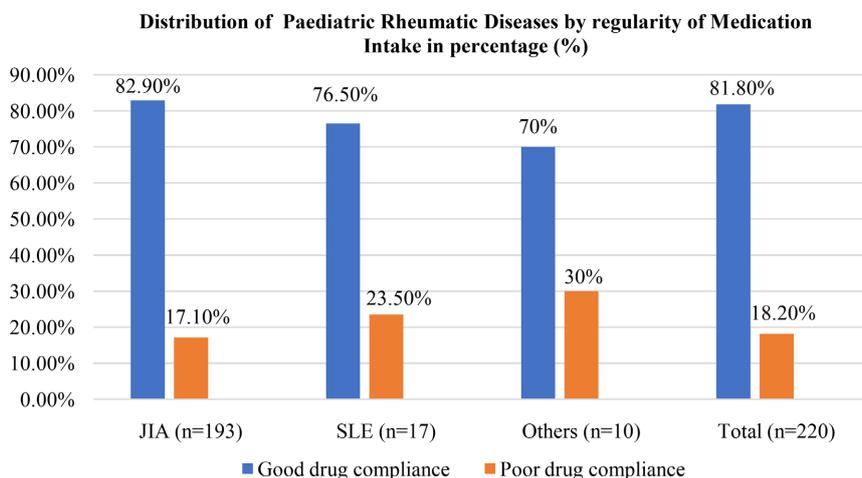
Figure 2. Distribution of Paediatric Rheumatic Disease patients by Irregularity of Medication (n = 220). p value < 0.0001; Z proportion test. JIA = Juvenile idiopathic arthritis, SLE = Systemic lupus erythematosus.

4. Discussion

In this cross-sectional observational study, a total of 220 patients with different types of PRDs were enrolled. The mean age of onset of PRD was around 8 years with male predominance. Among all the PRD cases, JIA was the most common. About 70.5% of the cases were irregular in their follow-up and 18.2% had poor drug compliance during the COVID-19 pandemic. Disease activity was markedly increased during the COVID-19 pandemic.

The mean age of onset of PRD children in this study was 8.01 ± 3.6 years (Table 1) which was similar to another study done in the same center where the mean age of onset was 8.33 ± 4.8 years [20]. Male predominance was seen with male: female ratio of 1.2:1 (Table 1). Previous studies from Bangladesh also found male predominance [20] [21]. Male predominance was also reported from Southeast Asia [22] [23]. This could be due to the socio-cultural background, where male children are given more attention. It is documented that in western world JIA and other PRDs are more common among girls [24] [25].

Kabir, *et al.* in a study found that most of the PRD patients attending pediatric rheumatology OPD, BSMMU were from outside Dhaka [14]. The present study also found similar findings, where 77.7% of participants were from outside the capital city Dhaka (Table 1). As, a greater number of patients registered in the clinic were from other 63 districts of Bangladesh, when the lockdown was imposed, patients could not attend BSMMU OPD.

All the epidemics/pandemics including SARS, MARS and Ebola had created threats towards the global public health and also the global economy over the last 30 years [5]. Because of the unusually serious, prolonged and ongoing course, there was almost total disruption of health care services all over the world during the COVID-19 era. Postponements of scheduled medical visits delayed seeking of help and lack of medication adherence worldwide lead to dere-

gulation of chronic diseases including PRDs [11]. Increased morbidity and mortality due to epidemics/pandemics also cause an increased demand on healthcare services [26]. Other chronic diseases including, malignancies, diabetes, chronic obstructive pulmonary disease, hypertension and mental health were also affected during COVID-19 pandemic due to difficulties in access to care [27].

In the present study the majority (70.5%) of the PRD cases had irregular follow-ups during the COVID-19 period (Figure 1). A study conducted to evaluate the impact of COVID-19 pandemic in the Arab countries found significant deleterious consequences of the COVID-19 pandemic on the rheumatology practice due to the limited access to health care and to fundamental drugs [28]. The COVID-19 pandemic had negative impact on patients with rheumatic disease in Latin America also [29]. They found that, disease activity increased, medication adherence decreased, and there were many hurdles to follow-up. Studies from Switzerland and Pakistan also reported similar findings, where majority of cases missed their follow-up during COVID-19 pandemic [8] [30]. Common reasons of missed follow-up in the present study included: fear of COVID-19 infection (57%), effects of lockdown (54.5%) and financial crisis (Table 2). The COVID-19 pandemic had a negative impact on the economic status of many families [28]. Many of the parents had to change their employment status and some of them even became jobless, which negatively affected regular follow-ups and drug compliance of PRD cases [31].

In the present study a total of forty PRD cases (18.2%) had irregular medication (Figure 2). A study conducted by Kabir, *et al.* in the same center in 2017 found 12.9% poor compliance among JIA patients during normal (non-COVID) time [14], which was much less than the COVID-19 pandemic time. The Turkish study found 22.3% of rheumatic patients had reduced or interrupted treatment [32] and a multicenter study in Saudi Arabia reported that 14.2% of rheumatic patients were non-adherent to their medications during COVID-19 pandemic [33]. Similar findings were reported from Switzerland, where the drug compliance decreased during the pandemic in comparison to before the pandemic [8].

Common reasons for poor compliance in the present study were: financial crisis, polypharmacy, fear of injection, side effects of medicines and non-availability of some medicines during the pandemic (Table 2). Kabir, *et al.* from our center found financial crisis, lack of awareness, access to traditional healers and polypharmacy as the common causes for poor drug compliance [14]. A study conducted among the Turkish adult rheumatic patients found that anxiety, not being able to reach the hospital and scarcity of drugs were common causes of poor drug adherence during the COVID pandemic [32].

The present study found that poor drug adherence was significantly associated with irregular follow-up (Table 3). Kabir, *et al.* also reported similar findings where most of patients from irregular follow-up group were also irregular in their medication [14]. Similarly, a study from the Latin America found a rela-

tionship between irregular follow-up and reduced drug adherence [29].

In the present study it is found that during the COVID pandemic, 51.3% of JIA patients had active disease or flare which was significantly higher than in pre-COVID-19 period, when it was only 20.7%. During this pandemic, all the pediatric rheumatologists of this center tried to help their patients with virtual consultation over telephone. But as the clinical condition and disease activity could not be assessed properly over telephone, maybe, medications including doses could not be modified properly and as a result, disease activity became higher. For any chronic illness including PRDs, regular follow-up, counseling and good drug adherence is essential to achieve and maintain inactive disease and remission. There were no significant changes in disease activity status among the patients who were maintaining clinical remission on medication (CRM) or clinical remission off medication (CR). Moreover, most of the CRM and CR cases adhered to their medication. This could be due to the fact that these children and their parents were very happy and optimistic about their inactive diseases, and as they were on minimum or no medication, they adhered to advice and counseling done by the pediatric rheumatologists over telephone despite of COVID-19 situation (Table 4). In Saudi Arab, it is reported that 30.1% rheumatic disease patients had active disease and 17.1% worsened during the COVID-19 period [33]. A multicenter study including 493 pediatric rheumatologists from 70 countries reported that 20% - 30% of 493 rheumatologists indicated that their patients had disease flares or delays in diagnosis due to postponed follow-up visits during COVID pandemic [34]. On the other hand, a study conducted in Canada did not find any anticipated delay in presentation or increased disease severity at presentation [35]. The reason behind this difference may be explained by their well-developed pediatric rheumatology service even at the primary health care level.

A significant number of SLE and other PRD cases also had higher disease activity level during COVID-19 period as many of them were not regular in their follow-ups (Table 5). Moreover, SLE and other PRD cases need to take a good number of medicines even if they have low disease activity status. So, maybe because of the reasons mentioned in Table 2, their regular follow-ups were interrupted, and drug compliance also became poor.

5. Conclusion

It may be concluded from this study that COVID-19 pandemic had significant negative effects on pediatric rheumatic disease management courses. The majority (70.5%) of PRD cases missed their follow-up during early phases of COVID-19 pandemic. A significant number of PRD cases (51.3%) had flare and higher or active disease states during the COVID-19 pandemic, which could be due to irregular follow-up and poor drug compliance.

Limitations

Single center and short time framed study.

Recommendations

Over the last two decades several new or emerging viral diseases including Dengue, SARS, MERS, Ebola and finally the COVID-19 pandemic are creating havoc in the form of epidemics or pandemics. These epidemics/pandemics are disrupting health services all over the world because of their direct and indirect effect on health care systems.

Children suffering from chronic diseases including rheumatic diseases, who need regular follow-up and long continued treatment, are more vulnerable in these situations. Policy makers along with specialists and experts from national and international level will have to plan for combating situations like these.

Acknowledgements

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix: I

Data collection sheet

(Questionnaire)

Date: [   ]

Study Title: Impact of the COVID-19 Pandemic on the Management Course of Children with Rheumatic Diseases in a Tertiary Care Hospital of Bangladesh

Investigator: Dr. Mohammad Zahidul Islam

<u>Section A: Particulars of the patient</u>

Case study No.: [ ] [ ] [ ]   Phone No.: [   ]

PRIC No.: [ ] [ ] [ ] [ ]

Name: [   ]

Age: [ ] Years [ ] Months

Gender: Male: [ ] Female: [ ]

Residence: Dhaka [ ] Outside Dhaka [ ]

<u>Section B: Disease related/ clinical profile</u>

<u>Clinical profile:</u>

Diagnosis: [   ]

Age of onset: [ ] Years [ ] Months

Disease duration: [ ] Years [ ] Months

Current disease status: DA [ ] DI [ ] CRM [ ] CR [ ] Flare [ ]

Previous disease status: DA [ ] DI [ ] CRM [ ] CR [ ] Flare [ ]

JADAS 27: [ ] CMAS: [ ] SLE DAI: [ ] SSDAI: [ ]

O/E: TJ: [ ] SJ: [ ] ROM: [ ] Enthesitis: [ ]

Fever: [ ] Rash: [ ] BP: [ ]

<u>Laboratory profile:</u>

ESR: [ ] Total count: [ ] Platelet count: [ ]

CRP: [ ] C3: [ ] C4: [ ] Anti-ds DNA: [ ]

Other investigations (when necessary):

Muscle enzymes: [ ] 24 hours UTP [ ]

Serum ferritin: [ ] Coombs test [ ]

<u>Section C: Follow-up related</u>

Number of total follow-up: [ ] times

Follow-up: Regular [ ] Irregular [ ]

If irregular: <3 months [ ] 3 - 6 months [ ] >6 months [ ]

Reason for irregular follow-up:

Lockdown [ ] Lack of transport [ ] Closure of OPD [ ]

Fear of COVID-19 infection [ ]

Non-availability of medicine, [ ] Financial crisis [ ]

Others (details)

…………………………………………………………………………………

<u>Section D: Drug related</u>

If irregular intake: Duration <3 months = 1, 3 - 6 months = 2, >6 months = 3)

	Regular	Irregular, Duration
DMARD: MTX:	☐	☐
Sulphasalazine:	☐	☐
Leflunamide:	☐	☐
Hydroxychloroquine	☐	☐
Thalidomide:	☐	☐
NSAID-Naproxen:	☐	☐
Indomethacin:	☐	☐
Corticosteroids:	☐	☐

Supporting drugs-

	Regular	Irregular, Duration
Calcium & vit D:	☐	☐
Folic acid:	☐	☐

Biological agents-

	Regular	Irregular, Duration
Tocilizumab:	☐	☐
Etanercept	☐	☐
Tofacitinib	☐	☐

Other Medicines, when needed…………………………………..

Reasons of Poor Drug Compliance:

COVID-19 related ☐ Financial crisis ☐ Lack of awareness ☐

Difficulty in communications ☐ Non-availability of medicine ☐

Chronicity of disease ☐

Polypharmacy, injection, side effects ☐ Traditional healers ☐

Familial disharmony ☐ Others (details) ☐

…………………………………………………………………………………