

Attitudes and Behaviours of Patients with Rheumatic Diseases during the early stages of the COVID-19 Outbreak.

Margaret HY Ma^{1,2}, Sen Hee Tay^{1,2}, Peter PM Cheung^{1,2}, Amelia Santosa^{1,2}, Yiong Huak Chan³, James WL Yip⁴, Anselm Mak^{1,2} and Manjari Lahiri^{1,2*}

1. Division of Rheumatology, University Medicine Cluster, National University Health System, Singapore.
2. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.
3. Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
4. National University of Singapore Saw Swee Hock School of Public Health, Singapore

*Corresponding Author:

Dr Manjari Lahiri

Email: manjari_lahiri@nuhs.edu.sg

Title: Senior Consultant, Rheumatology and Assistant Professor, Medicine

Address: Division of Rheumatology, University Medicine Cluster, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block, Level 10, Singapore, 119228

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Emails:

MHY Ma: margaret_ma@nuhs.edu.sg

SH Tay: sen_hee_tay@nuhs.edu.sg

PPM Cheung: peter_cheung@nuhs.edu.sg

A Santosa: amelia_santosa@nuhs.edu.sg

YH Chan: medcyh@nus.edu.sg

JWL Yip: James_yip@nuhs.edu.sg

A Mak: anselm_mak@nuhs.edu.sg,

M Lahiri: manjari_lahiri@nuhs.edu.sg

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- MHY Ma: study design, data plan, data analysis, data interpretation and writing of the manuscript
- SH Tay: study design, data plan, data analysis, data interpretation and writing of the manuscript
- PPM Cheung: study design, data plan, data analysis, data interpretation and writing of the manuscript
- A Santosa: study design, data plan, data analysis, data interpretation and writing of the manuscript
- YH Chan: data plan, data analysis, data interpretation and writing of the manuscript
- JWL Yip: study design, data acquisition and writing of the manuscript.
- A Mak: study design, data plan, data analysis, data interpretation and writing of the manuscript
- M Lahiri: conceived the study, study design, data plan, data analysis and writing of the manuscript.

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- The authors have no conflicts of interests.

ABSTRACT:

Objectives: To evaluate attitudes and behaviours of patients with rheumatic diseases during the COVID-19 pandemic.

Methods: An online survey delivered via text-message to 4695 patients on follow-up at a tertiary rheumatology centre. Latent class analysis was performed on the survey variables.

Results: 2239 (47.7%) responded to the survey and three clusters were identified. Cluster-3 (C3) was defined by patients most worried about COVID-19, were more likely to wear face-masks, and to alter or stop their medications. Patients in C3 were more likely to be female, Malay and unemployed.

Conclusion: We identified three clusters with different healthcare beliefs and distinct socio-demographics.

Word count: 100

INTRODUCTION

The novel coronavirus infection (COVID-19) has become a global pandemic [1]. While increasing age and comorbidities are proven risk factors for poor clinical outcomes [2], it is unclear [3-7] whether patients with rheumatic diseases should be considered high-risk both due to disease and immunosuppressive treatments, especially during the early stages of the pandemic. On the other hand, hydroxychloroquine (HCQ) has been used in the treatment of COVID-19 and anti-IL-6 for certain patients with cytokine storm [8,9].

COVID-19 has caused increased uncertainty and anxiety among patients, leading to changes in healthcare behaviours [10]. It is important to understand this in the context of rheumatological diseases. As such, we performed a study to explore their attitudes and behaviours, with an aim to identify subgroups of patients with higher needs who may benefit from closer follow-up during this period.

METHODS:

Patients seen in our tertiary rheumatology clinic in Singapore between March 1, 2019 and February 29, 2020 with Singapore mobile phones were extracted from our data warehouse using a data-anonymisation solution with a unique hashtag-key. These patients were sent a 25-question survey (see supplementary material) via short message service (SMS) on March 28, 2020, with a secure web-based survey tool (Research Database Capture, REDCap) [11]. A further 2 SMS reminders were sent on March 31 and April 9, 2020 if the survey was not completed. Data points were aggregated with demographics, diagnosis codes and prescriptions associated with the rheumatology visit; mobile numbers were removed to preserve anonymity. We used an unbiased, multidimensional approach to identify patients with different healthcare attitudes and behaviours and to see if these clusters predict disease characteristics and medication usage. LCA was performed to determine the appropriate number of clusters and the best fitting models were selected using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) [12]. A 3-cluster solution was obtained after examining the change in the AIC and BIC values between adjacent clusters. Twenty-two questionnaire responses were selected as input variables for LCA.

Missing data were inputted as “unknown” to make up a complete dataset. For survey responses, there were no missing data as the questions were all mandated. This analysis places subjects into clusters, suggested by the questionnaire data, not defined a priori. Differences between clusters were explored using chi-square test and Kruskal-Wallis test with Mann-Whitney-U and Bonferroni correction for pairwise and multiple comparisons respectively. STATAv10 and SPSSv25 were used. This study was approved by the National Health Group Domain Specific Review Board (NHG DSRB Reference: 2020/00248). Informed consent was not required since it was anonymised.

RESULTS:

Of 5085 eligible patients, the survey was sent to 4695 with Singapore mobile numbers: 2239(47.7%) responded by April 14, 2020 [mean(SD) age 53.5(15.9) years, 1567(70%) females, 1524(68.1%) Chinese]. 477(26.7%) had connective tissues disease (CTD) and 721(40.4%) had inflammatory arthritis (IA). 214(9.6%) were taking HCQ alone, 1032(46.1%) were taking immunosuppressants other than biologics and 95(4.2%) were taking biologic or targeted synthetic disease modifying anti-rheumatic drugs. Survey responders tended to be younger, more likely to be female, non-Chinese, more likely to have IA or CTD and less likely to have comorbid conditions (Table 1). 44(2.03%) had been tested for SARS-CoV-2 and only one was positive. 48(2.27%) of the patients' co-inhabitants tested positive.

The majority of patients obtained information on COVID-19 through multiple sources, including television (65.8%), social media (62.3%), the Singapore Ministry of Health (MOH) website and WhatsApp® channel (61.7%), newspaper (49.5%) or friends and family (50.5%). 162(7.4%) patients had contacted health care professionals (HCP) for COVID-19 advice and most(90.74%) were reassured by their advice. Patients were worried about COVID-19 [median(IQR) 73(50,89) on a 100-point visual analogue scale (VAS) with 100 being the most worried] and worried about going out [median(IQR) 70(50,81)]. 733(33.5%) had travelled abroad from December 1, 2019, to the time of the survey and 1020(47.3%) had cancelled travel plans. 1012 (46.4%) wore face-masks while well, despite this being discouraged by the government at the time of the survey. 2088(96%) sanitised hands more often. During the COVID-19 period, 255(11.7%) had seen their doctors more often than usual. 316(14.7%) admitted to not taking medications regularly even prior to the pandemic. Since the pandemic, 1991(94.8%) took their medications the same or more regularly than before. Of the 109(5.2%) patients who took their medications less regularly, 43.3% did so due to worries about COVID-19. 792(36.8%) and 792(36.8%) believed that their rheumatic condition and medications would increase their risk of COVID-19, respectively. 313(14.7%) (22% of those on HCQ) believed their medications would protect them from COVID-19. Only 868(41%) were up-to-date with their influenza and pneumococcal vaccinations.

Three clusters were found using LCA, classifying C1(295,13.2%), C2(703,31.4%) and C3(1241,55.4%). Discriminant analysis showed that 97.7% of the subjects were correctly classified with a cross-validation of 97.3% (Supplementary Figure 1). C3 was the group most worried about COVID-19 [median (IQR) VAS 86(78,97)] vs. C2 52(50,63), $p<0.001$ and vs. C1 20(10,29), $p<0.001$. This group had more contact with HCP (9% vs. 6% in C1, $p=0.01$), with more wearing face-masks(53% vs. 28%, $p<0.001$). They also decreased their social activities(80% vs 68%, $p<0.001$). They were also most worried that their condition(43% vs 20%, $p<0.001$) or medications(22% vs. 13%, $p<0.001$) would put them at higher risk of being infected. C3 also altered or stopped their medications more during COVID-19(11% vs 7%, $p=0.002$) and took

medication less regularly before COVID-19 (20% vs 16%, $p=0.02$). C3 obtained less information from newspapers (47% vs. 54%, $p=0.03$), and fewer were up-to-date with vaccinations (37% vs. 44%, $p=0.006$) (Table 2).

On examination of the demographic and clinical profiles of the generated clusters, patients in C3 were more likely to be female, of Malay race and unemployed. Rheumatic conditions and medication type were not different amongst the three clusters (Table 3). In a subset analysis of patients with IA or CTD and/or on immunomodulatory medications, patients with CTD were more likely to belong to C3, though other descriptors of group membership remained the same.

DISCUSSION:

Our study is the first to survey a wide spectrum of multi-ethnic patients with rheumatic diseases about COVID-19. We identified a large subset of patients who were more worried about COVID-19 due to their underlying disease and medications. These patients were more likely to contact HCP, modify their social behaviours and alter/stop medications. This group had a lower proportion of patients reading the newspaper, being adherent to their medications or being up to date with their vaccinations. This cluster represented a vulnerable socio-demographic group, with significantly more women, unemployment and belonging to an ethnic minority, but who were not different in the distribution of rheumatic diseases or immunosuppressive medications. Patients with such disadvantaged socio-demographic profiles are also similarly seen in other cohorts of rheumatic diseases (e.g. LUMINA cohort) [13]. Patients clustered in C3 may benefit from more rheumatology services.

In a US survey (response rate 7.5%), 530 patients with rheumatic diseases were significantly worried about risk of COVID-19 with 14% self-changing their medication or dose [14]. In our study, medication adjustments were only observed in 5%, possibly due to the patients' perception that their rheumatic disease itself posed a greater risk. However, increased handwashing, less travel and social activities among the general US population were similar to our findings [10].

Our study has several strengths. We were able to distribute the survey link via SMS to 92% of patients with a high response rate. We used a unique cluster analysis to avoid bias from testing for multiple outcomes. Our patients comprise a multi-ethnic population, representative of Singapore, which is predominantly Chinese (74%), followed by Malays (13%) and Indians (9%) [15], allowing us to study racial and cultural differences in attitudes and behaviour. However, while associations exist between socio-demographics and perceived risk of COVID-19, causation cannot be demonstrated due to the study design. We were limited by the cross-sectional nature of our survey, which did not allow us to determine the longitudinal stability of our clusters. Though not included in our survey, patient-perceived disease activity may have influenced their attitudes during and toward COVID-19 and would be thus informative to include in future studies. This survey was conducted mostly before stricter lockdown measures were implemented in Singapore on April 7, 2020; behaviour may since have changed.

The pathological and psychological impact of COVID-19 on patients with rheumatic diseases likely exists as a consequence of their immunosuppressive state and inherently heightened anxiety and depression levels [16]. While almost 20% of respondents were concerned that their medications would increase their risk for COVID-19, only a small proportion sought advice from their physicians. An effective platform for patients to express their concerns in the context of COVID-

19 will be fundamental to prevent unnecessary or even harmful unilateral changes of treatment by patients. Some rheumatological societies have published recommendations to address these issues; however, these additionally recommend cancellation of routine visits [17-19]. Rheumatologists will need to find novel ways to engage their patients proactively to allay anxiety. We have identified a subgroup of patients where these efforts should be most targeted.

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Table 1: Baseline Characteristics

*Comorbidities are based on diagnosis codes and are significantly under-coded as seen by proportion on anti-hypertensive drugs >> diagnosis codes for hypertension, diabetes, CVD and CKD combined

Supplementary Figure 1

Canonical discriminant analysis of the 3 clusters as well as their group centroids. The plot shows the clear discrimination of the 3 clusters based on the discrimination functions 1 and 2.

Table 2: Latent class analysis generation of three clusters

Cluster groups: C1/C2/C3 used the whole cohort of patients who had responded to questionnaire. Differences between clusters were tested using Kruskal–Wallis test for continuous measures and Pearson's chi-square test for categorical measures.

Table 3: Profile of three clusters

Cluster groups: C1/C2/C3 used the whole cohort of patients who had responded to questionnaire. A subgroup analysis was carried out on patients with a diagnosis of connective tissue disease, inflammatory arthritis and / or on immunosuppressive agents (IC1/IC2/IC3). Differences between clusters were tested using Kruskal–Wallis test for continuous measures and Pearson's chi-square test for categorical measures.

Table 1: Baseline Characteristics

	Overall Cohort (n=5085)	Survey Responders (n=2239)	Survey Non-Responders (n=2846)
Age (years), mean (SD)		53.5 (15.9)	59.2 (16.0)
Gender			
Female(%)	3450 (67.9)	1567 (70.0)	1883 (66.2)
Race			
Chinese(%)	3596 (70.7)	1524 (68.1)	2072 (72.8)
Malay(%)	483 (9.5)	249 (11.1)	234 (8.2)
Indian(%)	493 (9.7)	233 (10.4)	260 (9.1)
Other(%)	512 (10.1)	233 (10.4)	279 (9.8)
Diagnosis			
CTD(%)	946 (23.5)	477 (26.7)	469 (21.0)
IA(%)	1599 (39.8)	721 (40.3)	878 (39.3)
Crystal(%)	483 (12.0)	165 (9.2)	318 (14.2)
Non-inflammatory(%)	993 (24.7)	426 (23.8)	567 (25.4)
Comorbidities			
CVD(%)	397 (8.2)	138 (6.4)	259 (9.6)
Hypertension(%)	306 (6.3)	132 (6.1)	174 (6.4)
Diabetes mellitus(%)	337 (6.9)	134 (6.2)	203 (7.5)
CKD(%)	161 (3.3)	60 (2.8)	101 (3.7)
Cancer(%)	218 (4.5)	80 (3.7)	138 (5.1)
Rheumatological Medications			
Nil(%)	1647 (32.4)	699 (31.2)	948 (33.1)
HCQ alone(%)	464 (9.1)	214 (9.6)	250 (8.8)
IS including csDMARD(%)	2212 (43.5)	1032 (46.1)	1180 (41.4)
bDMARD or tsDMARD(%)	189 (3.7)	95 (4.2)	94 (3.3)
Gout medications(%)	573 (11.3)	199 (8.9)	374 (13.1)
Anti-Hypertensives			
Nil(%)	3496 (68.7)	1604 (71.6)	1892 (66.5)
ACEI / ARB(%)	933 (18.4)	387 (17.3)	546 (19.2)
Other Anti-hypertensives(%)	656 (12.9)	248 (11.1)	408 (14.3)
NSAID or COXIB (%)	1876 (36.9)	855 (38.2)	1021 (35.9)

*Comorbidities are based on diagnosis codes and are significantly under-coded as seen by proportion on anti-hypertensive drugs >> diagnosis codes for hypertension, diabetes, CVD and CKD combined
CTD: Connective tissue disease, includes systemic lupus erythematosus, immune mediated inflammatory myositis, systemic sclerosis, systemic vasculitis, sjogren's syndrome, mixed connective tissue disease, undifferentiated CTD
IA: Inflammatory arthritis, includes rheumatoid arthritis, psoriatic arthritis, axial and peripheral spondyloarthropathy, juvenile idiopathic arthritis, adult onset still's disease and undifferentiated inflammatory arthritis.
Non-inflammatory: includes primary antiphospholipid syndrome, osteoarthritis, osteoporosis, fibromyalgia, soft tissue rheumatism and miscellaneous conditions
CVD: cardiovascular disease, CKD: chronic kidney disease, HCQ: hydroxychloroquine, IS: immunosuppressant, csDMARD: conventional synthetic disease modifying anti-rheumatic drug, bDMARD: biologic disease modifying anti-rheumatic drug, tsDMARD: targeted synthetic disease modifying anti-rheumatic drug, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, NSAID: non-steroidal anti-inflammatory drug, COXIB: cyclooxygenase-2 inhibitor

Table 2: Latent class analysis generation of three clusters

Cluster groups: C1/C2/C3 used the whole cohort of patients who had responded to questionnaire. Differences between clusters were tested using Kruskal–Wallis test for continuous measures and Pearson's chi-square test for categorical measures.

	C1 (n=295)	C2 (n =703)	C3 (n =1241)	p value
Consider stopping medication (VAS 0-100 median IQR)	0 (0, 9)	2 (0, 24)	5 (0, 30)	<0.001
Worried about going out (VAS 0-100 median IQR)	21 (8, 30)	50 (47, 61)	80 (72, 91)	<0.001
Worried about COVID-19 (VAS 0-100 median IQR)	20 (10, 29)	52 (50, 63)	86 (78, 97)	<0.001
Where to get information (%):				
MOH website/WhatsApp	194 (66)	438 (62)	749 (60)	0.21
TV	178 (60)	474 (67)	822 (66)	0.89
Newspaper	160 (54)	364 (52)	585 (47)	0.03
Radio	77 (26)	201 (29)	378 (31)	0.30
Friends and family	139 (47)	373 (53)	620 (50)	0.19
Social media	170 (58)	442 (63)	784 (63)	0.20
Contact with health care workers (%)	18 (6)	36 (5)	108 (9)	0.01
Have you travelled since 1st Dec 2019 (%)	89 (30)	247 (35)	397 (32)	0.22
Have you cancelled your travel plans? (%)	134 (45)	330 (47)	556 (45)	0.68
Have you participated in social activities:				
Same (%)	93 (32)	132 (19)	234 (19)	<0.001
Less than before (%)	199 (68)	559 (78)	986 (80)	
More than before (%)	3 (1)	12 (2)	21 (2)	
Worn facemask even when well (%)	81 (28)	270 (38)	660 (53)	<0.001
Washing/sanitising hands more often (%)	266 (90)	668 (95)	1154 (93)	0.02
Seeing your doctor more (%)	28 (9.5)	74 (10.5)	152 (12.2)	0.29
Taking medication regularly before COVID-19 (%)	249 (84)	590 (84)	988 (80)	0.02
Taking medication regularly since COVID-19:				
Same (%)	273 (93)	667 (95)	1113 (92)	0.002
Less than before (%)	13 (4)	24 (3)	72 (6)	
More than before (%)	9 (3)	12 (2)	56 (5)	
Increased risk of COVID-19 because of your rheumatic condition (%)	59 (20)	205 (29)	528 (43)	<0.001
Your medication will protect you from COVID-19 (%)	39 (13)	90 (13)	184 (15)	0.43
Your medication will increase your risk of getting COVID-19 (%)	39 (13)	110 (16)	278 (22)	<0.001
Up to date with flu/pneumococcal vaccinations (%)	129 (44)	279 (40)	460 (37)	0.006

Table 3: Profile of three clusters

Cluster groups: C1/C2/C3 used the whole cohort of patients who had responded to questionnaire. A subgroup analysis was carried out on patients with a diagnosis of connective tissue disease, inflammatory arthritis and / or on immunosuppressive agents (IC1/IC2/IC3). Differences between clusters were tested using Kruskal–Wallis test for continuous measures and Pearson’s chi-square test for categorical measures.

	All patients (n =2239)				Patients with IA / CTD or on Immunomodulatory Therapy (n=1533)			
	C1 (n=295)	C2 (n=703)	C3 (n=1241)	P value	IC1 (n=183)	IC2 (n=488)	IC3 (n=862)	P value
Age, years, median (IQR)	55 (41-66)	53 (40-64)	55 (43-66)	0.03	52 (40-65)	51 (38-62)	54 (41-64)	0.008
Male(%)	113 (38.3)	223 (31.7)	336 (27.1)	<0.001	67 (36.6)	135 (27.7)	194 (22.5)	<0.001
Race								
Chinese (%)	216 (73.2)	493 (70.1)	815 (65.7)	<0.001	135 (73.8)	320 (65.6)	547 (63.5)	<0.001
Malay (%)	17 (5.8)	67 (9.5)	165 (13.3)		8 (4.4)	52 (10.7)	120 (13.9)	
Indian (%)	41 (13.9)	78 (11.1)	114 (9.2)		26 (14.2)	72 (14.8)	89 (10.3)	
Other (%)	21 (7.1)	65 (9.2)	147 (11.8)		14 (7.7)	44 (9.0)	106 (12.3)	
Unemployed (%)	109 (36.9)	269 (38.3)	584 (47.1)	<0.001	59 (32.2)	175 (35.9)	393 (45.6)	<0.001
Comorbidities								
Cancer (%)	10 (3.4)	28 (4)	42 (3.4)	0.78	4 (2.2)	11 (2.3)	23 (2.7)	0.86
CVD (%)	20 (6.8)	38 (5.4)	80 (6.4)	0.59	7 (3.8)	18 (3.7)	50 (5.8)	0.17
Diabetes mellitus (%)	14 (4.7)	45 (6.4)	75 (6)	0.60	9 (4.9)	33 (6.8)	45 (5.2)	0.45
Hypertension (%)	14 (4.7)	44 (6.3)	74 (6)	0.64	7 (3.8)	25 (5.1)	44 (5.1)	0.75
Anti-hypertensive drugs (%)	70 (23.7)	180 (25.6)	385 (31.1)	0.03	41 (22.4)	117 (23.9)	277 (32.2)	0.003
CKD (%)	9 (3.1)	16 (2.3)	35 (2.8)	0.71	5 (2.7)	8 (1.6)	17 (2.0)	0.66
Rheumatological diagnosis*								
IA (%)	98 (33.2)	243 (34.6)	380 (30.6)	0.25	94 (51.4)	245 (50.2)	382 (44.3)	0.01
CTD (%)	51 (17.3)	154 (21.9)	272 (21.9)		49 (26.8)	155 (31.8)	273 (31.7)	
Crystal arthritis (%)	24 (8.1)	51 (7.3)	90 (7.3)		-	-	-	
Non-Inflammatory (%)	67 (22.7)	126 (17.9)	233 (18.8)		-	-	-	
Medications								
Nil IS (%)	98 (33.2)	220 (31.3)	381 (30.7)	0.27	20 (10.9)	62 (12.7)	102 (11.8)	0.19
HCQ alone (%)	16 (5.4)	69 (9.8)	129 (10.4)		14 (7.7)	71 (14.5)	129 (15.0)	
IS including csDMARD (%)	138 (46.8)	315 (44.8)	579 (46.7)		133 (72.7)	320 (65.6)	579 (67.2)	
bDMARD or tsDMARD (%)	16 (5.4)	34 (4.8)	45 (3.6)		16 (8.7)	32 (6.6)	47 (5.5)	
Gout medications (%)	27 (9.2)	65 (9.2)	107 (8.6)		-	-	-	

*unknown = 450

CTD: Connective tissue disease, includes systemic lupus erythematosus, immune mediated inflammatory myositis, systemic sclerosis, systemic vasculitis, sjogren's syndrome, mixed connective tissue disease, undifferentiated CTD

IA: Inflammatory arthritis, includes rheumatoid arthritis, psoriatic arthritis, axial and peripheral spondyloarthropathy, juvenile idiopathic arthritis, adult onset still's disease and undifferentiated inflammatory arthritis.

Non-inflammatory: includes primary antiphospholipid syndrome, osteoarthritis, osteoporosis, fibromyalgia, soft tissue rheumatism and miscellaneous conditions

C1, C2, C3: Cluster 1, 2, 3; CVD: cardiovascular disease, CKD: chronic kidney disease, HCQ: hydroxychloroquine, IS: immunosuppressant, csDMARD: conventional synthetic disease modifying anti-rheumatic drug, bDMARD: biologic disease modifying anti-rheumatic drug, tsDMARD: targeted synthetic disease modifying anti-rheumatic drug, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, NSAID: non-steroidal anti-inflammatory drug, COXIB: cyclooxygenase-2 inhibitor