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Knowledge and Perceptions of Reactive Arthritis Diagnosis and Management Among Healthcare Workers During the COVID-19 Pandemic: Online Survey

Dana Bekaryssova,[1] **Mrudula Joshi**,[2] **Latika Gupta**,[3,4,5,6] **Marlen Yessirkepov**,[1] **Prakash Gupta**,[7] **Olena Zimba**,[8] **Armen Yuri Gasparyan**,[9] **Sakir Ahmed**,[10] **George D. Kitas**,[9,11] **and Vikas Agarwal** [3]

[1]Department of Biology and Biochemistry, South Kazakhstan Medical Academy, Shymkent, Kazakhstan
[2]Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, India
[3]Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
[4]Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK
[5]Department of Rheumatology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
[6]Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, The University of Manchester, Manchester, UK
[7]Virgen Milagrosa University Foundation College of Medicine, San Carlos City, Pangasinan, Philippines
[8]Department of Internal Medicine #2, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
[9]Departments of Rheumatology and Research and Development, Dudley Group NHS Foundation Trust (Teaching Trust of the University of Birmingham, UK), Russells Hall Hospital, Dudley, UK
[10]Department of Clinical Immunology and Rheumatology, Kalinga Institute of Medical Sciences (KIMS), KIIT University, Bhubaneswar, India
[11]Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK

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Address for Correspondence:
Sakir Ahmed, MD
Department of Clinical Immunology and Rheumatology, Kalinga Institute of Medical Sciences (KIMS), KIIT University, Kushabhadra Campus, 5, KIIT Road, Bhubaneswar 751024, India.
Email: sakir005@gmail.com

Vikas Agarwal, MD
Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, New PMSSY Rd, Raebareli Rd, Lucknow 226014, India.
Email: vikasagr@yahoo.com

ORCID iDs
Dana Bekaryssova
https://orcid.org/0000-0002-9651-7295
Mrudula Joshi
https://orcid.org/0000-0001-7312-351X
Latika Gupta
https://orcid.org/0000-0003-2753-2990
Marlen Yessirkepov
https://orcid.org/0000-0003-2511-6918

ABSTRACT

Background: Reactive arthritis (ReA) is an often neglected disease that received some attention during the coronavirus disease 2019 (COVID-19) pandemic. There is some evidence that infection with severe acute respiratory syndrome coronavirus 2 can lead to "reactive" arthritis. However, this does not follow the classical definition of ReA that limits the organisms leading to this condition. Also, there is no recommendation by any international society on the management of ReA during the current pandemic. Thus, a survey was conducted to gather information about how modern clinicians across the world approach ReA.
Methods: An e-survey was carried out based on convenient sampling via social media platforms. Twenty questions were validated on the pathogenesis, clinical presentation, and management of ReA. These also included information on post-COVID-19 arthritis. Duplicate entries were prevented and standard guidelines were followed for reporting internet-based surveys.
Results: There were 193 respondents from 24 countries. Around one-fifth knew the classical definition of ReA. Nearly half considered the triad of conjunctivitis, urethritis and asymmetric oligoarthritis a "must" for diagnosis of ReA. Other common manifestations reported include enthesitis, dermatitis, dactylitis, uveitis, and oral or genital ulcers. Three-fourths opined that no test was specific for ReA. Drugs for ReA were non-steroidal anti-inflammatory drugs, intra-articular injections, and conventional disease-modifying agents with less than 10% supporting biological use.

Prakash Gupta
https://orcid.org/0000-0002-1267-3769
Olena Zimba
https://orcid.org/0000-0002-4188-8486
Armen Yuri Gasparyan
https://orcid.org/0000-0001-8749-6018
Sakir Ahmed
https://orcid.org/0000-0003-4631-311X
George D. Kitas
https://orcid.org/0000-0002-0828-6176
Vikas Agarwal
https://orcid.org/0000-0002-4508-1233

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Author Contributions

Conceptualization: Bekaryssova D, Zimba O, Gasparyan AY. Formal analysis: Bekaryssova D, Joshi M, Gupta P, Ahmed S, Methodology: Bekaryssova D, Zimba O, Gupta L. Project administration: Zimba O, Ahmed S, Agarwal V. Supervision: Zimba O, Kitas GD, Agarwal V. Writing - original draft: Bekaryssova D. Writing - review & editing: Bekaryssova D, Joshi M, Gupta L, Yessirkepov M, Gupta P, Zimba O, Gasparyan AY, Ahmed S, Kitas GD, Agarwal V.

Conclusion: The survey brought out the gap in existing concepts of ReA. The current definition needs to be updated. There is an unmet need for consensus recommendations for the management of ReA, including the use of biologicals.

Keywords: Reactive Arthritis; Post-Infectious Arthritis; COVID-19; Definition; Treatment; Surveys and Questionnaires

INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) has set up new challenges in the management of persons with chronic diseases such as rheumatological disorders.[1,2] Various registries and surveys have helped provide real-world data on patients with rheumatic diseases. Analysis of data from electronic record databases and other registries has shown that COVID-19 outcomes are usually poorer in patients with rheumatic diseases.[3-7] However, the bulk of this data is limited to patients having common rheumatic diseases like rheumatoid arthritis, spondyloarthritis (SpA), systemic lupus erythematosus, or psoriatic arthritis. There is some evidence that patients with SpA may have better outcomes with COVID-19.[8] However, limited information is available about reactive arthritis (ReA) during the pandemic.

The classical definition of ReA encompasses arthritis that occurs around 2–4 weeks after a genitourinary or enteric infection and with no direct infection in the primary joint structures.[9-11] It is a sub-type of SpA. Arthritis occurs as a result of immune-mediated changes rather than the direct invasion of the joints by any pathogen.[12] Several pathognomonic features are sacroiliitis, uveitis, dactylitis or enthesitis. The presence of the HLA-B27 gene or a family history of SpA, psoriasis, or uveitis helps to categorize a patient as having ReA.[13] In countries where ReA is not commonly diagnosed, it may be misclassified as peripheral oligoarthritis or even psoriatic arthritis.[14]

ReA is prevalent in lower-income countries. In contrast, it is not so much known in Eastern Europe and Central Asia. Worldwide it is thought that the incidence of ReA is declining. However, it is still encountered in developing countries where infections are common. Several questions remain unanswered about the patterns of ReA worldwide, in the background of wider antibiotic use and immunosuppressants. HIV-related infections are on the rise globally and these also seem to play a role in the pathogenesis of ReA as a direct arthritogenic agent or causing immune dysfunction and deregulation in the production of cytokines predisposing to infection by other arthritogenic pathogens.[15,16]

Generally, COVID-19 presents with mild to modest musculoskeletal symptoms such as arthralgia and myalgia. It does not typically cause clinical arthritis. The pattern of profound inflammation and generation of pro-inflammatory cytokines is similar between COVID-19 and ReA.[17] The introduction of the term "post-COVID ReA" has led to many new questions.[10] Also, ReA after COVID-19 vaccination has been reported.[18] After the COVID-19 pandemic, the emergence of this "post-COVID-19 ReA" has raised an important question of whether we must persist with the traditional definitions of ReA or update it to include more diverse entities. There is a burning need to allow or disallow arthritides occurring after emerging infections to be called ReA. The controversies brought forth in ReA by the pandemic are best summarized elsewhere.[19]

The focus is particularly on therapeutic cytokine inhibition to counteract the pathological hyper-inflammatory disease state. However, none of the rheumatology societies or such international organizations has advised on the management of ReA during the current pandemic. Therefore, this survey was conducted to look at the patterns of ReA encountered by rheumatology practitioners and understand their choices, especially in the context of the COVID-19 pandemic.

METHODS

This survey was devised to cover the current knowledge and perceptions of healthcare workers (HCWs) regarding ReA diagnosis and management amidst the COVID-19 pandemic. An online platform (SurveyMonkey.com) was used to carry out the survey.

Survey design

The survey was designed to obtain information about the understanding of pathogenesis and specific features of ReA (arthritis, dactylitis, enthesitis, conjunctivitis, uveitis, oral and/or genital ulcers, sacroiliitis), clinical presentation, common test practices used for diagnosis, presence of preceding infection (urogenital, gastrointestinal and respiratory), the time interval between triggering infection and onset of arthritis and commonly used management strategies in ReA patients. The survey also obtained information regarding arthralgia and/or arthritis cases post COVID-19 infection and changes in ReA incidence over time as experienced by HCWs in their practice.

Three experts reviewed the questions over three rounds of discussion to finalize the wording and ensure content validity. The third round included dummy fill-ups of the online form to have a real feel. After finalization, the survey included 20 questions, of which 18 were multiple choice questions with a single answer to be chosen for 13 and multiple answers allowed for five questions. The two remaining questions needed numerical value entry only.

The respondents could change the answers before submission but not after it. All questions were made mandatory, such that partial responses were automatically discarded by the SurveyMonkey platform.

Sampling strategy

We employed a convenient sampling strategy. The questionnaire was circulated on social media platforms like Twitter and Facebook between 6th October 2021 and 23rd January 2022. The survey began with an informed consent document with all information pertaining to the survey mentioned therewith.

The survey link was open from the time the survey link was circulated on social media. The cover letter included details on the background and purpose of the study. Informed consent was taken at the beginning of the survey and no incentives were offered for survey completion.

Statistical analysis

The normality of data was checked by the Shapiro-Wilk test. Mostly descriptive statistics are presented. For graphical representations, Microsoft Excel (Microsoft, Redmond, WA, USA) was used to build figures. Chi-square tests were used to compare responses between groups.

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Results were considered to be significant at a *P* value of < 0.05. Statistical analysis was performed also using Microsoft Excel.

Confidentiality

The survey was partly anonymised with Internet Protocol (IP) addresses and emails of respondents being the only linked identifiers. These identifiers were used to ensure unique entries from each individual. Data handling was completely anonymous, with the IP addresses and email lists remaining with the first and corresponding author. Other authors had access to the synthesized data in tables without linked identifiers.

Ethics statement

Full ethics review was exempted by the Institutional Ethics Committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow (protocol number 2021-299-IMP-EXP-44). We adhered to our recommendations on online surveys during the COVID-19 pandemic[20] and the Checklist for Reporting Results of Internet E-surveys to report the data.[21]

RESULTS

Out of a total of 193 respondents, nearly half (88, 45.6%) were adult rheumatologists followed by general practitioners (24, 12.4%). Nearly one-third lived in Kazakhstan (59, 30.6%) followed by Turkey (41, 21.2%). There were responses from 22 other countries also. A detailed description of the demographics of the respondents is presented in **Table 1**.

Presenting features of ReA

More than half (123, 63.7%) of the respondents were aware of the definition of ReA along with its origin, with nearly one-third (42, 21.8%) knowing the definition. Based on observations in clinical practice, the period between contracting the infection and presenting with ReA was reported to be more than two weeks in nearly half the cases (99, 51.3%) (**Fig. 1**). Urogenital (140, 72.5%) and gastrointestinal (121, 62.7%) system infections were among the majority to precede ReA (**Fig. 2**). Nearly half of the respondents reported that the triad of conjunctivitis (81, 42.0%), urethritis (87, 45.1%), and asymmetric oligoarthritis (108, 56.0%) were the classic clinical presentation signs of ReA. More than one-third (76, 39.4%) reported dermatitis in addition to the classical triad (**Fig. 3**). Among the specific features of ReA, nearly three-fourths (141, 73.1%) reported mono or oligoarthritis predominantly in the lower limbs, followed by asymmetric oligoarthritis (136, 70.5%), conjunctivitis (122, 63.2%) and enthesitis (pain or tenderness at the insertion of the Achilles tendon or plantar fascia) (97, 50.3%) (**Fig. 4**).

Diagnosis of ReA

Among the tests employed to examine ReA patients in order to reach a diagnosis, C-reactive protein (132, 68.4%) was the most commonly used modality followed by a test for Chlamydia trachomatis (120, 62.2%), Joints imaging/ultrasonography (affected joints and sacroiliac joints) (118, 61.1%), HLA-B27 (116, 60.1%) and others. However, nearly three-fourths (138, 71.5%) reported that there are no specific tests for the diagnosis of ReA.

Treatment of ReA

Non-steroidal anti-inflammatory drugs were the most commonly (162, 83.9%) used drug for the management of ReA in practice settings, followed by Intraarticular corticosteroid injections (79, 40.9%), Methotrexate and other disease-modifying antirheumatic drugs (78, 40.4%) and others.

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Table 1. Baseline demographics

Variables	Response
Specialty	
Adult rheumatologist	88 (45.6)
Paediatric rheumatologist	6 (3.1)
Rheumatology nurse specialist	3 (1.6)
Resident	23 (11.9)
Intern	6 (3.1)
General practitioner	24 (12.4)
Internal medicine specialist	12 (6.2)
Other	31 (16.1)
Years in medical practice after graduation	
0–10	89 (46.1)
11–20	57 (29.5)
21–30	23 (11.9)
31–40	14 (7.3)
> 40	10 (5.2)
Practice setting	
Private clinic	36 (18.7)
Public clinic	65 (33.7)
Both private and public clinics	18 (9.3)
Teaching hospital/outpatient setting	74 (38.3)
Country	
Kazakhstan	59 (30.6)
Turkey	41 (21.2)
India	14 (7.6)
Morocco	13 (6.7)
Croatia	11 (5.7)
Age	
18–25	29 (15.0)
26–35	67 (34.7)
36–45	54 (28.0)
46–55	27 (14.0)
56–65	14 (7.3)
> 65	2 (1.0)
Gender	
Female	77 (39.9)
Male	78 (40.4)
Not specified	38 (19.7)

Values are presented as number (%).

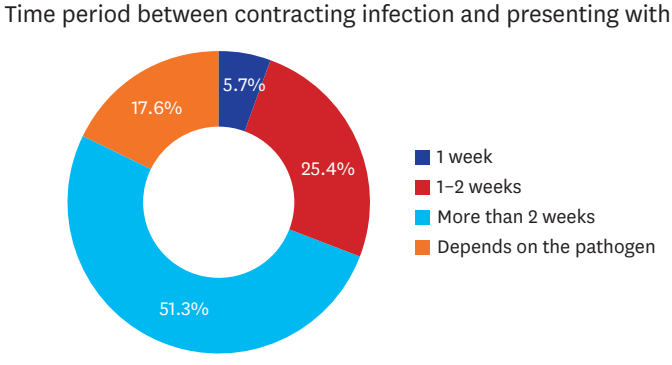

Fig. 1. Time period between contracting infection and presenting with ReA.
ReA = reactive arthritis.

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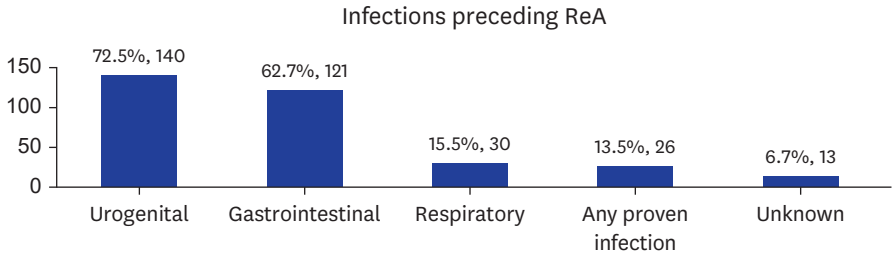

Fig. 2. Infections preceding ReA. Y axis depicts the number of respondents.
ReA = reactive arthritis.

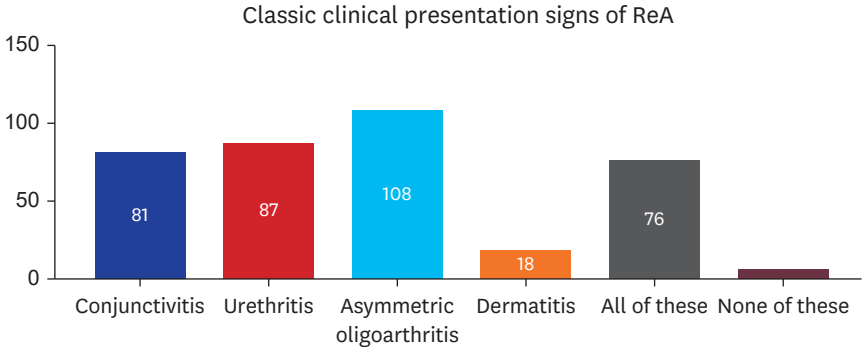

Fig. 3. Classic clinical presentation signs of ReA. Y axis depicts the number of respondents.
ReA = reactive arthritis.

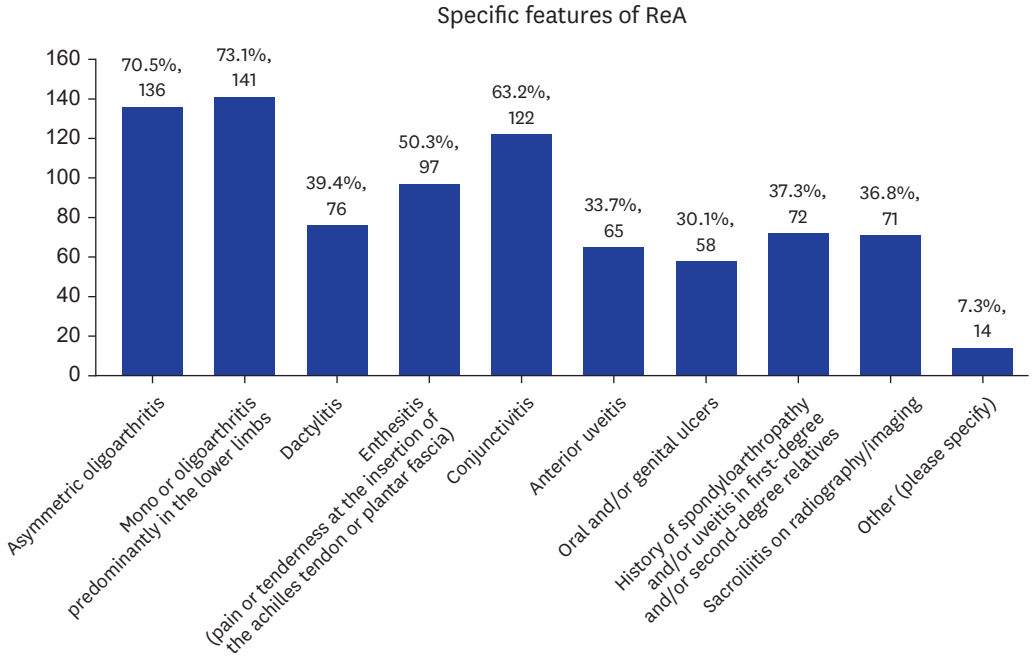

Fig. 4. Specific features of ReA. Y axis depicts the number of respondents.
ReA = reactive arthritis.

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Table 2 gives a detailed description of the Knowledge and perceptions of ReA diagnosis and management amidst the COVID-19 pandemic. **Table 3** gives a detailed description of the Knowledge and perceptions of ReA diagnosis and management in Kazakhstan and Turkey.

Table 2. Knowledge and perceptions of ReA diagnosis and management amidst the COVID-19 pandemic

Variables	Values
Presenting features	
Incubation period, wk	
1	11 (5.7)
1–2	49 (25.4)
≥ 2	99 (51.3)
Depends on the pathogen	34 (17.6)
Infections preceding ReA	
Urogenital	140 (72.5)
Gastrointestinal	121 (62.7)
Respiratory	30 (15.5)
Any proven infection	26 (13.5)
Unknown	13 (6.7)
Classic clinical presentation signs of ReA	
Conjunctivitis	81 (42.0)
Urethritis	87 (45.1)
Asymmetric oligoarthritis	108 (56.0)
Dermatitis	18 (9.3)
All of these	76 (39.4)
None of these	6 (3.1)
Other	3 (1.6)
Specific features of ReA	
Asymmetric oligoarthritis	136 (70.5)
Mono or oligoarthritis predominantly in the lower limbs	141 (73.1)
Dactylitis	76 (39.4)
Enthesitis (pain or tenderness at the insertion of the Achilles tendon or plantar fascia)	97 (50.3)
Conjunctivitis	122 (63.2)
Anterior uveitis	65 (33.7)
Oral and/or genital ulcers	58 (30.1)
History of spondyloarthropathy and/or uveitis in first-degree and/or second-degree relatives	72 (37.3)
Sacroiliitis on radiography/imaging	71 (36.8)
Other	14 (7.3)
Diagnosis of ReA	
Tests employed to examine ReA patients	
Clinical history and examination only	97 (50.3)
CRP	132 (68.4)
Uric acid in serum	59 (30.6)
Rheumatoid factor	89 (46.1)
Antinuclear antibodies	60 (31.1)
Antineutrophil cytoplasmic antibodies	37 (19.2)
HLA-B27	116 (60.1)
Test for anti-streptolysin O	63 (32.6)
Test for *Chlamydia trachomatis*	120 (62.2)
Test for *Mycoplasma*	62 (32.1)
Test for syphilis	62 (32.1)
Test for gonococcal infection	87 (45.1)
Test for HIV	59 (30.6)
Joints imaging/ultrasonography (affected joints and sacroilial joints)	118 (61.1)
Joint aspirate analysis	78 (40.4)
Other	8 (4.2)
Specific diagnostic tests employed	
Not sure	39 (20.2)
There are not any specific tests	138 (71.5)
Others	16 (8.3)

(continued to the next page)

Table 2. (Continued) Knowledge and perceptions of ReA diagnosis and management amidst the COVID-19 pandemic

Variables	Values
Treatment	
Commonly used treatment options for the management of ReA	
NSAIDs	162 (83.9)
Intraarticular corticosteroid injections	79 (40.9)
Oral corticosteroids	58 (30.1)
Intravenous (systemic) corticosteroids	21 (10.9)
Methotrexate and other disease-modifying antirheumatic drugs	78 (40.4)
Anti-TNF-alpha agents	15 (7.8)
Topical drug treatment	15 (7.8)
Joint support brace or tape	4 (2.1)
Other biologic agents	1 (0.5)
HCWs first preference as first line treatment for ReA	
NSAIDs	108 (56.0)
Intra-articular injections	6 (3.1)
A + B	51 (26.4)
Non-pharmacological only	2 (1.0)
Conventional synthetic disease-modifying antirheumatic drug (e.g., methotrexate, leflunomide, sulfasalazine, etc.)	17 (8.8)
Anti-TNF	4 (2.07)
Other	5 (2.6)
Subjects with persistent arthralgia and/or arthritis after recovering from COVID-19	
Yes	124 (64.3)
No	69 (35.8)
Online follow-up consultations/clinics for ReA patients	
Yes	64
No	129

Values are presented as number (%).
ReA = reactive arthritis, COVID-19 = coronavirus disease 2019, HIV = human immunodeficiency virus, CRP = C-reactive protein, NSAID = non-steroidal anti-inflammatory drug, TNF = tumor necrosis factor, HCW = healthcare worker.

DISCUSSION

This study aimed to identify the current knowledge and perceptions of HCWs regarding ReA diagnosis and management amidst the COVID-19 pandemic. The epidemiology of ReA has been evolving[15]and the COVID-19 pandemic has made it evolve further.

Nearly half of the survey respondents (88, 45.6%) were adult rheumatologists with up to 10 years of experience in medical practice after graduation (89, 46.1%). Nearly one-third of the respondents practised at a public clinic (65, 33.7%) and a teaching hospital/ outpatient setting respectively (74, 38.3%). The majority of the responses were from Kazakhstan (59, 30.6%) and Turkey (41, 21.2%).

ReA is inflammatory arthritis which manifests after several days to weeks after a genitourinary or gastrointestinal infection.[22] When the findings from Kazakhstan and Turkey are compared, we note that there is a significant difference in the percentage of respiratory infections preceding ReA, with the number of cases encountered being higher in Kazakhstan. It may point to the changing pattern in pathogens preceding ReA which could be a consequence of COVID-19 infection and its effects on individuals. Respondents from different parts of the world may be using different concepts or definitions of ReA.[23]

This perception of ReA occurring after respiratory infections is possibly the effect of the COVID-19 pandemic. ReA is often an orphan disease that may be neglected by physicians. However, the COVID-19 pandemic has brought it to the forefront.[24] Before this interest is lost, it

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Table 3. Knowledge and perceptions of ReA diagnosis and management in Kazakhstan and Turkey

Variables	Kazakhstan (n = 59)	Turkey (n = 41)	*P* value
Incubation period, wk			
1	10 (17.0)	0 (0)	0.002
1–2	11 (18.6)	10 (24.4)	0.827
≥ 2	19 (32.2)	27 (65.9)	0.238
Depends on the pathogen	19 (32.2)	4 (9.8)	0.002
Infections preceding ReA			
Urogenital	31 (52.5)	34 (82.9)	0.710
Gastrointestinal	20 (33.9)	34 (82.9)	0.057
Respiratory	13 (22.0)	4 (9.8)	0.029
Any proven infection	11 (18.6)	3 (7.3)	0.033
Unknown	7 (11.9)	0 (0)	0.008
Tests employed to examine ReA patients			
CRP	21 (35.6)	32 (78.1)	0.131
Uric acid in serum	22 (37.3)	9 (22.0)	0.020
Rheumatoid factor	32 (54.2)	18 (43.9)	0.048
Antinuclear antibodies	22 (37.3)	12 (29.3)	0.086
Antineutrophil cytoplasmic antibodies	21 (35.6)	5 (12.2)	0.002
HLA-B27	20 (33.9)	24 (58.5)	0.546
Test for anti-streptolysin O	27 (45.8)	9 (22.0)	0.003
Test for *Chlamydia trachomatis*	26 (44.1)	24 (58.5)	0.777
Test for *Mycoplasma*	19 (32.2)	9 (22.0)	0.059
Test for syphilis	23 (39.0)	8 (19.5)	0.007
Test for gonococcal infection	25 (42.4)	16 (39.0)	0.160
Test for HIV	12 (20.3)	10 (24.4)	0.670
Joints imaging/ultrasonography (affected joints and sacroiliac joints)	28 (47.5)	23 (56.1)	0.484
Joint aspirate analysis	14 (23.7)	21 (51.2)	0.237
Other	1 (1.7)	3 (7.3)	0.317
Commonly used treatment options for the management of ReA			
Non-steroidal anti-inflammatory drugs	38 (64.4)	38 (92.7)	1.000
Intraarticular corticosteroid injections	16 (27.1)	19 (46.3)	0.612
Oral corticosteroids	15 (25.4)	14 (34.2)	0.853
Intravenous (systemic) corticosteroids	19 (32.2)	1 (2.4)	-
Methotrexate and other disease-modifying antirheumatic drugs	18 (30.5)	16 (39.0)	0.732
Anti-TNF-alpha agents	3 (5.1)	1 (2.4)	0.317
Topical drug treatment	6 (10.2)	2 (4.9)	0.157
Joint support brace or tape	1 (1.7)	3 (7.3)	0.317
Other biologic agents	0 (0)	0 (0)	-
Subjects with persistent arthralgia and/or arthritis after recovering from COVID-19			0.115
Yes	28 (47.5)	26 (63.4)	
No	31 (52.5)	15 (36.6)	
Online follow-up consultations/clinics for ReA patients			0.641
Yes	18 (30.5)	8 (19.5)	
No	41 (69.5)	33 (80.5)	

Values are presented as number (%).
ReA = reactive arthritis, COVID-19 = coronavirus disease 2019, HIV = human immunodeficiency virus, CRP = C-reactive protein, TNF = tumor necrosis factor.

is imperative to update the definitions of ReA so that physicians worldwide recognise this entity in the same conceptual framework. Several newer pathogens beyond severe acute respiratory syndrome coronavirus 2 are being implicated in the pathogenesis of ReA.[25] Nevertheless, there is no consensus on how to include newer pathogens in the definition of ReA.[13]

Among the tests employed to examine ReA patients, there was a significant difference between Kazakhstan and Turkey when it came to the following tests: serum urate levels, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, test for anti-streptolysin O and test for syphilis, all of which is used in higher numbers in Kazakhstan. This may suggest the change in aetiology and origin of ReA over the years. However, regardless of the infectious agent and diagnostic modality, there has been no difference observed in the treatment

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of ReA.[26] The management goals of ReA in terms of providing symptomatic relief and preventing chronic complications are still prevalent.

This study also highlights the lack of clarity and consensus regarding the diagnosis and care of ReA. This is not new and has been acknowledged even whenever attempts have been made to structure working definitions.[19,27] Expanding the definition of ReA requires input from all parts of the world and this survey contains perspectives from central Asia that are often missing in the literature.[28] Since it is a relatively uncommon disease, it requires well-defined hypotheses and planning to establish clinically relevant case definitions.[29]

The limitations of the study include the snapshot picture of the data captured during the pandemic period. The pattern and chronicity may change in the future. It is also limited by the fact that the relationship between COVID-19 and ReA was not studied in great detail.

This survey highlights the varied interpretations of ReA by different respondents and the lack of consensus in management, especially during the COVID-19 pandemic. This calls for a united international effort for experts in the field to get together and formulate and update current definitions of ReA.

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