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Clinical Differentiation Between COVID-19-associated Reactive Arthritis and Urogenital Etiology Classic Reactive Arthritis

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Abstract To evaluate clinical differences between reactive arthritis associated with COVID-19 and urogenital etiology. **Materials and methods.** The study included 195 patients. The first group consisted of 135 patients who had suffered COVID-19, the second group consisted of 60 patients with reactive arthritis of urogenital etiology. General clinical, laboratory and instrumental studies of patients were assessed. **Results.** It was found that the average age of patients in the first group is 1.45 times greater than in the second. In the study participated more women than men: in the first group there were 1.8 times more women than men. In contrast, in the second group there were 1.4 times more men than women. In the first group, the disease manifests predominantly in a polyarticular form, and in the second group - in a mono- or oligo-articular form. **Conclusion.** Reactive arthritis associated with COVID-19 occurs primarily in older adults, is relatively more common in women, and tends to be poly-articular form.

Keywords COVID-19, Reactive arthritis, COVID-19 associated reactive arthritis, Urogenital etiology, Monoarthritis, Oligoarthritis, Polyarthritis, SARS-CoV-2 IgG

1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus [5]. SARS-CoV-2 affects people of all ages. However, patients older than 60 years and those with comorbid conditions are more likely to develop severe disease [3]. As with other respiratory diseases, patients with COVID-19 may experience various clinical symptoms in the musculoskeletal system. Arthralgia has been reported in more than 15% of patients with COVID-19, and myalgia in more than 45%. However, scientists have also emphasized that the extent of musculoskeletal damage is not related to the course and severity of COVID-19 [9]. However, the COVID-19 virus can trigger the production of various antibodies and cytokines in the body [15], and in patients with severe disease, autoantibodies against host cells may develop [14].

There is also information about various diseases associated with COVID-19, such as antiphospholipid syndrome, myositis, and systemic lupus erythematosus. Recent research also investigates the development of reactive arthritis in COVID-19 patients.

In their article, musculoskeletal injury in COVID-19: in Images, Chicago scientists studied muscles, nerves, joints, soft tissues, and bones using MRI, CT, and musculoskeletal ultrasound [8]. While signs of edema, necrosis, and atrophy were found in muscles, synovitis, and sometimes erosions were found in joints, hematoma, gangrene, COVID-finger, atypical ulcers, and signs of osteonecrosis and osteoporosis were found in soft tissues [9]. The most common symptom of the musculoskeletal system due to COVID-19 is myalgia, which is detected in almost 50% of patients [6]. Muscle damage is considered an important factor in the morbidity and mortality associated with RA [10]. Scientific sources from Indian scientists have highlighted the widespread involvement of the bone and joint system in COVID-19, similar to viral arthralgia [13]. Even after recovery from COVID-19, 27% of patients continued to have persistent joint pain [2].

Post-COVID-19 disease has been associated with a high incidence of inflammatory arthritis. Ursini et al. reported that 51% of patients had asymmetric monoarthritis or oligoarthritis. Of these, 20% had RA-specific features and 11% had persistent axial symptoms [12]. Jacoppo et al. have suggested that post-COVID-19 syndrome may be a trigger for the development of inflammatory arthritis [4]. Some sources indicate that COVID-19 and its vaccine can also induce inflammatory arthritis [12] and various less severe systemic diseases such as vasculitis, Still's disease, and dermatomyositis [1].

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Three articles compared the clinical presentation, course, and laboratory parameters of COVID-19-associated reactive arthritis with arthritis of urogenital etiology.

2. Material and Methods

The study was conducted in 2020-2024 at the Multidisciplinary Clinic of the Tashkent Medical Academy with the participation of patients who received inpatient and outpatient treatment in the departments of internal rehabilitation, rheumatology, cardiorheumatology and the Republican Rheumatology Center IADK. The study was carried out with a total of 195 participants. 135 patients with varying degrees of severity of COVID-19 and joint syndrome were selected for the study, and 60 patients with urogenital etiology diagnosed with ReA were chosen as the main group for comparison.

One specific criterion for selecting patients for the study of joints in patients with COVID-19 was the presence of various degrees of severity of COVID-19 and joint syndrome after the disease, and the absence of other rheumatic diseases before being selected for the study.

To confirm that patients with joint syndrome had been infected with COVID-19 and that joint syndrome was caused by SARS-CoV, SARS-CoV-2 IgG antibodies were detected in the blood serum. Patients with this antibody were included in the study. In group 2 patients, the detection of IgG to chlamydia and ureaplasma was one of the main criteria for confirming reactive arthritis of urogenital etiology. In addition, when selecting patients for the study of joint syndrome in patients with COVID-19, patients were excluded from the study in the following cases: with a history of other rheumatic diseases; patients with serologically positive results for chlamydia, ureaplasma, hepatitis B, C, AIDS; patients with positive serological markers such as RO, anti-ASSP, ANCA, ANA; patients with psoriasis or inflammatory bowel disease on examination or in history.

Thus, patients aged 18-70 were selected for the study. Women who had recently given birth and were pregnant, patients with severe and very severe chronic heart, kidney, and liver failure, and patients with unstable general conditions were excluded from the study. In addition, patients receiving genetically engineered biological drugs (infliximab, adalimumab, etanercept, IL-17 inhibitors secukinumab, ixekizumab) and synthetic antirheumatic drugs (sulfasalazine, methotrexate, leflunomide, azathioprine) were also excluded from the study.

Clinical, laboratory and instrumental examination methods were used in the general examination of patients. In the general clinical examination, the intensity of pain in the joints and the duration of morning stiffness were assessed using a visual analogue scale. Joint syndrome was assessed by the number of swollen joints, the number of painful joints. Laboratory examination methods included a complete blood and urine analysis, biochemical blood analysis, IgG chlamydia, ureaplasma; acute phase reactions: C-reactive protein (C-RP), rheumatoid factor - RF and ACCP, ANA (antinuclear antibody) to determine the presence of COVID-19 - IgG SARS-COV-2 was determined.

3. Results and Discussion

The average age of the patients participating in the study was 46.25±7.6 (min-20, max-70 years). Group 1 patients were found to be 1.18 times larger than the general group and 1.45 times larger than group 2 patients (Figure 1).

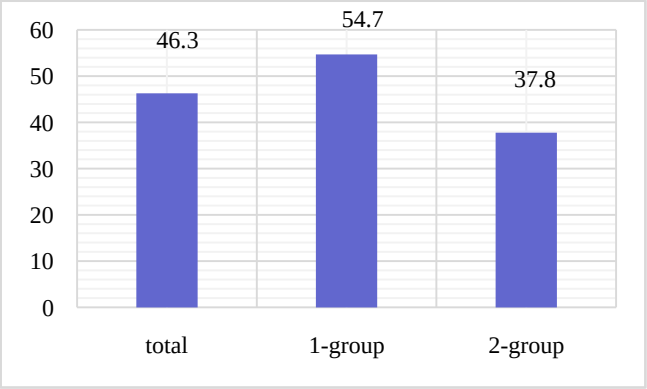

Figure 1. Average age of patients participating in the study, years

The figure above shows that in patients with COVID-19, joint syndrome was mainly found in older people compared to ReA. In group 1, the mode was 51 years old, and the median was 48 years old. Typically, ReA occurs in the population aged 18-40 years, with a peak rate at 20-29 years. When the gender difference was studied in the study, the ratio of men to women was 42.5% of the patients were men and 57.5% were women, with women being 1.35 times more common (Figure 2).

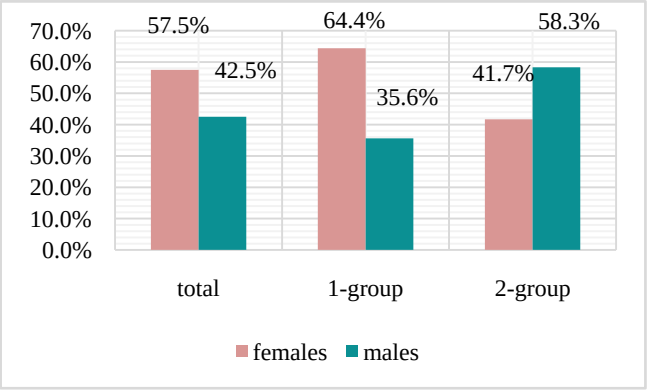

Figure 2. Gender ratio of patients participating in the study

As can be seen from the figure above, the proportion of women in the study was significant, with 1.8 times more women in Group 1. On the contrary, Group 2 had 1.4 times more men than women. The average duration of the joint syndrome ranged from 5 to 42 weeks. When analyzing the severity of COVID-19 in Group 1 patients, 63.7% of patients had mild disease, 27.4% had moderate disease, and 8.9% had severe disease (Figure 3).

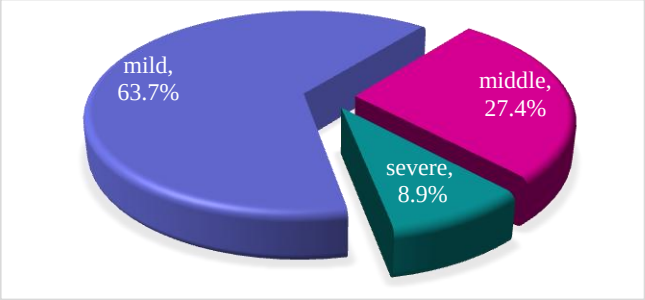

Figure 3. Severity of COVID-19 by patient

As can be seen from the figure above, 2/3 of the patients had a mild course of the disease, and almost all patients had symptoms such as fever, sore throat, and varying degrees of loss of smell and taste. These patients were treated at home. Patients with moderate and severe COVID-19 had symptoms of pneumonia of varying degrees along with the above symptoms and were treated in a hospital setting. Patients in group 2 did not have clear information about their COVID-19 infection, and the blood of these patients was negative for SARS-CoV-2 IgG.

The study analyzed the course of the disease by the type of joint damage (Figure 4).

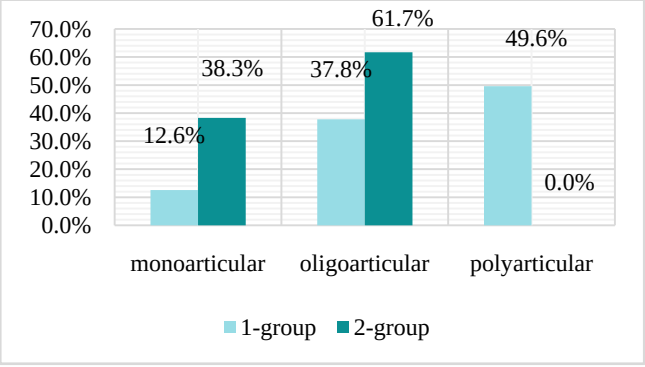

Figure 4. Patterns of progression of reactive arthritis in patients

The figure above shows that in group 1, COVID-19-associated reactive arthritis was predominantly oligo-polyarticular, while in group 2, reactive arthritis of urogenital etiology was predominantly mono-oligoarticular. Interestingly, the polyarticular form was detected only in group 2.

Disease activity was assessed by determining the VAS scale, duration of morning stiffness, number of swollen joints, and number of painful joints in patients (Table 1).

Table 1. Assessment of disease activity

№	Parameters	1-group n=135	2-group n=60
1	VAS, mm	7.34±1.76	5.2±2.4
2	Duration of morning stiffness, minutes	18.6±1.48	13.8±1,53*
3	Number of swelling joints	6.1±1.35	4.3±1.72
4	Number of painful joints	6.3±1.64	4.9±1.52
Note: The level of reliability of the difference when comparing groups 1 and 2:* -r<0.05, ** -or<0.01, *** -or<0.001			

The table shows that although all parameters differed between the groups, only the duration of morning stiffness was statistically significant.

The study determined the generally accepted laboratory parameters, but no significant differences were found between these laboratory parameters between the groups.

4. Conclusions

It is well known that arthritis of urogenital etiology occurs in a relatively young age group, affects men more often, and the disease has a mono-oligoarticular course. On the contrary, COVID-19-associated reactive arthritis occurs mainly in the elderly population, predominantly affects women, and has a tendency to polyarticular course, which is different from reactive arthritis of urogenital etiology in terms of its manifestation and course.

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