

ANNOTATION

**to the dissertation work of Ruskaya-Moroshan K.S. on the topic:
"Comprehensive assessment of risk factors and outcomes of coronavirus
infection in patients with a rheumatological profile during the pandemic in
Astana" submitted for the academic degree of Doctor of Philosophy (PhD) in
the specialty 8D10102 - "MEDICINE"**

Research Relevance. On January 30, 2020, the World Health Organization declared the outbreak of SARS-CoV-2 a public health emergency of international concern. Despite the official end of the pandemic, SARS-CoV-2 continues to cause new cases of infection, highlighting the ongoing relevance of COVID-19 and the need for further study of its impact on different population groups. COVID-19 acts as a "catalyst" for autoinflammatory processes of immune-inflammatory rheumatic diseases (IIRDs) due to the disruption of immune regulatory mechanisms, leading to a more severe course of infection, an increased risk of post-infectious exacerbations, or the emergence of new autoimmune phenomena [Nasonov E.L. et al., 2020]. According to meta-analyses [Wang Q et al., 2021; Conway et al., 2022; Xu et al., 2021], patients with IIRDs have a higher risk of severe disease progression and mortality from COVID-19. Rheumatic diseases per se are considered a risk factor for severe COVID-19 and present challenges in patient management [Roongta et al., 2020]. Another challenge is the regional variability in COVID-19 outcomes, influenced by epidemiological, climatic, and socio-demographic factors [Wang F. et al., 2022], which limits the direct extrapolation of international data to the Kazakhstani population of IIRDs patients and highlights the need for local studies. Unresolved questions regarding the course of IIRDs after COVID-19 remain worldwide, including the risk of chronic inflammation and post-infectious exacerbations.

Since the beginning of the pandemic, international expert communities have emphasized the importance of vaccination in the fight against COVID-19, however, IIRDs patients have not always been included in these studies, creating barriers to the widespread application of vaccination among this cohort in real-world clinical practice.

The disruption of mechanisms of innate, genetically determined, and acquired autoimmunity, accompanied by the development of chronic autoinflammation, underscores the relevance of studying the course of SARS-CoV-2 infection in patients with IIRDs. It also highlights the need to investigate COVID-19 in the context of its impact on the severity of the infectious process, the progression to chronic inflammation, the evaluation of vaccination opportunities in this patient population, and the development of optimized, personalized therapeutic strategies for rheumatology patients in the Republic of Kazakhstan. This dissertation research is aimed at addressing these aspects.

The Aim of the Study: to conduct a comprehensive analysis of the course and outcomes of COVID-19 in patients with IIRDs, considering risk factors for severe disease, the frequency and predictors of post-COVID exacerbations, as well as the assessment of the effectiveness and safety of vaccination against SARS-CoV-2.

Research Objectives

1. To study the structure of comorbid conditions in patients with IIRDs who have recovered from COVID-19.
2. To analyze the clinical course and outcomes of COVID-19 in rheumatology patients compared to the general population.
3. To identify and assess the significance of risk factors influencing the severity of COVID-19 in IIRDs patients.
4. To evaluate the dynamics of IIRDs progression in patients after COVID-19 in the post-pandemic period.
5. To analyze the frequency of COVID-19 vaccination and assess its safety profile in IIRDs patients.

Scientific Novelty. Based on a planned comprehensive study, for the first time in the Republic of Kazakhstan:

1. The clinical course of COVID-19 in IIRDs patients has been studied.
2. The frequency of hospitalization, oxygen therapy, and mechanical ventilation requirements in IIRDs patients with COVID-19 has been analyzed in comparison with the general population.
3. The impact of factors associated and not associated with rheumatic disease on the severe course of COVID-19 has been examined.
4. The dynamics of IIRDs progression after COVID-19 have been evaluated.
5. The effectiveness and safety of SARS-CoV-2 vaccines in a cohort of IIRDs patients have been investigated.

Theoretical and Practical Significance

For the first time in this geographic region, the clinical features of COVID-19 have been presented, and the long-term course of IIRDs following infection has been studied. Based on identified risk factors for IIRD exacerbations, a predictive model has been developed to assess the probability of subsequent exacerbations in IIRDs patients who have recovered from COVID-19. The identified risk factors for severe COVID-19 allow for timely prediction of adverse disease progression and the personalization of preventive measures.

The study has revealed a low level of vaccination among IIRDs patients, highlighting the need for increased attention from the healthcare system and medical institutions in promoting educational initiatives among both healthcare professionals and rheumatology patients. The importance of COVID-19 immunization for IIRDs patients has been emphasized.

Object of the study: 1. patients with IIRDs who have had COVID-19; 2. patients with IIRDs who received vaccination against SARS-CoV-2.

Subject of the study: 1. clinical characteristics of COVID-19 in patients with IIRDs; 2. risk factors for severe disease progression; 3. features of the post-COVID course of rheumatic diseases; 4. the effectiveness and safety of SARS-CoV-2 vaccination in this patient population.

Research methods. The study structure includes clinical, laboratory, instrumental, analytical, and statistical methods, as well as survey-based data collection. The mixed-methods study design included:

1. Retrospective case-control study – analysis of data from IIRDs patients who had COVID-19 (n = 140) and a control group without IIRD (n = 140).
 2. Retrospective-prospective cohort study – evaluation of IIRDs progression dynamics over 12 months following COVID-19 infection (n = 100).
 3. Retrospective cross-sectional study – assessment of vaccination rates, adverse events, and factors influencing vaccine refusal among IIRDs patients (n = 193).
- Statistical data processing was conducted using IBM SPSS STATISTICS (version 19).

The Main Provisions Submitted for Protection

1. Patients with IIRDs have an increased risk of severe COVID-19, characterized by higher rates of COVID-19-associated pneumonia, hospitalizations, and oxygen therapy.
2. Glucocorticoid use therapy (≥ 5 mg/day of prednisone-equivalent) and the presence of diabetes mellitus are significant risk factors for severe COVID-19 outcomes in rheumatology patients.
3. In Patients who have had coronavirus infection complicated by viral pneumonia and have comorbid conditions are at high risk of exacerbations of IIRD in the post-COVID period, requiring long-term monitoring.
4. Although COVID-19 vaccination demonstrates high efficacy and safety, its uptake remains low among patients with IIRDs, emphasizing the need for additional patient education and improved adherence to vaccination.

Conclusions

1. Among patients with IIRDs who had recovered from COVID-19, arterial hypertension (32.1% vs. 20.0%), lung diseases (16% vs. 9.3%), and diabetes mellitus (10.0% vs. 6.4%) were more frequently observed. The mean comorbidity index in the IIRD group was 6 points, which was higher than in the non-IIRD group (4 points).
2. At the onset of COVID-19, patients with IIRDs exhibited a higher frequency of musculoskeletal (up to 45.7%), respiratory, and intoxication syndromes (up to 43.6%). The most prevalent symptoms included arthralgia (45.7% vs. 26.4%, $p=0.001$), dyspnea (38.6% vs. 22.9%, $p=0.004$), and symptoms of irritability/depression (27.1% vs. 8.6%, $p<0.001$). CT-confirmed pneumonia occurred more frequently in the IIRD group (41.4% vs. 25.7%; $p<0.005$). The incidence of moderate, severe, and critical courses of SARS-CoV-2 infection was also higher (15.7% vs. 8.5%; $p=0.043$).
3. The risk of hospitalization due to COVID-19 was significantly higher in patients with IIRDs (25.7% vs. 7.8%; OR = 4.1; 95% CI: 2.0–8.4). Increasing age ($p=0.007$), glucocorticoid use at ≥ 5 mg/day prednisone equivalent ($p<0.001$), and longer duration of glucocorticoid therapy ($p<0.001$) were associated with an elevated risk of hospitalization. The use of biologic disease-modifying antirheumatic drugs (bDMARDs) was associated with a lower hospitalization rate ($p=0.011$).
4. Patients with COVID-19 and IIRDs more frequently required oxygen therapy (16.4% vs. 3.5%; $p=0.001$). Although the need for mechanical ventilation (3.5% vs. 1.4%) and the rate of complications (17.9% vs. 10.0%) were also higher in the IIRD

group, these differences did not reach statistical significance ($p = 0.447$ and $p = 0.085$, respectively).

5. According to the results of multivariate logistic regression analysis, the key risk factors for severe COVID-19 were diabetes mellitus and glucocorticoid use at doses ≥ 5 mg/day (prednisone equivalent).

6. The peak number of patients with high IIRD activity was observed at the 3-month follow-up mark — 51.0%. Exacerbations were more frequently recorded in patients with rheumatoid arthritis. The risk factors for experiencing two or more IIRD flares within one year after COVID-19 included COVID-19-associated pneumonia ($p=0.011$) and the presence of comorbid conditions ($p=0.024$).

7. Vaccination against SARS-CoV-2 in patients with IIRDs demonstrated high effectiveness (80.6%): all cases of subsequent infection were mild and resulted in full recovery.

8. Vaccination against SARS-CoV-2 showed a favorable safety profile: the overall incidence of post-vaccination adverse events was 66.7%, with 65.1% being mild. The only adverse event requiring medical assistance was a hypertensive crisis (1.6%). Subjective disease flares were reported by 24.2% of patients; however, no cases of objectively confirmed exacerbations were recorded.

Research results. In patients with IIRDs, COVID-19 tends to have a more severe course and more often requires hospitalization. Key risk factors for severe disease were identified. After recovery, a trend toward increased disease activity was observed. A prognostic model has been developed to assess the likelihood of IIRDs exacerbations in the post-COVID period. Despite the proven effectiveness and safety of vaccination, its coverage among this patient population remains low.

Practical Recommendations

1. Rheumatology patients with COVID-19 who receive GCs therapy ≥ 5 mg/day (prednisone equivalent) and those with diabetes mellitus should be considered high-risk for severe disease and require timely hospitalization and continuous monitoring in inpatient settings.

2. Patients who have had COVID-19, especially those with comorbid conditions and lung involvement due to coronavirus infection, require thorough clinical, laboratory, and instrumental monitoring, as well as treatment control, not only for 12 weeks but also for a significantly longer period—at least 12 months after recovering from COVID-19.

3. During periods of increased COVID-19 risk, GCs therapy in rheumatic patients should be minimized where possible, considering the clinical picture, to reduce the risk of severe infection.

4. COVID-19 immunization is recommended for patients with IIRDs, as vaccines have a high safety profile and reduce both the risk of infection and severe disease. Vaccination decisions should be individualized, taking into account disease activity and overall patient status, in close collaboration with the treating rheumatologist.

5. To integrate these recommendations into clinical practice, the development of local protocols is necessary to identify high-risk groups, optimize therapy, and increase vaccination rates among rheumatology patients.

Personal Contribution of the Author. The doctoral candidate independently conducted the planning of the research work, the collection of clinical material, the study of national and international scientific literature, the systematization, analysis, and interpretation of research data, as well as the writing and formatting of publications related to the study and the dissertation manuscript.

Validation of Dissertation Results. The dissertation materials were presented by the doctoral candidate at the 5th Congress of Rheumatologists of Kazakhstan "Rheumatology Today: Trends and Real Practice" (Almaty, September 29-30, 2022); the 9th Winter School of Rheumatologists of Kazakhstan and the Scientific and Practical Conference "Rheumatology of Kazakhstan: Achievements and Prospects. Continuity of Generations" (Almaty, December 2-3, 2022); the Congress of Therapists of Kazakhstan "Quality and Safety of Drug Therapy: Global Trends and Standards" (Astana, November 16-17, 2023); the 1st International Practical Conference "Astana Medical Forum 2024: Medicine of the Future – Integration of Science, Education, and Practice," dedicated to the 60th anniversary of Astana Medical University (Astana, October 14-15, 2024); and the International Scientific and Practical Conference "Progress in Rheumatology in 2024" (Moscow, December 5, 2024). The doctoral candidate also participated in English-language young scientist competitions. 1. The International Summit "Academy of the 21st Century: At the Forefront of Medical Education, Science, and Practice" (Astana, September 6-8, 2023). 2. Mid-term Symposium – APLAR 2024 and the 7th Congress of Rheumatologists of Kazakhstan (Almaty, April 26-27, 2024).

Publications on the Dissertation Topic. As a result of the study, eight scientific papers have been published: four in international peer-reviewed journals with an impact factor according to JCR, indexed in Web of Science Core Collection, Science Citation Index Expanded, Web of Science Core Collection (Clarivate Analytics), and Scopus; two in journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan; and one thesis in the proceedings of international conferences. Additionally, two author's certificates have been obtained.

Publications on the Dissertation Topic. The dissertation consists of 172 pages of computer-typed text and includes an introduction, three chapters (literature review, materials and research methods, original research results), a conclusion, summary of findings, practical recommendations, a reference list comprising 365 sources, and four appendices. The dissertation is illustrated with 17 figures and 26 tables.