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Research article

Mapping Early COVID-19 Clinical and Laboratory Profiles in Patients with Immune-Mediated Inflammatory Rheumatic Diseases: A Multicenter Case–Control Study

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Abstract: During the COVID-19 pandemic, patients with immune-mediated inflammatory rheumatic diseases (IMIRD) were placed in a "high-risk" category of poor outcomes because of chronic immune abnormalities and frequent comorbidities. Comparative data describing early clinical and laboratory findings in adults with and without IMIRD remain limited, particularly in Eastern Europe, and their relevance for early risk stratification and subsequent rehabilitation planning is insufficiently characterized. In this retrospective, multicenter case-control study, adults with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection admitted to three tertiary hospitals in Bucharest, Romania, were enrolled. Demographic, clinical, and baseline laboratory characteristics collected within the first 72 hours from symptom onset were compared between IMIRD patients (group A) and a control cohort (group B) without autoimmune diseases. COVID-19 severity was analyzed using univariable and multivariable ordinal logistic regression models, adjusting for age, sex, vaccination status, and comorbidity burden. 365 patients were included, of whom 211 had an IMIRD, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma (SSc), and axial spondyloarthritis (axSpA). In contrast with controls, IMIRD patients were predominantly female ($p < 0.001$), younger ($p = 0.012$), had higher vaccination rates ($p = 0.034$), and comorbidity burden ($p = 0.005$). In both univariable and multivariable analyses, IMIRD status was not independently linked to SARS-CoV-2 infection severity. This multicenter case-control study compares early clinical and laboratory features in IMIRD and non-IMIRD patients with COVID-19 in an underrepresented Eastern European setting. Early severity patterns may help identify patients at risk for post-acute functional problems. These findings support a thorough clinical assessment and rehabilitation-focused follow-up for IMIRD patients recovering from COVID-19.

Keywords: COVID-19, SARS-CoV-2, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, scleroderma, axial spondyloarthritis, case-control study, Physical and Rehabilitation Medicine, PRM

1. Introduction

SARS-CoV-2 infection has revealed considerable interindividual variability in clinical outcomes. Although notable progress has been made in apprehending its pathophysiology, it still, nowadays, constitutes a challenge to clarify how this infection manifests across different patient populations and clinical contexts [1–5] . At the population level, the COVID-19 pandemic temporarily reversed long-standing gains in life expectancy worldwide, underscoring the broad and heterogeneous impact of severe SARS-CoV-2 infection across age groups and health systems [6].

COVID-19 is very heterogeneous and can range from no symptoms to severe illness. Some demographic and clinical factors are linked to worse outcomes, but their impact is variable. Differences in age, comorbidity profiles, and healthcare organization reduce the applicability of results obtained in one setting to other clinical contexts, supporting the need for comparative analyses based on real-world data [7–11].

At the beginning of the COVID-19 pandemic, patients with IMIRD were considered at increased risk of poor outcomes. This assumption was mainly related to chronic immune dysregulation (caused by the disease itself and immunomodulatory treatments) and to cardiovascular and pulmonary comorbidities. Yet, follow-up evidence has been inconsistent, and several studies have failed to confirm a uniformly increased risk of severe disease or mortality. These results can indicate that COVID-19 severity in IMIRD adults may be influenced more by age, comorbidities, and early inflammatory response than by the underlying rheumatic disease itself [3,12–16].

Information from Eastern European countries remains limited, and regional factors that may influence COVID-19 outcomes in patients with IMIRD are still insufficiently described [17–20]. In addition, most published studies have focused on laboratory abnormalities recorded at later stages of hospitalization. In contrast, data describing clinical and laboratory findings at the time of initial presentation are relatively scarce, particularly in studies directly comparing IMIRD and non-IMIRD patients. Such early findings may nevertheless be relevant for clinical assessment and early risk evaluation [21,22].

From a Physical and Rehabilitation Medicine (PRM) standpoint, structured and advanced rehabilitation programs are not initiated during the acute phase of SARS-CoV-2 infection. However, in hospitalized patients with severe COVID-19 who are clinically stable, early bedside interventions are commonly recommended in order to limit complications related to a protracted period of immobilization and premature deconditioning. International recommendations from both European and American Societies support early, multidisciplinary, bedside rehabilitation interventions [23]. It is important to mention that for critically ill patients, interventions are generally limited to low-risk and preventive measures, such as positioning, passive range-of-motion, and secretion management. The transfer to dedicated rehabilitation settings is considered only once respiratory parameters are stable, radiological progression has been excluded, and no clinical deterioration is anticipated [24–26]. Recent clinical studies suggest that early bedside rehabilitation may be feasible and safe in selected hospitalized patients and may contribute to functional recovery [27]. In this context, early disease severity and inflammatory burden at presentation may be relevant for identifying patients at risk of subsequent functional decline and for planning post-acute follow-up [25,28].

Based on our previous analyses in patients with two of the most frequent IMIRD, namely RA [29,30] and axSpA [18], which consistently identified older age as a key determinant of COVID-19 severity and suggested disease-specific laboratory and comorbidity profiles, the present multicenter retrospective case-control study evaluated patients diagnosed with RA, axSpA, SLE and SSc who developed COVID-19 and compared them with a control cohort without autoimmune diseases evaluated in the same Romanian hospitals. The objectives of this study were to characterize, comparatively, the demographic, clinical, and laboratory profiles of these patients in the context of SARS-CoV-2 infection and to describe differences in COVID-19 severity across

groups within a real-world population. By focusing on an underrepresented Eastern European setting, this study aims to provide context-specific data on early severity patterns and clinical vulnerability relevant to both acute management and subsequent rehabilitation care.

2. Materials and Methods

2.1. Ethical Consideration

The present study was conducted in accordance with the Declaration of Helsinki and local regulations. Additionally, this study received approval from the Ethics Committee of the three hospitals where the research was conducted: "Bagdasar-Arseni" Teaching Emergency Hospital (No. 17071/17.04.2024), "Sfânta Maria" Clinical Hospital (No. 6655/21.03.2022), and Colentina Clinical Hospital (No. 19/18.07.2024). The patient data have been coded. All patients provided written informed consent to participate in the study, including consent for the General Data Protection Regulation (GDPR) and the use of electronically collected information exclusively for medical research.

2.2. Study Design and Objectives

This retrospective, multicenter, case-control observational study included adults with confirmed SARS-CoV-2 infection admitted to one of the three tertiary hospitals mentioned above in Bucharest, Romania, between 1 March 2020 and 31 December 2024.

Specifically, the study population, referred to as group A or IMIRD cohort, comprised 211 patients with RA, SLE, SSc, or axSpA. In contrast, a control cohort (group B) comprising 154 individuals with no other autoimmune or chronic inflammatory diseases was used for comparison. The control group was not individually or frequency matched to cases on any demographic or clinical variables. Together, the two cohorts comprised 365 patients with documented SARS-CoV-2 infection treated at the participating hospitals.

The main objective of the study was to compare demographic characteristics, clinical features, and paraclinical parameters between the two cohorts during the acute phase of COVID-19. In addition, the distribution of SARS-CoV-2 clinical severity was explored across the two groups.

To thoroughly characterize both cohorts, specific composite inflammatory indices were analyzed:

- Neutrophils-to-lymphocyte Ratio (NLR) = neutrophil count/lymphocyte count; widely used as a characteristic of systemic inflammation [21,31–34].
- Derived NLR (dNLR) = neutrophil count / (total leukocyte count – neutrophil count).
- Systemic Inflammation Response Index (SIRI) = (neutrophil count × monocyte count) / lymphocyte count, initially validated as a predictor of mortality in breast [35] and gastric cancers [36].
- Aggregate Index of Systemic Inflammation (AISI) = (neutrophil count × monocyte count × platelet count) / lymphocyte count [37–39].

To provide methodological robustness, the study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [40] (see Supplementary Table S1).

2.3. Eligibility Criteria

Adult patients (≥18 years) with confirmed SARS-CoV-2 infection were eligible for inclusion. COVID-19 diagnosis was established by reverse transcription polymerase chain reaction (RT-PCR) and/or rapid antigen testing [41].

For the IMIRD cohort, eligible patients had a documented diagnosis of RA, SLE, SSc, or axSpA, established by the treating physician. The control cohort consisted of patients with no history of IMIRD or other autoimmune conditions.

Clinical and paraclinical variables were limited to 72 hours following symptom onset to ensure robust comparability.

Exclusion criteria for both cohorts were: the presence of a concomitant infectious disease at presentation, except COVID-19; missing or unreliable data; and refusal to sign the informed consent.

Controls were retrospectively identified from the same hospitals and study period, based on fulfillment of eligibility criteria and the availability of clinical and laboratory data within the predefined 72-hour window from symptom onset.

As noted above, data were collected from the three involved hospitals using a standardized protocol.

All eligible patients who met the inclusion criteria during the study period were included in the analysis; thus, no a priori sample size calculation was performed.

2.4. Definition of COVID-19 severity

SARS-CoV-2 infection clinical severity was uniformly defined and used across both cohorts according to the World Health Organization (WHO) criteria, as outlined in the original guideline and applied in previous studies, including our previous work [18,30,42]. Based on these definitions, infection was classified into three ordered classes, consistently applied across both cohorts: mild (C1), moderate (C2), and severe or critical (C3) infection.

2.5. Data Sources and Variables

A standardized data collection protocol was used in each of the three hospitals, using the same forms and interview instruments. The information was obtained from patients' medical records, hospital databases, and, if necessary, from patients themselves through personal and through interviewing the patients personally and by phone after obtaining their prior informed consent. We collected and descriptively analyzed diverse variables, such as demographic, clinical, and laboratory data, as well as underlying conditions. Although laboratory analyses were performed at the respective hospital laboratories, all study sites used standard platforms with equivalent analytical methods and reference ranges, ensuring acceptable inter-center uniformity.

Statistical analyses were conducted on available case subsets for each variable, without imputing values to prevent causing artificial variability. The number of valid observations for every variable is reported in the respective tables.

2.6. Statistical Analysis

R software, version 4.4.1 [43], was used for all statistical analyses. Two-sided t tests and chi-squared tests or Fisher's exact tests, as appropriate, were used to compare continuous and categorical variables, respectively. Statistical significance was defined as a two-sided p-value < 0.05. Continuous variables were reported as mean ± standard deviation (SD), and categorical variables were expressed in absolute and relative frequencies (%).

For a formal comparison of SARS-CoV-2 severity between both cohorts, an ordinal logistic regression analysis was used. The outcome measure for these analyses was COVID-19 severity category (C1-C3), modeled as an ordinal variable, and cohort status (IMIRD vs non-IMIRD) was used as a single predictor. Additionally, to adjust for the differences between cohorts, a multivariable ordinal logistic regression model was designed. Covariates used included age, sex, vaccination status, and number of underlying conditions. The model's effectiveness was assessed by calculating Nagelkerke's R^2. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated. These analyses comprised a study population of 365 patients.

3. Results

3.1. Demographic and baseline characteristics

The IMIRD cohort (group A) comprised a total of 211 patients, of whom 90 (42.65%) had RA, 46 (21.80%) had axSpA, 45 (21.32%) had SLE, and 30 (14.21%) had SSc. The control cohort (group B) comprised a total of 154 patients with a range of other conditions (non-autoimmune). The sex ratio presented a significant difference ($p < 0.001$), with a large majority of females in group A (76%), as opposed to a fairly balanced sex ratio in group B, with 56% females and 44% males.

The mean age was significantly lower (p = 0.012) in group A (54 ± 14 years) than in group B (59 ± 16 years), and the difference in smoking was also significant, with group B having a higher percentage of smokers (24%) compared to group A (10%) (p < 0.001). Table 1 summarizes the observed data.

Table 1. Baseline demographic characteristics of the study population

Variable	Total (n = 365)	Group A (n = 211)	Group B (n = 154)	p-value
Sex, n (%)				<0.001
F	248 (68)	161 (76)	87 (56)	
M	117 (32)	50 (24)	67 (44)	
Age; Mean (SD)	56 (15)	54 (14)	59 (16)	0.012
Smoker n (%)				<0.001
Yes	58 (16)	21 (10)	37 (24)	
No	307 (84)	190 (90)	117 (76)	

3.2. Paraclinical findings

In the control group, a lower baseline oxygen saturation (SpO_2) at the onset of infection was observed (p = 0.031), which may be related to a higher proportion of smokers in this group. Additionally, this finding can indicate early respiratory distress in these patients.

Regarding baseline inflammatory parameters, the mean C-reactive protein (CRP) was 53±62 mg/L in group A and 46±64 mg/L in group B, with no statistically significant difference between the two populations (p = 0.38). In contrast, the levels of erythrocyte sedimentation rate (ESR) were significantly higher in the IMIRD cohort (44±33 mm/h) as compared to the control cohort (34±28 mm/h) (p = 0.04). This finding, however, should be interpreted cautiously, as ESR elevation indicates both acute and chronic inflammation (e.g., the presence of autoantibodies commonly encountered in patients with IMIRD). On the other hand, CRP is more specific to acute infection.

Composite inflammatory indices (NLR, SIRI, AISI, dNLR) exhibited similar values across groups, denoting a similar degree of systemic inflammatory activation at presentation. This result is further discussed in Section 4.

Patients in group A also had significantly lower fibrinogen levels (488±157 mg/dL) compared with those in group B (590±202 mg/dL) (p = 0.002). In the IMIRD cohort, serum D-dimer levels were higher (862±1219 ng/mL) than in the control cohort (514±953 ng/mL), with a difference that reached statistical significance (p = 0.045).

Table 2 summarizes the above-mentioned findings.

Table 2 – Paraclinical parameters assessed during acute SARS-CoV-2 infection – related to peripheral oxygenation, inflammation and coagulation variables

Variable	Total (N = 365)	Group A (N = 211)	Group B (N = 154)	p-value
SpO_2 (%), mean (SD)	**94.3 (6.2)**	**94.9 (5.9)**	**93.5 (6.6)**	**0.031**
Missing (n)	5	5	0	
CRP (mg/L), mean (SD)	49 (63)	53 (62)	46 (64)	0.38
Missing (n)	137	103	34	
ESR (mm/h), mean (SD)	**38 (30)**	**44 (33)**	**34 (28)**	**0.040**
Missing (n)	160	130	30	
Fibrinogen (mg/dL), mean (SD)	**541 (189)**	**488 (157)**	**590 (202)**	**0.002**

Missing (n)	241	152	89	
Procalcitonin (ng/mL), mean (SD)	0.57 (0.91)	0.41 (0.74)	0.64 (0.97)	0.13
Missing (n)	220	167	53	
D-dimer, mean (ng/mL) (SD)	**662 (1.084)**	**862 (1.219)**	**514 (953)**	**0.045**
Missing (n)	193	138	55	
NLR, mean (SD)	6.0 (7.9)	6.7 (9.4)	5.5 (6.6)	0.24
Missing (n)	112	103	9	
SIRI, mean (SD)	3.4 (4.45)	3.7 (4.77)	3 (4)	0.460
Missing (n)	112	103	9	
dNLR, mean (SD)	3.37 (3.98)	3.72 (4.38)	3.11 (3.64)	0.25
Missing (n)	112	103	9	
AISI, mean (SD)	861 (1282)	988 (1558)	766 (1025)	0.20
Missing (n)	112	103	9	

From a baseline hematologic perspective, individuals with IMIRD had lower mean hemoglobin levels (12.24±2.17 g/dL vs. 13.04±1.82 g/dL) and lower hematocrit levels (37.0±5.8% vs. 38.7±5.2%) compared with controls. Both differences were statistically significant ($p = 0.002$ and $p = 0.02$, respectively). These results may be attributable, at least in part, as inflammatory anemia is frequently observed in patients with active IMIRD. For other hematologic parameters, including absolute counts of leukocytes, lymphocytes, monocytes, and eosinophils, no statistically significant differences were observed between the two groups. Nonetheless, lymphocyte values tended to lie near or slightly below the lower limit of normal and monocyte counts showed a trend toward monocytopenia. Moreover, platelet counts were higher in group A (263±97 $\times 10^3/\mu L$) than in group B (240±97 $\times 10^3/\mu L$), although this difference did not achieve statistical significance ($p = 0.057$).

Regarding biochemical parameters, alanine aminotransferase (ALT) levels were lower in the IMIRD cohort (31±23 U/L) than in the control cohort (38±33 U/L), though the difference was marginally nonsignificant ($p = 0.057$). Interestingly, serum aspartate aminotransferase (AST) levels were identical. Serum creatinine values showed a tendency toward higher levels in group B (1.26±2.62 mg/dL) compared with group A (0.97±0.51 mg/dL), although this trend did not reach statistical significance.

Complete parameter-level data are presented in Table 3.

Table 3 – Paraclinical parameters assessed during acute SARS-CoV-2 infection – related to hematologic and biochemical variables

Variable	Total (N = 365)	Group A (N = 211)	Group B (N = 154)	p-value
Hemoglobin (g/dl), mean (SD)	**12.70 (2.01)**	**12.24 (2.17)**	**13.04 (1.82)**	**0.002**

Missing (n)	110	101	9	
Leukocytes (×10³/μL), mean (SD)	7.2 (3.6)	7.5 (3.8)	7.0 (3.4)	0.24
Missing (n)	111	101	10	
Lymphocytes (×10³/μL), mean (SD)	1.29 (0.78)	1.26 (0.75)	1.31 (0.80)	0.55
Missing (n)	110	101	9	
Neutrophils (×10³/μL), mean (SD)	5.2 (3.4)	5.6 (3.6)	4.9 (3.2)	0.15
Missing (n)	110	101	9	
Monocytes (×10³/μL), mean (SD)	0.62 (0.34)	0.60 (0.35)	0.63 (0.33)	0.40
Missing (n)	112	103	9	
Eosinophils (×10³/μL), mean (SD)	0.07 (0.10)	0.08 (0.12)	0.06 (0.09)	0.23
Missing (n)	112	103	9	
Hematocrit (%), mean (SD)	**38.0 (5.5)**	**37.0 (5.8)**	**38.7 (5.2)**	**0.020**
Missing (n)	112	103	9	
Platelets (×10³/μL), mean (SD)	*250 (97)*	*263 (96)*	*240 (97)*	*0.057*
Missing (n)	112	103	9	
AST (U/L), mean (SD)	38 (31)	38 (33)	38 (29)	0.99
Missing (n)	113	103	10	
ALT (U/L), mean (SD)	*35 (29)*	*31 (23)*	*38 (33)*	*0.057*
Missing (n)	113	103	10	
Creatine kinase (U/L), mean (SD)	184 (356)	173 (410)	191 (320)	0.78
Missing (n)	224	157	67	
Creatinine, mean (SD)	1.13 (2.01)	0.97 (0.51)	1.26 (2.62)	0.20
Missing (n)	115	103	12	

3.3. COVID-19-related treatments

The frequency of antiviral administration was approximately equal in both groups (24–25%) with no statistically significant difference (p = 0.83). This finding is consistent with the use of standardized treatment guidelines across centers. Use of immunomodulators (Tocilizumab, Hydroxychloroquine, or Anakinra) was higher in group A (9%) than in group B (4%), but this trend did not reach statistical significance (p = 0.056). This finding may reflect the particular immunologic context of patients suffering from IMIRD, where a heightened state of systemic inflammatory response can be expected. Moreover, clinicians may also be more familiar with these agents, given the patients' prior exposure to such therapies.

Antibiotics were used more often in the control cohort (55%) than in the IMIRD cohort (41%), a statistically significant difference (p = 0.012). Although seemingly counterintuitive, this pattern may reflect a more cautious approach in immunosuppressed patients, for whom dysbiosis and secondary complications – such as fungal infections or Clostridium difficile colitis – are well recognized and carefully managed. In addition, prescribing practices may vary by local protocols. Several studies have established the role of administering antibiotics such as azithromycin in early treatment guidelines in patients with SARS-CoV-2, taking into consideration prophylactic guidelines in cases with severe disease or important comorbidities [44–47].

An important mention is that only corticosteroids prescribed specifically for the acute COVID-19 episode were considered in the analysis. This therapy was administered more frequently in the control cohort (44%) than in the IMIRD cohort (34%); the difference did not reach statistical significance (p = 0.068). This distinction is relevant: some IMIRD patients were already receiving low-dose corticosteroids, which may

have discouraged the use of additional doses due to concerns about excessive immunosuppression. Moreover, multiple studies have reported an association between dosages of Prednisone of ≥10 mg/day in patients with worse outcomes in COVID-19 patients [12,13,15,17,18,48].

Another frequently prescribed treatment was anticoagulation. In the control cohort, this therapy was recommended in a higher proportion of patients (53%) than in the IMIRD cohort (37%), with this difference reaching statistical significance (p = 0.003). Detailed information on administered treatments is presented in Table 4.

Table 4. The allocation of COVID-19 treatments in both cohorts

Variable	Total (n = 365)	Group A (n = 211)	Group B (n = 154)	p-value
Antivirals, n (%)				0.83
Yes	88 (24)	50 (24)	38 (25)	
No	277 (76)	161 (76)	116 (75)	
Immunomodulators, n (%)				0.056
Yes	25 (7)	19 (9)	6 (4)	
No	340 (93)	192 (91)	148 (96)	
Antibiotics, n (%)				**0.012**
Yes	171 (47)	87 (41)	84 (55)	
No	194 (53)	124 (59)	70 (45)	
Glucocorticoids, n (%)				0.068
Yes	139 (38)	72 (34)	67 (44)	
No	226 (62)	139 (66)	87 (56)	
Anticoagulants, n (%)				**0.003**
Yes	161 (44)	79 (37)	82 (53)	
No	204 (56)	132 (63)	72 (47)	

3.4. Vaccination status and comorbidities

Vaccination status referred exclusively to immunization prior to SARS-CoV-2 infection; data on vaccine type, number of doses, and timing were not available for analysis. A significantly higher immunization rate (p=0.034) was observed in patients in the IMIRD cohort (27%) compared with controls (18%). This observation should be interpreted in the context of the relatively low overall vaccination coverage during the study period.

Moreover, patients in group A had a significantly higher number of associated diseases than those in group B (p=0.005). This observation underscores the important comorbidity burden in individuals with IMIRD.

To show patterns of comorbidities, arterial hypertension was chosen as the most common cardiovascular condition, and osteoporosis as the most frequent and important musculoskeletal comorbidity. Osteoarthritis, although frequent, was not highlighted because it is less relevant for COVID-19. Thyroid disorders included hypo-/hyperthyroidism, as well as autoimmune thyroiditis. Pulmonary conditions included asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and interstitial lung disease (ILD). For some conditions – hypertension, obesity, and cancer – there were no significant differences.

In contrast, thyroid disorders were more common in group A (21%) than in group B (6%), with a highly significant difference (p < 0.001). Pulmonary conditions were also more frequent in the IMIRD cohort (29%) compared with controls (14%) (p < 0.001). This is significant from a clinical point of view: ILD may be a severe extramusculoskeletal complication of RA, SLE, and SSc [49–51] and can further predispose to worse COVID-19 outcomes [52–55].

A significantly higher number of patients with IMIRD were diagnosed with osteoporosis (22%) when compared with controls (2%) (p < 0.001). This likely reflects the cumulative effects of chronic inflammation and long-term corticosteroid use, both

of which have been shown to lead to bone mass loss. Additionally, a greater proportion of neurological disorders was found in the control group ($p < 0.001$). Detailed information is presented in Table 5.

Table 5. COVID-19 vaccination and comorbidity profile of both cohorts

Variable	Total (n = 365)	Group A (n = 211)	Group B (n = 154)	p-value
Vaccination, n (%)				**0.034**
Yes	84 (23)	57 (27)	27 (18)	
No	281 (77)	154 (73)	127 (82)	
No. of comorbidities, mean (SD)	**4.7 (3.9)**	**5.2 (3.8)**	**4.0 (4.1)**	**0.005**
Arterial hypertension, n (%)				0.54
Yes	171 (47)	96 (45)	75 (49)	
No	194 (53)	115 (55)	79 (51)	
Obesity, n (%)				0.60
Yes	62 (17)	34 (16)	28 (18)	
No	303 (83)	177 (84)	126 (82)	
Thyroid diseases, n (%)				**<0.001**
Yes	54 (15)	45 (21)	9 (6)	
No	311 (85)	166 (79)	145 (94)	
Pulmonary diseases, n (%)				**<0.001**
Yes	82 (22)	61 (29)	21 (14)	
No	283 (78)	150 (71)	133 (86)	
Neoplasm, n (%)				0.14
Yes	25 (7)	18 (9)	7 (5)	
No	340 (93)	193 (91)	147 (95)	
Osteoporosis, n (%)				**<0.001**
Yes	50 (14)	47 (22)	3 (2)	
No	315 (86)	164 (78)	151 (98)	
Neurological diseases, n (%)				**<0.001**
Yes	36 (10)	10 (5)	26 (17)	
No	329 (90)	201 (95)	128 (83)	

3.5. SARS-CoV-2 severity

The pattern of COVID-19 outcomes was similar between the cohorts, as illustrated in Figure 1. Specifically, in group A, 135 patients (64.0%) had a mild illness, 37 adults (17.5%) presented with moderate infections, and 39 individuals (18.5%) were diagnosed with severe or critical infections. In group B, 92 patients (59.7%) had mild infections, 21 adults (13.6%) presented with moderate illness, and 41 individuals (26.6%) had severe or critical infections.

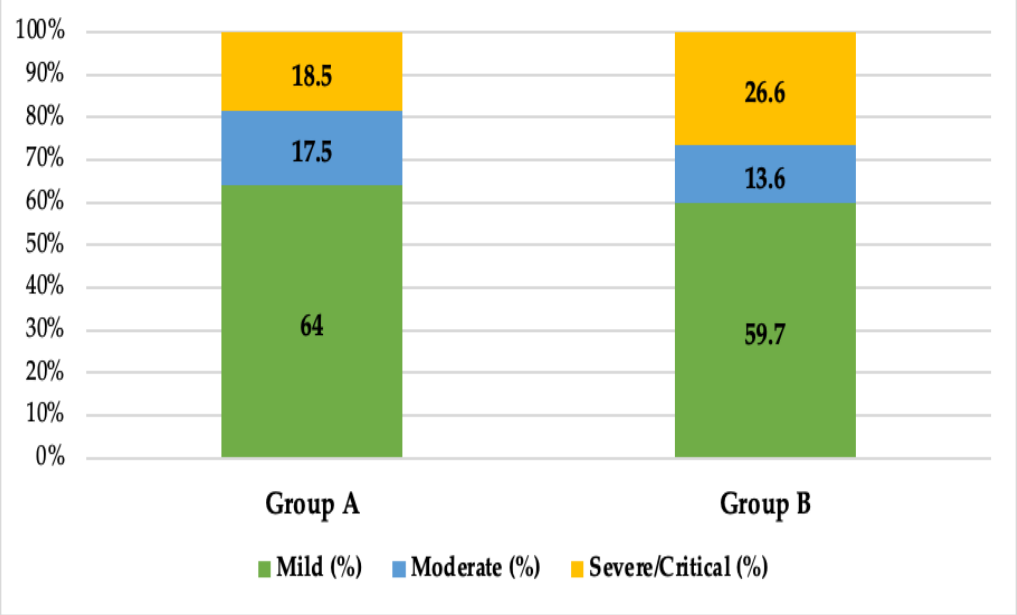

Figure 1. Distribution of COVID-19 severity by cohort.

To compare differences in SARS-CoV-2 infection severity, an ordinal regression model was used (refer to Section 2). The results revealed no statistically significant difference between the two groups (p = 0.225), as shown in Table 6.

Table 6. The results of the ordinal regression model regarding COVID-19 severity

	COVID-19 Severity		
Model parameters	*OR*	*CI*	*p-value*
1|2	1.83	1.39 – 2.42	**<0.001**
2|3	3.98	2.92 – 5.42	**<0.001**
Group [B]	1.29	0.85 – 1.96	0.225
Observations	365		

After adjustment for age, sex, vaccination status, and the number of comorbidities, the analysis showed that the association between cohort status and COVID-19 severity further attenuated and remained non-significant (OR 1.08, 95% CI 0.67–1.73; p = 0.752). In this multivariable model, the effect of each year of age on the odds of belonging to more severe clinical categories increased (OR = 1.04 per year; 95% CI: 1.02–1.06; p < 0.001). Unvaccinated patients had higher odds of severe COVID-19 compared with vaccinated individuals (OR = 2.51; 95% CI: 1.42–4.45; p = 0.002). Comorbidity burden was also associated with severity, with each additional comorbidity corresponding to an 8% increase in odds (OR = 1.08; 95% CI: 1.01–1.14; p = 0.015). The model yielded a Nagelkerke R^2 of 0.174, indicating that approximately 17% of the variability in disease severity was explained by the included covariates. The results are shown in Table 7 below.

Table 7. The results of the multivariable ordinal regression model regarding COVID-19 severity

		COVID-19 Severity	
Model parameters	*OR*	*CI*	*p-value*
1|2	62.33	19.39 – 200.36	**<0.001**
2|3	150.08	45.04 – 500.10	**<0.001**
Group [B]	1.08	0.67 – 1.73	0.752
Sex [M]	1.26	0.78 – 2.04	0.339
Age	1.04	1.02 – 1.06	**<0.001**
Vaccination [No]	2.51	1.42 – 4.45	**0.002**
No. of comorbidities	1.08	1.01 – 1.14	**0.015**
Observations		365	
R^2 Nagelkerke		0.174	

4. Discussion

To our knowledge, this is among the most detailed Romanian analyses, comparing demographic, clinical, and baseline laboratory characteristics, as well as COVID-19 outcomes between patients with RA, SLE, SSc, or axSpA and non-autoimmune controls. In contrast to Western Europe, where large multicenter studies are available, information for Eastern European populations remains limited, making our results relevant in this context.

The IMIRD cohort was mainly female and significantly younger than non-IMIRD patients ($p < 0.001$ and $p = 0.012$, respectively). Both characteristics have been associated with a more favorable course of COVID-19, as shown by large rheumatology-specific registries, such as the COVID-19 Global Rheumatology Alliance (GRA) [56,57] and SAR-COVID [58], and population-based analyses [12,18,59–64]. Moreover, the distribution of sex is consistent with the established evidence of a significant female preponderance in RA, SLE, and SSc patient populations. Furthermore, axSpA, previously thought to be predominantly found in men, now has a more balanced male-to-female ratio of 3:1 [18,30,65–67]. From a PRM perspective, these results are clinically significant, as advanced age and male gender have been associated with an increased risk of functional decline, immobility, and recovery from acute COVID-19. This may be partly attributed to inflammaging, frequent vitamin D deficiency, and sarcopenia in older populations, all of which have been associated with adverse COVID-19 outcomes and impaired functional recovery [23,62,68–73].

Smoking, a known risk factor for severe SARS-CoV-2 infection, disrupts the innate immune response, increases angiotensin-converting enzyme 2 (ACE2) receptor expression in the respiratory epithelium and oxidative stress, impairs mucociliary clearance, causes vasoconstriction, and promotes a prothrombotic state [56,74,75]. Smoking was significantly more common in group B, a finding that should be considered when interpreting the slightly higher proportion of severe cases observed in that cohort.

From a laboratory perspective, IMIRD patients displayed higher ESR values and chronic inflammation–related hematologic abnormalities, including lower hemoglobin and hematocrit levels, which are frequently observed in these patients and may increase their risk of poor COVID-19 outcomes [14,21,76–78]. Taking into consideration the elevated CRP and ESR levels, a corresponding increase in fibrinogen would have also been anticipated. However, these patients had lower-than-expected fibrinogen levels and elevated D-dimer levels, suggesting differential activation of the coagulation and fibrinolytic pathways. Nonetheless, fibrinogen and D-dimer are affected by various factors in SARS-CoV-2 infection (including acute-phase dynamics, chronic inflammation, and anticoagulant exposure) [79–81]. Notably, anticoagulant therapy was more frequently administered in the control group, making differential anticoagulant exposure an unlikely explanation for this pattern. A more plausible interpretation involves chronic immune activation and pre-existing endothelial dysfunction in IMIRDs, which may promote sustained coagulation pathway engagement and increased fibrinolytic turnover during SARS-CoV-2 infection. As COVID-19 severity has repeatedly been linked to a procoagulant state, these parameters should be interpreted in the context of systemic inflammation and underlying disease-related factors [82–85]. Early inflammatory burden and anemia have been linked to muscle wasting, fatigue, and reduced exercise tolerance in acute and post-acute SARS-CoV-2, factors that directly influence rehabilitation trajectories and work disability [27,86–90].

The lack of significant differences in composite inflammatory markers between the two cohorts further supports the observation that, at the onset of infection, systemic inflammatory responses were similar. This constitutes a clinically meaningful negative finding. Despite a well-known immune imbalance in patients with IMIRD, this analysis shows that both patient groups had a similar extent of systemic inflammatory activation within the pre-specified 72-hour timeframe of symptoms. This could help explain why there were no significant differences between the two patient groups in overall disease severity and supports the hypothesis that host factors such as age, co-existing illness, and specific treatment exposure may be stronger drivers of outcomes than IMIRD status per se. This finding is concordant with early comparative evidence from a retrospective matched-cohort study by Hsu et al. [91], which reported similar baseline inflammatory profiles between patients with systemic rheumatic diseases and non-rheumatic controls.

Additionally, COVID-19 treatments were administered differently between the two groups. This finding requires careful interpretation. The choice of a certain therapy is influenced by multiple factors, such as clinical judgment, paraclinical factors, expected prognosis, and comorbid conditions, and perhaps most importantly, local recommendations and resource availability. This has been well described in the literature as the process of "confounding by indication": clinicians tend to prescribe antibiotics, anticoagulation, and systemic corticosteroids to patients with more severe respiratory compromise or higher perceived risk, which can bias unadjusted comparisons of treatment rates. Moreover, in some IMIRD patients receiving Hydroxychloroquine - which also has antiviral characteristics and was thought to delay infection, a hypothesis later dismissed - Azithromycin is often avoided because of the risk of QT interval prolongation and subsequent arrhythmias, providing further rationale for the lower use of antibiotics in group A [92–95]. Therefore, the treatment patterns reported in this research should be interpreted as markers of clinical decision-making within the acute-care context, not as causal determinants of outcomes [46,96,97].

Another aspect worth mentioning is that patients with IMIRD exhibited a higher number of comorbidities than the control cohort. The "burden" of comorbidities is well documented in the literature as a factor associated with more severe SARS-CoV-2 outcomes, including persistent symptoms (anosmia, fatigue, cognitive impairment, dyspnea, cough) [98], increased oxygen supplementation [58,98], higher hospitalization rates [17,48,58,99], and mortality [11,58].

Overall, our data show that COVID-19 severity did not differ significantly between patients with and without IMIRD, despite clear demographic and clinical differences between groups. Both univariable and multivariable ordinal regression analyses showed that, after adjustment for age, sex, vaccination status, and comorbidity burden, IMIRD status was not independently associated with SARS-CoV-2 severity. In contrast, older age, lack of prior vaccination, and greater comorbidity burden were associated with more severe clinical courses.

Our findings concerning the distribution of COVID-19 severity in our cohort also correlate with evidence from large rheumatology registries, which suggest that having a diagnosis of RA, SLE, SSc, or axSpA does not necessarily predispose to poor SARS-CoV-2 outcomes after adjusting for key host factors. These observations emphasize that it is important to assess IMIRD susceptibility in a wider context that incorporates the burden of comorbidities, including pulmonary diseases, IMIRD activity, and treatment with immunomodulators, as previously highlighted in the literature [56,58,100]. On the other hand, other population-based studies and meta-analyses have reported increased risks of severe SARS-CoV-2 outcomes compared with the general population. However, such associations likely reflect heterogeneity in disease distribution, baseline risk profiles, and treatment exposures across IMIRD populations. In this context, our findings support a careful interpretation of IMIRD status as an isolated risk factor for COVID-19 severity [1,3,101].

Importantly, the consequences go beyond the acute phase. As we recently showed in a study [88] examining the same cohort of IMIRD patients during the post-acute period, individuals with these pathologies may be particularly vulnerable to a constellation of persistent symptoms after SARS-CoV-2 infection, all of which are significantly associated with various paraclinical biomarkers.

An additional strength of the present study is the focus on early laboratory assessment, restricted to the first 72 hours from symptom onset. In contrast to studies relying on peak inflammatory values during hospitalization, this strategy permitted a more accurate comparison of baseline inflammatory activation between IMIRD and non-IMIRD patients, minimizing confounding by disease progression and treatment effects.

Several limitations need to be considered. The retrospective design limits the ability to make causative deductions. In addition, even if this research was conducted in three hospitals, the findings reflect the experience of a single national healthcare system; therapeutic practices evolved over time, and hence caution should be exercised when generalizing from one Eastern European country to another. The patients in the IMIRD group include various diseases with different immunopathology and organ involvement (RA, axSpA, SLE, and SSc), and COVID-19 risk is not expected to be uniform across these conditions, particularly in patients with cardiopulmonary involvement. Treatment strategies and comorbidity profiles also vary across IMIRD subtypes and may influence outcomes, as delineated in the literature [49,52,60,102–104].

Although this research represents a real clinical case mix, subgroup-specific analyses were not statistically robust due to the limited number of participants per IMIRD subtype and incomplete data on key modifiers (e.g., ILD extent, pulmonary hypertension, functional parameters). Future disease-specific analyses in phenotypically well-characterized cohorts are necessary and part of forthcoming efforts.

5. Conclusions

The present multicenter study provides early-stage comparative real-world results from an understudied population of Eastern European adults with IMRD and supports the hypothesis that COVID-19 outcomes in IMRD patients vary and are influenced by host-related factors.

From a PRM point of view, disease severity in the early phase of infection, age, comorbidity burden, pulmonary involvement, anemia, and inflammation status are

key factors that help create profiles of patients at risk of functional decline or prolonged recovery in the post-acute phase of the infection. The coexistence of chronic musculoskeletal disease and cardiopulmonary comorbidities among the IMRD groups emphasizes the need for early risk stratification, as well as continuity of care through both the acute and post-acute phases of rehabilitation.

Future prospective, disease-specific studies incorporating functional assessments are warranted to better define severity determinants and rehabilitation trajectories in IMIRD populations.

Abbreviations

The following abbreviations are used in this manuscript:

ACE 2 – Angiotensin-converting enzyme 2
AISI – Aggregate Index of Systemic Inflammation
ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
axSpA – Axial spondyloarthritis
CI – Confidence interval
COPD – Chronic obstructive pulmonary disease
COVID-19 – Coronavirus disease 2019
CRP – C-reactive protein
dNLR – Derived neutrophil-to-lymphocyte ratio
ESR – Erythrocyte sedimentation rate
F – Female
GCP - Good Clinical Practice
GDPR – General Data Protection Regulation
GRA – Global Rheumatology Alliance
ILD – Interstitial lung disease
IMIRD – Immune-mediated inflammatory rheumatic disease
M – Male
N - Number
NLR – Neutrophil-to-lymphocyte ratio
OR – Odds Ratio
RA – Rheumatoid Arthritis
RT-PCR – Reverse transcription polymerase chain reaction
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
SD – Standard Deviation
SIRI – Systemic Inflammation Response Index
SLE – Systemic lupus erythematosus
SpO_2 – Peripheral oxygen saturation
SSc – Systemic sclerosis
STROBE – Strengthening the Reporting of Observational Studies in Epidemiology
WHO – World Health Organization

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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