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*Research article*

# Risk Factors for COVID-19 Mortality in Patients with Rheumatoid Arthritis: A National Registry-Based Cohort Study

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**Abstract:** The Coronavirus Disease 2019 (COVID-19) pandemic has shown considerable variability in mortality risk among different patient groups, and people with chronic immune-mediated and inflammatory diseases, such as rheumatoid arthritis (RA), may have an increased risk of this outcome. While many studies have examined various aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, we still do not fully understand what predicts mortality, especially among RA patients in Central and Eastern Europe. As RA patients are frequently managed by Physical and Rehabilitation Medicine (PRM) clinicians, it is important to recognize mortality-associated risk profiles to better tailor rehabilitation care. This research was an observational, retrospective registry-based study that included adult RA patients with SARS-CoV-2 infection between March 2020 and December 2023. Data was compiled from the Romanian Registry of Rheumatic Diseases (RRBR). We analyzed demographics, comorbidities, RA and COVID-19 characteristics. Mortality was the primary outcome. Binary logistic regression was used to identify independent predictors of death, and the final multivariable model was obtained through backward stepwise selection, with multicollinearity assessed using variance inflation factors (VIF). The study included 270 RA patients, of whom 6.66% died. Mortality was associated with age ⩾65.5 years (OR 11.1, 95% CI 3.16 – 55.6, p<0.001), lung involvement during COVID-19 (OR 27.2, 95% CI 4.69 – 540, p=0.003), and smoking status (OR 0.10, 95% CI 0.02–0.43, p=0.003). RA disease duration, extra-articular manifestations, comorbidities, and antirheumatic treatment categories were not associated with mortality. In this national RA cohort, COVID-19–related mortality was driven mainly by age, lung involvement, and smoking, rather than by RA-specific disease characteristics. While statistically significant, the wide confidence intervals reflect the limited number of events and suggest cautious interpretation of the effect size. These factors are also linked to reduced functional reserve and poorer recovery potential. From a PRM perspective, recognizing such risk profiles may support appropriate clinical watchfulness and post-acute management in RA patients following SARS-CoV-2 infection.

**Keywords:** COVID-19, SARS-CoV-2, rheumatoid arthritis, cohort study, mortality, risk factors, Romanian Registry of Rheumatic Diseases, RRBR, aging, smoking, registry-based study

## 1. Introduction

The heterogeneity of the clinical manifestations and outcomes associated with COVID-19 varies from asymptomatic infection to severe respiratory failure and death. Certain clinical outcomes of SARS-CoV-2 infection carry greater weight when assessing disease impact in different patient groups. For instance, large-scale studies and meta-analyses have found that advanced age, male gender, and pre-existing cardiovascular, metabolic, and pulmonary conditions remain the major determinants for mortality associated with SARS-CoV-2 infection, whereas excessive inflammatory responses contribute to the progression of the infection in severe cases [1–6]. Despite substantial advances in understanding the pathophysiology of COVID-19, predicting mortality at the individual patient level remains challenging, particularly in populations with baseline immune alterations [7–10].

In addition, other population studies reported an excess mortality and a decline in life expectancy during the pandemic, reflecting both direct and indirect effects of COVID-19. However, by 2023, age-standardized mortality rates and life expectancy had largely returned to pre-pandemic levels. Nevertheless, considerable heterogeneity persisted across populations and age groups. Incomplete recovery persists in a considerable proportion of countries, particularly among older adults and populations with comorbid conditions [11].

In parallel, the pandemic brought a lot of uncertainties to healthcare delivery, leading to reduced medical attendance, delayed diagnoses, anxiety, and interruptions in the management of chronic diseases. Indirect effects of the pandemic may have increased the risk for adverse outcomes among populations or patient groups with underlying inflammatory and comorbidities [12].

Rheumatoid arthritis (RA) represents a paradigmatic model of chronic systemic inflammatory disease, characterized by persistent immune activation and a high burden of cardiometabolic and pulmonary comorbidities. In addition, many patients are exposed to immunomodulatory therapies, which initially raised concerns regarding susceptibility to severe COVID-19 and fatal outcomes. However, evidence regarding SARS-CoV-2–related mortality in RA has remained heterogeneous and, at times, conflicting. Although some large observational studies reported increased risk compared to the general population, other studies suggested that increased mortality in RA patients could be mainly attributed to increased age and comorbidities, such as interstitial lung disease (ILD), rather than RA-specific factors [12–16].

With respect to rehabilitation, patients with RA constitute a separate entity, in which COVID-19-related outcomes should be interpreted in relation to pre-existing levels of inflammation. Chronic systemic inflammation in RA individuals is strongly related to muscle catabolism, decreased physical performance, and increased prevalence of sarcopenia and frailty, even in the absence of overt illness [12,17–19]. SARS-CoV-2 infection is considered to be another inflammatory and catabolic stressor, which may lead to deconditioning and functional decline in RA patients. These individuals often require continuous rehabilitation care, especially those with long-standing disease. Thus, it is essential to identify clinical predictors of COVID-19 mortality to avoid underestimating disease severity and to ensure appropriate risk stratification, monitoring, and clinical decision-making within rehabilitation settings. In this context, predictors of fatal outcomes may also signal an increased risk of adverse functional trajectories among survivors [20–22].

Despite the increase in studies on the outcomes of patients with COVID-19 and RA, there remain gaps in current knowledge. Most studies have been conducted to assess the severity, the rate of hospitalization, and combined outcomes, with the risk of death considered as a secondary endpoint or a proxy for the severity of the illness.

Additionally, there is a lack of studies on outcomes in patients with RA, and the results have been difficult to generalize due to differences in healthcare systems, pandemic phases, and the variables analyzed. It is also worth emphasizing the lack of studies from national rheumatology registries in Central and Eastern Europe, considering the different demographic characteristics, patterns of comorbidities, healthcare access, treatment patterns, and pandemic responses compared to Western Europe or the US, all of which can significantly influence the outcomes in patients with RA [14–16,23–28].

The RRBR is a real-world model for collecting longitudinal outcomes in patients with immune-mediated inflammatory rheumatic diseases (IMIRD) in Romania, including experience with SARS-CoV-2 infection [29–32]. Even though the pandemic has passed, the infection is still present and still causes deaths. Building on prior registry-based analyses that explored predictors of COVID-19 severity in other rheumatic disease subsets [33], the present study focuses specifically on RA and aims to identify clinical predictors of mortality following SARS-CoV-2 infection in this population.

## 1. Material and Methods

### *1.1. Ethical Considerations*

This study was conducted following the principles of the Declaration of Helsinki, national regulations and Good Clinical Practices (GCP) standards. Written informed consent, including authorization under the General Data Protection Regulation (GDPR), was obtained from all enrolled patients at the time of their initial registration in the RRBR and at every medical visit. This consent explicitly encompassed permission to use electronic medical data for research purposes while ensuring patient anonymity through the systematic coding of personal identifiers. This study is part of the Doctoral Research and has approval from the Scientific Research Ethics Committee of the "Sfânta Maria" Clinical Hospital (No. 6655/21.03.2022), with all procedures conducted in accordance with established ethical guidelines for retrospective registry-based research.

### *1.2. Study Design*

This observational, retrospective cohort study used anonymized data from the RRBR and included patients who had both RA and SARS-CoV-2 infection between March 1, 2020, and December 31, 2023.

### *1.3. Data Source and Registry Infrastructure*

Data were prospectively collected in the RRBR at the point of initiation of biological or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) therapy for each enrolled patient. Data is stored in a secure environment on a protected server. Voluntary contributions from participating rheumatologists ensured the data's geographical representation. Information on adverse events and complications - including infectious episodes - is added to the patient's medical history during the routine follow-up visit or when significant clinical events require documentation. To maintain the integrity of the data and to reduce the potential bias, a deliberate separation was made between the data analysis and the data collection; specifically, the person who was in charge of the raw data extraction and anonymization was not involved in the statistical analysis. Moreover, all the data were subjected to rigorous harmonization, quality verification, and consolidation before the statistical analysis.

### *1.4. Eligibility Criteria*

To be included in the study, patients had to be 18 years of age or older with a confirmed diagnosis of RA, based on clinical and paraclinical findings and supported by established classification criteria [34], and to have been infected with SARS-CoV-2 during the designated period. The diagnosis of COVID-19 was confirmed by the results of the Rapid Antigen Detection and reverse transcription-polymerase chain reaction tests. All included patients had received at least one course of biological therapy.

The patients were excluded from the study if they were part of the pediatric population (<18 years old) or if the COVID-19 diagnosis remained uncertain or was inadequately documented. Patients with incomplete registry data regarding essential variables were also excluded to maintain rigor

*1.5. Study Variables*

The analytical framework incorporated multiple variable categories spanning demographic, clinical, and treatment-related domains.

Demographic characteristics included: sex, age at COVID-19 diagnosis, smoking history (yes/no), residence (urban/rural), and education level (elementary/secondary/university degree). Smoking status was included as a binary variable (Yes = reference category; No), such that odds ratios (OR) <1 indicate a lower mortality risk among non-smokers compared with smokers.Clinical variables covered a thorough assessment of co-existing diseases present before or during the infection. Detailed characterization of RA-specific features included disease duration (calculated from the initial RA diagnosis to COVID-19 onset), the presence and type of extra-articular manifestations, and all immunosuppressive and immunomodulatory therapies that were administered to patients at the time of SARS-CoV-2 infection.

Regarding the COVID-19 episode, we collected data on symptoms, duration of infection, antibiotic use, disease progression, and mortality outcome.

*1.6. Study Objectives*

The main goal of this study was to identify clinical factors that predict death in RA patients with COVID-19. We focused on mortality because it is the most important and reliably recorded outcome in the registry framework. The secondary goal was to comprehensively describe the study cohort, including their demographics, clinical features, treatments, and infection-related information, to better understand this patient population.

*1.7. Statistical Analysis*

The data calculations were performed using R statistical software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) [35]. Descriptive analyses for all the variables under investigation were computed. Continuous variables are represented as the mean with standard deviations (SD) or the median with interquartile range if the data is skewed. Categorical variables are expressed as frequencies and percentages.

To establish the predictive relationship between the variables and the fatal outcomes, univariate and multivariate binary logistic regression analyses were used. In the regression analysis, the dependent variable was a binary outcome: death related to or associated with COVID-19. The independent variables were the previously mentioned variables.

The Receiver Operating Characteristic (ROC) curve was employed to identify the optimal age cutoff for mortality prediction. The discriminative ability of the cutoff was also determined using the area under the curve (AUC).

In the univariate regression analysis, the variables under investigation were analyzed individually to identify connections meriting further investigation.

The associations of predictor variables with mortality were determined by calculating ORs and their corresponding confidence intervals (CIs) at 95%. Statistical significance was determined using a conventional alpha threshold of 0.05; p-values below this level were considered significant.

The final multivariate model of prediction was designed using the backward stepwise selection algorithm and included all candidate predictors identified through univariate screening. To ensure validity, multicollinearity between the predictor variables in the final model was also determined using VIFs. This approach confirms that the final model includes variables that are independently associated with mortality while considering confounding effects.

## 2. Results

### 2.1. Demographics

Of the 9,300 patients in the registry diagnosed with RA, 270 (3%) had a confirmed COVID-19 diagnosis during the study period, and 18 individuals had died. Thus, the overall case fatality rate was 6.66%.

The deceased patients had a mean age of 68.1 ± 6.2 years, with a median of 69 years (range 53-79). ROC analysis indicated that an age of≥65.5 years was a significant threshold for distinguishing between survival and death, with an AUC of 0.740 (Figure 1). Using the univariate analysis, the results showed that patients aged 65.5 years or older had a 7.39-fold higher mortality risk than younger patients (OR 7.39, 95% CI: 2.56–26.7, p < 0.001). Each additional year of age was associated with a 9% increase in mortality risk (OR 1.09, 95% CI: 1.03–1.15, p = 0.003).

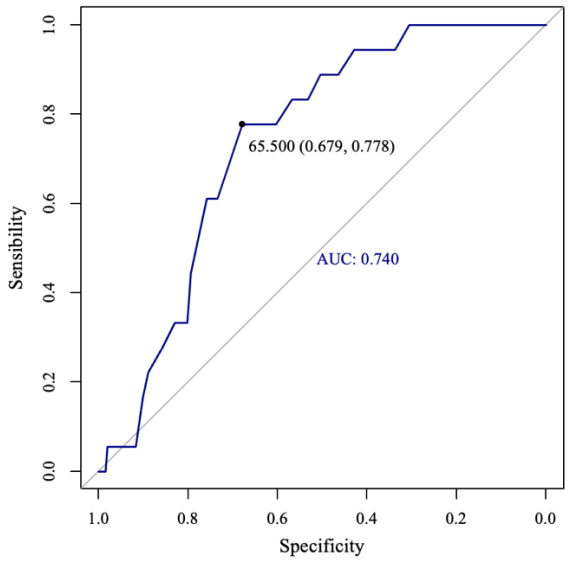


Figure 1 – The results of the ROC analysis regarding mortality age.

AUC: area under the curve

The demographic composition of the study cohort was representative of that commonly found in RA cases, with 229 female patients (84.8%) and 41 male patients (15.2%). Among the patients who died during the study period, there were 14 female patients and 4 male patients. The statistical analysis revealed no significant difference in mortality rate between sexes (OR 1.66; 95% CI: 0.45-4.93; p=0.394).

Regarding residential distribution, 188 patients (69.6%) lived in urban areas, with 10 deaths (5.3% case mortality rate), while 82 patients (30.4%) lived in rural areas, with 8 deaths (9.8% case mortality rate). Although rural patients had a higher mortality rate compared to their urban counterparts, the difference was not statistically significant (OR 0.52; 95% CI: 0.20-1.41; p=0.185).

The analysis of the education level revealed that 205 patients (76%) had completed elementary or secondary education, with 16 deaths (7.8% case mortality rate), while 65 patients (24%) had higher education, with only 2 deaths (3.1% case mortality rate). Although higher education may have a protective effect against mortality rate, the difference was not statistically significant (OR 0.38, 95% CI: 0.06–1.37, p = 0.199).

Smoking status was documented for all patients, with 32 individuals (11.9%) identified as current smokers and 238 (88.1%) as non-smokers. Five deaths occurred among smokers (15.6% case fatality) compared to 13 among non-smokers (5.5% case fatality). Univariate analysis indicated that non-smokers had a significantly reduced mortality risk (OR 0.31, 95% CI: 0.11–1.03, p = 0.039).

Detailed information is provided in Table 1.

| Predictor | N | Deaths N | OR (95% CI) | p-value |
|---|---|---|---|---|
| Age (years ± SD) | 270 | 18 | 1.09 (1.03 to 1.15) | 0.003 |
| Age category (years) | | | | |
| < 65.5 | 175 | 4 | — | |
| >= 65.5 | 95 | 14 | 7.39 (2.56 to 26.7) | <0.001 |
| Sex | | | | |
| F | 229 | 14 | — | |
| M | 41 | 4 | 1.66 (0.45 to 4.93) | 0.394 |
| Smokers | | | | |
| Yes | 32 | 5 | — | |
| No | 238 | 13 | 0.31 (0.11 to 1.03) | 0.039 |
| Education level (n, %) | | | | |
| Elementary + High School | 205 | 16 | — | |
| Higher Education | 65 | 2 | 0.38 (0.06 to 1.37) | 0.199 |
| Residence (n, %) | | | | |
| Rural | 82 | 8 | — | |
| Urban | 188 | 10 | 0.52 (0.20 to 1.41) | 0.185 |

**Table 1 – The results of the univariate regression analysis for demographic variables**

### 2.2. RA-Specific Disease Characteristics

a) Disease duration

The mean disease duration among deceased patients was 20 ± 11 years, compared to 16 ± 10 years in the surviving cohort. Each additional year of RA was associated with a 4% increase in mortality risk, though this association was marginal non-significant (OR 1.04, 95% CI: 0.99 to 1.08, p = 0.085).

b) Extra-musculoskeletal manifestations

Rheumatoid nodules were documented in 32 patients, with no deaths recorded in this subgroup (p = 0.122). Sicca syndrome affected 29 patients, among whom 2 deaths occurred, yielding no significant association with mortality (p = 0.958). Vasculitis was documented in 6 patients without any fatalities (p = 0.987), and Raynaud's syndrome was present in 4 patients, also without deaths (p = 0.801). Pulmonary fibrosis was identified in 34 patients, with 4 deaths occurring in this group; however, the association with mortality did not reach statistical significance (OR 0.47, 95% CI: 0.16–1.75, p = 0.212). Ocular involvement was reported in 6 patients, with a single death (p = 0.342).

c) DMARDs

All 18 deceased patients were receiving treatment in monotherapy with biological or targeted synthetic (b/ts)DMARDs at the time of SARS-CoV-2 infection. The distribution among fatal cases included 3 patients treated with TNF-$\alpha$ inhibitors, 3 with IL-6 receptor inhibitors, 7 with rituximab, and 5 with tsDMARDs.

Among individuals who received an association with a conventional synthetic (cs)DMARD, the distribution was as follows: 8 patients received Methotrexate, 7 Sulfasalazine, 7 Leflunomide, 2 Hydroxychloroquine, and 1 Azathioprine. No deaths occurred among these 25 patients compared with the biologics group (p = 0.218).

### 2.3. Comorbidity Burden

The cardiovascular comorbidities formed the largest group of comorbidities, with hypertension being identified in 132 (48.9%) patients from the study population. Among this group, there were 13 fatalities. In contrast, those without hypertension had a significantly lower risk of death (OR 0.34, 95% CI: 0.11–0.94, p = 0.049). Ischemic heart disease was present in 54 patients, of whom 4 died. There were no differences in mortality risk between this group and the patients without ischemic heart disease (OR 0.86, 95% CI: 0.32–2.74, p = 0.807). Additionally, there were 15 cases of congestive heart failure (CHF), with 3 fatalities; patients without CHF exhibited a four-fold reduction in mortality risk (OR 0.25, 95% CI: 0.07–1.18, p = 0.047). Peripheral vascular disease was identified in 33 patients, with 2 deaths, showing no significant association (p = 0.882).

In the pulmonary comorbidity category, a history of tuberculosis was noted among 24 patients. This is of particular interest with regard to the administration of immunosuppressive therapy. There were 3 fatalities among these patients, although the association with mortality was not significant (p = 0.241).

The metabolic and endocrine category included diabetes mellitus, from which 35 patients suffered, with 3 fatalities, as well as thyroid disease among 45 patients with 2 fatalities, neither of which demonstrated significant mortality associations (p = 0.630 and p = 0.517, respectively). Osteoporosis was the second most frequent comorbidity, as expected, and recorded among 72 patients with 5 fatalities (p = 0.912), while osteoarthritis was recorded in 33 patients, yielding 2 deaths (p = 0.882). A history of stroke was identified among 10 patients, with 2 fatalities (p = 0.108). Malignancy was recorded among 10 patients, with no deaths reported (p = 0.731). These results are also summarized and illustrated in Table 2.

| Predictor | N | Deaths N | OR (95% CI)[1] | p-value |
|---|---|---|---|---|
| RA disease duration | 270 | 18 | 1.04 (0.99 to 1.08) | 0.085 |
| Rheumatoid nodules | | | | |
| Yes | 32 | 0 | — | |
| No | 238 | 18 | 5.41 (0.71 to 699.24) | 0.122 |
| Sicca syndrome | | | | |
| Yes | 29 | 2 | — | |
| No | 241 | 16 | 0.96 (0.25 to 6.28) | 0.958 |
| Vasculitis | | | | |
| Yes | 6 | 0 | — | |
| No | 264 | 18 | 0.97 (0.10 to 129.02) | 0.987 |
| Raynaud's syndrome | | | | |
| Yes | 4 | 0 | — | |
| No | 266 | 18 | 0.67 (0.06 to 90.00) | 0.801 |
| Pulmonary fibrosis | | | | |
| Yes | 34 | 4 | — | |
| No | 236 | 14 | 0.47 (0.16 to 1.75) | 0.212 |
| Ocular involvement | | | | |
| Yes | 6 | 1 | — | |
| No | 264 | 17 | 0.34 (0.05 to 6.79) | 0.342 |
| Treatment | | | | |
| b/tsDMARDs | 245 | 18 | — | |

| Predictor | N | Deaths N | OR (95% CI)[1] | p-value |
|---|---|---|---|---|
| csDMARDs | 25 | 0 | 0.24 (0.01 to 1.85) | 0.218 |
| Pulmonary tuberculosis | | | | |
| Yes | 24 | 3 | — | |
| No | 246 | 15 | 0.45 (0.14 to 2.07) | 0.241 |
| Arterial hypertension | | | | |
| Yes | 132 | 13 | — | |
| No | 138 | 5 | 0.34 (0.11 to 0.94) | 0.049 |
| Ischemic heart disease | | | | |
| Yes | 54 | 4 | — | |
| No | 216 | 14 | 0.86 (0.32 to 2.74) | 0.807 |
| CHF | | | | |
| Yes | 15 | 3 | — | |
| No | 255 | 15 | 0.25 (0.07 to 1.18) | 0.047 |
| Diabetes mellitus | | | | |
| Yes | 35 | 3 | — | |
| No | 235 | 15 | 0.73 (0.22 to 3.26) | 0.630 |
| Thyroid diseases | | | | |
| Yes | 45 | 2 | — | |
| No | 225 | 16 | 1.65 (0.45 to 10.7) | 0.517 |
| Osteoarthritis | | | | |
| Yes | 33 | 2 | — | |
| No | 237 | 16 | 1.12 (0.30 to 7.31) | 0.882 |
| Osteoporosis | | | | |
| Yes | 72 | 5 | — | |
| No | 198 | 13 | 0.94 (0.34 to 3.03) | 0.912 |
| Stroke | | | | |
| Yes | 10 | 2 | — | |
| No | 260 | 16 | 0.26 (0.06 to 1.83) | 0.108 |
| Malignancies | | | | |
| Yes | 10 | 0 | — | |
| No | 260 | 18 | 1.59 (0.19 to 208.51) | 0.731 |

**Table 2 –The results of the univariate regression analysis for RA-specific variables**

### 2.4. COVID-19 Clinical Manifestations

Respiratory symptom classification revealed distinct mortality trends. Upper airway involvement (UAI) alone accounted for 136 (50.4%) cases, of which only 1 patient died. In contrast, pulmonary (lung) involvement accounted for 134 (49.6%) cases, of which 17 deaths were recorded. Differences between groups were statistically significant; patients with pulmonary involvement had a much higher risk of mortality than those with UAI (OR 19.6, 95% CI: 3.94–356, $p = 0.004$).

When evaluating the effect of antibiotics, it was found that 46 patients received antibiotics during the course of COVID-19, and 9 deaths were recorded. Of the 224 patients who did not receive antibiotics, 9 died. There was a significant reduction in mortality in the group that did not receive antibiotics (OR 0.17, 95% CI: 0.06–0.47, $p < 0.001$). This association likely reflects the well-known "confounding by indication" phenomenon, as antibiotic therapy was preferentially administered to patients with more severe presentations or suspected bacterial superinfection, rather than representing a causal relationship. Detailed information is presented in the table below.

| Predictor | N | Deaths N | OR (95% CI)1 | p-value |
|---|---|---|---|---|
| Respiratory symptoms | | | | |
| UAI | 136 | 1 | — | |
| Pulmonary | 134 | 17 | 19.6 (3.94 to 356) | 0.004 |
| Antibiotic | | | | |
| Yes | 46 | 9 | — | |
| No | 224 | 9 | 0.17 (0.06 to 0.47) | <0.001 |

**Table 3 - The results of the univariate regression analysis for COVID-19 specific variables**

### 2.5. Multivariate Analysis and Final Predictive Model

To refine the documentation of mortality predictors as completely and accurately as possible, variables with univariate p-values < 0.10 were included in multiple univariate binomial logistic regressions, with the initial model shown in Table 4. The cutoff of 0.10 was selected to ensure that potentially important marginal associations were not prematurely excluded. VIF analysis revealed acceptable levels of multicollinearity, with values ranging from 1.1 to 2.9. Although antibiotic use was significantly associated with mortality in univariate analysis, it was not retained in the final multivariate model, as it was considered a proxy marker of disease severity and subject to confounding by indication.

| **Predictor** | **N** | **Deaths (N)** | **OR (95% CI)** | **p-value** | **VIF** |
|---|---|---|---|---|---|
| Age (years ± SD) | 270 | 18 | 1.01 (0.91 to 1.13) | 0.85 | 2.9 |
| Age category (years) | | | | | 2.9 |
| < 65.5 | 175 | 4 | — | | |
| >= 65.5 | 95 | 14 | 8.65 (1.15 to 86.9) | 0.047 | |
| RA disease duration | 270 | 18 | 1.04 (0.99 to 1.10) | 0.11 | 1.1 |
| Respiratory symptoms | | | | | 1.2 |
| UAI | 136 | 1 | — | | |
| Pulmonary | 134 | 17 | 36.4 (5.65 to 781) | 0.002 | |
| Smokers (n) | | | | | 1.6 |
| Yes | 32 | 5 | — | | |
| No | 238 | 13 | 0.06 (0.01 to 0.31) | <0.001 | |
| Arterial hypertension | | | | | 1.2 |
| Yes | 132 | 13 | — | | |
| No | 138 | 5 | 0.64 (0.15 to 2.40) | 0.52 | |
| CHF | | | | | 1.1 |
| Yes | 15 | 3 | — | | |
| No | 255 | 15 | 0.28 (0.06 to 1.66) | 0.13 | |

**Table 4 – The results of the multiple univariate binomial logistic regressions for variables of interest**

Using the reverse selection method based on p-values and VIFs of the predictors, a final model was developed, with three independent predictors included (Table 5).

Patients aged at least 65.5 years were found to have an increased mortality risk by 11.1-fold (OR 11.1; CI: 3.16-55.6; p<0.001; VIF: 1.3). Lung involvement increased the mortality risk by 27.2-fold (OR 27.2; CI: 4.69-540; p = 0.003; VIF: 1.1). Non-smoking (with smoking as the reference category) was independently associated with lower mortality (OR 0.10; CI: 0.02-0.43; p = 0.003; VIF: 1.4). The final model indicated minimal multicollinearity with all VIF values below 1.5.

However, although arterial hypertension and CHF were found to be predictors in the univariate analysis, they did not have an independent effect in the multivariate analysis after controlling for age and pulmonary involvement.

| Predictor | N | Deaths N | OR (95% CI) | p-value | VIF |
|---|---|---|---|---|---|
| Age category (years) | | | | | 1.3 |
| < 65.5 | 175 | 4 | — | | |
| >= 65.5 | 95 | 14 | 11.1 (3.16 to 55.6) | <0.001 | |
| Respiratory symptoms | | | | | 1.1 |
| UAI | 136 | 1 | — | | |
| Pulmonary | 134 | 17 | 27.2 (4.69 to 540) | 0.003 | |
| Smokers | | | | | 1.4 |
| Yes | 32 | 5 | — | | |
| No | 238 | 13 | 0.10 (0.02 to 0.43) | 0.003 | |

**Table 5 – The results of the final multivariate logistic regression**

## 4. Discussions

To the best of our knowledge, this study is the first to examine COVID-19-associated mortality among patients with the most common IMIRD, namely RA, enrolled in the RRBR. The 6.66% death rate in this cohort is noteworthy, especially when compared to the 1.9% mortality rate documented by the World Health Organization for the general population [36], and is a clear indication of the patient's vulnerability and cannot be regarded as a mere statistical difference. This variation is particularly relevant for clinical practice, including for PRM clinicians, demanding enhanced vigilance, individualized risk stratification, and customized therapeutic strategies in line with the principles of the P4-Medicine paradigm: Preventive, Predictive, Participatory, and Personalized [37,38].

The multivariate analysis crystallized three independent mortality predictors, each warranting careful consideration. Pulmonary involvement emerged as the paramount determinant, conferring a 27-fold elevation in mortality risk. This finding resonates powerfully with established pathophysiological understanding of SARS-CoV-2 infection. It is well documented that the virus targets the pulmonary epithelium, utilizing the abundant number of angiotensin-converting enzyme 2 receptors (ACE2), which are maximally concentrated on the alveolar surface. The large surface area, coupled with an imbalance in cytokine release, makes it conducive to acute respiratory distress syndrome, which is a major cause of mortality [39–43]. In RA, this is particularly a cause for concern because the underlying pulmonary reserve is compromised by underlying ILD, chronic obstructive pulmonary disease, or medication-related pulmonary toxicity that further erodes physiologic reserve, narrowing the margin between clinical stability and decompensation [44–48].

Older age was the second independent predictor, with a mortality risk elevenfold higher for patients 65.5 years and older. This likely reflects the convergence of multiple age-related factors. Immunosenescence in RA is characterized by the expansion of late-differentiated, senescent T cells and a reduction in early-differentiated subsets, leading to impaired adaptive immunity and persistent low-grade inflammation [49,50]. In addition, older patients accumulate multiple comorbidities—including cardiovascular, neurological, metabolic, psychiatric, and renal conditions—

which further increase vulnerability [15,51–57]. Sarcopenia and frailty, both associated with disease activity and reduced physiological reserve, may further compromise resilience during acute infection [17,19,58].

From a rehabilitation perspective, older RA patients with COVID-19 are at a higher risk for deconditioning, muscle wasting, and functional decline [17,19,58]. Even those who survive may need long recovery periods, including physical therapy, better nutrition, and gradual exercise to regain their previous abilities [22,59]. Given the rapid expansion of wearable and mobile health technologies, continuous evaluation and long-term monitoring of these developments are essential to ensure their safe and clinically meaningful integration into patient care [60].

Smoking emerged as the third independent predictor of mortality, amplifying death risk by about ten times. The mechanisms involved in the association of smoking and mortality risk are complex. Tobacco exposure affects the pulmonary homeostasis through several pathways. It impairs mucociliary clearance, prolonging pathogen retention in the airways, and increases ACE2 receptor expression in the respiratory epithelium, potentially facilitating viral entry [61–63]. Smoking also amplifies inflammatory mediator cascades, including tumor necrosis factor-alpha, transforming growth factor-beta, and several interleukins, while inducing oxidative stress, epithelial injury, endothelial dysfunction, and prothrombotic states [13,61–66]. For RA patients—already managing chronic inflammation and immune dysregulation—superimposed smoking-related pathology creates a convergence of risk-enhancing mechanisms of vulnerabilities when confronted with respiratory viral challenge [67–73].

Regarding the other potential predictors evaluated, our analysis showed that although some, such as arterial hypertension or CHF, were associated with mortality in the univariate analysis, they were not subsequently validated as independent predictors in the multivariate model. This observation is not in line with the data from the literature, which, by using different methods of assessment and varying degrees of precision, found that cardiovascular diseases and COVID-19 mortality are correlated [74–77]. However, cardiovascular comorbidity, despite being non-significant as an independent predictor, is probably an important contributor to the risk burden as it is a major cause of mortality and disability by itself. Prudent clinical practice entails comprehensive cardiovascular assessment and optimization in patients with RA, particularly those facing infectious challenges [74,78–80].

This study has some important limitations. First, the retrospective nature and reliance on data from a Rheumatology Registry may introduce the risk of incomplete information, including underreporting of COVID-19 cases. Another limitation was the lack of data on RA severity, as measured by disease activity indices, as well as on specific treatments for SARS-CoV-2 infection. The limited number of deaths may also have affected model stability and contributed to the wide confidence intervals observed for some predictors. While the direction of associations was consistent, confirmation in larger samples is warranted. An important constraint of this registry-based study must be stated. Because of strict data protection regulations, as described in the Informed Consent forms, it has not been possible to obtain specific laboratory results or clinical details that would require direct patient interaction, such as symptom diaries, home monitoring data, and infection sequelae. Although these limitations make it more difficult to draw definite conclusions, they reflect the necessary balance between complete data acquisition and rigorous protection of patient privacy.

## 5. Conclusions

In this RRBR-derived national cohort, COVID-19–related mortality in individuals with RA was associated with older age, lung involvement during acute infection, as

well as smoking. On the contrary, RA-specific characteristics, such as extra-musculoskeletal manifestations or b/tsDMARDs, did not influence the risk of death associated with SARS-CoV-2 infection. These findings should be interpreted in the context of the limited number of fatal events, which may influence the precision of effect estimates.

Patients with RA are commonly treated within rehabilitation services, often presenting with reduced exercise tolerance, chronic pain, and comorbid conditions. In those with advanced age or documented pulmonary involvement during COVID-19, rehabilitation planning should include careful respiratory evaluation, gradual progression of aerobic workload, monitoring of oxygen saturation during exertion, and closer medical supervision in the early post-infectious phase. Recognition of these risk profiles is essential to avoid underestimating infection-related vulnerability and to ensure safe and individualized rehabilitation programs.

**Abbreviations**

The following abbreviations are used in this manuscript:

ACE 2 – Angiotensin-converting enzyme 2
AUC – Area Under the Curve
bDMARDs - Biologic Disease-Modifying Antirheumatic Drugs
CHF - Congestive Heart Failure
CI – Confidence interval
COVID-19 – Coronavirus Disease 2019
csDMARDs - Conventional Synthetic Disease-Modifying Antirheumatic Drugs
F – Female
GCP Good Clinical Practice
GDPR – General Data Protection Regulation
ILD – Interstitial lung disease
IMIRD – Immune-mediated inflammatory rheumatic disease
M – Male
N – Number
OR – Odds Ratio
RA – Rheumatoid Arthritis
ROC – Receiver Operating Characteristic
RRBR - Romanian Registry of Rheumatic Diseases
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
SD – Standard Deviation
tsDMARDs – Targeted Synthetic Disease-Modifying Antirheumatic Drugs
VIF – Variance Inflation Factors

**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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