Trends in severe outcomes in SARS-CoV-2-positive hospitalized patients with rheumatic diseases: a monocentric observational and case-control study in northern Italy

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SUMMARY

Rheumatic disease patients are at greater risk of infection due to their disease, comorbidities, and immunosuppressive therapy. COVID-19 outcomes in this patient setting appeared to be similar to those of the general population. However, data on this topic were mainly related to small studies on a limited number of patients. Consequently, to date, this field remains poorly explored, particularly in the pre-vaccine era. This monocentric study aimed to describe the intrahospital mortality in rheumatic patients with SARS-CoV-2 consecutively hospitalized from 21 February to 31 December 2020, before anti-SARS-CoV-2 vaccine administration spread, compared with non-rheumatic patients. Of 2491 included patients, 65 [3%, median (interquartile range) age 75 (64.76-82.239 years, 65% women] were suffering from rheumatic diseases. A total of 20 deaths were reported [case fatality rate 31%, 95% confidence interval (CI): 19-42] compared with 433 deaths (19%, 95% CI: 17-20) in patients without rheumatic diseases (p=0.024). However, the rheumatic disease was not associated with a significant increase in univariate mortality hazards (hazard ratio 1.374, 95% CI: 0.876-2.154), and after adjustment (hazard ratio 1.199, 95% CI: 0.759-1.894) by age, sex and Charlson comorbidity index. The incidence of intensive care unit admission, death, and discharge in the case-control study was comparable between rheumatic and non-rheumatic patients. The presence of rheumatic diseases in SARS-CoV-2-hospitalized patients did not represent an independent risk factor for severe disease or mortality.

Key words: *SARS-CoV-2, rheumatic diseases, severe outcomes, intrahospital mortality.*

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INTRODUCTION

The COVID-19 pandemic has spread globally over the past years, with more than 15 million confirmed cases and over 160,000 deaths in Italy from 21 February 2020 to 14 April 2022 (1). Lombardy (northern Italy) was the first region in Europe to be affected by COVID-19, which quickly led to an exponential increase in the number of hospitalizations and intensive care unit (ICU) admissions caused by infection complications. The pandemic progression in Lombardy led to 2,640,897 confirmed cases and over 39,000 deaths (1), among 9,965,046 inhabitants by 1 January 2022 (2). As the COVID-19 pandemic continues worldwide, severe COVID-19 outcomes remain a major concern for patients with rheumatic and musculoskeletal diseases (3). Indeed, patients with rheumatic diseases are at a higher risk of infection attributed to multiple factors, such as disease activity, comorbidities, and immunosuppressive therapy (4). Immunological considerations support a possible link between infection risk and immune system alterations in this group of patients due to the disease itself or the associated therapeutic regimen. In particular, immunosuppression

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and comorbidities have been associated with an increased risk of severe infection in people with rheumatic diseases (5). Therefore, during the pandemic, patients with rheumatic and musculoskeletal diseases have received particular attention regarding the hospitalization risk and severe outcomes caused by the SARS-CoV-2 infection. Several studies have reported COVID-19 outcomes based on data from the general population, but little is known about disease-specific subgroups, including patients with rheumatic diseases (6). Although few studies found that the risk of hospitalization caused by COVID-19 was higher in these patients (7, 8), COVID-19 outcomes in rheumatic patients appeared to be similar to those of the general population. However, these data were mainly related to small studies on a limited number of patients (9-16). Consequently, to date, this field remains poorly explored, particularly in the pre-vaccine era. This observational study aimed to investigate the outcomes of a monocentric cohort of rheumatic patients hospitalized for COVID-19 in Lombardy, comparing them with those of non-rheumatic patients before the use of anti-SARS-CoV-2 vaccines spread.

MATERIALS AND METHODS

Study design, setting, and participants

This was a retrospective observational cohort study based on the review of administrative health data and electronic case records of the inpatients consecutively admitted to Niguarda Hospital between 21 February and 8 November 2020. Niguarda is one of the largest general hospitals in the north of Milan (Lombardy) within a metropolitan area with 3,279,944 inhabitants (January 2020) and hosts all the medical and surgical disciplines for adults and children, including a 24-hour Emergency Department with 96,588 visits and 32,612 hospital admissions covering every intensity of care in 2019.

Within this study, all inpatients were eligible if they were positive for the SARS-CoV-2 infection, certified by the positivity of nasopharyngeal swab to the SARS-CoV-2 genome, regardless of the presence of respiratory disease. Swab tests were processed at Niguarda Hospital, and a documented result of test positivity from other health facilities was not a reason for exclusion. Inpatients who developed COVID-19 symptoms and/or tested positive for the SARS-CoV-2 genome after 48 hours from the negative test at admission were excluded, as they could be considered possible hospital-acquired infections. All the included patients were followed from the first day of elective or urgent admission to the hospital until the day of discharge, death, or 17 January 2021. A rheumatologist identified rheumatic patients by reviewing the electronic charts. Rheumatic diseases included inflammatory arthropathies and connective tissue diseases (hereafter termed rheumatic diseases).

The study was conducted following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and within the protocol approved by the Ethics Committee Milano Area 3 (register number 249-13052020). Written informed consent was obtained from all individual participants included in the study.

Outcome measurements

The study's primary aim was to compare the case fatality rate (CFR) of rheumatic and non-rheumatic patients. CFR was calculated as the proportion of observed in-hospital deaths (all-cause mortality) over the total number of included inpatients diagnosed with SARS-CoV-2 during the observation period. Time-specific CFRs were also calculated, and to this aim, the study period was divided into the following three intervals, consistent with trends in hospital admissions due to SARS-CoV-2 infection:

1) first wave (or wave 1): from 21 February to 31 May 2020;
2) intermediate phase: between 1 June and 30 September 2020;
3) second wave (or wave 2): from 1 October to 8 November 2020.

Secondary outcomes were defined from the time of admission to the following events: admission to the ICU, death, or discharge. Both single and composite outcomes re-

flecting complex definitions of in-hospital SARS-CoV-2 infection prognosis were considered to investigate the secondary endpoints.

A case-control study was also performed to further remove the possible role of confounders in assessing the association between rheumatic disease and time-to-event endpoints. Controls were defined as patients admitted to the same hospital for COVID-19 but without any rheumatic disease.

Statistical analysis

The distribution of patients' characteristics at admission was described using absolute numbers and percentages for categorical variables, and median and interquartile range (IQR) for continuous variables. The distribution of these characteristics between rheumatic and non-rheumatic patients was compared using the Chi-square test and Mann-Whitney test for categorical and continuous variables, respectively. The CRF with 95% confidence interval (CI) was estimated according to the Wald method. The association of the rheumatic disease diagnosis with two competing time-to-event endpoints was analyzed. These were composite endpoints defined as the time from admission to in-hospital mortality or admission to ICU. A single endpoint was defined as the time from admission to discharge from the hospital (without ICU). Patients transferred to another hospital were treated as censored observations. For each endpoint, the crude incidence was estimated using the Aalen-Johansen estimator separately for rheumatic and non-rheumatic patients, and the curves were compared using the Gray test. Uni- and multi-variable cause-specific Cox models were also fitted to assess the association between rheumatic disease and endpoints adjusting for wave, age, gender, and Charlson comorbidity index. The same analyses were repeated for the other two competing time-to-event endpoints: time from admission to in-hospital mortality (with or without ICU) and time from admission to discharge from the hospital (with or without ICU).

The following matching algorithm was applied to perform the case-control study. For each rheumatic patient, one patient among the non-rheumatic population with common characteristics was selected: same wave, same gender, similar age (absolute difference ≤5 years), and same Charlson comorbidity index (*i.e.*, 1, 2, 3, 4 or ≥5). For all rheumatic patients, it was possible to find a suitable match. If two or more suitable matching patients were found, one was randomly selected. The crude incidence between rheumatic and non-rheumatic patients was estimated and compared for each endpoint on the matched sample. The analyses were performed using R 4.0.3 (R Core Team, 2020. R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

During the study period, 2634 patients admitted to the Niguarda Hospital tested positive for the SARS-CoV-2 infection. A total of 143 patients developed COVID-19 symptoms and/or tested positive for SARS-CoV-2 after 48 hours from admission and consequently were not considered (*Supplementary Figure 1*). Among the remaining 2491 patients, 65 presented with a diagnosis of rheumatic disease (*Supplementary Table I*). Most patients were admitted during the second COVID-19 wave (57.9% of non-rheumatic patients, 64.6% of rheumatic patients); no rheumatic patients were admitted during the intermediate wave (Table I). Consequently, all non-rheumatic patients of the intermediate wave (n=130) were excluded from the subsequent analysis.

Rheumatic patients were mainly females (64.6% *vs* 35.1%, p<0.001), significantly older [median (IQR): 75 years (64.76-82.23) *vs* 65 (52.23-78.03), p<0.001] and with more comorbidities [Charlson comorbidity index median (IQR): 5 (4-8) *vs* 3 (1-5), p<0.001) compared with non-rheumatic patients (Table I). In particular, rheumatic patients were more likely to have a history of congestive heart failure (12.3% *vs* 5.2%, p=0.025), chronic obstructive pulmonary

disease (15.4% *vs* 7.6%, p=0.04), and moderate to severe chronic kidney disease (16.9% *vs* 8.6%, p=0.03) (Table I). Additional characteristics of patients with rheumatic diseases are presented in *Supplementary Table I*. Characteristics of patients with rheumatic diseases at admission were homogeneous between the first and second wave (*Supplementary Table II*).

Case fatality rate in rheumatic and non-rheumatic patients

During the study period, the overall CFR was 19.2% (95% CI: 17.6-20.8; the number of deaths/number of cases: 453/2361). Among rheumatic patients, CFR was 30.8% (95% CI: 19.5-42.0; the number of deaths/cases: 20/65). Among non-rheumatic patients, CFR was 18.9% (95% CI: 17.3-20.4; the number of deaths/cases: 433/2296), and this difference was statistically significant (Fisher test, p=0.024). CFR was comparable between the first and second wave for rheumatic patients (30.4% *vs* 31.0%, respectively, p=1) but not for non-rheumatic patients (21.3% *vs* 17.3%, respectively, p=0.019) and the overall population (21.6% *vs* 17.7%, respectively, p=0.021) (Table II).

Secondary outcomes

After 30 days from the admission, the crude incidence of admission to the ICU or death before the admission to the ICU was 37.5% (95% CI: 25.2-49.8) and 26.7% (95% CI:

Table I - Comparison of patients' characteristics at the time of admission.

Variables	Rheumatic disease		p value*
	No (n=2426)	Yes (n=65)	
Gender female, n (%)	851 (35.1)	42 (64.6)	**<0.001**
Current pregnancy, n (%)	13 (0.5)	0 (0)	1
Age at admission (years), median (IQR)	65.02 (52.23-78.03)	75.35 (64.76-82.23)	**<0.001**
Wave, n (%):			0.135
First (21 February - 31 May 2020)	891 (36.7)	23 (35.4)	
Intermediate (1 June - 31 September 2020)	130 (5.4)	0 (0)	
Second (1 October - 31 December 2020)	1405 (57.9)	42 (64.6)	
Emergency room stay (days), n (%):			**0.748**
Not admitted to the emergency room	1324 (62.1)	44 (71.0)	
1	771 (36.2)	18 (29.0)	
2	21 (1.0)	0 (0)	
3	9 (0.4)	0 (0)	
4	6 (0.3)	0 (0)	
5	1 (0)	0 (0)	
Outcome, n (%)			**0.035**
Death	443 (18.3)	20 (30.8)	
Discharge	1513 (62.4)	33 (50.8)	
Transferred to another hospital	470 (19.4)	12 (18.5)	
Length of stay (days), median (IQR)	13 (8-21)	16 (8-25)	0.274
Admission to ICU, n (%)	292 (12.0)	6 (9.2)	0.621
History of, n (%):			
Asthma	78 (3.6)	2 (3.3)	1
Myocardial infarction	231 (9.5)	10 (15.4)	0.174
Congestive heart failure	125 (5.2)	8 (12.3)	**0.025**
Peripheral vascular disease	146 (6.0)	6 (9.2)	0.423

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Variables	Rheumatic disease		p value*
	No (n=2426)	Yes (n=65)	
Cerebrovascular accident or transient ischemic attack	248 (10.2)	8 (12.3)	0.738
Dementia	173 (7.1)	5 (7.7)	1
Chronic obstructive pulmonary disease	185 (7.6)	10 (15.4)	**0.040**
Peptic ulcer disease	59 (2.4)	2 (3.1)	1
Hemiplegia	51 (2.1)	2 (3.1)	0.920
Liver disease	92 (3.8)	3 (4.6)	0.991
Moderate to severe chronic kidney disease	209 (8.6)	11 (16.9)	**0.036**
Solid tumor	349 (14.4)	13 (20)	0.279
AIDS	11 (0.5)	0 (0)	1
Diabetes	403 (16.6)	15 (23.1)	0.229
Leukemia	25 (1.0)	0 (0)	0.847
Linfoma	50 (2.1)	1 (1.5)	1
Charlson comorbidity index (0-37 score), median (IQR)	3 (1-5)	5 (4-8)	**<0.001**
Charlson comorbidity index (estimated 10-year survival), median (IQR)	77 (21-96)	21 (0-53)	**<0.001**
Charlson comorbidity index, n (%):			**<0.001**
Score 0	416 (17.2)	0 (0)	
Score 1	307 (12.7)	1 (1.5)	
Score 2	329 (13.6)	5 (7.7)	
Score 3	282 (11.6)	8 (12.3)	
Score 4	296 (12.2)	11 (16.9)	
Score ≥5	792 (32.7)	40 (61.5)	

Statistically significant p values are reported in bold. *Chi-square test for categorical variables and Mann-Whitney test for continuous variables. ICU, intensive care unit; IQR, interquartile range.

24.8-28.6), respectively, for rheumatic and non-rheumatic patients (p=0.141; Figure 1A). The crude incidence of discharge before ICU was 42.4% (95% CI: 29.6-55.2) in rheumatic patients and 58.8% (95% CI: 56.6-61.0) in non-rheumatic patients (p=0.010; Figure 1B). At 30 days after admission, the crude incidence of in-hospital

Table II - Case fatality rate with 95% confidence interval according to time intervals (waves) and rheumatic disease.

Wave	Rheumatic disease	No	Yes	Total
1	Number of patients	891	23	914
	Number of deaths	190	7	197
	CFR, % (95% CI)	21.3 (18.6-24.0)	30.4 (11.6-49.2)	21.6 (18.9-24.2)
2	Number of patients	1405	42	1447
	Number of deaths	243	13	256
	CFR, % (95% CI)	17.3 (15.3-19.3)	31.0 (17.0-44.9)	17.7 (15.7-19.7)
Overall*	Number of patients	2296	65	2361
	Number of deaths	433	20	453
	CFR, % (95% CI)	18.9 (17.3-20.4)	30.8 (19.5-42.0)	19.2 (17.6-20.8)

*Patients of the intermediate wave (n=130, all without rheumatic disease) were excluded.
CFR, case fatality rate; CI, confidence interval.

death was 33.5% (95% CI: 21.4-45.7) *vs* 19% (95% CI: 17.3-20.7), p=0.026 (Figure 1C), and the crude incidence of discharge was 43.5% (95% CI: 30.8-56.2) *vs* 60.9% (95% CI: 58.8-63.1), p=0.009 (Figure 1D), respectively, for rheumatic and non-rheumatic patients.

According to the Cox univariate analysis, the presence of a rheumatic disease was not significantly associated with a higher hazard of ICU or death compared to non-rheumatic diseases (Table III). The discharge hazard with or without ICU was significantly lower in rheumatic patients (Table III). In the same analysis, older age and higher Charlson comorbidity index were significantly associated with a higher hazard of ICU or death. The hazard of ICU or death without ICU was notably higher during the first wave and was significantly associated with the male gender (Table III). Multiple Cox model analyses adjusting for wave, age, gender, and the Charlson comorbidity index indicated that the rheumatic disease was not remarkably associated with a higher hazard of ICU or death, or discharge compared to the absence of rheumatic conditions (Table IV).

In the case-control study, the crude incidence for each endpoint (ICU admission, death, discharge) was comparable between rheumatic and non-rheumatic patients (Figure 2 and *Supplementary Table III*).

DISCUSSION

The impact of SARS-CoV-2 infection on patients with rheumatic diseases is currently unclear, especially in non-vaccinated subjects. Between February and November 2020, 2634 patients were admitted to Niguarda Hospital with a diagnosis of SARS-CoV-2 infection. Of this group, 2491 were included in the present study, and 65

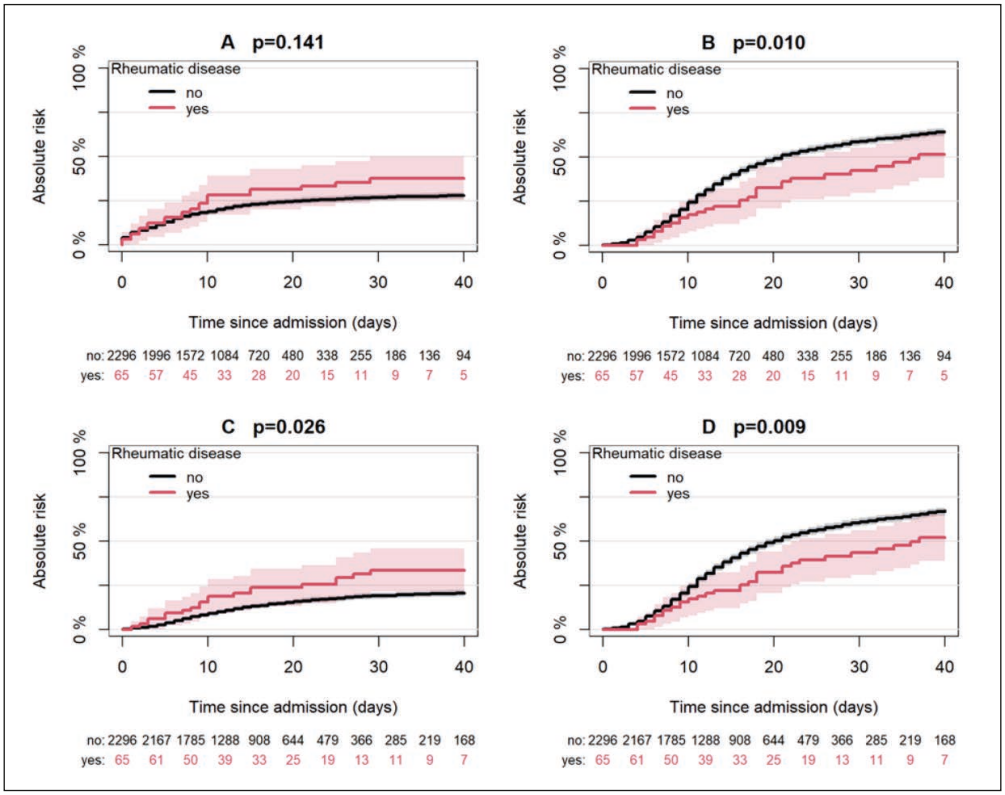

Figure 1 - Crude incidence (Aalen-Johansen estimates) of admission to intensive care unit or death before intensive care unit (A), discharge before intensive care unit (B), death in hospital (C), and discharge (D) by presence/absence of rheumatic disease (n=2361, patients of the intermediate wave were excluded).

Table III - Univariate cause-specific Cox models hazard ratios with 95% confidence interval to assess the association of patients' characteristics at baseline with each event (n=2361, data of the intermediate wave were excluded).

c	ICU or death without ICU (n=622), HR (95% CI)	Discharge without ICU (n=1335), HR (95% CI)
Wave (1 as reference)	0.612 (0.523-0.716)	0.965 (0.863-1.079)
Age (per 10-year increment)	1. 210 (1.149-1.275)	0.769 (0.748-0.791)
Gender (female as reference)	1.327 (1.119-1.573)	1.035 (0.926-1.156)
Charlson comorbidity index (score 0 as reference)		
Score 1	1.686 (1.144-2.485)	0.943 (0.784-1.134)
Score 2	1.558 (1.069-2.272)	0.669 (0.559-0.802)
Score 3	1.712 (1.180-2.485)	0.447 (0.368-0.544)
Score 4	1.667 (1.159-2.398)	0.339 (0.278-0.412)
Score ≥5	2.163 (1.577-2.966)	0.251 (0.213-0.296)
Rheumatic disease (no as reference)	1.193 (0.785-1.813)	0.608 (0.420-0.879)
	Death (n=453), HR (95% CI)	**Discharge (n=1432), HR (95% CI)**
Wave (1 as reference)	0.903 (0.750-1.088)	1.111 (0.999-1.236)
Age (per 10-year increment)	1.688 (1.565-1.821)	0.791 (0.769-0.814)
Gender (female as reference)	1.059 (0.872-1.286)	0.956 (0.858-1.065)
Charlson comorbidity index (score 0 as reference)		
Score 1	1.737 (0.760-3.970)	0.741 (0.622-0.883)
Score 2	2.893 (1.373-6.097)	0.623 (0.523-0.741)
Score 3	5.470 (2.695-11.106)	0.521 (0.432-0.628)
Score 4	6.887 (3.442-13.781)	0.450 (0.373-0.544)
Score ≥5	10.101 (5.197-19.633)	0.346 (0.296-0.404)
Rheumatic disease (no as reference)	1.374 (0.876-2.154)	0.671 (0.474-0.949)

ICU, intensive care unit; HR, hazard ratio; CI, confidence interval.

presented a rheumatic disease. These patients were more likely to be female, over 75 years old, and with a higher comorbidity rate than non-rheumatic patients. A CFR of 30.8% was reported among rheumatic patients during the study period. Among non-rheumatic patients, the CFR was 18.9%, and this difference was statistically significant (p=0.024).

Nevertheless, our findings suggest that the prognosis of SARS-CoV-2 infection is more likely to be related to other risk factors rather than rheumatic disease. Indeed, we observed no significant correlation between rheumatic disease and ICU admission or death. Else, in this study, a poor outcome from COVID-19 was associated with older age, the presence of comorbidities, and the male gender rather than the presence of rheumatic conditions. For instance, the surprisingly limited number of patients with rheumatic disease admissions from a large cohort of a general hospital referral hospital may be consistent with these findings.

Only a few studies reported a case-control analysis of patients with COVID-19 and rheumatic diseases. In our study, the case-control analysis showed that the crude incidence for each endpoint (ICU admission, death, discharge) was comparable between rheumatic and non-rheumatic patients.

Our observations align with most of the previous studies on rheumatic patients in the pre-vaccine era. The COVID-19 Global Rheumatology Alliance analyzed the largest cohort of patients with COVID-19 and rheumatic disease, describing 710 patients (8, 17). Similar to our cohort, rheumatic patients were mainly females, and the most

Table IV - Multivariable cause-specific Cox models hazard ratios with 95% confidence interval to assess the association of patients' characteristics at baseline with each event (n=2361, data of the intermediate wave were excluded). Adjustments in the multivariable model were performed for wave, age, gender, and Charlson comorbidity index.

Factors	ICU or death without ICU (n events=622), HR (95% CI)	Discharge without ICU (n events=1335), HR (95% CI)
Wave (1 as reference)	0.582 (0.496-0.682)	1.105 (0.986-1.238)
Age (per 10-year increment)	1.321 (1.205-1.448)	0.870 (0.829-0.913)
Gender (female as reference)	1.520 (1.277-1.808)	0.894 (0.798-1)
Charlson comorbidity index (score 0 as reference)		
Score 1	1.128 (0.747-1.703)	1.184 (0.965-1.452)
Score 2	0.907 (0.591-1.391)	0.894 (0.725-1.103)
Score 3	0.814 (0.512-1.293)	0.672 (0.524-0.862)
Score 4	0.655 (0.398-1.080)	0.553 (0.424-0.721)
Score ≥5	0.783 (0.481-1.277)	0.435 (0.335-0.564)
Rheumatic disease (no as reference)	1.285 (0.840-1.965)	0.815 (0.561-1.184)
	Death (n events=453), HR (95% CI)	**Discharge (n events=1432), HR (95% CI)**
Wave (1 as reference)	0.714 (0.591-0.862)	1.291 (1.157-1.44)
Age (per 10-year increment)	1.544 (1.382-1.724)	0.840 (0.801-0.881)
Gender (female as reference)	1.424 (1.165-1.739)	0.825 (0.739-0.92)
Charlson comorbidity index (score 0 as reference)		
Score 1	0.969 (0.419-2.243)	0.956 (0.788-1.160)
Score 2	1.178 (0.539-2.572)	0.890 (0.726-1.091)
Score 3	1.717 (0.791-3.729)	0.817 (0.644-1.035)
Score 4	1.643 (0.739-3.654)	0.760 (0.591-0.977)
Score ≥5	2.133 (0.967-4.706)	0.623 (0.487-0.796)
Rheumatic disease (no as reference)	1.199 (0.759-1.894)	0.792 (0.557-1.126)

HR, hazard ratio; ICU, intensive care unit; CI, confidence interval.

reported diagnosis was rheumatoid arthritis. Otherwise, our patients were more likely to be over 65 years and have a higher rate of comorbidities.

Other comparative studies were conducted on smaller cohorts of patients with diverse or selected rheumatic diseases, most concluding that this condition was not clearly associated with severe COVID-19 outcomes compared to the general population or that additional risk was marginal (9-16, 18-22). Moreover, outcomes of COVID-19 appeared to be primarily influenced by comorbidities and particular disease states or treatments (3, 23, 24).

Systematic reviews and meta-analyses were also provided. Conway *et al*. considered 100 studies (the majority with a low risk of bias) and found an increased prevalence of SARS-CoV-2 infection in rheumatic patients compared to the general population (25). The rates of hospitalization, ICU admission, and mechanical ventilation were similar in rheumatic patients and the general population. In contrast, the mortality rate increased in patients with a rheumatic disease [odds ratio (OR): 1.74; 95% CI: 1.08-2.80], yet unadjusted for confounding factors and with a remarkable heterogeneity (I^2=83%) (25). Accordingly, a limitation of this meta-analysis was the small number of studies that included adjusted risk estimates. Indeed, the meta-analysis was limited to unadjusted numbers resulting in data interpretation difficulties because of the potential imbalance of other risk factors between rheumatic patients and general populations. Other-

wise, the provided risk-adjusted analysis of COVID-19-related outcomes assessed in the few studies with adjusted risk ratios yielded conflicting results (25). This could be due to the heterogeneity in the study design or SARS-CoV-2 testing rates, which may reflect wide regional variation in outcomes from geographically diverse studies (26).

A systematic review with meta-analysis provided by Bellou et al. did not find an association between the presence of rheumatological diseases and a higher mortality risk. Nevertheless, also this meta-analysis focused on unadjusted effect estimates (27). Another systematic literature review by Kroon and collaborators suggested that rheumatic patients were not at higher risk of contracting SARS-CoV-2 nor a worse prognosis of COVID-19 than the general population (28).

Lastly, in contrast with our findings, the results from a recent national surveillance study promoted by the Italian Society for Rheumatology, including 668 patients with rheumatic diseases and COVID-19 during the first wave (between March and November 2020), showed that death risk increased (OR: 3.10, 95% CI: 2.29-4.12), independently from the differences in age and sex distributions compared with official data from the Italian population (29). Such a finding was confirmed even after considering the potential influence of surveillance bias (OR: 2.08, 95% CI: 1.55-2.73). However, the burden of comorbidities, which is known to be a major confounder, was not considered.

This study presents some limitations. Firstly, patients with rheumatic diseases were identified by reviewing the electronic records and confirmed by a rheumatologist.

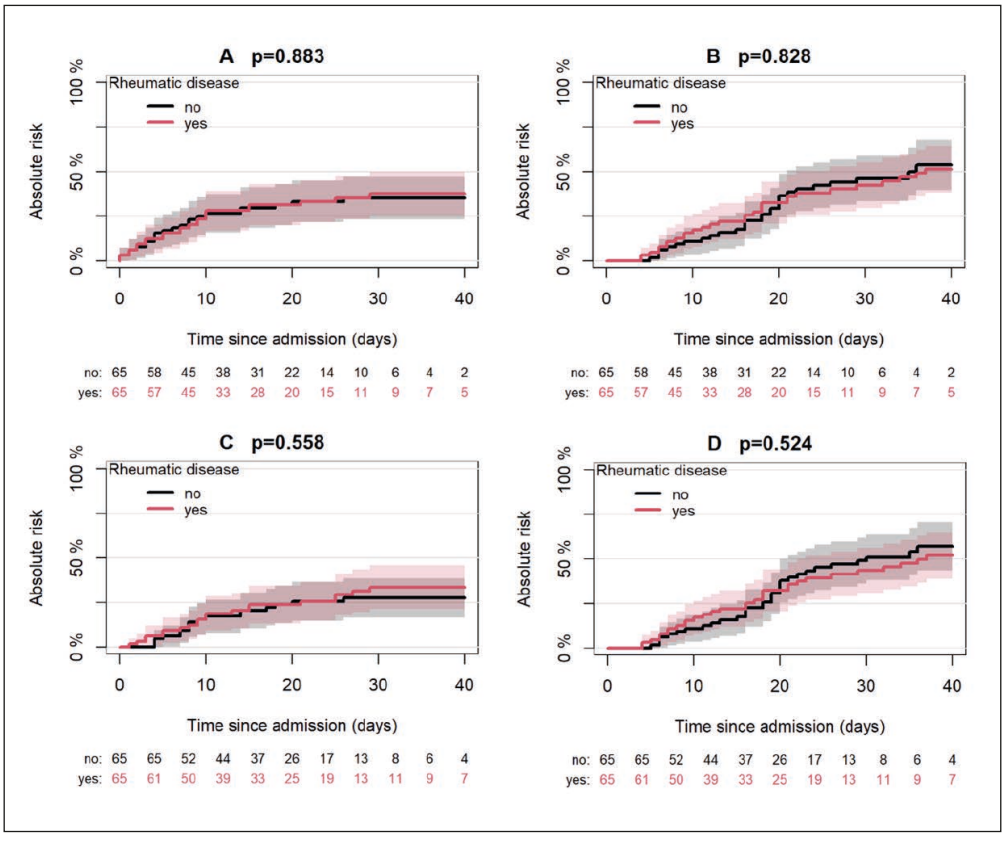

Figure 2 - Crude incidence (Aalen-Johansen estimates) of admission to intensive care unit or death before intensive care unit (A), discharge before intensive care unit (B), death in hospital (C), and discharge (D) by presence/absence of rheumatic disease in the case-control study.

However, misclassification issues (*i.e.*, incorrect diagnosis) and underestimation of this population may be hypothesized due to under-reporting by attending physicians during the admission. In addition, the retrospective design may generate measurement errors for assessing the confounding. However, the use of electronic and administrative data and hard outcomes were expected to protect from this bias. Lastly, the case-control design may have generated sampling bias. However, the random selection and matching from a vast cohort of controls from a general hospital were expected to reduce such bias.

For instance, our small sample did not allow the stratification of rheumatic patients based on diagnosis and treatment. Nevertheless, according to the study by Kroon *et al*., no consistent differences in the risk of developing severe COVID-19 were found between different categories of rheumatic patients (28).

In the SARS-CoV-2 vaccine era, vaccination coverage in patients with rheumatic disease is still not full (30, 31) and is prone to improvements (32). Unvaccinated patients, including those with rheumatic disease, are more prone to significant outcomes, such as hospitalization, ICU, and death, than vaccinated ones (33). In hospitalized unvaccinated patients, the rheumatic disease is not a clear prognostic factor for major events if age, sex, and other comorbidities are considered. This finding may support the physician in hospitalized patient management and communication of hospital outcomes.

CONCLUSIONS

Our findings suggest that in the case of SARS-CoV-2 infection, the presence of rheumatic diseases is not a clear prognostic factor for major events such as ICU and death. Otherwise, the high incidence of comorbidities among people with a rheumatic disease that is known to be associated with poor outcomes of SARS-CoV-2 infection should be carefully evaluated. In the case of hospitalized unvaccinated rheumatic patients, this finding may be used to support physicians in patient management and communication of hospital outcomes.

Contributions

NU, DPB, MGV, OME, CR, conceptualization, investigation and methodology; NU, CG, FDG, AD, data curation; DPB, MGV, NU, statistical analysis; NU, OME, supervision; NU, DPB, writing – original draft. All authors contributed to the formal analysis, reviewed and edited the manuscript and gave approval to submit.

Ethics approval and consent to participate

The study was conducted following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and within the protocol approved by the Ethics Committee Milano Area 3 (register number 249-13052020).

Patient consent for publication

All the participants provided an informed consent form. However, patients' consent for publication is not required as this manuscript does not include details, images, or videos related to the participants.

Availability of data and materials

Data and materials are available upon reasonable request.

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REFERENCES

1. Civil Protection Department, Presidency of the Council of Ministers, Italian Government. Coronavirus dashboards. Available from: http://arcg.is/C1unv. Accessed: 14/05/2022.
2. ISTAT. Popolazione e famiglie. Available from: https://www.istat.it/it/popolazione-e-famiglie?dati. Accessed: 10/12/2022.
3. Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol. 2022; 18: 191-204.
4. Meroni PL, Zavaglia D, Girmenia C. Vaccina-

tions in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs. Clin Exp Rheumatol. 2018; 36: 317-28.
5. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis with its comorbidity and treatment. Rheumatology. 2013; 52: 53-61.
6. Huang Y, Chen Z, Wang Y, Han L, Qin K, Huang W, et al. Clinical characteristics of 17 patients with covid-19 and systemic autoimmune diseases: a retrospective study. Ann Rheum Dis. 2020; 79: 1163-9.
7. Freites Nuñez DD, Leon L, Mucientes A, Rodriguez-Rodriguez L, Font Urgelles J, Madrid García AM, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020; 79: 1393-9.
8. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for covid-19 in people with rheumatic disease: data from the covid-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis. 2020; 79: 859-66.
9. Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F. Brescia Rheumatology covid-19 study group. Covid-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. Lancet Rheumatol. 2020; 2: e549-56.
10. Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al. Clinical outcomes of hospitalised patients with covid-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis. 2020; 79: 1544-9.
11. Pang R, Zhao J, Gan Z, Hu Z, Xue X, Wu Y, et al. Evolution of covid-19 in patients with autoimmune rheumatic diseases. Aging (Albany NY). 2020; 12: 23427-35.
12. Faye AS, Lee KE, Laszkowska M, Kim J, Blackett JW, McKenney AS, et al. Risk of adverse outcomes in hospitalized patients with autoimmune disease and covid-19: a matched cohort study from new york city. J Rheumatol. 2021; 48: 454-62.
13. Montero F, Martínez-Barrio J, Serrano-Benavente B, González T, Rivera J, Molina Collada J, et al. Coronavirus disease 2019 (Covid-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. Rheumatol Int. 2020; 40: 1593-8.
14. Cordtz R, Lindhardsen J, Soussi BG, Vela J, Uhrenholt L, Westermann R, et al. Incidence and severeness of covid-19 hospitalization in patients with inflammatory rheumatic disease: a nationwide cohort study from Denmark. Rheumatology (Oxford). 2021; 60: SI59-67.
15. Serling-Boyd N, D'Silva KM, Hsu TY, Wallwork R, Fu X, Gravallese EM, et al. Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis. 2021; 80: 660-6.
16. D'Silva KM, Jorge A, Cohen A, McCormick N, Zhang Y, Wallace ZS, et al. Covid-19 outcomes in patients with systemic autoimmune rheumatic diseases compared to the general population: a US multicenter, comparative cohort study. Arthritis Rheumatol. 2021; 73: 914-20.
17. Gianfrancesco MA, Hyrich KL, Gossec L, Strangfeld A, Carmona L, Mateus EF, et al. Rheumatic disease and covid-19: initial data from the covid-19 global rheumatology alliance provider registries. Lancet Rheumatol. 2020; 2: e250-3.
18. Enginar AU, Gundogdu M. The course of covid-19 in patients with Behçet's disease. Reumatologia. 2021; 59: 356-61.
19. Hsu TY, D'Silva KM, Patel NJ, Wang J, Mueller AA, Fu X, et al. Laboratory trends, hyperinflammation, and clinical outcomes for patients with a systemic rheumatic disease admitted to hospital for covid-19: a retrospective, comparative cohort study. Lancet Rheumatol. 2021; 3: e638-47.
20. Kjeldsen J, Nielsen J, Ellingsen T, Knudsen T, Nielsen RG, Larsen MD, et al. Outcome of covid-19 in hospitalized patients with chronic inflammatory diseases. a population based national register study in Denmark. J Autoimmun. 2021; 120: 102632.
21. Thompson K, Shah A, Grunbaum A, Oyesanmi O. Investigation into the effect of covid-19 infection on length of hospital stay and mortality in patients with rheumatoid arthritis. Cureus. 2022; 14: e22685.
22. Peach E, Rutter M, Lanyon P, Grainge MJ, Hubbard R, Aston J, et al. Risk of death among people with rare autoimmune diseases compared with the general population in England during the 2020 covid-19 pandemic. Rheumatology (Oxford). 2021; 60: 1902-9.
23. Andersen KM, Bates BA, Rashidi ES, Olex AL, Mannon RB, Patel RC, et al. Long-term use of immunosuppressive medicines and in-hospital covid-19 outcomes: a retrospective cohort study using data from the national covid cohort collaborative. Lancet Rheumatol. 2022; 4: e33-41.
24. Curtis JR, Zhou X, Rubin DT, Reinisch W, Yazdany J, Robinson PC, et al. Characteristics, comorbidities, and outcomes of sars-cov-2 infection in patients with autoimmune conditions treated with systemic therapies: a population-based study. J Rheumatol. 2022; 49: 320-9.
25. Conway R, Grimshaw AA, Konig MF, Putman M, Duarte-García A, Tseng LY, et al. Sars-Cov-2 infection and Covid-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. Arthritis Rheumatol. 2022; 74: 766-75.

26. Mazumder A, Arora M, Sra MS, Gupta A, Behera P, Gupta M, et al. Geographical variation in case fatality rate and doubling time during the covid-19 pandemic. Epidemiol Infect. 2020; 148: e163.
27. Bellou V, Tzoulaki I, van Smeden M, Moons KGM, Evangelou E, Belbasis L. Prognostic factors for adverse outcomes in patients with Covid-19: a field-wide systematic review and meta-analysis. Eur Respir J. 2022; 59: 2002964.
28. Kroon FPB, Najm A, Alunno A, Schoones JW, Landewé RBM, Machado PM, et al. Risk and prognosis of sars-cov-2 infection and vaccination against sars-cov-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform eular recommendations. Ann Rheum Dis. 2022; 81: 422-32.
29. Zanetti A, Carrara G, Landolfi G, Rozza D, Chighizola CB, Alunno A, et al. Increased COVID-19 mortality in patients with rheumatic diseases: results from the control-19 study by the Italian Society for Rheumatology. Clin Exp Rheumatol. 2022; 40: 2038-43.
30. Krasselt M, Baerwald C, Seifert O. Covid-19 vaccination coverage in patients with rheumatic diseases in a german outpatient clinic: an observational study. Vaccines (Basel). 2022; 10: 253.
31. Putman M, Kennedy K, Sirotich E, Liew JW, Sattui SE, Moni TT, et al. Covid-19 vaccine perceptions and uptake: results from the covid-19 global rheumatology alliance vaccine survey. Lancet Rheumatol. 2022; 4: e237-40.
32. Goulenok T, Francois C, Mendes C, Farhi F, Alexandra JF, Rouzaud D, et al. Improving covid-19 vaccine coverage in patients with autoimmune and inflammatory diseases. J Rheumatol. 2022; 49: 118-9.
33. Papagoras C, Fragoulis GE, Zioga N, Simopoulou T, Deftereou K, Kalavri E, et al. Better outcomes of covid-19 in vaccinated compared to unvaccinated patients with systemic rheumatic diseases. Ann Rheum Dis. 2022; 81: 1013-6.