Different Covid-19 Outcomes Among Systemic Rheumatic Diseases: A Nation-wide Cohort Study

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Running Title: Covid-19 in Systemic Rheumatic Diseases

Keywords: Covid-19; Rheumatoid Arthritis; Ankylosing Spondylitis; Psoriatic Arthritis; Systemic Lupus Erythematosus; Systemic Sclerosis

Objectives: To investigate Covid-19-associated risk of hospitalization and death in rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) in comparison with the general population during pandemic's first year and compare their overall mortality with 2019.

Methods: Interlinking nation-wide electronic registries, we recorded confirmed Covid-19-associated infections, hospitalizations and deaths, and all-cause deaths between 1-March-2020 and 28-February-2021 in all adults with RA, AS, PsA, SLE, and SSc under treatment (n=74,970, median age 67.5, 51.2, 58.1, 56.2, 62.2 years, respectively) and in matched (1:5) on age, sex, and region of domicile random comparators from the general population. Deaths from all causes during 2019 were also recorded.

Results: Compared to the general population incidence rates (IR) for Covid-19-associated hospitalization were higher in RA [IR ratio (IRR):1.71(1.50-1.95)], SLE [2.0(1.4-2.7)] and SSc [2.28(1.29-3.90)], while Covid-19-associated death rates were higher in RA [1.91(1.46-2.49)]. When focusing only on SARS-CoV-2 infected subjects, after adjusting for age and gender, the odds ratio for Covid-19 associated death was higher in RA [1.47(1.11- 1.94)] and SSc [2.92(1.07-7.99)] compared to the general population. All-cause mortality rate compared to the general population increased in RA during the first pandemic year (IRR:0.71) with reference to 2019 (0.59) and decreased in SSc (IRR:1.94 vs 4.36).

Conclusion: Covid-19 may have more severe impact in patients with systemic rheumatic disease than the general population. Covid-19-related mortality is increased in subgroups of patients with specific rheumatic diseases, underscoring the need for priority vaccination and access to targeted treatments.

Key Messages

- RA, SLE and SSc patients have higher Covid-19-associated hospitalization risk compared to the general population.
- RA patients have higher risk of Covid-19-associated death compared to the general population.
- All-cause mortality during pandemic-associated lock-down increased versus 2019 in RA and decreased in SSc.

Introduction:

Over the last two years, corona virus disease 2019 (Covid-19) has been associated with increased morbidity and mortality in the general population[1]. Evidence, however, regarding systemic rheumatic diseases which affect almost 2% of the population[2] is not conclusive. In the systematic literature review performed to inform the respective European Alliance of Associations for Rheumatology recommendations, no signal for increased mortality in systemic rheumatic diseases compared to the general population was detected[3]. Similar results were presented in a recent meta-analysis examining data from 26 observational studies[4]. On the other hand, a large meta-analysis of 71 studies showed that patients with systemic rheumatic disease displayed increased odds for mortality[5]. The same uncertainty also applies to the question whether systemic rheumatic disease patients are more susceptible to contracting Covid-19, with systematic literature reviews and meta-analyses again having discordant results[3–5]. To make matters more complicated, the known increased rates of concomitant comorbidities, including arterial hypertension, cardiovascular disease, diabetes, and malignancy[6–12] may have a major additional impact. In any case, whether a propensity of systemic rheumatic disease patients towards more severe Covid-19 associated outcomes, as found in some studies, is true for some or for all diseases remains unclear.

During the first year of the pandemic, Greece implemented a strict lockdown policy limiting Covid-19-associated deaths to 6,504. In this setting, by interlinking data from national electronic registries between March 2020, when the Covid-19 pandemic started in our country, and February 2021, when vaccination became available to patients with systemic rheumatic diseases, we aimed to investigate the Covid-19-

associated risk of hospitalization and death in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) in comparison with the general population. Furthermore, we sought to assess the risk of Covid-19-associated hospitalization and death following infection, focusing only on SARS-CoV-2 infected subjects from out cohort, with or without underlying systemic rheumatic disease. Finally, we aimed to compare overall mortality of RA, AS, PsA, SLE and SSc during the first year of the pandemic, with their overall mortality in the pre-Covid-19 year.

Methods:

Setting:

The first confirmed case of Covid-19 in Greece was identified on 26 February 2020. Until 28 February 2021 there had been 191,100 confirmed cases and 6,504 Covid-19 associated deaths reported in the country. During the first year of the pandemic several measures were implemented to contain transmission of the virus, including a strict lock-down from 23 March 2020 until 14 May 2020; schools and tourist enterprises did not reopen until 1 June 2020 and 1 July 2020, respectively. A second pandemic wave in November 2020 led to a new lockdown from 7 November 2020, with measures remaining in place until after March 2021 in some regions, including Athens, the country's capital. On the other hand, priority vaccination against Covid-19 in Greece became available for patients with systemic rheumatic disease in mid-March 2021.

Data Sources:

In Greece, an electronic database for social security services (IDIKA) operates since 2011, currently covering 99% of the country's population of about 11,000,000 people. Information about prescribed medications, medical diagnoses (based on the specific International Classification of Disease [ICD-10]), age, gender and region of domicile derived from this database can be linked to the nationwide death records as well as to the national Covid-19 digital registry, which includes data on hospitalizations and deaths of all confirmed Covid-19 cases in the country.

Study Population:

In this nationwide, population-based cohort study we identified all adult patients with RA, AS, PsA, SLE, and SSc alive on 1-March-2020. For this purpose, we used our published data[13] derived from the electronic prescription database for social security services (IDIKA). This data included all adult (aged ≥18years old) patients who had filled at least one prescription for corticosteroids, conventional synthetic disease modifying anti-rheumatic drugs (DMARDs), immunosuppressants, biologic DMARDs, targeted synthetic DMARDs, advanced vasodilatory medications or antifibrotic agents between 1-January-2015 and 31-December-2019 with a diagnosis of either RA, AS, PsA, SLE or SSc, based on prespecified for each disease ICD-10 codes. A detailed list of relevant ICD-10 (**Supplementary Table S1**) and ATC-5 codes **(Supplementary Table S2**) for diagnoses and medications of interest, respectively, is shown in the supplementary material available at *Rheumatology* online. Each of the 74,970 patients identified in total, was matched to 5 random referents from the general population for gender and age, as well as for region of domicile

For all subjects in our cohort, we retrieved data on age, gender and death from all causes and by crosslinking with the national Covid-19 registry, data on SARS-CoV-2 infection confirmed by reverse-transcriptase-polymerase-chain-reaction or antigen-detecting rapid diagnostic testing, as well as Covid-19-associated hospitalization and death, during the study period i.e. between 1 March 2020 and 28 February 2021.

To compare incidence rates of death from all causes during the first year of the pandemic in our cohort with the respective incidence rates from the pre Covid-19 era, we identified all adult patients with RA, AS, PsA, SLE and SSc alive on 1-January-2019 and again matched each patient to 5 random referents from the general population for gender, age and region of domicile, using the same methodology as described above. This comparison cohort included all patients aged 18 years or older, who had filled at least one prescription for the above-mentioned medications of interest with a diagnosis of RA, AS, PsA, SLE or SSc, as specified above, between 1-January-2015 and 31-December-2018. For these patients we recorded death from all causes between 1-January 2019 and 31-12-2019.

Following approval of our formal request, the Greek Ministry of Health granted us permission to use anonymized data deposited in the social security services (IDIKA) database and the National Covid-19 digital registry, according to the European legislation for General Data Protection Regulation, (27 April 2016) and the Greek national laws (4600/2019, 4624/2019, 3892/10, 3418/2005).

Statistical Analysis:

Continuous variables were presented as median (Q1-Q3) and categorical variables were reported as numbers and percentages. Incidence rates per 1000 person-years and patient to referent incidence rate ratios (IRR) were estimated for a. SARS-CoV-2 infection, b. Covid-19 associated hospitalization and c. Covid-19-related death for RA, AS, PsA, SLE and SSc patients and their matched referents from the general population. Binary logistic regression analysis was further conducted for each disease group and its referents, to estimate Odd Ratios (OR) for Covid-19 related hospitalization and death, in SARS-CoV-2 infected subjects in our cohort, using subjects free of underlying systemic rheumatic disease as the reference category. All logistic regression models were adjusted for age, gender and underlying disease. Incidence rates of death from all causes and patient to referent IRR were estimated for RA, AS, PsA, SLE and SSc patients and for their matched population referents during two different time periods, the first extending from 1 January 2019 to 31 December 2019 and the second from 1 March 2020 to 28 February 2021. In all analyses age was treated as a continuous variable, increasing by year. There were no missing data on covariates we selected to record. The level of statistical significance was set at a p-value of ≤ 0.05. Statistical analysis was performed using the Stata statistical software package (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

Results:

Cohort demographics

Our search of the IDIKA database, using the above-described criteria, retrieved 40,014 RA patients (79% female), 9,566 AS patients (43% female), 13,405 PsA patients (55% female), 9,960 SLE patients (90% female) and 2,025 SSc patients (88% female). RA patients were older compared to other systemic rheumatic disease patients with a

median (Q1-Q3) age of 67.5 (57.4 to 76.0) years, followed by SSc [62.2 (51.7 to 71.0) years], PsA [58.1 (48.6 to 68.0) years], SLE [56.2 (45.2 to 67.2) years] and AS patients [51.2 (41.9 to 60.4) years]. Total follow-up was 74,765 person-years for systemic rheumatic disease patients and 372,019 person-years for their matched comparators. **Table 1** shows demographics of systemic rheumatic disease patients and their matched referents from the general population. SARS-CoV-2 infections, Covid-19 related hospitalizations and deaths occurring in our cohort between 1 March 2020 and 28 February 2021 are also shown in **Table 1**.

Comparison of patients with RA, AS, PsA, SLE and SSc with matched population referents

Table 2 shows incidence rates per 1000 patient-years for Covid-19 associated infection, hospitalization, and death among patients with RA, AS, PsA, SLE and SSc, and their matched population comparators. Rates of infection were higher among patients with systemic rheumatic diseases compared to their matched referents [IRR 1.33 (1.23 to 1.44) for RA, IRR: 1.28 (1.10 to 1.49) for AS, IRR: 1.23 (1.07 to 1.40) for PsA, IRR: 1.21 (1.03 to 1.42) for SLE and IRR: 1.52 (1.08 to 2.11) for SSc, respectively]. Regarding rates of hospitalization, these were higher among patients with RA [IRR: 1.71 (1.50 to 1.95)], SLE [IRR: 2.0 (1.4 to 2.7)] and SSc [IRR: 2.28 (1.29 to 3.90)] compared to their matched population referents. Finally, mortality rates were only found to be higher among RA patients compared to their matched comparators from the general population [IRR: 1.91 (1.46 to 2.49)].

Subgroup analyses among SARS-CoV-2 infected subjects

To investigate for potential differences between patients with systemic rheumatic disease infected with SARS-CoV-2, we performed a subgroup analysis, using infected subjects without underlying rheumatic disease as the reference group. After adjustment for age and sex, we found that the odds ratio for Covid-19 associated hospitalization was higher in SSc, (OR: 2.84, 95% CI: 1.51 to 5.36) followed by SLE (OR: 2.19 95% CI: 1.55 to 3.09) and RA patients, (OR: 1.55, 95% CI: 1.30 to 1.84). Regarding Covid-19 associated death once infected, SSc patients had the worse outcomes in comparison to the general population (OR: 2.92, 95% CI: 1.07 to 7.99), followed by RA patients (OR: 1.47, 95% CI: 1.11 to 1.94). No difference in Covid-19 associated mortality was found between patients with AS, PsA or SLE and the general population **(Figure 1)**.

Overall mortality of RA, AS, PsA, SLE and SSc patients during the first pandemic year in comparison to the pre-Covid-19 year.

For RA, AS, PsA, SLE, and SSc patients in our cohort and their matched referents from the general population we estimated Incidence Rates (IR) of death from all causes per 1000 person-years for the time period under study, as shown in **Table 3**. The comparison cohort for the year 2019 included 36,589 RA patients [79.9% female, 66.7 (56.7-75.2) years median (Q1-Q3) age], 8,527 AS patients [41.5% female, 50.7 (41.3-59.7) years median age], 12,025 PsA patients [55.0% female, 57.4 (47.9-67.3) years median age], 10,073 SLE patients [89.7% female, 55.3 (44.3-66.5) years median age] and 1,938 SSc patients [88.4% female, 61.8 (51.5-70.9) years median age]. Using all-cause mortality data from the comparison cohort we estimated death rates per 1000 person-years in the pre-Covid-19 era, between 1-1-2019 and 31-12-2019 **(Table. 3)**. Interestingly, using 2019 as the reference year, all-cause mortality was higher for RA patients in comparison to the general population during the first year of the pandemic in Greece, [IRR (95% CI) for death from all causes: 0.71 (0.67 to 0.74) in 2020-21 vs 0.59 (0.55 to 0.63) in 2019], whereas it decreased by more than half for SSc patients [IRR (95% CI) for death from all causes: 1.94 (1.74 to 2.17) in 2020-21 vs 4.36 (4.30 to 4.43) in 2019]. No difference was found for AS, PsA and SLE patients.

Discussion

Our 12-month study, analysing data derived from merging large nationwide databases covering the entire Greek population, shows that unvaccinated patients with RA, SLE and SSc have a higher probability for hospitalization due to Covid-19, while patients with RA also have a higher Covid-19 associated mortality rate compared to the general population. Given the well-established association of older age with an increased risk of Covid-19-related death, the higher mortality in RA patients, who are older than patients with AS, PsA, SLE and SSc, could be partly explained by the age-associated burden of comorbidities which are known to be more frequent in any systemic rheumatic disease[6–12].

Regarding the risk of SARS-CoV-2 infection, we found that patients with the systemic rheumatic diseases under study had higher probability to contract Covid-19 compared to the general population, in agreement also with two general population-

based cohort studies [14, 15] and two recent-metanalyses[4, 5]. This finding could be explained by higher susceptibility of these individuals to Covid-19 infection although the possibility that these patients were more frequently tested cannot be excluded. Therefore, whether a tendency to contract the infection more easily, together with the increased comorbidity burden, can explain the higher Covid-19 associated death risk found in RA patients compared to the general population needs further study[16]. Along these lines, when we focused only on subjects infected with SARS-CoV-2, adjusting for age and gender, we found that, patients with SSc and RA infected with Covid-19, displayed an increased Odds Ratio both for Covid-19 hospitalization and death compared to the general population.

To investigate whether the pandemic had an effect on all-cause mortality for rheumatic patients, we further analyzed the age and gender-adjusted mortality between 2019 and 2020 across all rheumatic patient groups. This effect of the pandemic can be direct due to Covid-19 infection, but also indirect due to reduced access to care as a result of the stringent public health measures, or any other factor affecting mortality in the population. Our data indicate that in comparison to matched population referents, all-cause mortality for patients with RA increased during the first year of the pandemic compared to 2019, suggesting that Covid-19 affected this population. Recently, a systematic analysis was published, estimating the excess mortality due to the Covid-19 pandemic during the two-year period 2020-2021, in many different countries and territories of the world. According to this analysis 20,800 deaths due to Covid-19 have been registered in Greece during the first two years of the pandemic, leading to a reported Covid-19 mortality rate of 104.1 with an estimated excess mortality rate of 127.1 (95% CI: 117.0 to 137.2) per 100,000[17].

On the other hand, all-cause mortality decreased by more than half for patients with SSc. This difference could reflect the extent and efficacy of self-protective measures taken by patients with SSc, a large proportion of them having clinically significant interstitial lung disease[18]. This finding is of particular interest and shows that when vulnerable populations with chronic diseases are compliant to public health measures, all-cause mortality can be reduced during a pandemic. This highlights the importance of non-pharmaceutical interventions among SSc patients and further supports the need for public health risk communication during a global health crisis. It should be noted

that a similarly impressive reduction in all-cause mortality was reported in the same setting, i.e. during the early Covid-19 lockdown in Greece, for patients with idiopathic pulmonary fibrosis, possibly due to the implementation of public health measures against Covid-19, such as social distancing, use of face masks and hands hygiene[19].

To the best of our knowledge only one previous nation-wide study assessing mortality risk of unvaccinated patients with chronic inflammatory arthritis versus the general population has been published[20]. This was a 6-month study in Sweden, a country where public measures were far less strict, especially during the first pandemic wave, compared to the rest of the world. The authors reported that death rates were increased when adjusting only for age, sex and region of domicile, but this risk was mitigated when additionally adjusting for comorbidities and socioeconomic factors. The adjusted HR for Covid-19 associated death in all inflammatory joint diseases examined in this study was 1.18 (95% CI 0.97 to 1.44), while the adjusted HR for Covid-19 associated death in RA was 1.27 (1.02 to 1.59), compared with matched general population comparator subjects, which is, indeed, significantly higher. The authors concluded that, in absolute terms, risks of serious outcomes from Covid-19 in patients with inflammatory joint disease are strongly affected by age and the presence of comorbidities. Our findings, in accordance with the Swedish nation-wide study, also indicate an increased likelihood of death due to Covid-19 among RA patients in comparison to the general population, while no difference could be shown among the other inflammatory arthritis groups examined.

A second nationwide 5-month study from South Korea included 133,609 adult subjects tested for SARS-CoV-2 (3.65% tested positive), of whom 8,297 had inflammatory rheumatic diseases. In comparison to the general population, patients with rheumatic disease had a 19% increased likelihood of testing positive for SARS-CoV-2, 26% higher risk of severe Covid-19 outcomes and 69% higher risk of Covid-19 associated death. Patients with rheumatic diseases receiving higher corticosteroid doses (≥10 mg prednisolone per day) were particularly vulnerable to developing worse Covid-19 associated outcomes[21]. Notably, our results are in line with this study, as well as with the results of a meta-analysis by Conway et al. reporting an OR of 1.74 (95%CI: 1.08 to 2.80) for Covid-19-related death in systemic rheumatic disease patients in comparison with the general population[5]. It should be here noted

that both our study and the meta-analysis of Conway et al. could not adjust for comorbidities, disease severity or disease duration, due to the lack of the corresponding data in the data sources used. This important limitation should be taken in account when interpreting these findings, given the high frequency of comorbidities among patients with systemic rheumatic disease[6–12] and the strong influence that comorbidities and disease activity exert on Covid-19 associated outcomes in this patient population[22, 23].

As regards hospitalization rates, there are four nation-wide studies, one from Sweden[20], two from Denmark[15, 24] and one from Iceland[25], in line with our findings, while two meta-analyses[4, 5] report different results on this matter. This could be interpreted in light of several differences between countries, such as local guidelines, intensity of pandemic wave, saturation level of health care system, access to healthcare facilities and other confounders[26]. Increased hospitalization rates could be possibly also due, at least in part, to lower threshold for admission of patients suffering from a systemic rheumatic disease. Besides, in concert with our results various factors have been previously identified to associate with Covid-19-related hospitalization, including male gender, higher age and specific diseases like RA, vasculitis, and connective tissue diseases[23, 24, 27–30]. Importantly, vaccination[15] and treatment with biologic agents has been negatively associated with hospital admission in other studies [4, 28, 31].

In general, findings about Covid-19 related outcomes in systemic rheumatic disease patients should be interpreted with caution[32]. Inconsistencies between various studies may pertain to ethnic or racial differences[33], to the heterogeneity of systemic rheumatic disease and their treatment, differences in the intensity of pandemic waves and the capacity of health care system, but also to the different study designs or timing of data acquisition with regard to the implementation of patient vaccination policies[15]. That said, we should note that our study was performed before vaccination was available among systemic rheumatic disease patients in Greece.

A recently published study also raised some concerns about high rate of biases (e.g participation and ascertainment bias) occurring in the studies being published about

this topic[34]. This was also noted in a recent systematic literature review performed to inform respective EULAR recommendations[3]. In the strengths of our study, one can include the following: firstly, it is a nationwide study examining the whole population of our country (approximately 11 million people) during the whole first year of the pandemic. To further strengthen our methodology, matching with the general population was adjusted for area of residence, limiting biases concerning access to healthcare facilities and regional differences in Covid-19 incidence rate. Despite the fact that population coverage of the IDIKA database is very high, there is always a risk that patients with a lower socioeconomic status, usually being followed up in public hospitals, are overrepresented in the database compared to patients from the private sector, who would expectedly be able to afford to buy their medications. To eliminate selection bias, we limited our requirements for inclusion in the cohort to one filled prescription with any of the above-mentioned medications of interest between 2015-2019. Therefore, only a very small minority of patients consistently buying their rheumatology drugs over the counter for 5 consecutive years would not have been captured. Also, in contrast to other studies, we have examined simultaneously five major systemic rheumatic diseases in the same population which also allowed us to make comparison between diseases.

One major weakness of our study, as mentioned above, is the inability to adjust our findings for disease duration, disease activity and the presence of comorbidities. However, in the sense that comorbidities now tend to be seen as an inherent component of systemic rheumatic disease, we believe that it is hard to decipher whether the higher Covid-19 associated death rate observed in certain of these patient' subgroups should be attributed to the systemic rheumatic disease per se or to the concomitant presence of other diseases. It is also worth mentioning that no adjustment was made in our analysis for use of rheumatic disease specific treatments, such as corticosteroids, conventional synthetic, targeted synthetic or biologic DMARDs. Some previous studies have, indeed, reported an association of certain treatments, namely corticosteroids at a dose of ≥10mg prednisolone/day[28], or rituximab[35] with a worse Covid-19 outcome, while other medications were found to have a beneficial effect, with tocilizumab[36] or baricitinib[37] for example, now being used to treat severe Covid-19 infections. Although data on medication usage for our cohort could be retrieved from the database, other potential confounders such as disease

duration, disease severity, comorbidities, treatment adherence or timing of treatment with regard to the occurrence of SARS-CoV-2 infection could not be addressed, which would have undermined the robustness of our results. Therefore, we deemed best not to include medication usage in our analysis.

Conclusions

Covid-19 outcomes clearly differ between patients with RA, AS, PsA, SLE and SSc. The probability of death from Covid-19 was found higher in RA patients versus matched referents from the general population. Furthermore, once infected with SARS-CoV-2, both RA and SSc patients had worse Covid-19-associated outcomes compared to the general population, implying that priority vaccination policies and access to targeted therapeutic approaches are important, especially for older patients and specific patient subgroups. The increased death rate is probably attributable to the presence of comorbidities, which are inherent to the chronic inflammatory process characterizing systemic rheumatic diseases. Further studies could help in effective risk stratification for systemic rheumatic disease patients and therefore result in better outcomes.

List of abbreviations

AS: Ankylosing Spondylitis
CI: Confidence Interval
Covid-19: Corona virus disease 2019
DMARDs: Disease Modifying Anti-Rheumatic Drugs
EULAR: European League Against Rheumatism
ICD-10: International Classification of Disease-10
OR: Odds Ratio
PsA: Psoriatic Arthritis
RA: Rheumatoid Arthritis
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SLE: Systemic Lupus Erythematosus
SRD: Systemic Rheumatic Disease
SSc: Systemic Sclerosis

Declarations

Authors' contributions: VKB contributed to study design, curation of data and drafting the manuscript, GEF contributed to study design and drafting the manuscript, IT, KM, AT and PM contributed to data curation, GK contributed to statistical analysis, GV and DP contributed to study design and statistical analysis, MT contributed to study design and critically revised the manuscript, PPS conceived the original idea, supervised the project and contributed to study design, writing and reviewing the manuscript.

Ethics approval and consent to participate: The Data Protection Office of the Greek Ministry of Health (17 Aristotelous str, 10187, Athens, Greece, email: dpo@moh.gov.gr / gdpr@moh.gov.gr), gave ethical approval for this work, granting permission for the use of anonymized data deposited in the social security services (IDIKA) database and the national Covid-19 digital registry, according to the European legislation for General Data Protection Regulation, (27 April 2016) and the Greek national laws (4600/2019, 4624/2019, 3892/10, 3418/2005).

Patient and Public Involvement statement: Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Consent for publication: Not applicable

Competing interests: The authors have declared no conflicts of interest.

Funding: This work was partly supported by the Kleon Tsetis Foundation, in the context of promoting academic research initiatives within its COVID-19 response framework

Availability of data and materials: The data that support the findings of this study are available from the Data Protection Officer of the Greek Ministry of Health but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from

the authors upon reasonable request and with permission of the Data Protection Officer of the Greek Ministry of Health.

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Table 1. Demographics and number of Covid-19-associated infections, hospitalizations, and deaths recorded among patients and population referents.

Demographics and number of SARS-CoV-2 infections, number of Covid-19-associated hospitalizations and deaths recorded between 1-3-2020 and 28-2-2021 among patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and their matched population referents.

	RA		**AS**		**PsA**		**SLE**		**SSc**	
	Patients N=40014	**Population referents N=200070**	**Patients N=9566**	**Population referents N=47830**	**Patients N=13405**	**Population referents N=67025**	**Patients N=9960**	**Population referents N=49800**	**Patients N=2025**	**Population referents N=10125**
Female gender, N (%)	31782 (79.4)	158910 (79.4)	41287 (43.1)	20635 (43.1)	7402 (55.2)	37010 (55.2)	8948 (89.8)	44740 (89.8)	1786 (88.2)	8930 (88.2)
Median age (Q1-Q3) at study entry	67.5 (57.4-76.0)		51.2 (41.9-60.4)		58.1 (48.6-68.0)		56.2 (45.2-67.2)		62.2 (51.7-71.0)	
SARS-CoV-2 infection N (%)	767 (1.92)	2860 (1.43)	221 (2.31)	860 (1.80)	285 (2.13)	1156 (1.72)	197 (1.98)	812 (1.63)	49 (2.42)	161 (1.59)
Covid-19 hospitalization N (%)	315 (0.79)	914 (0.46)	42 (0.44)	154 (0.32)	65 (0.48)	260 (0.39)	59 (0.59)	151 (0.30)	21 (1.04)	46 (0.45)
Covid-19 death N (%)	79 (0.20)	205 (0.10)	3 (0.03)	21 (0.04)	10 (0.07)	41 (0.06)	9 (0.09)	25 (0.05)	5 (0.25)	9 (0.09)

Table 2. Patient to matched population referent incidence rate ratios of Covid-19-associated infections, hospitalizations, and deaths. Incidence Rates (IR) per 1000 person years with 95% Confidence Intervals (CI) for Covid-19 infection, hospitalization and death among rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) patients and their matched referents from the general population. Patient to population referents Incidence Rate Ratios (IRR) with 95% CI have been estimated for each disease group. IRR indicating a statistically significant difference between patients and their matched population referents are denoted in bold.

	RA			AS			PsA			SLE			SSc		
	patients	Population referents	IRR	patients	Population referents	IRR	patients	Population referents	IRR	patients	Population referents	IRR	patients	Population referents	IRR
Covid-19 infection IR (95% CI)	19.2 (17.9 to 20.7)	14.4 (13.9 to 15.0)	**1.33 (1.23 to 1.44)**	23.1 (20.3 to 26.4)	18.0 (16.9 to 19.3)	**1.28 (1.10 to 1.49)**	21.3 (19.0 to 23.9)	17.3 (16.4 to 18.4)	**1.23 (1.07 to 1.40)**	19.8 (17.2 to 22.8)	16.4 (15.3 to 17.6)	**1.21 (1.03 to 1.42)**	24.3 (18.4 to 32.2)	16.0 (13.7 to 18.7)	**1.52 (1.08 to 2.11)**
Covid-19 Hospitalization IR (95% CI)	7.9 (7.1 to 8.8)	4.6 (4.3 to 4.9)	**1.71 (1.50 to 1.95)**	4.4 (3.2 to 5.9)	3.2 (2.8 to 3.8)	1.36 (0.94 to 1.93)	4.9 (3.8 to 6.2)	3.9 (3.5 to 4.4)	1.25 (0.93 to 1.64)	5.9 (4.6 to 7.7)	3.0 (2.6 to 3.6)	**2.0 (1.4 to 2.7)**	10.4 (6.8 to 16.0)	4.6 (3.4 to 6.1)	**2.28 (1.29 to 3.90)**

Covid-19 Deaths IR (95% CI)	2.0 (1.6 to 2.5)	1.0 (0.9 to 1.2)	**1.91 (1.46 to 2.49)**	0.3 (0.1 to 1.0)	0.4 (0.3 to 0.7)	0.71 (0.14 to 2.39)	0.8 (0.4 to 1.4)	0.6 (0.5 to 0.8)	1.22 (0.54 to 2.47)	0.90 (0.5 to 1.74)	0.50 (0.3 to 0.8)	1.80 (0.74 to 3.98)	2.5 (1.0 to 6.0)	0.9 (0.5 to 1.7)	2.78 (0.73 to 9.23)

Table 3. All-cause mortality among patients and population referents during the pandemic (2020-21) and pre-Covid-19 (2019) era.
Incidence Rates (IR) per 1000 person years with 95% Confidence Intervals (CI) for death from all causes among rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) patients and their matched referents from the general population. Data are presented for two different time periods: a. 1-3-2020 to 28-2-2021 and b.1-1-2019 to 31-12-2019. Patient to population referents Incidence Rate Ratios (IRR) with 95% CI have been estimated for each disease group for the different time periods under study.

Deaths from all causes	**RA**			**AS**			**PsA**			**SLE**			**SSc**		
	IR (95% CI)		IRR (95% CI)	IR (95% CI)		IRR (95% CI)	IR (95% CI)		IRR (95% CI)	IR (95% CI)		IRR (95% CI)	IR (95% CI)		IRR (95% CI)
	patients	pop. referents		patients	pop. referents		patients	pop. referents		patients	pop. referents		patients	pop. referents	
a. 2020-2021	15.1 (13.9 to 16.3)	21.2 (20.6 to 21.9)	0.71 (0.65 to 0.77)	3.8 (2.7 to 5.2)	5.8 (5.2 to 6.6)	0.65 (0.44 to 0.92)	6.1 (4.9 to 7.5)	11.5 (10.7 to 12.3)	0.53 (0.41 to 0.66)	10.0 (8.2 to 12.1)	9.6 (8.8 to 10.5)	1.04 (0.83 to 1.29)	22.3 (16.7 to 29.9)	11.5 (9.6 to 13.8)	1.94 (1.34 to 2.76)
b. 2019	9.0 (8.1 to	15.3 (14.7 to	0.59 (0.52 to 0.66)	3.4 (2.4 to	6.0 (5.3 to	0.57 (0.38 to	9.2 (7.7 to	17.9 (16.9 to	0.51 (0.42 to	14.1 (12.0 to	13.8 (12.8 to	1.02 (0.85 to 1.23)	42.3 (34.0 to	9.7 (7.9 to	4.36 (3.20 to

	10.0)	15.9)		4.9)	6.8)	0.84)	11.1)	19.0)	0.63)	16.7)	14.9)		52.7)	11.9)	5.96)

Figure

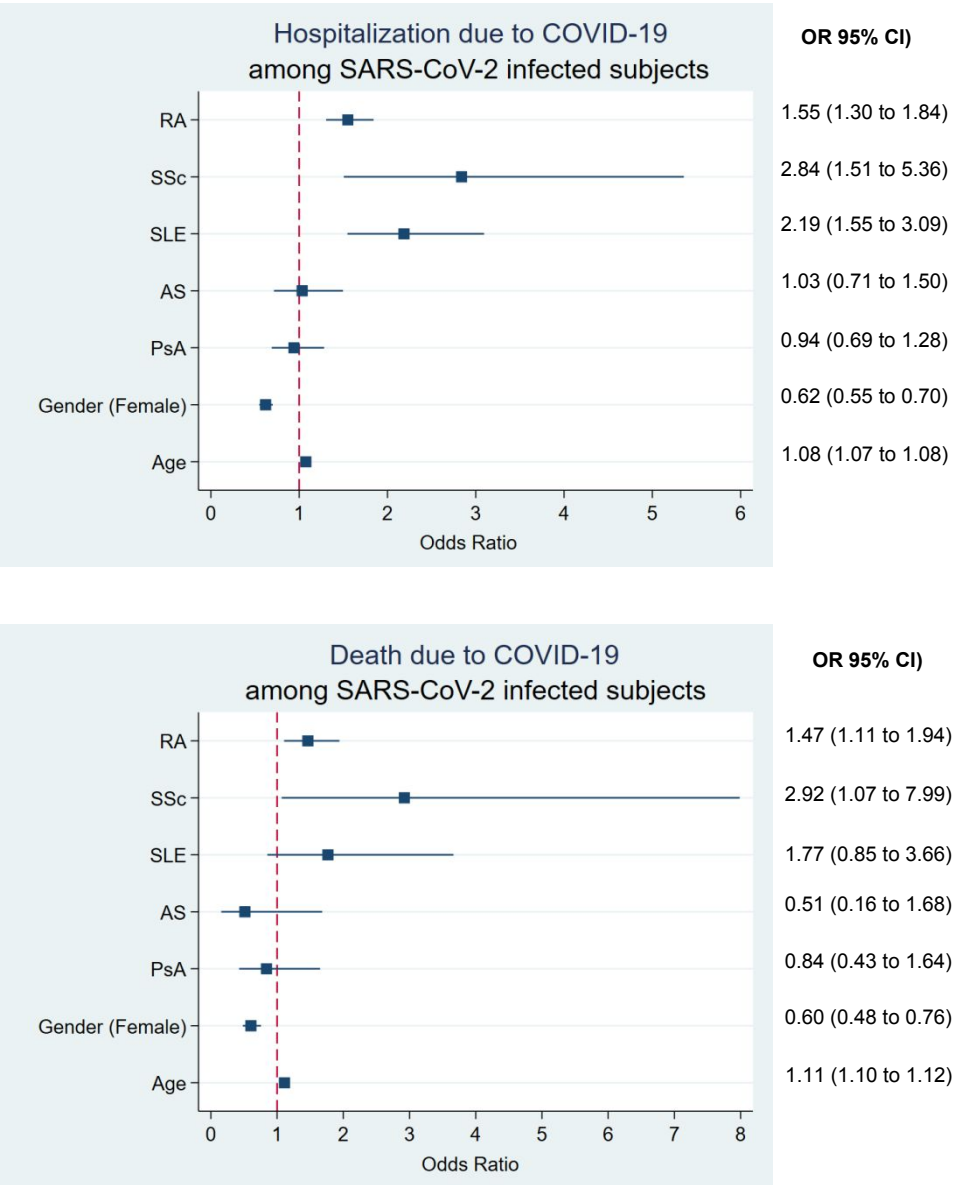

Figure 1. Logistic regression analysis assessing odd ratios for Covid-19-associated hospitalization and death among SARS-CoV-2 infected subjects

Odds Ratio with 95% Confidence Intervals for hospitalization and death due to Covid-19 focusing only on subjects infected with SARS-CoV-2 between 1-3-2020 and 28-2-2021. Model adjusted for underlying systemic rheumatic disease, age and

gender. SARS-CoV-2 infected subjects without underlying systemic rheumatic disease are used as the reference category. RA: Rheumatoid Arthritis, SSc: Systemic Sclerosis, SLE: Systemic Lupus Erythematosus, AS: Ankylosing spondylitis and PsA: Psoriatic Arthritis.