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Temporal Trends in COVID-19 outcomes in People with Rheumatic Diseases in Ireland: data from the COVID-19 Global Rheumatology Alliance registry

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Abstract

Objectives

Although evidence is accumulating globally, data on outcomes in rheumatic disease and COVID-19 in Ireland are limited. We used data from the COVID-19 Global Rheumatology Alliance (C19-GRA) to describe time-varying COVID-19 outcomes for people with rheumatic disease in Ireland.

Methods

Data entered into the C19-GRA provider registry from Ireland between 24th March 2020 and 9th July 2021 were analysed. Differences in the likelihood of hospitalisation and mortality according to demographic and clinical variables were investigated using Chi-squared test or Fisher's exact test, as appropriate. Trends in odds of hospitalisation and mortality over time were investigated using logistic regression with the time period as a categorical variable.

Results

Of 212 cases included, 59.4% were female and median age was 58.0 years (range 13-96). Of the 212 cases, 92 (43%) were hospitalized and 22 (10.4%) died. Increasing age, a diagnosis of gout, ever smoking, glucocorticoid use, having comorbidities, and specific comorbidities of cancer, cardiovascular, and pulmonary disease were more common in those hospitalised. A diagnosis of inflammatory arthritis, csDMARD and/or b/tsDMARD use were less frequent in those hospitalised. Increasing age, a diagnosis of gout, ever smoking, having comorbidities and specific comorbidities of obesity, cardiovascular and pulmonary disease were more common in those who died. Odds of hospitalisation or mortality did not change over time.

Conclusion

No temporal trend was observed in either COVID-19 related hospitalisation or mortality outcomes for people with rheumatic disease in Ireland.

Key words

Rheumatic disease; COVID-19; biologics; hospitalisation.

Key messages

1. The current study includes 212 cases of COVID-19 in people with rheumatic disease reported in Ireland.

2. Of the COVID-19 cases reported, 43% were hospitalized and 10% died.

3. COVID-19 outcomes for people with rheumatic disease did not show the temporal improvements observed in the general population.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting Coronavirus disease 2019 (COVID-19) continue to present a global health crisis. Significant improvements in COVID-19 outcomes have been demonstrated over time (1-5). This may relate to accumulating clinical experience leading to an improvement in care (6) along with beneficial effects of several immunomodulating treatments in severe COVID-19 (7-10). It is unclear whether outcomes for people with rheumatic disease who develop COVID-19 are also improving, with some studies reporting improved outcomes (4, 11). Since outcomes following SARS-CoV-2 infection may also vary depending on the geography and ethnicity of affected populations, it is important to explore outcomes in different locations and over time (12-16).

We have previously reported predictors of hospitalisation in people with rheumatic disease who developed COVID-19 in the first five months of the pandemic in Ireland (17). In this study we examine temporal trends in COVID-19 outcomes in people with rheumatic disease in Ireland in the first 16 months of the pandemic.

Methods

COVID-19 Global Rheumatology Alliance

Data regarding individuals with rheumatic disease with COVID-19 are entered into one of two parallel international data portals hosted in the United States and United Kingdom. Details of the C19-GRA registries have been published previously (18, 19).

Data collection

Cases in this study were entered into the C19-GRA provider registry from 24th March 2020 to 9th July 2021. Data were collected on baseline rheumatic disease status including demographic and clinical variables such as age, sex, smoking status, rheumatic disease diagnosis, disease activity (as

per the physician's global assessment (remission, low, moderate, or high/severe)), and comorbidities. Medications were categorised as previously described (17). Disease-modifying antirheumatic drugs (DMARDs) were grouped as conventional synthetic DMARDs (csDMARDs) or biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) (18). Rheumatic diseases were categorised as 1) inflammatory arthritis (IA), 2) gout, 3) vasculitis, connective tissue diseases, and all other diagnoses ('other'). Data collected regarding COVID-19 infection included method of diagnosis, place of diagnosis, COVID-19 symptoms, and outcomes of COVID-19 disease including hospitalisation, ventilation, and death.

Demographic and clinical continuous variables were reported as median (IQR) and categorical variables as number and percentage (%). Hospitalisation and mortality probability were calculated for each category of the key demographic and clinical variables. Differences in the likelihood of hospitalisation and mortality according to demographic and clinical variables were investigated using Chi-squared test or Fisher's exact test, as appropriate.

Trends in the odds of hospitalisation and mortality between timing of diagnosis were investigated using logistic regression with hospitalisation or mortality as the dependent variable and wave as a categorical predictor. Each case was categorized under a wave using the date of diagnosis as follows: Wave 1 (weeks 10-31), 1st March 2020 – 1st August 2020; Wave 2 (week 32-47), 2nd August 2020 – 21st November 2020; and Wave 3 (week 48 onwards), 22nd November 2020 – 9th July 2021 (20). The COVID-19 vaccination programme in Ireland began on 29th December 2020, with 1 million vaccine doses administered by April 2021, and 90% of adults fully vaccinated by September 2021. Appropriate confounders were identified as those demographic and clinical variables that were associated with both the outcome of interest as well as with timing/wave of diagnosis. These confounders were corrected for in each model. The significance of any suspected trend was tested using the "contrast" post-estimation command.

A sensitivity analysis was performed restricting our results to two institutions employing a rigorous case-finding methodology. These institutions contacted all patients requesting that they notify the rheumatology service if they developed COVID-19 (as part of clinical care), all admissions to the institutions with COVID-19 were screened for rheumatic disease cases, and finally all positive SARS-CoV-2 PCR tests were back-referenced against people attending the rheumatology services using medical record linkage.

All statistical analyses were performed using STATA IC15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) and graphs were prepared using GraphPad Prism version 6 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com).

This study was approved by the Irish National Research Ethics Committee for COVID-19 (20-NREC-COV-010). The committee waived the need for written informed consent as the data were fully anonymised.

Results

The 212 cases had a median age of 58.0 years (IQR:45.5-73.0) and the majority were female (59.4%). Most had IA (136/212 64.2%) with the balance having gout (35/212, 16.5%) and CTD or other diagnoses (50/212, 23.6%). The majority of patients (46.2%) were in remission, with 35.6% of cases having low disease activity. Seventy cases (33%) had no comorbidities; among those with comorbidities, cardiovascular and pulmonary diseases were the most prevalent (42% and 17.5%, respectively). Just under half of cases were hospitalized (92/212, 43%) and 22 (10.4%) died.

Hospitalisation outcome

Demographic and clinical details according to hospitalisation are shown in Table 1. Increasing age, a diagnosis of gout, ever smoking, glucocorticoid use, having comorbidities, and specific comorbidities of cancer and cardiovascular and pulmonary disease were more common in those hospitalised.

Patients at either high or low disease activity were more likely to be hospitalised. A diagnosis of IA, csDMARD and/or b/tsDMARD use were less frequent in those hospitalised.

Mortality outcome

Demographic and clinical details according to mortality are shown in Table 1. Increasing age, a diagnosis of gout, ever smoking, having comorbidities and specific comorbidities of obesity, cardiovascular and pulmonary disease were more common in those who died.

Hospitalisation and Mortality outcomes according to wave of diagnosis

The majority of people (n=115, 54.2%) were diagnosed during the first wave of the pandemic in Ireland, with 8.9% (n=19) in the second wave and 36.3% (n=77) in the third wave. Hospitalisation occurred in 49/115 (44.1%) during the first wave, 2/19 (11.1%) during the second wave, and 41/77 (54%) during the third wave. Death occurred in 10/115 (8.7%) during the first wave, 1/19 (5.3%) during the second wave, and 11/77 (14.3%) during the third wave. A diagnosis of IA, disease activity, cardiovascular disease, or obesity were differentially represented in the three waves (Supplementary Table S1, available at *Rheumatology* online). They were thus inserted as confounders, along with age and gender, in the logistic regression model investigating the odds of hospitalisation across waves. Likewise, disease activity, cardiovascular disease and obesity were both added as confounders, along with age and gender, in the respective model for mortality.

Cases diagnosed during wave 2 displayed a decrease in the likelihood of hospitalisation compared to wave 1, whereas cases diagnosed during wave 3 had increased hospitalisation odds compared to wave 1 , but all changes were non-significant, as was the quadratic trend in the odds for hospitalisation between the three waves.

In terms of mortality, cases diagnosed in each successive wave demonstrated again non-statistically significant increased likelihoods of mortality, and a non-statistically increasing linear trend in the odds of mortality across waves (Figure 1).

The sensitivity analysis restricting our results to the two institutions with rigorous case-finding methodology, reporting 59% of cases, did not alter the overall results.

Discussion

This is the largest and most detailed report of people with rheumatic disease and COVID-19 from Ireland. We have previously reported associations of clinical features with hospitalisation (17). We did not identify any reduction in odds for hospitalisation or mortality over time. This lack of change in odds of hospitalisation and mortality over time was in contrast to other data where clear improvements in COVID-19 outcomes have been demonstrated for non-rheumatic disease patients over time (1, 2, 21). Likely contributors are better general care measures as well as targeted treatments such as glucocorticoids and tocilizumab (7, 8). One explanatory hypothesis may be that people with rheumatic diseases, who may be receiving long-term immunomodulating treatments, may be less likely to benefit from the use of these treatments in the setting of subsequent severe COVID-19. Alternatively, our small sample size may have limited ability to demonstrate a change. The roll out of the COVID-19 vaccine in Ireland occurred in conjunction with the third COVID-19 wave and may have impacted on our findings.

Previous studies in rheumatic disease patients have suggested some improvement in outcomes over time (4, 5, 11). A cohort study from Boston of 143 rheumatic disease patients demonstrated a reduction in rates of mechanical ventilation, but not of hospitalisation or mortality, over time (11). An exposure scored matched analysis study of 8540 rheumatic disease patients using the US TriNetX

electronic health record database reported a reduction in the risks of hospitalisation, mechanical ventilation, and mortality when comparing a late cohort to an early cohort (4). The findings of these studies, and the current work, must be interpreted with cognisance of the limitations, including selection bias, unmeasured confounders, and possible artefact related to the identification of milder cases over time as testing capacity expanded (5).

Our study has several limitations. While this is the largest study of people with rheumatic disease and COVID-19 from Ireland, the statistical power of our study is limited by the low number of cases; we did not undertake multivariable analyses due to this. The C19-GRA is a physician-entered registry and is limited by selection bias with a likely tendency to report more severe cases. There is also the possibility that the reporting of cases varied over time potentially influencing our results. However, restricting our data to the two institutions with rigorous case ascertainment did not alter the overall findings. The C19-GRA is also a case-based registry with no denominator population, therefore inferences cannot be made about the incidence of COVID-19 in people with rheumatic diseases. Additionally, the C19-GRA is by design restricted to people with rheumatic disease and COVID-19, therefore, comparisons cannot be made to people with non-rheumatic disease and COVID-19 nor to rheumatic disease in the absence of COVID-19.

In conclusion our findings demonstrate no difference in hospitalisation or mortality in patients with rheumatic disease across the first three COVID-19 waves in Ireland.

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version to be published. PCR, JWL and RG directed the work and contributed to the analysis and interpretation of the data. They drafted, and revised, the manuscript critically for important intellectual content and gave final approval of the version to be published.

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Data sharing statement: Request for access to data from the registry should be made to the Data Access and Sharing Committee of the COVID-19 Global Rheumatology Alliance.

Data availability: The data underlying this article are available on reasonable request to the corresponding author.

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Table 1 - Hospitalisation outcome according to demographic and clinical factors in people with rheumatic disease diagnosed with COVID-19

	All Participants (n=212)	Not hospitalised (n=113)	Hospitalised (n=92)	p-value	Alive (n=190)	Deceased (n=22)	p-value
Gender, N(%)							
Female	126 (59.4)	72 (59.0)	50 (41.0)	0.17	114 (90.5)	12 (9.5)	0.62
Male	86 (40.6)	41 (49.4)	42 (50.6)		76 (88.4)	10 (11.6)	
Age (years), N(%)							
18-29	8 (3.8)	6 (85.7)	1 (14.3)		8 (100.0)	0 (0.0)	**<0.01**[a]
30-49	54 (25.8)	42 (80.8)	10 (19.2)	**<0.01**[a]	54 (100.0)	0 (0.0)	
50-65	67 (32.1)	46 (70.8)	19 (29.2)		62 (92.5)	5 (7.5)	
>65	80 (38.3)	17 (21.5)	62 (78.5)		63 (78.8)	17 (21.2)	
Most common rheumatic disease diagnoses*, N(%)							
Inflammatory arthritis[¥]	136 (64.2)	91 (70.0)	39 (30.0)	**<0.01**	126 (92.7)	10 (7.3)	0.05
Gout	35 (16.5)	2 (5.7)	33 (94.3)	**<0.01**	27 (77.1)	8 (22.9)	**0.01**[a]
Connective Tissue Disease and Other[∞]	50 (23.6)	23 (47.9)	25 (52.1)	0.25	45 (90.0)	5 (10.0)	0.29
Disease Activity, N (%)							
1	96 (46.2)	34 (36.6)	59 (63.4)		81 (84.4)	15 (15.6)	0.19[a]
2	74 (35.6)	54 (75.0)	18 (25.0)	**<0.01**[a]	70 (94.6)	4 (5.4)	
3	30 (14.4)	21 (70.0)	9 (30.0)		27 (90.0)	3 (10.01)	
4	5 (2.40)	1 (20.0)	4 (80.0)		5 (100.0)	0 (0.0)	
No comorbidities, N(%)	70 (33.0)	58 (85.3)	10 (14.7)	**<0.01**	69 (98.6)	1 (1.4)	**<0.01**
Most common comorbidities, N(%)							
Cancer	10 (4.3)	1 (11.1)	9 (88.9)	**0.01**[a]	7 (77.8)	2 (22.2)	0.24[a]
Cardiovascular Disease[◊]	89 (42.0)	23 (26.4)	64 (73.6)	**<0.01**	70 (78.7)	19 (21.3)	**<0.01**[a]
Pulmonary Disease[◊]	37 (17.5)	9 (24.3)	28 (75.7)	**<0.01**	26 (70.3)	11 (29.7)	**<0.01**[a]
Neurological / Neuromuscular / Psychiatric Disease	10 (4.7)	3 (30.0)	7 (70.0)	0.12	8 (80.0)	2 (20.0)	0.28[a]
Obesity	20 (9.4)	11 (55.0)	9 (45.0)	0.99	14 (70.0)	6 (30.0)	**<0.01**[a]
Smoking Status, N(%)							
Never	120 (56.6)	72 (60.5)	47 (39.5)	**<0.01**	110 (91.7)	10 (8.3)	**0.02**
Ever	54 (25.5)	15 (28.3)	38 (71.7)		43 (79.6)	11 (20.4)	
Unknown	38 (17.9)						
Medication prior to COVID-19 diagnosis, N(%)							
Steroids	33 (15.6)	11 (34.4)	21 (65.6)	**0.01**	26 (78.8)	7 (21.2)	0.06
Steroids 10mg or more	15 (7.1)	4 (28.6)	10 (71.4)	**0.04**	12 (80.0)	3 (20.0)	0.19
csDMARD monotherapy[v]	61 (28.8)	39 (67.2)	19 (32.8)	**0.03**	56 (91.8)	5 (8.2)	0.51
b_tsDMARD (monotherapy or in combinationwith csDMARD)[≠]	81 (38.2)	56 (70.0)	24 (30.0)	**0.00**	75 (92.6)	6 (7.4)	0.27
No complications, N(%)	162 (76.4)	155 (95.7)	7 (4.3)	**<0.01**	155 (95.7)	7 (4.3)	**<0.01**
Most common complications, N(%)							
ARDS	10 (4.7)	3 (30.0)	7 (70.0)	**<0.01**[a]	3 (30.0)	7 (70.0)	**<0.01**[a]
Sepsis	9 (4.3)	4 (44.4)	5 (55.6)	**<0.01**[a]	4 (44.4)	5 (55.6)	**<0.01**[a]

Concominant Infection	14 (6.6)	9 (64.3)	5 (35.7)	**0.01** [a]	9 (64.3)	5 (35.7)	**<0.01** [a]
Thromboembolism	11 (5.2)	10 (89.6)	1 (9.1)	1.00 [a]	10 (90.9)	1 (9.1)	1.00
AKI or renal failure	7 (3.3)	2 (28.6)	5 (71.4)	**<0.01** [a]	2 (28.6)	5 (71.4)	**<0.01** [a]
Deceased, N(%)	22 (10.4)	0 (0.0)	22 (100.0)	**<0.01**	-	-	

P-value from Pearson's Chi Square test, unless a=Fisher's Exact test

$ Patients could be diagnosed with more than one rheumatic diseases

¥ Inflammatory Arthritis diagnosis includes: Axial spondyloarthritis (including ankylosing spondylitis) | Psoriatic arthritis | Other spondyloarthritis (including reactive arthritis) | Juvenile idiopathic arthritis, oligo | Juvenile idiopathic arthritis, poly | Systemic juvenile idiopathic arthritis | Rheumatoid arthritis | Other inflammatory arthritis

∞ Connective tissue diesease and other diagnoses include: NCA-associated vasculitis (e.g., GPA, EGPA) | Other vasculitis including Kawasaki disease | Anti-phospholipid antibody syndrome | Autoinflammatory syndrome (including TRAPS, CAPS, FMF) | Behcet's | Chronic recurrent multifocal osteomyelitis | Giant cell arteritis | IgG4-related disease | Inflammatory myopathy (e.g. dermatomyositis, polymyositis) | Inclusion body myositis (IBM) | Mixed connective tissue disease | Ocular inflammation | Polymyalgia rheumatica | Sarcoidosis | Sjogren's syndrome | Systemic lupus erythematosus | Systemic sclerosis | Undifferentiated connective tissue disease | Localised scleroderma (morphea) | Other

◊ Cardiovascular Diseases include Cerebrovascular disease, CVD, Hypertension, Diabetes and Renal Disease; Pulmonary Diseases include Asthma, COPD and Interstitial Lung Disease

√ csDMARD monotherapy includes: Antimalarials (including hydroxychloroquine, chloroquine, mepacrine/quinacrine) | Apremilast | Azathioprine / 6-MP | | Cyclosporine | Leflunomide | Methotrexate | Mycophenolate mofetil / mycophenolic acid | Sulfasalazine | Tacrolimus | Thalidomide / lenalidomide

≠ b/tsDMARD thrapy includes: Abatacept | Belimumab | CD-20 inhibitors (including rituximab, ofatumumab) | Cyclophosphamide | IL-1 inhibitors (including anakinra, canakinumab, rilonacept) | IL-6 inhibitors (including tocilizumab, sarilumab) | IL-12 inhibitors (ustekinumab) | IL 23 inhibitors (guselkumab, risankizumab) | IL-17 inhibitors (including secukinumab, ixekizumab) | JAK inhibitors (including tofacitinib, baricitinib, upadacitinib) | TNF-inhibitors (including infliximab, etanercept, adalimumab, golimumab, certolizumab, and biosimilars) | Rituximab within the last 12 months

Figure 1 – Odds for hospitalisation and mortality according to wave of diagnosis