

ORIGINAL RESEARCH

Factors associated with severe COVID-19 in people with idiopathic inflammatory myopathy: results from the COVID-19 Global Rheumatology Alliance physician-reported registry

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ABSTRACT

Objectives To investigate factors associated with severe COVID-19 in people with idiopathic inflammatory myopathy (IIM).

Methods Demographic data, clinical characteristics and COVID-19 outcome severity of adults with IIM were obtained from the COVID-19 Global Rheumatology Alliance physician-reported registry. A 3-point ordinal COVID-19 severity scale was defined: (1) no hospitalisation, (2) hospitalisation (and no death) and (3) death. ORs were estimated using multivariable ordinal logistic regression. Sensitivity analyses were performed using a 4-point ordinal scale: (1) no hospitalisation, (2) hospitalisation with no oxygen (and no death), (3) hospitalisation with oxygen/ventilation (and no death) and 4) death.

Results Of 348 patients, 48% were not hospitalised, 39% were hospitalised (and did not die) and 13% died. Older age (OR=1.59/decade, 95% CI 1.31 to 1.91), high disease activity (OR=3.50, 95% CI 1.25 to 9.83; vs remission), ≥2 comorbidities (OR=2.63, 95% CI 1.39 to 4.98; vs none), prednisolone-equivalent dose >7.5 mg/day (OR=2.40, 95% CI 1.09 to 5.28; vs no intake) and exposure to rituximab (OR=2.71, 95% CI 1.28 to 5.72; vs conventional synthetic disease-modifying antirheumatic drugs only) were independently associated with severe COVID-19. In addition to these variables, in the sensitivity

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ There is a paucity of data about the factors associated with a severe outcome of COVID-19 for people with idiopathic inflammatory myopathy (IIM).

WHAT DOES THIS STUDY ADD?

⇒ This is the first international data set of people with IIM with COVID-19.
⇒ Older age, male sex, higher comorbidity burden, high disease activity, prednisolone-equivalent glucocorticoid dose >7.5 mg/day and exposure to rituximab were factors associated with severe COVID-19.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FUTURE DEVELOPMENTS?

⇒ The findings from this study will enable risk stratification for patients with IIM.
⇒ These findings will inform the development of tailored management strategies and evidence-based recommendations for patients with IIM.

analyses, male sex (OR range: 1.65–1.83; vs female) was also significantly associated with severe outcomes, while COVID-19 diagnosis after 1 October 2020 (OR range:

0.51–0.59; vs on/before 15 June 2020) was significantly associated with less severe outcomes, but these associations were not significant in the main model (OR=1.57, 95% CI 0.95 to 2.59; and OR=0.61, 95% CI 0.37 to 1.00; respectively).

Conclusions This is the first large registry data on outcomes of COVID-19 in people with IIM. Older age, male sex, higher comorbidity burden, high disease activity, prednisolone-equivalent dose >7.5 mg/day and rituximab exposure were associated with severe COVID-19. These findings will enable risk stratification and inform management decisions for patients with IIM.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a group of rare inflammatory muscle diseases, including dermatomyositis, polymyositis, anti-synthetase syndrome, immune-mediated necrotising myopathies and inclusion body myositis. People with IIM have been included in reports on patients with rheumatic diseases infected with SARS-CoV-2,^{1–6} but there are little granular data in the literature specifically about outcomes for people with IIM with SARS-CoV-2 infection, probably due to its low prevalence. People with IIM may be at an increased risk of poor COVID-19 outcomes due to being treated with immunosuppressives, especially rituximab and glucocorticoids, having IIM-associated features such as interstitial lung disease, and the increased incidence of IIM as age increases.⁷

Our aim was to investigate factors associated with severe COVID-19 in people with IIM.

METHODS

Data source

Data were obtained from the collaborative COVID-19 Global Rheumatology Alliance and European Alliance of Associations for Rheumatology (EULAR) registry, an observational, voluntary, physician-reported database containing anonymous data on patients with a pre-existing rheumatic condition and a confirmed/presumptive COVID-19 diagnosis.^{8,9}

Patients with a physician-reported diagnosis of IIM, diagnosed with COVID-19 between 5 March 2020 and 27 August 2021, were included in the analyses. The database hosts, University of California San Francisco (USA) and University of Manchester (UK), checked the data to ensure no duplicates in the data entries.

Treatment prior to COVID-19 infection

Data on exposure to antirheumatic therapies for IIM at the time of COVID-19 infection were collected: conventional synthetic disease-modifying antirheumatic drugs (csDMARDs—hydroxychloroquine, leflunomide, methotrexate, sulfasalazine), immunosuppressive drugs (azathioprine, cyclophosphamide, ciclosporin, mycophenolate mofetil/mycophenolic acid, tacrolimus), biological DMARDs (bDMARDs—abatacept, anakinra, canakinumab, tocilizumab, sarilumab, ixekizumab, secukinumab, adalimumab, certolizumab, etanercept,

golimumab, infliximab, rituximab), targeted synthetic DMARDs (Janus kinase inhibitors (JAKi) and apremilast), intravenous immunoglobulin (IVIg), and glucocorticoid treatment (prednisolone-equivalent dose).

COVID-19 outcome

The primary outcome of interest was an ordinal COVID-19 severity scale, which included the following mutually exclusive groups: (1) no hospitalisation, (2) hospitalisation (without death), and (3) death.

Statistical analysis

Categorical variables were summarised as number and percentage while continuous variables were summarised as mean and SD.

Multivariable ordinal logistic regression was used to analyse the data. Associations were estimated using ORs, 95% CIs and p values. The effect size of a categorical predictor gives the chance in odds of being one level higher on the ordinal COVID-19 severity scale compared with the reference category of the predictor variable, while for a continuous predictor, it gives the chance in odds of being one level higher on the ordinal COVID-19 severity scale for a unit increase in the continuous predictor. Cases without outcome data were excluded from the models. Missing data were assumed to be missing at random. Multiple imputation of missing data was performed to get pooled estimates for glucocorticoid dose, disease activity, hypertension/cardiovascular disease, diabetes mellitus and chronic renal disease.

Model covariates included age (continuous, analysed by decade), sex (female or male), pandemic calendar period (17 March 2020 to 15 June 2020, 16 June 2020 to 30 September 2020, 1 October 2020 to 27 August 2021), the number of comorbidities (none, one, two or more) or the individual comorbidities (hypertension or other cardiovascular disease (coronary artery disease, congestive heart failure, arrhythmia), interstitial lung disease, other chronic lung disease (obstructive lung disease (COPD/asthma), restrictive lung disease, other lung disease), diabetes mellitus, chronic renal disease (chronic renal insufficiency and end stage renal disease), cancer and obesity (defined by body mass index (BMI) ≥ 30 kg/m²), disease activity at the time of COVID-19 diagnosis using physician's global assessment (remission, low, moderate, high) and region (Europe, North America, other). Medication was categorised as follows for the multivariable ordinal logistic regression analysis (mutually exclusive categories): (1) no DMARD; (2) csDMARD only (monotherapy or combination therapy; used as reference category); (3) azathioprine monotherapy; (4) mycophenolate monotherapy; (5) azathioprine/mycophenolate combination therapy (except combination with b/tsDMARDs, including rituximab); (6) any other immunosuppressive monotherapy or combination therapy (except combination with b/tsDMARDs, including rituximab); (7) b/tsDMARD monotherapy or combination therapy (except rituximab, grouped separately); (8)

rituximab (monotherapy or combination therapy with any other drug). IVIg and prednisolone-equivalent dose (0 mg/day, 0–7.5 mg/day, >7.5 mg/day) were analysed separately in the multivariable model.

The primary model included the number of comorbidities as a predictor variable (as a reflection of the overall comorbidity burden) and a secondary model was built listing each individual comorbidity as a predictor. Sensitivity analyses were performed using a 4-point mutually exclusive ordinal COVID-19 severity outcome scale defined by (1) no hospitalisation, (2) hospitalisation with no oxygen (without death), (3) hospitalisation with oxygen/ventilation (without death), and (4) death.

Results were considered statistically significant when *p* value <0.05. Data clean-up was performed using RStudio4 and data were analysed using R V.4.0.2.

RESULTS

Patient characteristics

Complete hospitalisation and death outcome data were available for 348 individuals with IIM. None of the patients had inclusion body myositis. Four-fifths of cases (81.9%) originated from Europe and North America (table 1 and online supplemental table 1). Mean age was 53 (15.5) years, and most people in the study were female (64.1%) and of white ethnicity/race (55.3%). Common comorbidities included cardiovascular disease or hypertension (40.1%), interstitial lung disease (25%) and obesity (21.8%) (table 1). Most patients had a laboratory-confirmed diagnosis of COVID-19 (87.1%). About a quarter (27.5%) were reported to be taking between 0 and 7.5 mg/day prednisolone-equivalent dose, whereas 36.1% were reported to be taking >7.5 mg/day prednisolone. Just over two-thirds of patients were in remission/low disease activity (70.5%). The most prescribed DMARDs/immunosuppressants were methotrexate (25%), mycophenolate (20.4%), rituximab (18.1%), hydroxychloroquine (14.9%) and azathioprine (14.7%).

COVID-19 severity

There were 12.9% (45/348) deaths and 39.1% (136/348) were hospitalised, while 48.0% (167/348) were not hospitalised. Of those who were hospitalised, oxygenation/ventilation status was known for 100 individuals (73.5%): 34% (34/100) were hospitalised with no oxygenation/ventilation required, while 66% (66/100) required oxygenation/ventilation (table 2).

In the primary analysis (table 3), there were higher odds of severe COVID-19 with increasing age (OR=1.59 for each additional decade of life, 95% CI 1.31 to 1.91), case reporting from a region other than North America or Europe (OR=4.55, 95% CI 2.37 to 8.76; vs Europe), history of two or more comorbidities (OR=2.63, 95% CI 1.39 to 4.98; vs none), presence of high disease activity (OR=3.50, 95% CI 1.25 to 9.83; vs remission), glucocorticoid intake >7.5 mg/day of prednisolone-equivalent dose (OR=2.40, 95% CI 1.09 to 5.28; vs none) and rituximab

Table 1 Demographics and clinical characteristics of patients with idiopathic inflammatory myopathy and COVID-19 (N=348)

| Characteristics | |
|--|-------------|
| Age, mean (SD), years | 53.0 (15.5) |
| Age group, n (%) | |
| <30 | 26 (7.5) |
| 30–49 | 108 (31.0) |
| 50–65 | 136 (39.1) |
| >65 | 78 (22.4) |
| Gender, n (%) | |
| Female | 223 (64.1) |
| Race/ethnicity, n (%)* | |
| White | 157 (55.3) |
| Black | 34 (12.0) |
| Latinx | 68 (23.9) |
| Other | 25 (8.8) |
| Missing data | 64 |
| Region, n (%) | |
| Europe | 162 (46.6) |
| North America | 123 (35.3) |
| South America | 43 (12.4) |
| Other† | 20 (5.7) |
| Pandemic calendar period, n (%) | |
| 17 March 2020 to 15 June 2020 | 129 (37.2) |
| 16 June 2020 to 30 September 2020 | 51 (14.7) |
| 1 October 2020 to 27 August 2021 | 167 (48.1) |
| Comorbidities, n (%) | |
| Hypertension | 125 (25.9) |
| Other cardiovascular disease | 46 (36.2) |
| Hypertension or other cardiovascular disease | 139 (40.1) |
| Diabetes | 59 (17.0) |
| Chronic renal disease | 16 (4.6) |
| Interstitial lung disease | 87 (25.0) |
| Other chronic lung disease | 26 (7.5) |
| Cancer | 24 (6.9) |
| Obesity | 76 (21.8) |
| Ever smoker | 84 (31.1) |
| Comorbid count‡, n (%) | |
| None | 139 (39.9) |
| One | 101 (29.0) |
| Two or more | 108 (31.0) |
| Disease activity, n (%)* | |
| Remission | 91 (29.8) |
| Low disease activity | 124 (40.7) |
| Moderate disease activity | 62 (20.3) |
| High disease activity | 28 (9.2) |
| Missing data | 43 |
| csDMARDs, n (%) | |
| MTX | 87 (25.0) |

Continued

Table 1 Continued

| Characteristics | |
|--|------------|
| LEF | 7 (2.0) |
| SSZ | 1 (0.3) |
| HCQ | 52 (14.9) |
| Immunosuppressants, n (%) | |
| AZA | 51 (14.7) |
| CSA | 10 (2.9) |
| MMF | 71 (20.4) |
| TAC | 5 (1.4) |
| CYC | 10 (2.9) |
| bDMARDs, n (%) | |
| RTX | 63 (18.1) |
| Abatacept | 5 (1.4) |
| Anti-IL1 | 2 (0.6) |
| Anti-IL17 | 1 (0.3) |
| Anti-TNF | 1 (0.3) |
| tsDMARDs | |
| Apremilast | 2 (0.6) |
| JAKi, n (%) | 4 (1.1) |
| IVIg, n (%) | 26 (7.5) |
| Glucocorticoids (prednisolone-equivalent dose) | |
| No glucocorticoids | 111 (36.4) |
| >0 to 7.5 mg/day | 84 (27.5) |
| >7.5 mg/day | 110 (36.1) |
| DMARD/immunosuppressant medication category, n (%) | |
| No DMARD/immunosuppressant | 70 (20.1) |
| csDMARD only (HCQ/MTX/SSZ/LEF monotherapy or combination therapy) | 81 (23.3) |
| AZA monotherapy | 32 (9.2) |
| MMF monotherapy | 43 (12.4) |
| AZA/MMF combination therapy (except combination with RTX or b/tsDMARDs) | 27 (7.8) |
| CSA/CYC/TAC monotherapy or combination therapy (except RTX/b/tsDMARDs) | 17 (4.9) |
| b/tsDMARD monotherapy or combination therapy (except RTX) | 15 (4.3) |
| RTX (monotherapy or combination therapy with any other drug) | 63 (18.1) |
| *Missing data excluded from the denominator when calculating percentages. | |
| †Comorbid count includes hypertension, other cardiovascular disease, diabetes, chronic renal disease, chronic lung disease, cancer and obesity (BMI≥30). | |
| ‡Other regions with available patient data included South America, Eastern Mediterranean, South-East Asia and Western Pacific. | |
| AZA, azathioprine; bDMARD, biologic DMARD; BMI, body mass index; CSA, ciclosporin; csDMARD, conventional synthetic DMARD; CYC, cyclophosphamide; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; IL, interleukin; IVIg, intravenous immunoglobulin; JAKi, Janus kinase inhibitors; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; SSZ, sulfasalazine; TAC, tacrolimus; TNF, tumour necrosis factor; tsDMARD, targeted synthetic DMARD. | |

Table 2 Frequencies and proportions of outcomes in the ordinal COVID-19 severity scale (N=348)

| Outcomes | n (%) |
|---|------------|
| No hospitalisation | 167 (48.0) |
| Hospitalisation | 136 (39.1) |
| No oxygenation | 34 (34)* |
| Oxygenation/ventilation | 66 (66)* |
| Missing data | 36 |
| Death | 45 (12.9) |
| *Missing data excluded from the denominator when calculating percentages. | |

exposure (OR=2.71, 95% CI 1.28 to 5.72; vs csDMARD exposure only). Male gender (OR=1.59, 95% CI 0.95 to 2.59) was also associated with worst COVID-19, whereas COVID-19 diagnosis after 1 October 2020 was associated with less severe COVID-19 (OR=0.61, 95% CI 0.37 to 1.00), although these two associations were not statistically significant.

In the secondary analysis with comorbidities as individual covariates, male sex (OR=1.65, 95% CI 1.01 to 2.71) and calendar period on/after 1 October 2020 (OR=0.59, 95% CI 0.35 to 0.97) emerged as significant variables in the model (online supplemental table 2). All the previously identified variables were also associated with severe outcomes in this model: age, region, high disease activity, glucocorticoids >7.5 mg/day and rituximab exposure (online supplemental table 2).

Results of the sensitivity analyses are presented in online supplemental tables 3 and 4. Similarly to the results of the primary analysis, age, male sex, history of two or more comorbidities, high disease activity, glucocorticoids >7.5 mg/day and rituximab exposure were associated with severe COVID-19, whereas COVID-19 diagnosis after 1 October 2020 was associated with less severe COVID-19.

DISCUSSION

In our study of 348 patients with IIM, we have identified factors associated with severe COVID-19, namely, older age, male sex, region other than North America/Europe, history of two or more comorbidities, high disease activity, prednisolone-equivalent intake of >7.5 mg/day and rituximab exposure. COVID-19 diagnosis later in the pandemic was associated with less severe COVID-19.

The increased odds of more severe COVID-19 in people with IIM with age is consistent with reports on people with other rheumatic diseases^{10–12} and non-rheumatic populations.^{13–15} An increased number of comorbidities being a contributor to COVID-19 severity has also been reported in inflammatory bowel disease¹⁶ and in the general population.^{10–12} Increased glucocorticoid use and high disease activity are also associated with an increased risk of COVID-19 severity consistent with other rheumatic^{10,12} and non-rheumatic diseases, such as inflammatory bowel disease,¹⁶ although the possibility of

Table 3 Multivariable ordinal logistic regression analysis of factors associated with the 3-point ordinal COVID-19 severity outcome scale (no hospitalisation, hospitalisation, death), with comorbidity count instead of comorbidities listed individually (N=348, primary analysis)

| | OR (95% CI) | P value |
|---|----------------------------|------------------|
| Age (per decade) | 1.59 (1.31 to 1.91) | <0.001 |
| Male sex | 1.57 (0.95 to 2.59) | 0.076 |
| Region | | |
| Europe | REF | n/a |
| North America | 0.87 (0.48 to 1.58) | 0.648 |
| Other | 4.55 (2.37 to 8.76) | <0.001 |
| Pandemic calendar period | | |
| On/before 15 June 2020 | REF | n/a |
| 16 June to 30 September 2020 | 0.55 (0.26 to 1.20) | 0.132 |
| On/after 1 October 2020 | 0.61 (0.37 to 1.00) | 0.051 |
| Comorbidities | | |
| None | REF | n/a |
| One | 1.41 (0.73 to 2.74) | 0.305 |
| Two or more | 2.63 (1.39 to 4.98) | 0.003 |
| Disease activity | | |
| Remission | REF | n/a |
| Low/moderate disease activity | 1.19 (0.63 to 2.25) | 0.594 |
| High disease activity | 3.50 (1.25 to 9.83) | 0.018 |
| Glucocorticoid (prednisolone-equivalent dose) | | |
| No glucocorticoids | REF | n/a |
| >0 to 7.5 mg/day | 1.08 (0.57 to 2.05) | 0.820 |
| >7.5 mg/day | 2.40 (1.09 to 5.28) | 0.031 |
| IVIg | 0.42 (0.15 to 1.18) | 0.101 |
| DMARD/immunosuppressant medication category | | |
| csDMARD only (HCQ/MTX/SSZ/LEF monotherapy or combination therapy) | REF | n/a |
| No DMARD/immunosuppressant | 1.85 (0.90 to 3.78) | 0.094 |
| AZA monotherapy | 1.78 (0.71 to 4.43) | 0.216 |
| MMF monotherapy | 1.25 (0.54 to 2.89) | 0.601 |
| AZA/MMF combination therapy (except combination with RTX or b/tsDMARDs) | 0.77 (0.27 to 2.15) | 0.615 |
| CSA/CYC/TAC monotherapy or combination therapy (except RTX/b/tsDMARDs) | 1.61 (0.54 to 4.79) | 0.386 |
| b/tsDMARD monotherapy or combination therapy (except RTX) | 1.65 (0.50 to 5.43) | 0.411 |
| RTX (monotherapy or combination therapy with any other drug) | 2.71 (1.28 to 5.72) | 0.009 |

Statistically significant OR are highlighted in bold.

AZA, azathioprine; bDMARD, biologic DMARD; CSA, ciclosporin; csDMARD, conventional synthetic DMARD; CYC, cyclophosphamide; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; IL, interleukin; IVIg, intravenous immunoglobulin; JAKi, Janus kinase inhibitors; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; SSZ, sulfasalazine; TAC, tacrolimus; TNF, tumour necrosis factor; tsDMARD, targeted synthetic DMARD.

confounding by indication has been raised as a potential explanation for the glucocorticoid association.¹⁷ In our data set, patients with high disease activity were 3.5 times more likely to have severe COVID-19 outcome compared with those in remission, and those on doses of >7.5 mg/day of prednisolone-equivalent glucocorticoids were 2.4 times more likely to have a severe COVID-19 outcome. Other studies have also identified rituximab as

an important risk factor of COVID-19 adverse outcomes in other conditions.¹⁻³

The strength of this study is the collaborative work by rheumatologists that allowed the collection of a large number of entries into the registry in a short space of time for what is considered a relatively rare condition.¹⁸ There is a higher representation of patients from the USA and Europe in this study, possibly due to reporting

bias from increased provider awareness of this database. Physicians may also be more aware of hospitalisations and deaths of their patients due to COVID-19 rather than those who were not hospitalised, as well as more aware of patients who are sicker at baseline or have more complex disease (regardless of outcome), which may contribute to reporting bias. Another limitation of our study is the absence of a control group. Therefore, this study cannot be used to comment on hospitalisation or death rates, as selection bias may exist, and comparisons with hospitalisation or death rates in other subgroups of patients or with the general population should not be made. Moreover, we caution against interpreting our estimates causally. There is likely unmeasured confounding dependent on the particularities of health systems and case reporting differences. We tried to address this by limiting the research questions to those that could be answered with this data set and by accounting for potential confounders in our analyses. The WHO clinical progression scale¹⁹ was not used in our study, limiting direct comparisons to be made with other studies. This was due to the absence of data granularity and statistical feasibility. However, the ordinal severity scale used in our study includes merged components from the WHO clinical progression scale and minimises missing data and data overfitting. Another limitation of the study is that the cause of hospitalisation was not explicitly included in the dataset. However, it may be inferred that COVID-19 was the cause of hospitalisation as this physician-reported database captures COVID-19 cases in patients with rheumatic diseases where physicians inputting data were asked “Was the patient hospitalised during the illness?” and “What was the maximum level of care required during the illness?”. Due to the nature of this registry, granular data about auto-antibody profiles are not available. Vaccination status was not available for the patients in this dataset. However, the calendar period used in this study (1 October 2020 to 27 August 2021) may act as a surrogate for the COVID-19 vaccine era being the time period in which the vaccination roll-out commenced.

In conclusion, analysis of this large registry data set has identified factors associated with severe outcomes due to COVID-19 in adult patients with IIM, consistent with the reported literature in other rheumatic diseases, providing insights into future risk stratification of patients with IIM.

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