High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry

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ABSTRACT

Objectives To evaluate risk factors associated with unfavourable outcomes: emergency care, hospitalisation, admission to intensive care unit (ICU), mechanical ventilation and death in patients with immune-mediated rheumatic disease (IMRD) and COVID-19.

Methods Analysis of the first 8 weeks of observational multicentre prospective cohort study (ReumaCoV Brasil registry). Patients with IMRD and COVID-19 according to the Ministry of Health criteria were classified as eligible for the study.

Results 334 participants were enrolled, a majority of them women, with a median age of 45 years; systemic lupus erythematosus (32.9%) was the most frequent IMRD. Emergency care was required in 160 patients, 33.0% were hospitalised, 15.0% were admitted to the ICU and 10.5% underwent mechanical ventilation; 28 patients (8.4%) died. In the multivariate adjustment model for emergency care, diabetes (prevalence ratio, PR 1.38; 95% CI 1.05 to 1.77; p=0.020), oral glucocorticoids (GC) (PR 2.24; 95% CI 1.36 to 3.71; p<0.001) and pulse therapy with methylprednisolone (PR 1.65; 95% CI 1.26 to 2.85; p=0.002), no use of tumour necrosis factor inhibitor (TNFi) (PR 2.51; 95% CI 1.16 to 5.45; p=0.004) and methylprednisolone pulse therapy (PR 2.50; 95% CI 1.59 to 3.92; p<0.001) for ICU admission, oral GC (PR 2.24; 95% CI 1.36 to 3.71; p<0.001) and pulse therapy with methylprednisolone (PR 1.65; 95% CI 1.00 to 2.68; p=0.0043) were associated with death with methylprednisolone or cyclophosphamide (PR 2.86; 95% CI 1.59 to 5.14; p<0.018).

Conclusions Age >50 years and immunosuppression with GC and cyclophosphamide were associated with unfavourable outcomes of COVID-19. Treatment with TNFi may have been protective, perhaps leading to the COVID-19 inflammatory process.
of developing more severe forms of COVID-19. Moreover, Brazil is a country of continental dimensions, with important regional differences in relation to socioeconomic status, basic sanitation and access to health, and the evolution of patients with COVID-19 and IMRD may assume a different behaviour from other parts of the world.

The primary aim of this paper was to describe the patients included in the first 8 weeks of the ReumaCoV Brasil register, evaluating the factors associated with the following outcomes: (1) need for emergency care (patients who went to the hospital, except those who were seen in an outpatient clinic), (2) hospitalisation (more than 24 hours of hospital permanence), (3) intensive care unit (ICU) admission, (4) mechanical ventilation and (5) death. Our hypothesis was that patients with IMRD and high-grade immunosuppression could have an unfavourable evolution compared with those with less immunosuppression.

METHODS

The complete study methodology was previously published. Briefly, the ReumaCoV Brasil is a multicentre, observational, prospective cohort study carried out to monitor adult IMRD patients with COVID-19 diagnosis, using a convenience sample, whose data collection began 20 May 2020, with inclusion scheduled until December 2020, with 43 participating research centres. This paper will present the analysis of data for the first 8 weeks of inclusion in the study.

Eligible patients were selected based on the identification of a case of COVID-19 by the researcher, through telephone contact, outpatient consultation or during hospitalisation for COVID-19. Inclusion criteria were: (1) age over 18, (2) COVID-19 diagnosis, according to the Brazilian Health Minister (BMH) (figure 1) and (3) prior diagnosis of IMRD, according to the American College of Rheumatology or the European League against Rheumatism criteria. Exclusion criteria were other immunodeficiency diseases, past organ or bone marrow transplantation, neoplasms within the last 5 years, current chemotherapy, HIV diagnosis and thymus diseases.

Demographic data such as age, sex, work situation and social isolation during the pandemic, as well diagnosis and treatment of IMRD, comorbidities (https://www.who.int/classifications/icd/icdonlineversions/en/), clinical characteristics, treatment and evolution of COVID-19 were collected using a Research Electronic Data Capture (REDCap) database (https://www.project-redcap.org/), through telephone call or face-to-face interview, if permitted by local health recommendations. In case of hospitalisation, the data were collected directly.
with the patient, if possible, or from medical records. In cases where death was notified, data were collected directly from a family member, who authorised the inclusion of the data in the register.

For data analysis, a database was built using the REDCap database, which was exported to the SPSS program, V.21, where the analysis was performed. To characterise the profile of the patients, the percentage of frequencies were calculated, and the frequency distribution of the evaluated factors was constructed. For the quantitative variables, the median and IQR statistics were calculated. In order to verify which factors influenced the outcomes, the contingency table was constructed and the Chi-square test for the independence sample was applied. In cases where the assumptions of the $\chi^2$ test were violated, Fisher’s exact test was applied. In addition, prevalence ratios (PR) and the respective CI were calculated. Since the objective of the study was to assess the evolution of the most severe forms of COVID-19 in patients with IMRD, the IUC and death outcomes were analysed only among patients who were hospitalised.

All conclusions were drawn considering the significance level of 5%. The variables that showed statistical significance of up to 20% in the bivariate analysis were included in the Poisson multivariate adjustment. Variables with a 5% significance remained in the final model. The OR was calculated to assess the chance of a COVID-19 symptom occurring in patients with laboratory confirmed disease.

This study was registered at the Brazilian Registry of Clinical Trials—REBEC, RBR-33YTQC. All patients read and signed the informed consent form before inclusion.

RESULTS

Results are reported in accordance with STROBE guidelines. Between 20 May 20 and 24 July 2020, 334 IMRD patients with a diagnosis of COVID-19 were included in the register. The median age was 45 years (IQR=51–57) and 81.4% were female. In regard to their work situation, 186 (55.0%) patients were active at the time of SARS-CoV-2 infection; among the inactive, most were retired or on work leave due to rheumatic disease (69.0%); 126 (37.3%) patients reported a profession that dealt directly with the public (public attendance, health, security, education); 159 (47.0%) patients reported no social isolation during the pandemic; 159 (47.0%) reported close contact with a confirmed case of COVID-19, with 104 (30.8%) events occurring at home. The most common comorbidities were hypertension (35.8%), obesity (15.7%) and diabetes (11.5%); smoking was reported by 4.4% of patients. Regarding rheumatic disease diagnosis, systemic lupus erythematosus (SLE) (32.9%) and rheumatoid arthritis (RA) (28.4%) were the most frequent. Hydroxychloroquine (HCQ) (118/338; 34.9%), oral glucocorticoids (GC) (116/338; 34.2%), tumour necrosis factor inhibitor (TNFi) (75/338; 22.2%) and methotrexate (68/338; 20.1%) were the most common rheumatic disease treatments. All patients included were COVID-19 confirmed cases, according to BMH recommendations (figure 1), most of them classified according to lab criterion (76.8%), mostly through RT-PCR (n=175; 51.8%). Table 1 describes demographic and clinical data of the sample.

In regard to COVID-19 symptoms, the most frequent were headache (58.0%), cough (56.5%) and fever (51.2%). Twelve asymptomatic patients (3.6%) were included because they presented a positive RT-PCR for SARS-CoV-2, collected due to contact with a confirmed case of COVID-19.

The median duration of symptoms was 12 days (IQR=10) and 102 patients (30.2%) still had symptoms at study entry. The most common medications used to treat COVID-19 were analgesics (n=166, 49.6%) and azithromycin (n=165, 49.3%), HCQ (n=66, 19.7%) and oral GC (n=71, 20.6%), at a dosage above >30 mg/day in 44.1% of patients. Pulse therapy with GC was used by 14 (4.2%) patients.

Regarding the main outcomes, emergency care was required in 160 patients (48%); 110 (33.0%) patients were hospitalised, 50 (15.0%) were admitted to the ICU, 35 (10.5%) underwent mechanical ventilation and 28 (8.4%) died. Among the 28 patients who died, 24 (85.7%) were women, and the median age was 53 years (IQR=36–69). The diagnosis was SLE in 11 patients, 4 were RA, 2 axial spondyloarthritis, 5 systemic sclerosis and 6 had other diseases; 5 (17.9%) patients were using pulse therapy with methylprednisolone and 5 (17.9%) patients were using pulse therapy with cyclophosphamide.

Table 2 describes the binary associations between the need for emergency care and explanatory variables only in the COVID-19 lab confirmed group. There was a statistically significant difference in relation to being inactive at work (PR 1.42, 95% CI 1.13 to 1.78; p=0.002), the presence of diabetes (PR 1.49, 95% CI 1.18 to 1.87; p=0.008), and having hypertension (PR 1.30, 95% CI 1.05 to 1.62; p=0.020), hypothyroidism (PR 1.52, 95% CI 1.17 to 1.98; p=0.030), kidney disease (PR 1.49, 95% CI 1.13 to 1.97; p=0.046), using oral corticosteroids (PR1.60, 95% CI 1.30 to 1.97; p<0.001) and methylprednisolone pulse therapy (PR 1.86, 95% CI 1.65 to 2.08; p=0.018). Not using TNFi was associated with an increased prevalence rate for hospitalisation (PR 1.53; 95% CI 1.07 to 2.18; p=0.007).

No differences were observed regarding age, gender, social isolation, heart and lung disease, obesity, smoking, HCQ, methotrexate, leflunomide or rheumatic disease diagnosis.

In the multivariate adjustment using the Poisson model for emergency care, diabetes, kidney disease, use of oral GC and pulse therapy with methylprednisolone remained significant (table 3).

Table 4 shows the binary associations between the primary outcomes: hospitalisation, ICU, mechanical ventilation, death and explanatory variables. For hospitalisation, a statistically significant association was observed with age >50 years (PR 1.91; 95% CI 1.26 to
Regarding admission to the ICU, a statistically significant association was observed with oral GC (PR 2.15, 95% CI 1.32 to 3.48; p=0.001), not using TNFi (PR 2.59; 95% CI 0.88 to 7.57; p=0.007), oral GC dose above 20 mg/day (PR 2.86, 95% CI 1.59 to 5.14; p=0.018) (table 4). In multivariate analysis using the Poisson model, oral GC and pulse therapy with methylprednisolone remained statistically significant (table 3). None of the

### Table 1 Demographic and clinical characteristics of 334 patients with confirmed or suspected COVID-19 and rheumatic diseases

| Variables                                      | n   | %    |
|------------------------------------------------|-----|------|
| Female                                         | 275 | 81.4 |
| Age, median (IQR)                              | 45  | 31–57|
| Professions that deal with the public          | 126 | 37.3 |
| Active at work                                 | 186 | 55.0 |
| Retired/ work leave due rheumatic disease*     | 230 | 69.0 |
| Social isolation                               | 159 | 47.0 |
| Close contact with a confirmed case of COVID-19| 159 | 47.0 |
| **Comorbidities**                              |     |      |
| Hypertension                                   | 121 | 35.8 |
| Obesity                                        | 53  | 15.7 |
| Diabetes                                       | 39  | 11.5 |
| Hypothyroidism                                 | 20  | 5.9  |
| Lung disease                                   | 32  | 9.4  |
| Heart disease                                  | 25  | 7.4  |
| Dyslipidaemia                                  | 22  | 6.5  |
| Fibromyalgia                                   | 12  | 3.6  |
| Kidney disease                                 | 21  | 6.2  |
| Smoking                                        | 15  | 4.4  |
| Alcoholism                                     | 8   | 2.4  |
| Depression                                     | 7   | 2.1  |
| **Rheumatic diseases diagnostic**              |     |      |
| Systemic lupus erythematosus                   | 110 | 32.9 |
| Rheumatoid arthritis                           | 95  | 28.4 |
| Axial Spondyloarthritis                        | 45  | 13.5 |
| Systemic sclerosis                             | 23  | 6.9  |
| Psoriatic arthritis                            | 23  | 6.9  |
| Vasculitis                                     | 10  | 3.3  |
| Others                                         | 28  | 8.3  |
| **Rheumatic disease treatment**                |     |      |
| Hydroxychloroquine                             | 118 | 34.9 |
| Oral corticosteroids                           | 116 | 34.3 |
| Methotrexate                                   | 68  | 20.1 |
| Azathioprine                                   | 42  | 12.4 |
| Leflunomide                                    | 23  | 11.8 |
| Mycophenolate mofetil                          | 21  | 6.2  |
| TNFi                                           | 75  | 22.2 |
| Non-TNFi                                       | 41  | 12.1 |
| Rituximab                                      | 13  | 3.8  |
| Anti-IL-17                                     | 12  | 3.6  |
| Tocilizumab                                    | 9   | 2.7  |
| Belimumab                                      | 3   | 0.9  |
| Abatacept                                      | 3   | 0.9  |

Continued
| Variables            | Emergency care |          |          | p-value | PR 95% CI |
|----------------------|----------------|----------|----------|---------|-----------|
|                      | Yes (n, %)     | No (n, %)|          |         |           |
| Age                  |                |          |          |         |           |
| Up to 50 years       | 81 (52.9)      | 72 (47.1)| 0.429*   | 1.00;   | –         |
| >50 years            | 58 (58.0)      | 42 (42.0)| 1.10;    | 0.88 to | 1.37      |
| Sex                  |                |          |          |         |           |
| Male                 | 25 (53.2)      | 22 (46.8)| 0.769*   | 1.00;   | –         |
| Female               | 115 (55.6)     | 92 (44.4)| 1.04;    | 0.78 to | 1.40      |
| Work situation       |                |          |          |         |           |
| Inactive             | 73 (65.2)      | 39 (34.8)| 0.002*   | 1.42;   | 1.13 to 1.78 |
| Active               | 63 (46.0)      | 74 (54.0)| 1.00;    | –       |           |
| Skin colour          |                |          |          |         |           |
| White                | 78 (56.9)      | 59 (43.1)| 0.529*   | 1.07;   | 0.86 to 1.34 |
| Non white            | 62 (53.0)      | 55 (47.0)| 1.00;    | –       |           |
| Geographic distribution |              |          |          |         |           |
| Non-southeast        | 58 (49.6)      | 59 (50.4)| 0.101*   | 1.00;   | –         |
| Southeast            | 82 (59.9)      | 55 (40.1)| 1.21;    | 0.96 to | 1.52      |
| Hypertension         |                |          |          |         |           |
| No                   | 81 (49.7)      | 82 (50.3)| 0.020*   | 1.00;   | –         |
| Yes                  | 59 (64.8)      | 32 (35.2)| 1.3      | 1.05 to | 1.62      |
| Obesity              |                |          |          |         |           |
| No                   | 113 (53.6)     | 98 (46.4)| 0.267*   | 1.00;   | –         |
| Yes                  | 27 (62.8)      | 16 (37.2)| 1.17     | 0.90 to | 1.52      |
| Diabetes             |                |          |          |         |           |
| No                   | 116 (52.0)     | 107 (48.0)| 0.008*   | 1.00;   | –         |
| Yes                  | 24 (77.4)      | 7 (22.6) | 1.49     | 1.18 to | 1.87      |
| Lung disease         |                |          |          |         |           |
| No                   | 121 (54.3)     | 102 (45.7)| 0.461*   | 1.00;   | –         |
| Yes                  | 19 (61.3)      | 12 (38.7)| 1.13     | 0.83 to | 1.53      |
| Cardiovascular disease |              |          |          |         |           |
| No                   | 124 (53.7)     | 107 (46.3)| 0.144*   | 1.00;   | –         |
| Yes                  | 16 (69.6%)     | 7 (30.4) | 1.3      | 0.96 to | 1.74      |
| Dyslipidaemia        |                |          |          |         |           |
| No                   | 129 (54.4)     | 108 (45.6)| 0.411*   | 1.00;   | –         |
| Yes                  | 11 (64.7)      | 6 (35.3) | 1.19     | 0.82 to | 1.72      |
| Hypothyroidism       |                |          |          |         |           |
| No                   | 127 (53.4)     | 111 (46.6)| 0.030*   | 1.00;   | –         |
| Yes                  | 13 (81.3)      | 3 (18.8) | 1.52     | 1.17 to | 1.98      |
| Kidney disease       |                |          |          |         |           |
| No                   | 128 (53.6)     | 111 (46.4)| 0.046*   | 1.00;   | –         |
| Yes                  | 12 (80.0)      | 3 (20.0) | 1.49     | 1.13 to | 1.97      |
| Smoking              |                |          |          |         |           |
| No                   | 136 (56.0)     | 107 (44.0)| 0.228†   | 1.54    | 0.70 to 3.39 |
| Yes                  | 4 (36.4)       | 7 (63.6) | 1.00;    | –       |           |

Continued
Before including the use of TNFi in the binary analysis, it was tested whether there was an association with the use of biologicals of all classes as a group, and an association was observed with the ICU outcome (p=0.001). However, when we separated the groups into biological TNFi (p=0.006) and non TNFi (p=0.089), the difference remained only for the TNFi group. For this reason, only this group was included in the binary analysis and Poisson model.

**DISCUSSION**

Brazil is the country with the third highest number of cases of COVID-19 in the world, with the first case confirmed 26 February 2020, and counting 4123000 cases and 126203 deaths through 6 September 2020. To the best of our knowledge, ReumaCoV Brasil is the largest cohort of patients with COVID-19 and underlying IMRD from a single country. Our results demonstrate that age over 50, diabetes, kidney disease, use of oral GC, not using TNFi, pulse therapy with methylprednisolone and cyclophosphamide were associated with a higher prevalence of worse outcomes of COVID-19 in patients with IMRD. We did not find any association between the variables and the need for mechanical ventilation.

The first published report regarding COVID-19 in patients with rheumatic diseases suggested that there would be no greater risk in relation to the general population or with other comorbidities. Since then, some studies addressed the risk and severity of COVID-19 infection in people with IMRD, confirming this initial impression, except for hospitalisation in patients exposed to high GC doses. However, evidence on COVID-19 risk

| Variables            | Emergency care | p-value | PR 95% CI |
|----------------------|----------------|---------|-----------|
|                      | Yes (n, %)     | No (n, %) |           |
| No                   | 133 (54.5)     | 111 (45.5) | 0.519†   | 1.00; –   |
| Yes                  | 7 (70.0)       | 3 (30.0)   | 1.28      | 0.84 to 1.96 |
| Alcoholism           |                |          |           |
| No                   | 137 (55.9)     | 108 (44.1) | 0.049†   | 3.91      | 0.64 to 24.11 |
| Yes                  | 1 (14.3)       | 6 (85.7)   | 1.00      | –         |
| Depression           |                |          |           |
| No                   | 137 (55.2)     | 111 (44.8) | 1.000†   | 1.1       | 0.49 to 2.48 |
| Yes                  | 3 (50.0)       | 3 (50.0)   | 1.00      | –         |
| TNFi                 |                |          |           |
| No                   | 119 (59.5)     | 81 (40.5)  | 0.007*   | 1.53      | 1.07–2.18   |
| Yes                  | 21 (38.9)      | 33 (61.1)  | 1.00      | –         |
| HCQ                  |                |          |           |
| No                   | 86 (51.2)      | 82 (48.8)  | 0.079*   | 1.00      | –         |
| Yes                  | 54 (62.8)      | 32 (37.2)  | 1.23      | 0.98 to 1.53 |
| Oral GC              |                |          |           |
| No                   | 80 (46.2)      | 93 (53.8)  | <0.001   | 1.00      | –         |
| Yes                  | 60 (74.1)      | 21 (25.9)  | 1.6       | 1.30 to 1.97 |
| GC dosage            |                |          |           |
| <20mg/day            | 43 (69.4)      | 19 (30.6)  | 0.133†   | 1.00      | –         |
| ≥20mg/day            | 17 (89.5)      | 2 (10.5)   | 1.29      | 1.03 to 1.62 |
| Intravenous GC       |                |          |           |
| No                   | 133 (53.8)     | 114 (46.2) | 0.018†   | 1.00      | –         |
| Yes                  | 7 (100.0)      | 0 (0)      | 1.86      | 1.65 to 2.08 |
| CYC                  |                |          |           |
| No                   | 133 (54.3)     | 112 (45.7) | 0.193†   | 1.00      | –         |
| Yes                  | 7 (77.8)       | 2 (22.2)   | 1.44      | 1.00 to 2.09 |

*p value of the χ² test for independence; †p value of Fisher’s exact test.

CYC, cyclophosphamide pulse therapy; GC, glucocorticoids; HCQ, hydroxychloroquine; Methyl, methylprednisolone e pulse therapy; PR, prevalence ratio; TNFi, tumour necrosis factor inhibitor.
Almost half of the patients in our study required emergency care, being more prevalent among patients with diabetes, kidney disease and chronic users of corticosteroids, either oral or in the form of pulse therapy. Among those who sought emergency care, there was the need for hospitalisation in two thirds of cases, especially in older patients, those who were treated with methylprednisolone pulse therapy and those who did not use TNFi. The prevalence is higher than those reported in most published studies,11–16 and similar to that reported in an Italian cohort by Fredi et al.17 One possible explanation for these differences is the lower social conditions in Brazil, which makes patients more susceptible to more severe conditions, besides the difference in the patient’s disease profile and medications, raising the need for greater concern for patients in developing countries. In accordance with ReumaCov Brazil, most of the studies have found advanced age associated with a higher risk of hospitalisation.13 15–18

Chronic GC use, both oral and pulse therapy, was associated with all outcomes, except mechanical ventilation. Other previous studies describe similar results with oral GC, with doses ranging from 5 to 10 mg11 12 14 19; however, none of these studies described the impact of pulse therapy with methylprednisolone to treat IMRD in COVID-19 outcomes. Although recent studies have shown that the use of GCs in the moderate to severe acute phase of COVID-19 has led to a benefit,20 21 the effect seems to be deleterious in patients on chronic use, probably associated increased risk of infection with higher dose of GC,22 due to impairment of innate immune responses with a reduction in neutrophil recruitment and a delay in viral clearance.23

The result that associated lower prevalence of hospitalisation and ICU admission in patients using TNFi therapy is similar to that described in other studies12–14 and could not be demonstrated to all classes of biologicals. We must also consider that the number of patients using non-TNFi biologicals was lower (12.1%), therefore, the data should be interpreted with caution. However, other studies, including populations with different diseases, have shown similar results, which demonstrates that there must be a biological plausibility for this effect.11 24 25 Gianfrancesco et al also reported that TNFi use was associated with reduced odds of hospitalisation (OR 0.40, 95% CI 0.19 to 0.81), a finding that was not seen with conventional DMARDs alone or in combination with biologics or Janus kinase inhibitors.11

A possible explanation for the TNFi effect on COVID-19 could be inflammation control, based on the evidence that patients with more severe COVID-19 have higher levels of cytokines as TNF and IL-6,26–28 and the TNF inhibition in animal models has led to a protection against SARS-CoV-2 infection,29 induces a rapid decrease of IL-6 and IL-1 concentrations in patients with active RA,30 triggers a reduction of adhesion molecules and vascular endothelial growth factor, which is partly responsible for capillary leak,31 with a consequence of less leucocyte traffic to inflamed tissues.32 A similar effect was also observed in other viral infections, such as Chikungunya fever, where the use of TNFi was associated with better outcomes.33

Twenty-eight patients died, accounting for 8.4% of the total of our series and 17.5% of hospitalised

| Variables                          | PR     | 95% CI      | P value* |
|------------------------------------|--------|-------------|----------|
| Emergency care                     |        |             |          |
| Diabetes                           |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 1.38   | 1.11 to 1.73| 0.004    |
| Kidney disease                     |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 1.36   | 1.05 to 1.77| 0.020    |
| Oral GC                            |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 1.49   | 1.21 to 1.85| <0.001   |
| Intravenous GC                     |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 1.38   | 1.14 to 1.67| 0.001    |
| Hospitalisation                    |        |             |          |
| Age                                |        |             |          |
| Up to 50                           | 1.00   | –           | –        |
| >50                                | 1.89   | 1.26 to 2.85| 0.002    |
| TNFi                               |        |             |          |
| No                                 | 2.51   | 1.16 to 5.45| 0.020    |
| Yes                                | 1.00   | –           | –        |
| Intravenous GC                     |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 2.50   | 1.59 to 3.92| <0.001   |
| Intensive care unit admission      |        |             |          |
| Oral GC                            |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 2.24   | 1.36 to 3.71| 0.002    |
| Intravenous GC                     |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 1.65   | 1.0 to 2.68 | 0.043    |
| SLE                                |        |             |          |
| No                                 | 1.00   | –           | –        |
| Yes                                | 1.72   | 1.04 to 2.88| 0.036    |

*P value of the Wald test
PR, prevalence ratio; TNFi, tumour necrosis factor inhibitor; GC, glucocorticoids; SLE, systemic lupus erythematosus.
| Variables       | Hospitalisation (n, %) | ICU* (n, %) | Death* (n, %) |
|----------------|------------------------|------------|--------------|
|                | Yes      | No      | P value   | 95% CI     | Yes      | No      | P value   | 95% CI     | Yes      | No      | P value   | 95% CI     |
| Age            |          |          |           |            |          |          |           |            |          |          |           |            |
| Up to 50 years | 29 125  | 23 58   | 0.002     | 1.91;      | 13 33    | 0.949†   | 1.02;     | 1.91       |          |          |           |            |
|                | -18.8    | -81.2   | 1.26 to 2.91 | -28.4     | -71.6   | 0.92 to 2.31 | -28.3     | -71.7     |          |          |           |            |
| >50 years      | 36 64    | 24 34   |            |            | 15 37    |          | 0.54 to 1.91 |            |          |          |           |            |
|                | -36 -64  | -41.4 -58.6 |            |            |          |          |            |            |          |          |           |            |
| SLE            |          |          |           |            |          |          |           |            |          |          |           |            |
| No             | 46      | 132     | 0.982     | 1.01;      | 33 55   | 0.200†   | 1.39;     | 1.35;      | 17      | 50      | 0.352†   | 1.35;     |
|                | -25.8    | -74.2   | 0.64 to 1.58 | -37.5     | -62.5   | 0.83 to 2.35 | -25.4     | -74.6     |          |          |           |            |
| Yes            | 20      | 57      |            |            | 14 38   | 1.000‡  | 1.35;     | 1.35;      | 11      | 21      |          | 1.35;     |
|                | -26 -74  | -26.9 -73.1 |            |            |          |          |            |            |          |          |           |            |
| Anti-TNF       |          |          |           |            |          |          |           |            |          |          |           |            |
| No             | 60      | 141     | 0.005     | 2.89;      | 44 75   | 0.042†  | 2.60;     | 2.55;      | 26      | 64      | 1.000†   | 1.30;     |
|                | -29.9    | -70.1   | 1.23 to 5.88 | -37 -63   | 0.88 to 7.57 | -28.9 -71.1 | 1.000†  | 1.30;     |          |          |           |            |
| Yes            | 6       | 48      |            |            | 3 18    | 0.493‡  | 2.21      | 2.21       | 2       | 7       | 1.000‡   | 2.21      |
|                | -11.1 -88.9 | -14.3 -85.7 |            |            |          |          |            |            |          |          |           |            |
| Oral GC        |          |          |           |            |          |          |           |            |          |          |           |            |
| No             | 36      | 138     | 0.006     | 1.82;      | 18 62   | 0.001†  | 2.15;     | 2.55;      | 13      | 37      | 0.610†   | 1.18;     |
|                | -20.7    | -79.3   | 1.21 to 2.74 | -22.5     | -77.5   | 1.32 to 3.48 | -26 -74   | 0.63 to 2.21 |          |          |           |            |
| Yes            | 30      | 51      |            |            | 29 31   | 1.000‡  | 1.18;     | 1.18;      | 15      | 34      |          | 1.18;     |
|                | -37 -63  | -48.3 -51.7 |            |            |          |          |            |            |          |          |           |            |
| Oral GC        |          |          |           |            |          |          |           |            |          |          |           |            |
| <20 mg/day     | 18      | 44      | 0.007     | 2.18;      | 18 25   | 0.111†  | 1.55;     | 1.00†      | 10      | 23      | 1.00†    | 1.03;     |
|                | (29,0)   | -71     | 1.29 to 3.66 | -41.9     | -58.1   | 0.94 to 2.54 | -30.3 -69.7 | 0.42 to 2.52 |          |          |           |            |
| ≥20 mg/day     | 12      | 7       |            |            | 11 6    |          | 5 11      | 1.00†      |          |          |           |            |
|                | -63.2 -38.8 | -64.7 -35.3 |            |            |          |          |            |            |          |          |           |            |
| HCQ            |          |          |           |            |          |          |           |            |          |          |           |            |
|               | Continued |          |           |            |          |          |           |            |          |          |           |            |
| Variables | Hospitalisation | ICU* | Death* |
|-----------|----------------|------|--------|
|           | (n, %)         | (n, %) | P value | (n, %) | (n, %) | P value | (n, %) | (n, %) | P value |
|           | Yes            | No    | RP | Yes | No | RP | Yes | No | RP |
| No        | 46             | 122   | 0.448 | 1.19; | 1.19; | 0.250† | 1.34; | 0.752† | 1.11; |
|           | −27.4          | −72.6 | 0.75 to 1.88 | −37.2 | −62.8 | 0.80 to 2.23 | −27.3 | −72.7 | 0.58 to 2.13 |
| Yes       | 20             | 67    | 0.250† | 0.250† | 1.19; | 1.19; | 0.752† | 1.11; |
|           | −23            | −77   | −27.8 | −72.2 | −37.2 | −62.8 | −27.3 | −72.7 |
| CYC       | No             | 62    | 184 | 0.196 | 1.76; | 1.76; | 0.042‡ | 2.26; | 0.018‡ | 2.86; |
|           | −25.2          | −74.8 | 0.82 to 3.78 | −31.6 | −68.4 | 1.33 to 3.85 | −25 | −75 |
| Yes       | 4              | 5     | 0.042‡ | 0.042‡ | 1.76; | 1.76; | 0.752† | 1.11; |
|           | −44.5          | −55.6 | −71.4 | −28.6 | −71.4 | −28.6 |
| Methyl    | No             | 61    | 187 | 0.0142 | 2.90; | 2.90; | 0.042‡ | 2.26; | 0.018‡ | 2.86; |
|           | −24.6          | −75.4 | 1.73 to 4.87 | −31.6 | (68.4) | 1.33 to 3.85 | −25 | −75 |
| Yes       | 5              | 2     | 0.042‡ | 0.042‡ | 2.90; | 2.90; | 0.752† | 1.11; |
|           | −71.4          | −28.6 | −71.4 | −28.6 | −71.4 | −28.6 |

*Calculated only for hospitalised patients
†P value of the \( \chi^2 \) test for independence;
‡P value of Fisher’s exact test.

anti-TNF, tumour necrose factor inhibitor; CYC, cyclophosphamide pulse therapy; GC, glucocorticoids; HCQ, hydroxychloroquine; ICU, intensive care unit; Methyl, methylprednisolone pulse therapy; RP, prevalence ratio; SLE, systemic lupus erythematosus.
patients, which is quite similar to the data found in other cohorts. The factors associated with mortality in these various studies were variable, but the use of oral GC was the common factor for most of them. In our study deaths were associated with pulse therapy with methylprednisolone and cyclophosphamide. The impact of these medications on both hospitalisation and mortality may be due to the greater number of patients with SLE included in our cohort when compared with others, but also the greater number of SLE among the deaths. It is noteworthy that patients treated with these medications have more severe disease, especially in SLE. This fact calls attention to the evaluation of treatment alternatives during the COVID-19 pandemic, with lower doses of GC and other immunosuppressants than cyclophosphamide, once this is possible.

HCQ was not protective against COVID-19. Despite some initial promising in vitro results, this hypothesis was not supported by our results or by the results of other studies performed in pre-exposed and postexposition prophylaxis using HCQ, as well as more recent randomised clinical trials, including mild-moderate and severe forms of COVID-19. More recently, Gianfrancesco et al reported no association of antimalarial use (OR 0.94, 95% CI 0.57 to 1.57) with hospitalisation.11

Patients with rheumatic diseases had greater need for ICU hospitalisation and presented over a threefold increased risk of requiring mechanical ventilation. Here, we report that 35 out of 50 patients in the ICU required invasive mechanical ventilation, corresponding to 70% of the patients in the ICU. This represents a need for ventilatory assistance in a higher proportion than described in other cohorts of IMRD patients and in the general population.40

Other important points addressed by our study deserve to be highlighted, as they demonstrate a different profile from other data previously published. As in the other series, there was a predominance of females, probably reflecting the higher prevalence of IMRD in women. However, different from other studies, our patients were younger and most of those who died were women under the age of 60 (median 53 years). Considering the median age of 45 years of patients in our cohort, and the mean age of the patients that died, it suggests that immunosuppression is a relevant factor associated with mortality in COVID-19. The immunosuppressed, younger patients can be more vulnerable, and should be considered as a group for shielding. Although our patients were younger, more than two-thirds were not working, and among those who were active at work, most performed activities involving care or contact with the public, which may have favoured infection by SARS-CoV-2. Less than half reported social isolation, suggesting a lack of confidence in social distancing measures or for being considered as breadwinners. Compared with other cohorts, in which SLE patients comprise 6.5%–19.0%, we have found a higher proportion (32.9%). Some cohorts that evaluated only SLE patients demonstrated a higher rate of hospitalisation with no difference between those who used or did not use HCQ and also with no difference in relation to the need for mechanical ventilation or extracorporeal membrane oxygenation.

Although the most recent systematic review and meta-analysis has shown the IMRD patients are more susceptible to the COVID-19, including unfavourable outcomes, when SLE patients are separately analysed, particularly in case–control studies, this finding does not seem to be an absolute true. It probably reflects a selection bias, frequently reported by observational studies, similar to our findings, since most research centres have a great number of SLE patients, with easy access to the researcher and to hospital. In addition, these patients could have been more frequently hospitalised because the clinician may have considered the potential severity of the disease in the COVID-19 scenario. In the multivariate analysis, having a diagnosis of SLE was considered as a possible protective effect for ICU. Nonetheless, it is worth emphasising that SLE patients may have the combination of infection and disease activity in the context of immunosuppression and the rheumatologist needs to individualise the treatment weighing benefits and risks. Interestingly, the current reports have not shown reactivation of underlying IMRD after the COVID-19. Thus, large and longitudinal studies are necessary to address this relevant issue.

In the 74 Latin American patients with rheumatic diseases and COVID-19 reported from the COVID-19 Global Rheumatology Alliance Physician-Reported Registry there were more RA patients (35%) than SLE patients (22%), while in our sample the proportion of SLE patients (32.9%) was greater than the RA (28.4%).

Although hypertension and diabetes were the most frequent comorbidities, as described in other cohorts, we observed that diabetes and renal diseases were the two diseases associated with emergency care at the final model. Of interest, we found 15.7% of obesity, which was not frequently described in other cohorts, but almost the same to one multicentric cohort. A strength of our study is that we included patients from different states of Brazil, a continental country, with most of the patients with confirmed diagnosis of COVID-19 based on positive COVID-19 RT-PCR testing. In addition, the 8-week interim analysis is related to the first weeks of community viral transmission, a relevant finding simulating the pandemic epidemiological curve in Brazil.

As a limitation of the study, many cases may be not included in the cohort because they were not tested or have not been confirmed, usually for presenting a benign evolution of the disease. Since in the Brazilian public health system only hospitalised patients were being tested, this may have become a selection bias, including only the most severely ill patients. Because this is a national register, patients were treated in different services, possibly with different physical and personnel characteristics—a fact that may have interfered with the
results. The availability of healthcare in Brazil can be different when it comes to the public or private health system. Regarding treatment, it was not possible to evaluate the association between COVID-19 with the combination use of different immunosuppressants or DMARDs combination.

Another limitation is related to main endpoints, including hospitalisation, need of mechanical ventilation and death, because they could not be adjusted for potential bias, such as access to healthcare systems, availability of hospital beds, strategies to mitigate the community viral transmission, heterogeneous expertise of medical team.\textsuperscript{39,40} Physicians’ beliefs on the risk of poor outcome in IMRD patients, especially those under immunosuppression, could have driven decision making, such as the need of ICU and medications given earlier. However, it is also important to consider that some patients enrolled in our registry had active and severe underlying IMRD. Therefore, the unfavourable evolution of them could occur itself, regardless of COVID-19.

Brazil is a country with a heterogeneous population, with variations in socioeconomic, cultural, ethnic and health status. The fact that we included representative patients from all Brazilian geographic regions allows our results to be generalised to Brazil and possibly to Latin American countries, with the same population pattern. Future studies comparing the different populations are needed to confirm whether these data occur similarly or not in the rest of the world.

In conclusion, the results of first 8 weeks of the ReumaCoV Brazil registry showed that aspects related to the patients with IMRD (age >50 years), and those related to their treatment (immunosuppression with GC and cyclophosphamide) were associated with unfavourable outcomes of the SARS-CoV-2 infection. Treatment with TNFi, on the other hand, may have been protective, perhaps leading to the control of COVID-19 inflammatory process, but randomised controlled trials to prove this effect are needed.

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Correction: High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry

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The article has been corrected since it was published online. The authors want to alert the readers on missing to include co-author Felipe Omura in the authors' list. He has been identified one of the authors who had a vital contribution towards the preparation of the paper.

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