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Outcomes with and without outpatient SARS-CoV-2 treatment for patients with COVID-19 and systemic autoimmune rheumatic diseases: a retrospective cohort study

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Summary

Background Some patients with systemic autoimmune rheumatic disease and immunosuppression might still be at risk of severe COVID-19. The effect of outpatient SARS-CoV-2 treatments on COVID-19 outcomes among patients with systemic autoimmune rheumatic disease is unclear. We aimed to evaluate temporal trends, severe outcomes, and COVID-19 rebound among patients with systemic autoimmune rheumatic disease and COVID-19 who received outpatient SARS-CoV-2 treatment compared with those who did not receive outpatient treatment.

Methods We did a retrospective cohort study at Mass General Brigham Integrated Health Care System, Boston, MA, USA. We included patients aged 18 years or older with a pre-existing systemic autoimmune rheumatic disease, who had COVID-19 onset between Jan 23 and May 30, 2022. We identified COVID-19 by positive PCR or antigen test (index date defined as the date of first positive test) and systemic autoimmune rheumatic diseases using diagnosis codes and immunomodulator prescription. Outpatient SARS-CoV-2 treatments were confirmed by medical record review. The primary outcome was severe COVID-19, defined as hospitalisation or death within 30 days after the index date. COVID-19 rebound was defined as documentation of a negative SARS-CoV-2 test after treatment followed by a newly positive test. The association of outpatient SARS-CoV-2 treatment versus no outpatient treatment with severe COVID-19 outcomes was assessed using multivariable logistic regression.

Findings Between Jan 23 and May 30, 2022, 704 patients were identified and included in our analysis (mean age 58·4 years [SD 15·9]; 536 [76%] were female and 168 [24%] were male, 590 [84%] were White and 39 [6%] were Black, and 347 [49%] had rheumatoid arthritis). Outpatient SARS-CoV-2 treatments increased in frequency over calendar time (p<0·0001). A total of 426 [61%] of 704 patients received outpatient treatment (307 [44%] with nirmatrelvir–ritonavir, 105 [15%] with monoclonal antibodies, five [1%] with molnupiravir, three [<1%] with remdesivir, and 347 [49%] had rheumatoid arthritis). Outpatient SARS-CoV-2 treatments increased in frequency over calendar time (p<0·0001). A total of 426 [61%] of 704 patients received outpatient treatment (307 [44%] with nirmatrelvir–ritonavir, 105 [15%] with monoclonal antibodies, five [1%] with molnupiravir, three [<1%] with remdesivir, and six [1%] with combination treatment). There were nine (2·1%) hospitalisations or deaths among 426 patients who received outpatient treatment compared with 49 (17·6%) among 278 who did not receive outpatient treatment (odds ratio [adjusted for age, sex, race, comorbidities, and kidney function] 0·12, 95% CI 0·05–0·25). 25 (7·9%) of 318 patients who received oral outpatient treatment had documented COVID-19 rebound.

Interpretation Outpatient treatment was associated with lower odds of severe COVID-19 outcomes compared with no outpatient treatment. These findings highlight the importance of outpatient SARS-CoV-2 treatment for patients with systemic autoimmune rheumatic disease and COVID-19 and the need for further research on COVID-19 rebound.

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Introduction

Outpatient SARS-CoV-2 treatment options include monoclonal antibodies, remdesivir, and oral medications such as nirmatrelvir–ritonavir and molnupiravir.12–14 For patients with systemic autoimmune rheumatic disease, effective COVID-19 treatments are important because altered immunity and immunosuppression might affect vaccine response14–16 and COVID-19 severity.17 COVID-19 rebound is a complication after treatment, characterised by recurrence of symptoms and test positivity after regimen completion.18–21 However, there is a paucity of data on outcomes with and without outpatient SARS-CoV-2 treatment among patients with systemic autoimmune rheumatic disease and COVID-19, and on the prevalence of rebound COVID-19. The trials showing efficacy of outpatient SARS-CoV-2 treatments were done before the emergence of contemporary viral variants and the introduction of COVID-19 vaccines.22–24 Also, although these trials focused on people at high risk of progressing to severe COVID-19, people who were immunosuppressed, such as those with systemic autoimmune rheumatic disease, were infrequently enrolled (eg, 0% in the nirmatrelvir–ritonavir trial and 4% in the outpatient remdesivir trial).12–14 Thus, the potential benefit of outpatient SARS-CoV-2 treatment
We searched PubMed on Dec 2, 2022, for articles published from database inception to Dec 2, 2022, with no language restrictions, using the terms: ((‘rheumatic’ or ‘immunosuppressed’) AND “COVID-19” AND (“outpatient” OR “nirmatrelvir” OR “molnupiravir”) NOT ((review) OR (editorial) OR “case report”)). The search yielded 86 articles. Many of the articles pertained to vaccine response rather than SARS-CoV-2 infection. A single-centre study in 2022 investigated breakthrough COVID-19 among patients with immune-mediated inflammatory diseases who had received B-cell-depleting therapy. The authors found that outpatient treatment with monoclonal antibodies was associated with lower risk of severe COVID-19 compared with no outpatient treatment, but this analysis was performed before the SARS-CoV-2 omicron variant was dominant and before oral outpatient treatment options were available. A large study in Israel using administrative data found that only 4737 (2.6%) of 180351 patients at high risk of severe COVID-19 in early 2022 were treated with nirmatrelvir-ritonavir, and this treatment was associated with lower risk of severe COVID-19, but the study did not focus on patients with systemic autoimmune rheumatic disease and immunosuppression. We found no studies that investigated COVID-19 rebound (recurrence of symptoms and test positivity after regimen completion) after oral outpatient SARS-CoV-2 treatment.

Evidence before this study

We aimed to evaluate outpatient SARS-CoV-2 treatments and outcomes, including COVID-19 rebound, in patients with systemic autoimmune rheumatic diseases and COVID-19. First, we examined temporal trends and the proportion of patients receiving SARS-CoV-2 outpatient treatment (monoclonal antibodies, oral medications, or remdesivir). Second, we compared severe COVID-19 outcomes among patients who received outpatient SARS-CoV-2 treatment with those who did not receive outpatient treatment. Third, we examined the prevalence of COVID-19 rebound among patients with systemic autoimmune rheumatic disease who received oral outpatient SARS-CoV-2 treatment.

Methods

Study design and participants

We did a retrospective cohort study at Mass General Brigham Integrated Health Care System, Boston, MA, USA. Mass General Brigham is a multicentre health-care system that includes 14 hospitals and primary care or specialty outpatient centres. We included patients aged 18 years or older with a pre-existing systemic autoimmune rheumatic disease who had COVID-19 onset between Jan 23 and May 30, 2022. This study was approved by the Mass General Brigham Institutional Review Board. Patient informed consent was not required for this retrospective study.

We identified patients with COVID-19 using an electronic query of the Mass General Brigham Research Patient Data Registry, which gathers data from the electronic health record. We identified COVID-19 as a positive SARS-CoV-2 PCR or antigen test, or a positive COVID-19 flag in the electronic health record, or both. At Mass General Brigham, a positive COVID-19 flag indicates a confirmed diagnosis of COVID-19 and captures patients with a positive test outside of the Mass General Brigham health-care system, including home rapid antigen assay reported to health-care providers or clinics and when ordering or administering outpatient treatments. The index date was defined as the date of the first positive test or flag within the study dates.

From this cohort of patients with COVID-19, we identified patients who had a pre-existing systemic autoimmune rheumatic disease at onset of COVID-19. We previously described identification of systemic autoimmune rheumatic diseases at Mass General Brigham using administrative data for COVID-19 studies in detail, validated with a 90% positive predictive value. Briefly, systemic autoimmune rheumatic diseases were defined as at least two International Classification of Diseases (ICD)-10 codes (appendix p 2) for a systemic autoimmune

Added value of this study

To our knowledge, this is one of the first studies to evaluate outpatient SARS-CoV-2 treatments among patients with systemic autoimmune rheumatic disease that includes oral outpatient treatment options and quantifies the prevalence of COVID-19 rebound. Even among a cohort of patients with rheumatic disease and immunosuppression who were mostly vaccinated against SARS-CoV-2, outpatient treatment was associated with substantially reduced odds of severe COVID-19 outcomes compared with no outpatient treatment. At least 8% of patients with systemic autoimmune rheumatic disease who received oral outpatient treatment had COVID-19 rebound.

Implications of all the available evidence

These results should encourage clinicians to prescribe—and patients with systemic autoimmune rheumatic disease and COVID-19 to seek—prompt outpatient SARS-CoV-2 treatment. This research provides an early estimate of the prevalence of COVID-19 rebound after oral outpatient SARS-CoV-2 treatment, which could be used to quantify this risk to clinicians and patients with systemic autoimmune rheumatic disease and encourage future research.
Among patients who received oral outpatient SARS-CoV-2 treatment, we performed medical record review to identify patients who had COVID-19 rebound documented in the electronic health record. As in a previous study, COVID-19 rebound was defined as: completion of oral outpatient regimen, documentation of negative then newly positive SARS-CoV-2 tests within 7 days of regimen completion, and recurrence in COVID-19 symptoms (after improvement in most or all symptoms) within 7 days of regimen completion. Patients who had little or no improvement in symptoms throughout follow-up were not considered to have COVID-19 rebound. Patients with prolonged viral shedding without a negative test in the interim were not considered to have rebound COVID-19.

We classified each patient’s systemic autoimmune rheumatic disease diagnosis using ICD-10 codes, as described previously. Immunomodulatory medications were identified using prescription data preceding the index date. For conventional synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), we separately considered the most recent prescriptions. For CD20 inhibitors, we classified exposure if last received within 1 year before the index date, due to lengthy effects that can impact vaccine response and COVID-19 severity.

We used an electronic query to identify most covariates. Demographic factors were age, sex, race (White, Black, Asian, other, or unknown), and ethnicity (Hispanic or Latinx, or non-Hispanic). We measured area-level social deprivation using median household income by zip code area. Lifestyle factors were BMI (continuous) and smoking status (never, past, current, or missing). We calculated the Charlson Comorbidity Index from ICD-10 codes in the 1 year before the index date. We also identified individual components of the Charlson Comorbidity Index as well as interstitial lung disease, which has been previously associated with worse COVID-19 outcomes. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation without the race multiplier. We categorised eGFR as less than 30 mL/min/1.73 m² (severely decreased kidney function), 30 mL/min/1.73 m² to less than 60 mL/min/1.73 m² (moderately decreased kidney function), or 60 mL/min/1.73 m² or greater (normal kidney function), because this affects nirmatrelvir-ritonavir dosing and eligibility.

COVID-19 vaccine types and dates were extracted from patients’ electronic health record. Vaccination status was classified as unvaccinated, partially vaccinated, two doses of mRNA vaccine or one dose of adenovirus vaccine, or additional vaccine doses. For patients initially classified as unvaccinated or partially vaccinated, we reviewed their medical records to accurately classify vaccination status. For patients who had received vaccines, we also calculated time from last dose to the index date, because immunity wanes over time. Electronic query identified previous
COVID-19 before the current episode. Medical record review determined tixagevimab–cilgavimab use.23

Statistical analysis
We plotted the total number of COVID-19 cases per calendar week in the study period and subdivided this by outpatient treatment received (nirmatrelvir–ritonavir, molnupiravir, monoclonal antibodies, remdesivir, combination treatment, or no outpatient treatment). We used the χ² test to calculate the p value for trend of the proportion of patients who received outpatient treatment across the ordinal variable of calendar week. We reported baseline characteristics using descriptive statistics according to outpatient treatment exposure status.

The primary analysis compared any outpatient SARS-CoV-2 treatment versus no outpatient treatment for the outcome of severe COVID-19. We used an unadjusted logistic regression model to calculate the odds ratios (ORs) and 95% CIs for severe COVID-19. In the multivariable model, we included age, Charlson Comorbidity Index, eGFR, and race (White or non-White) as possible confounders. We used directed acyclic graphs (appendix p 5) to choose these as potential confounders that might influence both the decision to prescribe outpatient treatment as well as the risk of severe COVID-19. As there were relatively few outcomes in the group who received outpatient treatment, we also performed an analysis using Poisson regression to obtain risk ratios (RRs) to negate sparse-data bias.24,25

We performed similar analyses for other comparisons of outpatient treatments for risk of severe COVID-19: nirmatrelvir–ritonavir versus no outpatient treatment, monoclonal antibodies versus no outpatient treatment, nirmatrelvir–ritonavir versus no outpatient treatment and all other treatments, monoclonal antibodies versus no outpatient treatment and all other treatments, and nirmatrelvir–ritonavir versus monoclonal antibodies. We were unable to investigate molnupiravir, outpatient remdesivir, or combination treatment use because few patients received these therapies. We also performed several sensitivity analyses. First, we only considered severe COVID-19 outcomes that occurred at least 1 day after the index date. Second, we only considered severe COVID-19 outcomes that occurred at least 1 day after the index date up to day 14. Third, we performed medical record review of all severe outcomes masked to outpatient treatment (table 1). The proportion of patients who received outpatient SARS-CoV-2 treatment increased over calendar time (figure 1); 20 (35%) of 57 patients who received outpatient SARS-CoV-2 treatment increased during the first week of the study compared with 44 (65%) of 68 during the last full week of the study (p for trend <0·0001 across all calendar weeks).

A total of 426 (61%) of 704 patients received any outpatient SARS-CoV-2 treatment (307 [44%] with nirmatrelvir–ritonavir; 105 [15%] with monoclonal antibodies; five [1%] with molnupiravir; three [<1%] with remdesivir; and six [1%] with combination treatment; four with nirmatrelvir–ritonavir and monoclonal antibodies; two with molnupiravir and monoclonal antibodies). A total of 278 (39%) patients received no outpatient SARS-CoV-2 treatment (table 1). Patients who received outpatient treatment were more likely to be female (331 [78%] of 426 patients vs 205 [74%] of 278) and White (367 [86%] vs 223 [80%]), less likely to have severe kidney impairment (six [1%] vs nine [3%]), and less likely to be unvaccinated (nine [2%] vs 18 [6%]) than those who received no outpatient treatment.
347 (49%) of 704 patients had rheumatoid arthritis, 113 (16%) had psoriatic arthritis, and 87 (12%) had systemic lupus erythematosus (table 2). 484 (69%) of 704 patients used conventional synthetic DMARDs, most frequently methotrexate (232 [33%]) and hydroxychloroquine (214 [30%]). 258 (37%) patients used biologic DMARDs, most frequently tumour necrosis factor inhibitors (144 [20%]). Characteristics of patients that used other outpatient treatments are shown in the appendix (pp 6–7).

Among 704 patients, a total of 58 (8·2%) hospitalisations and three (0·4%) deaths occurred within 30 days of the COVID-19 index date (table 3). The composite primary outcome of hospitalisation or death (severe COVID-19)
within 30 days of the COVID-19 index date occurred in 58 (8·2%) patients. Of the patients who received outpatient SARS-CoV-2 treatment, nine (2·1%; including one death) of 426 had severe COVID-19 compared with 49 (17·6%; two deaths) of 278 patients who did not receive outpatient treatment. Of 307 patients treated with nirmatrelvir–ritonavir, four (1·3%; one death) had severe COVID-19 outcomes. Of 105 patients treated with monoclonal antibodies, five (4·8%) had hospitalisations. No severe COVID-19 outcomes occurred among the 14 patients who received molnupiravir, remdesivir, or combination treatment. Among 27 unvaccinated patients, two (7·4%) had severe COVID-19 outcomes; neither of these patients had received outpatient treatment.

Of the three deaths, one was in an older man (who did not receive outpatient treatment) with giant cell arteritis treated with prednisone and methotrexate who was admitted to hospital with COVID-19 pneumonia and progressed to multi-organ failure; one was in an older man (who did not receive outpatient treatment) with metastatic prostate cancer and psoriatic arthritis treated with etanercept who was admitted to hospital with COVID-19 pneumonia, generalised weakness, and fatigue without substantial recovery; and one was in an older woman (who received outpatient treatment with nirmatrelvir–ritonavir) with rheumatoid arthritis treated with methotrexate who was admitted to hospital with fever and severe abdominal pain, found to have peritoneal carcinomatosis, and died after intestinal perforation.

Of the patients with severe COVID-19 outcomes in the primary analysis, 46 (79%) of 58 were adjudicated to have COVID-19 as either a primary or partial contributor to the hospitalisation, and 29 (63%) of 46 had COVID-19 pneumonia as the primary reason for hospitalisation.

After adjustment for age, Charlson Comorbidity Index, eGFR, and race, patients who received any outpatient SARS-CoV-2 treatment had an adjusted OR for severe COVID-19 of 0·12 (95% CI 0·05–0·25) compared with those who did not receive outpatient treatment (table 4). The results of the Poisson regression were similar to the primary analyses (adjusted RR 0·16, 95% CI 0·08–0·32; appendix p 8).

In the secondary analyses, nirmatrelvir–ritonavir (adjusted OR 0·08, 95% CI 0·03–0·24) and monoclonal
antibodies (0·20, 0·07–0·54) were each associated with lower odds of severe COVID-19 compared with no outpatient treatment. Patients who received nirmatrelvir–ritonavir had an adjusted OR for severe COVID-19 of 0·46 (95% CI 0·11–1·97) compared with those who received monoclonal antibodies (table 4).

| Rheumatic disease diagnosis | Outpatient treatment | No outpatient treatment (n=278) |
|-----------------------------|----------------------|---------------------------------|
|                             | Any treatment (n=426)* | Nirmatrelvir–ritonavir (n=307) | Monoclonal antibodies (n=105) |

| Rheumatic disease diagnosis | Outpatient treatment | No outpatient treatment (n=278) |
|-----------------------------|----------------------|---------------------------------|
|                             | Any treatment (n=426)* | Nirmatrelvir–ritonavir (n=307) | Monoclonal antibodies (n=105) |

| Immunomodulatory medications | Oral glucocorticoid | Any conventional synthetic DMARDs† | Methotrexate | Any conventional synthetic DMARDs† |
|-------------------------------|---------------------|------------------------------------|--------------|------------------------------------|
|                               | 18 (4%)             | 284 (67%)                          | 138 (22%)    | 205 (67%)                          |
|                               | 6 (2%)              | 71 (68%)                           | 32 (30%)     | 200 (72%)                          |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
| Immunosuppressive medications | Oral glucocorticoid | Any conventional synthetic DMARDs† | Methotrexate | Any conventional synthetic DMARDs† |
|                               | 18 (4%)             | 284 (67%)                          | 138 (22%)    | 205 (67%)                          |
|                               | 6 (2%)              | 71 (68%)                           | 32 (30%)     | 200 (72%)                          |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
|                               | 6 (2%)              | 32 (10%)                           | 30 (9%)      |                                    |
|                               | 12 (11%)            | 94 (34%)                           | 97 (35%)     |                                    |
| Data are n (%). ANCA=antineutrophil cytoplasmic antibodies. CTLA-4=cytotoxic T-lymphocyte-associated protein 4. DMARD=disease-modifying antirheumatic drug. IL=interleukin. JAK=Janus kinase. TNF=tumour necrosis factor. *Characteristics of other outpatient treatments (five patients received molnupiravir, three received remdesivir, and six received combination treatment [four received nirmatrelvir–ritonavir and monoclonal antibodies and two received molnupiravir and monoclonal antibodies]) are shown in the appendix (pp 6–7). †Some patients were on more than one medication.

Table 2: Rheumatic disease characteristics at COVID-19 onset by outpatient SARS-CoV-2 treatment status
### Table 4: ORs for severe COVID-19 (hospitalisation or death) within 30 days after the index date

|                                      | All patients (n=704) | Outpatient treatment (n=426) | No outpatient treatment (n=278) |
|--------------------------------------|----------------------|------------------------------|---------------------------------|
|                                      |                      | Any outpatient treatment     | Nirmatrelvir-ritonavir (n=307) | Monoclonal antibodies (n=105) |
| Hospitalisation                      | $58$ (8.2%)         | $9$ (2.1%)                   | $4$ (1.3%)                      | $5$ (4.8%)                     |
| Death                                | $3$ (0.4%)          | $1$ (0.2%)                   | $1$ (0.3%)                      | $0$                            |
| Severe COVID-19 (hospitalisation or death) | $58$ (8.2%)         | $9$ (2.1%)                   | $4$ (1.3%)                      | $5$ (4.8%)                     |
| COVID-19 rebound†                    | NA                   | NA                           | $24$ (31.1%)                    | $0$                            |

Data are n (%) or n/N (%). NA=not applicable. *There were no severe COVID-19 outcomes among patients who received molnupiravir, three received remdesivir, and six received combination treatment (four received nirmatrelvir-ritonavir and monoclonal antibodies and two received molnupiravir and monoclonal antibodies). †Within 7 days after completion of the oral outpatient regimen. ‡The denominator for COVID-19 rebound also includes four patients who received nirmatrelvir-ritonavir in combination with monoclonal antibodies; there was also one COVID-19 rebound case among seven (14.3%) patients who received molnupiravir.

### Table 3: COVID-19 outcomes within 30 days after the index date by outpatient SARS-CoV-2 treatment status

|                                      | Unadjusted | Multivariable model 1* | Multivariable model 2† |
|--------------------------------------|------------|------------------------|------------------------|
| **Primary analysis**                 |            |                        |                        |
| Any outpatient treatment vs no outpatient treatment | $0.10$ (0·05–0·21) | $0.12$ (0·05–0·25) | $0.13$ (0·06–0·28) |
| **Secondary analyses**               |            |                        |                        |
| Nirmatrelvir-ritonavir vs no outpatient treatment | $0.06$ (0·02–0·17) | $0.08$ (0·03–0·24) | $0.09$ (0·03–0·27) |
| Monoclonal antibodies vs no outpatient treatment | $0.23$ (0·09–0·60) | $0.20$ (0·07–0·54) | $0.21$ (0·08–0·57) |
| Nirmatrelvir-ritonavir vs no outpatient treatment and all other treatments | $0.08$ (0·03–0·23) | $0.12$ (0·04–0·34) | $0.13$ (0·04–0·37) |
| Monoclonal antibodies vs no outpatient treatment and all other treatments | $0.52$ (0·20–1·32) | $0.35$ (0·13–0·97) | $0.35$ (0·13–0·99) |
| Nirmatrelvir-ritonavir vs monoclonal antibodies | $0.26$ (0·07–1·00) | $0.46$ (0·11–1·97) | $0.43$ (0·10–1·86) |

Data are OR (95% CI). OR=odds ratio. *Model 1 was adjusted for continuous age, continuous Charlson Comorbidity Index, continuous estimated glomerular filtration rate, and race. †Model 2 was adjusted for the covariates listed in Model 1 and zip code area median household income.

Findings from our primary analysis remained robust across all subgroup analyses (figure 2). Results were similar among the subgroup of patients with rheumatoid arthritis and patients receiving specific immunomodulatory medications (ie, methotrexate and hydroxychloroquine; appendix p 9).

In the first sensitivity analysis that considered only severe COVID-19 outcomes that occurred at least 1 day after the index date, severe COVID-19 outcomes occurred in 38 (5·4%) of 704 patients (nine [2·1 %] of 426 who received any outpatient SARS-CoV-2 treatment vs 29 [10·4%] of 278 who did not receive outpatient treatment; adjusted OR 0·28, 95% CI 0·12–0·62; appendix p 11). In the third sensitivity analysis, we excluded 12 of the 58 severe COVID-19 outcomes adjudicated to be unrelated to COVID-19 (appendix p 12); patients who received any outpatient SARS-CoV-2 treatment had an adjusted OR for severe COVID-19 outcomes of 0·13 (95% CI 0·05–0·29) compared with those who received no outpatient treatment (appendix p 12).

25 (7·9%) of 318 patients who received oral outpatient SARS-CoV-2 treatment had documented COVID-19 rebound. Among 311 patients who received nirmatrelvir-ritonavir, 24 (7·7%) had COVID-19 rebound. Among seven patients who received molnupiravir, one (14·3%) had COVID-19 rebound. Characteristics of patients who had COVID-19 rebound are shown in the appendix (pp 13–15).

### Discussion

In this contemporary cohort of patients with systemic autoimmune rheumatic disease and COVID-19, outpatient SARS-CoV-2 treatment with antivirals or monoclonal antibodies was associated with substantially lower odds of severe COVID-19 outcomes compared with no outpatient treatment. Outpatient COVID-19 treatment increased in frequency over the study period; the most common outpatient treatments were nirmatrelvir–ritonavir, 24 (7·7%) had COVID-19 rebound. Among seven patients who received molnupiravir, one (14·3%) had COVID-19 rebound. Characteristics of patients who had COVID-19 rebound are shown in the appendix (pp 13–15).
### Table A

| Age (years) | Severe outcomes (n) | Participants (n) | OR (95% CI) |
|-------------|---------------------|------------------|-------------|
| <65         | 27                  | 454              | 0.05 (0.01-0.20) |
| ≥65         | 31                  | 250              | 0.20 (0.08-0.54) |

**Sex**
- Male: 18 / 168
- Female: 40 / 536

**Charlson Comorbidity Index**
- 0–1: 9 / 372
- ≥2: 49 / 332

**eGFR (mL/min per 1.73 m²)**
- ≥30: 53 / 689
- <30: 5 / 15

**Vaccination status**
- Unvaccinated: 2 / 27
- Two mRNA vaccine doses or one adenovirus vaccine dose: 17 / 112
- Additional doses: 39 / 565

**Duration since last vaccine dose (months)**
- ≤6: 34 / 395
- >6: 21 / 281

**Overall**
- Total: 58 / 704

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### Table B

| Age (years) | Severe outcomes (n) | Participants (n) | OR (95% CI) |
|-------------|---------------------|------------------|-------------|
| <65         | 27                  | 386              | 0.07 (0.02-0.33) |
| ≥65         | 26                  | 199              | 0.11 (0.02-0.54) |

**Sex**
- Male: 16 / 145
- Female: 37 / 440

**Charlson Comorbidity Index**
- 0–1: 9 / 334
- ≥2: 44 / 251

**eGFR (mL/min per 1.73 m²)**
- ≥30: 48 / 576
- <30: 5 / 9

**Vaccination status**
- Unvaccinated: 2 / 26
- Two mRNA vaccine doses or one adenovirus vaccine dose: 16 / 97
- Additional doses: 35 / 462

**Duration since last vaccine dose (months)**
- ≤6: 31 / 323
- >6: 19 / 235

**Overall**
- Total: 53 / 585

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### Table C

| Age (years) | Severe outcomes (n) | Participants (n) | OR (95% CI) |
|-------------|---------------------|------------------|-------------|
| <65         | 25                  | 235              | *           |
| ≥65         | 29                  | 148              | 0.35 (0.11-1.11) |

**Sex**
- Male: 16 / 95
- Female: 38 / 288

**Charlson Comorbidity Index**
- 0–1: 7 / 169
- ≥2: 47 / 214

**eGFR (mL/min per 1.73 m²)**
- ≥30: 49 / 369
- <30: 5 / 14

**Vaccination status**
- Unvaccinated: 2 / 19
- Two mRNA vaccine doses or one adenovirus vaccine dose: 16 / 69
- Additional doses: 36 / 295

**Duration since last vaccine dose (months)**
- ≤6: 31 / 220
- >6: 20 / 143

**Overall**
- Total: 54 / 383

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Figure 2: Forest plots of subgroup analyses for odds of severe COVID-19 outcomes (hospitalisation or death) within 30 days after the index date

(A) Any outpatient SARS-CoV-2 treatment versus no outpatient treatment. (B) Nirmatrelvir-ritonavir versus no outpatient treatment. (C) Monoclonal antibodies versus no outpatient treatment. All ORs are adjusted for continuous age, continuous CCL, continuous eGFR, and race. eGFR=estimated glomerular filtration rate. OR=odds ratio. *Model did not converge due to few outcomes.
Articles

Patients with systemic autoimmune rheumatic disease have increased risk of SARS-CoV-2 infection and severe outcomes compared with the general population.6,26 Thus, even with improving COVID-19 outcomes, some severe outcomes compared with the general population.26

Thus, even with improving COVID-19 outcomes, some severe outcomes compared with the general population.26 A large study in Israel using administrative data investigated nirmatrelvir–ritonavir use among patients at high risk of severe COVID-19 early in 2022 and found that few patients received nirmatrelvir–ritonavir, but those who did had lower risk of severe COVID-19 than those who did not receive this treatment. However, the study was not focused on patients with systemic autoimmunity rheumatic disease who were at risk of severe COVID-19 due to immunosuppression.28 In this context, our novel findings regarding the substantially lower odds of severe COVID-19 associated with outpatient SARS-CoV-2 treatment are an important reminder to clinicians to consider early outpatient treatment for patients with systemic autoimmune rheumatic disease and COVID-19. We observed a strong association between outpatient treatment and lower risk of severe COVID-19 (adjusted OR 0.12). This result is similar to the pivotal clinical trial for nirmatrelvir–ritonavir that observed a RR of 0.11 for severe COVID-19 compared with placebo.3 To further evaluate the potential effect of sparse-data bias, we did a sensitivity analysis using Poisson regression and confirmed the robustness of our results. Importantly, our findings persisted across all subgroups examined, including in younger (<65 years) patients and those who remained unvaccinated during this study period characterised by predominance of the highly contagious omicron SARS-CoV-2 variants. Most patients in the outpatient treatment group in our study received nirmatrelvir–ritonavir and monoclonal antibodies; few received molnupiravir (1%), remdesivir (<1%), or combination treatment (1%). Whether similar patterns of benefit will be observed in other centres or with receipt of these less frequently used treatments requires further investigation.

COVID-19 rebound is characterised by re-emergence of test positivity and symptoms after completion of oral outpatient SARS-CoV-2 treatments.8 Rebound might have societal effects related to extension of isolation along with health effects and reduced quality of life from prolonged viral infection. The exact mechanisms of COVID-19 rebound are unknown, but it might reflect incomplete viral eradication at the completion of oral treatment. People with systemic autoimmune rheumatic disease have altered underlying immunity and are immunosuppressed, with some known to have prolonged viral shedding,9 so it is possible that patients with immunosuppression could have higher risk of COVID-19 rebound. We found that 7.9% of patients with systemic autoimmune rheumatic disease who received oral monotherapy for COVID-19 had documented COVID-19 rebound. Because our study was retrospective, and we required documentation of recurrent positive test results and symptoms to confirm rebound cases, 7.9% is likely to be an underestimate of the true incidence of COVID-19 rebound. Notably, no patients in our study who had documented COVID-19 rebound were subsequently hospitalised, which is reassuring. Overall, this finding highlights the need for further research on COVID-19 in this vulnerable population, including prospective ascertainment of COVID-19 rebound, possible relationships with severe COVID-1919 and long-COVID, and consideration of longer courses of oral treatment regimens.

Monoclonal antibodies were the first outpatient treatment shown to be effective in preventing severe COVID-19 among patients at high risk.1 Pre-exposure prophylaxis with monoclonal antibodies might also reduce severe outcomes, and among patients with systemic autoimmunity rheumatic disease who received B-cell-depleting therapy, monoclonal antibodies might be effective, even after vaccination.21,22 Our study adds to the literature by investigating all patients with systemic autoimmunity rheumatic disease, not only those at highest risk of severe outcomes due to B-cell depletion. Compared with no outpatient treatment, monoclonal antibodies were associated with substantially lower odds of severe COVID-19. These patients might have had high clinical suspicion to progress to severe COVID-19. Indeed, patients with systemic autoimmunity rheumatic disease who received monoclonal antibodies had more comorbidities and worse kidney function than those who did not receive outpatient treatment. Even with oral options available, many clinicians and patients might choose to receive monoclonal antibodies, due to contraindications for the use of nirmatrelvir–ritonavir or to avoid COVID-19 rebound after oral medications. In the analysis that compared nirmatrelvir–ritonavir with monoclonal antibodies, there was no significant difference between these treatments, which suggests that they might be similarly effective. Our findings were robust across many subgroups and sensitivity analyses that shortened the window for severe COVID-19 outcomes and excluded some severe outcomes that might not have been related to COVID-19 or where COVID-19 was diagnosed after hospitalisation. We had access to individual medical record data and were able to provide clinical detail on the severe COVID-19 outcomes and confirm that the majority of hospitalisations in this analysis were due to COVID-19, rather than an incidental diagnosis.

This study has some limitations. First, the sample was from a single geographical area with a high COVID-19 vaccination coverage, so might not be generalisable to other settings. However, we still detected significant differences in severe COVID-19 risk that might be even more pronounced in populations with lower vaccination...
coverage. Second, we might not have identified all COVID-19 cases, particularly in those who used home antigen tests and did not inform their health-care provider of the results. Thus, the true denominator of patients with systemic autoimmune rheumatic disease and COVID-19 might be larger than our study reported. However, people at high risk of severe COVID-19 might be more likely to seek testing and treatment, which might have therefore biased our findings towards the null. Third, some of the severe COVID-19 outcomes might have been due to incidentally diagnosed COVID-19 from screening during hospitalisations for other reasons or could have been nosocomial infections. Our findings remained robust in a sensitivity analysis that required a time separation between the index date and outcome. Fourth, it is possible that the results might have been affected by unmeasured confounding that might include specific contraindications to nirmatrelvir–ritonavir, social determinants of health, and access to care. However, in the additional multivariable analysis that adjusted for area-level household income, the results were similar. Fifth, although the results were robust across many subgroups and sensitivity analyses, we performed many comparisons and some subgroups were small, so these results should be considered exploratory and interpreted with caution. Although we were able to detect associations, the precision of effect size estimates was low due to relatively few outcomes, resulting in wide 95% CIs, so the magnitude of the associations should be interpreted with caution. Although we attempted to correct for possible sparse-data bias by also calculating RRs for analyses in which point estimates for ORs were far from the null, this still might not have completely overcome this issue due to few outcomes in the group who received outpatient treatment. Finally, we relied on medical documentation to identify cases of COVID-19 rebound. It is possible that some patients had COVID-19 rebound and it was not documented. Therefore, we presented only descriptive results, and this estimate should be viewed as conservative.

In conclusion, we found that outpatient SARS-CoV-2 treatment was associated with reduced odds of severe COVID-19 outcomes compared with no outpatient treatment. Over time, more patients with systemic autoimmune rheumatic disease received outpatient SARS-CoV-2 treatment, mostly with nirmatrelvir–ritonavir or monoclonal antibodies. The proportion of patients who received outpatient treatment who had confirmed COVID-19 rebound was at least 7·9%, a conservative estimate due to the stringent definition we used that required documentation. These findings should encourage outpatient SARS-CoV-2 treatment among patients with systemic autoimmune rheumatic disease.

Contributors
GQ, ZSW, and JAS designed the study, were responsible for the acquisition, analysis, and interpretation of the data, and drafted and revised the manuscript. XW was involved in the analysis and interpretation of the data. All authors were involved in the data acquisition, interpretation, and revision of the manuscript. ZSW and JAS are joint senior authors. GQ, XW, ZSW, and JAS directly accessed and verified the underlying data reported in the manuscript. All authors approved the final version of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests
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Data sharing
Data are available upon request to the corresponding author with appropriate institutional review board approval.

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