A SIMPLE, HOME-THERAPY ALGORITHM TO PREVENT HOSPITALIZATION OF COVID-19 PATIENTS: A RETROSPECTIVE OBSERVATIONAL MATCHED-COHORT STUDY

Brief title:
COVID-19 home therapy

Fredy Suter MD\textsuperscript{1}, Elena Consolaro MD\textsuperscript{2}, Stefania Pedroni MD\textsuperscript{2}, Chiara Moroni MD\textsuperscript{2}, Elena Pastò MD\textsuperscript{2}, Maria Vittoria Paganini MD\textsuperscript{2}, Grazi P ravettoni MD\textsuperscript{3}, Umberto Cantarelli MD\textsuperscript{4}, Nadia Rubis res nurse\textsuperscript{5}, Norberto Perico* MD\textsuperscript{5}, Annalisa Perna MSC\textsuperscript{5}, Tobia Peracchi StatSciD\textsuperscript{5}, Piero Ruggenenti* MD\textsuperscript{1,5}, Giuseppe Remuzzi *MD\textsuperscript{5},

\textsuperscript{1}Azienda Socio-Sanitaria Territoriale (ASST) Papa Giovanni XXIII, Bergamo, Italy
\textsuperscript{2}ATS Insubria, Varese, Italy
\textsuperscript{3}Ospedale Circolo di Busto Arsizio, Varese, Italy
\textsuperscript{4}ASL Teramo, Teramo, Italy
\textsuperscript{5}Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy

* equally contributed

Correspondence to:
Norberto Perico MD,
Istituto di Ricerche Farmacologiche IRCCS,
Centro di Ricerche Cliniche per Malattie Rare Aldo e Cele Daccò,
Via GB Camozzi 3, 24020 Ranica, Bergamo, Italy.
Email: norberto.perico@marionegri.it

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
**SUMMARY**

**Background.** Effective simple, home-treatment algorithms implemented on the basis of a pathophysiologic and pharmacologic rationale to accelerate recovery and prevent hospitalization of patients with early coronavirus disease 2019 (COVID-19) would have major implications for patients and health care providers.

**Methods.** This academic, matched-cohort study compared outcomes of 90 consecutive consenting patients with mild COVID-19 treated at home by their family physicians from October 2020 to January 2021 according to the proposed recommendation algorithm with those of 90 age-, sex-, and comorbidities- matched patients who received other therapeutic regimens. Primary outcome was time to resolution of major symptoms. Secondary outcomes included prevention of hospitalization. Analyses were by intention-to-treat.

**Findings.** All patients achieved complete remission. The median [IQR] time to resolution of major symptoms was 18 [14-23] days in the ‘recommended’ schedule cohort and 14 [7-30] days in the matched ‘control’ cohort (p=0·033). Minor symptoms persisted in a lower percentage of patients in the ‘recommended’ than in the ‘control’ cohort (23·3% versus 73·3%, respectively, p<0·0001) and for a shorter period (p=0·0107). Two patients in the ‘recommended’ cohort were hospitalized compared to 13 (14·4%) controls (Log-rank test, p=0·0038). Prevention algorithm abated the days and cumulative costs of hospitalization by >90% (from 481 to 44 days and from 296 to 28 thousand Euros, respectively. 1·2 patients had to be treated to save one hospitalization event.

**Interpretation.** Implementation of an early, home-treatment algorithm failed to accelerate recovery from major symptoms of COVID-19, but almost blunted the risk of hospitalization and related treatment costs.
RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 19, 2021, using the search terms (“2019-nCoV” or “SARS-CoV-2” or “COVID-19”) and (“early” or “outpatient” or “treatment” or “home”). Our search did not identify any randomised clinical trials or observational studies that assessed the effectiveness of treatment regimens targeting early mild symptoms of COVID-19 in the outpatient setting.

Added value of this study

In this fully academic, observational matched-cohort study, we found that early home-treatment of 90 consecutive patients with mild COVID-19 by their family physicians according to the proposed recommendation algorithm, designed on the basis of a pathophysiologic and pharmacologic rationale, significantly reduced the risk of hospitalisation compared to 90 age-, sex-, and comorbidities-matched patients who received other therapeutic regimens. Days of hospitalization and related treatment costs were reduced by more than 90%. Just 1.2 patients needed to be treated to save one hospitalization event. The ‘recommended’ schedule cohort required a few more days to achieve resolution of major symptoms, including fever, dyspnea, musculoskeletal pain, headache and cough compared to the ‘control’ cohort. Symptoms, such as anosmia and ageusia/dysgeusia, persisted less commonly and for a shorter period in the ‘recommendation’ than in the ‘control’ cohort.

Implications of the available evidence

The finding that the implementation of the proposed simple treatment algorithm during the initial, mild phase of COVID-19 has the potential to prevent disease progression, eventually limiting the need of hospital admission may have major implications for patients and health care providers. Indeed, preventing hospitalisations due to worsening of COVID-19 will not only save lives, but will...
also contribute to remarkably reduce treatment costs and to reshape health care systems that are overburdened because of the pandemic effects.
INTRODUCTION

The newly recognised disease COVID-19 is caused by the Severe-Acute-Respiratory-Syndrome Coronavirus 2 (SARS-CoV-2), which rapidly spread globally late 2019, reaching pandemic proportions. The clinical spectrum of SARS-CoV-2 infection is wide, encompassing asymptomatic infection, mild upper respiratory tract illness and mild extrapulmonary symptoms, and severe viral pneumonia with respiratory failure and even death. Given the rising global death toll associated with the pandemic, in the last year we have witnessed a race to find drug/biological treatments to save the lives of hospitalised severely ill patients, as well as to develop vaccines. To this purpose, randomised clinical trials have been performed or are underway to test experimental drug candidates, or repurposed medicines. Nonetheless, to limit the number of hospitalisation and deaths due to severe illness, thus avoiding pushing the hospitals to their limits and remarkably reducing the tremendous treatment costs for health care providers, it would be crucial to focus on primary care physicians and initial mild symptoms in COVID-19 patients at home.

As with other acute viral infections, early initiation of treatment for COVID-19 might improve clinical outcomes. For COVID-19, most primary care physicians have initially treated their patients according to their judgment with various treatment regimens they believed more appropriate founded on their know-how. We have recently published a note on how we were treating patients at home based on the pathophysiologic and the pharmacologic rationale and the available clinical evidence of efficacy in COVID-19 for each of the recommended class of drugs. This consists of anti-inflammatory agents, especially relatively selective cyclooxygenase-2 (COX-2) inhibitors, given early in the course of the disease at the very onset of symptoms, even before nasopharyngeal swab an approach that is intended to limit excessive host inflammatory responses to the viral infection. Others have debated the same issue for corticosteroids and also mentioned the risk of secondary infections and other complications.
Moreover COVID-19 patients are exposed to the risk of thromboembolic events and anticoagulant prophylaxis is recommended, unless contraindicated.\textsuperscript{13,14} However, no randomised clinical trials have been performed so far in COVID-19 patients to compare the effectiveness of different regimens targeting early symptoms at home. Comparative analysis of patient cohorts in everyday clinical practice with adjustment for possible confounding bias may offer a good alternative to randomised clinical trials to evaluate the effectiveness of novel therapies.\textsuperscript{15,16} Thus, we used this approach in a retrospective observational matched-cohort study to compare the outcomes of a cohort of COVID-19 patients treated at home by their family physicians according to a therapeutic paradigm based on the proposed recommendations \textsuperscript{10} with the outcomes of a cohort of similar patients treated with other therapeutic regimens.
PATIENTS AND METHODS

Study design and participants
In this retrospective observational study, two matched cohorts of COVID-19 patients were included. The ‘Recommended schedule’ cohort included 90 patients treated at home by their family doctors according to the published proposed recommendations from October 2020 to January 2021. It involved available family physicians of the Bergamo, Varese, Teramo provinces who had followed the proposed recommendations and expressed their interest to participate in the study with the engagement of their patients. They applied the recommended treatment algorithm (see Supplementary Methods) at the onset of, or within few days, from the beginning of symptoms. The doctors were asked to fill an online questionnaire after collection of the consent form signed by the patients. To this purpose, patients received detailed information by their physicians on the objective and design of the study. The questionnaire includes information on the outcomes of COVID-19 symptoms/illness suitable to address the primary, secondary and safety aims of the observational study. The study coordinator, the Istituto di Ricerche Farmacologiche Mario Negri IRCCS, promoted the project through online institutional media. Patients were eligible if male and female adults (≥ 18 years old), with early mild symptoms of COVID-19, who started the recommended treatment, without waiting results of a nasopharyngeal swab, if any. Subjects who required immediate hospital admission because of severe COVID-19 symptoms at onset, according to family doctor opinion, were excluded. Ninety COVID-19 patients matched by age, sex, concomitant diseases (hypertension, diabetes, cardiovascular diseases, obesity, chronic kidney disease) and symptoms at onset of illness who had been enrolled in the “Study of the Genetic Factors That Influence the Susceptibility to and Severity of COVID-19” (the ORIGIN study) and treated at home by family physicians with drug regimens not necessarily guided by those proposed in the recommendations, served as controls. Also in this cohort individuals who needed immediate hospitalization according to family physician judgment because
of severe symptoms of illness at onset, were not included. ORIGIN is a large study of the Istituto di Ricerche Farmacologiche Mario Negri IRCCS with the general aim to explore whether variations in inter-individual genetic signature in the population of COVID-19 patients living in the Bergamo province, could explain the observed different responses to SARS-CoV-2 viral infection and thus different clinical features of the disease (ClinicalTrials.gov; NCT04799834). ORIGIN collects, among others, all clinical information planned for the analysis of the ‘Recommended schedule’ cohort. Till now more than 5000 consenting subjects have joined the ORIGIN study.

The COVER study has been approved by the Centralised Ethical Committee for all COVID-19 trials in Italy based at the Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, Rome (Parere n° 263, January 31, 2021) and registered at the ClinicalTrials.gov (NCT04794998). All COVER participants provided written informed consent to enter the study.

Outcomes and definitions

The primary outcome was the time (in days) from beginning the proposed recommended treatments or other therapeutic regimens to resolution of major symptoms (time to complete remission). “Complete remission” was defined as complete recovery from major symptoms, ie no fever, dyspnea and/or SpO2 >94%, cough, rhinitis, pain (myalgia, arthralgia, chest pain, headache, sore throat), vertigo, nausea, vomiting or diarrhoea, nor sicca syndrome or red eyes.

Secondary outcomes included. 1) Days between the onset of symptoms and the start of anti-inflammatory therapy in the two treatment cohorts. 2) Compliance to the algorithm in the cohort adopting the proposed treatment recommendations, defined as adherence to recommended schedule, daily dose of drugs and duration of treatment. 3) Rate of complete remission, as defined above, in the two treatment cohorts. 4) Rate of remission with persistence of very mild symptoms in the two cohorts. This was termed “partial remission”, and defined as recovery from major COVID-19 symptoms, but persistence of symptoms such as anosmia, ageusia/dysgeusia, lack of appetite, fatigue.
In addition, time of persistence of these symptoms (<30 days, or 30 to 60, or >60 days after “complete remission”) was assessed. 5) Rate of patients worsening with severe dyspnea requiring hospitalisation in the two treatment cohorts.

We predefined potential baseline confounders, such as age, sex, and concomitant diseases that potentially enhance the risk of severe COVID-19 illness. \(^{18-20}\)

In addition, serious (SAE) and non-serious adverse events (AE) related to the administered treatments were assessed. The severity/non-severity of the observed events and their causal relationships with treatments were defined by the family doctor in charge of the patients.

**Sample size and statistical analyses**

Given the results of a recently published study \(^{21}\) and considering the characteristics of our COVID-19 patient population, we assumed that our ‘control cohort’ may have a longer time to resolution of symptoms (time to complete remission), expected to be equal to 20 days (SD: 10 days) and that in the ‘recommended schedule’ cohort it would be shortened to 15 days. With the above assumptions a sample size of 86 per group (172 total) would achieve 90% power to reject the null hypothesis of equal means when the population mean difference is \(\mu_1 - \mu_2 = 20 - 15 = 5\) days with a standard deviation for both groups of 10 days and with a significance level (alpha) of 0.05 using a two-sided two-sample equal-variance t-test. Accounting for a 20% drop-out rate, 108 per group (i.e. 216 total) needed to be included.

‘Recommended schedule’ and ‘control’ cohorts were expected to be sufficiently comparable at baseline. However, a matching was carried out between the two groups. \(^{22}\) Scores were built with a logistic regression by using the "Propensity Score" SAS procedure, which considered at least the following baseline variables: age, sex, comorbidities, and COVID-19 symptoms at onset. Continuous variables were analysed through descriptive statistics and reported as mean (SD) or median [IQR], as appropriate. Within-group changes with respect to baseline were analysed with paired t-test or
Wilcoxon signed-rank test, as appropriate. For survival data a Log-rank test was used. Statistically significant differences were assumed at 5% level of probability.

**Role of the funding source**

The study was partially supported by the generous donation of Fondazione Cav. Lav. Carlo Pesenti (Bergamo - Italy) to the Istituto di Ricerche Farmacologiche Mario Negri IRCCS. The Fondazione Cav. Lav. Carlo Pesenti had not any role in study design, in the collection, analysis and interpretation of data; in writing the report; and in the decision to submit the paper for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication.
RESULTS

From October 2020 to January 2021, seven family physicians, who expressed interest to participate in this retrospective study, reported 90 consecutive consenting participants with early symptoms of COVID-19 they treated at home according to the proposed recommendations ('recommendation' cohort). All these individuals had confirmed SARS-CoV-2 infection by positive nasopharyngeal swabs. Height-height of the 90 individuals identified from the ORIGIN dataset who had been matched for age, sex, and major concomitants diseases ('control' cohort) presented with COVID 19 from March to May 2020 and two participants on October 2020 and January 2021. All were COVID-19 cases confirmed by nasopharyngeal swab or by serology tests, and treated at home by their family doctors with regimens they believed more appropriate founded on their know-how. Both cohorts had a slight prevalence of females (56.7%) and were comparable for age range, with most individuals being 41 to 65 years old (Table 1). Similarly, distribution of concomitant diseases was well balanced in the two groups, with a few more individuals with hypertension and chronic kidney disease in the ‘recommended’ cohort than in the ‘control’ cohort. The most common symptoms at the onset of the disease were musculoskeletal pain (91.1% vs 83.3%) and fever (80.0% vs 78.9%), followed by fatigue (73.3% vs 76.7%), cough (60.0% vs 45.6%) and headache (56.7% vs 41.1%) in both cohorts (Table 1). More patients in the ‘recommended’ cohort had rhinitis at onset (26.7% vs 8.9%, p=0.003), while diarrhea (14.4% vs 30.0%, p=0.019) and dyspnea (20.0% vs 36.7%, p=0.02) were significantly more frequent in the ‘control’ cohort. On average, dyspnea occurred 4 to 5 days after the onset of symptoms in the ‘recommended’ cohort.

Primary outcome

The median time to resolution of major symptoms (complete remission) was 18 days [IQR: 14-23] in the ‘recommendation’ cohort, slightly but significantly longer (p=0.033) than in the matched
‘control’ cohort (14 days, IQR: 7-30) (Figure 1 A). Time to complete remission was comparable in the females (median [IQR], ‘recommended’ cohort: 18 days [14-23]; ‘control’ cohort: 15 days [8-30], p=0·116) and males (median [IQR], ‘recommended’ cohort: 16 days [12-23]; ‘control’ cohort: 10 days [6-30], p=0·128) of the two cohorts (Figure 1B). Similarly, there was no significant difference as for the time to complete remission between the two cohorts for less than 65 years old patients. The median time to resolution was, however, significantly longer in the ‘recommended’ than in the ‘control’ cohort for elderly individuals (> 66 years old) (Figure 1C).

**Secondary outcomes**

Two of the 90 patients (2·2%) in the ‘recommended’ cohort were hospitalised as compared to 13 of the 90 (14·4%) in the ‘control’ cohort (Figure 2A). In the ‘recommended’ cohort one of the patients was hospitalised due to interstitial pneumonia (Table 2). However, he started taking spontaneously at home paracetamol before contacting his doctor, which has to be considered a protocol violation. The other patients in this cohort was admitted to the hospital 11 days after complete remission of COVID-19 symptoms and SARS-CoV-2 negative nasopharyngeal swab, due to dyspnea developed few days after right frontal lobe trauma post syncopal episode that was related to a documented pulmonary embolism (Table 2). All patients in the ‘control’ cohort were hospitalised due to dyspnea secondary to interstitial pneumonia (Table 2). Event rate was significantly lower in the ‘recommended’ than in the ‘control’ cohort (Log-rank test, p=0·0038) (Figure 2A). The median [IQR] of days of hospitalization was numerically lower in the ‘recommended’ than in the ‘control’ cohort (22.0 days [7.0-37.0] vs 32.5 days [15-0-56.5], p=0.465) (Table 2). Cumulative number of days in ICU, in sub-intensive care units, and ordinary units were respectively 11, 1, and 32 in the ‘recommended’ cohort, and 104, 13, and 364 in the ‘control’ cohort (Figure 3A). Thus, overall, there were only 44 days of hospitalization in the “recommended” cohort as compared to 481 in controls (9.1%). Consistently, cumulative hospitalization costs were 28,335 Euros vs 296,243 Euros in controls (9.6%) (Figure 3B).
Only 1.2 [95% CI: 1.1 to 1.3] patients were needed to treat with the home-therapy algorithm to save one hospitalisation event.

In the ‘recommended’ cohort 66 out of 90 patients were given a relatively selective COX-2 inhibitor (nimesulide or celecoxib) (Table 3). Twenty patients received other NSAIDs, including aspirin (n=7). Thirteen patients were prescribed ibuprofen or indomethacin or acetaminophen (paracetamol), which made the non-adherence to the recommended anti-inflammatory regimen in 14·4% of the cohort (Table 3). On the other hand, in the ‘control’ cohort, none of the patients received relatively selective COX-2 inhibitors and only one was given aspirin (Table 3). Moreover, in this cohort most of the patients were treated with paracetamol (n=45), and the remaining with ketoprofen or ibuprofen. Thirty percent of patients in the ‘recommended’ cohort and 9·2% in the ‘control’ cohort were given corticosteroids (p=0·001) (Table 3). More patients were prescribed antibiotics (p<0·001) as well as anticoagulants (p=0·004) in the ‘recommended’ than in the ‘control’ cohort (Table 2). Regarding the antibiotic therapy, in the ‘recommended’ cohort, 49% of treated patients were given azithromycin and 15·7% amoxicillin/clavulanic acid. Seven patients in the ‘recommended’ cohort and six in the ‘control’ cohort required gently oxygen supply at home for decreasing oxygen saturation or following a first episode of dyspnea or wheezing (Table 3).

A sensitivity analysis of hospital admissions was repeated after excluding patients who spontaneously started treatment with paracetamol before contacting their family doctors in the ‘recommended’ cohort and the related matched patients in the ‘control’ cohort. Similarly to the intention-to-treat analysis, event rate was still significantly lower in the ‘recommended’ than in the ‘control’ cohort (Log-rank test, p=0·0035) (Figure 2B).

In the ‘recommended’ cohort, the anti-inflammatory treatment with NSAIDs started at home on a median of 2 days [IQR: 1-3] after the onset of COVID-19 symptoms. In both cohorts all patients achieved complete remission, defined as resolution of major symptoms (Table 4). Nonetheless, symptoms, like anosmia, ageusia/dysgeusia, lack of appetite and fatigue, persisted in a lower
percentage of patients in the ‘recommended’ than in the ‘control’ cohort (23·3% vs 73·3%, respectively, p<0·0001). In particular, this significant difference was documented in the subgroups of patients in whom these symptoms persisted less than 30 days or more than 60 days (Table 4).
**DISCUSSION**

In this fully academic observational, matched cohort study we found that early treatment of COVID-19 patients at home by their family doctors according to the proposed recommendation regimen almost completely prevented the need of hospital admission (the most clinically relevant outcome) due to progression toward a more severe illness, as compared to patients in the ‘control’ cohort who received treatments by their family physicians according to what they believe more appropriate based on their know-how. This translated into more than 90% reduction in the overall numbers of days of hospitalization and in the related treatment costs. Considering that differences in early at home treatment regimens were negligible, the cost effectiveness of the home-therapy algorithm was terrific. This was consistent with finding that only 1.2 patients were needed to treat to save one hospitalization event. The ‘recommended’ cohort required a few more days to reach resolution of major early symptoms, including fever, musculoskeletal pain, headache, and cough, than in the ‘control’ cohort. Minor symptom, such as anosmia, ageusia/dysgeusia, persisted less frequently and for a shorter period of time in the ‘recommended’ than in the ‘control’ cohort. Why treatment effect on risk of hospitalization was so different from treatment onset on disease duration is matter of speculation. One plausible explanation is that we were not testing disease-modifying treatments, but rather comparing different symptomatic regimens. In other words, the early home-therapy regimen could not appreciably affect the duration of the diseases, but could affects disease phenotype with consequent remarkably reduced need for hospitalization. The results is even more surprising considering that controls presented with symptoms during the first epidemic wave when the health care system was pushed to its limit and not all patients in need might have access to the hospital because of strong limitations of available resources. Thus, lower hospitalization rate of patients given at home-therapy according to guidelines was not an issue of reduced hospital access.
The pillars of the proposed treatment recommendation are three-fold: i) intervene at the very onset of mild/moderate symptoms at home; ii) start treatment as early as possible after the family doctor has been called by the patient without waiting the results of a nasopharyngeal swab; iii) rely on particular non-steroidal anti-inflammatory drugs, unless contraindicated. Indeed, after the initial exposure to SARS-CoV-2, patients typically develop symptoms that underline an inflammatory process within 5 to 6 days on average. Insights into the pathogenic mechanism underlying SARS-CoV-2 infection highlight the critical role of inflammatory hyper-response, characterised by tissue leucocyte infiltration, macrophage activation, widespread endothelial damage, complement–induced blood clotting and systemic microangiopathy, in disease progression. Accumulating evidence suggests that this hyper-inflammatory reaction, rather than the virus itself, underpins the progression to severe COVID-19 cases, and pro-inflammatory cytokines and macrophages seem to be integral to the initiation and propagation of this process. Therefore, the recommendation of starting treatment of early COVID-19 symptoms with NSAIDs, whose best characterised mechanisms of action is inhibition of the cyclooxygenase (COX) activity of prostaglandin H synthase 1 and 2, also referred to as COX-1 and COX-2. COX-2 has a great effect on proinflammatory cytokines and its inhibition does not blunt immune response against viral disease. The COX-2 selectivity of a particular drug is a continuous variable in relation to the relative drug concentration required to inhibit by 50% COX-1 and COX-2 enzymes in whole blood assays. Substantial overlap in COX-2 selectivity is found among some coxibs (e.g., celecoxib) and some traditional NSAIDs (e.g., nimesulide). The experimental evidence that celecoxib decreased cytokine levels (TNF-α, G-CSF and IL-6) in bronchoalveolar lavage fluid in mice with influenza A infection, and the overlap in COX-2 selectivity between this coxib and nimesulide, was the rationale to recommend these two drugs for treatment of early COVID-19 symptoms at home, if not contraindicated. Adherence to this recommendation was high (73.3%) in the study ‘recommended’ cohort. Conversely, we found that in the ‘control’ cohort none of the patients received a COX-2 inhibitor, and most of them were given...
paracetamol, a drug with very mild anti-inflammatory activity. Paracetamol is suggested as a safe and recommendable alternative for the early management of pain and fever in COVID-19 patients. However, it should be taken into account that besides being a negligible anti-inflammatory drug, paracetamol reduces plasma and tissue glutathione levels when given at relatively low doses, which might exacerbate COVID-19 illness, as recently hypothesised. Although more selective inhibition of COX-2 is desirable to limit the gastrointestinal toxicity seen with less selective COX-2 inhibitors, physicians may be aware of the finding that the use of NSAIDs has been associated with higher rates of cardiovascular events. Moreover, nimesulide can associate with a risk of hepatotoxicity, very low when the drug is administered at recommended time of exposure and daily dosage. Nonetheless, in the ‘recommended’ cohort, treatment with nimesulide or celecoxib was safe and well tolerated, with only one patient reporting epigastric pain. This may explain the low rate of the use of aspirin in this cohort, which according to the proposed recommendations should be given as an alternative treatment to nimesulide and celecoxib when signs of toxicity or contraindications to these drugs are brought to the attention of the family physician. Nonetheless, aspirin could be a potentially alternative treatment for COVID-19 at home, since it has been previously shown to reduce plasma levels of inflammatory cytokines in patients with chronic stable angina, and even to have antiviral activity against RNA viruses of the respiratory tract. The treatment effect of this drug is supported by the findings of a retrospective cohort study on 412 adult patients hospitalised with COVID-19 showing that aspirin administration was independently associated with reduced risk of mechanical ventilation, intensive care unit admission, and in-hospital mortality. According to the recommendation algorithm, corticosteroids were not used at the onset of symptoms but only after a mean of 8 days in the 30% of patients in the ‘recommended’ cohort in whom fever, myalgia/arthralgia or cough persisted. A patient in this cohort was already receiving corticosteroids chronically due to connectivitis disease. Indeed, corticosteroids exert their anti-inflammatory effects mainly by inhibiting pro-inflammatory genes that encode for cytokines, chemokines, inflammatory...
enzymes to control the inflammatory process and restore homeostasis.\textsuperscript{34} However, the use of corticosteroids in COVID-19 patients has been controversial, due to the risk of prolonging the presence of the virus in the respiratory tract and blood, and the incidence of complications, as shown in previous observational studies in patients with coronavirus pneumonia induced by SARS and MERS.\textsuperscript{35,36} Nevertheless, none of the patients in the ‘recommended’ cohort given corticosteroids showed particular side effects related to the used of these medicines. Based mainly on the positive findings of reduced mortality in hospitalised patients of the large RECOVERY trial, a WHO guidance strongly recommended for systemic corticosteroids in patients with severe COVID-19, except in those not receiving respiratory support, who did not benefit from the treatment.\textsuperscript{37} In the early phase of COVID-19, when patients are not hospitalised, available data are scanty, but some evidence indicates that prompt intervention with corticosteroids can reverse or at least attenuate the initial lesions in the lungs.\textsuperscript{12,38}

Apart from causing patients to be bedridden even with mild symptoms, there is evidence that in SARS-CoV-2 infection dysregulation of coagulation cascade and fibrinolytic systems occur, creating a high risk of thromboembolic events and death for patients.\textsuperscript{39} Thus, the use of low-molecular weight (LMW) heparin at the prophylactic dose has been recommended for the management of COVID-19 patients. However, only 16\% of patients in the ‘recommended’ cohort were actually treated prophylactically with LMW heparin because bedridden, without side effects. This suggests the need of further educational programs for family physicians on this topic.

The use of antibiotics in non-hospitalized COVID-19 patients is not mandatory, but sometimes necessary, since there is evidence that patients may die of secondary bacterial infections rather than of viral infection. Thus, as indicated in the proposed recommendations, antibiotics were prescribed to patients in both cohorts only when needed, not on the routine basis. This is in line with the very recent findings of the PRINCIPLE trial that do not justify the routine use of azithromycin for shortening time to recovery or reducing risk of hospitalisation in individuals with suspected COVID-
19 illness in the community.\textsuperscript{40} This has important implications, since indiscriminate use of antibiotics could favor the development of antimicrobial resistance.

\textit{Limitations and strengths}

The relative small sample size and the non-randomised design were major limitations, although time to resolution of major COVID-19 symptoms were consistent with the power calculation. Analyses were retrospective, but they were performed according to the pre-defined study protocol and statistical plans. At variance with data in the ‘recommended’ cohort collected by family physicians, outcome data of the ‘control’ cohort were obtained from patients questionnaire and interview referring to events occurring many months before the survey, which may have resulted in underestimation of time to resolution of COVID-19 symptoms and of adverse event rates, but not on hospitalization rate. Indeed the date of hospital admission was well documented by the hospital discharge letter.

Moreover, data from the ‘control’ cohort were obtained when hospital structures were under huge pressure because of the first ‘wave’ of the COVID-19 pandemic, which may have resulted in postponed or avoided hospitalization of patients in need. Findings of remarkably higher hospitalization in the ‘control’ cohort patients despite this potential bias, provided additional, indirect evidence, of the protective effect of the proposed recommended treatment protocol against hospitalization because of worsening of COVID-19 symptoms.

Furthermore, the time to complete remission of symptoms in the two cohorts was quite similar. This could be reasonable, considering that the adopted treatments were targeting symptoms and were not specific against the virus. Therefore, it is expected that the time of viral clearance would be comparable in the two cohorts independently of the symptomatic therapy used, but symptoms will be attenuated to the extent of not requiring hospital admission.
The proposed recommendation algorithm suggests to upgrade the treatment toward the use of corticosteroids or to start anticoagulant prophylaxis also based on hematochemical tests that document increase of inflammatory indexes (CRP, neutrophil count) and/or D-dimer, respectively, in addition to clinical judgment. However, fulfilling this lab test requirement in the early phase of the illness did result unfeasible, since all patients had confirmation of SARS-CoV-2 infection and thus they were quarantined at home, making it impossible for them to reach the laboratory center.

Strength of the COVER study includes the formal evaluation of a treatment recommendation algorithm for family doctors targeting early symptoms in the community designed according to a pathophysiologic and pharmacologic rationale. Several recommendations on how to treat COVID-19 patients at home have been recently proposed, including those of the Italian Ministry of Health, but none of them has been formally tested for their ability to prevent or limit the progression of early phase of the illness to the need of hospitalisation. Albeit in a retrospective observational design, the COVER study documents the ability of the proposed recommendation algorithm to almost completely prevent hospital admission of COVID-19 patients with early symptoms managed at home. This provides the background and a hypothesis generating finding to design future prospective trials.

In conclusion, we found that few simple treatments, as reported in the proposed recommendation algorithm, show benefit among outpatients in the early phase of COVID-19. This reasoned approach may have the potential to avert clinical deterioration of the illness limiting the need of hospitalization, in addition to shorten the duration of minor symptoms, such as anosmia, dysgeusia and fatigue that affect patient’s quality of life, with substantial public health and societal implications and effects.
REFERENCES

1. Johns Hopkins CSSE. COVID-19 Map - Johns Hopkins Coronavirus Resource Center. Accessed March 19, 2021. Available at: https://www.coronavirus.jhu.edu.

2. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26: 1017–32.

3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.

4. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020; 323: 1824–36.

5. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. Science 2020; 367: 1412–3.

6. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021; 384: 693–704.

7. World Health Organization. “Solidarity” clinical trial for COVID-19 treatments. Updated 15 October 2020. Accessed 17 March 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.

8. Perico N, Fagiuoli S, Di Marco F, et al. Bergamo and Covid-19: How the Dark Can Turn to Light. Front Med (Lausanne) 2021; 8: 609440.

9. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. J Antimicrob Chemother 2003; 51: 123–9.

10. Suter F, Perico N, Cortinovis M, Remuzzi G. A recurrent question from a primary care physician: How should I treat my COVID-19 patients at home? An update Clin Med Invest 2020; 5: 1-9. doi: 10.15761/CMI.1000218.

11. Baghaki S, Yalcin CE, Baghaki HS, Aydin SY, Daghan B, Yavuz E. COX2 inhibition in the treatment of COVID-19: Review of literature to propose repositioning of celecoxib for randomized controlled studies. Int J Infect Dis 2020; 101: 29–32.

12. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience 2020; 14: 1023.

13. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 18: 1023–6.

14. Eparine a basso peso molecolare nella terapia dei pazienti adulti con COVID-19 (aggiornamento al 26/11/2020). Disponibile in: https://www.aifa.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della-malattia-covid19.
15 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003; **158**: 915–20.

16 Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med* 2008; **5**: e67.

17 Perico N, Suter F, Remuzzi G. A recurrent question from a primary care physician: How should I treat my COVID-19 patients at home? *Clin Med Invest* 2020;5:1-8. Published: May 25, 2020. doi: 10.15761/CMI.1000207.

18 ERA-EDTA Council, ERACODA Working Group. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant* 2021; **36**: 87–94.

19 Grasselli G, Greco M, Zanella A, *et al*. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med* 2020; **180**: 1345–55.

20 Gansevoort RT, Hilbrands LB. CKD is a key risk factor for COVID-19 mortality. *Nat Rev Nephrol* 2020; **16**: 705–6.

21 Ganz-Lord FA, Segal KR, Rinke ML. COVID-19 symptoms, duration, and prevalence among healthcare workers in the New York metropolitan area. *Infect Control Hosp Epidemiol* 2020; : 1–7.

22 Cummings P, McKnight B. Analysis of Matched Cohort Data. The Stata Journal 2004; **4**: 274–281.

23 Li Q, Guan X, Wu P, *et al*. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; **382**: 1199–207.

24 Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021; **17**: 46–64.

25 FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345**: 433–42.

26 Carey MA, Bradbury JA, Rebollos YD, Graves JP, Zeldin DC, Germolec DR. Pharmacologic inhibition of COX-1 and COX-2 in influenza A viral infection in mice. *PLoS One* 2010; **5**: e11610.

27 Ghanem CI, Pérez MJ, Manautou JE, Mottino AD. Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacol Res* 2016; **109**: 119–31.

28 Sestili P, Fimognari C. Paracetamol-Induced Glutathione Consumption: Is There a Link With Severe COVID-19 Illness? *Front Pharmacol* 2020; **11**: 579944.

29 Coxib and traditional NSAID Trialists’ (CNT) Collaboration, Bhala N, Emberson J, *et al*. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; **382**: 769–79.

30 Donati M, Conforti A, Lenti MC, *et al*. Risk of acute and serious liver injury associated to nimesulide and other NSAIDs: data from drug-induced liver injury case-control study in Italy. *Br J Clin Pharmacol* 2016; **82**: 238–48.
31 Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999; **100**: 793–8.

32 Glatthaar-Saalmüller B, Mair KH, Saalmüller A. Antiviral activity of aspirin against RNA viruses of the respiratory tract—an in vitro study. *Influenza Other Respir Viruses* 2017; **11**: 85–92.

33 Chow JH, Khanna AK, Kethireddy S, *et al.* Aspirin Use Is Associated With Decreased Mechanical Ventilation, Intensive Care Unit Admission, and In-Hospital Mortality in Hospitalized Patients With Coronavirus Disease 2019. *Anesth Analg* 2021; **132**: 930–41.

34 Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. *Neuroimmunomodulation* 2015; **22**: 20–32.

35 Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006; **3**: e343.

36 Arabi YM, Mandourah Y, Al-Hameed F, *et al.* Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med* 2018; **197**: 757–67.

37 Lamontagne F, Agoritsas T, Siemieniuk R, *et al.* A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021; **372**: n526.

38 Lee K-Y. Pneumonia, Acute Respiratory Distress Syndrome, and Early Immune-Modulator Therapy. *Int J Mol Sci* 2017; **18**. DOI:10.3390/ijms18020388.

39 Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020; **127**: 104362.

40 PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021; published online March 4. DOI:10.1016/S0140-6736(21)00461-X.

41 Ministero della Salute. Gestione domiciliare dei pazienti con infezione da SARS-CoV-2. 30 November 2020. Available at: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=5201. Accessed on 19 March 2021.
LEGENDS TO THE FIGURES

Figure 1. Time to complete remission.
Time to complete remission in the two treatment cohorts (primary outcome, Panel A), in the two treatment cohorts according to sex (Panel B), and in the two treatment cohorts according to age range (Panel C). Data are median and interquartile range. Grey histograms, recommended treatment cohort; white histograms, control cohort. Between-group differences were assessed by Mann-Whitney test.

Figure 2. Kaplan-Meier curves for hospital admission.
Kaplan-Meier curves show the proportion of patients who required hospitalisation in the two treatment cohorts (Panel A), and after excluding patients who spontaneously started treatment with paracetamol before contacting their family doctors in the “recommended” cohort and the related matched patients in the “control” cohort (Panel B). Grey line, recommended treatment cohort; black line, control cohort. Between-group differences were assessed by Log-rank test.

Figure 3. Cumulative days of hospitalisation and related costs in the two study cohorts.
Cumulative days of hospitalisation in the ‘recommended’ treatment cohort and in the ‘control’ cohort, according to stay in ordinary ward (white), subintensive care unit (black) and intensive care unit (grey) (Panel A). Cumulative costs for hospitalisation in the ‘recommended’ treatment cohort and in the ‘control’ cohort, according to stay in ordinary ward (white), subintensive care unit (black) and intensive care unit (grey) (Panel B).
SUPPLEMENTARY METHODS

Summary of proposed recommendations

Recommended treatments should start immediately when COVID-19 early symptoms appear without waiting results of a nasopharyngeal swab, if any. The recommended drugs can be used unless contraindicated according to the summary of product characteristics.

I. Non-steroidal anti-inflammatory drugs (NSAIDs)

Relatively selective COX-2 inhibitors §‡ (for myalgias and/or arthralgias or other painful symptoms)

‡ based on the ratio of concentrations of the various NSAIDs required to inhibit the activity of COX-1 and COX-2 by 50 percent (IC50) in assays of whole blood

#unless contraindicated

Nimesulide *

100 mg b.i.d p.o, after a meal, for a maximum of 12 days.

Or

Celecoxib *

Initial oral dose of 400 mg, followed by a second dose of 200 mg on the first day of therapy. In the following days, up to a maximum of 400 mg (200 mg twice a day) should be given as needed for a maximum of 12 days

* Should the patient have fever (≥ 37.3 °C) or develop laboratory signs of hepatotoxicity associated with nimesulide or there are contraindications to celecoxib, these drugs should be substituted with aspirin (a COX-1 and COX-2 inhibitor) (500 mg twice a day p.o. - after a meal). These treatments should be associated with a proton pump inhibitor (e.g. lansoprazole - 30 mg/day; or omeprazole - 20 mg/day; or pantoprazole - 20 mg/day).

After approximately 3 days from the onset of symptoms (or more days are elapsed and the physician sees the patient for the first time), a series of hematochemical tests should be performed (blood cell count, D-dimer, CRP, creatinine, fasting blood glucose, ALT). Should inflammatory indexes (CRP, neutrophil count), ALT, and D-dimer be in the normal range, nimesulide/celecoxib (or aspirin) treatment will continue.
II. Corticosteroids*

Dexamethasone *(for persistent fever or musculoskeletal pain or when few days later hematochemical tests were repeated and even mild increase of inflammatory indexes - CRP, neutrophil count - are documented, or cough and oxygen saturation (SpO2) <94-92% occur)*

8 mg p.o for 3 days, then tapered to 4 mg for a further 3 days, and then to 2 mg for 3 days. That makes 42 mg dexamethasone total over 9 days.

*Duration of corticosteroid treatment also depends on the clinical evolution of the disease*

III. Anticoagulants

*Low-molecular weight (LMW) heparin* *(when the hematochemical tests show even a mild increase of D-dimer or for thromboembolism prophylaxis for bedridden patients)*

Enoxaparin, at the prophylactic daily dose of 4000 U.I subcutaneously - i.e. 40 mg enoxaparin. Treatment recommended for at least 7-14 days, independently of the patient recovering mobility.

*unless contraindicated (e.g., ongoing bleeding or platelet count <25 x 10⁹/L)*

IV. Oxygen therapy

Gentle oxygen supply in the early phase of the disease, possibly before pulmonary symptoms manifest, in the presence of progressively decreasing oxygen saturation – as indicated by oximeter – or following a first episode of dyspnoea or wheezing.

Conventional oxygen therapy is suggested when the respiratory rate is >14/min and oxygen saturation (SpO₂) <94-92%, but is required with SpO₂ <90% at room air. With liquid oxygen, start with 8-10 litre/min and monitor SpO₂ every 3-4 hours. Titrate oxygen flow rate to reach target SpO₂ >94%. Then the rate of oxygen administration can be reduced to 4-5 litre/min (but continue SpO₂ monitoring every 3-4 hours). With gaseous O₂, start with 2.5-3.0 litre/min, but monitor SpO₂ more frequently than with liquid oxygen, and titrate flow rates to reach target SpO₂ >94%. Should patients be poorly responsive to high O₂ administration, consider hospitalisation, if feasible.

V. Antibiotics

*Azithromycin* *(with bacterial pneumonia or suspected secondary bacterial upper respiratory tract infections, or in particularly fragile patients, or when hematochemical inflammatory indexes (CRP, neutrophil count) are markedly altered)*

500 mg/day p.o for 6-10 days depending on the clinical judgement

* Should the patient be at risk of or with a history of cardiac arrhythmia or present other contraindications, cefixime (400 mg/day p.o for 6-10 days) or amoxicillin/clavulanic acid (1gr three times a day for 6-10 days) can be considered as alternative to azithromycin.
Table 1. Demographic and early symptoms associated with COVID-19 illness in the two treatment cohorts.

| Demographic characteristics | Overall (n=180) | Recommended treatment cohort (n=90) | Control cohort (n=90) | P value |
|-----------------------------|----------------|-----------------------------------|----------------------|---------|
| **Demographic characteristics** |                |                                   |                      |         |
| Age, years                  |                |                                   |                      |         |
| 18-40                       | 34 (18.89)     | 17 (18.89)                        | 17 (18.89)           | 1.000   |
| 41-65                       | 90 (50.00)     | 45 (50.00)                        | 45 (50.00)           | 1.000   |
| 66-75                       | 26 (14.44)     | 13 (14.44)                        | 13 (14.44)           | 1.000   |
| >75                         | 30 (16.67)     | 15 (16.67)                        | 15 (16.67)           | 1.000   |
| Males, n (%)                | 78 (43.33)     | 39 (43.33)                        | 39 (43.33)           | 1.000   |
| **Comorbidities, n (%)**    |                |                                   |                      |         |
| Cardiovascular disease      | 32 (17.78)     | 16 (17.78)                        | 16 (17.78)           | 1.000   |
| Hypertension                | 57 (31.67)     | 31 (34.44)                        | 26 (28.89)           | 0.522   |
| Diabetes mellitus           | 16 (8.89)      | 8 (8.89)                          | 8 (8.89)             | 1.000   |
| Overweight/Obesity          | 31 (17.22)     | 16 (17.78)                        | 15 (16.67)           | 1.000   |
| Chronic kidney disease      | 2 (1.11)       | 2 (2.22)                          | 0 (0)                | 0.497   |
| **Early symptoms, n (%)**   |                |                                   |                      |         |
| Fever                       | 143 (79.44)    | 72 (80.00)                        | 71 (78.89)           | 1.000   |
| Myalgia                     | 100 (55.56)    | 50 (55.56)                        | 50 (55.56)           | 1.000   |
| Arthralgia                  | 57 (31.67)     | 32 (35.6)                         | 25 (27.78)           | 0.336   |
| Tiredness/exhaustion        | 135 (75.00)    | 66 (73.3)                         | 69 (76.7)            | 0.731   |
| Dyspnea                     | 51 (28.33)     | 18 (20.00)                        | 33 (36.7)            | 0.020   |
| Chest pain                  | 23 (12.78)     | 10 (11.1)                         | 13 (14.4)            | 0.656   |
| Headache                    | 88 (48.89)     | 51 (56.7)                         | 37 (41.1)            | 0.052   |
| Lack of appetite            | 68 (37.7)      | 28 (31)                           | 40 (44.4)            | 0.090   |
| Cough                       | 95 (52.7)      | 54 (60.0)                         | 41 (45.6)            | 0.073   |
| Sore throat                 | 37 (20.56)     | 22 (24.4)                         | 15 (16.7)            | 0.268   |
| Rhinitis                    | 32 (17.78)     | 24 (26.7)                         | 8 (8.9)              | 0.003   |
| Vomiting/nausea             | 34 (18.89)     | 13 (14.4)                         | 21 (23.3)            | 0.182   |
| Diarrhoea                   | 40 (22.2)      | 13 (14.4)                         | 27 (30.0)            | 0.019   |
| Red eyes                    | 20 (11.1)      | 7 (7.8)                           | 13 (14.4)            | 0.235   |
| Vertigo                     | 5 (2.7)        | 3 (3.3)                           | 2 (2.2)              | 1.000   |
| Sicca syndrome              | 3 (1.6)        | 0 (0)                             | 3 (3.3)              | 0.246   |
| Anosmia                     | 100 (55.56)    | 46 (51.1)                         | 54 (60.0)            | 0.294   |
| Ageusia                     | 102 (56.7)     | 45 (50.0)                         | 57 (63.3)            | 0.098   |

Data are numbers (percentages). Between-group differences were assessed by Fisher’s exact test.
| Cohort | Reason for hospital admission                      | Hospitalisation (days) | Oxygen therapy* (yes/no) | CPAP (yes/no) | CPAP (days) | Mechanical ventilation (yes/no) | Mechanical ventilation (days) | ICU admission (yes/no) | ICU admission (days) | Sequelae at discharge (yes/no) |
|--------|----------------------------------------------------|------------------------|--------------------------|---------------|-------------|--------------------------------|-------------------------------|----------------------|----------------------|-------------------------------|
| Control| Dyspnea (interstitial pneumonia)                   | 60                     | Yes                      | Yes           | 3           | Yes                            | 17                           | Yes                  | 17                   | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 8                      | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 5                      | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 68                     | Yes                      | Yes           | 3           | Yes                            | 14                           | Yes                  | 14                   | Yes, persistence of decreased muscle tone |
| Control| Dyspnea (interstitial pneumonia)                   | 10                     | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 41                     | Yes                      | No            | -           | Yes                            | 25                           | Yes                  | 25                   | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 35                     | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 23                     | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 50                     | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control| Dyspnea (interstitial pneumonia)                   | 20                     | Yes                      | No            | -           | No                             | -                            | No                   | -                    | No                             |
| Control | Dyspnea (interstitial pneumonia, small pulmonary embolism in stila bronches of the right lung) | 128 | Yes | Yes | 7 | Yes | 48 | Yes | 48 |
|---------|---------------------------------------------------------------------------------------------|-----|-----|-----|---|-----|----|-----|----|
| Control | Dyspnea (interstitial pneumonia)                                                            | 30  | Yes | No  | - | No  | -  | No  | -  |
| Control*| Dyspnea (interstitial pneumonia)                                                            | Yes | No  | -   | No | -   | No | -   |   |
| 'Recommended' | Dyspnea (massive bilateral pulmonary embolism and left iliac-femoral deep vein thrombosis, after right frontal lobe trauma post-syncopeal episode) | 7   | Yes | No  | - | No  | -  | No  | -  |
| 'Recommended' | Dyspnea (interstitial pneumonia)                                                            | 37  | Yes | Yes | 1 | Yes | 11 | Yes | 11 |

*Conventional oxygen therapy (oxygen delivered by nasal tube, nasal cannula or face mask). ° This patients did not provide the hospital discharge letter. CPAP, continuous positive airway pressure; ICU, intensive care unit.
Table 3. Treatment at home in the two study cohorts.

| Recommended treatment cohort (n=90) | Control cohort (n=90) | P value |
|-------------------------------------|----------------------|---------|
| **Relatively selective COX-2 inhibitors** | | |
| Nimesulide                          | 31/66 (46·97)        | 0/76 (0) | P<0·001 |
| Celecoxib                           | 33/66 (50·00)        |         |         |
| Etoricoxib                          | 2/66 (3·03)          |         |         |
| **Other NSAIDs**                    | 20/86 (23·26)        | 53/77 (68·83) | P<0·001 |
| Aspirin                             | 7/86 (8·14)          | 1/77 (1·30) |         |
| Ketoprofen                          | 0/86 (0)             | 2/77 (2·60) |         |
| Ibuprofen                           | 5/86 (5·81)          | 4/77 (5·19) |         |
| Indomethacin                        | 2/86 (2·33)          | 0/77 (0)  |         |
| Paracetamol                         | 6/86 (6·98)          | 45/77 (58·44) |         |
| Unknown                             | 0/86 (0)             | 1/77 (1·30) |         |
| **Corticosteroids**                | 27/90 (30·00)°       | 7/76 (9·21) | P=0·001 |
| **Anticoagulants**                 | 15/90 (16·67)        | 2/76 (2·63) | P=0·004 |
| **Antibiotics**                     | 51/90 (56·67)        | 23/77 (29·87) | P<0·001 |
| **Azithromycin**                   | 25/51 (49·02)        | -        |         |
| **Amoxicillin and clavulanic acid** | 8/51 (15·69)        | -        |         |
| **Need of oxygen**                  | 7/90 (7·78)          | 6/77 (7·79) | P=1·000 |

Data are n/N (percentages). COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs. * Need for oxygen therapy at home. Between-group differences were assessed by Fisher’s exact test. ° A patient was on chronic corticosteroid therapy due to connectivitis.
### Table 4. Secondary outcomes.

|                                      | Recommended treatment cohort (n=90) | Control cohort (n=90) | P value |
|--------------------------------------|-------------------------------------|-----------------------|---------|
| Time from symptoms onset and start of anti-inflammatory therapy (days) | 2 [1-3]                            | -                     | -       |
| Rate of complete remission*          | 90/90 (100)                         | 90/90 (100)           | P=1·000 |
| Rate of partial remission°           | 21/90 (23·3)                        | 66/90 (73·3)          | P<0·0001|
| Persistence of minor symptoms (days) |                                     |                       |         |
| < 30                                 | 11/21 (52·4)                        | 13/65 (20·0)          | P=0·0107|
| 30-60                                | 5/21 (23·8)                         | 16/65 (24·6)          |         |
| > 60                                 | 5/21 (23·8)                         | 36/65 (55·4)          |         |
| Rate of hospitalisation              | 2/90 (2·2)                          | 13/90 (14·4)          | P=0·0053|
| Rate of hospitalisation§             | 1/84 (1·2)                          | 11/84 (13·1)          | P=0·007 |

Data are n/N (percentages) or median [interquartile range], as appropriate. * defined as complete recovery from major symptoms, ie no fever, SpO₂ >94% and/or no dyspnea, no cough, no rhinitis, no pain (myalgia, arthralgia, chest pain, headache, sore throat), no vertigo, no nausea, vomiting or diarrhoea, no sicca syndrome or red eyes; ° defined as recovery from major COVID-19 symptoms, but persistence of symptoms such as anosmia, ageusia/dysgeusia, lack of appetite, fatigue. § Sensitivity analysis performed excluding patients who spontaneously started treatment with paracetamol before contacting their family doctors in the “recommended” cohort and the related matched patients in the “control” cohort.
Figure 1
Figure 2

(A) Proportion of patients who required hospitalisation over 90 days.

| Patients at risk | 'Recommended' | 'Control' |
|------------------|---------------|-----------|
| 90               | 29            | 56        |
|                  | 14            | 42        |
|                  | 4             | 11        |

P = 0.0038

(B) Proportion of patients who required hospitalisation over 90 days.

| Patients at risk | 'Recommended' | 'Control' |
|------------------|---------------|-----------|
| 84               | 25            | 53        |
|                  | 11            | 40        |
|                  | 4             | 10        |

P = 0.0035
Figure 3

A

Cumulative days of hospitalisation

'Recommended' cohort

'Control' cohort

B

Cumulative costs of hospitalisation (Euro)

'Recommended' cohort

'Control' cohort

28,335

296,243

Figure 3