Aging Clinical and Experimental Research (2022) 34:2585–2590
https://doi.org/10.1007/s40520-022-02181-1

SHORT COMMUNICATION

Potential of outpatient steroid therapy in elderly patients with early COVID-19

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Received: 13 May 2022 / Accepted: 10 June 2022 / Published online: 4 July 2022

Abstract

Corticosteroids lower mortality in hospitalized patients with COVID-19 pneumonia requiring oxygen support. In this observational retrospective study (September 2020–June 2021), we explored the association between receiving home corticosteroids without oxygen supply and 30-day mortality in hospitalized patients with COVID-19 pneumonia. Among a total of 794 COVID-19 pneumonia patients, 763 were included into the study (males 68%; mean age 65 ± 12 years), of whom 197 (26%) received home corticosteroids (mean daily prednisone equivalent-dose 40 mg ± 12 mg; range 10–50 mg; median 50 mg; IQR 25–50 mg; for 4 days). The overall 30-day mortality of the study population was 12%. The risk of death—adjusted for age, comorbidities, administration of remdesivir and respiratory failure severity—was lower (HR 0.405; $p = 0.024$) in patients receiving home corticosteroids. After stratifying the study population by age categories, home corticosteroids were associated with an adjusted decrease in mortality risk in patients > 77 years (HR 0.346; $p = 0.040$). Home corticosteroids may lower the 30-day mortality in elderly COVID-19 patients.

Keywords COVID-19 · Corticosteroids · Outpatient · Pneumonia · Elderly · All-cause mortality

Introduction

The therapeutic management of outpatients with mild COVID-19 not requiring oxygen supply consists of symptomatic treatment using antipyretics, analgesics and antitussives [1]. More recently, several therapeutic options are available for the treatment of non-hospitalized patients at high risk of disease progression. In fact, antispike neutralizing antibodies (e.g. sotrovimab) and novel antivirals (remdesivir, molnupiravir and ritonavir/nirmatrelvir) have demonstrated to reduce medically attended visit or hospitalization in high-risk outpatients. However, the effect of these therapies in reducing mortality is low [2–5]. The Recovery trial demonstrated dexamethasone to lower 28-day mortality among hospitalized patients with COVID-19 pneumonia requiring either invasive mechanical ventilation (IMV) or oxygen alone but not in those with no oxygen need [6]. WHO recommends against the use of dexamethasone or other systemic glucocorticoids to treat patients with mild to moderate COVID-19 who do not require hospitalization and supplemental oxygen [7]. Early corticosteroid therapy is a double-edge sword that can mitigate inflammation and delay viral clearance at a time when control of viral replication is crucial, as previously observed in patients with SARS-Cov-1 in 2003 [8]. On the other hand, late use and high or medium doses rather than early use and low dose of glucocorticoids were significantly associated with a high risk of viral clearance delay in a recent review and meta-analysis on the effect of steroid use on the viral shedding in COVID-19 [9].

Corticosteroids are often prescribed in real-life even in outpatients without oxygen support by general practitioners. However, data evaluating the possible benefits of corticosteroids in the very early phase of COVID-19 are lacking. We aimed to explore the association between home

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administration of corticosteroids compared to usual care and 30-day all-cause mortality in hospitalized patients with COVID-19 pneumonia.

Patients and methods

We performed an observational retrospective study analyzing data on adults hospitalized with COVID-19 pneumonia. All patients had PCR-confirmed SARS-Cov-2 infection and were consecutively admitted from September 2020 to June 2021 to the Infectious Diseases Unit, University Hospital, Trieste, Italy. Demographics (age and gender) and clinical characteristics including obesity, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and immune deficit were collected at hospital admission. Data on corticosteroid therapy before hospital admission were collected including time from onset of symptoms to corticosteroid therapy, overall corticosteroid (prednisone equivalent) dose [10], and treatment duration. Because of inter-patient variability of corticosteroid drug and dosage, home steroid therapy was managed as a dichotomic variable (yes or no). The highest respiratory support received during hospitalization (oxygen via masks or high-flow nasal cannula, non-invasive or invasive mechanical ventilation) was considered as a marker of respiratory failure severity. Other relevant care administered during hospitalization, including remdesivir, heparin/oral anticoagulants, and corticosteroids, were collected as well. Patients not undergoing corticosteroids during their hospital stay were excluded. All-cause 30-day mortality was considered as primary outcome.

Continuous variables were presented as means ± standard deviations (SD). The between-group comparisons were analyzed via Student's *t* test for independent samples after determining whether or not equal variance could be attributed to the subgroups as per Levene's test. Nominal variables were shown as a number and percentage and the respective contingency tables were analyzed using χ test or Fisher's exact test, as appropriate. The different time of death according to having received or not steroids before hospital admission was explored. Observations were right-censored until 30-days from hospitalization. Both unadjusted and adjusted survival analyses were carried out. To assess a possible hierarchy between mortality predictors, an exploratory analysis was conducted through recursive regression trees, showing three statistically significant different ($p < 0.001$) age strata: < 68, 68–77, and > 77 years. Multivariable Cox proportional-hazards models with forward stepwise selection were adjusted for confounders significantly related to the occurrence of 30-day death in bivariate analyses. The results were presented as an adjusted proportional-hazard ratio (HR) and 95% confidence intervals (CI).

Since multivariable analysis showed patient's age as a strong independent risk factor of death, separate Cox regressions for patients belonging to the previously identified age strata were computed for sensitivity analysis. *P* value < 0.05 was set for statistical significance.

Results

A total of 794 COVID-19 pneumonia patients (534 males, 67.2%; mean age 65.3±13.6 years) with COVID-19 pneumonia were admitted to the study ward. After excluding subjects not undergoing corticosteroids therapy during their hospital stay ($n = 31$; 3.9%), 763 patients were included into the study; 197 (26%) of them received home corticosteroids and none oxygen supply before hospital admission. The main characteristics of the study population are reported in Table 1.

The mean time from COVID-19 onset and the start of home steroids was 5.8 ± 3.2 days. The mean duration of steroid therapy was 3.7 ± 1.9 days. The overall dose of prednisone dose-equivalent steroid per patient was 147.4 ± 85.6 mg, corresponding approximately to a mean of prednisone 40 ± 12 mg daily (range 10–50 mg; median 50 mg; IQR 25–50 mg) for 4 days. Compared to untreated ones, corticosteroid home treated subjects were younger and had a lower prevalence of pre-existing hypertension, COPD and immunodeficiency conditions, and received less frequently antivirals in hospital, while no further between-group difference was found (Table 1). No between-group difference was found in home-administered steroid dose according to the considered age-strata (< 68 years: 40.6 ± 13.0 mg; 68–77 years: 43.9 ± 11.6 mg; > 77 years: 38.5 ± 13.5 mg; $p = 0.286$). Patients were admitted to the hospital after a mean of 9.4 ± 3.1 days from COVID-19 onset. All patients but one received either heparin or anticoagulants during hospitalization, so that this variable was not further considered in data analyses. Patients belonging to 68–77 age group underwent NIV or IMV in a higher percentage as compared to the other age-strata (< 68: $n = 188$, 44.2%; 68–77: $n = 86$, 51.5%; > 77: $n = 62$, 36.8%; $p = 0.025$).

The overall 30-day mortality was 12.2%. In patients who received home corticosteroids the crude mortality was significantly lower compared to patients who did not (no home steroids: $n = 86/566$, 15.2%; home steroids: $n = 7/197$, 3.6%; $p < 0.001$). Mortality was also significantly associated with older age, hypertension, COPD and immunodeficiency, as well as with a higher respiratory support; conversely, mortality was lower for patients treated with remdesivir (Table 2).

Figure 1 shows the results of survival analyses. Patients undergoing home corticosteroids showed a lower crude mortality risk ($p < 0.001$) compared to untreated patients. This finding was confirmed by multivariable Cox regression analysis adjusted for comorbidities (hypertension, COPD and immunodeficiency), in-hospital administration of remdesivir

Table 1 Main baseline social-demographic and clinical characteristics of the full study population and of subgroups undergoing or not steroid therapy before hospital admission

Variable	All patients ($n=763$)	No home steroids ($n=566$)	Home steroids ($n=197$)	p value
Sex (male)	520 (68.2%)	385 (68.0%)	135 (68.5%)	0.895
Age (years)	65.2 ± 13.6	66.6 ± 14.0	61.4 ± 11.7	< 0.001
Age categories				
< 68 years	425 (55.7%)	284 (66.8%)	141 (33.2%)	–
68–77 years	167 (21.9%)	134 (80.2%)	33 (19.8%)	< 0.001
> 77 years	171 (22.4%)	147 (86.0%)	24 (14.0%)	–
BMI (kg/m^2)	27.4 ± 4.9	27.5 ± 5.1	27.3 ± 4.5	0.644
BMI ≥ 30 kg/m^2	202 (26.6%)	154 (27.4%)	48 (24.5%)	0.435
Hypertension	382 (50.1%)	304 (53.7%)	78 (39.6%)	0.001
Diabetes	146 (19.1%)	114 (20.1%)	32 (16.2%)	0.231
COPD	51 (6.7%)	48 (8.5%)	3 (1.5%)	< 0.001
Immunodeficency	45 (5.9%)	41 (7.2%)	4 (2.0%)	0.007
Hospital heparin	732 (95.9%)	542 (95.8%)	190 (96.4%)	0.674
Hospital remdesivir	115 (15.1%)	94 (16.6%)	21 (10.7%)	0.044
Higher respiratory support				
None-oxygen*	426 (55.8%)	313 (55.3%)	113 (57.4%)	–
NIV	289 (37.9%)	213 (37.6%)	76 (38.6%)	0.325
IMV	48 (6.3%)	40 (7.1%)	8 (4.1%)	–

BMI body mass index, *COPD* Chronic obstructive pulmonary disease, *NIV* non-invasive mechanical ventilation, *IMV* invasive mechanical ventilation

*No support or oxygen through mask or high-flow nasal cannulae.

Table 2 Social-demographic and clinical characteristics of the patients according to mortality at 30-day follow-up

Variable	Survived ($n=670$)	Dead ($n=93$)	p value
Sex (male)	462 (69.0%)	58 (62.4%)	0.201
Age categories			
< 68 years	417 (62.2%)	8 (8.6%)	–
68–77 years	146 (21.8%)	21 (22.6%)	< 0.001
> 77 years	107 (16.0%)	64 (68.8%)	–
BMI ≥ 30 kg/m^2	179 (26.8%)	23 (25.3%)	0.758
Hypertension	316 (47.2%)	66 (71.0%)	< 0.001
Diabetes	125 (18.7%)	21 (22.6%)	0.367
COPD	35 (5.2%)	16 (17.2%)	< 0.001
Immunodeficency	32 (4.8%)	13 (14.0%)	< 0.001
Hospital interventions			
Heparin	641 (95.7%)	91 (97.8%)	0.319
Remdesivir	111 (16.6%)	4 (4.3%)	0.001
Higher respiratory support			
None-oxygen*	375 (56.0%)	51 (54.8%)	–
NIV	259 (38.7%)	30 (32.3%)	0.016
IMV	36 (5.4%)	12 (12.9%)	–

BMI body mass index, *COPD* Chronic obstructive pulmonary disease, *NIV* non-invasive mechanical ventilation, *IMV* invasive mechanical ventilation

*No support or oxygen through mask or high-flow nasal cannulae.

and respiratory failure severity (i.e., the highest received respiratory support), demonstrating a significantly decreased (by 59%) proportional-risk of 30-day death in patients who received home corticosteroids. Other variables significantly associated to mortality were age, immunodeficiency and the severity of pneumonia as described by requiring IMV (Table 3). After stratifying the study population according to identified age categories, home corticosteroids were associated with a statistically significant decrease in mortality risk in patients older than 77 years in a multivariable Cox regression model adjusted for the above described covariates (Fig. 1). Based on this finding, patients belonging to over-77 age group receiving or not home steroids were compared as a further sensitivity analysis. No statistically significant difference was found neither according to respiratory failure severity ($p=0.474$), nor to prevalence of comorbidities (hypertension: $p=0.267$; diabetes: $p=0.489$; COPD: $p=0.535$; immunodeficiency: $p=0.221$; obesity: $p=1.000$).

Discussion

The severity of COVID-19 pneumonia remains unacceptably high and antivirals have demonstrated little impact on COVID-19 mortality. Dexamethasone therapy lowers mortality in hospitalized patients with COVID-19 pneumonia requiring oxygen, especially in those treated after 7 days

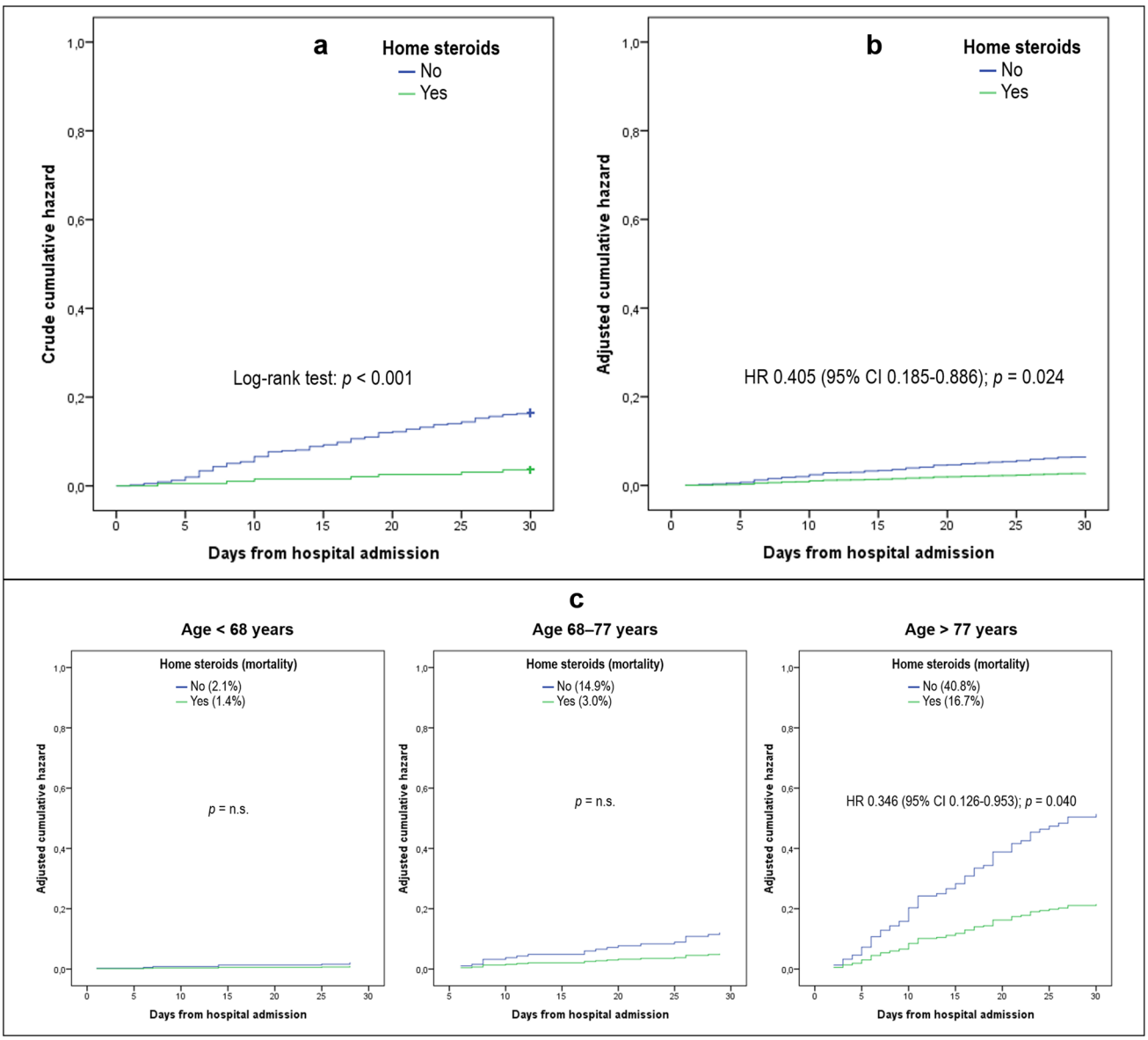

Fig. 1 Crude **a** and adjusted **b** Kaplan–Meier curves for the proportional-risk of 30-day death in patients receiving or not home steroid therapy in the whole study population and adjusted Kaplan–Meier risk curves **c** for patients belonging to the study age strata. *HR* hazard ratio, *CI* confidence interval

from symptoms [6]. Although no benefit of corticosteroids in COVID-19 hospitalized patients who do not require oxygen was reported, no harm has been equally demonstrated [6]. To date, the best timing for administering corticosteroids in SARS-CoV-2 infection remains undefined. Indeed, there are no data on the use of corticosteroids in non-hospitalized patients with COVID-19 not requiring oxygen support.

In the present study, almost a quarter of 763 patients with COVID-19 pneumonia were treated with home corticosteroids by their general practitioners. After a mean of six days from the onset of COVID-19 onset, these patients received approximately prednisone 40 mg daily (or equivalent) for a mean duration of 4 days. Compared with untreated ones, corticosteroid treated patients were younger and had a lower prevalence of some pre-existing comorbidities. This was probably due to the unspecified role of steroids in the early phase of COVID-19. However, the administration of this steroid regimen was found to lower the risk of 30-day death and this benefit was particularly evident in the elderly patient population. This finding was confirmed by multivariable and sensitivity analyses adjusted for age categories, main comorbidities, administration of remdesivir and respiratory failure severity. Severe illness typically occurs around one week

Table 3 Results of stepwise cox regression of 30-day mortality on study variables

Predictor	HR (95% CI)	*p* value
Home steroids (yes)	0.416 (0.191–0.907)	0.027
Age categories		
< 68 years	1.000	–
68–77 years	5.430 (2.387–12.350)	< 0.001
> 77 years	23.591 (11.194–49.718)	< 0.001
Immunodeficency (yes)	2.053 (1.131–3.726)	0.018
Higher respiratory support		
None-oxygen*	1.000	–
NIV	*0.879 (0.557–1.387)*	*0.579*
IMV	3.582 (1.826–7.023)	< 0.001

Variable excluded from the final regression model: Remdesivir, Hypertension, Chronic obstructive pulmonary disease

HR hazard ratio, *CI* confidence interval, *NIV* non-invasive mechanical ventilation, *IMV* invasive mechanical ventilation.

*No support or oxygen through mask or high-flow nasal cannulae.

after the beginning of symptoms related to SARS-CoV-2 infection and risk factors for COVID-19 mortality include mainly older age, male gender, lung disease, cardiovascular disease, hypertension, diabetes and obesity [11]. Our data show that COVID-19 patients aged > 77 years had the highest death risk and were those who benefited mostly from home corticosteroids. The latter finding is not unexpected since the aging process is associated with increased levels of systemic pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines ("inflamm-aging") [12].

The present study has several weaknesses. First, this is a retrospective observational study, where information regarding home corticosteroids were evaluated as a dichotomic variable and corticosteroid dosages were mainly reported by patients or their caregivers. Second, this is an Italian monocentric study and conclusions cannot be generalized. The third limitation is the lack of longitudinal data on SARS-CoV-2 clearance by serial nasopharyngeal samples. Lastly, we could not investigate the side effects of home corticosteroids regimens. In fact, since all of our patients received corticosteroid therapy following hospital admission, steroid side effects could not be attributable to a defined timing of treatment. Nonetheless, we explored for the first time the potential role of home corticosteroids in patients hospitalized for COVID-19 pneumonia. Our findings show that early corticosteroid therapy may lower the 30-day mortality in COVID-19 patients not receiving concomitant home oxygen supply who were subsequently hospitalized and treated with usual care, especially in the older ones. Given the retrospective nature of the study caution is needed in interpreting our results; however, early outpatient steroid therapy did not affect negatively the outcome in our patients with COVID-19 pneumonia.

Since the elderly patient population is precisely the one with the highest mortality due to COVID-19 [13], there is high priority to confirm our data by a running well-designed prospective randomized controlled study.

Authors contribution Conceptualization: RL, SDB; data curation: MDL, VZ, GB, DG; methodology: GS, MB; writing—original draft preparation: RL; supervision: SDB, GS, GB, RL; writing—review and editing: SDB, GS, RL. All authors read and approved the final manuscript included the names and order of authors.

Declarations

Conflict of interest The authors declare they have no financial or non-financial interests that are directly or indirectly related to the work submitted for publication

Ethics approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard. This study was approved by the Regional Ethics Committee of Trieste University Hospital (No. 2020-OS-072).

Informed consent All participants provided informed consent prior to participation.

References

1. National Institute for Health and Care Excellence (NICE) in collaboration with NHS England and NHS Improvement (2020) Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. BMJ 369:m1461. https://doi.org/10.1136/bmj.m1461
2. Gupta A, Gonzalez-Rojas Y, Juarez E et al (2021) Early treatment for covid-19 with sars-cov-2 neutralizing antibody sotrovimab. N Engl J Med 385:1941–1950. https://doi.org/10.1056/NEJMoa2107934
3. Gottlieb RL, Vaca CE, Paredes R et al (2022) Early remdesivir to prevent progression to severe covid-19 in outpatients. N Engl J Med 386:305–315. https://doi.org/10.1056/NEJMoa2116846
4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB et al (2022) Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. N Engl J Med 386:509–520. https://doi.org/10.1056/NEJMoa2116044
5. Hammond J, Leister-Tebbe H, Gardner A et al (2022) Oral nirmatrelvir for high-risk, nonhospitalized adults with covid-19. N Engl J Med. https://doi.org/10.1056/NEJMoa2118542
6. Group TRC, The RECOVERY Collaborative Group (2021) Dexamethasone in hospitalized patients with covid-19. N Engl J Med 384:693–704. https://doi.org/10.1056/nejmoa2021436
7. Sterne JAC, Murthy S, Diaz JV et al (2020) Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 324:1330. https://doi.org/10.1001/jama.2020.17023
8. Lee N, Allen Chan KC, Hui DS et al (2004) Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA

concentrations in adult patients. J Clin Virol 31:304–309. https://doi.org/10.1016/j.jcv.2004.07.006
9. Jianbo L, Xuelian L, Yue Z et al (2021) Association between glucocorticoids treatment and viral clearance delay in patients with COVID-19: a systematic review and meta-analysis. BMC Infect Dis 21:1063. https://doi.org/10.1186/s12879-021-6548-z
10. Czock D, Keller F, Rasche F (2005) Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet 44:61–98
11. Williamson EJ, Walker AJ, Bhaskaran K et al (2020) Factors associated with COVID-19-related death using opensafely. Nature 584:430–436. https://doi.org/10.1038/s41586-020-2521-4
12. Meftahi GH, Jangravi Z, Sahraei H et al (2020) The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging." Inflamm Res 69:825–839. https://doi.org/10.1007/s00011-020-01372-8
13. Prendki V, Tiseo G, Falcone M (2022) Caring for older adults during the COVID-19 pandemic. Clin Microbiol Infect. https://doi.org/10.1016/j.cmi.2022.02.040