Use of chronic medications and risk of severe death due to COVID-19 in hospitalised patients

María Larrosa-García,[1] Sonia Garcia-Garcia ,[1] Javier Louro,[2] Adrián Sánchez-Montalvá,[3] Julia Sampol Sirvent,[4] Salvador Augustín Recio,[5] Alfredo Guillén del Castillo,[5] Judit Riera-Arnau ,[6] Maria Queralt Gorgas,[1] Marta Miarons[1]

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[1]Pharmacy Department, Vall d'Hebron University Hospital, Barcelona, Spain
[2]Department of Epidemiology and Evaluation, IMIM, Hospital del Mar INAD, Barcelona, Spain
[3]Infectious Diseases Department, Vall d'Hebron University Hospital, Barcelona, Spain
[4]Pneumology Department, Vall d'Hebron University Hospital, Barcelona, Spain
[5]Internal Medicine Department, Vall d'Hebron University Hospital, Barcelona, Spain
[6]Pharmacology Department, Vall d'Hebron University Hospital, Barcelona, Spain

Correspondence to
Sonia Garcia-Garcia, Vall d'Hebron University Hospital, Barcelona 08035, Spain; sonia.17.gg@gmail.com

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ABSTRACT

Objectives To evaluate the potential association between chronic exposure to medication and death related to COVID-19.

Methods This is a retrospective cross-sectional study that included all patients hospitalised due to COVID-19 from 11 March to 4 June 2020 in our centre. Chronic patient medication was classified by the Anatomical Therapeutic Chemical (ATC) classification; demographic and clinical data were analysed. Multivariate logistic regression models were used to estimate the adjusted odds ratios (aOR) of death for each drug exposure; each aOR represents an independent model adjusted by clinical factors related to COVID-19 mortality.

Results The study included 978 patients with a mean (SD) age of 64.5 (17.7) years who were predominantly male (531, 54.3%). Of all 978 patients, 182 (18.61%) died during the follow-up of the study. The most common Charlson Comorbidity Index (CCI) was 0, 4.2% were smokers, 16.7% were obese, 47.4% had hypertension, and 19.4% were diabetic. Most patients (70.8%) were prescribed at least one treatment, 32.5% used >5 treatments, and 8.6% >10. Our data suggest that COVID-19 hospitalised patients taking trimethoprim and analogues, leukotriene receptor antagonists, calcineurin inhibitors, aldosterone antagonists, selective immunosuppressants, propulsives, insulins and analogues, and benzodiazepine derivatives have a higher risk of death.

Conclusions This study investigated the association between chronic exposure to drugs and the risk of death in COVID-19 patients. Our results have shed some light on the impact of chronic drug exposure on the risk of severe COVID-19; however, further research is needed to increase the understanding about its relevance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The global pandemic of COVID-19 requires the identification of possible clinical predisposing or protective factors.
⇒ It has been reported that male sex and older age, among other factors, are associated with a worse prognosis. However, data regarding drugs indicated for other diseases as being potentially beneficial or harmful are scarce.

WHAT THIS STUDY ADDS

⇒ The present study widely investigates the association between drugs and the risk of severe COVID-19, increasing the understanding of their association.
⇒ COVID-19 hospitalised patients previously using insulins and analogues, leukotriene receptor antagonists and calcineurin inhibitors, among other treatments, had significantly higher odds of death than patients not taking those drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results have shed some light regarding the impact of chronic treatments on COVID-19, even if the evidence is not strong enough to advise against the use of any groups of drugs.
⇒ Further research is needed in order to increase understanding about the impact of chronic drug exposure on the risk of severe COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially fatal disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The estimated mortality of diagnosed cases with COVID-19 ranges from 2.3–15.2%, depending on patient population, diagnostic strategies and, probably, additional poorly characterised factors.[1] Several studies have reported that clinical conditions such as hypertension, cardiovascular disease, cerebrovascular disease, diabetes and chronic kidney disease are associated with a higher risk for severe complications and death in the case of COVID-19.[2]

The use of certain chronic medications has also been suggested as a risk factor influencing COVID-19 prognosis. Initial concerns related antihypertensive medication with poor COVID-19 outcome; however, those fears were rapidly disproved.[3 4] There is accumulating data suggesting that antidiabetic oral drugs, such as sodium-glucose cotransporter-2 inhibitors (SGLT2i) and metformin, act as protective factors in the case of SARS-CoV-2 infection.[5 6] The impact of immunomodulation therapies on COVID-19 disease remains controversial. On the one hand, they may impair the natural immune response against the virus,[7 8] and on the other hand, immunosuppressants could minimise immune system over-activation; in fact, dexamethasone, tocilizumab and anakinra have been used to control exacerbated immune responses to COVID-19.[9–13] Finally, anticoagulant therapy appears to be associated with a better prognosis and lower

mortality in patients meeting sepsis-induced coagulopathy criteria or with notably elevated D-dimer.[14–18]

Given the uncertainties, the current research aims to analyse the potential effect of chronic treatments on clinical outcomes of hospitalised patients with COVID-19.

METHODS

Study setting and COVID-19 pharmacological treatment

We conducted a retrospective cross-sectional study analysing patients with SARS-CoV-2 infection. This cohort included 978 patients who were admitted to the emergency department because of COVID-19 from 11 March to 4 June 2020 in the Vall d'Hebron University Hospital, which is located in northern Barcelona; it provides care for >430 000 people and has an emergency department with 71 beds. Patients with mild SARS-CoV-2 infection were discharged following the home care institutional protocol. Hospitalised patients with moderate-severe COVID-19 were treated according to the hospital's clinical protocol available at the time of hospitalisation. During hospitalisation, maintaining usual medication for chronic diseases was at the discretion of the treating physicians.

Ethical consideration

The Institutional Review Board provided ethical clearance for this study (reference number: PR (AG) 240/2020). Patients were asked for an oral consent. If patients were unable to give oral consent, the Institutional Review Board granted a waiver of informed consent. The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association as established in the 18th General Assembly and its modifications.[19] The Organic Law 3/2018, of 5 December, on the Protection of Personal Data and Guarantee of Digital Rights was applied.

Microbiological diagnosis

Laboratory-confirmed COVID-19 was defined as a positive SARS-CoV-2 polymerase-chain-reaction (PCR) result from any respiratory sample (nasopharyngeal swab, sputum, bronchoalveolar lavage or aspirate or tracheal aspirate). The commercial Allplex 2019-nCoV multiplex real-time PCR assay (Seegene, South Korea) was used for the detection of three target genes of SARS-CoV-2 (E and N genes and RNA-dependent RNA polymerase).

Data collection and outcomes

Data were collected from the time of COVID-19 diagnosis until an outcome (death, discharge or hospitalised after 28 days of hospitalisation) was reached. We obtained patients' sociodemographic characteristics, epidemiological history, comorbidities and chronic medications from electronic medical records. Information about therapy during hospitalisation and tests on respiratory samples and supportive measures needed was also collected. Blood test results, vital signs, symptoms and physical examination were evaluated on admission and weekly during hospitalisation. We used Research Electronic Data Capture software (REDCap, Vanderbilt University) for data recording. Three investigators independently reviewed all the collected data.

Definition of study variables and outcomes

Age and gender were collected at the time of hospitalisation. Smoking status was self-reported and stratified into active smokers, ex-smokers and no smokers. Previous medical conditions were recorded from the electronic medical record system. The age-adjusted Charlson Comorbidity Index (CCI)[20] was calculated. The main outcome was in-hospital death due to COVID-19.

Drug exposure

Chronic medication was defined as drugs taken for at least a 3-month period before admission. Information about chronic treatments was obtained from the Integrated Electronic prescription System (SIRE), a drug management programme that coordinates drug prescription and dispensing within the Catalan Public Healthcare System. Chronic treatments were analysed according to the Anatomical Therapeutic Chemical (ATC) classification system.[21]

In case <10 people used any drug from an ATC group it was excluded from analysis.

Statistical analysis

Descriptive statistics are expressed as median and range or mean and SD for continuous variables and absolute number and percentage for categorical variables. We evaluated the differences in the mean age of those patients who died using the Mann-Whitney U test. For the remaining variables we assessed the differences in the proportion of patients who died using the χ^2 test. Multivariate logistic regression models were used to estimate the adjusted odds ratio (aOR) and 95% confidence interval (95% CI) of death for each drug exposure. Each aOR represents an independent model adjusted by age, gender, CCI, arterial hypertension, smoking status, diabetes and obesity. We represented the different aOR for every drug exposure using forest plots. Since there were a high number of drug categories, we stratified the results by statistical significance. All analyses were performed using the statistical software R version 4.0.3 (Development Core Team, 2014).

RESULTS

Baseline characteristics of patients

At the end of the follow-up, 978 patients had been diagnosed with confirmed COVID-19 and admitted to the hospital. Table 1 shows baseline demographic and clinical characteristics of all patients during the time of the study.

The patients' mean (SD) age was 64.5 (17.7) years and they were predominantly male (531 (54.3%)). The most common CCI was 0, and 58.2% of the patients had no or mild comorbidity (CCI 0, 1 and 2). The percentage of smokers was 4.2%, 16.7% of patients were obese, 47.4% had hypertension and 19.4% were diabetic. Regarding chronic treatments, 70.8% of patients included in the study used at least one chronic medication before hospital admission, 32.5% used >5 drugs and 8.6% >10. Of the 978 patients, 182 (18.6%) died during the follow-up of the study. Non-survivors were significantly older than survivors (mean (SD) age 78.2 (10.5) vs 61.4 (17.6) years, p<0.001). The proportion of non-survivors among male patients was significantly higher than among females (111 (20.9%) vs 71 (15.9%), p=0.044). The proportion of non-survivors increased significantly as the CCI increased (p<0.001). There were higher proportions of non-survivors among ex-smokers (65 (29.4%)) and active smokers (9 (22.0%)) than among no smokers (108 (15.3%)). No differences were found in patients with obesity (p=0.462). The proportion of non-survivors was also higher in patients with arterial hypertension (136 (29.3%) vs 46 (8.9%), p<0.001) and in diabetic patients (52 (27.4%) vs 130 (16.5%), p<0.001). There was a higher proportion of non-survivors as the number of drugs chronically used by patients increased, ranging from 17 (5.9%) non-survivors in the group of patients

Table 1 Baseline demographic and clinical characteristics of patients

	Total	Death		
	N (978)	No (796) N (%)	Yes (182) N (%)	P value*
Age (mean)	64.5	61.4	78.2	<0.001
Gender				
Male	531	420 (79.1%)	111 (20.9%)	0.044
Female	447	376 (84.1%)	71 (15.9%)	
Charlson Comorbidity Index				
0	181	180 (99.4%)	1 (0.6%)	<0.001
1	137	136 (99.3%)	1 (0.7%)	
2	121	113 (93.4%)	8 (6.6%)	
3	130	103 (79.2%)	27 (20.8%)	
4	114	86 (75.4%)	28 (24.6%)	
5	96	68 (70.8%)	28 (29.2%)	
6	76	45 (59.2%)	31 (40.8%)	
7	41	24 (58.5%)	17 (41.5%)	
8	30	17 (56.7%)	13 (43.3%)	
9	18	8 (44.4%)	10 (55.6%)	
10	14	9 (64.3%)	5 (35.7%)	
>10	20	7 (35.0%)	13 (65.0%)	
Smoking status				
Active	41	32 (78.0%)	9 (22.0%)	<0.001
Ex	221	156 (70.6%)	65 (29.4%)	
No	704	608 (86.4%)	108 (15.3%)	
Obesity				
No	815	660 (81.0%)	155 (19.0%)	0.462
Yes	163	136 (83.4%)	27 (16.6%)	
Arterial hypertension				
No	514	468 (91.1%)	46 (8.9%)	<0.001
Yes	464	328 (70.7%)	136 (29.3%)	
Diabetes				
No	788	658 (83.5%)	130 (16.5%)	0.001
Yes	190	138 (72.6%)	52 (27.4%)	
Number of chronic treatments				
0	286	269 (94.1%)	17 (5.9%)	<0.001
1	92	86 (93.5%)	6 (6.5%)	
2	77	72 (93.5%)	5 (6.5%)	
3	78	63 (80.8%)	15 (19.2%)	
4	61	47 (77.0%)	14 (23.0%)	
5	66	53 (80.3%)	13 (19.7%)	
6	51	38 (74.5%)	13 (25.5%)	
7	51	35 (68.6%)	16 (31.4%)	
8	56	40 (71.4%)	16 (28.6%)	
9	44	21 (47.7%)	23 (52.3%)	
10	32	21 (65.6%)	11 (34.4%)	
>10	84	51 (60.7%)	33 (39.3%)	
Intensive care unit admission	132	109 (82.6%)	23 (17.4%)	0.707

not exposed to any drug to 33 (39.3%) in those exposed to >10 drugs (p<0.001). Risk of death was not statistically different between patients admitted to the intense care unit or not (18.8% vs 17.4%, p=0.707).

Chronic drug exposure and COVID-19 related mortality

The median number of chronic drugs used by patients was 3 (range 0–18); 286 (29.2%) patients did not have any active prescription at the time of hospital admission and 318 (32.5%) patients were taking >10 drugs.

As shown in figure 1, we found statistically significant higher odds of death due to COVID-19 in those patients who had been exposed to trimethoprim and derivatives (aOR 5.15, 95% CI 1.89 to 14.02), leukotriene receptor antagonists (aOR 4.77, 95% CI 1.61 to 14.14), calcineurin inhibitors (aOR 3.65, 95% CI 1.58 to 8.41), aldosterone antagonists (aOR 3.13, 95% CI 1.05 to 9.35), selective immunosuppressants (aOR 2.99, 95% CI 1.31 to 6.78), propulsives (aOR 2.79, 95% CI 1.01 to 7.69), insulins and analogues (aOR 2.40, 95% CI 1.18 to 4.89) and benzodiazepine derivatives (antiepileptics) (aOR 2.05, 95% CI 1.27 to 3.31) in comparison with patients who did not use these treatments.

Other ATC groups showed a tendency towards either higher or lower risk of death due to COVID-19, but they were not statistically significant (online supplemental figure 1).

DISCUSSION

The global pandemic caused by SARS-CoV-2 requires the identification of factors that influence the severity of COVID-19. The literature describes different pharmacology groups that could alter the prognosis of SARS-CoV-2 infection. The present study examines the association between the chronic use of drugs and death in COVID-19 hospitalised patients. We found that COVID-19 hospitalised patients previously using trimethoprim and derivatives, leukotriene receptor antagonists, aldosterone antagonists, propulsives, insulins and analogues, selective immunosuppressants, calcineurin inhibitors and benzodiazepine derivatives (antiepileptics) had potentially higher odds of death than other patients.

In our study, adjustments by age, gender, CCI, arterial hypertension, smoking status, diabetes and obesity were made because these factors have been identified as strong predictors of mortality in people with SARS-CoV-2 infection.[22–26] We have found that the mortality rate was 18.6%, which is consistent with other studies performed in COVID-19 hospitalised patients. The study of Roso-Llorach *et al* found that the highest 30-day mortality rate was reported during the first wave (17%) and decreased afterwards, remaining stable at 13% in the second and third waves (overall 30% reduction).

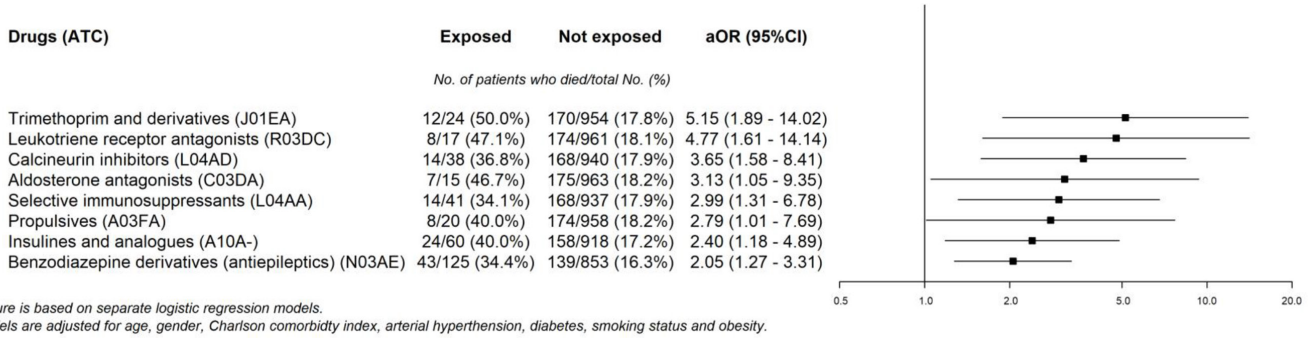

Figure 1 Adjusted odds ratios (aOR) of COVID-19 mortality by previous exposure to chronic treatments (significant results).

Regarding the association of drugs and death, the use of the combination of trimethoprim and derivatives is related to a higher incidence of death due to COVID-19. Since this drug is most commonly used as prophylactic treatment for *Pneumocystis jirovecii* in patients with an impaired immune system due to oncohaematologic diseases,[27] HIV[28] or organ transplantation,[29] we suggest that the increased mortality might be related to the immunosuppression status.

We have also found that the use of leukotriene receptor antagonists, which includes montelukast, was related to a higher mortality rate. Montelukast reduces inflammation and leads to smooth muscle relaxation in the small airways, and has been suggested as a treatment for COVID-19.[30 31] The use of montelukast by patients with severe asthma could explain its relationship within higher COVID-19 mortality; however, the relationship between asthma and severe COVID-19 remains uncertain.[32 33]

Aldosterone antagonists have been identified as risk factors of death due to COVID-19. However, some authors have hypothesised that spironolactone could have a protective effect against COVID-19.[34 35] A greater use of these treatments among polymedicated patients with cardiovascular diseases,[36] which have been related to a worse prognosis in COVID-19 infection,[37] could have impacted our results.

Selective immunosuppressants and calcineurin inhibitors were related to increased risk of death. Some studies have suggested that serum concentrations of pro-inflammatory cytokines are associated with COVID-19 severity, so it could be expected that immunosuppressive drugs could act as a protective factor for severe disease.[38] Nevertheless, it is well known that these drugs increase the risk of severe infections[39] and involve faster infection disease progression. During the early viral replication phase, immunosuppression therapy may lead to higher viral load peak, higher direct tissue damage and cytokine storm release. Consequently, immunosuppressant therapy (associated with comorbidities) could impair the immune system's ability to fight the virus and involve a worse prognosis of COVID-19 in transplant recipients[29 39 40] and patients with autoimmune diseases,[41–43] as has been reported by others.[44 45]

The positive correlation found between propulsives and poor prognosis may be attributable to various unknown facts. Propulsive drugs are widely used in oncology patients[46 47] and palliative care.[48] In this group of fragile patients, a higher mortality after COVID-19 is to be expected.[49]

Insulins and analogues constitute a therapeutic regimen for diabetes mellitus, a chronic and low-grade inflammatory disease. Yu *et al*[50] conducted a retrospective study analysing hospitalised diabetic patients with COVID-19 and found that insulin was related to higher mortality, as we have observed. Authors have suggested that insulin may have a deleterious effect by increasing the pro-inflammatory cytokine levels and lung inflammation, as has been proven by several in vitro, in vivo and clinical studies.[51 52]

Benzodiazepine derivatives (antiepileptics) were related to a higher risk of death. Asaadi-Pooya *et al*[53] and other authors have stated that it is highly likely that some patients with severe COVID-19 have central nervous system involvement and neurological manifestations. [54–56]

We did not identify any ATC group related to a lower risk of death, even if other antihistamines for systemic use and β-blocking agents, non-selective among others, showed a tendency towards having a protective effect, as shown in online supplemental figure 1. These ATC groups might have a protective effect that could not be identified as statistically significant in our study due to the limited sample and/or confounders effect.

The pathogenesis of distress syndrome in the clinical context of COVID-19 may be related to the direct effect of SARS-CoV-2 on alveolar epithelial cells and to the indirect effects of infection-related hypoxia, severe inflammatory response and microvascular pulmonary thrombosis.[57] Given that the thrombogenic features of COVID-19 potentially cause a progressive disease course, anticoagulation may protect against severe COVID-19; however, evidence regarding the potential beneficial effect of anticoagulants is controversial. In a retrospective cohort study including severely ill COVID-19 patients, a decrease in 28 day-mortality was observed in heparin users versus non-users in specific subgroups of patients.[14] Our results did not show any beneficial effect of anticoagulants in COVID-19 patients, as has been found in other retrospective studies.[57–59]

It has been hypothesised that drugs that act on the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), may affect the susceptibility to and severity of COVID-19.[3 4 60 61] However, currently available results show that the use of ACEIs or ARBs are not associated with an increased risk of severity of COVID-19,[3 4] as the results of our study show. Other studies analysing our population, conducted in Spain[62] and specifically in Catalonia,[63] as well as other European countries,[64] agree with our findings.

Finally, glucocorticoids for systemic use have been associated with better outcomes when administered to patients with severe COVID-19[13]; specifically, the RECOVERY trial has shown that corticoid administration leads to lower mortality in patients requiring oxygen support or mechanical ventilation.[65] However, chronic exposure to glucocorticoids was associated with higher odds of hospitalisation in patients with inflammatory bowel disease,[66] and rheumatic and musculoskeletal diseases.[67] We have found that there was a tendency towards higher risk of death in patients who were chronically exposed to corticoids, and we hypothesise that the time of administration plays a key role in corticosteroids effect: chronic use of systemic corticosteroids may worsen COVID-19 prognosis by suppressing the immune response and allowing virus replication, whereas corticoid use in the hyperinflammation phase of COVID-19 disease may prevent multiple organ failure and acute respiratory distress syndrome.[68 69]

We found that the mortality rate was 18.6%, which is consistent with other studies performed in COVID-19 hospitalised patients. The study of Roso-Llorach *et al* found that the highest 30-day mortality rate was reported during the first wave (17%) and decreased afterwards, remaining stable at 13% in the second and third waves (overall 30% reduction).[70]

Our study has some limitations that might reduce our ability to establish a causal relationship between chronic drug exposure and severe COVID-19, and should be considered when interpreting the results. First, there are biases on exposure; for example, we only analysed the impact of ATC groups that were used by >10 patients because we considered that the information available in these cases was insufficient to draw conclusions. Second, we considered that patients were exposed to treatment if they had an active electronic medical prescription from 3 months before hospital admission; however, we cannot affirm that patients were actually taking their medication. This could lead to an underestimation of these drugs' impact on COVID-19. Third, we did not evaluate over-the-counter treatments, which could interfere with the results of the prescribed drugs and might cause interaction in their effect. Fourth, we included patients admitted to the hospital due to COVID-19; therefore, even if we detect that chronic exposure to drugs belonging to

a certain ATC group is a risk factor for severe COVID-19, this might not apply to the whole population taking the drug in the community. We assumed that patients who were not hospitalised and had COVID-19 overcame the infection and survived, but we cannot affirm that there were not severe COVID-19 cases outside the hospital. Fifth, chronic treatment use is related to certain health conditions or chronic diseases; this implies that exposure to the drug could act as a confounder. We reduced the risk of bias and the confounder effect by adjusting for different parameters including age, gender, CCI, arterial hypertension, diabetes, smoking status and obesity; however, we cannot affirm that the risk of bias was completely erased. Finally, we are aware that multiple comparisons may increase the chances of finding significant results even if they do not exist. Therefore, our study should be interpreted with caution, and the results should help to generate hypotheses.

In this study, we analysed the relationship between exposure to chronic treatments before COVID-19 and the risk of death in hospitalised COVID-19 patients. COVID-19 prognosis depends on a myriad of factors, some of which remain to be identified, making it challenging to detect individual risk or protective factors; however, making efforts to detect drugs that might exert an effect on COVID-19 outcomes is crucial in order to optimise chronic treatments in the context of the SARS-CoV-2 pandemic and potentially identify treatments for COVID-19. We have observed that the use of certain drugs including trimethoprim and derivatives, leukotriene receptor antagonists, aldosterone antagonists, propulsives, insulins and analogues, selective immunosuppressants, calcineurin inhibitors and benzodiazepine derivatives (antiepileptics) are related to a potential higher risk of severe COVID-19. Evidence is not strong enough to advise against the use of any groups of drugs; however, our results have shed some light regarding the impact of chronic treatments on COVID-19 and they should be taken into consideration. Further research is needed in order to increase understanding about the impact of chronic drug exposure on the risk of severe COVID-19.

Twitter María Larrosa-García @laresiLarrosa and Judit Riera-Arnau @J_Riera_Farcli

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ORCID iDs
Sonia Garcia-Garcia http://orcid.org/0000-0002-7505-4770
Judit Riera-Arnau http://orcid.org/0000-0001-7591-0218

REFERENCES

1 Baud D, Qi X, Nielsen-Saines K, *et al*. Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis* 2020;20:773.
2 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239–42.
3 Reynolds HR, Adhikari S, Pulgarin C, *et al*. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. *N Engl J Med Overseas Ed* 2020;382:2441–8.
4 Mancia G, Rea F, Ludergnani M, *et al*. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020;382:2431–40.
5 Rey JR, Merino Llorens JL, Iniesta Manjavacas ÁM. Influence of statin treatment in a cohort of patients admitted for COVID-19. *Med Clin* 2022;158:586–95.
6 Fernandez-Fernandez B, D'Marco L, Górriz JL, *et al*. Exploring sodium glucose co-transporter-2 (SGLT2) inhibitors for organ protection in COVID-19. *J Clin Med* 2020;9. doi:10.3390/jcm9072030. [Epub ahead of print: 28 06 2020].
7 Scheen AJ, Metformin SAJ. Metformin and COVID-19: from cellular mechanisms to reduced mortality. *Diabetes Metab* 2020;46:423–6.
8 Remuzzi A, Remuzzi G, Zoccai GB. Immunosuppression for hyperinflammation in COVID-19 : a double-edged sword? AauAuthoritarianism and the threat of infectious diseases. *Lancet* 2020.
9 Rizk JG, Kalantar-Zadeh K, Mehra MR, *et al*. Pharmaco-immunomodulatory therapy in COVID-19. *Drugs* 2020;80:1267–92.
10 Sánchez-Montalvá A, Sellarés-Nadal J, Espinosa-Pereiro J. Early outcomes of tocilizumab in adults hospitalized with severe COVID-19 - the Vall d'Hebron COVID-19 prospective cohort study. *medRxiv* 2020.
11 Ceribelli A, Motta F, De Santis M, *et al*. Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. *J Autoimmun* 2020;109:102442.
12 Langer-gould A, Smith JB, Gonzales EG. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. *Int J Infect Dis* 2020;99:291–7.
13 Wang Y, Jiang W, He Q. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. *medRxiv* 2020.
14 Tang N, Li D, Wang X, *et al*. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–7.
15 Danzi GB, Loffi M, Galeazzi G, *et al*. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J* 2020;41:1858.
16 Cui S, Chen S, Li X, *et al*. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:1421–4.
17 Minet C, Potton L, Bonadona A, *et al*. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care* 2015;19:1–9.
18 Malato A, Dentali F, Siragusa S, *et al*. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. *Blood Transfus* 2015;13:559–68.
19 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
20 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
21 World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). World Health Organization, 2015. Available: http://www.who.int/classifications/atcddd/en/ [Accessed 01 Jan 2021].
22 Ssentongo P, Ssentongo AE, Heilbrunn ES, *et al*. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. *PLoS One* 2020;15:e0238215–6.
23 Fang X, Li S, Yu H. Epidemiological comorbidity factors with severity and prognosis. *Aging* 2020;12:12493–503.
24 Dorjee K, Kim H, Bonomo E, *et al*. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: a comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. *PLoS One* 2020;15:e0243191–27.
25 Berenguer J, Ryan P, Rodríguez-Baño J, *et al*. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect* 2020;26:1525–36.
26 Petrilli CM, Jones SA, Yang J, *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966.
27 Lee LYW, Cazier J-B, Starkey T, *et al*. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. *Lancet Oncol* 2020;21:1309–16.
28 Ho H-E, Peluso MJ, Margus C, *et al*. Clinical outcomes and immunologic characteristics of coronavirus disease 2019 in people with human immunodeficiency virus. *J Infect Dis* 2021;223:4–9.

29 Miarons M, Larrosa-García M, García-García S, *et al*. COVID-19 in solid organ transplantation: a matched retrospective cohort study and evaluation of immunosuppression management. *Transplantation* 2021;105:138–50.
30 Citron F, Perelli L, Deem AK, *et al*. Leukotrienes, a potential target for Covid-19. *Prostaglandins Leukot Essent Fatty Acids* 2020;161:102174.
31 Barré J, Sabatier J-M, Annweiler C. Montelukast drug may improve COVID-19 prognosis: a review of evidence. *Front Pharmacol* 2020;11:1344.
32 Choi YJ, Park J, Lee HS. Early view effect of asthma and asthma medication on the prognosis of patients with COVID-19. *Eur Respir J* 2021;57:2002226.
33 Boyce JH-, Gunnell J, Drake J. Asthma and COVID-19 : review of evidence on risks and management considerations. *BMJ Evid Based Med* 2020.
34 Cadegiani FA, Wambier CG, Goren A. Spironolactone: an anti-androgenic and anti-hypertensive drug that may provide protection against the novel coronavirus (SARS-CoV-2) induced acute respiratory distress syndrome (ARDS) in COVID-19. *Front Med* 2020;7:1–5.
35 Cadegiani FA, Goren A, Wambier CG. Spironolactone may provide protection from SARS-CoV-2: targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RaaS). *Med Hypotheses* 2020;143:110112–2.
36 Funder JW. Spironolactone in cardiovascular disease: an expanding universe? *F1000Res* 2017;6:1738–7.
37 Li B, Yang J, Zhao F, *et al*. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020;109:531–8.
38 Chen G, Wu D, Guo W, *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130:2620–9.
39 Zhang H, Dai H, Xie X. Solid organ transplantation during the COVID-19 pandemic. *Front Immunol* 2020;11.
40 Trapani S, Masiero L, Puoti F, *et al*. Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: a nationwide population-based study. *Am J Transplant* 2021;21:2509–21.
41 Feng Y, Ling Y, Bai T, *et al*. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med* 2020;201:1380–8.
42 Safavi F, Nourbakhsh B, Azimi AR. B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. *Mult Scler Relat Disord* 2020;43:102195.
43 Baker D, Amor S, Kang AS, *et al*. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. *Mult Scler Relat Disord* 2020;43:102174.
44 Fishman JA, Grossi PA. Novel coronavirus-19 (COVID-19) in the immunocompromised transplant recipient: #Flatteningthecurve. *Am J Transplant* 2020;20:1765–7.
45 Michaels MG, La Hoz RM, Danziger-Isakov L, *et al*. Coronavirus disease 2019: implications of emerging infections for transplantation. *Am J Transplant* 2020;20:1768–72.
46 Einhorn LH, Rapoport B, Navari RM, *et al*. 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following multiple-day chemotherapy, high-dose chemotherapy, and breakthrough nausea and vomiting. *Support Care Cancer* 2017;25:303–8.
47 Harder S, Herrstedt J, Isaksen J, *et al*. The nature of nausea: prevalence, etiology, and treatment in patients with advanced cancer not receiving antineoplastic treatment. *Support Care Cancer* 2019;27:3071–80.
48 To THM, Agar M. Prescribing for nausea in palliative care : a cross-sectional national survey. *J Palliat Med* 2014;17:1032–6.
49 Sorouri M, Kasaeian A, Mojtabavi H, *et al*. Clinical characteristics, outcomes, and risk factors for mortality in hospitalized patients with COVID-19 and cancer history: a propensity score-matched study. *Infect Agent Cancer* 2020;15:1–11.
50 Yu B, Li C, Sun Y, *et al*. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. *Cell Metab* 2021;33:65–77.
51 Brundage SI, Kirilcuk NN, Lam JC, *et al*. Insulin increases the release of proinflammatory mediators. *J Trauma* 2008;65:367–72.
52 Filgueiras LR, Capelozzi VL, Martins JO, *et al*. Sepsis-induced lung inflammation is modulated by insulin. *BMC Pulm Med* 2014;14:177.
53 Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. *J Neurol Sci* 2020;413:116832.
54 Cabezudo-García P, Ciano-Petersen NL, Mena-Vázquez N, *et al*. Incidence and case fatality rate of COVID-19 in patients with active epilepsy. *Neurology* 2020;95:e1417–25.
55 Sepehrinezhad A, Shahbazi A, Negah SS. COVID-19 virus may have neuroinvasive potential and cause neurological complications: a perspective review. *J Neurovirol* 2020;26:324–9.
56 Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. *Mult Scler Relat Disord* 2020;46:102535.
57 Bikdeli B, Madhavan MV, Jimenez D, *et al*. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;75:2950–73.
58 Maldonado E, Tao D, Mackey K. Antithrombotic therapies in COVID-19 disease: a systematic review. *J Gen Intern Med* 2020;35:2698–706.
59 Russo V, Di Maio M, Attena E, *et al*. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. *Pharmacol Res* 2020;159:104965.
60 Grover A, Oberoi M. A systematic review and meta-analysis to evaluate the clinical outcomes in COVID-19 patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. *Eur Heart J Cardiovasc Pharmacother* 2020:1–10.
61 Şenkal N, Meral R, Medetalibeyoğlu A, *et al*. Association between chronic ACE inhibitor exposure and decreased odds of severe disease in patients with COVID-19. *Anatol J Cardiol* 2020;24:21–9.
62 de Abajo FJ, Rodríguez-Martín S, Lerma V, *et al*. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020;395:1705–14.
63 Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, *et al*. Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. *PLoS One* 2020;15:e0239571.
64 Trifirò G, Massari M, Da Cas R, *et al*. Renin-angiotensin-aldosterone system inhibitors and risk of death in patients hospitalised with COVID-19: a retrospective Italian cohort study of 43,000 patients. *Drug Saf* 2020;43:1297–308.
65 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11.
66 Brenner EJ, Ungaro RC, Gearry RB, *et al*. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020;159:481–91.
67 Montero F, Martínez-Barrio J, Serrano-Benavente B, *et al*. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. *Rheumatol Int* 2020;40:1593–8.
68 Robinson PC, Morand E. Divergent effects of acute versus chronic glucocorticoids in COVID-19. *Lancet Rheumatol* 2021;3:e168–70.
69 Wu J, Huang J, Zhu G, *et al*. Systemic corticosteroids and mortality in severe and critical COVID-19 patients in Wuhan, China. *J Clin Endocrinol Metab* 2020;105:e4230–9.
70 Roso-Llorach A, Serra-Picamal X, Cos FX, *et al*. Evolving mortality and clinical outcomes of hospitalized subjects during successive COVID-19 waves in Catalonia, Spain. *Glob Epidemiol* 2022;4:100071.