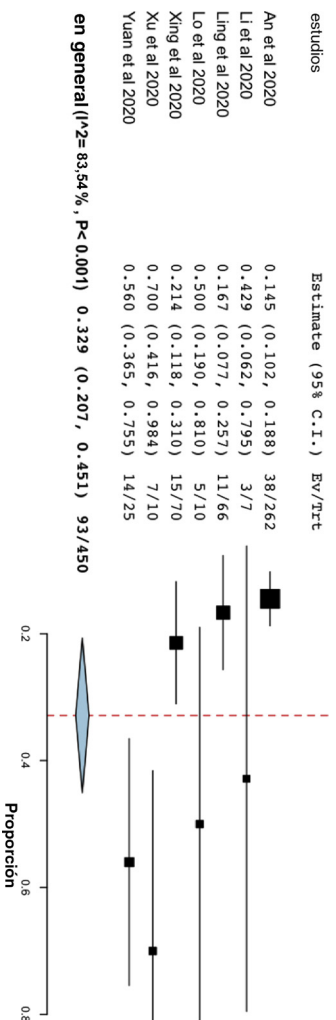




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



**Figure 1** Forest plot of the seven studies estimating the pooled prevalence of re-detectable positive SARS-CoV-2 RNA test among recovered patients.

## References

- An J, Liao X, Xiao T, Qian S, Yuan J, Ye H, et al. Clinical characteristics of the recovered COVID-19 patients with re-detectable positive RNA test. *medRxiv*. 2020, doi:10.1101/2020.03.26.20044222.
- Chen D, Xu W, Lei Z, Huang Z, Liu J, Gao Z, et al. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. *Int J Infect Dis*. 2020;93:297–9, doi:10.1016/j.ijid.2020.03.003.
- Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, et al. Positive RT-PCR test results in patients recovered from COVID-19. *JAMA*. 2020, doi:10.1001/jama.2020.2783.
- Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)*. 2020, doi:10.1097/CM9.0000000000000774.
- Lo IL, Lio CF, Cheong HH, Lei CI, Cheong TH, Zhong X, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. *Int J Biol Sci*. 2020;16:1698–707, doi:10.7150/ijbs.45357.
- Qu YM, Kang EM, Cong HY. Positive result of SARS-CoV-2 in sputum from a cured patient with COVID-19. *Travel Med Infect Dis*. 2020, doi:10.1016/j.tmaid.2020.1016.19.
- Xinglaj Y, Ni W, Wu Q, Li W, Li G, Tong J, et al. Prolonged presence of SARS-CoV-2 in feces of pediatric patients during the convalescent phase. *medRxiv*. 2020, doi:10.1101/2020.03.11.20033159.
- Z. S. Ulhaq<sup>a,\*</sup>, G. V. Soraya<sup>b</sup>, F. A. Fauziah<sup>c</sup>  
<sup>a</sup> Department of Biochemistry, Faculty of Medicine and Health Sciences, Maulana Malik Ibrahim Islamic State University of Malang, Batu, Indonesia  
<sup>b</sup> Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia  
<sup>c</sup> Scaling Up Nutrition Secretariat, Ministry of National Development Planning, Indonesia

\*Corresponding author.

E-mail address: zulhaq@kedokteran.uin-malang.ac.id (Z.S. Ulhaq).

2254-8874/ © 2020 Elsevier España, S.L.U. and Sociedad Española de Medicina Interna (SEMI). All rights reserved.



## Is chronic obstructive pulmonary disease a protective factor in SARS-CoV-2 infection? The importance of bronchodilator treatment<sup>☆</sup>

### ¿Es la enfermedad pulmonar obstructiva crónica un factor protector en la infección por SARS-CoV-2? La importancia del tratamiento broncodilatador

Dear Director,

Globally, viruses play an important role in exacerbations of chronic obstructive pulmonary disease (COPD). In a sys-

tematic review of infections in patients with COPD that required hospital admission, it was observed that the rhinovirus, respiratory syncytial virus (RSV), and influenza virus were the most prevalent agents, followed by parainfluenza and coronavirus. Coronavirus is the most frequent upper respiratory tract infection and is predominant during the winter months.<sup>1</sup>

In a study conducted in Spain, 26% of patients admitted during the flu season presented with COPD as a comorbidity.<sup>2</sup> Other authors have reported a somewhat lower prevalence of COPD in patients with the flu (17.3%) and an even lower prevalence of COPD in patients with RSV infection (7.6%).<sup>3</sup> There are also studies which have evaluated the presence of COPD as a comorbidity in other coronavirus infections such as SARS, with a rate of 6%,<sup>4</sup> and MERS, with a rate of 13%.<sup>5</sup>

In regard to the current SARS-CoV-2 pandemic, it was initially considered that people with chronic lung diseases could be more prone to presenting with symptoms of the

<sup>☆</sup> Please cite this article as: Boixeda R, Campins L, Juanola J, Force L. ¿Es la enfermedad pulmonar obstructiva crónica un factor protector en la infección por SARS-CoV-2? La importancia del tratamiento broncodilatador. *Rev Clin Esp*. 2020;220:526–529.

infection or to developing a more severe infection. However, published case series show a low prevalence of patients with COPD: 6.6% in the United States of America,<sup>6</sup> 3% in Italy,<sup>7</sup> and just 1.4% in China.<sup>8</sup>

This low prevalence could give rise to different interpretations. First, the strict lockdown imposed by public health authorities could explain that these patients, who are supposedly more vulnerable to SARS-CoV-2 infection, had closely followed social distancing protocols, thus decreasing the risk of contact.

Second, there could be a protective effect that is not well established in the physiopathology of chronic respiratory disease, with a different immune response that could prevent infection in these patients or condition milder symptoms. One piece of data in favor of this protection against infection can be concluded from the study by Mehta et al.,<sup>6</sup> which analyzes factors associated with a positive result on a SARS-CoV-2 diagnostic test in a sample of 184,772 people. Of the total number of tests, 1735 (9.4%) were positive whereas in patients with COPD, only 114 (6.4%) were positive ( $p < .001$ ). Therefore, it seems that COPD as a comorbidity is associated with a lower probability of having COVID-19.

Third, it has been hypothesized that baseline inhaled treatments, such as inhaled corticosteroids and bronchodilators, could have a protective effect against SARS-CoV-2 infection. *In vitro* studies on inhaled corticosteroids (budesonide), either alone or in combination with other bronchodilators (glycopyrronium bromide and formoterol), have demonstrated a suppression of HCoV-229E coronavirus replication.<sup>9</sup>

Likewise, another study on inhaled corticosteroids that included just 3 patients, conducted in Japan and without a control group, observed a lower requirement for ventilatory support.<sup>10</sup> On this matter, a systematic review was recently published on the possible protective effect of inhaled corticosteroids; it was unable to establish either a beneficial or detrimental effect of this treatment.<sup>11</sup> Similarly, in an Italian study on a cohort of patients with COVID-19, patients with SARS-CoV-2 infection were compared to the general population. No influence on progress related to either short- or long-term inhaled corticosteroids or beta-adrenergic agonists was noted.<sup>7</sup>

Tiotropium bromide is one of the main treatments for COPD and is usually used in approximately 30% of patients treated in primary care.<sup>12</sup> Recent studies have demonstrated how tiotropium reduces neutrophils and macrophages as well as IL-6 and gamma interferon levels in the airways of rats exposed to tobacco smoke and infected with the A/PR/8/34 (H1N1) influenza virus. The effect was greater than what was observed with fluticasone and roflumilast.<sup>13</sup> This potential anti-inflammatory effect with cytokine inhibition in animal models could explain a greater protective effect of tiotropium versus other inhaled therapies in SARS-CoV-2 infection.

We have analyzed the prevalence of COPD in patients treated for COVID-19 in our center, specifically evaluating their baseline treatment with inhalers as a potential protective factor against SARS-CoV-2 infection.

A retrospective, observational study was carried out in the Mataró Hospital which identified patients hospitalized with a clinical and/or microbiological diagnosis of SARS-CoV-2 from March 10 to April 22, 2020. A diagnosis of COPD was established when the physician had recorded it on the medical record or when a compatible spirometry was available. Treatments with inhaled corticosteroids and anticholinergics were also recorded.

During the study period, 487 patients were identified. Of them, 78 (16%) had a clinical diagnosis and 409 (84%) had a microbiological diagnosis of SARS-CoV-2 infection. Of the patients identified, 62.2% were men. The mean age was  $64.9 \pm 15.1$  years and the overall mortality rate was 20.5%. Of all patients, 25 had a diagnosis of COPD (5.1%), 17 of which (68%) had spirometric confirmation. Within the group of patients with COPD, the mean age was  $72.7 \pm 9.1$  years and they had a greater mortality rate of 44%.

We compared the baseline treatment of patients with COPD in our COVID-19 cohort with other published series of patients with hospital admission due to COPD exacerbation related to other respiratory pathogens or those in stable clinical condition. We did not note any differences in the use of inhaled corticosteroids between both groups. However, the use of tiotropium was significantly lower in patients with COPD who had been hospitalized for COVID-19 in relation to other cohorts of patients with stable COPD and without SARS-CoV-2 infection and controlled in primary care (12% vs. 29.5% and 31.7%,  $p < .03$ ) (Table 1 Table 1).

The analysis of our cohort of patients with SARS-CoV-2 confirms a low prevalence of patients with COPD (5.1%). These patients were older ( $p = .02$ ), had greater mortality ( $p = .03$ ), and there was a low percentage of patients treated with tiotropium ( $p = .034$ ).

Given the discordance in the available information, large studies are needed that evaluate the presence of COPD and baseline treatments as possible protective factors against SARS-CoV-2 infection, with special attention paid to treatment with tiotropium, which appeared to have a protective effect in our study.

Likewise, it seems necessary to evaluate different prognostic factors that allow for confirming whether presence of COPD is associated with a worse disease prognosis or if there are other confounding factors that explain this higher mortality, such as age or the establishment of therapeutic limitations related to the comorbidity itself or the healthcare resources available in the context of a pandemic.

## Appendix A. Members of the COCOHMAT (COhorte COvid del Hospital de MATaró) Group

ABS Cirera-Molins (Joaquim Oyon, Mariona Ferrer, Antonia Llinares, Astrid Arkesteijn, Amaia Erraiz, Tàtiana Rejon, Evora Igual, Mireia Carmona, Axel Muñoz, Patricia Prado, Andrea Ventura), Cardiology Department (Berta Ferreiro), Endocrinology Department (Elena Guanyabens), Pharmacy

**Table 1** Treatment with inhaled corticosteroids and anticholinergics in patients with COPD in series of patients hospitalized due to SARS-CoV-2, severe exacerbation of COPD, and patients in the stable phase (primary care).

	Patients	IC	AC	LTAC	Tiotropium
<i>Severe SARS-CoV-2 infection</i>					
Boixeda et al. (Mataró Hospital)	25	16 (64)	17 (68)	11 (44)	3 (12)*
<i>Severe COPD exacerbation</i>					
Casas-Mendez et al. <sup>14</sup>	465	293 (63)	363 (77.5)	158 (33.9)	–
<i>Stable COPD</i>					
Morros et al. <sup>12</sup>	3837	2224 (57.9)	1763 (45)	–	1134 (29.5)*
De Oliveira et al. <sup>15</sup>	180	167 (92.8)	–	–	57 (31.7)*

The data are shown in absolute values (percentage).

AC: anticholinergics; IC: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease; LTAC: long-term anticholinergics.

\*  $p < .03$ .

Department (Laia Pérez, Azhara Sanchez, Javier Delgado, Marc Bitlloch), Geriatrics Department (Nicolás Morón, Franz Sancho, Adrian Oller, Cristina Borrellas), Hematology Department (Esther Plensa), Internal Medicine Department (Raquel Arànega, Carlos Lopera, Laia Arbonés, Javier Fernández, Ainhoa Rex, Marta Parra, Aleix Serrallonga, María Fernanda Solano, María Larrousse, Montserrat Mauri, Concepció Falgà, Sandra Bacca, Paula Fernández, Laura Pacho, Miquel Martín), Pulmonology Department (Alejandro Robles, Xavier Vilà, Laura Ovejero, Pilar Ortega), Oncology Department (Susana Martínez, Irene Ortiz), Pediatrics Department (Anna Vidal, Pamela Calderón, Julio Baena, Ingrid Badia), Rehabilitation Department (Adrián Ruiz).

## References

- Zwaans WAR, Mallia P, van Winden MEC, Rhode GGU. The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease- A systematic review. *J Clin Virol*. 2014;61:181–8, doi:10.1016/j.jcv.2014.06.025.
- Godoy P, Romero A, Soldevila N, Torner N, Jané M, Martínez A, et al. Influenza vaccine effectiveness in reducing severe outcomes over six influenza season, a case-case analysis, Spain, 2010/11 to 2105/16. *Euro Surveill*. 2018;23(43):pii=1700732.
- Malosh RE, Martin ET, Callear AP, Petrie JG, Luring AS, Lamerato L, et al. Respiratory syncytial virus hospitalization in middle-aged and older adults. *J Clin Virol*. 2017;96:37–43, doi:10.1016/j.jcv.2017.09.001.
- Chen CY, Lee CH, Liu CY, Wang JH, Wang LM, Perng RP. Clinical features and outcomes of severe acute respiratory syndrome and predictive factors respiratory distress syndrome. *J Chin Med Assoc*. 2005;68(1):4–10.
- Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk factors for primary Middle East Respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. *Emerg Infect Dis*. 2016;22(1):49–55, doi:10.3201/eid2201.151340.
- Mehta N, Kalra A, Nowacki AS, Anjewierden S. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020, published online May 5. doi:10.1001/jamacardio.2020.1855.
- Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med*. 2020;382:2431–40, doi:10.1056/NEJMoa2006923.
- Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Akdis CA, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020;00:1–12, doi:10.1111/all.14238.
- Yamaya M, Nishimura H, Deng X, Sugawara M, Watanabe O, Nomura K, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus RNA replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. *Respir Investig*. 2020;58(3):155–68, doi:10.1016/j.resinv.2019.12.005.
- Iwabuchi K, Yoshie K, Kurakami Y, Takahashi K, Kato Y, Morishima T. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia. Report of three cases. *J Infect Chemother*. 2020;26(6):625–32, doi:10.1016/j.jiac.2020.04.007.
- Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systemic review and clinical perspective. *Eur Respir J*. 2020, doi:10.1183/13993003.01009-2020, in press.
- Morros R, Vedia C, Giner-Soriano M, Casellas A, Armado E, Baena JM. Neumonías adquiridas en la comunidad en pacientes con enfermedad obstructiva crónica tratados con corticoides inhalados u otros broncodilatadores. Estudio PNEUMOCORT. *Aten Primaria*. 2019;51(6):333–40, doi:10.1016/j.aprim.2018.02.007.
- Bucher H, Duechs MJ, Tilp C, Jung B, Erb KJ. Tiotropium attenuates virus-induced pulmonary inflammation in cigarette smoke-exposed mice. *J Pharmacol Exp Ther*. 2016;357:606–18, doi:10.1124/jpet.116.232009.
- Casas-Mendez F, Abadías MJ, Yuguero O, Bardés I, Barbé F, de Batlle J. Treatment strategies after acute exacerbations of chronic obstructive pulmonary disease: Impact on mortality. *PLoS ONE*. 2018;13(12):e0208847, https://doi.org/10.1371/journal.pone.0208847.
- De Oliveira JCM, de Carvalho Aguiar I, de Oliveira Beloto ACN, Santos IR, Leitão Filho FS, Malosa Sampaio LM, et al. Clinical significance in COPD patients followed in a real practice. *Multidisciplinary Respiratory Medicine*. 2013;8:43, doi:10.1186/2049-6958-8-43.

R. Boixeda<sup>a,b,c,\*</sup>, L. Campins<sup>d</sup>, J. Juanola<sup>b,e,f</sup>, L. Force<sup>a,f</sup>, on behalf of the COCOHMAT group<sup>1</sup>

<sup>a</sup> Servicio de Medicina Interna, Hospital de Mataró, Consorci Sanitari del Maresme (CSDM), Mataró, Barcelona, Spain

<sup>b</sup> Grup d'Estudi al Maresme de la Pneumònia Adquirida en la Comunitat i la MPOC (GEMP@C), Mataró, Barcelona, Spain

<sup>c</sup> *Universidad de Barcelona, CIBERES Barcelona, Barcelona, Spain*

<sup>d</sup> *Servicio de Farmacia, Hospital de Mataró, CSDM, Mataró, Barcelona, Spain*

<sup>e</sup> *Servicio de Neumología, Hospital de Mataró, CSDM, Mataró, Barcelona, Spain*

<sup>f</sup> *Escola de Ciències de la Salut, Tecnocampus, Universitat Pompeu Fabra, Barcelona, Spain*

\* Corresponding author.

*E-mail addresses:* [rboixeda@cscdm.cat](mailto:rboixeda@cscdm.cat), [rboixeda@ub.edu](mailto:rboixeda@ub.edu) (R. Boixeda).

<sup>1</sup> In Appendix A the remaining members of the COCOHMAT (COhort COvid of the Hospital de MATaró) group are listed.

2254-8874/ © 2020 Elsevier España, S.L.U. and Sociedad Española de Medicina Interna (SEMI). All rights reserved.

## COVID-19 in healthcare workers at the Olot Regional Hospital (Girona)<sup>☆</sup>



### COVID-19 en trabajadores sanitarios del Hospital comarcal de Olot (Girona)

Dear Director,

Spain is the country with the most healthcare professionals (HP) affected by the coronavirus 2019 disease (COVID-19) in the world. A report from April 2020 by the European Centre for Disease Prevention and Control notes that 20% of COVID-19 cases in Spain affected this group whereas in Italy, the percentage was 10% and in the United States of America and China, it was 3% and 3.8%, respectively.<sup>1</sup> As of May 14, 2020, a total of 236,611 COVID-19 cases had been reported to the National Epidemiological Surveillance Network, of which 39,349 corresponded to HP.<sup>2</sup>

An observational, prospective study was performed on COVID-19 infections among HP at the Olot Regional Hospital of La Garrotxa (ORHG), a regional hospital in Girona with 136 hospitalization beds in 4 units: units 3 and 4 (U3/U4) with 64 beds for acute patients, and units 1 and 2 (U1/U2) with 72 beds for chronic/community healthcare. U3 was isolated and destined exclusively for the care of COVID-19 patients.

All HP in the hospital were included in the study; only those who did not provide consent were excluded. In a first period (starting on March 11, 2020, when the first case of COVID-19 was diagnosed in the hospital), all HP with symptoms were attended to in the Occupational Health Department in order to diagnose COVID-19. In a second period (starting April 21, 2020, when the last COVID-19 cases were diagnosed in HP), a PCR test was given to HP who did not present with symptoms or who tested negative in the first period.

To diagnose COVID-19, confirmation by means of a positive PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in nasopharyngeal smear samples was required. For the serologic tests, capillary blood sam-

ples were used (rapid detection of SARS-CoV-2 antibodies by means of immunochromatography).

The Ethics Committee of the Dr. Josep Trueta University Hospital of Girona approved the study and informed consent was obtained from all participants.

Of a total of 493 HP, 198 (40.1%) consulted with the Occupational Health Department. Of those, 81 (16.4% of the staff) were diagnosed with COVID-19 (Table 1). The majority were women (median age of 43 years) in professional categories in direct contact with patients, particularly nurses and nursing aides, and most (52%) worked in U1/U2 (chronic/community healthcare). The majority of HP consulted for respiratory symptoms, but they also presented with other symptoms (the most frequent were headache and abnormalities in taste or smell). Three HP required hospital admission due to pneumonia, one of which required treatment in the ICU with intubation and mechanical ventilation. Progress was favorable in all cases. The majority had a negative PCR test at 14 days, but in nearly a third, it took 21, 28, or up to 35 days for them to test negative.

The second period included 412 HP: 117 who had symptoms during the first period but had a negative PCR test and 295 who did not have symptoms. Seventy-seven could not or did not want to participate in the study and the remaining 345 underwent PCR and serologic tests. 100% of the PCR tests were negative and in 28 cases (8.1%), the serologic tests were positive (6 cases for IgM, 11 cases for IgG, and 11 cases for both).

The majority of the HP affected by COVID-19 were women, with a median age of 43 years, a characteristic similar to the few COVID-19 series in HP reported in other countries such as the United States of America,<sup>3,4</sup> China,<sup>5</sup> and Holland.<sup>6</sup> As in these series, the majority presented with respiratory symptoms. Furthermore, a non-negligible proportion of cases also experienced other symptoms, such as headache or digestive abnormalities.<sup>4,6</sup> 53% of cases reported abnormalities in taste or smell. This percentage is much higher than in other series on HP with COVID-19 (7%–16%),<sup>4,6</sup> but is similar to the rate found in a study on the prevalence of these symptoms in mild cases of COVID-19.<sup>7</sup>

The majority of cases were mild and there was only one ICU admission. Nevertheless, the mortality rate due to COVID-19 in HP reported to date is 49 cases in

<sup>☆</sup> Please cite this article as: Trullàs JC, Vilardell I, Blasco M, Heredia J. COVID-19 en trabajadores sanitarios del Hospital comarcal de Olot (Girona). *Rev Clin Esp.* 2020;220:529–531.