

Research Article

Assessing the impact of long-term inhaled corticosteroid therapy on patients with COVID-19 and coexisting chronic lung disease: A multicenter retrospective cohort study

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Abstract

Background

Patients with chronic lung disease (CLD), such as asthma or chronic obstructive pulmonary disease, were expected to have an increased risk of clinical manifestations and severity of COVID-19. However, these comorbidities have been reported less frequently than expected. Chronic treatment with inhaled corticosteroids (ICS) may impact the clinical course of COVID-19. The main objective of this study is to know the influence of chronic treatment with ICS on the prognosis of COVID-19 hospitalized patients with CLD.

Methods

A multicenter retrospective cohort study was designed, including patients hospitalized with COVID-19. Epidemiological and clinical data were collected at admission and at seven days, and clinical outcomes were collected. Patients with CLD with and without chronic treatment with ICS were compared.

Results

Two thousand five hundred ninety-eight patients were included, of which 1,171 patients had a diagnosis of asthma and 1,427 of COPD (53.37% and 41.41% with ICS, respectively). No differences were found in mortality, transfer to ICU, or development of moderate-severe ARDS. Patients with chronic ICS had a longer hospital stay in both asthma and COPD patients (9 vs. 8 days, $p = 0.031$ in asthma patients), (11 vs. 9 days, $p = 0.018$ in COPD patients); although they also had more comorbidity burden.

Conclusions

Patients with chronic inhaled corticosteroids had longer hospital stays and more chronic comorbidities, measured by the Charlson comorbidity index, but they did not have more

severe disease at admission, evaluated with qSOFA and PSI scores. Chronic treatment with inhaled corticosteroids had no influence on the prognosis of patients with chronic lung disease and COVID-19.

INTRODUCTION

SARS-CoV-2 develops a respiratory disease with systemic involvement.¹ Severity of the disease is variable; in a Chinese study with 72314 cases² including outpatients and patients admitted to hospital, 14% had severe pneumonia, and 5% were critical cases. Also, another Chinese study¹ reported that 15-20% of the inpatients required ventilatory support. Overall mortality has been reported from 21 to 28% in hospitalized patients,^{3,4} and it rises to 61.5 to 62% in patients in an Intensive Care Unit (ICU)^{4,5}

Patients with chronic lung diseases (CLD), particularly chronic obstructive pulmonary disease (COPD) and asthma, would be expected to be at increased risk of SARS-CoV-2 infection and more severe COVID-19 course.⁶⁻¹² However, none of these diseases are main comorbidities in patients with COVID-19.^{6,13} Only 0.95% - 5.1% of admitted patients with COVID-19 had a CLD.^{14,15} A study reported a lower risk of hospital admission for COVID-19 in patients with COPD and asthma.¹⁶

It has been hypothesized that chronic inhaled corticosteroids (ICS) could affect the development of SARS-CoV-2 infection.^{6,15} In patients with COPD and asthma, ICS has been associated with an increased risk of upper respiratory infections, and ICS has been associated with a higher prevalence of pneumonia.¹⁷ Furthermore, in-vitro models suggest that ICS could delay virus clearance.¹⁷ In contrast, ICS alone or in combination with bronchodilators has been shown to suppress coronavirus replication and cytokine production in HCoV-229 coronavirus infection in in-vitro models.¹⁸ Moreover, ciclesonide suppresses viral replication of SARS-CoV-2 in-vitro, ICS downregulates the SARS-CoV-2 receptor ACE2 in-vitro in COPD patients, and long-term use of inhaled corticosteroids for controlling asthma is likely to have a beneficial modulatory effect on COVID-19.¹⁹⁻²¹

Taking into account the contradictory data on the possible benefits^{6,14-16,18-21} or harms^{6,17} of inhaled corticosteroids (which are administered worldwide to the majority of asthmatic and COPD patients¹⁶) on the prognosis of COVID-19, we have carried out this study to investigate the influence that chronic ICS may have on the prognosis of COVID-19 hospitalized patients with CLD.

METHODS

STUDY DESIGN AND PARTICIPANTS

This is a multicenter retrospective cohort study of patients with SARS-CoV2 infection, aged ≥ 18 years, who were hospitalized between March and September 2020 in Spain and included in the SEMI-COVID-19 Network.³ The registry is an initiative of the Spanish Society of Internal Medicine (SEMI, for its initials in Spanish), which included 17,416 cases by September 2020, and its characteristics have been

described elsewhere.^{3,12} Data are collected retrospectively and include epidemiological and clinical characteristics, such as comorbidities, symptoms, physical examination findings, laboratory and diagnostic imaging test results, and clinical outcomes. STROBE Statement Guidelines were followed in the study's design and reporting.

DEFINITIONS AND DATA SOURCE

COVID-19 was defined as compatible symptoms and a positive result on either polymerase chain reaction (PCR) of a nasopharyngeal sample or serology test for SARS-CoV-2. Chronic lung disease (CLD) was defined as an antecedent of COPD or asthma diagnosed by pulmonary function tests or clinical criteria of chronic bronchitis. Clinical criteria of chronic bronchitis is clinically characterized by a persistent cough lasting at least three months over two or more consecutive years.²² These changes significantly impair lung compliance and pulmonary function.^{23,24} Chronic bronchitis is associated with a diminished quality of life, a more rapid decline in lung function, increased frequency of exacerbations, and a higher risk of mortality, as highlighted in research by Kim et al. in 2016 and 202.^{25,26} Pulmonary function tests are used in the evaluation, classification and grading of a variety of forms of lung diseases with the performance of basic spirometry with or without other additional tests such as spirometry before and after a bronchodilator, lung volumes and quantification of carbon monoxide diffusing capacity. Chronic ICS use was retrieved from electronic medical records. Patients with a long-term prescription written in the past 12 months were included. Fever was considered as an axillary temperature of 38°C or more.³

OUTCOME MEASURES

The primary outcome of this study was in-hospital mortality. Secondary outcomes were the development of moderate-severe Acute Respiratory Distress Syndrome (ARDS) according to the Berlin 2012 criteria,²⁷ transfer to an ICU, requirement of invasive mechanical ventilation, and length of stay (LOS).

The increase of inflammatory parameters (c-reactive protein, ferritin, interleukin 6, D-Dimer, lymphocyte, lactate dehydrogenase and fibrinogen) were also analyzed, comparing their values at admission and on day +7 of hospitalization and comparing the difference of medians.

STATISTICAL ANALYSIS

Continuous variables were expressed by mean, standard deviation (SD) or median, and interquartile range (IQR). Categorical variables were summarized in terms of frequencies and percentages. Differences between groups were determined using the chi-square test or Fisher's exact test for categorical variables; the Mann-Whitney U test, Student's

t-test or analysis of variance were used for continuous variables, as appropriate. *P* values <0.05 were considered statistically significant. Cases with missing data were excluded from the analysis. The SPSS statistical package version 22.0 (SPSS, Chicago, IL) was used.

ETHICAL ASPECTS

Scientific and ethical permission to conduct this study was obtained from the Provincial Research Ethics Committee of Málaga (Spain). Personal data were processed in strict compliance with Spanish Law 14/2007 on Biomedical Research; Regulation (EU) 2016/679 of the European Parliament and of the Council of April 2016 on the protection of natural persons concerning the processing of personal data and on the free movement of such data (General Data Protection Regulation); and Spanish Organic Law 3/2018 on Personal Data Protection and the Guarantee of Digital Rights.

RESULTS

Of the 17,416 patients included in the SEMI-COVID Network by September 2020, 2,598 patients had CLD, of which 1,171 patients had a diagnosis of asthma and 1,427 of COPD (see [Figure 1](#)). The mean age was 76.7 years (IQR 69.7–83.9) in COPD patients and 65.6 years (IQR 52.6–76.8) in patients with asthma. Both asthma patients with ICS and COPD patients with ICS had a significantly higher mean age [(asthma patients: 66.6 years vs. 63.4 years, $p < 0.001$), (COPD patients: 77.5 years vs. 76.6 years, $p = 0.009$)]. 79.1% of COPD patients were male, and 40.2% of asthma patients were male. Most of the patients (66.8% asthma patients and 94.5% COPD patients) had an adjusted Charlson Comorbidity Index of 3 or more points, being more frequent in those with ICS [(72.2% vs. 60.6%, $p < 0.001$ in asthma patients); (96.1% vs. 93.3%, $p = 0.025$ in COPD patients)]. The most frequent comorbidities in asthma patients were hypertension (47.4%), diabetes (15%) and heart failure (6.7%). In comparison, the most frequent comorbidities in COPD patients were hypertension (67.6%), cancer (31.6%) and diabetes (28.2%). In COPD patients, the severity of the condition was assessed with FEV1. As may be expected, patients with ICS had a more severe COPD. Other epidemiological characteristics of the patients may be seen in [Table 1](#).

The most frequent symptoms in chronic respiratory patients triggered by the COVID-19 infection were dyspnea (70.9% and 71.3% in asthma and COPD patients, respectively), fever (62.4% in asthma patients and 52.9% in COPD patients) and dry cough (59.9% in asthma patients and 48.5% in COPD patients). Dry cough was significantly more frequent in patients without ICS [(59.4% vs. 60.6%, $p = 0.001$ in asthma patients), (45.2% vs. 50.8%, $p = 0.006$ in COPD patients)]. In comparison, productive cough was significantly more frequent in patients with ICS [(23.1% vs. 15.6%, $p < 0.001$ in asthma patients), (29.6% vs. 22.2%, $p = 0.006$ in COPD patients)]. Dyspnea was more frequent in patients with ICS, being statistically significant in COPD patients (76.1% vs. 67.9%, $p = 0.001$). At lung auscultation, wheezing and roncus were more frequent in both asthma

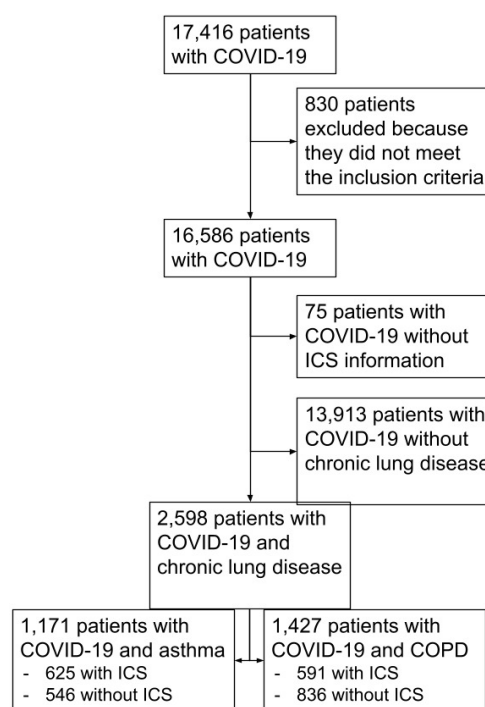


Figure 1. Flowchart of patients with COVID-19 included in the SEMI-COVID Network with chronic lung disease.

and COPD patients with ICS. Other clinical data are shown in [Table 2](#).

Regarding the inflammatory parameters ([Table 3](#)), there was a significant decrease in CRP and IL6 in all groups, except in COPD patients with ICS, where the decrease was not statistically significant ($p = 0.087$). Ferritin increased in all groups but was statistically significant only in COPD patients (with ICS $p = 0.001$, without ICS $p = 0.003$). D-dimer also increased in all groups but was not statistically significant in COPD patients with ICS ($p = 0.062$). Lymphocytes increased in asthma patients (statistically significant in asthma patients with ICS, $p = 0.041$) and decreased in COPD patients (statistically significant in COPD patients without ICS, $p = 0.045$).

Patients with chronic ICS had a longer hospital stay in asthma and COPD patients (9 vs. 8 days, $p = 0.031$ in asthma patients), (11 vs. 9 days, $p = 0.018$ in COPD patients). No differences were found in-hospital mortality, transfer to ICU, or the development of moderate-severe ARDS ([Table 4](#)).

DISCUSSION

In our study, we aimed to investigate the influence of chronic treatment with ICS on the prognosis of COVID-19 hospitalized patients with CLD. We found that patients with COVID-19 and chronic ICS did have more dyspnea and productive cough at admission, as well as a longer hospital stay. Chronic treatment with ICS in patients with asthma and COPD did not influence in-hospital mortality or other prognostic factors such as transfer to ICU, development of

Table 1. Epidemiological characteristics of patients diagnosed with COVID-19 with asthma and chronic obstructive pulmonary disease according to chronic treatment with or without inhaled corticosteroids.

	Asthma				COPD			
	Total (n = 1171)	With ICS (n = 625)	Without ICS (n = 546)	p	Total (n = 1427)	With ICS (n = 591)	Without ICS (n = 836)	p
Age (years, Median [IQR])	65.6 [52.6-76.8]	66.6 [56.8-77.3]	63.4 [47.3-76.3]	<0.001	76.7 [69.7-83.9]	77.5 [70.2-84.4]	76.6 [70.4-83.1]	0.009
Sex (male), n (%)	471 (40.2)	252 (40.3)	219 (40.1)	0.952	1128 (79.1)	469 (79.4)	659 (78.8)	0.895
Active smokers, n (%)	56 (4.8)	30 (4.8)	26 (4.8)	0.958	196 (13.7)	71 (12)	125 (14.9)	0.118
Former smokers, n (%)	261 (22.3)	162 (25.9)	99 (18.1)	0.001	888 (62.2)	392 (66.3)	496 (59.3)	0.009
Moderate-severe dependence, n (%)	123 (10.5)	57 (9.1)	66 (12.1)	0.145	333 (23.3)	137 (23.2)	196 (23.4)	0.222
Charlson ≥ 3 , n (%)	782 (66.8)	451 (72.2)	331 (60.6)	<0.001	1348 (94.5)	568 (96.1)	780 (93.3)	0.025
FEV ₁ , mean (SD)	-	-	-	-	58.6 (17.9)	57.5 (17.8)	61.6 (17.9)	0.008
Hypertension, n (%)	555 (47.4)	317 (50.7)	238 (43.6)	0.014	964 (67.6)	414 (70.1)	550 (65.8)	0.079
Diabetes mellitus type 2, n (%)	176 (15)	90 (14.4)	86 (15.8)	0.566	403 (28.2)	176 (29.8)	227 (26.4)	0.283
Heart failure, n (%)	78 (6.7)	44 (7.1)	34 (6.2)	0.639	244 (17.1)	107 (18.1)	137 (16.4)	0.393
Stroke, n (%)	14 (1.2)	3 (0.5)	11 (2)	0.027	51 (3.6)	15 (2.5)	36 (4.3)	0.078
Moderate-severe chronic kidney disease, n (%)	48 (4.1)	26 (4.2)	22 (4)	0.910	168 (11.8)	67 (11.3)	101 (12.1)	0.739
Cancer, n (%)	49 (4.2)	24 (3.8)	25 (4.6)	0.561	154 (10.8)	65 (11)	89 (10.6)	0.863
Dementia, n (%)	63 (5.4)	28 (4.5)	35 (6.4)	0.155	162 (11.4)	64 (10.8)	98 (11.7)	0.612
qSOFA	83 (7.1)	40 (6.4)	43 (7.9)	0.306	221 (15.5)	89 (15.1)	132 (15.8)	0.656
CURB65	395 (33.7)	223 (35.7)	172 (31.5)	0.190	952 (66.7)	417 (70.6)	535 (64)	0.030
PSI IV-V	96 (8.2)	44 (7)	52 (9.5)	0.110	323 (22.6)	139 (23.5)	184 (22)	0.745

COPD, Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; IQR, interquartile range; FEV₁, Forced Expiratory Volume in the 1st second; SD, standard deviation; qSOFA, Quick Sequential Organ Failure Assessment; CURB65, Confusion, Uremia, Respiratory rate, Blood pressure, age ≥ 65 ; PSI IV-V, Pneumonia Severity Index.

moderate-severe ARDS or requirement of invasive mechanical ventilation.

At the beginning of the SARS-CoV-2 pandemic, it was suggested that patients with CLD could have a worse prognosis.¹¹ Influence of chronic ICS was controversial since its use is a known risk factor for pneumonia,^{28,29} but it was also suggested that it may improve prognosis due to its inhibition of viral replication.¹⁹ The STOIC and PRINCIPLE trials published later showed that inhaled budesonide in outpatients reduced time to recovery after early COVID-19, and a recently published clinical trial suggests that using inhaled budesonide may reduce the risk of worsening in hospitalized patients with COVID-19 pneumonia.^{30,31}

In our results, patients treated with chronic corticosteroid therapy (both asthma and COPD) had a higher mean age and more comorbidities, just as was inferred in other articles, compared to patients without ICS. Patients with CLD treated with chronic ICS did not have more severe disease at admission, according to qSOFA and CURB-65,

despite having more comorbidities (Charlson ≥ 3 83.8%). In addition, the severity of COPD (assessed with FEV₁) was associated with an increased use of inhaled corticosteroids, as expected.^{32,33}

Asthma and COPD patients treated with chronic ICS did not have higher in-hospital mortality, coinciding with other studies,^{17,29,34} nor had higher rates of moderate-severe ARDS, transfer to ICU or requirement of invasive mechanical ventilation. Similar results were found by Sen P. et al. in patients with COPD who tested positive for COVID-19.³⁵ However, both asthma and COPD patients treated with ICS had a longer hospital stay. The fact that these patients had a longer hospital stay could be due to factors such as older age and comorbidity measured with the Charlson comorbidity index.

In our study, patients with CLD treated with chronic ICS had a more frequently productive cough, as suggested by Hasan et al. in a study that associates ICS with the risk of respiratory infection.²⁸

Table 2. Clinical characteristics of patients diagnosed with COVID-19 with asthma and chronic obstructive pulmonary disease according to chronic treatment with or without inhaled corticosteroids.

	Asthma				COPD			
	Total (n = 1171)	With ICS (n = 625)	Without ICS (n = 546)	p	Total (n = 1427)	With ICS (n = 591)	Without ICS (n = 836)	p
Dry cough, n (%)	702 (59.9)	371 (59.4)	331 (60.6)	0.001	692 (48.5)	267 (45.2)	425 (50.8)	0.006
Productive cough, n (%)	229 (19.6)	144 (23.1)	85 (15.6)	<0.001	361 (25.3)	175 (29.6)	186 (22.2)	0.016
Arthromyalgia, n (%)	384 (32.8)	206 (33)	178 (32.6)	0.851	314 (22)	127 (21.5)	187 (22.4)	0.746
Ageusia, n (%)	109 (9.3)	50 (8)	59 (10.8)	0.158	56 (3.9)	18 (3)	38 (4.5)	0.168
Anosmia, n (%)	79 (6.7)	36 (5.8)	43 (7.9)	0.200	53 (3.7)	18 (3)	35 (4.2)	0.320
Asthenia, n (%)	528 (45.1)	279 (44.6)	249 (45.6)	0.991	586 (41.1)	252 (42.6)	334 (40)	0.297
Anorexy, n (%)	192 (16.4)	105 (16.8)	87 (15.9)	0.635	263 (18.4)	104 (17.6)	159 (19)	0.578
Pharyngodynia, n (%)	114 (9.7)	59 (9.4)	55 (10.1)	0.844	119 (8.3)	51 (8.6)	68 (8.1)	0.770
Headache, n (%)	165 (14.1)	95 (15.2)	70 (12.8)	0.207	93 (6.5)	34 (5.8)	59 (7)	0.330
Febricula (T ^a 37.5-38°C), n (%)	251 (21.4)	140 (22.4)	111 (20.3)	0.414	332 (23.3)	153 (25.9)	179 (21.4)	0.250
Fever (T ^a > 38°C), n (%)	731 (62.4)	389 (62.2)	342 (62.6)	0.988	755 (52.9)	305 (51.6)	450 (53.8)	0.120
Dyspnea, n (%)	830 (70.9)	458 (73.3)	372 (68.1)	0.061	1018 (71.3)	450 (76.1)	568 (67.9)	0.001
Confusion, n (%)	89 (7.6)	42 (6.7)	47 (8.6)	0.226	243 (17)	100 (16.9)	143 (17.1)	0.886
Tachypnea (>20 bpm), n (%)	372 (31.8)	195 (31.2)	177 (32.4)	0.613	659 (46.2)	279 (47.2)	380 (45.5)	0.703
Crackles, n (%)	564 (48.2)	301 (48.2)	263 (48.2)	0.972	779 (54.6)	313 (52.9)	466 (55.7)	0.380
Wheezing, n (%)	221 (18.9)	139 (22.2)	82 (15)	0.002	212 (14.9)	117 (19.8)	95 (11.4)	<0.001
Roncus, n (%)	160 (13.7)	103 (16.5)	57 (10.4)	0.003	354 (24.8)	174 (29.4)	180 (21.5)	0.001

COPD, Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; bpm, breaths per minute; T^a, temperature.

It has been suggested that chronic ICS may reduce the inflammation produced by SARS-CoV-2.^{17,19,21} We analyzed the evolution of inflammatory parameters of these patients during admission and observed that chronic ICS did not have an influence. To our knowledge, this is the first multicenter study that evaluates the evolution of these parameters, which have been related to poor prognosis in COVID-19,³⁶ in patients with chronic ICS.

The main strength of this study is its multicenter, nationwide design and the large number of patients included. The main limitation is that only inpatients were included; therefore, the results may be different for outpatients. Another important limitation is that the different types of ICS were not analyzed separately, so their different degrees of systemic effects could influence the results. Because of the study's retrospective design, some patients had incomplete information regarding their use of inhaled corticosteroids; these patients were not included, as described in the flow chart (Figure 1). It should be taken into account that the study was developed during the first and second waves of COVID-19 in Spain with different strains of SARS-CoV-2

than from those currently existing and without any vaccination.

The outcomes of this study support the maintenance of ICS in patients admitted for COVID-19. Despite its limitations, its results are very useful in clinical practice since the patients in this study have epidemiological characteristics similar to those in subsequent pandemic waves.³⁷

CONCLUSIONS

Patients with chronic inhaled corticosteroids had longer hospital stay and more chronic comorbidities, measured by the Charlson comorbidity index, but they did not have more severe disease at admission, evaluated with qSOFA and PSI scores. Chronic treatment with ICS had no influence on the prognosis of patients with chronic lung disease and COVID-19.

Table 3. Variation of inflammatory parameters in patients with asthma and chronic obstructive pulmonary disease admitted to hospital due to COVID-19 according to chronic treatment with or without inhaled corticosteroids.

			At admission	At 7 days control	p
Asthma	With ICS	CRP	54 [19-128]	21 [6-68]	<0.001
		Ferritin	462 [200-930]	531 [243-1004]	0.065
		IL-6	26.1 [9.7-62.9]	16 [4.2-60]	0.003
		D-dimer	620 [336-940]	666 [356-1206]	<0.001
		Lymphocytes	990 [700-1300]	1120 [720-1580]	0.041
	Without ICS	CRP	52 [16-113]	20 [5-57]	<0.001
		Ferritin	475 [186-899]	538 [228-948]	0.066
		IL-6	24.8 [5.5-59.9]	10.2 [2.1-35]	<0.001
		D-dimer	520 [289-1085]	598 [338-1254]	0.016
		Lymphocytes	1030 [770-1400]	1200 [800-1700]	0.083
COPD	With ICS	CRP	78 [26-152]	40 [10-128]	<0.001
		Ferritin	547 [248-1047]	691 [350-1178]	0.001
		IL-6	24.1 [11.4-52]	16.5 [5.1-45.4]	0.087
		D-dimer	818 [408-1375]	831 [434-1625]	0.062
		Lymphocytes	890 [590-1200]	840 [542-1037]	0.085
	Without ICS	CRP	76 [23-147]	35 [11-118]	<0.001
		Ferritin	493 [256-979]	611 [287-1283]	0.003
		IL-6	32.1 [15.1-86.6]	24.5 [9.6-81]	0.031
		D-dimer	835 [480-1434]	900 [461-1913]	0.001
		Lymphocytes	820 [560-1220]	733 [533-1000]	0.045

COPD, Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; CRP, c-reactive protein; IL-6, Interleukin 6.

Table 4. Prognostic factors of patients with a history of asthma and COPD diagnosed with COVID-19 according to chronic treatment with or without inhaled corticosteroids

	Asthma				COPD			
	Total (n = 1171)	With ICS (n = 625)	Without ICS (n = 546)	p	Total (n = 1427)	With ICS (n = 591)	Without ICS (n = 836)	p
In-hospital mortality, n (%)	166 (14.2)	87 (13.9)	79 (14.5)	0.802	525 (36.8)	233 (39.4)	292 (34.9)	0.084
Moderate-severe ARDS, n (%)	260 (22.2)	137 (21.9)	123 (22.5)	0.778	526 (36.9)	233 (39.4)	293 (35)	0.106
Sepsis, n (%)	60 (5.1)	32 (5.1)	28 (5.1)	0.983	117 (8.2)	50 (8.5)	67 (8)	0.770
Pulmonary thromboembolism, n (%)	22 (1.9)	13 (2.1)	9 (1.6)	0.744	21 (1.5)	6 (1)	15 (1.8)	0.324
Transfer to ICU, n (%)	126 (10.8)	63 (10.1)	63 (11.5)	0.450	102 (7.1)	38 (6.4)	64 (7.7)	0.405
Invasive mechanical ventilation, n (%)	100 (8.5)	52 (8.3)	48 (8.8)	0.754	79 (5.5)	30 (5.1)	49 (5.9)	0.558
Non-invasive mechanical ventilation, n (%)	66 (5.6)	34 (5.4)	32 (5.9)	0.800	135 (9.5)	70 (11.8)	65 (7.8)	0.013
Hospital stay (days), Median [IQR]	9 [5-13]	9 [6-14]	8 [5-12]	0.031	9 [5-16]	11 [6-17]	9 [5-15]	0.018

COPD, Chronic Obstructive Pulmonary Disease; ICS, inhaled corticosteroids; ARDS, Acute Respiratory Distress Syndrome; ICU, Intensive Care Unit; IQR, interquartile range.

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ETHICAL APPROVAL

Scientific and ethical permission to conduct this study was obtained from the Provincial Research Ethics Committee of Málaga (Spain).

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form and declare no conflict of interest.

AI STATEMENT

The authors confirm no generative AI or AI-assisted technology was used to generate content.

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