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ORIGINAL RESEARCH

Impact of Dexamethasone on Respiratory Sequelae in the Follow-Up of Hospitalized Patients with Sars-Cov-2 Pneumonia

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Introduction: Dexamethasone has been shown to reduce 28-day mortality in COVID-19 patients requiring oxygen, but its effect on long-term pulmonary complications remains unclear. This study aimed to assess whether treatment with dexamethasone in the acute phase of SARS-CoV-2 pneumonia improves post-COVID clinical outcomes.

Methods: This longitudinal retrospective study analysed patients hospitalized for SARS-CoV-2 pneumonia between March 2020 and April 2021. Patients were stratified according to dexamethasone treatment during hospitalization. They were evaluated 3–9 months post- discharge using clinical assessments, pulmonary function tests, and imaging studies. We compared the demographic, clinical, and functional characteristics according to dexamethasone treatment. Multivariate linear and logistic regression models were used to assess the association between dexamethasone and main outcome follow-up variables.

Results: In a study of 1,011 patients hospitalized for SARS-CoV-2 pneumonia, 663 received dexamethasone treatment while 348 did not. During post-COVID follow-up, dexamethasone-treated patients reported less dyspnea (28.4% vs 37.6%, p=0.003); showed better lung function, particularly in DLCO (76.9% vs 69.9%, p<0.001), and better performance in the 6-minute walk test (435 meters vs 405 meters, p=0.002) Radiologically, these patients had lower degrees of reticulation (4,4% vs 9,5%; p=0,009), septal thickening (5,8% vs 10,5%; p=0,012) and fibrosis (3,5% vs 15,6%; p=<0,001). Although rates of bronchial involvement were similar, dexamethasone-treated patients had less bronchiolitis but more bronchiectasis and bronchial thickening. Dexamethasone treatment increased DLCO by 9.25 points (95% CI: 0.50–18.00; p=0.038) and significantly reduced the risk of fibrosis (OR=0.24; 95% CI: 0.12–0.49) in multivariate analysis.

Conclusion: Patients treated with dexamethasone showed improved post-COVID respiratory outcomes, including less dyspnea, better lung function, and fewer signs of fibrosis. These findings suggest that dexamethasone is associated with improved outcomes after severe COVID-19 pneumonia.

Keywords: long-term complications, lung fibrosis, dyspnea, COVID-19

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the etiological agent responsible for coronavirus disease 2019 (COVID-19), caused by zoonotic transmission in late 2019 in Wuhan.[1] While many cases are mild or asymptomatic a proportion of patients develop SARS-CoV-2 pneumonia that requires hospital care; this can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support.[2] Initially, no effective treatments for COVID-19 were known; various treatment modalities were applied, many of them based on expert recommendations or prior experience in treating similar illnesses. The use of corticosteroids was one of the first

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treatments investigated, but the results it yielded were controversial. Some studies suggested that corticosteroid use might not be the most suitable strategy,[3] but others argued that, given the intense inflammatory response associated with SARS-CoV-2 pneumonia, it might constitute a valid therapeutic option, complementing other treatments such as antivirals.[4,5]

In July 2020, a meta-analysis of ongoing clinical trials concluded that the administration of systemic corticosteroids was associated with reduced 28-day all-cause mortality compared to usual care or placebo.[6] A later clinical trial demonstrated that dexamethasone is an effective treatment for patients with SARS-CoV-2 pneumonia requiring oxygen therapy or other ventilatory support, who presented lower mortality at 28 days than those who did not receive this drug.[6] Therefore, treatment with dexamethasone represented a significant change in the management of SARS-CoV-2 pneumonia in patients with oxygen therapy requirements.

However, after the acute phase, many patients develop pulmonary complications during follow-up. Recent evidence indicates that a significant proportion of COVID-19 survivors experience persistent respiratory sequelae, such as diffusion impairment and fibrotic changes lasting up to one year. The emergence of post-COVID interstitial lung disease (ILD) further underscores the need to understand long-term pulmonary consequences and potential irreversible damage[7,8] Although dexamethasone has demonstrated beneficial effects during the acute phase of severe COVID-19, evidence regarding its long-term impact on respiratory sequelae remains scarce A study published in the United Kingdom, evaluated health-related quality of life (HRQoL) before hospitalization and one year after discharge, and showed that systemic corticosteroid treatment for acute COVID-19 was unable to mitigate the significant reduction in HRQoL one year after hospital discharge.[9] To date, however, no studies have specifically evaluated long-term respiratory sequelae in relation to acute dexamethasone treatment.

The aim of this study was to compare post-COVID respiratory outcomes (lung function, imaging findings, and dyspnea) in patients with severe COVID-19 pneumonia who received dexamethasone during the acute phase with those not treated with corticosteroids during the earlier stages of the pandemic, in order to determine whether dexamethasone is associated with improved respiratory sequelae during follow-up.

Methods

Patients and Design

A longitudinal retrospective study was designed involving all patients seen at a specialized post-COVID-19 respiratory sequelae clinic who had required hospitalization for SARS-CoV-2 pneumonia between March 2020 and April 2021. The patients were evaluated between three and nine months after hospital discharge. Each patient underwent a clinical interview, physical examination, chest high-resolution computed tomography (HRCT), spirometry, carbon monoxide (CO) transfer test and 6-min walking test (6MWT).

The patients were divided into two groups: those who were admitted from July 2020 onwards and received dexamethasone treatment, and those who were admitted between March and June 2020, prior to the use of dexamethasone as a treatment for SARS-CoV-2 pneumonia. Dexamethasone was administered according to prevailing recommendations (6 mg once daily, orally or intravenously, for up to 10 days or until hospital discharge). Patients excluded from the study were those who did not attend follow-up visits (due to lack of post-COVID evaluation), those not treated with dexamethasone starting from the second wave (July 2020 to April 2021, when it had become standard of care), and those who did not require oxygen therapy, as they were not candidates for dexamethasone treatment. During the study period, the strains included were the wild-type strain or Wuhan strain, the Alpha variant (B.1.1.7), which reached Spain in late 2020, and the Beta (B.1.351) and Gamma (P.1) variants, which were less widespread in this country. Given the retrospective design, treatment allocation was not randomized and may have been influenced by temporal and clinical factors, including differences in disease severity between pandemic waves.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (Hospital Vall d'Hebron Ethics Committee approval (PR [AG]222/2020). All subjects signed an informed consent document prior to their participation.

Baseline Data

The following data were collected from the hospital admission: demographic variables (sex, age, body mass index (BMI), smoking status) and clinical variables such as comorbidities. Laboratory data at admission (leukocytes, platelets, D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), and interleukin-6 (IL-6)) were also recorded. Disease was defined as severe if the patient needed FiO2 <40%, very severe if they needed FiO2> 40%, and critical if they needed ventilatory support.[10] The treatment received during hospitalization was also documented. The indications for the different treatments at our center are attached in Table S1.

Follow-Up Visit

Clinical evaluation included the degree of dyspnea using the modified Medical Research Council (mMRC) scale and the presence of other respiratory symptoms. A comprehensive physical examination was performed. Additionally, a complete pulmonary function study, including forced spirometry and lung diffusion capacity for carbon monoxide (DLCO), was conducted for all participants. The tests were carried out using an ultrasonic spirometer incorporated into a complete Viasys pulmonary function system (VYaire-Vyntus Body) according to the guidelines of the European Respiratory Society and the American Thoracic Society.[11] All data were expressed as percentages of the predicted values published by the Global Lung Function Initiative (GLI).[12,13] For forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and DLCO, values below 80% were considered low, while for the FEV1/FVC ratio, values below 70% were considered low. The 6MWT was performed according to the 2014 ERS/ATS Statement guidelines.[14] A HRCT scan of the chest with 1 mm slices at 10 mm intervals during maximum inspiration was performed during follow-up. All imaging features were independently interpreted by a radiologist and a pulmonologist. For controversial images, another radiologist was consulted. The HRCT scans were evaluated for the following features: location (unilateral or bilateral) and distribution (central, peripheral, or both) of the lesion, type of lesion (single, multiple, or diffuse), presence of ground-glass opacity, consolidation, linear opacities, reticulation, and/or mixed pattern, and interstitial changes (septal thickening, crazy paving and fibrosis). Airway involvement was also assessed, and if present, the characteristics of the airway (bronchial wall thickening, bronchiectasis, tracheomalacia, and bronchiolitis) were evaluated. The chest CT scans were evaluated following the descriptions provided in the Fleischner Society guidelines for Radiology.[15] DLCO and presence of fibrosis at the HRCT scan were defined as main follow-up outcome variables.

Statistical Analysis

A descriptive analysis of the demographic, clinical, and functional characteristics of all patients was conducted, with stratification by dexamethasone treatment. Absolute frequencies and corresponding percentages were calculated for qualitative variables. Quantitative variables with a normal distribution were described using the mean and standard deviation, while those that did not follow a normal distribution were described using the median and 25th-75th percentiles.

Demographic, clinical, and functional characteristics of patients treated with dexamethasone were compared with those not treated using the Student's *t*-test for normally distributed quantitative variables and the Mann–Whitney *U*-test for non-normally distributed variables. For qualitative variables, the Chi-square test or Fisher's exact test was applied as appropriate.

Multivariate linear and logistic regression models were employed to assess the association between dexamethasone treatment and alveolar-capillary diffusion and the presence of fibrosis on follow-up CT scans respectively. Potential confounding factors were tested and included in the final models if (i) they were related to both the exposure and the outcome, (ii) they were modified (>10% change in the regression coefficient) the estimates of the remaining variables, or (iii) there was documented evidence in the literature supporting an association with the outcome variables analysed.

Results were considered statistically significant if $p<0.05$. Analyses were performed using the STATA 18.0 statistical software package (StataCorp, College Station, TX, USA).

Results

A total of 1,448 patients who had been hospitalized for SARS-CoV-2 pneumonia between March 2020 and April 2021 were evaluated at the post-COVID medical unit. All patients were diagnosed with pneumonia based on radiological findings on chest X-rays and a positive SARS-CoV-2 test. Patients who did not require oxygen therapy during hospitalization and those not treated with dexamethasone during the second and third waves were excluded, resulting in a final analysis of 1,011 patients. The patients were divided into two groups: 348 patients who were not treated with dexamethasone (first wave) and 663 patients who were treated with dexamethasone, further subdivided into 311 patients from the second wave and 352 patients from the third wave (Figure 1).

Demographic characteristics are shown in Table 1. Regarding comorbidities, patients treated with dexamethasone had a higher prevalence of obesity, with 309 patients (46.6%), and gastroesophageal reflux disease, with 32 patients (4.8%), compared to those not treated with dexamethasone, among whom 139 patients (39.9%) had obesity and three (0.9%) had gastroesophageal reflux disease, indicating a significant difference between the two groups (p=0.043 and p=0.001 respectively). No other significant differences were observed in baseline demographic characteristics or comorbidities between the two groups (Table 1).

Patients treated with dexamethasone had a shorter hospital stay than those not treated, with median values of 10 days (6–16) versus 17 days (10–34) respectively (p-value < 0.001). Additionally, 259 (39.1%) of the patients treated with dexamethasone were admitted to the ICU, compared to 200 (57.5%) of those not treated (p-value < 0.001). ICU stay was also shorter for the treated group, with a median of 8 days (5–16) compared to 12 days (6–24) for the untreated group (p-value = 0.007). Patients treated with dexamethasone required a lower FiO_2, and fewer needed ventilatory support during hospitalization; they presented lower rates of acute respiratory distress, and fewer secondary infections, septic shock, and deep vein thrombosis Table 2 presents the remaining hospitalization variables according to dexamethasone treatment.

Regarding post-COVID-19 follow-up, patients treated with dexamethasone were seen later, after a median of 180 days (109–262) compared to 92 days (61–182) for those not treated (p-value < 0.001). Clinically, patients treated with dexamethasone experienced proportionally lower levels of dyspnea, recorded in 188 patients (28.4%) compared to 131 patients (37.6%) in the non-dexamethasone group (p-value = 0.003). Comparing patients treated with dexamethasone between the second and third waves, those from the later wave reported significantly less dyspnea. There were no significant differences in the other symptoms reported during the follow-up consultations. In pulmonary function tests, the DLCO of patients treated with dexamethasone was better at 76.9% (15.6), compared to 69.9% (20.7); similarly, patients from the third wave had better DLCO values than those from the second wave. There were no differences in the other spirometry values. Regarding the 6MWT, patients treated with dexamethasone walked a greater distance and had a better average oxygen saturation (Table 3).

Radiologically, there were no differences in the number of pathological chest CT scans across the different groups. However, there were differences in the type of parenchymal involvement, with a notable decrease in reticulation observed in the dexamethasone-treated group (23 [4.4%]) compared to the non-dexamethasone group (28 [9.5%]). As for interstitial changes, there were clear differences between the groups: patients treated with dexamethasone had significantly fewer septal thickenings (30 [5.8%]) and less fibrosis (18 [3.5%]) compared to those not treated with dexamethasone, who presented 31 (10.5%) cases of septal thickening and 46 (15.6%) cases of fibrosis. It is important to note that in this case, there were no differences between patients in the second and third waves, during which time both groups received dexamethasone. In the thoracic CT scans, no clear differences were observed in the percentage of bronchial involvement between the two groups. However, differences were noted in the type of bronchial involvement; patients treated with dexamethasone exhibited fewer cases of bronchiolitis – 37 cases (10.3%) compared to 61 cases (33.3%) in the untreated group (p<0.001). Additionally, patients treated with dexamethasone showed a higher prevalence of bronchiectasis, which was recorded in 269 cases (74.9%) compared to 117 cases (63.9%) in the non-treated group (p=0.007), and greater bronchial thickening, recorded in 227 cases (63.2%) compared to 70 cases (38.3%) among those not treated (p<0.001) (Table 4).

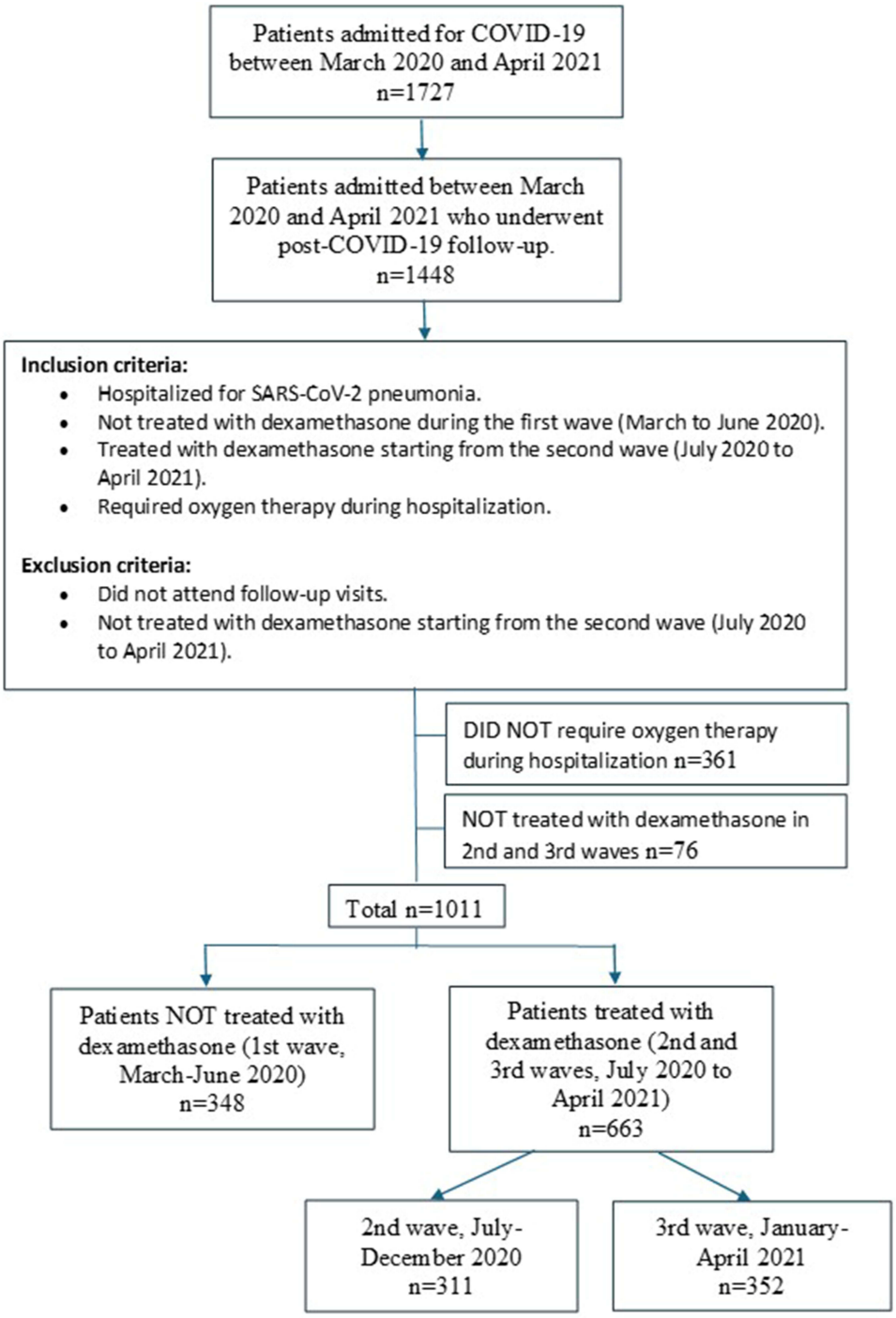

Figure 1 Patient Flowchart.

In the multivariate analysis, a linear regression model was created to evaluate the association between dexamethasone treatment and alveolar-capillary diffusion, adjusted for potential confounding factors such as age, sex, severity during hospitalization, and time from discharge to post-COVID visit. The model showed a mean DLCO of 81.24 (71.22–91.26) with a significant improvement of 9.25 (0.50–18.00), p=0.038, among patients treated with dexamethasone, even after adjustment for confounding variables. In the logistic regression model assessing the association between dexamethasone treatment and the presence of fibrosis on follow-up CT scans, adjusted for confounding factors, it was found that patients treated with dexamethasone had a lower likelihood of fibrosis on follow-up, with an OR (95% CI) of 0.24 (0.12–0.49) (Table 5).

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Table 1 Baseline Demographic Characteristics of the Study Population According to Dexamethasone Treatment

	Total (n=1011)	No Dexamethasone Treatment (n=348)	Dexamethasone Treatment (n=663)	p-value
Age at admission (years), mean (SD)	58.9 (12.7)	57.8 (13.1)	59.5 (12.5)	0.044
Sex, female, n (%)	387 (38.3)	138 (39.7)	249 (37.6)	0.514
BMI (kg/m^2), mean (SD)	29.5 (5.0)	29.1 (5.0)	29.7 (4.9)	0.073
Race, n (%):				0.547
White	729 (72.1)	254 (73.0)	475 (71.6)	
Asian	10 (1.0)	5 (1.4)	5 (0.8)	
Black	11 (1.1)	5 (1.4)	6 (0.9)	
Hispanic/Latino	247 (24.4)	81 (23.2)	166 (25.0)	
Other	14 (1.4)	3 (1.0)	11 (1.7)	
Smoking status, n (%):				0.790
Active smokers	44 (4.4)	15 (4.3)	29 (4.4)	
Former smokers	351 (34.7)	116 (33.3)	235 (35.4)	
Non-smokers	616 (60.9)	217 (62.4)	399 (60.2)	
Pack-years, median (IQR)	32.2 (22.8)	25 (11–40)	30 (18–50)	0.016
Comorbidities, n (%):				
Hypertension	423 (41.8)	147 (42.2)	276 (41.6)	0.851
Obesity	448 (44.3)	139 (39.9)	309 (46.6)	0.043
Diabetes	219 (21.7)	69 (19.8)	150 (22.6)	0.305
Renal insufficiency	73 (7.2)	26 (7.5)	47 (7.1)	0.823
Immunosuppression	50 (5.0)	20 (5.6)	30 (4.5)	0.394
Ischemic heart disease	53 (5.2)	12 (3.5)	41 (6.2)	0.064
Heart failure	28 (2.8)	11 (3.2)	17 (2.6)	0.583
Atrial fibrillation	42 (4.2)	15 (4.3)	27 (4.1)	0.857
Solid cancer	91 (9.0)	34 (9.8)	57 (8.6)	0.536
Leukemia	18 (1.8)	8 (2.3)	10 (1.5)	0.366
Psychiatric disorder	129 (12.8)	43 (12.4)	86 (13.0)	0.781
Gastroesophageal reflux	35 (3.5)	3 (0.9)	32 (4.8)	0.001
Respiratory comorbidities, n (%):				
Asthma	45 (4.5)	13 (3.7)	32 (4.8)	0.424
Obstructive sleep apnea (OSA)	78 (7.7)	24 (6.9)	54 (8.1)	0.503
Chronic obstructive pulmonary disease (COPD)	51 (5.0)	14 (4.0)	37 (5.6)	0.282
Bronchiectasis	12 (1.2)	3 (0.9)	9 (1.4)	0.490
Cystic fibrosis	1 (0.1)	0 (0.0)	1 (0.2)	0.999

(*Continued*)

Table 1 (Continued).

	Total (n=1011)	No Dexamethasone Treatment (n=348)	Dexamethasone Treatment (n=663)	p-value
Pulmonary arterial hypertension	9 (0.9)	5 (1.4)	4 (0.6)	0.288
Pulmonary fibrosis	2 (0.2)	2 (0.6)	0 (0.0)	0.118
Other interstitial lung disease	11 (1.1)	5 (1.4)	6 (0.9)	0.526
Scoliosis/kyphosis	9 (0.9)	1 (0.3)	8 (1.2)	0.176
Thoracic trauma	8 (0.8)	2 (0.6)	6 (0.9)	0.722

Table 2 Hospitalization Variables According to Dexamethasone Treatment

	Total (n=1011)	Without Dexamethasone Treatment 1st Wave (n=348)	With Dexamethasone Treatment (n=663)	p-value	Dexamethasone Treatment		p-value
					2nd Wave (n=311)	3rd Wave (n=352)	
Duration of hospital stay (days), median (p25-p75)	12 (7–21)	17 (10–34)	10 (6–16)	<0.001	10 (6–17)	9 (6–15)	0.046
ICU admission, n (%)	459 (45.4)	200 (57.5)	259 (39.1)	<0.001	122 (39.2)	137 (38.9)	0.935
Duration of ICU stay (days), median (p25-p75)	10 (5–20)	12 (6–24)	8 (5–16)	0.007	11 (5–21)	7 (5–14)	0.008
Oxygen therapy (yes), n (%)	1011 (100)	348 (100)	663 (100)	NA	311 (100)	352 (100)	NA
FiO_2<40	487 (48.2)	109 (31.3)	378 (57.0)	<0.001	177 (56.9)	201 (57.1)	0.961
FiO_2>40	524 (51.8)	239 (68.7)	285 (43.0)		134 (43.1)	151 (42.9)	
Ventilatory support							
None, n (%)	509 (50.3)	112 (32.2)	397 (59.9)	<0.001	185 (59.5)	212 (60.2)	0.846
High-flow nasal cannula (HFNC), n (%)	448 (44.3)	182 (52.3)	266 (40.1)	<0.001	127 (40.8)	139 (39.5)	0.724
Non-invasive ventilation (NIV), n (%)	43 (4.3)	29 (8.3)	14 (2.1)	<0.001	9 (2.9)	5 (1.4)	0.188
Invasive mechanical ventilation (IMV), n (%)	241 (23.8)	138 (39.7)	103 (15.5)	<0.001	55 (17.7)	48 (13.6)	0.151
Extracorporeal membrane oxygenation (ECMO), n (%)	7 (0.7)	6 (1.7)	1 (0.1)	0.008	0 (0.0)	1 (0.3)	0.999
Type Rx of lung involvement at hospital admission							
Alveolar infiltrate, n (%)	929 (91.9)	308 (88.5)	621 (93.7)	0.004	282 (90.7)	339 (96.3)	0.003
Pleural effusion, n (%)	2 (0.3)	2 (0.6)	0 (0.0)	0.118	0 (0.0)	0 (0.0)	-
Interstitial pattern, n (%)	117 (11.6)	68 (19.5)	49 (7.4)	<0.001	38 (12.2)	11 (3.1)	<0.001
Atelectasis, n (%)	5 (0.5)	2 (0.6)	3 (0.5)	0.999	1 (0.3)	2 (0.6)	0.999
Other, n (%)	5 (0.5)	1 (0.3)	4 (0.6)	0.665	4 (1.3)	0 (0.0)	0.048
Laterality							
Unilateral, n (%)	97 (9.6)	37 (10.6	60 (9.1)	0.421	32 (10.3)	28 (7.9)	0.290

(*Continued*)

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Table 2 (Continued).

	Total (n=1011)	Without Dexamethasone Treatment 1st Wave (n=348)	With Dexamethasone Treatment (n=663)	p-value	Dexamethasone Treatment		p-value
					2nd Wave (n=311)	3rd Wave (n=352)	
Bilateral, n (%)	913 (90.4)	311 (89.4)	602 (90.9)		278 (89.7)	324 (92.1)	
Extent of lung involvement, n (%)							
<33%	311 (32.8)	81 (23.3)	250 (37.8)	<0.001	115 (37.1)	135 (38.4)	0.180
33-66%	470 (46.5)	166 (47.7)	304 (45.9)		152 (49.0)	152 (43.2)	
>66%	209 (20.7)	101 (29.0)	108 (16.3)		43 (13.9)	65 (18.5)	
Secondary complications							
Acute respiratory distress, n (%)	440 (43.5)	179 (51.4)	261 (39.4)	<0.001	122 (39.2)	139 (39.5)	0.945
Heart failure, n (%)	18 (1.8)	5 (1.4)	13 (1.9)	0.626	7 (2.3)	6 (1.7)	0.613
Septic shock, n (%)	28 (2.8)	19 (5.5)	9 (1.4)	<0.001	6 (1.9)	3 (0.9)	0.230
Acute cardiac injury, n (%)	8 (0.8)	4 (1.2)	4 (0.6)	0.465	1 (0.3)	3 (0.9)	0.627
Acute kidney injury, n (%)	79 (7.8)	31 (8.9)	48 (7.3)	0.355	20 (6.5)	28 (7.9)	0.451
Secondary infection, n (%)	248 (24.5)	107 (30.8)	141 (21.3)	0.001	63 (20.3)	78 (22.2)	0.550
Pneumothorax, n (%)	15 (1.5)	5 (1.4)	10 (1.5)	0.924	5 (1.6)	5 (1.4)	0.851
Cerebrovascular accident, n (%)	8 (0.8)	4 (1.2)	4 (0.6)	0.353	1 (0.3)	3 (0.9)	0.380
Pulmonary embolism, n (%)	47 (4.7)	15 (4.3)	32 (4.8)	0.771	18 (5.8)	14 (3.9)	0.278
Deep vein thrombosis, n (%)	42 (4.2)	24 (7.0)	18 (2.7)	0.001	9 (2.9)	9 (2.6)	0.790
Corticosteroid treatment							
Corticosteroids (yes), n (%)	756 (74.8)	93 (26.7)	663 (100)	<0.001	311 (100)	352 (100)	NA
Type of corticosteroids							
Prednisone, n (%)	30 (4.0)	19 (20.4)	11 (1.7)	<0.001	2 (0.6)	9 (2.6)	0.054
Methylprednisolone, n (%)	105 (13.9)	80 (86.0)	25 (3.8)	<0.001	11 (3.5)	14 (4.0)	0.766
Dexamethasone, n (%)	663 (87.7)	0 (0.0)	663 (100)	<0.001	311 (100)	352 (100)	NA
Hydrocortisone, n (%)	7 (0.9)	7 (7.5)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	NA
Cumulative dose of corticosteroids, median (p25-p75)	375 (375–375)	577 (356–1125)	375 (375–375)	<0.001	375 (375–375)	375 (375–375)	0.561
Other treatments							
Hydroxychloroquine, n (%)	328 (32.4)	327 (93.7)	1 (0.2)	<0.001	1 (0.3)	0 (0.0)	0.469
Lopinavir/ritonavir, n (%)	257 (25.4)	257 (73.9)	0 (0.0)	<0.001	-	-	-
Darunavir/cobicistat, n (%)	26 (2.6)	26 (7.5)	0 (0.0)	<0.001	-	-	-
Antibiotics, n (%)	585 (57.9)	335 (96.3)	250 (37.7)	<0.001	133 (42.8)	117 (33.2)	0.012
Baricitinib, n (%)	1 (0.10)	0 (0.0)	1 (0.15)	0.999	0 (0.0)	1 (0.3)	0.999
Remdesivir, n (%)	56 (5.5)	6 (1.7)	50 (7.5)	<0.001	50 (16.1)	0 (0.0)	<0.001
Tocilizumab, n (%)	179 (17.7)	156 (44.8)	23 (3.5)	<0.001	19 (6.1)	4 (1.1)	<0.001
Convalescent plasma, n (%)	7 (0.7)	0 (0.0)	7 (1.1)	0.103	6 (1.9)	1 (0.3)	0.055

Table 3 Clinical and Functional Data During Post-COVID-19 Follow-Up According to Dexamethasone Treatment

	Total (n=1011)	Without Dexamethasone Treatment 1st Wave (n=348)	With Dexamethasone Treatment (n=663)	p-value	Dexamethasone Treatment		p-value
					2nd Wave (n=311)	3rd Wave (n=352)	
Time from discharge to post-COVID consultation (days), median (p25-p75)	144 (92–251)	92 (61–182)	180 (109–262)	<0.001	138 (103–261)	238 (123–262)	<0.001
Symptoms							
Cough, n (%)	71 (7.0)	23 (6.6)	48 (7.2)	0.709	19 (6.1)	29 (8.2)	0.291
Expectoration, n (%)	17 (1.7)	6 (1.7)	11 (1.7)	0.939	5 (1.6)	6 (1.7)	0.922
Dyspnea, n (%)	319 (31.6)	131 (37.6)	188 (28.4)	0.003	105 (33.8)	83 (23.6)	0.004
Chest pain, n (%)	35 (3.5)	14 (4.0)	21 (3.2)	0.480	12 (3.9)	9 (2.6)	0.340
Dyspnea (mMRC; 0–4), Median (p25-p75)	1 (1–2)	1 (1–2)	1 (1–2)	0.989	1 (1–2)	1 (1–2)	0.174
Pulmonary function							
FVC (% predicted), mean (SD)	90.4 (17.8)	91.2 (19.1)	90.0 (17.0)	0.477	88.3 (17.2)	91.5 (16.6)	0.026
FEV1 (% predicted), mean (SD)	92.7 (19.3)	94.3 (21.4)	91.9 (18.0)	0.075	90.5 (18.3)	93.1 (17.7)	0.091
FEV1/FVC (%), mean (SD)	80.7 (7.6)	81.6 (8.1)	80.2 (7.2)	0.005	80.3 (7.2)	80.1 (7.3)	0.724
DLCO (% predicted), mean (SD)	74.4 (20.2)	69.9 (20.7)	76.9 (15.6)	<0.001	74.9 (19.0)	78.8 (19.9)	0.013
KCO (% predicted), mean (SD)	85.1 (17.6)	81.1 (16.8)	87.4 (17.7)	<0.001	85.0 (15.7)	89.7 (19.1)	<0.001
Six-minute walk test							
Distance (m), median (p25-p75)	420 (360–480)	405 (360–465)	435 (360–480)	0.002	435 (360–480)	435 (375–484)	0.233
Baseline SpO2 (%), mean (SD)	96.9 (1.7)	96.3 (1.8)	97.3 (1.9)	<0.001	96.8 (1.9)	98.0 (1.7)	<0.001
Lowest SpO2 (%), mean (SD)	93.2 (4.1)	92.6 (4.2)	93.7 (3.8)	<0.001	93.2 (3.5)	94.3 (4.2)	<0.002
Mean SpO2 (%), mean (SD)	94.9 (3.1)	94.2 (3.1)	95.4 (3.0)	<0.001	94.9 (2.9)	96.0 (3.1)	<0.001

Discussion

The present study demonstrates that patients treated with dexamethasone experienced less dyspnea, had better DLCO, walked a greater distance in the six-minute walk test and had a better average oxygen saturation in post-COVID-19 follow-up. Radiologically, a notable decrease in reticulation, significantly fewer septal thickenings and less fibrosis were observed in the dexamethasone-treated group compared to the non-dexamethasone group. In consonance with previous studies, our results also indicate associations between dexamethasone treatment during hospitalization and shorter hospital and ICU stays, and lower FiO_2 and ventilatory support requirements.

The lack of effective treatments for COVID-19 during the early stages of the pandemic posed a huge challenge. Many of the therapeutic options available were experimental or had limited efficacy. Subsequently, clinical trials were published supporting the use of certain medications such as remdesivir, tocilizumab, and dexamethasone.[5,6,16–23] Dexamethasone has been identified as an effective treatment for all patients requiring respiratory support.[7,21] Nevertheless, the doses and the period of treatment are debated.[19,20,22]

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Table 4 Description of Chest CT Findings During Post-COVID-19 Follow-Up According to Dexamethasone Treatment

	Total (n=1011)	Without Dexamethasone Treatment 1st Wave (n=348)	With Dexamethasone Treatment (n=663)	p-value	Dexamethasone Treatment		p-value
					2nd Wave (n=311)	3rd Wave (n=352)	
Pathological, n (%)	816 (81.9)	294 (84.7)	522 (80.4)	0.093	251 (81.5)	271 (79.5)	0.517
Parenchymal Involvement, n (%)							
Ground-glass opacity	209 (25.6)	73 (24.8)	136 (26.1)	0.009	65 (25.9)	71 (26.2)	0.449
Consolidation	6 (0.7)	5 (1.7)	1 (0.2)		1 (0.4)	0 (0.0)	
Linear opacities	54 (6.6)	21 (7.1)	33 (6.3)		11 (4.4)	22 (8.1)	
Reticulation	51 (6.3)	28 (9.5)	23 (4.4)		13 (5.2)	10 (3.7)	
Mixed type	373 (45.7)	122 (41.5)	251 (48.1)		123 (49.0)	128 (47.2)	
None	123 (15.1)	45 (15.3)	78 (14.9)		38 (15.1)	40 (14.8)	
Interstitial							
Septal thickening, n (%)	61 (7.5)	31 (10.5)	30 (5.8)	0.012	11 (4.4)	19 (7.0)	0.197
Crazy paving, n (%)	4 (0.5)	2 (0.7)	2 (0.4)	0.622	0 (0.0)	2 (0.7)	0.500
Fibrosis, n (%)	64 (7.8)	46 (15.6)	18 (3.5)	<0.001	8 (3.2)	10 (3.7)	0.753
No, n (%)	690 (84.6)	223 (75.9)	467 (89.5)	<0.001	224 (89.2)	243 (89.7)	0.874
Bronchial Involvement							
Bronchial Involvement, n (%)	542 (66.4)	183 (62.2)	359 (68.8)	0.058	175 (69.7)	184 (67.9)	0.653
Type of bronchial involvement							
Bronchiectasis, n (%)	386 (71.2)	117 (63.9)	269 (74.9)	0.007	121 (69.1)	148 (80.4)	0.014
Bronchial thickening, n (%)	297 (54.8)	70 (38.3)	227 (63.2)	<0.001	109 (62.3)	118 (64.1)	0.717
Bronchiolitis, n (%)	98 (18.1)	61 (33.3)	37 (10.3)	<0.001	29 (16.6)	8 (4.4)	<0.001
Tracheomalacia, n(%)	18 (3.3)	7 (3.8)	11 (3.1)	0.640	2 (1.1)	9 (4.9)	0.062

Notes: Mixed type: patient presents two of the other conditions.

Although it has been demonstrated that dexamethasone represents a major step forward in COVID-19 treatment, many individuals continue to experience symptoms such as shortness of breath, persistent cough, and reduced lung capacity months after their initial infection. In this context, one of the largest meta-analyses (which included 46 studies evaluating radiological changes and 50 studies assessing lung function) found that approximately 50% of patients presented inflammatory sequelae, 29% fibrotic changes on imaging, and 38% impaired DLCO, with a median follow-up period of 3 months in COVID-19 cases.[24] Therefore, the evidence indicates that many patients present respiratory sequelae at both the clinical and imaging levels, as well as in pulmonary function tests.[25,26]

Due to the initial uncertainty regarding lung lesions following SARS-CoV-2 pneumonia, Culebras et al conducted a study on 50 post-COVID-19 patients with suspected diffuse interstitial lung disease. The most common histological finding was organizing pneumonia (32%), followed by lymphoplasmacytic interstitial infiltrate (18%), patchy

Table 5 Adjusted Analysis Using a Multiple Linear Regression Model of the Relationship Between Dexamethasone Treatment During Hospital Admission and the Value of Alveolar-Capillary Diffusion Assessed at Follow-Up, and Adjusted Analysis Using a Logistic Regression Model of the Relationship Between Dexamethasone Treatment and the Presence of Fibrosis in Follow-Up CT Scans

	DLCO (% Predicted)	
	Coefficient† (IC 95%)	p
Constant*	81.24 (71.22–91.26)	<0.001
Dexamethasone treatment	9.25 (0.50–18.00)	0.038
Age at admission (years)	−0.25 (−0.34- −0.15)	<0.001
Sex (male)	3.54 (1.01–6.00)	0.005
BMI (kg/m^2)	0.92 (0.67–1.71)	<0.001
Fibrosis on admission X-ray	−1.27 (−5.01–2.47)	0.506
Lung transplant patient	−27.16 (−44.76- −9.56)	0.003
FiO_2>40%	−5.71 (−8.66- −2.76)	<0.001
Non-invasive ventilation (NIV)	−6.32 (−9.76- −2.88)	<0.001
Invasive mechanical ventilation (IMV)	−10.27 (−16.55- −4.01)	0.001
Hydroxychloroquine on admission	10.22 (1.52–18.91)	0.021
Tocilizumab on admission	−1.97 (−5.64–1.70)	0.292
Duration of hospital stay (days)	−0.06 (−0.11- −0.01)	0.025
Time from discharge to post-COVID consultation	0.03 (0.02–0.05)	0.021
	Presence of fibrosis on follow-up CT scan	
	OR (IC 95%)	p
Dexamethasone treatment	0.24 (0.12–0.49)	<0.001
Age at admission (years)	1.04 (1.02–1.07)	0.001
Sex (Male)	1.35 (0.74–2.45)	0.330
BMI (kg/m^2)	0.93 (0.87–0.99)	0.032
Fibrosis on admission X-ray	0.71 (0.31–1.01)	0.409
FiO_2>40%	2.45 (1.07–5.61)	0.034
Non-invasive ventilation (NIV)	2.62 (1.38–4.99)	0.003
Tocilizumab on admission	0.77 (0.39–1.51)	0.452
Time from discharge to post-COVID consultation	0.98 (0.99–1.00)	0.467

Notes: *: Adjusted mean value based on the multiple linear regression equation corresponding to the mean DLCO (% predicted) in a subject with average values for continuous variables and the reference category for categorical variables. †: The coefficients represent an increase or decrease in percentage units of DLCO for (i) each unit of the continuous variables, or (ii) the difference relative to the reference category in the categorical variables.

collagenous scarring (8%), and minimal or normal findings in 26% of patients. Since organizing pneumonia has been identified as the most common pulmonary sequela following SARS-CoV-2 pneumonia, it is reasonable to suggest that corticosteroids administered in the acute phase may aid recovery in these patients.[27] Organizing pneumonia is a diffuse interstitial lung disease (ILD) characterized by a pattern of lung tissue repair following injury, such as that caused by

SARS-CoV-2 pneumonia, that can progress to fibrotic changes observed in chest computed tomography (CT), particularly in cases that advance without treatment. Therefore, administering anti-inflammatory treatment in the acute phase, when an inflammatory response occurs,[28] may improve recovery from viral injury, reducing repair defects and subsequent fibrotic changes.

In this regard, the present study demonstrated clinical improvement and enhanced lung function in the group treated with dexamethasone during follow-up, suggesting that the anti-inflammatory effects of the drug during the acute phase may contribute to improved long-term respiratory outcomes, although this interpretation remains speculative and cannot be directly confirmed by our data. Radiological assessments further reinforce these clinical findings, as patients treated with dexamethasone exhibited fewer fibrotic changes such as septal thickening and fibrosis than the untreated group. Other studies have suggested that dexamethasone in the acute phase of COVID-19 may be a factor that may reduce post-COVID-19 syndrome by controlling inflammation.[29,30] Although it appeared that symptoms were decreasing in these patients, Leavy et al's study showed no improvements in quality of life or other secondary outcomes, such as lung function, in patients treated with systemic corticosteroids one year after COVID-19 infection.[9] This apparent divergence may reflect that HRQoL is influenced by multiple factors beyond respiratory status, and thus may not fully align with functional or radiological findings. Moreover, the broader literature regarding corticosteroids and long-COVID remains heterogeneous, with some studies reporting conflicting or null results. It is worth noting that data on lung function in many patients in that study were incomplete (for example, other diagnostic tests such as chest CT were not always available) which limits the assessment of its impact. Additionally, the baseline quality of life questionnaire prior to hospitalization was assessed retrospectively.[9] In the present study, the sequelae following pneumonia caused by SARS-CoV-2 can be evaluated better, as all patients underwent a clinical evaluation combined with functional respiratory tests and chest CT scans. This apparent divergence may reflect that HRQoL is influenced by multiple factors beyond respiratory status, and thus may not fully align with functional or radiological findings. Moreover, the broader literature regarding corticosteroids and long-COVID remains heterogeneous, with some studies reporting conflicting or null results. It is worth noting that data on lung function in many patients in that study were incomplete (for example, other diagnostic tests such as chest CT were not always available) which limits the assessment of its impact.

Although, as previously mentioned, in the present study we observed differences in parenchymal involvement in patients treated/not treated with dexamethasone, no differences were observed in terms of airway involvement between the two groups. In this regard, in patients with COVID-19 infection, intense and persistent inflammation in the airways can cause tissue damage and deterioration of the epithelial barrier function of the airways, thus producing alterations in the airway.[28] The results of the present study suggest that dexamethasone treatment produces a change in the type of alterations in the airway, reducing the degree of bronchiolitis but increasing the bronchiectasis. This finding may be influenced by factors such as ICU-related injury or timing of follow-up, and further studies will be needed to clarify its significance.

This study has several limitations. First, its retrospective design may introduce bias. An important limitation of our study is the overlap between dexamethasone treatment and pandemic wave, with untreated patients largely hospitalized during the first wave and treated patients in later waves. This temporal grouping coincides with evolving standards of care, ICU capacity, and circulating viral variants, all of which could influence outcomes independently of corticosteroid use. Although we adjusted for follow-up interval and markers of disease severity in multivariate analyses, residual confounding from unmeasured factors—including improvements in ICU management, access to rehabilitation, and differences in comorbidities—cannot be excluded. Therefore, the observed associations between dexamethasone and improved long-term respiratory outcomes should be interpreted with caution. Second, the follow-up period also varied between groups, with dexamethasone-treated patients generally being seen later, a difference that may have influenced the assessment of long-term outcomes. However, multivariate analysis shows that differences in DLCO and fibrosis on chest CT in dexamethasone- treated/non-treated patients remained significant, even after adjusting for the time from discharge to post-COVID consultation. Third, although these patients received other treatments that might influence disease progression, the use of antivirals, tocilizumab, or convalescent plasma among dexamethasone-treated patients was limited and unlikely to account for the observed outcomes. In addition, we did not perform a specific subgroup analysis of ICU patients, although this could be of interest given their higher risk of long-term sequelae. Moreover,

fibrosis severity was not quantified, and only its presence was reported, which limits interpretability. Finally, as no adjustment for multiple testing was performed, the risk of type I error cannot be excluded.

In conclusion, this study suggests that dexamethasone treatment during hospitalization for severe COVID-19 may be associated with improved long-term respiratory outcomes, including reduced dyspnea, better lung function, and fewer radiological signs of pulmonary fibrosis. These findings indicate a potential association between dexamethasone use in the acute phase and better long-term recovery, although causality cannot be established given the retrospective design.

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