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Effectiveness of corticosteroids on chest high-resolution computed tomography features of COVID-19 pneumonia

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Abstract

Objective: The aim of our study was to assess the effect of a short-term treatment with low-moderate corticosteroid (CS) doses by both a quantitative and qualitative assessment of chest HRCT of COVID-19 pneumonia.

Methods: CORTICOVID is a single-center, cross-sectional, retrospective study involving severe/critical COVID-19 patients with mild/moderate ARDS. Lung total severity score was obtained according to Chung and colleagues. Moreover, the relative percentages of lung total severity score by ground glass opacities, consolidations, crazy paving, and linear bands were computed. Chest HRCT scores, P/F ratio, and laboratory parameters were evaluated before (pre-CS) and 7–10 days after (post-CS) methylprednisolone of 0.5–0.8 mg/kg/day.

Findings: A total of 34 severe/critical COVID-19 patients were included in the study, of which 17 received Standard of Care (SoC) and 17 CS therapy in add-on. CS treatment disclosed a significant decrease in HRCT total severity score [median = 6 (IQR: 5–7.5) *versus* 10 (IQR: 9–13) in SoC, $p < 0.001$], as well in single consolidations [median = 0.33 (IQR: 0–0.92) *versus* 6.73 (IQR: 2.49–8.03) in SoC, $p < 0.001$] and crazy paving scores [mean = 0.19 (SD = 0.53) *versus* 1.79 (SD = 2.71) in SoC, $p = 0.010$], along with a significant increase in linear bands [mean = 2.56 (SD = 1.65) *versus* 0.97 (SD = 1.30) in SoC, $p = 0.006$]. GGO score instead did not significantly differ at the end of treatment between the two groups. Most post-CS GGO, however, derived from previous consolidations and crazy paving [median = 1.5 (0.35–3.81) *versus* 2 (1.25–3.8) pre-CS; $p = 0.579$], while pre-CS GGO significantly decreased after methylprednisolone therapy [median = 0.66 (0.05–1.33) *versus* 1.5 (0.35–3.81) pre-CS; $p = 0.004$]. CS therapy further determined a significant improvement in P/F levels [median P/F = 310 (IQR: 235.5–370) *versus* 136 (IQR: 98.5–211.75) in SoC; $p < 0.001$], and a significant increase in white blood cells, lymphocytes, and neutrophils absolute values.

Conclusion: The improvement of all chest HRCT findings further supports the role of CS adjunctive therapy in severe/critical COVID-19 pneumonia.

Keywords: ARDS, chest high-resolution computed tomography, corticosteroids, COVID-19, P/F

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Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 is the seventh identified coronavirus responsible for the highly contagious COVID-19 infection. COVID-19 rapidly spread worldwide, reaching pandemic proportion during the first months of 2020. While most infected patients are either asymptomatic or develop mild, flu-like symptoms, several cases evolve toward an interstitial pneumonia, which may further move into an acute respiratory distress syndrome (ARDS) and, eventually, lead to death.

The natural history of COVID-19 disease seems to pursue three progressive stages. SARS-CoV-2, mainly transmitted through respiratory droplets, primarily replicate in the mucosal epithelium of both upper and lower respiratory tract. In some cases, the virus can spread through the bloodstream to tissues, involving mainly alveolar epithelium and endothelium, which express higher concentration of the SARS-CoV-2 receptor, the angiotensin-converting enzyme 2 (ACE2). During this phase, a rapid viral replication and cell damage may result in vascular leakage and pulmonary inflammation, mediated by a profuse production of cytokines and chemokines by both innate and adaptive immune cells. In few cases, the disease proceeds to the most severe stage, characterized by a systemic hyperinflammation syndrome.[1] Pathological findings of severe COVID-19 pneumonia show inflammatory infiltrates dominated by lymphocytes, diffuse alveolar damage, pulmonary edema, and hyaline membrane formation suggestive of ARDS.[2]

The progressive alveolar and interstitial pulmonary injury and inflammation can be detected on chest computed tomography (CT) that, though nonspecific for viral etiology, plays a crucial role in both early diagnosis and management of COVID-19 pneumonia.[3] Multifocal and bilateral ground glass opacities (GGOs) usually involving the peripheral and subpleural regions of lower pulmonary lobes are the main early CT signs. The increase in both numbers and densities of GGOs spreading to central area and middle-upper zones with the appearance of crazy paving pattern and consolidations is indicative of a progression of the disease, whereas the appearance of linear bands and/or reduction of either GGOs or consolidations is suggestive of disease improvement.[4] Thus, the modification of CT chest images seems to match with the clinical evolution of COVID-19 pneumonia and may help physician to tailor the treatment of the disease. Taking into account the central role of the host response in the pathogenesis of COVID-19 pneumonia, a therapeutic approach to the disease is focused on the immunomodulatory agents that can act on the pulmonary and systemic hyperinflammatory state. Currently, the use of systemic corticosteroids (CS) in COVID-19, highly controversial during the first months of pandemic, has been strongly recommended in patients with severe and critical disease by the World Health Organization (WHO) guideline panel, as well as by other academic and health organizations. In fact, based on data from two meta-analyses of eight randomized trials, CS have been demonstrated effective in reducing 28-day mortality. Up to now, the evaluation of corticosteroid therapy through a systematic monitoring of chest CT features of COVID-19 pneumonia has been never performed.

Thus, aim of the present study is to assess the effects of a short-term treatment with CS on radiological features in a selected cohort of severe and critical COVID-19 patients.

Methods

Study design and participants

CORTICOVID is a cross-sectional single-center, case-control, retrospective study on severe/critical COVID-19 patients admitted to the Sub-Intensive Care Unit of A.O.R.N. Ospedali dei Colli, Cotugno Hospital, Naples (Italy), in a time period of 1 month, from 15 March to 15 April 2020.

All patients were diagnosed as COVID-19 on positive nasopharyngeal specimen at real-time reverse transcription polymerase chain reaction (RT-PCR). Enrolled patients were classified as affected by either severe COVID-19 pneumonia (in the presence of fever, cough, dyspnea, fast breathing, one among respiratory rate >30 breaths/min, severe respiratory distress, or $SpO_2<90\%$ on room air) or critical with mild ARDS [P/F between 200 and 300 mmHg, with either positive end expiratory pressure (PEEP) or continuous positive airway pressure (cPAP) $\geqslant 5$ cm H_2O] or moderate ARDS (P/F between 100 and 200 mmHg, with PEEP $\geqslant 5$ cm H_2O).

As the WHO advised against the use of CS at the beginning of SARS-CoV-2 pandemic, a group of patients was treated with standard of care (SoC) prescribed in March 2020, which included azithromycin, hydroxychloroquine sulfate, antivirals (lopinavir/ritonavir or darunavir/cobicistat), and anti-interleukin-6 receptor antibody (tocilizumab).[5] As the pandemic progressed, some evidence from retrospective observational studies reported a reduction of mortality in patients treated with CS. Hence, another group of patients received, in addition to SoC, intravenous low-to-moderate dose of CS, that is, methylprednisolone of 0.5–0.8 mg/kg/day for 7–10 days, and then gradually tapered according to clinical conditions. All participants

gave their written informed consent to participate in the study, which was approved by the local ethics committee of University of Campania 'Luigi Vanvitelli' and A.O.R.N. Ospedali dei Colli and is in accordance with the 1976 Declaration of Helsinki and its later amendments.

Data collection

General, anthropometric, clinical, laboratory, and instrumental parameters were collected from medical records on an electronic database by a team of trained physicians. In depth, at baseline, the following data were considered: demographic characteristics, smoking status, period from onset of illness to admission, symptoms and signs (fever, cough, shortness of breath, fatigue), known comorbidities [obesity, deep venous thrombosis, arterial hypertension, chronic artery disease (CAD), chronic obstructive pulmonary disease (COPD), and diabetes], concomitant therapies with renin-angiotensin-aldosterone system (RAAS) inhibitors [angiotensin II receptor blockers (ARBs) and/or angiotensin-converting enzyme (ACE) inhibitors], and severity of illness scores [CURB65 (confusion, urea, respiratory rate, blood pressure, and 65 years of age or older), MEWS (Modified Early Warning Score), and SOFA (Sequential Organ Failure Assessment)].

Before (pre-SoC and pre-CS) and after standard of care or corticosteroid (post-SoC and post-CS) therapy, we furtherly collected the following parameters: score of chest high-resolution computed tomography (HRCT) scan, P/F ratio, and laboratory test (peripheral blood count cells). As well, side effects were also assessed.

HRCT score

A quantitative and a qualitative HRCT imaging analysis was performed by two blinded expert radiologists and final scores were determined by consensus, in case of an inconsistency. According to Chung and colleagues, each of the five lung lobes was scored for the degree of involvement, as follows: score 0 (no involvement; 0%); score 1 (minimal involvement; 1–25%); score 2 (mild involvement; 26–50%); score 3 (moderate involvement; 51–75%); and score 4 (severe involvement; 76–100%). Finally, an overall lung 'total severity score' was computed as the sum of the five lobe scores (range of possible scores, 0–20).[6] Then, for each lobe, we evaluated the relative percentages of the following thoracic imaging findings, defined in accordance to the Fleischner Society glossary: (a) GGOs, (b) consolidations, (c) crazy paving pattern, and (d) linear bands.[7] On the basis of their percentages in every lobe, first, we calculated the lobe score by each chest image; second, we summed them; and finally, we obtained the lung score ascribable to each chest CT images. In this way, a quantitative and a qualitative chest CT analysis was performed.

Statistical analysis

Categorical data were expressed as number and percentage, while continuous variables as either median and interquartile range (IQR) or mean and standard deviation, based on their distribution assessed by the Shapiro–Wilk test. Between-groups differences at baseline were tested, according to the normal/not normal distribution, either by the parametric paired Student's t test or by the nonparametric Wilcoxon signed-rank test, while categorical data were analyzed by the Fisher's exact test.

Comparison of groups at the end of treatment was performed by generalized estimating equations (GEE) model with cluster as group variable,[8] further adjusting for baseline values as covariate. Distribution of dependent variable and link function was used as appropriate (gaussian and identity for continuous variable, binomial and logit for dichotomous variable). Bivariate correlations were expressed by the Pearson's correlation coefficient, which assumes a value ranging between −1 and +1. Negative values are expression of an inverse correlation between variables. All correlations were also complemented by appropriate graphs.

A p value of <0.05 was considered statistically significant. Data were analyzed using SPSS Software, Version 24 (IBM, Armonk, New York, USA) and STATA 15.5 software (StataCorp. 2015, StataCorp LP, College Station, TX, USA).

Results

A total of 34 severe/critical COVID-19 patients were finally included in the study, of which 17 received SoC therapy *versus* 17 CS therapy. SoC and CS groups did not differ as for baseline characteristics. Median age was 62 (IQR: 56.3–64) years, mostly men (82.4%) with a median body mass

index (BMI) of 28 (IQR: 26.8–30) kg/m^2, and more than half of patients were smokers or ex-smokers (57.6%).

Patients presented at hospitalization with a median body temperature of 37.4°C (IQR: 36.4–38°C) and symptoms preexisting from almost 6 (IQR: 4–7) days. Among previous comorbidities, obesity (67.6%) and arterial hypertension (64.7%) were the most frequent, while diabetes was recorded in 20.6% of the patients.

On admission, both ACE inhibitors and ARBs were not largely prescribed (14.7% and 23.5%, respectively). Severity of illness was measured according to validated scores. In depth, mean CURB65 Score was 1.59 ± 1.01, MEWS Score 2.24 ± 1.84, and SOFA Score 3.53 ± 1.76.

Moreover, as for SoC therapy, most of patients were under combined therapy with hydroxychloroquine and azithromycin (85.3%). As well, the 78.5% also underwent antiviral treatment, while 19 patients (55.9%) were administered tocilizumab. All data are shown in Table 1.

At baseline, patients who had undergone SoC therapy were characterized by a significantly higher lymphopenia than those under CS [median a.v. (absolute value) 0.66 *versus* 1.28, $p = 0.003$] and significantly lower levels of monocytes (median a.v. 0 *versus* 0.12, $p = 0.011$). As for HRCT score at baseline, all analyzed parameters, indeed, did not significantly differ between the two groups, as well P/F values. All data are shown in Table 2.

We thus searched for possible differences between the two groups at the end of the different treatments, with parameters at the end of intervention as dependent variable and group allocation and parameters at baseline as covariates.

We observed a significant improvement in HRCT parameters in patients following intravenous treatment with methylprednisolone. The median time between first and second HRCT was of 8.5 (IQR: 5–14) days. In particular, CS treatment disclosed a significant decrease in HRCT total severity score [median = 6 (IQR: 5–7.5) *versus* 10 (IQR: 9–13) in SoC, $p < 0.001$], and in the scores of consolidations [median = 0.33 (IQR: 0–0.92) *versus* 6.73 (IQR: 2.49–8.03) in SoC, $p < 0.001$] and crazy paving [mean = 0.19 (SD = 0.53) *versus* 1.79 (SD = 2.71) in SoC, $p = 0.010$], along with a significant increase in linear bands [mean = 2.56 (SD = 1.65) *versus* 0.97 (SD = 1.30) in SoC, $p = 0.006$] (Table 2, Figure 1). GGO score instead did not significantly differ at the end of treatment between the two groups. Given the significant HRCT improvements after CS therapy compared with SoC, we better focused on this subgroup and analyzed more in depth GGO after CS therapy. We observed that most post-CS GGO derived from previous consolidations and crazy paving [median = 1.5 (0.35–3.81) *versus* 2 (1.25–3.8) pre-CS; $p = 0.579$], while pre-CS GGO significantly decreased after therapy with methylprednisolone [median = 0.66 (0.05–1.33) *versus* 1.5 (0.35–3.81) pre-CS; $p = 0.004$] (Figure 2).

Some examples of clear HRCT modification following CS therapy in patients affected by critical COVID-19 are shown in Figure 3. Indeed, in Figure 4, we can observe some examples of patients with critical COVID-19 in which the HRCT score either did not change or the change was very little, although the analysis of the relative percentages of thoracic imaging findings was suggestive of a resolution phase.

Of note, as for blood count examinations, we observed an improvement in lymphocytes in the CS subgroup, while lymphopenia persisted in the SoC group even at the end of treatment [median = 1.83 (IQR: 0.82–2.29) *versus* 0.82 (IQR: 0.63–1.37) in SoC, $p < 0.001$]. Finally, CS therapy was significantly associated with an increase of neutrophils a.v. [5.89 (4.87–10.25) *versus* 4.14 (3.18–8.80) in SoC, $p < 0.001$] and WBC [9.04 (7.94–12.90) *versus* 7.45 (4.87–11.86) in SoC, $p < 0.001$].

Moreover, the addition of CS therapy further determined a significant improvement in P/F levels at the end of treatment [median P/F = 310 (IQR: 235.5–370) *versus* 136 (IQR: 98.5–211.75) in SoC; $p < 0.001$]. All data are shown in Table 2.

Except for a case of exacerbation of hyperglycemia in a type 2 diabetic patient managed with insulin, no side effects occurred during CS therapy.

Discussion

In this study, we assessed the effects of a short-term treatment with CS on radiological parameters in severe COVID-19 patients. We documented an

Table 1. Baseline characteristics of the study population, both overall and as single subgroups ($N = 34$).

Parameter	Overall population ($N = 34$)	SoC ($n = 17$)	CS ($n = 17$)	
Age, years, median (IQR)	62 (56.3–64)	62 (53.5–63.5)	62 (57–64)	0.786
Sex, M/F, *n* (%)	28 (82.4)/6 (17.6)	14 (82.4)/3 (17.6)	14 (82.4)/3 (17.6)	1.000
BMI, kg/m^2, median (IQR)	28 (26.75–30)	28 (26–30)	28 (27–31)	0.870
Smoking habit, *n* (%)				0.393
Yes/ex	19 (57.6)	11 (64.7)	8 (50)	
No	14 (42.4)	6 (35.3)	8 (50)	
Temperature, °C, median (IQR)	37.4 (36.4–38)	37.5 (36.4–37.9)	37.0 (36.4–38.0)	0.658
Cough, *n* (%)	25 (73.5)	12 (70.6)	13 (76.5)	1.000
Shortness of breath, *n* (%)	4 (11.8)	2 (11.8)	2 (11.8)	1.000
Fatigue, *n* (%)	19 (55.9)	8 (47.1)	11 (64.7)	0.491
Days symptoms before hospitalization, median (IQR)	6 (4.0–7.0)	6 (4.0–7.0)	6.0 (3.0–8.0)	1.000
Comorbidities, *n* (%)				
Obesity	23 (67.6)	11 (64.7)	12 (70.6)	0.714
DVT	1 (2.9)	1 (5.9)	–	1.000
Arterial hypertension	22 (64.7)	12 (70.6)	10 (58.8)	0.721
Diabetes	7 (20.6)	4 (23.5)	3 (17.6)	0.671
CAD	1 (2.9)	1 (5.9)	–	1.000
COPD	1 (2.9)	1 (5.9)	–	1.000
RAAS inhibitors, *n* (%)				
ACE inhibitors	5 (14.7)	2 (11.8)	3 (17.6)	1.000
ARBs	8 (23.5)	4 (23.5)	4 (23.5)	1.000
Severity of illness scores, mean (SD)				
CURB65 Score	1.59 (1.01)	1.44 (1.09)	1.75 (0.93)	0.391
MEWS Score	2.24 (1.84)	2.00 (1.71)	2.47 (1.97)	0.471
SOFA Score	3.53 (1.76)	3.88 (1.75)	3.19 (1.76)	0.276
Therapy, *n* (%)				0.419
Azithromycin	3 (8.8)	1 (5.9)	2 (11.8)	0.267
Hydroxychloroquine sulfate	2 (5.9)	–	2 (11.8)	
Both	29 (85.3)	16 (94.1)	13 (76.4)	
Antiviral therapy, *n* (%)				0.106
Lopinavir/ritonavir	18 (53)	6 (35.3)	12 (70.6)	
Darunavir/cobicistat	8 (23.5)	5 (29.4)	3 (17.6)	
None	8 (23.5)	6 (35.3)	2 (11.8)	
Tocilizumab, *n* (%)	19 (55.9)	8 (47.1)	11 (64.7)	0.491

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; CS, corticosteroid; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CURB65, confusion, urea, respiratory rate, blood pressure, and 65 years of age or older; DVT, deep vein thrombosis; F, female; IQR, interquartile range; M, male; MEWS, Modified Early Warning Score; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; SoC, standard of care; SOFA, Sequential Organ Failure Assessment.

Table 2. Differences in HRCT, laboratory parameters, and P/F between SoC and CS group at baseline and at the end of the study ($N = 34$).

Parameter	Baseline		End of treatment		p*	p**
	SoC ($n = 17$)	CS ($n = 17$)	SoC ($n = 17$)	CS ($n = 17$)		
HRCT features						
HRCT Total Severity Score, median (IQR)	7 (5.5–11)	10 (6.5–13.5)	10 (9–13)	6 (5–7.5)	0.205	<0.001
GGO score, median (IQR)	1.5 (0.25–3.38)	2.13 (0.63–3.68)	1.5 (0.63–3.37)	2.25 (1.84–3.75)	0.540	0.690
Consolidation score, median (IQR)	3.15 (0.71–4.35)	5.25 (2.25–8.69)	6.73 (2.49–8.03)	0.33 (0–0.92)	0.045	<0.001
Crazy paving score, mean (SD)	2.71 (2.71)	1.50 (2.45)	1.79 (2.71)	0.19 (0.53)	0.150	0.010
Linear band score, mean (SD)	0 (0)	0.20 (0.43)	0.97 (1.30)	2.56 (1.65)	0.245	0.006
Laboratory test						
Hgb, g/dL, median (IQR)	13.6 (12.3–15.1)	12.7 (11.35–14.55)	12.2 (11.4–13.95)	12.65 (11.30–13.68)	0.102	<0.001
RBC (10^6), median (IQR)	4.53 (4.22–5.32)	4.64 (3.99–4.87)	4.17 (3.84–4.85)	4.27 (3.91–4.59)	0.191	<0.001
WBC (10^3), median (IQR)	6.06 (4.10–9.49)	7.45 (4.87–11.86)	6.39 (3.03–8.45)	9.04 (7.94–12.90)	0.276	<0.001
Lymphocytes, median (IQR)						
%	12.4 (8.8–15.9)	13.8 (9.35–28.25)	14.7 (11.85–22.85)	17.55 (10.70–28.93)	0.246	0.009
(a.v.)	0.66 (0.52–0.91)	1.28 (0.69–1.60)	0.82 (0.63–1.37)	1.83 (0.82–2.29)	0.003	<0.001
Monocytes, median (IQR)						
%	4.6 (3–8.5)	8.4 (6.95–11)	8.3 (4.3–13.4)	8.8 (6–11.38)	0.024	<0.001
(a.v.)	0.33 (0.15–0.45)	0.63 (0.41–0.75)	0.46 (0.34–0.62)	0.81 (0.61–1.21)	0.001	0.997
Neutrophils, median (IQR)						
%	82.8 (76.8–89)	76 (55–80.9)	74 (57.35–80.5)	70.7 (59.2–80.98)	0.040	<0.001
(a.v.)	4.29 (3.1–6.85)	4.14 (3.18–8.80)	4.18 (1.91–6.09)	5.89 (4.87–10.25)	0.970	<0.001
Eosinophils, median (IQR)						
%	0 (0–0.6)	1.6 (0.75–2.55)	0.9 (0–2)	0.60 (0–1.1)	0.001	0.417
(a.v.)	0 (0–0.5)	0.12 (0.045–0.30)	0.05 (0–0.1)	0.05 (0–0.12)	0.011	0.043
PLT (10^3), median (IQR)	210 (148–239)	251 (207–305.5)	238 (206.5–331)	245 (181.75–429)	0.019	0.042
P/F, median (IQR)	103 (93–138)	138 (100.5–241)	136 (98.5–211.75)	310 (235.5–370)	0.114	<0.001

a.v., absolute value; CS, corticosteroid; GGO, ground glass opacity; Hgb, hemoglobin; HRCT, high-resolution computed tomography; IQR, interquartile range; PLT, platelets; RBC, red blood cells; SD, standard deviation; SoC, standard of care; WBC, white blood cells.Laboratory reference ranges: Hgb = 14–18 (g/dL); RBC = 4.30–5.90 × 10^6; WBC = 4.50–11.0 × 10^3; lymphocytes = 25–55% (a.v.: 1.5–5/mm^3); monocytes = 2–10% (a.v.: 0.1–0.9/mm^3); neutrophils = 40–75% (a.v..: 2–8/mm^3); eosinophils = 0.5–6% (a.v..: 0.02–0.6/mm^3); PLT = 150–400 × 10^3. *The p values indicate differences at baseline between the two subgroups. **The p values calculated by applying a regression model with parameters at the end of intervention as dependent variable and group allocation and parameters at baseline as covariates.

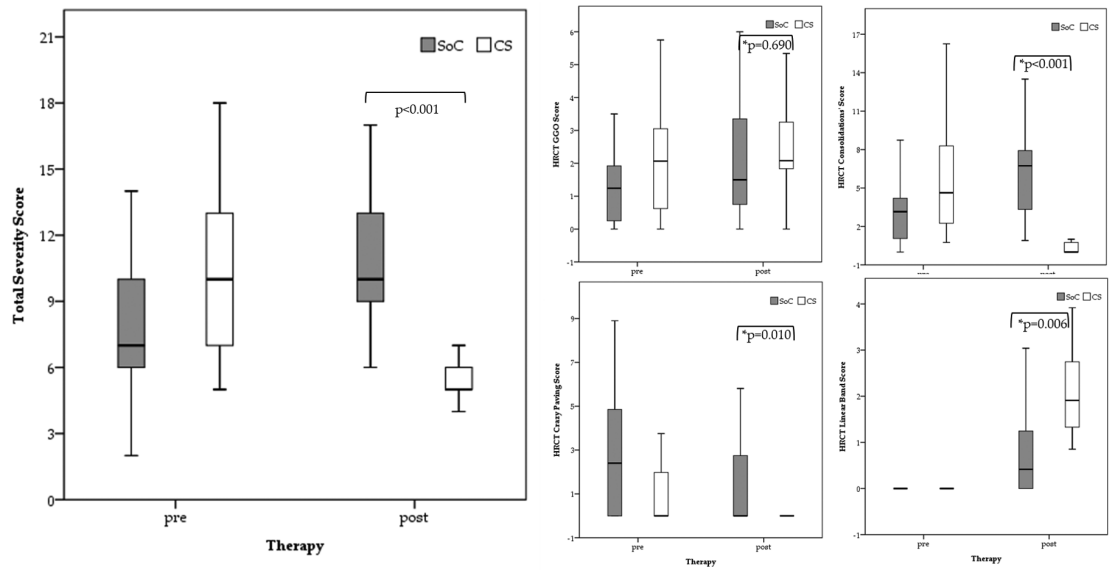

Figure 1. HRCT scores' modifications pre- and post-CS (corticosteroid therapy) compared with Standard of Care (SoC).
HRCT, high-resolution computed tomography.
*The *p* values were calculated applying a regression model with parameters at the end of intervention as dependent variable and group allocation and parameters at baseline as covariates.

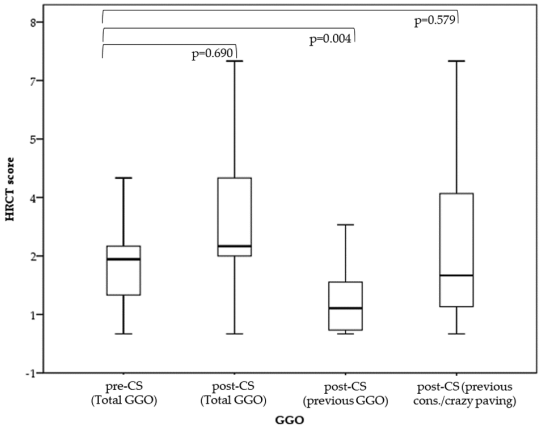

Figure 2. Pre- and post-corticosteroid (CS) therapy GGO score.
GGO, ground glass opacity; HRCT, high-resolution computed tomography.

improvement of HRCT total severity score following corticosteroid therapy, with modifications of chest images suggestive of an ongoing resolution of COVID-19 pneumonia. Particularly, we observed a significant reduction of both consolidations and crazy paving pattern associated with an increase of linear bands. Although GGO score did not significantly change, when we analyzed more in depth the evolution of GGO, corticosteroid therapy displayed a significant decrease of pre-CS GGO while most post-CS GGO derived from previous consolidations and crazy paving. The improvement of chest CT images was associated with a significant improvement of P/F ratio and hematological parameters.

The efficacy of systemic CS, compared either with usual care or with placebo, in reducing mortality in critically ill patients with COVID-19 has been demonstrated in a recent meta-analysis of several randomized controlled trials.[9] In particular, the Recovery Trial has shown that low dose of dexamethasone reduced deaths in patients hospitalized with COVID-19 who required oxygen therapy or mechanical ventilation; in contrast, no benefit was seen among COVID-19 patients who did not need any respiratory support.[10] Among CS, immediately after dexamethasone, methylprednisolone is the drug that has the greatest anti-inflammatory and the least mineralocorticoid power. In the METCOVID trial, Jeronimo and colleagues observed that a short course of methylprednisolone did not reduce mortality in the overall population hospitalized with COVID-19 but only in the subgroup of patients over 60 years of age.[11] In our study, the median age in both treatment groups was 62 years. Moreover, Wu and colleagues, in a retrospective study, showed that the treatment with methylprednisolone significantly reduced the risk

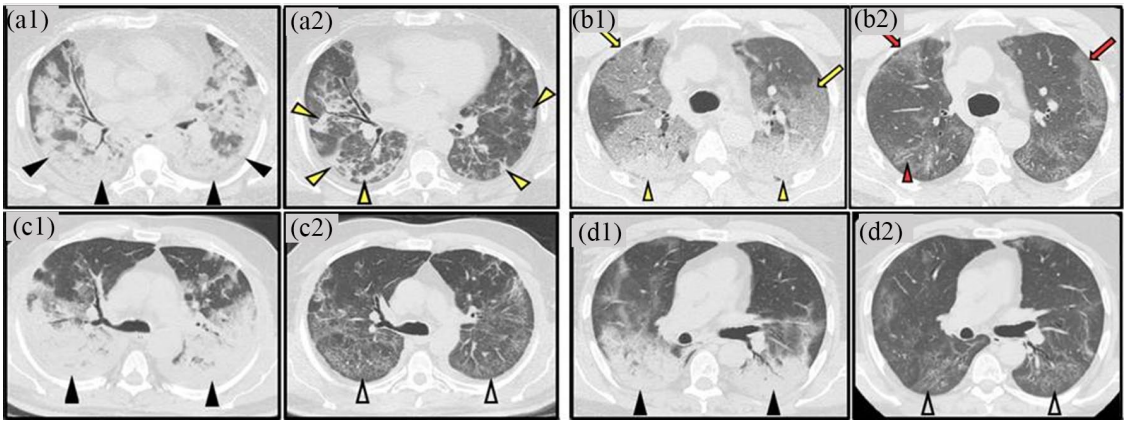

Figure 3. Axial chest HRCTs suggestive of a clear improvement of lung total severity score after CS therapy. (a.1). Pre-CS: subtotal consolidations of RML, lingula, and LLs (black arrow heads). (a.2) Post-CS: some small patches of consolidations, linear bands, and GGOs (yellow arrow heads). Reduction of lung total score, consolidations, crazy paving, and increase of GGO and linear bands. (b.1) Pre-CS: extensive and widespread areas of crazy paving (yellow arrows) with consolidation foci (yellow arrow heads) in the ULs. (b.2) Post-CS: some residual GGO (red arrows) and linear parenchymal bands (red arrowhead) in the ULs. Reduction of lung total score, consolidations, and crazy paving, and increase of GGO and linear bands. (c.1). Pre-CS: massive consolidation of the ULs (black arrow heads). (c.2) Post-CS: in both ULs residual diffuse and irregular reticulation (void arrow heads). Reduction of lung total score, consolidations, crazy paving, GGO, and increase of linear bands. (d.1) Pre-CS: extensive consolidation of the apical segments of LLs (black arrow heads). (d.2) Post-CS: complete regression of consolidations with residual diffuse and irregular reticulation (void arrowheads) in LLs. Reduction of lung total score and consolidations, and increase of crazy paving, GGO, and linear bands.
CS, corticosteroid; GGO, ground glass opacity; HRCT, high-resolution computed tomography; LLs, lower lobes; RML, right middle; ULs, upper lobes.

of death among COVID-19 patients with ARDS.[12] Very few studies, however, have investigated in depth the effect of a short-term treatment with CS on chest CT images in COVID-19 patients.

CT scan has been revealed as a key diagnostic tool not only in the early detection of COVID-19 pneumonia but also in monitoring disease progression and therapeutic response. According to previous studies, the main chest HRCT features associated with SARS-CoV-2 pneumonia are GGOs, consolidations, crazy paving pattern, and linear bands. Four stages of COVID-19 chest CT manifestations have been described: (a) early, characterized by either single or multiple patchy or conglomerate GGOs (sometimes with a crazy paving pattern); (b) advanced, characterized by an increase in density and extent of earlier findings coexisting with new lesions similar to those of early stage; (c) severe, showing diffuse lung consolidations, with air bronchograms and bronchial dilation associated with patchy GGOs; and (d) dissipation stage characterized by a gradual resolution of GGO and consolidations, with some residual curvilinear areas of density.[4]

In our study, all enrolled patients showed consolidations before starting corticosteroid therapy indicative of a severe COVID-19 disease.[13] Intravenous methylprednisolone determined a significant reduction of consolidations and crazy paving pattern, leaving residual GGOs and subpleural parenchymal bands suggestive of patients' recovery.[4] Similar to our study, Su and colleagues described three COVID-19 patients successfully treated with a tailored corticosteroid therapy according to the disease severity assessed on the basis of quantitative analysis of the images of serial CT scans.[14]

Consistent with our data, Wang and colleagues reported a significant association between an early administration of methylprednisolone (1–2 mg/kg/day) and a rapid improvement of body temperature, SpO_2, and chest CT scan in severe COVID-19 pneumonia compared with patients not receiving any corticosteroid treatment.[15]

In contrast, Yuan suggested that corticosteroid might have a negative effect on lung injury

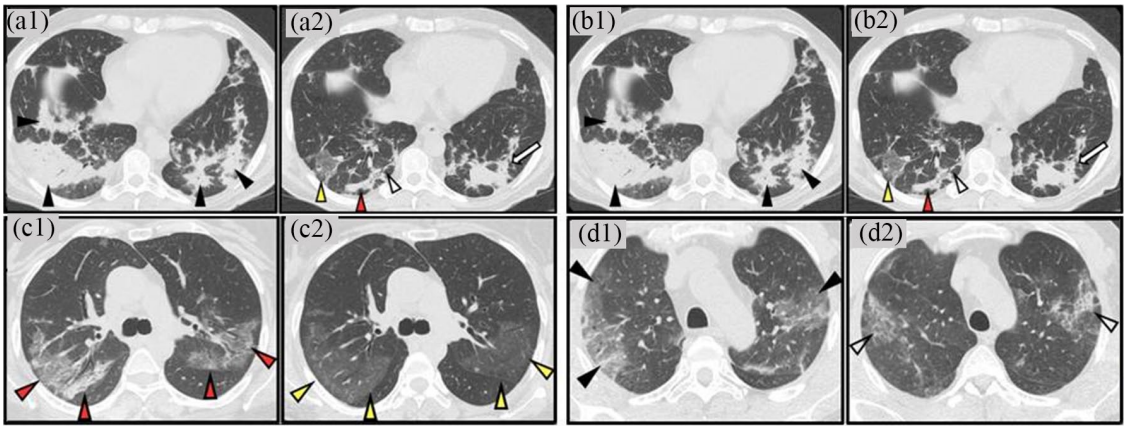

Figure 4. Axial chest HRCT of patients with a lung total severity score that did not change or the change was very little but the analysis of the relative percentages of thoracic imaging findings was suggestive of a resolution phase. (a.1) Pre-CS: several broad consolidations (black arrow heads) in the LLS. (a.2) Post-CS: in the RLL, relief of some GGOs (yellow arrowhead), small patches of consolidations (red arrowhead) and linear bands (white arrowhead). In the LLL, modest reduction in size and a change in the morphology of consolidations (white arrow). Lung total severity score changed from 10 to 9, along with a reduction of consolidations and an increase of GGOs and linear bands. (b.1) Pre-CS: extensive consolidation in the RLL (yellow arrows) and some small GGO in the LLL (yellow arrow heads). (b.2) Post-CS: residual small consolidations (red arrow) and some linear parenchymal bands (red arrowhead) in the RLL and tiny GGO in the LLL. (white arrow heads). Lung total score changed from 7 to 5, along with a reduction of consolidations and crazy paving, and an increase of GGO and linear bands. (c.1) Pre-CS: mixed areas with GGOs and consolidations (red arrow heads) in ULs (c.2). Post-CS: replacement of the mixed areas with more subtle GGOs (yellow arrow heads) in ULs. Lung total scores pre- and post- CS were the same, while consolidations and crazy paving reduced, and GGOs and linear bands increased. (d.1) Pre-CS: large subpleural GGO in ULs (black arrowheads). (d.2) Post-CS: residual irregular reticulation (void arrow heads) in ULs. Lung total score changed from 5 to 4 but we observed a reduction of consolidations and increase of GGO and linear bands.
CS, corticosteroid; GGOs, ground glass opacity; HRCT, high-resolution computed tomography; LLs, lower lobes; RLL, right lower lobe; ULs, upper lobes.

recovery, as patients in corticosteroid group had a CT score that increased on day 7 and then declined subsequently, while the score of noncorticosteroid group exhibited a trend of continuous decline.[16] The authors, however, studied nonsevere COVID-19 pneumonia, while our enrolled patients were affected by severe/critical pneumonia. In our study, we performed a quantitative and qualitative analysis of lung involvement before and after corticosteroid therapy, which has emerged, in our opinion, very useful. As an example, in some patients (Figure 3, panels c.1–c.2), treatment with intravenous methylprednisolone did not change the total lung severity score, although corticosteroid therapy replaced lung involvement mainly due to consolidations with GGOs, suggestive of a resolution phase.

In conclusion, despite the retrospective design of the study and the relatively small sample size, the HRCT improvements observed from the addition of CS therapy further support the treatment with low-dose intravenous methylprednisolone in patients affected by COVID-19 pneumonia.

Authors Contributions

GF, CC, and MM contributed to conception and design; AA contributed to experimental procedures; PI, ML, GP, and MF were involved in acquisition of data; PCP was involved in data analysis; PCP, CC, and MM interpretated the data; CC, PCP, and MM drafted the article; GF, CC, and MM critically revised the article for important intellectual content; all authors approved the final version to be published.

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Supplemental material

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