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PULSE THERAPY WITH HIGH DOSES OF CORTICOSTEROIDS INCREASES SURVIVAL IN PATIENTS WITH INTERSTITIAL PNEUMONIA WITH COVID-19

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Annotation

COVID-19 is a disease caused by the SARS-CoV-2 virus, originally described in Wuhan, China in December 2019. It is postulated that 80% of the infected population experience no symptoms or mild symptoms, and 20% are hospitalized with 5% in need of intensive care, with a mortality rate of 50% in these cases [1–3]. The course of the disease is divided into three phases: the first phase is characterized by a viral infection of the respiratory tract; secondary pulmonary phase, characterized by pulmonary infection with a non-hypoxic stage (phase IIA) and turning into a hypoxic stage (phase IIB); and the third hyperinflammatory phase [4]. A clinical study has shown that, depending on the age of the patient, individual phases of COVID -19 may be more or less virulent: while tolerance to the first virulent phase decreases with age, the last hyper-inflammatory phase can be life -threatening . threatens younger patients .

Keywords: COVID-19, pneumonia, pulse therapy, corticosteroids, hyperinflammatory reaction.

Introduction

The hyperinflammatory phase has the highest mortality rate. This hyperinflammatory response is characterized by the production pro- inflammatory cytokines of an early response, which can lead to multiple organ failure and death [5–7]. Due to the urgency of this pandemic, many interventions have been tried to counteract this hyperinflammatory response. Some of these interventions include drugs that block IL-6 (such as Tosilizumab , IL-1 (Anakinra) or corticosteroids at various doses. However, the use of the latter has proven to be controversial and continues to be a subject of controversy.

In this study, we are investigating whether there is an association between high-dose pulsed corticosteroids (GCs) and reduced risk of death in COVID -19 patients with high levels of inflammation along with other interventions. To explore some of the diagnostic criteria that can be used to determine which patients may benefit the most

from corticosteroids, we also analyze differences in laboratory markers between survivors throughout the course of COVID-19.

Relevance

Covid _19 Pneumonia is still one of the leading pathologies in the group of respiratory diseases. Which is the most dangerous virus for humanity. The incidence rate of COVID 19 in most countries is 70-82, varying depending on the age, gender, race and socioeconomic conditions of the populations surveyed [2]. According to the latest WHO data published in 2020, deaths from lung diseases in Uzbekistan reached 25.132 or 64.26% of total mortality. Age-adjusted mortality is 26.42 per 100,000 population, and according to these indicators, Uzbekistan is among the top ten in the world. The presence of treatment and complication is one of the unfavorable factors affecting the course and prognosis of covid pneumonia . Taking into account the frequent fatal outcome, it is important to timely identify and adequately correct decompensation of concomitant pathology (heart failure, cardiac arrhythmias, decompensation of diabetes mellitus), since lethality in this category of patients is often due to decompensation of conditions.

Purpose and Task

To test whether increased survival in patients with COVID-19 is associated with a risk of hyperinflammatory response to high-dose pulsed corticosteroid (GCS) therapy with methylprednisolone or dexamethasone .

Provide some initial diagnostic criteria using laboratory markers to stratify these patients.

Materials and Methods

This is a prospective study that met 106 inclusion criteria. 22 patients (20.75%) received corticosteroids using at least 1.5 mg per kg body weight every 24 hours of methylprednisolone or dexamethasone equivalent . Multivariate Cox regression (control for comorbidities and other treatments) was performed to determine if corticosteroids (among other interventions) were associated with a reduction in mortality. We also conducted a 30-day course of laboratory marker analysis between survivors to identify potential markers for patient stratification.

Methods

We recruited all patients who were admitted to the Samarkand city hospital in the department of pulmonology and allergology. With confirmed or suspected COVID-19 from December 10, 2020 to May 20, 2020 and who were over 18 years of age. 106 met

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the criteria for inclusion in the definition of SARS-CoV-2 by PCR or serology (n=90.90, 2%) or with high clinical suspicion (n=15.38, 9%), defined as the presence of bilateral pulmonary infiltrate or lymphopenia with similar clinical manifestations. All patients were of Uzbek origin. In accordance with the rules of the local ethical committee, oral consent was obtained from patients who joined the study and recorded in the medical record of each patient.

Table #1

	General (n = 106)	Survivors (n=271)	non-survivors (n = 47)	P value
	64.9(14.1)	63.3(13.6)	73.9(13.7)	<0.001
Floor				
Zhenshina	132(41.5%)	112(41.3%)		20 (42.6%)
Man	186 (58.5%)	159 (58.7%)		27 (57.4%)
P value Days with illness before hospitalization	7.79 (5.48)	8 (5.53)	6.55 (5.04)	0.078
qSOFA	0.433 (0.83)	0.331 (0.78)	1.08(0.859)	<0.001
Chesnt-ra results ^^^_		one		
Both lungs affected	217(68.2%)	183 (67.5%)	34 (72.3%)	0.612
One lung affected	59(18.6%)	49 (18.1%)	10 (21.3%)	0.684
None	42(13.2%)	39(14.4%)	3 (6.38%)	0.165
NIH Clinical Presentation				
Minor	0(0%)	0(0%)	0(0%)	
Moderate	19 (6%)	19 (6%)	0(0%)	
Severe & Critical	299 (94%)	252 (92.9 %)	47 (100%)	
Heat	241 (76%)	210 (77.5%)	31 (67.4%)	0.14
Dyspnea	164 (51.6%)	136 (50.2%)	28 (59.6%)	0.27
cough	66.66(63.3%)	59(65.6%)	7.66(50%)	0.016
Asthenia	52.6 (49.8%)	43.3 (48.1%)	9.33 (59.6%)	0.052 _
Anosmia	18 (5.66%)	17 (6.27%)	1 (2.13%)	0.49
Agevsia	22 (6.92%)	20 (7.38%)	2 (4.26%)	0.754
Obesity	48(15.2%)	40 (14.9%)	8 (17%)	0.664
Smoking				
Former smoker	20 (6.29%)	17 (6.27%)	3 (6.38%)	one
Yes	39(12.3%)	30(11.1%)	9(19.1%)	0.146
COPD	24 (7.55%)	17 (6.27%)	7 (14.9%)	0.065
Asthma	26 (8.18%)	23 (8.49%)	3 (6.38%)	0.779
hypertension	164(51.6%)	141 (52%)	23 (48.9%)	0.753
chronic heart disease	28(8.81%)	22 (8.12%)	6 (12.8%)	0.275
atrial fibrillation	36(11.3%)	28 (10.3%)	8 (17%)	0.21
Immunosuppressant	13 (3.77%)	8 (2.95%)	4 (8.51%)	0.084
Tumor	35(11%)	26 (9.59%)	9(19.1%)	0.073
ACE inhibitor	131 (41.2%)	115(42.4%)	16 (34%)	0.336
Corticosteroids before hospitalization	19 (5.97%)	14 (5.17%)	5 (10.6%)	0.175
Diabetes	75 (23.6%)	61 (22.5%)	14 (29.8%)	0.27
Vitamin D level	17.6(33.7)	18.1 (35.3)	12.5(10.9)	0.173

We conducted a prospective observational study in which clinical data were collected from all eligible patients and compared retrospectively. Upon arrival at the hospital, we recorded the following: age, sex, date of onset of COVID-19 symptoms, and presence of dyspnea, cough, fever, asthenia, and oxygen saturation level on a pulse oximeter . The following comorbidities from the medical history were also recorded : arterial hypertension, smoking, chronic obstructive pulmonary disease (COPD), asthma, chronic heart disease (CHD), atrial fibrillation, diabetes mellitus, and whether the patient was taking any oral or inhaled corticosteroids. Before hospitalization (regardless of duration) were you taking against cancer or immunosuppressive therapy (i.e., patients who were taking immunosuppressive drugs, had human immunodeficiency virus (HIV), or were immunosuppressed due to long-term oral or inhaled corticosteroid therapy). In addition, we recorded whether patients were taking an angiotensin -converting enzyme (ACE) inhibitor/ angiotensin receptor blocker (ARB). Each of these patients underwent PCR for SARS-CoV-2 and/or serological analyzes (IgM and IgG) tests.

We collected the results of all laboratory tests performed from the start of hospitalization to the end point of death or hospital discharge. All patients in the intensive care unit underwent laboratory tests every 24 hours . Patients outside the intensive care unit underwent laboratory tests every 48 hours if they did not show worsening of symptoms (in these cases they were checked every 24 hours). Levels of 40 markers were measured in these laboratory tests, including hemogram, glomerular filtration rate, creatinine kinase , triglycerides, lactate dehydrogenase , interleukin 6 (IL-6), ferritin , HIV serology, immunoglobulins and vitamin D, international normalized ratio. (INR), prothrombin time and partial thromboplastin time (see Table B 1 for a complete list). Upon arrival at the hospital, we also took a chest X-ray and performed a rapid assessment of the organ failure associated with sepsis [9].

During their stay in the hospital, we assessed the need for oxygen supplementation and the maximum required oxygen flow (we considered high oxygen requirements, oxygen volumes exceeded 10 L per min); artificial ventilation of the lungs (invasive or non-invasive); and the need for intensive care. We also registered all medications taken during their hospital stay: hydroxychloroquine , groprinosin , immunoglobulin therapy, tosylizumab , anakinra , azithromycin , vitamin D supplements, anticoagulant and corticosteroid therapy. For anticoagulant therapy, we used either low molecular weight heparin (LMWH) or direct-acting oral anticoagulants at three different dosages: prophylactic 3500–4000 IU per day; intermediate 5,000–6,000 IU per day; or full 115–150 IU per kg per day (in all cases this medication was used throughout the entire hospital stay).

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	Hazard coefficient	
Age	P=0.0 10	1.050(1.012-1.09)
sex life	P=0.065	0.429(0.174-1.05)
hypertension	P=0. 291	0.561 (0.191-1.64)
COPD	P=0. 347	1 . 733 (0.553-5.44)
Asthma	P=0. 258	2 . 235 (0.55 4 -9.02)
chronic heart disease	P=0. 927	1 . 060 (0.312-3.59)
atrial fibrillation	P=0. 387	1.674 (0.521-5.38)
Obesity	P=0. 714	1 . 238 (0.393-3.90)
Tumor	P=0.0 85	2.447(0.881-6.79)
ACE inhibitors	P=0. 299	0.581(0.209-1.62)
Pre-corticosteroids	P=0. 489	0.456(0.049-4.22)
Immunosuppressants	P=0. 588	1.738(0.235-12.89)
Required high volume of oxygen	P <= 0.001	28.853(10.483-79.41)
Diabetes	P=0. 661	1.219-(0.502-2.96)
qSOFA	P= 1.1	1.000(0.702-1.42)
Hydroxochloroquine	P=0.0 43	0.248(0.063-0.96)
Azithromycin	P=0. 980	1.012(0.373-2.74)
Groprinosin	P=0. 43	1.507(0.544-4.17)
Interferon	P=0. 988	0.991(0.295-3.34)
Low dose corticosteroid	P=0. 232	0.538(0.194-1.49)
high dose corticosteroid	P <= 0.002	0.086(0.021-0.36)
Vitamin D	P=0. 123	0.164(0.016-1.64)

Within corticosteroid therapy, we distinguished between high-dose corticosteroid pulse therapy and low-dose corticosteroid therapy. High-dose corticosteroid pulse therapy was defined as a daily dose of methyl prednisolone or dexamethasone

equivalent of at least 1.5 mg/kg/24 hours. The standard duration of pulse therapy with high doses of corticosteroids was 3 days. In some patients who did not improve after 3 days, the course of treatment was extended to 5 days. In two patients, the course of treatment was reduced to 2 days due to the observed significant recovery. High-dose corticosteroid pulses were given to patients according to criteria previously proposed based on empirical observations and guidelines used for macrophage activation syndrome [10]: either IL-6 at a concentration of at least 40 pg /mL, or two of them: ferritin , triglycerides. and D - dimer at least 300 mg/ml, 300 mg/l and 1000 mg/ml, respectively. GCS was administered immediately after determining the levels of these markers, regardless of whether the patient was in the intensive care unit or in the pulmonology department. Not all patients who met these criteria received pulsed high-dose corticosteroids: out of 53 patients, 16 received pulsed high-dose corticosteroids. There were also 6 patients who received pulsed high doses of corticosteroids due to their critical clinical status, even though they did not meet these criteria for high inflammation. These 6 patients were receiving high-dose corticosteroid pulse therapy because they developed severe respiratory failure and did not respond to standard clinical treatment for COVID-19 at the time, including pharmacological (hydroxychloroquine , azithromycin , and lopinavir-ritonavir) and physical interventions (e.g. changes in posture). Low-dose corticosteroid therapy is defined as less than 1.5 mg/kg/24 hours of methylprednisolone or dexamethasone equivalent and is given to patients who have had bronchospasm , according to standard clinical guidelines.

To test for associations between outcome and demographic and clinical variables at admission, Student's t-tests or Fisher's t-tests were performed for numerical and categorical variables, respectively (Table 1).

A multivariate Cox regression model was fitted to assess treatment effect for the entire cohort using the following covariates : age, gender, hypertension, chronic obstructive pulmonary disease, asthma, chronic heart disease, atrial fibrillation, obesity, tumor, ACE inhibitors/ARBs, whether the patient was taking corticosteroids during hospitalization, whether the patient was immunosuppressed, whether the patient was given large volumes of oxygen (>10 L), diabetes, qSOFA , hydroxychloroquine , azithromycin , lopinavir / ritonavir , interferon, low-dose corticosteroids, corticosteroids, vitamin D supplementation, and anticoagulant therapy (in an intermediate, full or prophylactic dose). Using this multivariate Cox model, hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Differences in laboratory markers among survivors during the first month of illness were calculated by time trend fitting using a regression spline. A moderate F-test was

then performed on the interaction parameter time: survival/ non- survival to assess the significance between the two groups. P values were adjusted for multiple testing and false detection rate, CRF was calculated using the method of Benjamini and Hochberg (function R p.adjust). The significance level taken into account in all analyzes was 0.05. All statistical analyzes were performed using R (version 3.6.0).

Results

Cohort characteristics

We recruited all patients who were admitted to the Samarkand city hospital in the department of pulmonology and allergology. FROM confirmed or suspected COVID-19 from December 10, 2020 to May 20, 2020 and who were over 18 years old as specified in the methods. According to the recommendations of the GIN [16], of the 106 patients included in our study, 7 patients were moderate (6.3%). The remaining patients were severe or critical (n = 94.64.4%). Unfortunately, we cannot distinguish between severe and critical patients as we have no data on respiratory or multi-organ failure and not all critical patients were admitted to intensive care due to overcrowding at the height of the pandemic. Patients were admitted to the hospital an average of 7.79 days after the first symptoms of COVID-19. The median age was 54.9 (SD 13.1), ranging from 19 to 86 years. 62 men (58.5%) and 44 women (41.5%). All patients were of Uzbek origin. Hypertension and diabetes mellitus were present in 51.6% and 23.6% of patients, respectively. Other comorbid conditions were infrequent (less than 10%) and did not show any statistically significant difference between survivors and non-survivors (Table 1). As previously reported [12, 13], vitamin D levels differed significantly between survivors and non-survivors (p = 0.025). None of the treatments prior to hospitalization (i.e. Corticosteroids and ACE inhibitors/ARBs) showed statistically significant differences between survivors and non-survivors.

Study Endpoint

We aimed to explore which factors and interventions were associated with improved survival using multivariate Cox regression analysis. Of the 106 patients included in the study, 16 died (14.15%). Table 2 provides a complete list of therapeutic interventions and patient oxygen requirements.

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Table number 2

	General (n = 106)	Recovered (n = 271)	Not recovered (n = 47)	P value
Nutrition for oxygen supplement	259(81.4%)	215 (79.3%)	44 (93.6%)	0.024
Requires a high volume of oxygen	74 (23.9%)	38 (14.4%)	44 (93.6%)	<0.001
VI Mechanical assisted ventilation (non-invasive)				
CPAP	3 (0.943%)	2 (0.743%)	1 (2.22%)	0.372
High flow oxygen	27 (8.49%)	18 (6.69%)	9 (20%)	0.007
Entered intensive care	25 (7.91%)	12 (4.44%)	13 (28.3%)	<0.001
Hydroxychloroquine	297 (93.4%)	257 (94.8%)	40(85.1%)	0.022
Azithromycin	281 (88.6%)	244 (90.4%)	37 (78.7%)	0.042
Groprinosin	209 (65.7%)	180 (66.4%)	29 (61.7%)	0.618
Interferon	37(11.7%)	27(10%)	10(21.3%)	0.045
High dose corticosteroids PT	64(20.1%)	60 (22.1%)	4(8.51%)	0.031
Low dose corticosteroids	68(21.4%)	57 (21%)	11 (23.4%)	0.702
Immunoglobulins	3 (0.943%)	3(1.11%)	0(0%)	one
Vitamin D supplements	37(11.6%)	36 (13.3%)	1 (2.13%)	0.025
Anticoagulants: prophylactic dose.	233(73.3%)	200 (74.6%)	33 (70.2%)	0.589
Anticoagulants: intermediate dose	24 (7.55%)	22 (8.18%)	2 (4.26%)	0.551

COPD, continuous positive airway pressure. High doses of corticosteroids PT, pulse therapy with high doses of corticosteroids. DOAC, direct acting oral anticoagulants. LMWH, low molecular weight heparin. Numeric variables are presented as mean (standard deviation). Categorical variables are presented as total numbers with percentages. P-values were calculated using Student's t-test (numerical variables) or Fisher's exact test (categorical variables).

Multivariate Cox regression controlling for clinical covariates as well as all treatments patients received (Fig. 1, see Methods) revealed a statistically significant increase in the risk of death with age (RR 1.05 [95% DD 1.01–1, 09]; P = 0.009) and high volumes of oxygen demand (> 10 L, HR 28.85 [95% DN 10.48–79.41]; P < 0.001). Preventive anticoagulation showed a less statistically significant adverse effect (RR 2.99 [95% CI 1.05–8.50], P = 0.04). No other interventions showed a statistically significant increase in mortality. Pulse therapy with high doses of corticosteroids showed a statistically significant reduction in mortality (RR = 0.087 [95% CI 0.021–0.36]; P < 0.001). Hydroxychloroquine was the only other intervention that showed some statistical evidence of a reduction in mortality, albeit only at a P < 0.05 level (RR = 0.249 [95% DA 0.064–0.96]; P = 0.043).

Analysis of the dynamics of laboratory markers of all 40 analyses.

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We analyzed the dynamics of forty different laboratory markers during the first month of disease onset, distinguishing between COVID-19 survivors and non-survivors, n = 106 (Methods and Table B1).

Table No. B 1

All forty laboratory analyzed and tested. P-value and False Conversion Rate (FFR) included 30-day time analysis between survivors and non-survivors. Markers with statistically significant changes are highlighted in green.

Laboratory markers	P value	Rate (FCR)	unit of measurement	Normal values
Urea	1.27E-63	5.86E-62	mg / dL	[10 - 50]
lactate dehydrogenase	9.45E-52	2.17E-50	U/L	[0 - 250]
C-reactive protein	1.19E-49	1.82E-48	mg /L	[0.0 - 5.0]
Hemoglobin	3.00E-36	3.44E-35	g/ dL	[13.0 - 18.0]
Absolute neutrophil count	6.73E-30	6.20E-29	x 10^3/ µL	[2.00 - 7.50]
platelets	8.18E-30	6.27E-29	x 10^3/ µL	[130 - 450]
Glomerular rate filtration	6.86E-24	4.51E-23	mL / min	
Gamma glutamin transferase	1.53E-23	8.79E-23	U/L	[8 - 61]
fibrinogen	3.51E-21	1.79E-20	mg / dL	[150 - 400]
D -dimer	4.92E-18	2.26E-17	ng / mL	[0 - 500]
Interleukin 6	1.03E-17	4.30E-17	pg / mL	[0.00 - 7.00]
Percentage of eosinophils	1.95E-15	7.46E-15	%	[0.00 - 6.00]
Medium corpuscular volume	5.38E-13	1.90E-12	fL	[82.0 - 95.0]
Glucose	1.17E-11	3.83E-11	mg / dL	[74 - 106]
Total basophils	2.76E-10	8.48E-10	x 10^3/ µL	[0.00 - 0.10]
Alanine transaminase	3.16E-10	9.09E-10	U/L	[0 - 41]
Total protein content	9.25E-05	2.24E-04	g/ dL	[6.4 - 8.3]
Partial thromboplastin time	2.08E-04	4.78E-04	Seg	[25.0 - 37.0]
Triglycerides	2.69E-04	5.90E-04	mg / dL	[30 - 150]
Aspartate transaminase	5.49E-04	1.15E-03	U/L	[0 - 40]
Medium corpuscular hemoglobin	7.19E-04	1.44E-03	pg	[27.0 - 32.0]
Average corpuscular hemoglobin concentration	8.94E-04	1.71E-03	g/ dL	[32.0 - 36.0]
Troponin T high sensitivity	1.34E-03	2.47E-03	ng /L	[0.0 - 14.0]
Total monocytes	1.52E-03	2.68E-03	x 10^3/ µL	[0.00 - 1.00]
red blood cells	6.75E-03	1.15E-02	x 10^6/ µL	[4.00 - 5.50]
prothrombin time	1.20E-02	1.97E-02	Seg	[11.0 - 14.0]
fibrinogen	2.46E-02	3.88E-02	mg / dL	[150 - 400]
Total number of lymphocytes	2.53E-02	3.88E-02	x 10^3/ µL	[1.00 - 4.00]
total bilirubin	7.69E-02	1.11E-01	mg / dL	[0.1 - 1]
Creatine kinase	1.18E-01	1.51E-01	U/L	[39 - 308]
Leukocyte	1.17E-01	1.51E-01	x 10^3/ µL	[3.70 - 9.70]
Percentage of leukocytes	1.18E-01	1.51E-01	%	[20.00 - 45.00]
Percentage of Monocytes	1.14E-01	1.51E-01	%	[2.00 - 10.00]
Prothrombin time (percentage)	2.07E-01	2.57E-01	%	[70 - 120]
Albumin	2.96E-01	3.58E-01	g/ dL	[3.5 - 5.2]
Hemocrit	5.20E-01	5.98E-01	%	[40.0 - 54.0]
Neutrophy l (percentage)	5.14E-01	5.98E-01	%	[40.00 - 75.00]
Average platelet volume	5.93E-01	6.65E-01	fL	[7.0 - 11.0]
Basophils (percent)	7.95E-01	8.31E-01	%	[0.00 - 1.00]
Creatinine	9.17E-01	9.37E-01	mg / dL	[0.70 - 1.20]
Eosinophils	9.92E-01	9.92E-01	x 10^3/ µL	[0.00 - 0.30]

Statistically significant levels (CLF <0.05) were found for thirty markers (see Table B 1). Among these, we highlight time differences in the following pro- inflammatory markers: IL-6, ferritin , lactate dehydrogenase (LDH), D - dimer , and C -reactive protein (CRP , Fig. 2a). Because of its utility in clinical decision making, we also highlight overall temporal differences in platelets, total neutrophils, troponin T , total lymphocytes, procalcitonin , glomerular filtration rate (CRP), and triglycerides (Figure 2b).

Following this temporal analysis of pro- inflammatory markers in survivors , we could suggest initial COVID-19-specific criteria for diagnosing the development of a COVID -19 hyperinflammatory response as follows: Patients with IL-6 >=40 mg/mL and/or two of the following: C α-reactive protein >= 100 mg/L, D- dimer >= 1000 ng /mL, ferritin >= 500 ng /mL, and lactate dehydrogenase >= 300 U /L (Fig. 2a, marked with red line).

Discussion

In this study, we show that in patients infected with SARS-CoV-2, the use of pulsed corticosteroids can increase survival. Several studies have reported that the use of corticosteroids may not be useful in diseases caused by other coronaviruses (such as SARS-CoV-1 and MERS- CoV) [8]. On the contrary, even without published scientific data [16], other authors [15-18] recommended their use to stop hyperinflammatory response after the observed hyperinflammatory phase and its similarity to the inflammatory phases seen in other diseases such as hemophagocytic syndrome or macrophage activation syndrome [19]. In this study, we define pulsed high-dose corticosteroids as doses of at least 125 mg of methylprednisolone or dexamethasone equivalent acting on the disease. Previous studies in patients with COVID-19 found no clinical difference between doses of methylprednisolone above 125 mg [10,20,21]. We also tested low dose corticosteroids and found no statistically significant difference in results. However, they were used for no more than five days, so it cannot be ruled out that they can be effective with a longer course of treatment.

To determine which patients may develop a hyperinflammatory response, and therefore decide which patients should be given glucocorticosteroids, we mainly followed the criteria previously proposed based on empirical observations and the guidelines used for macrophage activation syndrome (IL-6> = 40 pg) . / ml and / or two of the following: D - dimer >= 1000 ng / ml, ferritin > = 300 ng / ml and triglycerides > = 300 mg / dl) [10]. However, despite the similarities between the inflammatory response seen in this disease and COVID-19, our temporal analysis of pro- inflammatory markers between survivors and non-survivors showed some

notable differences from which we could derive specific criteria for diagnosis . development of a hyperinflammatory response to COVID -19. Returning to the criteria proposed by [10], we would keep the same thresholds for IL-6 (IL-6 >= 40 pg /mL) and D- dimer (D - dimer >= 1000 ng /mL) . ml) and raise the ferritin limit to 500 ng /ml, since both survivors and non-survivors had a mean ferritin level of over 300 ng /ml. We did not observe clear differences that could differentiate between survivors and non-survivors in terms of triglyceride levels, because of this we removed this marker and instead propose to include C-reactive protein and lactate dehydrogenase as indirect markers of inflammation at >= 100 mg/kg . L and >= 300 U /L, respectively.

Patients included in this study were also taking other drugs, including the anti-inflammatory drug tosilizumab (used in 5 patients with IL-6 levels above 40 pg /mL). Although we observed a survival rate of 73.1% in patients treated with tosilizumab , the overall results were not statistically significant (which may be due to the small sample size). However, the observed trend towards increased survival is consistent with data published by] and Campins. et al [22]. In their study, they found increased survival of tosilizumab in patients with early intervention and multiple doses.

The role of hydroxycholoquine in COVID-19 remains controversial. In our study, we found only a minor association between hydroxycholoquine use and increased survival. Although this study was not designed to assess the role of hydroxycholoquine in survival, this marginal association may be consistent with what was reported in previous studies in which they found hydroxychloroquine to be effective in inhibiting SARS-CoV-2 in vitro [23] . In contrast, randomized clinical trials such as RECOVERY [24] and the study by Cavalcanti et al [25] did not find an increase in survival in patients with COVID-19. However, the clinical study by Cavalcanti only looked at patients with mild and/or moderate COVID-19, and the RECOVERY study did not look at patients who were hospitalized with severe disease. To date, there is not enough evidence to suggest that hydroxycholoquine is effective in increasing the survival of patients with COVID-19, and more research is needed to analyze the effect of hydroxycholoquine on COVID-19. With regard to other antiviral therapies, although some potential beneficial effects have been described for azithromycin [26], groprinosin [27] and interferon [28], we did not find a statistically significant increase in survival with either of them or with their combination . and from them.

Extensive blood clotting has also been observed in COVID-19 [29-33], which may indicate the need for antithrombotic therapy in all patients with high D- dimer levels or indicate initial disseminated intravascular coagulation [34]. However, this is still a matter of debate, and recent studies have also questioned the need for a full dose of

anticoagulant if there is no additional clinical evidence to support this need. In our study, although we found a non-significant association between prophylactic anticoagulant therapy and mortality, our analyzes were not designed to ask this question, but instead looked at interventions that affect overall inflammation associated with death. Thus, we do not conclude that the prophylactic dose increases the risk of death. To answer this question, we would have to specifically stratify patients based on D- dimer levels . Further research should evaluate different types of anticoagulants and their association with disease outcomes.

Results

GCS preparations showed a statistically significant reduction in mortality (HR = 0.087 [95% CI 0.021–0.36]; P < 0.001). An analysis of a 30-day course of laboratory tests for markers showed marked differences in pro- inflammatory markers between survivors . As diagnostic criteria for identifying patients at risk of developing a COVID -19 hyperinflammatory response, we suggest the following parameters (IL-6 >= 40 mg/mL or two of the following: C-reactive protein >= 100 mg/L, D- dimer >= 1000 ng /ml, ferritin >=500 ng /ml and lactate dehydrogenase >=300 U/l).

Conclusions

Corticosteroids may be an effective intervention to increase COVID-19 survival in patients at risk of developing a hyperinflammatory response to COVID-19, laboratory marker tests can be used to stratify these patients who should be prescribed corticosteroids. This study is not a randomized clinical trial (RCT). In the future, an RCT is needed to confirm the effectiveness of corticosteroids in improving survival and life extension in COVID-19.

Other studies have shown that corticosteroid therapy does not affect the time of virus clearance [27]. Unfortunately, in our study, we did not conduct follow-up to quantify viral clearance. It would be interesting to assess whether glucocorticosteroids affect viral clearance time, and we hope that future studies may shed light on this topic.

This study has some serious limitations, including that all patients were from the same center and the same ethnic group. Moreover, even though we performed a multivariate analysis to account for any possible confounding effects, there may be different imbalances between patient groups. This study is not a randomized clinical trial, so a causal relationship cannot be established. However, there is a promising effect of high-dose corticosteroid pulse therapy in improving severe/critical disease progression of COVID-19 and increasing survival in patients at risk of developing a hyperinflammatory response. We also propose some initial criteria using pro-

inflammatory markers to diagnose these patients. Future multicenter randomized clinical trials should be conducted to confirm the efficacy of pulsed therapy with high pulsed corticosteroids to increase survival in COVID-19.

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