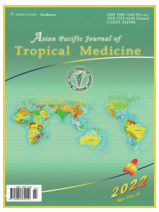

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Outcome of patients with severe COVID−19 pneumonia treated with high−dose corticosteroid pulse therapy: A retrospective study

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ABSTRACT

Objective: To assess the effectiveness of high-dose corticosteroid pulse therapy and evaluate possible factors associated with 28-day mortality in hospitalised patients with severe COVID-19 pneumonia.

Methods: We conducted a single-centre retrospective cohort study on hospitalised patients with clinical, epidemiological, and/or radiologically confirmed and suspected COVID-19 at Bitlis Tatvan State Hospital in Turkey between December 1, 2020 and June 1, 2021. All data of the study participants were recorded, and all patients received intravenous high-dose corticosteroid pulse therapy. The Ordinal Scale for Clinical Improvement (OSCI), Charlson Comorbidity Index and Total Severity Score were calculated. Univariate and multivariate Cox regression models were performed to evaluate the clinical and laboratory parameters that may affect the 28-day mortality.

Results: A total of 126 patients were included in the analysis. The 28-day mortality rate of the patients was 22.2%. Laboratory and clinical improvement were observed in 77.8% (98/126) of patients after high-dose corticosteroid pulse therapy. There was a statistically significant difference between the survivors and non-survivors in terms of age, platelet count, neutrophil/lymphocyte ratio, and OSCI, Charlson Comorbidity Index, and Total Severity Score (P<0.001). Multivariate Cox regression analysis revealed that age [*HR* 1.047 (95% *CI* 1.01-1.08)], use of prophylactic anticoagulation [*HR* 0.838 (95% *CI* 0.79-0.89)], and bacterial co-infection [*HR* 3.966 (95% *CI* 1.40-11.21)] were significant determinants of mortality. Early C-reactive protein (CRP) response, decreased oxygen requirement, and improving respiratory rate/OSCI scores after administration of high-dose corticosteroid pulse therapy could contribute to clinical improvement.

Conclusions: CRP response, needed oxygen and OSCI scores can be used as prognostic factors to select patients who will benefit from high-dose corticosteroid pulse therapy.

KEYWORDS: Corticosteroid; Coronavirus disease 2019 (COVID-19); Mortality; Prognostic factors

1. Introduction

Coronaviruses (CoVs) are enveloped positive-stranded RNA viruses causing mild to severe respiratory and intestinal infections[1,2]. In December 2019, a new coronavirus belonging to the genus *Betacorona virus*, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an unusual viral pneumonia outbreak in Wuhan, China[3,4]. The World Health Organisation (WHO) named the disease coronavirus disease 2019 (COVID-19) and declared the viral outbreak a global pandemic on March 11, 2020[5,6].

Significance

This study highlighted that bacterial coinfection and older age are important factors related to mortality for COVID-19 pneumonia patients who received high-dose corticosteroid pulse therapy. Early CRP response improved respiratory rate/OSCI scores, and decreased oxygen need after pulse steroid treatment might contribute to clinical improvement.

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The clinical spectrum of the COVID-19 infection varies from asymptomatic carriage, mild forms, and moderate forms that require hospitalisation (pneumonia) to severe forms that result in death[7,8]. Patients with COVID-19 progress to acute respiratory distress syndrome (ARDS), multiple organ failure, and death due to excessive release of proinflammatory cytokines which is defined as a cytokine storm[9,10].

Various antiviral therapies have been used to treat COVID-19 around the world[11]. In the absence of effective antiviral therapy, current clinical management of the disease is primarily supportive care[12]. Considering the pathogenesis of cytokine storm in severe COVID-19 cases, anti-inflammatory treatments, such as corticosteroids, tocilizumab, or anakinra have been administered[13,14].

Corticosteroids have been widely used as adjuvant therapy during SARS-CoV, MERS-CoV, and influenza virus outbreaks, but the results are controversial[14]. On the one hand, it is thought to inhibit tissue damage by reducing the inflammatory response; but on the other hand, it is feared that it may inhibit cell-mediated immunity (*i.e.*, reducing antigen presentation, lymphocyte proliferation, *etc.*), which could reduce viral clearance and also the increase of the risk of secondary infections and adverse effects[14,15]. Studies have reported that corticosteroid treatment increases mortality in SARS-CoV and MERS-CoV, delays viral clearance, increases not only mortality but also hospital infections, and prolongs intensive care unit (ICU) stay in influenza pneumonia[16,17].

Despite the lack of previous evidence of a clear benefit for patient survival outcomes (due to their hypothetical benefits on pulmonary function and potential effects in reducing the number of patients requiring invasive procedures), corticosteroids have been used in clinical practice for the management of COVID-19 hospitalized patients[15].

Although the WHO initially recommended against the use of corticosteroids for COVID-19 patients, based on studies on other viral pneumonia, recent randomised trials have shown positive effects[14,18,19].

A large UK-based randomised clinical trial of Randomised Assessment of COVID-19 Therapy included 6 245 patients. A 10-day course of dexamethasone (6 mg/day) appeared to reduce the 28-day mortality in patients given oxygen without invasive mechanical ventilation, whereas no survival benefit was observed in those who did not receive respiratory support[18].

Based on this information, we analysed whether there is a relationship between any clinical and/or laboratory characteristics and response to high-dose corticosteroid pulse therapy (HDCPT) in patients with severe COVID-19 pneumonia, and differences in clinical features and laboratory markers between survivors and non-survivors to identify possible predictors associated with mortality. Therefore, we planned a retrospective observational study to determine the patients who may benefit from HDCPT.

2. Subjects and methods

2.1. Study design

Patients who received inpatient treatment with the diagnosis of COVID-19 at Bitlis Tatvan State Hospital between December 1, 2020 and June 1, 2021 were included in this single-centre retrospective cohort study. Our institution is a 400-bed secondary-level state hospital in Turkey. A total of 126 subjects met the inclusion criteria, which included those with PCR-detected SARS-CoV-2 (n=120, 95.2%) or clinically compatible signs and symptoms (n=6, 4.8%) who had bilateral pulmonary infiltrates on computed tomography (CT) and lymphopenia with high clinical suspicion.

The probable and definitive diagnosis of COVID-19 pneumonia and all treatment strategies were based on guidelines prepared by the Ministry of Health Scientific Committee[20]. Patients were included in the study if they met the following inclusion criteria: 1) ≥18 years of age, 2) had SpO_2 of <92%, 3) had positive nasal or nasopharyngeal RT-PCR test results, 3) had strong computed tomography (CT) scan findings consistent with COVID-19 pneumonia, 4) who received intravenous 250 mg or more of methylprednisolone (or equivalent steroid therapy) (high-dose corticosteroid pulse therapy, HDCPT for at least 1 day, 5) agreed to give informed consent. Individuals were excluded from the study if they met the following criteria: 1) <18 years of age, 2) were pregnant or lactating women, 3) had active malignancies and immunosuppression, 4) had mild to moderate pneumonia findings, 5) had a clinical response to standard therapy. The results are reported in accordance with the STROBE guidelines.

2.2. Ethical statement

This study was approved by the Marmara University Clinical Research Ethics Committee (09.2021.711 issue/04.06.2021 date). Informed consent was obtained from the patients participating in the study according to the local ethics committee regulations.

2.3. Data collection

Demographic, clinical, laboratory, and radiological data of the study participants were obtained from electronic medical records. Clinical findings and laboratory data were evaluated during hospitalisation: from day 0 to day 3 high-dose corticosteroid pulse therapy, recovery, hospital discharge, or death and followed up 1 week after hospital discharge. All medications taken during their hospital stay and

COVID-19 vaccine information were also recorded. Routine blood examinations and CT scans were also conducted on all inpatients.

Disease severity at admission was defined according to the COVID-19 Diagnosis and Treatment Guidelines[21]. The WHO Ordinal Scale for Clinical Improvement (OSCI) was used to measure disease severity over time. OSCI distinguishes various levels of COVID-19 clinical severity, with a score ranging from 0 to 8 according to the specific treatments required[22].

Comorbidities of the patients were recorded. The Charlson Comorbidity Index (CCI), which predicts the risk of death and includes 17 comorbidities, was used to evaluate the prognostic burden of comorbid diseases[23,24]. The Total Severity Score (TSS), developed by Kunwei *et al*, was used to assess the severity of lung involvement. The thoracic CT images at the time of diagnosis were used for the assessment[25]. To determine the degree of oxygen demand, a varying supplementary scoring system between 0 and 6 was used. Oxygen was given to the patients to ensure that the SpO_2 level was above 92% as standard[26].

2.4. Administration of methylprednisolone and other drugs

For anticoagulation therapy, enoxaparin sodium was given during the hospital stay to all inpatients without contraindication and was also prescribed at discharge. All patients were given favipiravir (2 × 1600) mg loading dose and (2 × 600) mg maintenance therapy (5-10 days), according to the COVID-19 Adult Patient Treatment Guidelines[21].

Low-dose methylprednisolone or equivalent steroid therapy [(1-1.5) mg/kg/day] was added to patients who needed oxygen therapy support because of respiratory distress (SpO_2 ≤92%). HDCPT (250 or 500 mg) methylprednisolone was added to patients who were unresponsive to pharmacological treatment, were clinical deteriorating (increased OSCI score), needed non-invasive or invasive mechanical ventilation, had levels of C-reactive protein (CRP) 10 times the upper limit of normal value [10 × (0-5) mg/L], ferritin >500 ng/mL, with severe pneumonia (≥50% lung involvement) in lung CT, and with lymphopenia (<800/μL). As for maintenance steroid treatment, (1-1.5) mg/kg/day methylprednisolone was continued.

The decision to prescribe steroids was at the discretion of the treating physician. All undesirable/adverse effects experienced by the patients during the study related to methylprednisolone treatment were identified and recorded. Mortality rate, time from initiation of treatment to death, and length of hospital stay in recovered patients were evaluated.

2.5. Outcomes

The primary outcome was all-cause mortality within 28 days among COVID-19 patients who received HDCPT. Secondary outcomes included the intensive care unit (ICU) admission, patient's oxygen demand, time to discharge from the hospital, and adverse events.

2.6. Statistical analysis

IBM SPSS version 22 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. Results were presented as numbers (*n*) and percentages (%) for categorical variables and as mean ± standard deviation or median (IQR or Q1-Q3 value) for continuous variables. Analysis of categorical variables was conducted by using the *Chi*-square test or Fisher's exact test. The normality assumption for continuous variables was confirmed by the Kolmogorov-Smirnov test. For comparison of independent continuous variables between survivors and non-survivors, Student's *t*-test or the Mann-Whitney *U* test was used depending on whether the statistical hypotheses were fulfilled or not. For time-dependent variables, repeated measures analysis of variance was conducted to compare the differences between groups and within groups. To assess the survival analysis, a univariate Cox regression model was fit to the entire cohort and then a multivariate Cox model was used to analyse the variables that were significant in univariate models. Potentially confounding variables (covariates) were included in the multivariate model based on clinical experience and the COVID-19 literature at the time. Hazard ratios (*HR*s) and 95% confidence intervals (*CI*s) were computed and reported. The statistical level of significance for all tests was considered to be 0.05.

3. Results

3.1. Characteristics of patients at admission

A total of 1953 patients who were hospitalised with COVID-19 pneumonia between December 1, 2020 and June 1, 2021 were defined as the cohort. After exclusion of pregnant patients and patients <18 years old, 1895 patients were evaluated and HDCPT was given to 149 patients. Another 14 and 9 patients were excluded from the study because of discontinuation of follow-up and active malignancy/immunosuppression, respectively. Finally, 126 patients were included in the study (Figure 1).

According to the National Institutes of Health (NIH) guidelines[27], all 126 (100%) patients included in the study had severe COVID-19 pneumonia. The SARS-CoV-2 nasal or nasopharyngeal RT-PCR test results were positive in 120 (95.2%) patients. The remaining 6 patients had bilateral pulmonary infiltrates on CT with high clinical suspicion for COVID-19. Table 1 presents the demographic and

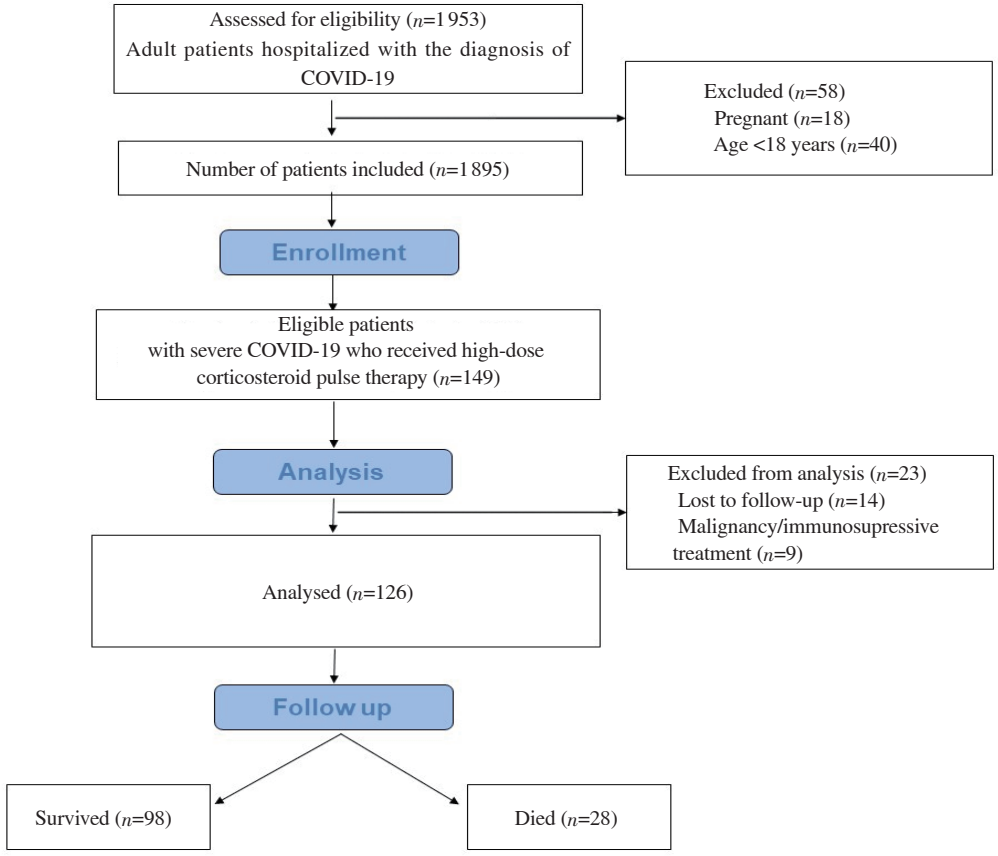

Figure 1. Flowchart of the enrolment, analysis inclusion/exclusion criteria, and follow-up of the COVID-19 patients treated with high-dose corticosteroid pulse therapy.

clinical characteristics of the patients.

Of the 126 patients, 81 (64.3%) were male and 45 (35.7%) were female. The mean age of the patients was (58.0 ± 15.7) (range, 19-88 years). A total of 98 (77.8%) of the patients survived. Non-survivors were older compared to survivors (P<0.001) (Table 1). Comorbidities were present in 87 (69.0%) patients, with hypertension as the most common (43.7%). As shown in Table 1, apart from age and hypertension, which were significantly higher and more prevalent in the non-survivors, respectively, no significant difference was found between the two groups in terms of the other demographic and clinical characteristics.

3.2. Treatments and outcomes

The mean duration from the onset of symptoms to presentation was (8.3 ± 4.0) days, and the median (IQR) hospital stay was 15.0 (11.0) days. All patients received favipiravir for a median (IQR) of 10.0 (5.0) days and enoxaparin for 30.0 (10.0) days. During the follow-up period, 110 patients received antibiotic treatment for a mean of (12.0 ± 7.4) days. Forty-eight (38.1%) patients received colchicine, 11 (8.7%) patients received intravenous immunoglobulin (IVIG) treatment, and 8 (6.3%) patients received anakinra (Table 2). The median duration from symptom onset and hospitalisation to pulse steroid administration was (11.8 ± 4.5) days and 4.0 (4.0) days, respectively. Patients received 1 440 (645) mg of total steroids for a median of 14.5 days (12.0) (Table 2).

Side effects due to HDCPT treatment were seen in 43 (34.1%) patients. The most common side effect is glucose dysregulation (n=36, 28.6%). Mild to moderate gastrointestinal system bleeding was seen in 5 (4.0%) patients.

Bacterial co-infection was found in 16 patients. The specimens included blood in 6 patients, urine in 5 patients, sputum in 4 patients, and blood, urine, and sputum in 1 patient (P<0.001). These positive cultures were considered clinically co-infections.

A total of 46 (36.5%) patients were transferred into the ICU. Invasive and non-invasive mechanical ventilation was required in 26 patients (20.6%) and 20 patients (15.9%), respectively. The median (IQR) ICU stay was significantly higher in non-survivors 14.0 (12.0) than in survivors 5.5 (7.0) (P=0.003).

The CCI was 3.5 (3.0) in non-survivors and 1.0 (3.0) in survivors, and the difference was statistically significant (P<0.001) (Table 2).

3.3. Time course analysis of laboratory results and scores

The OSCI score correlated with increased mortality, it was higher in non-survivors at all time points (Figure 2). According to another classification system, we used to determine the degree of the patient's oxygen demand, and the severity of the oxygen demand was graded from 0 to 6. There was a statistically significant difference between the groups in terms of oxygen demand (P<0.001). Oxygen needs gradually increased in non-survivors but decreased in survivors. It was determined that a one-unit increase in oxygen demand doubled the mortality rate (Figure 3).

Table 1. Patient demographics and clinical characteristics.

Characteristics	Total (n=126)	Mortality		P value
		Survivors (n=98)	Non-survivors (n=28)	
Age, mean±SD, year	58.0±15.7	54.5±15.1	70.3±10.7	<0.001
Sex, n (%)				
Female	45 (35.7)	38 (38.8)	7 (25.0)	0.180
Male	81 (64.3)	60 (61.2)	21 (75.0)	
Symptoms, n (%)				
Fever	38 (30.2)	30 (30.6)	8 (28.6)	0.957
Dyspnoea	92 (73.0)	68 (69.4)	24 (85.7)	0.086
Cough	63 (50.0)	50 (51.0)	13 (46.4)	0.402
Sore throat	8 (6.3)	7 (7.1)	1 (3.6)	0.494
Myalgia	30 (23.8)	25 (25.5)	5 (17.9)	0.402
Arthralgia	18 (14.3)	14 (14.3)	4 (14.3)	0.999
Fatigue	83 (65.9)	67 (68.4)	16 (57.1)	0.269
Headache	12 (9.5)	11 (11.2)	1 (3.6)	0.502
Diarrhea	2 (1.6)	2 (2.0)	0 (0.0)	0.446
Nausea	8 (6.3)	6 (6.1)	2 (7.1)	0.845
Chest pain	5 (4.0)	3 (3.1)	2 (7.1)	0.329
Flutter	2 (1.6)	2 (2.0)	0 (0.0)	0.446
Smoking, n (%) (n=115, missing data was available)				
Non-smoker	84 (73.0)	67 (74.4)	17 (68.0)	0.705
Smoker	17 (14.8)	12 (13.3)	5 (20.0)	
Ex-smoker	14 (12.2)	11 (12.2)	3 (12.0)	
*Comorbid conditions, n (%)				
Hypertension	55 (43.7)	37 (37.8)	18 (64.3)	0.013
Diabetes	25 (19.8)	16 (16.3)	9 (32.1)	0.064
Coronary artery disease	6 (4.8)	4 (4.1)	2 (7.1)	0.502
COPD	10 (7.9)	6 (6.1)	4 (14.3)	0.159
Drugs, n (%)				
Antidiabetic	18 (14.3)	13 (13.3)	5 (17.9)	0.540
Immunosuppressive	1 (0.8)	0 (0.0)	1 (3.6)	0.060
Antiarrhythmic	12 (9.5)	10 (10.2)	2 (7.1)	0.626
Antidepressants/Antipsychotic	5 (4.0)	5 (5.1)	0 (0.0)	0.223
Antithyroid	1 (0.8)	0 (0.0)	1 (3.6)	0.060
Inhaled corticosteroids/β2 adrenergic agonists	11 (8.7)	9 (9.2)	2 (7.1)	0.736
ACE inhibitors / ARBs (n=116, missing data was available)	36 (31.0)	26 (29.2)	10 (37.0)	0.441

COPD: chronic obstructive pulmonary disease; ACE inhibitors/ARBs: angiotensin-converting enzyme inhibitors and an angiotensin receptor blockers. For categorical variables, *Chi*-square test (or Fisher's exact) was applied. Normally distributed data were expressed as the mean±SD; between-group comparisons were performed using an independent samples t-test. *Some patients had more than one comorbidity. Non-smokers, defined as smoking <100 cigarettes/lifetime; ex-smokers, defined as abstinence from smoking for at least 15 years on the day before the start of therapy; smokers, defined as smoking >100 cigarettes/lifetime, or smoking >100 cigarettes/lifetime but abstinence from smoking for less than one year on the day before the start of therapy.

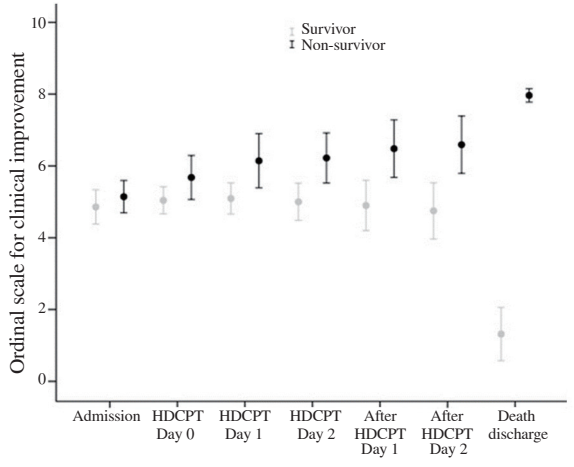

Figure 2. Time-course analysis of Ordinal Scale for Clinical Improvement (OSCI) in the survivors and non-survivors. The chart shows that the OSCI is higher in survivors than non-survivors at each time point. While it constantly increased depending on the time in the non-survivors group, it either stayed constant or decreased in the survivors. Data are expressed as mean±SD.

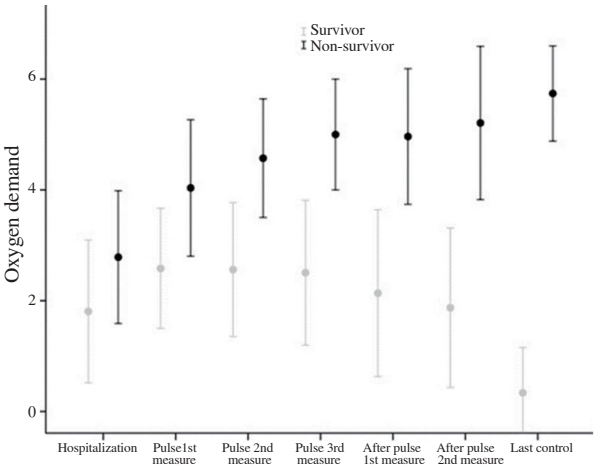

Figure 3. Time-course analysis of oxygen demand in the survivors and non-survivors. Oxygen demand increased gradually in the non-survivors and decreased gradually in the survivors. Data are expressed as mean±SD.

Table 2. The comparison of drug, vaccination and clinical evaluation scores between the survivors (*n*=98) and the non-survivors (*n*=28).

Parameters	Total (*n*=126)	Mortality		*P* value
		Survivors (*n*=98)	Non-survivors (*n*=28)	
Intensive care unit admission, *n* (%)				
No	80 (63.5)	80 (81.6)	0 (0.0)	<0.001
Yes	46 (36.5)	18 (18.4)	28 (100.0)	
No-intubation	20 (15.9)	17 (17.3)	3.0 (10.7)	<0.001
Intubation	26 (20.6)	1.0 (1.0)	25 (89.3)	
Symptom-hospitalization time, mean±SD, d	8.3±4.0	8.6±4.2	7.1±3.2	0.119
Symptom-pulse steroid duration, mean±SD, d	11.8±4.5	12.1±4.4	11.0±4.9	0.267
Hospitalization-pulse steroid duration, median (IQR), d*	4.0 (4.0)	4.0 (4.0)	3.5 (5.0)	0.843
Average length of hospital stay, median (IQR), d*	15.0 (11.0)	14.0 (10.0)	19.0 (15.0)	0.078
Average length of intensive care unit stay, median (IQR), d*	10.0 (11.0)	5.5 (7.0)	14.0 (12.0)	<0.001
Favipiravir, median (IQR), d*	10.0 (5.0)	8.0 (5.0)	10.0 (2.0)	0.008
Enoxaparin, median (IQR), d*	30.0 (10.0)	30.0 (0.0)	18.0 (14.0)	<0.001
Pre-pulse therapy (Low-dose steroid therapy)				
Duration of corticosteroid, median (IQR), d*	2.0 (3.0)	2.0 (3.0)	3.0 (5.0)	0.239
Dose of corticosteroid, median (IQR), mg *	120 (160)	120 (160)	140 (260)	0.546
Post-pulse therapy (Maintenance steroid theraphy)				
Duration of corticosteroid, median (IQR), d*	9.0 (10.0)	8.5 (10.0)	10.0 (15.0)	0.281
Dose of corticosteroid, median (IQR), mg*	455 (485)	423.5 (403.0)	690 (1 010.0)	0.013
Total corticosteroid (Pre-Pulse+Post Pulse+Pulse)				
Duration of corticosteroid, median (IQR), d*	14.5 (12.0)	14.0 (11.0)	16.5 (13.75)	0.092
Dose of corticosteroid , median (IQR), mg*	1 440 (645)	1 390 (575)	1 670 (1 087.25)	0.011
Intravenous immunoglobulin, *n* (%)	11 (8.7)	2 (2.0)	9 (32.1)	<0.001
Colchicine	48 (38.1)	42 (42.9)	6 (21.4)	0.037
Duration of colchicine, mean±SD, d	9.0±3.2	8.8±3.1	10.6±3.9	0.426
Anakinra, *n* (%)	8 (6.3)	6 (6.1)	2 (7.1)	0.845
Antibiotics, *n* (%)	110 (87.3)	82 (83.7)	28 (100.0)	0.094
Beta lactam	34 (30.9)	28 (34.1)	6 (21.4)	
Quinolone	36 (32.7)	33 (40.2)	3 (10.7)	
Beta lactam+Quinolone	24 (21.8)	19 (23.2)	5 (17.9)	
Beta lactam+Quinolone+Vancomycin/Teicoplanin/Linezolid (anyone)	6 (5.5)	1 (1.2)	5 (17.9)	
Beta lactam+Quinolone+Colistin	9 (8.2)	0 (0.0)	9 (32.1)	
Other, *n* (%)	1 (0.9)	1 (1.2)	0 (0.0)	
Duration of antibiotic therapy, median (IQR), d*	10.0 (8.0)	7.5 (7.0)	16.5 (14.0)	<0.001
Bacterial co-infection, *n* (%)	16 (12.7)	4 (4.1)	12 (42.9)	<0.001
Vaccine, *n* (%)	8 (7.1)	8 (9.4)	0 (0.0)	0.092
Ordinal scale for clinical improvement [after HDCPT (0 day)], median (IQR)*	5.0 (0.0)	5.0 (0.0)	6.0 (1.0)	<0.001
Charlson Comorbidity Index, median (IQR)*	2.0 (2.0)	1.0 (3.0)	3.5 (3.0)	<0.001
Total Severity Score, median (IQR)*	8.0 (8.0)	7.0 (7.0)	12.0 (13.0)	0.022

d: day; mg: miligram; IQR: interquartile range. For categorical variables, *Chi*-square test (or Fisher's exact) was applied. Normally distributed data were expressed as the mean ± SD; between-group comparisons were performed using an independent samples *t*-test. *Non-normally distributed data were expressed as the median (IQR); between-group comparisons were performed using the Mann Whitney *U*-test.

TSS was used to evaluate the CT findings of the patients during hospitalisation. The median (IQR) TSS was significantly higher in non-survivors 12.0 (13.0) than in survivors 7.0 (7.0) (*P*=0.022). It was observed that patients with higher total scores regarding lung involvement based on CT had higher mortality rates.

Time-dependent changes in respiratory rates were different between the groups (*P*<0.001). Initially, the mean respiratory rate per minute of non-survivors differed by two units from that of the survivors (*P*=0.028).

HDCPT day 0 laboratory parameters were compared between survivors and non-survivors: the levels of creatinine, lactate dehydrogenase, and haemoglobin were significantly higher in non-survivors (*P*<0.001). Although ferritin, AST, WBC, and CRP values were higher in non-survivors than in survivors, the difference was not statistically significant (Supplementary Table 1).

Table 3 summarises the laboratory parameters on admission, HDCPT day 0, and HDCPT day 3. Although the CRP value was similar in both groups at the time of hospitalisation, HDCPT day 2 showed a decrease in the CRP value in survivors, whereas the CRP value further increased in non-survivors. It was observed that CRP response was not obtained after HDCPT in patients who died, as the increase in the CRP value was statistically significant (Figure 4 and 5) (*P*<0.001). Additionally, CRP and neutrophil to lymphocyte ratio (NLR) of survivors and non-survivors were examined before and after HDCPT, and their changes over time were compared (Figure 4 and 6). The NLR of survivors and non-survivors was similar at the time of hospitalisation, but it increased over time in non-survivors, whereas it decreased in survivors after HDCPT treatment (Figure 6).

Table 3. The comparison of parameters at admission, 0 and 3 days of high-dose corticosteroid pulse therapy.

Parameter [median (range)]	On admission (a)	HDCPT (0 day) (b)	HCPT (3 day) (c)	*P* value (a *vs.* b)	*P* value (a *vs.* c)	*P* value (b *vs.* c)
Hemoglobin (g/dL, normal range: 11-17)	14.1 (13-15.2)	13.7 (12.3-14.7)	13.5 (12.1-14.2)	<0.001	<0.001	<0.001
White blood cell counts ($\times10^9$/L, normal range: 4-10)	6.1 (4.7-9.0)	7.9 (5.1-11.0)	10.3 (7.3-12.9)	<0.001	<0.001	<0.001
Neutrophil ($\times10^9$/L, normal range: 1.3-7.4)	4.5 (3.2-7.7)	6.7 (3.9-9.7)	8.7 (5.9-11.4)	<0.001	<0.001	<0.001
Lymphocytes ($\times10^9$/L, normal range: 0.9-5.3)	0.9 (0.6-1.2)	0.6 (0.4-1.0)	0.7 (0.4-1.0)	<0.001	<0.001	0.193
Platelets (1000 u/L), normal range: 150-450)	185 (145-232)	219 (165-287)	285 (214-368)	<0.001	<0.001	<0.001
C-reactive protein (mg/L, normal range: 0-5)	109 (48-157)	118 (69-156)	33 (15-64)	0.125	<0.001	<0.001
Ferritin (μmol/L, normal range: 30-220)	222 (129-415)	346 (189-614)	331 (158-549)	<0.001	0.033	0.123
Lactate dehydrogenase, (U/L, normal range: 0-248)	354 (289-473)	395 (320-519)	366 (281-617)	0.153	0.090	0.708
Aspartate aminotransferase (U/L, normal range: 0-31)	36 (27-46.3)	34 (24.0-48.3)	28 (22-45.2)	0.215	0.266	0.567
Alanine aminotransferase (U/L, normal range: 0-45)	26 (16-37.3)	26.5 (18-43)	41 (26-79)	0.015	<0.001	<0.001
Creatinine (mg/dL, normal range: 0.8-1.5)	1 (0.8-1.2)	0.9 (0.7-1.0)	0.8 (0.6-0.9)	<0.001	<0.001	0.010

HDCPT: high-dose corticosteroid pulse therapy. Results were presented as median (Q1-Q3). Repeated measures analysis was conducted to compare the differences within groups.

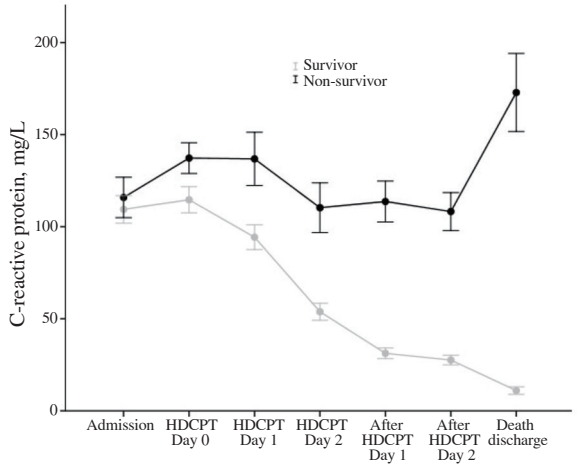

Figure 4. Time-course analysis of C-reactive protein (CRP) levels in the survivors and non-survivors that received high-dose corticosteroid pulse therapy (HDCPT) from hospitalization to discharge or death. Data are expressed as mean±SE.

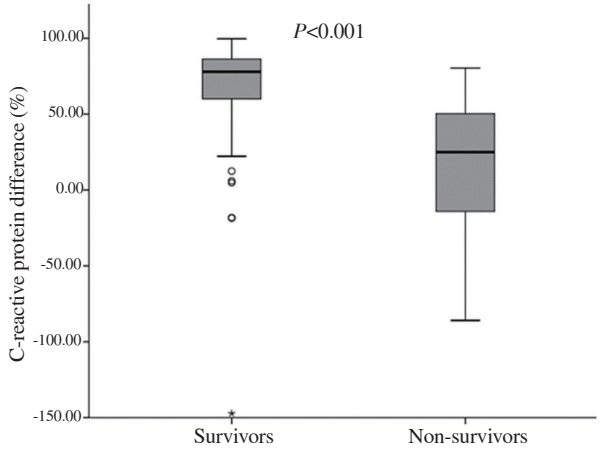

Figure 5. C-reactive protein response of patients who received high-dose corticosteroid pulse therapy (HDCPT) was significantly reduced in patients who survived when HDCPT 0 and 2nd day C-reactive protein values were compared. Between-group comparisons were performed using the Mann Whitney *U*-test. Data are expressed as median (IQR).

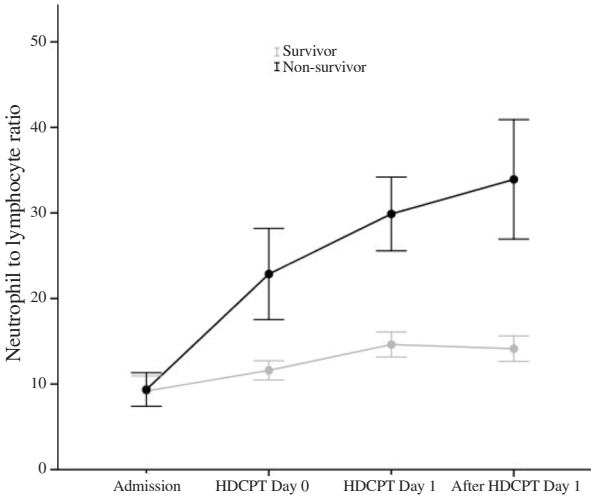

Figure 6. Time-course analysis of neutrophil to lymphocyte ratio in the survivors and non-survivors that received high-dose corticosteroid puls therapy (HDCPT) from hospitalization to discharge or death. Data are expressed as mean±SE.

3.4. Multivariate Cox regression analysis

We aimed to investigate which factors are associated with mortality using the multivariate Cox regression analysis. Multivariate Cox regression analysis revealed that age, bacterial co-infections, and use of prophylactic anticoagulation affected mortality *HR* 1.047 (95% *CI* 1.01-1.08, *P*=0.021), *HR* 3.966 (95% *CI* 1.40-11.21, *P*=0.009) and *HR* 0.838 (95% *CI* 0.79-0.89, *P*<0.001), respectively. In our study, older age, and bacterial co-infection were found to increase mortality (Table 4).

4. Discussion

In this retrospective cohort study, we analysed the clinical symptoms and laboratory findings of patients with severe COVID-19

Table 4. Univariate and multivariate Cox regression model mortality in patients with high-dose corticosteroid pulse therapy.

Parameters	Univariate Cox regressions		Multivariate Cox regression	
	HR (95% *CI*)	*P* value	*HR* (95% *CI*)	*P* value
Age, year	1.043 (1.01-1.08)	0.010	1.047 (1.01-1.08)	0.021
Sex	1.437 (0.60-3.43)	0.415		
Smoking	1.088 (0.62-1.92)	0.771		
Diabetes	2.514 (1.09-5.79)	0.031	1.482 (0.51-4.28)	0.467
Hypertension	0.875 (0.38-1.99)	0.752		
Coronary artery disease	0.416 (0.06-3.13)	0.395		
Charlson Comorbidity Index	1.219 (1.00-1.48)	0.049		
Dose of corticosteroid, mg	1.000 (0.99-1.01)	0.793		
Use of prophylactic anticogulation, d	0.868 (0.83-0.91)	<0.001	0.838 (0.79-0.89)	<0.001
Duration of antibiotic therapy, d	0.997 (0.96-1.04)	0.880		
Bacterial co-infection	2.461 (1.13-5.34)	0.023	3.966 (1.40-11.21)	0.009
Total Severity Score	1.071 (0.99-1.15)	0.056		
Needed oxygen [after HDCPT (0 day)]	1.629 (1.15-2.31)	0.006	0.780 (0.47-1.31)	0.348
CRP difference, %	0.989 (0.98-0.99)	0.001	0.996 (0.99-1.01)	0.459
NLR, % [after HDCPT (0 day)]	1.007 (0.99-1.02)	0.383		

HDCPT: high-dose corticosteroid pulse therapy; *HR*: hazard ratio; *CI*: confidence interval; CRP: C-reactive protein; NLR: neutrophil/lymphocyte ratio; d: day; mg: miligram. To assess the survival analysis variables which were statistically significant when survivor and non-survivor groups were compared regardless of time, used in a univariate Cox regression model. Then a multivariate Cox model was used to analyze the variables that were significant in univariate models.

pneumonia treated with HDCPT to predict their survival. We contributed to the literature by identifying prognostic factors to help patients who will benefit from HDCPT. The mean age of our patients was (58.0 ± 15.7) years, and most (64.3%) were men. Our study confirmed that older age was associated with mortality in COVID-19 patients, which was consistent with the literature[28,29]. Fatigue, cough, and shortness of breath were the most common symptoms at the time of admission. The most common comorbidities were hypertension and diabetes, as previously reported, but these were not associated with mortality[30–32].

After HDCPT, improvement was observed in laboratory and clinical parameters of 98 patients. Although 18 of the 98 surviving patients were admitted to the ICU and one needed invasive mechanical ventilation, all 98 patients were discharged.

Our study showed that administration of HDCPT of the disease resulted in 28-day mortality rate of 22.2%, similar to earlier reports with rates ranging between 5.9% and 25.7%[18,33–36].

In a retrospective cohort study conducted in Madrid, in-hospital mortality was significantly lower in patients treated with steroids than in controls (13.9% *vs.* 23.9%; *P*=0.044). In terms of mortality, it was reported that there was no difference between the patients who received the initial regimen of 1 mg/kg/day methylprednisolone or pulse steroids[33].

In a comparative observational study with patients with COVID-19 pneumonia and high inflammatory markers, it was reported that 2-week methylprednisolone would be effective in improving the prognosis of patients with COVID-19 pneumonia[34]. In another study from Spain, Pascual *et al.* divided 259 patients with severe SARS-CoV-2 pneumonia into three different groups and compared them on hospital admission to ICU admission and death. They reported that patients treated with pulsed glucocorticoids (≥250 mg) had a more favourable course with less mortality and less admission to the intensive care unit than other groups[35]. Our study was compared with the study, the rate of admission in the intensive care unit was higher but required invasive mechanical ventilation and the mortality rate was similar to the pulse-treated group.

In a single-blinded randomised controlled clinical trial in Iran involving severely hospitalised patients with confirmed COVID-19 in the early pulmonary phase of the disease, it was reported that methylprednisolone pulse therapy could be an effective therapeutic agent for severe COVID-19 patients in the pulmonary phase[36].

The surviving patients in our cohort had significantly lower levels of NLR, CRP, and lactate dehydrogenase on HCPT 3 days. Although CRP was similar on admission and HDCPT day 0, it decreased significantly on HDCPT day 3. In non-surviving patients, CRP response could not be obtained after HDCPT. The HDCPT day 0 and 3-day ferritin levels were significantly higher than those on admission and were similar in both groups. We could suggest that CRP could be more beneficial compared to ferritin levels to evaluate early treatment response. Unlike our study, in a study by Edalatifard *et al*, although the CRP and ferritin values were high at the time of hospitalisation, they gradually decreased on HDCPT day 3 and after HDCPT treatment (discharge or death)[36].

The time from the onset of symptoms to the use of steroids varies in studies. In our study, the median time from the onset of symptoms to pulse steroid use was (11.8 ± 4.5) days, which ranged from 8 to 14 days in other studies[18,33–36]. By contrast, randomised study in Brazil reported that in 50% of patients, low dose methylprednisolone was non-efficacious when administered within the third week of disease[37].

However, the question remains on whether patients should use short-term pulsed steroids or lower doses over a longer period of time. For this reason, there are no definite recommendations about which corticosteroid should be administered, at what dose, when to start, and for how long, which should be clarified by further studies.

We found that patients with high TSS based on CT images had high mortality rates, but statistical significance could not be reached in the regression analysis might be explained by the small sample size.

One of the important factors affecting mortality in our study was the presence of bacterial infection. Although the infection rate in the survivor group was 4.1%, this rate was 12.7% in the non-survivors. Although total steroid dosage didn't affect mortality after being

evaluated with regression analysis, increased steroid exposure in a non-survivor group may be an additional factor for bacterial co-infection. Contrary to our study, a quantitative meta-analysis that included eight randomised clinical studies and had data on infection rate in three studies showed no significant difference between the steroid group (18.3%) and the standard care group (22.4%) in terms of co-infection rate[38]. On the other hand, 82 (83.7%) survivors and 28 (100%) non-survivors received antibiotic treatment, and empirical antibiotic therapy is non-efficacious in survival in our study.

We also found that mortality was lower in patients who were given HDCPT and colchicine. The use of colchicine in the treatment of COVID-19 is supported by the GRECCO randomised clinical trial, the clinical primary endpoint rate was 14% in the control group *versus* 1.8% in the colchicine group. Colchicine statistically significantly improved the time to clinical worsening in patients[39].

Coagulation abnormalities have been reported in the majority of severe COVID-19 patients, and significant mortality in COVID-19 patients has been attributed to abnormal coagulopathy[40]. In Turkey, early phase anticoagulant therapy was included in the treatment protocol for hospitalised COVID-19 patients[20]. Therefore, anticoagulation therapy was given to all patients in our study, which showed that there was a positive effect of enoxaparin on mortality in patients who were given enoxaparin for a longer period.

Despite their beneficial effects, systemic use of corticosteroids can lead to a variety of adverse events[41,42]. In our study, side effects were seen in 43 (34.1%) patients, including hyperglycaemia in 36 (28.6%) patients. Similar to our study, higher rates of hyperglycaemia or need for insulin were reported in patients receiving corticosteroids in the MetCOVID and GLUCOCOVID studies[37,43].

Our study has some limitations. Firstly, due to the retrospective nature of the study, there is no control group. HDCPT treatment was given in our center according to the severity of the disease as stated by the national guidelines. All patients were from a single-center and from a single ethnic group. Six patients were included in the study who had bilateral pulmonary infiltrates on CT with high clinical suspicion for COVID-19 despite being PCR negative. Other limitations are the lack of viral load measurements, the inability to measure *D*-dimer and procalcitonin values in all patients due to laboratory problems, sample size, a small number of clinical cases, and a short follow-up period.

In conclusion, bacterial co-infection and older age are important factors related to mortality for COVID-19 pneumonia patients treated with pulse steroid treatment. Early CRP response and improving respiratory rate/OSCI scores, and decreased oxygen need after pulse steroid treatment can be promising signs for survival. We think that it would be useful to determine the criteria using pro-inflammatory markers and evaluate patients according to these criteria for early diagnosis of these patients and to identify patients who may benefit from treatment. The patient group with the best risk/benefit ratio, optimal timing, appropriate dosing, and duration for the correct treatment have not yet been clarified. Therefore, the efficacy of HDCPT therapy and determining its potential impact and roles to improve survival rates in patients with COVID-19 are needed to confirm.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

HNK and AA participated in the study design. HNK, AA, SNO, GZ, and HAY collected data. HNK and MA performed the analysis, contributed to data interpretation, and wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

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