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ORIGINAL ARTICLE

# C-Reactive Protein Levels during High Dose Steroid Treatment for COVID-19 Pneumonia

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ABSTRACT

Objectives: Inflammation is the main cause of systemic damage in SARS-COV2 infections. Steroid treatment has been shown to reduce mortality in COVID-19. However, there is no index to monitor treatment responses to steroids. Here, we evaluated the validity of serial C-reactive-protein (CRP) follow-up for predicting the outcome in the patients receiving steroid therapy.

Material and methods: In our retrospective cohort study, four hundred twenty-five patients were included. All patients received dexamethasone 6 mg/day or equivalent dose of steroid as much as needed with the onset of hypoxia (SaO2 ≤ 93%). We divided patients into two groups according to outcome (deceased/discharged). We then compared demographic, clinical and laboratory features between the groups. Lastly, we evaluated the thresholds of CRP decline associated with COVID-19 associated mortality at 3th, 5th days and at the end of treatment.

Results: COVID 19 associated mortality rate of the cohort was 6.1% (26/425). In multivariate analysis, in which survival was evaluated, parameters related to death due to COVID-19 in the steroid group were high NEWS-2 score (0.82, CI 95 % 0.68-0.97, p=0.02), increased Charlson comorbidity index (0.68,CI 95% 0.51-0.90,p= 0.007) and absolute CRP level at the end of treatment (0.97,CI 95%, p<0.001). In addition, cut-off levels of CRP reduction related to COVID-19-associated mortality during steroid therapy were found as follows: less than 33% (sensitivity 75%, specificity 64.1%) on day 3, less than 43.5% (sensitivity 81.8%, specificity 70.8%) on day 5 and less than 55% at the end of the treatment (sensitivity 80.7%, specificity 71.8%).

Conclusions: Serial CRP measurement from the third day of steroid therapy can be used to predict mortality in COVID-19 patients receiving steroids.

Keywords: coronavirus disease 2019, mortality, c-reactive protein, steroid treatment.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a multi-systemic disorder that is mainly characterized by severe lung disease [1]. Enhanced inflammatory response to the virus is thought to be the main cause for the lung damage [2]. Moreover, this uncontrolled inflammation is accepted as one of the unfavourable prognostic factors [3].

RECOVERY trial has shown that the steroid is the only proven treatment option that reduces the mortality in severe COVID-19 cases. In this trial, the patients randomised to receive steroid therapy in the form of 6 mg/day dexamethasone up to 10 days and to receive usual care [4]. According to the results of the study, mortality rates were lower in patients who received dexamethasone and were hypoxic on the day of randomization. [5]. As expected, not all patients on dexamethasone treatment have responded to the treatment similarly. Moreover, there is no known indicators showing the success of the steroid treatment yet. Early detection of non-responders to the steroid treatment can guide clinicians for administering other anti-inflammatory treatment options such as anti-cytokine therapies as soon as possible.

C-reactive protein (CRP) is an acute phase reactant that is synthesized by liver in response to various inflammatory signals [6]. CRP is also one of the prognostic factors for COVID-19 [7]. Furthermore, as the severity of the lung involvement increases, there will be a corresponding increase in CRP values [8]. In addition, serial CRP measurements can be used to evaluate the treatment response to tocilizumab in the patients with severe COVID-19 pneumonia [9].

In this study we evaluated the capability of serial CRP measurements to predict the response to the steroid treatment. We also evaluated factors associated with COVID-related mortality while the patient was receiving steroid therapy.

## MATERIAL AND METHODS

Four hundred twenty-five COVID-19 patients over the age of 18 years hospitalized in a tertiary health-care facility between July and September 2020 were retrospectively included in the study. The inclusion criteria to the study were 1) the patients with hypoxia (oxygen saturation ≤ 93%) and/or in need of oxygen therapy due to COVID-19, 2) the patients who received dexamethasone 6 mg/day or equivalent dose of steroid at the onset of hypoxia unless the patients had corticosteroid contraindications (uncontrolled hypertension, glaucoma, uncontrolled hyperglycemia, hypersensitivity to any component of formulation) or active infection. The COVID-19 patients with any corticosteroid contraindication, pregnant or nursing women and patients with concomitant bacterial or fungal infection at time of hypoxia and/or in need of oxygen supplementation were excluded. In our institute, COVID-19 is diagnosed through two different approaches. First, with Polymerase Chain Reaction (PCR) positivity. Second, the individuals with a negative PCR test with all of the three criteria: (a) fever and/or respiratory symptoms, (b) compatible chest imaging findings [10] and (c) decreased lymphocyte count with normal or decreased white blood cell count. The management of COVID-19 treatments, hospitalization and discharge decisions were taken according to the COVID-19 Guidelines of the Ministry of Health of The Republic of Turkey [11]. The length of the steroid treatment was decided by consultant clinician based on clinical progress of the patient.

We collected data from COVID-19 patients retrospectively from the hospital's medical database. We obtained the demographic properties of the patients (age, gender), co-morbidities, presenting COVID-19 related symptoms, results of SARS-CoV-2 PCR tests, treatment history for COVID-19 during hospitalization, outcome of the patients, intensive care unit admission/stay, requirement of mechanical ventilation, duration of hospitalization, time from hospitalization to steroid treatment and time from onset of the symptoms to initiation of steroid treatment, length of steroid treatment, laboratory values at the onset of hypoxia [normal blood levels of biochemical parameters include aspartate aminotransferase (AST) (5-40 U/L), alanine aminotransferase (ALT) (7-56 U/L), creatinine (0.6-1.0 mg/dL), creatinine kinase (CK) (22-198 U/L) , lactate dehydrogenase (LDH) (140-280 U/L), D-dimer, ferritin, CRP (0-5 mg/dl) and total blood counts ], length of steroid treatment.

The levels of ALT, AST, creatinine, CK, LDH, CRP were classified according to the laboratory reference ranges as normal, low, or high. However, ferritin and D-dimer levels were classified based upon their levels related to unfavourable prognosis in COVID-19. These cut- off levels were specified as 300 mg/mL for ferritin and 1000 mg/L for D-dimer. Also, we focused on lymphocyte counts at total blood counts. Lymphocyte level lower than $1x10^9$ per litre was accepted as cut-off value for severe disease [12]. Moreover, the severity of co-morbidities was defined by the Charlson comorbidity index score [13]. In addition, NEWS-2 score was used to determine the severity of the cases. These scores were classified as low (0-4), medium (5-6) and high (≥7) [14]. Also, we have defined hypoxia if the oxygen saturation is 93% or lower [11].

CRP values were measured serially at the beginning of steroid treatment, on the 3rd day, on the 5th day and finally at the end of the treatment. Furthermore, we analysed patients' individual CRP changes during treatment by comparing the CRP level on the first day of steroid treatment (basal CRP level).

Additionally, we dichotomized the patients based upon their prognosis (discharged or deceased). We then compared the demographic, laboratory, treatment related features, prognosis, and serial CRP changes between the groups.

This study was approved by both the Local Research Ethics Committee (30.12.2020 514/192/46) and Turkish Health Ministry (2020-12-05T17_11_39) prior to data collection and carried out in compliance with the Helsinki Declaration.

### Statistical analyses

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). In order to determine if the data were normally distributed, the Kolmogorov-Smirnov test was performed. None of the parameters was distributed normally. Therefore, comparisons of the continuous variables and categorical variables were performed by Mann-Whitney U test and Chi-square test, respectively. We evaluated the factors related to mortality in the patients receiving steroid with binary logistic regression (Backward LR methods) method. The outcome of these analyses was surviva we included (all variables p<0,05 in univariate analyses plus possible confounding factor gender) age, gender, CRP values at the onset and at the end of the steroid treatment (absolute values), baseline d-dimer values, time from symptoms to steroid treatment, severity of the disease (absolute values of NEWS score) and co- morbidities (absolute values of Charlson comorbidity index score) and high baseline transaminases and creatinine levels to the multivariate analysis model. We also performed ROC analyses to find threshold CRP decline in serial measurements related to mortality associated with COVID-19. To determine the threshold changes for associated mortality of COVID-19, we specified the percent change in CRP values at day 3, day 5 and at the end of treatment compared to day 1 with ROC curves. We presented the intersection of highest sensitivity and specificity. Area under curve measurements were made in all CRP measurements to determine the validity of CRP changes to predict mortality. All values were shown as median (IQR). P-value lower than 0.05 was considered as statistically significant.

## RESULTS

Two hundred fifty-nine of the patients were male. Median age of the patients was 61.0 (50.5-72.0) years. The PCR positivity for SARS-COV-2 was 87.5%. More than two thirds of the patients had high or medium NEWS-2 scores. Most frequent presenting symptoms of the patients were cough, shortness of breath and malaise. In addition, hypertension was the most frequent co-morbidity of the patients. Mortality rate of the cohort was 6.1% (26/425). Thirty patients (7.1%) had requirement of intensive care unit. Lastly, 23 (5.4%) of the patients received mechanical ventilation. Demographic and disease related features of the COVID-19 patients were shown in Table 1.

In our study, we found that deceased patients in our cohort were older, had shorter duration between onset of symptoms to onset of hypoxia (treatment), had more severe disease and had higher co-morbidity burden than those who were discharged. In addition, patients who died had higher baseline CRP levels, d-dimer values and more patients in this group had creatinine and transaminase levels higher than upper limits. Comparison of demographic and disease related features between the patients classified according to outcome was shown at Table 2. Also, in multivariate analysis multivariate analysis, in which survival was evaluated, NEWS-

 

**Table 1.** Demographic and disease related features of the COVID-19 patients

| | **n= 425** |
|---|---|
| Age (year) | 61 (50.5-72.0) |
| Gender (M/F) | 259/166 |
| Positive PCR n(%) | 372 ( 87.5) |
| Time from onset of symptoms to initiation of steroid treatment (day) | 6 (3.0-8.5) |
| Time to hospitalization to steroid treatment (day) | 1(1-1) |
| Length of hospitalization (days) | 6 (5-9) |
| Length of steroid treatment (days) | 5.0(3.0-7.0) |
| **NEWS-2 score** | 3 (1.0-5.5) |
| Low | 263 (61.9) |
| Medium | 84 (19.8) |
| High | 78 (18.3) |
| **Presenting symptoms n (%)** | |
| Cough | 260 (61.2) |
| Shortness of breath | 234 (55.1) |
| Fever | 158 (37.2) |
| Myalgia | 95 (22.4) |
| Headache | 29 (6.8) |
| Nasal discharge | 2 (0.5) |
| Sore throat | 16 (3.8) |
| Loss of taste or smell | 10 (2.4) |
| Malaise | 178 (41.9) |
| Diarrhoea | 28 (6.6) |
| Nausea/vomiting | 56 (13.2) |
| Loss of appetite | 42 (9.9) |
| **Co-morbidities n(%)** | |
| Diabetes mellitus | 132 (31.1) |
| Hypertension | 188 (44.2) |
| Coronary arterial disease | 82 (19.3) |
| COPD | 21 (4.9) |
| Asthma | 36 (8.5) |
| Malignancy | 30 (7.1) |
| **Obesity** | |
| Chronic renal disease | 24(5.6) |
| Rheumatic diseases | 9 (2.1) |
| Charlson comorbidity index score | 3 (1-5) |
| **Treatment n(%)** | |
| Hydroxychloroquine | 116 (27.3) |
| Favipravir | 376 (88.5) |
| Antibiotherapy | 118 (27.8) |
| **Outcome n(%)** | |
| Intensive care unit requirement | 30 (7.1) |
| Mechanical ventilation requirement | 23 (5.4) |
| Mortality | 26 (6.1) |

M: Male; F: Female; PCR: polymerase chain reaction for SARS Cov2; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; MV: Mechanical ventilation; NEWS-2: National Early Warning Score -2 Obesity: BMI≥25 kg/m$^2$

2 score (0.82 CI 95 % 0.68-0.97, p=0.02), Charlson comorbidity index score (0.68, CI 95% 0.51-0.90, p= 0.007) and CRP levels at the end of treatment (0.97, CI 95% 0.96-0.98, p<0.001) were found to be significantly associated with mortality in our cohort (Table 3).

In the deceased group, median CRP values were higher than those who were discharged at the beginning of steroid treatment, on the 3rd day, on the 5th day and finally at the end of the treatment. Furthermore, changes of the median CRP values on the 3rd day, on the 5th day and at the end of the treatment were significantly different between the groups. In all serial measurements, patients in discharged group showed higher improvement in CRP values. The main CRP reduction in discharged group occurred within the first five days of the treatment (Figure 1).

Finally, we conducted ROC analyses to determine the threshold CRP decline associated with mortality on day 3, day 5 and the end of the treatment. All three ROC curves were statistically valid for predicting mortality (Figure 2). Here, the cut- off CRP reductions for mortality was defined less than 33% (sensitivity 75%, specificity 64.1%) on day 3, less than 43.5% (sensitivity 81.8%, specificity 70.8%) on day 5 and less than 55% at the end of the treatment (sensitivity 80.7%, specificity 71.8%) from baseline (Table 4).

## DISCUSSION

In our study where we evaluated the CRP levels during steroid therapy, we showed that serial CRP

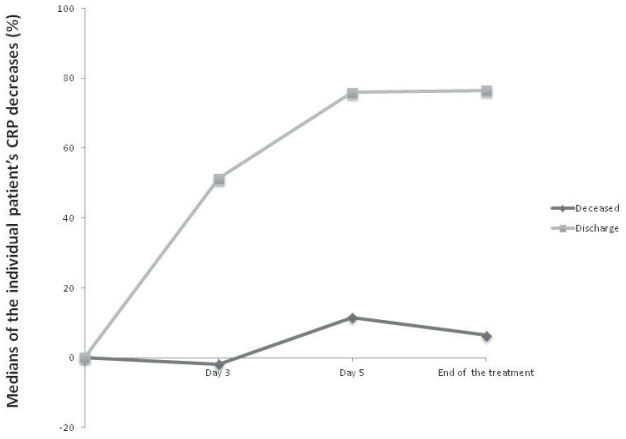


**Figure 1.** CRP decrease percentages of patients receiving steroid therapy

**Table 2.** Comparison of demographic and disease related features between the patients classified according to outcome

| | **Deceased n=26** | **Discharged n= 399** | **p** |
|---|---|---|---|
| Age (years) | 64 (72.0-77.5) | 60 (50.0-71.0) | **<0.001** |
| Gender (M/F) | 17/9 | 242/157 | 0.63 |
| Positive PCR test, n (%) | 25 (96.2) | 347 (87.0) | 0.22 |
| Time from onset of symptoms to initiation of steroid treatment (day) | 3.0 (2.0-7.0) | 6.0 (3.0-9.0) | **0.02** |
| Time to hospitalization to steroid treatment (day) | 1.0 (1.0-1.0) | 1.0 (1.0-1.0) | 0.50 |
| Length of hospitalization (day) | 10.5(7.0-14.5) | 6 (5.0-9.0) | **<0.001** |
| Length of steroid treatment (days) | 10.0(5.75-12.5) | 5.0(4.0-7.0) | **<0.001** |
| **NEWS-2 score** | 6 (4.5-7.0) | 3 (1.0-5.0) | **<0.001** |
| Low | 6 (23.1) | 257 (64.5) | **<0.001** |
| Medium | 9 (34.5) | 75 (18.7) | |
| High | 11 (42.4) | 67 (16.8) | |
| Charlson comorbidity index score | 5 (4-7) | 3 (1-5) | **<0.001** |
| **Laboratory** | | | |
| Baseline Median CRP values | 141.5 (63.5-170.7) | 66.0 (30.0-122.0) | **<0.001** |
| Median CRP values (Day 3) | 129.0 (55.5-182.0) | 30.0 (14.0-64.0) | **<0.001** |
| Median CRP values (Day 5) | 133.5 (85.2-176.5) | 17.0 (7.5-38.5) | **<0.001** |
| Median CRP values (End of the treatment) | 173.0 (66.0-236.5) | 5.0 (13.0-30.0) | **<0.001** |
| ΔCRP (Day 3) % | 1.9 (-37.5-39.8) | -51.3 (-71.7- -10.0) | **<0.001** |
| ΔCRP (Day 5) % | -11.6 (41.3- 103.3) | -75.9 (-88.0- -27.2) | **<0.001** |
| ΔCRP (End of the treatment) % | -6.4 (-44.0-202.8) | -76.5 (-89.8- -51.0) | **<0.001** |
| Transaminases (>35 IU/L) | 15 (57.7) | 150 (37.6) | **0.04** |
| Creatinine (>1.2 mg/dL) | 14 (53.8) | 96 (24.1) | **0.002** |
| LDH (>240 U/L) | 20 (76.9) | 258 (64.7) | 0.20 |
| D-dimer (≥1000 ng/mL) | 17 (65.4) | 157 (39.3) | **0.008** |
| Lymphocyte count (≤1x109/L) | 15 (57.7) | 190 (47.6) | 0.31 |
| Ferritin (≥300 mg/mL) | 17 (65.4) | 213 (57.4) | 0.57 |
| **Treatment n(%)** | | | |
| Hydroxychloroquine | 4 (15.4) | 112 (28.1) | 0.35 |
| Favipravir | 25 (96.2) | 351 (88.0) | 0.34 |
| Antibiotherapy | 23 (88.5) | 95 (23.8) | **<0.001** |
| **Outcomes n(%)** | | | |
| Intensive care unit requirement | 24 (92.3) | 6 (1.5) | **<0.001** |
| Mechanical ventilation requirement | 23 (88.5) | 0 | |

M: Male; F: Female; PCR: SARS Cov2 polymerase chain reaction ; ICU: Intensive care unit; MV: Mechanical ventilation; NEWS-2: National Early Warning Score -2; CRP: C reactive protein; LDH: Lactate dehydrogenase. ΔCRP: Median CRP changes of the individual patients as compared to baseline values

**p<0.05 was shown bold**

measurements during the treatment can be used to predict the outcome of the steroid treatment.

Several cytokines were found to be associated with the disease severity of the COVID-19 [15]. Based upon these data, it was predicted that anti-inflammatory treatment may be an option for COVID-19. Subsequently, both the results of the recovery trial and other anti-inflammatory treatments with tocilizumab; or baricitinib, remsedevir combination has some promising results [15-17].

There were several parameters that can help to predict the prognosis of the COVID-19 patients. Features related to severe disease in physical examination, high inflammation parameters/acute phase reactants, laboratory parameters showing

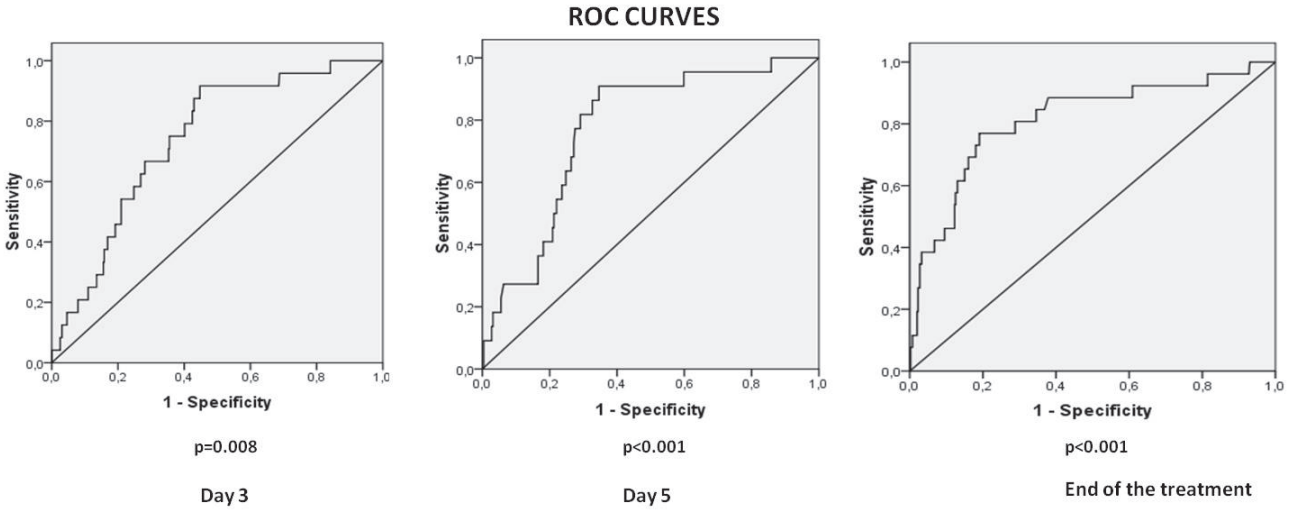


**Figure 2.** ROC curves for CRP changes of the patients receiving steroid therapy

**Table 3.** Multivariate analyses of the factors related to the mortality of patients on steroid treatment

| | OR | %95 CI | p |
|---|---|---|---|
| Age | 0.96 | 0.89-1.03 | 0.30 |
| Gender | 0.80 | 0.22-2.97 | 0.74 |
| Time from onset of symptoms to initiation of steroid treatment | 1.02 | 0.86-1.22 | 0.74 |
| **NEWS-2 score** | **0.82** | **0.68-0.97** | **0.02** |
| **Charlson comorbidity index score** | **0.68** | **0.51-0.90** | **0.007** |
| Baseline Median CRP values | 0.99 | 0.90-1.00 | 0.82 |
| **Median CRP values (at the end of the treatment)** | **0.97** | **0.96-0.98** | **<0.001** |
| Transaminases (>35 IU/L) | 0.30 | 0.80-1.10 | 0.07 |
| Creatinine (>1.2 mg/dL) | 0.52 | 0.13-2.02 | 0.35 |
| D-dimer (≥1000 ng/mL) | 0.81 | 0.23-2.87 | 0.75 |

NEWS-2: National Early Waning Score -2; CRP: C reactive protein; LDH: Lactate dehydrogenases

The outcome of the analyses was survival

**p<0.05 was shown bold**

**Table 4.** Relationship between mortality and CRP value changes from baseline

| CRP decrease from baseline (%) | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | OR (%95 CI) | p |
|---|---|---|---|---|---|---|
| **Day 3** | | | | | | |
| < 33 | 75 | 64.1 | 11.3 | 97.6 | 5.3 (1.6-9.6) | <0.001 |
| **Day 5** | | | | | | |
| < 43.5 | 81.8 | 70.8 | 19.5 | 97.8 | 10.9 (3.5-33.4) | <0.001 |
| **End of the treatment** | | | | | | |
| < 55 | 80.7 | 71.8 | 15.4 | 98.2 | 10.3(3.8-28.1) | <0.001 |

Values are for mortality

specific tissue damage, high interleukin (IL)-6 levels and increased Sequential Organ Failure Assessment (SOFA) scores was found to be associated with unfavourable prognosis [18-21]. In addition, CRP levels higher than 10 mg/dl was related to intense inflammation and unfavourable outcome [22]. As expected, normalization of these features would indicate improvement [23]. However, the use of specific parameters to predict the response of the treatments has not been shown yet. Recently, it has been shown that CRP levels would be used to track the response of tocilizumab treatment [9].

Dexamethasone treatment has been shown to reduce 28-day mortality in hypoxemic COVID-19 patients [5]. However, no clinical or laboratory

indicators have been shown to predict the response of the therapy. According to the original article, the only feature related to treatment success was the need for oxygen support. In our study, we presented in multivariate analyses that disease severity, high co-morbidity burden and CRP levels at the end of the treatment will be negative prognostic factors in the patients receiving steroid treatment. Both multiple co-morbidities and high disease severity are also known as unfavourable outcome indices [24,25]. However, differently in our study, we showed that CRP response to the treatment may be related to the outcome of the patients receiving steroid therapy. Our results show the importance of CRP level monitoring for assessment of the treatment success.

Serial CRP level measurements can be used to predict the outcome of steroid treatment. According to our results, there was a significant decrease in median CRP levels between the deceased and discharged patient groups as early as the third day of the treatment. Furthermore, this difference increased throughout the treatment. Therefore, rapid, and persistent CRP reduction can be considered an important feature of steroid responders. We think that daily CRP level monitoring will be important for the patient follow up and clinical assessment.

In our study, we showed that CRP changes during the steroid treatment might predict that CRP response lower than certain thresholds at serial CRP follow up would be an indicator of mortality. The threshold levels in our study would not be specific to predict mortality in the patients receiving steroid treatment, but they suggest that monitoring CRP levels would be valuable. Reduction levels in CRP values should be followed closely concomitant with clinical parameters. In addition, non-responders will be candidates for other anti-inflammatory treatment options such as anti-cytokine therapies.

The study has some limitations; firstly, we evaluated only changes in CRP levels to predict treatment response for steroid therapy. The composite indices would be more predictive of treatment response. Additionally, we do not have any specific treatment protocol for steroid therapy. This would limit the generalizability of our results. Lastly, we did not exclude respiratory viral infections other than COVID-19.

In conclusion, serial CRP measurements will be useful for predicting the unfavourable prognosis in patients receiving steroid as early as the third day of the therapy. Patients with low-level declines in CRP levels during treatment may be considered candidates for aggressive immunosuppressive therapies to prevent further clinical worsening.

## Author contribution

Study conception and design: AB, MET; data collection: EK, NE; analysis and interpretation of results: MET; draft manuscript preparation: AB, MET. All authors reviewed the results and approved the final version of the manuscript.

## Ethical approval

This study was approved by both the Local Research Ethics Committee and Turkish Health Ministry prior to data collection and carried out in compliance with the Helsinki Declaration. (Kartal Dr. Lutfi Kırdar City Hospital IRB Approval Date: 30.12.2020, Approval number: 514/192/46).

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The authors declare that the study received no funding.

## Conflict of interest

The authors declare that there is no conflict of interest.

 

## REFERENCES


[1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020; 109:102433.

[2] Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. J Med Virol. 2020; 92(4):424-432.

[3] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; 46(5):846-848.

[4] Buttgereit F, da Silva JA, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002; 61(8):718-722.

[5] Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.

[6] Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol. 2005; 288(5):H2031-2041.

[7] Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020; 14:1753466620937175.

[8] Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020; 146(1):128-136 e124.

[9] Cassone G, Dolci G, Besutti G, et al. Acute-phase reactants during tocilizumab therapy for severe COVID-19 pneumonia. Clin Exp Rheumatol. 2020; 38(6):1215-1222.

[10] Yang Q, Liu Q, Xu H, Lu H, Liu S, Li H. Imaging of coronavirus disease 2019: A Chinese expert consensus statement. Eur J Radiol. 2020; 127:109008.

[11] Guidance To Covid-19 (SARS Cov2 Infection). Turkish Health Ministry; 2020. https://hsgm.saglik.gov.tr/tr/covid-19-i-ngilizce-dokumanlar.html. Accessed 18.05.2020.

[12] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054-1062.

[13] D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. Methods Inf Med. 1993; 32(5):382-387.

[14] Smith GB, Redfern OC, Pimentel MA, et al. The National Early Warning Score 2 (NEWS2). Clin Med (Lond). 2019; 19(3):260.

[15] Ghazavi A, Ganji A, Keshavarzian N, Rabiemajd S, Mosayebi G. Cytokine profile and disease severity in patients with COVID-19. Cytokine. 2021; 137:155323.

[16] Rosas IO, Brau N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021; 384(16):1503-1516.

[17] Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021; 384(9):795-807.

[18] Hou W, Zhang W, Jin R, Liang L, Xu B, Hu Z. Risk factors for disease progression in hospitalized patients with COVID-19: a retrospective cohort study. Infect Dis (Lond). 2020; 52(7):498-505.

[19] Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020; 15(11):e0241955.

[20] Lagadinou M, Salomou EE, Zareifopoulos N, Marangos M, Gogos C, Velissaris D. Prognosis of COVID-19: Changes in laboratory parameters. Infez Med. 2020; 28(suppl 1):89-95.

[21] Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta. 2020; 510:475-482.

[22] Qin L, Li X, Shi J, et al. Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. J Med Virol. 2020; 92(11):2684-2692.

[23] Liu Y, Zhang X, Qiao J, et al. A Controllable Inflammatory Response and Temporary Abnormal Coagulation in Moderate Disease of COVID-19 in Wuhan, China. J Clin Med Res. 2020; 12(9):590-597.

[24] Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. Diabetes Obes Metab. 2020; 22(10):1915-1924.

[25] Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020; 395(10229):1014-1015.