Early and Significant Reduction in C-Reactive Protein Levels After Corticosteroid Therapy Is Associated With Reduced Mortality in Patients With COVID-19

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BACKGROUND: Corticosteroids may be beneficial in a subset of patients with coronavirus disease 2019 (COVID-19), but predictors of therapeutic response remain unknown. C-reactive protein (CRP) is a routinely measured biomarker, and reduction in its levels after initiation of therapy may predict inpatient mortality.

METHODS: In this retrospective cohort study, the charts of patients who were admitted to Montefiore Medical Center between March 10, 2020, and May 2, 2020 for the management of COVID-19 were examined. Of all patients who met inclusion criteria, patients who received corticosteroid treatment were categorized as CRP responders (≥50% CRP level reduction) and CRP nonresponders (<50% CRP level reduction) based on change in CRP within 72 hours of corticosteroid treatment initiation. The outcomes of interest were two-fold: (1) CRP response after treatment with corticosteroid, and (2) differences in mortality among patients with CRP response compared those without.

RESULTS: Of 2,707 patients admitted during the study period, 324 received corticosteroid treatment. Of patients who received corticosteroid treatment, CRP responders had reduced risk of death compared with risk among CRP nonresponders (25.2% vs 47.8%; unadjusted odds ratio [OR], 0.37; 95% CI, 0.21-0.65; $P < .001$). This effect remained strong and significant after adjustment for potential confounders (adjusted OR, 0.27; 95% CI, 0.14-0.54; $P < .001$).

CONCLUSION: Reduction in CRP by 50% or more within 72 hours of initiating corticosteroid therapy potentially predicts inpatient mortality. This may serve as an early biomarker of response to corticosteroid therapy in patients with COVID-19. *Journal of Hospital Medicine* 2021;16:XXX-XXX. © 2021 Society of Hospital Medicine

Novel coronavirus disease 2019 (COVID-19) has affected more than 108 million persons and is responsible for approximately 2.4 million deaths worldwide.[1] In the United States, 27 million cases of COVID-19 have been reported, and the disease has caused more than 482,000 deaths.[2] The clinical presentation of COVID-19 varies widely, with the most severe presentation characterized by acute respiratory distress syndrome and a marked systemic inflammatory response. Corticosteroids have emerged as a potential therapeutic option in a subset of patients. Results from the recently published RECOVERY trial suggest a substantial mortality benefit of dexamethasone in patients who require mechanical ventilation, with a risk reduction of approximately 33%.[3] In addition, a recent large retrospective study demonstrated a reduction in the risk of mechanical ventilation or mortality with corticosteroid therapy in a prespecified subset of patients with C-reactive protein (CRP) levels ≥20 mg/dL, which indicates a high burden of inflammation.[4]

Some patients with severe COVID-19 experience a positive feedback cascade of proinflammatory cytokines, called the cytokine storm, which can worsen lung injury and, in some cases, progress to vasodilatory shock and multiorgan failure.[5] This complication's cytokine cascade includes interleukin (IL) 6, IL-1β, and CC chemokine ligand 3 (CCL3), which are released by airway macrophages and are heavily implicated in the maladaptive forms of immune response to COVID-19.[6,7] The cytokine IL-6 is the primary signal for the production of CRP, and corticosteroids have been shown, both in vitro and in vivo, to reduce the production of IL-6 and other cytokines by airway macrophages.[6] Levels of CRP have been shown to correlate with outcomes in COVID-19 and bacterial pneumonias.[7,8] Reduction in CRP levels following the institution of therapy, known as CRP response, has been shown to predict outcomes in other inflammatory conditions, such as osteomyelitis, hidradenitis suppurativa, and some cases of bacterial pneu-

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monia.[8-10] Similar CRP response in hemophagocytic lymphohistiocytosis, an entity which closely resembles cytokine storm syndrome, has been shown to correlate with disease activity in patients following treatment with an IL-1 antagonist.[11] Whether the CRP response as a response to therapeutics in COVID-19 is associated with improved outcomes remains unknown.

Laboratory measurement of CRP levels offers several advantages over the measurement of interleukins. Notably, the half-life of CRP is approximately 19 hours, which is comparable across different age groups and inflammatory conditions because its concentration depends primarily on synthesis in the liver, and a decreased level suggests decreased stimulus for synthesis.[8] This makes CRP a useful biomarker to assess response to therapy, in contrast to interleukins, which have short half-lives, are variable in heterogeneous populations, and can be difficult to measure. In addition, CRP measurement is rapid and relatively inexpensive.

We hypothesized that reduction in CRP levels by 50% or more within 72 hours after the initiation of corticosteroids in patients with COVID-19 is associated with reduced inpatient mortality and may be an early indicator of therapeutic response.

METHODS

Study Participants

In this retrospective cohort study, we reviewed all adult patients admitted to Montefiore Medical Center (Bronx, New York) for COVID-19 between March 10, 2020, and May 2, 2020. Patients must have been discharged (alive or deceased) by the administrative censor date (May 2, 2020) to be included. Patients who died within the first 48 hours of admission were excluded to allow sufficient time for corticosteroid treatment to take effect. For inclusion in the corticosteroid group, patients needed to have received at least 2 consecutive days of corticosteroid treatment beginning within the first 48 hours of admission with a total daily dose of 0.5 mg/kg prednisone equivalent or greater. Patients who received treatment-dose corticosteroids later in the hospital course were excluded (Appendix Figure).

Comparison Group and Outcome

We examined trends in CRP levels for patients who received corticosteroids vs trends among patients who did not receive corticosteroids. In addition, among patients who were treated with corticosteroids, we compared the inpatient mortality of those who did have a reduction in CRP level after treatment with inpatient mortality of those who did not have a reduction in CRP level after treatment. First, CRP level trends over time were examined in all patients and compared between those who received corticosteroid treatment and those who did not. Then, patients who received corticosteroids were categorized based on changes in CRP levels after beginning corticosteroids. The first CRP level obtained during the first 48 hours of admission was used as the initial CRP level. For each patient, the last CRP level within the 72 hours after initiation of treatment was used to calculate the change in CRP level from admission. A patient was considered to be a "CRP responder" if their CRP level decreased by 50% or more within 72 hours after treatment, and a "CRP nonresponder" if their CRP level did not drop by at least 50% within 72 hours of treatment. Patients who did not have a CRP level measured within the initial 48 hours of admission or a subsequent CRP measured in the 72 hours after treatment were considered to have an "undetermined CRP response" and excluded from the mortality analysis.

We observed a rise in CRP starting around day 6 among patients treated with corticosteroids and performed a post hoc analysis to determine if this was due to a selection effect, whereby patients staying in the hospital longer had higher CRP levels or represented an actual rise. In order to address this, we performed a stratified analysis comparing the trends in CRP levels among patients with a length of stay (LOS) of 7 or more days with trends among those with an LOS shorter than 7 days.

Statistical Analysis

To characterize differences in patients who received corticosteroids and those who did not, we examined their demographic, clinical characteristics, and admission laboratory values, using chi-square test for categorical variables and Kruskal-Wallis test for continuous variables (Table 1). The change in CRP levels from day 0 (presentation to the hospital) in both groups was plotted in a time-series analysis. For each day in the time series, the 95% CIs for the changes in CRP were computed using the *t* statistic for the corresponding distribution. The Kruskal-Wallis test was used to assess the significance of differences between groups at 72 hours after initiation of treatment.

After categorizing patients by CRP response, we compared demographic, clinical, and laboratory characteristics of patients who were CRP responsive with those of patients who were not, using the same tests of statistical inference mentioned above. To compare time to inpatient mortality differences between CRP response groups, Kaplan-Meier survival curves were generated and statistical significance determined via log-rank test. Univariable logistic regression was used to estimate the odds ratio of inpatient mortality between comparison groups in an unadjusted analysis. Last, to examine the independent association between CRP response and mortality, we constructed a multivariate model that included variables that were significantly associated with mortality in univariable analysis and considered to be important potential confounders by the authors. Details on variable selection for the model are listed in Appendix Table 1.

Data Collection

Data were directly extracted from our center's electronic health record system. Data processing and recoding were performed using the Python programming language (version 2.7.17) and data analysis was done using Stata 12 (StataCorp LLC; 2011). This study was approved by the institutional review board of the Albert Einstein College of Medicine.

RESULTS

Corticosteroids vs No Corticosteroids

Between March 10, 2020, and May 2, 2020, a total of 3,382 adult patients were admitted for COVID-19 at Montefiore Medical Center. Of these, 2,707 patients met the study inclusion criteria, and 324 of those received corticosteroid treatment. Their demographic characteristics, comorbidities, and admission

TABLE 1. **Characteristics Among Patients Who Received Corticosteroid and Those Who Did Not**

	No corticosteroids (N = 2,383)	Received corticosteroids (N = 324)	*P* Value
Age, median (IQR), y	66 (54-77)	67 (57-77)	.23
Female, No. (%)	1,079 (45.3)	155 (47.8)	.64
BMI, median (IQR), kg/m^2	28.3 (24.6-32.7)	28.7 (23.9-34.7)	.19
Full code, No. (%)	1904 (79.9)	217 (67.0)	<.001
Charlson Comorbidity Index, median (IQR)	3 (1-4)	3 (2-4)	.25
Hypertension, No. (%)	1485 (62.3)	188 (58.0)	.14
Asthma/COPD, No. (%)	480 (20.1)	118 (36.4)	<.001
Ever smoker, No. (%)	129 (5.4)	23 (7.1)	.22
Diabetes, No. (%)	899 (37.7)	124 (38.3)	.85
ESRD, No. (%)	96 (4.0)	9 (2.8)	.27
Initial WBC count, median (IQR), k/μL	6.8 (5.3-9.3)	9 (6.6-12.7)	<.001
Initial neutrophil count, median (IQR), k/μL	5.2 (3.6-7.5)	7.5 (5-10.8)	<.001
Initial lymphocyte count, median (IQR), k/μL	1 (0.7-1.4)	0.9 (0.7-1.3)	.03
Initial creatinine, median (IQR), mg/dL	1.1 (0.8-1.8)	1.2 (0.8-2.3)	.07
Initial CRP, median (IQR), mg/dL	8.3 (4.1-15.9)	16.3 (9.1-23.3)	<.001
Initial LDH, median (IQR), mg/dL	366 (281-482)	516 (385-680)	<.001
Initial ferritin, median (IQR), ng/mL	724 (344-1,376)	1,058 (613-1,986)	<.001
Initial fibrinogen, median (IQR), mg/dL	619 (507-730)	686 (577-822)	<.001
Initial D-dimer, median (IQR), μg/mL	1.4 (0.8-2.9)	2.5 (1.3-8.3)	<.001
Initial procalcitonin, median (IQR), ng/mL	0.2 (0.1-0.5)	0.5 (0.2-2.1)	<.001
Initial IL-6, median (IQR), pg/mL	33.0 (16-64)	31.5 (10-90)	.81
Death, No. (%)	463 (19.4)	133 (41.1)	<.001

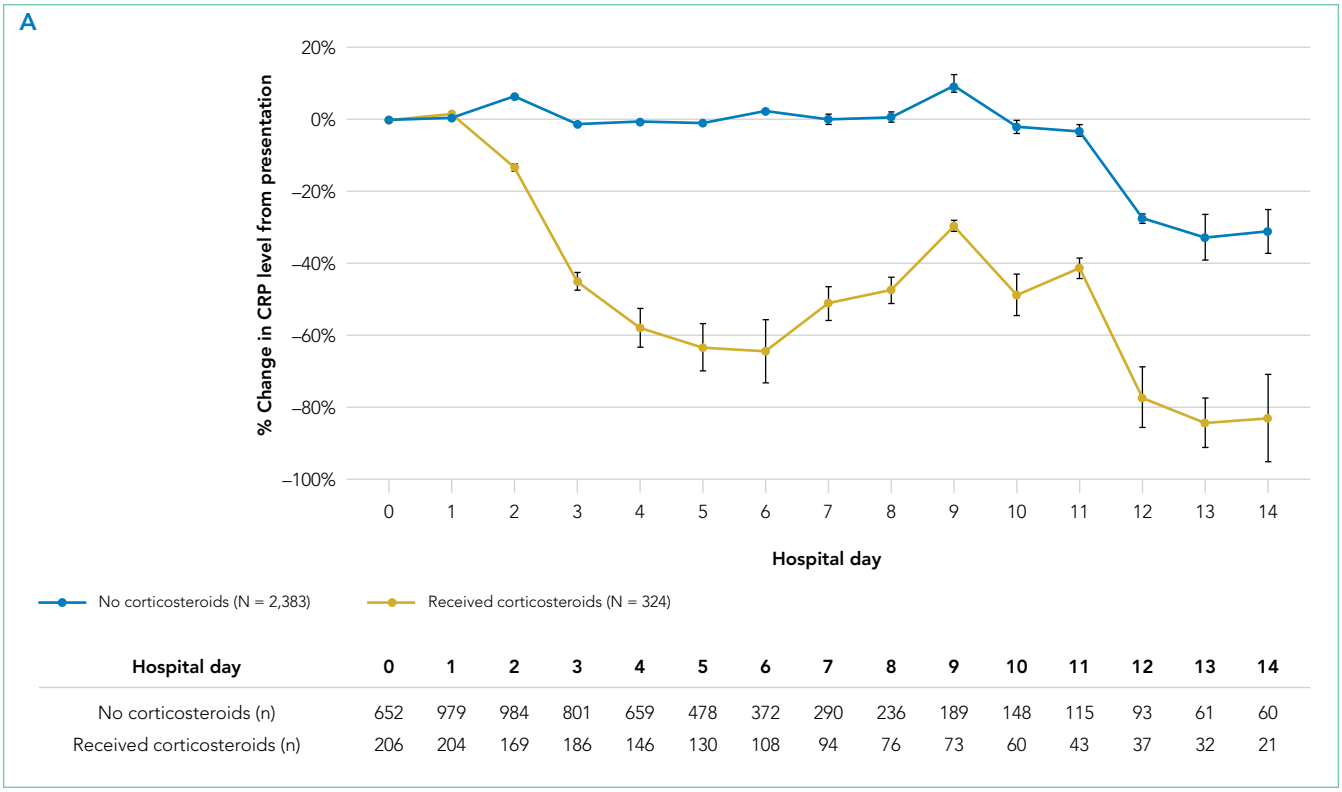
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESRD, end-stage renal disease; IL-6, interleukin-6; IQR, interquartile range; LDH, lactate dehydrogenase; WBC, white blood cell.

lab values are shown in Table 1. Patients who received corticosteroids were older, had higher comorbidity scores, were more likely to have asthma or chronic obstructive pulmonary disease, and were less likely to be full code status, compared with patients who did not receive corticosteroids. Patients who received corticosteroids also had higher initial white blood cell (WBC) and neutrophil counts but lower lymphocyte count. The two groups were comparable in initial creatinine level. Additional patient characteristics and addmission lab values are shown in Appendix Table 2.

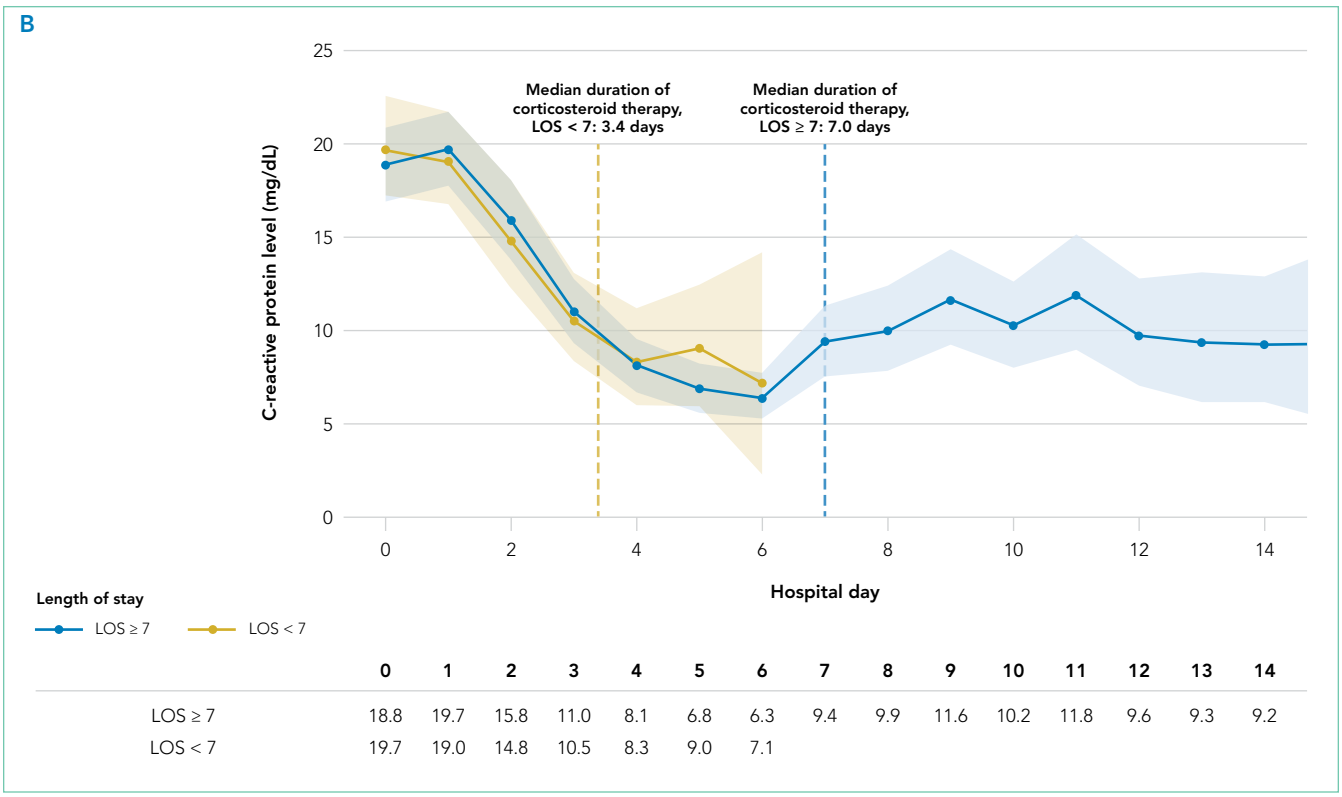
Average change in CRP levels by hospital day for those who received corticosteroids and those who did not are shown in Figure 1A. Among patients who received corticosteroid treatment, there was a significant decrease in CRP level at 72 hours of treatment ($P < .001$). In the post hoc analysis of trends in CRP levels, we found that CRP levels among those treated with corticosteroids started to rise around day 6 after the initial drop. This trend was observed even after removing patients with shorter LOS (<7 days) (Figure 1B). The median durations of corticosteroid therapy were 3 days among patients whose LOS was less than 7 days and 6 days among those whose LOS was 7 days or greater. The rise in CRP level was seen at day 5 and day 7 within each group, respectively. Crude death rate was 41.7% among patients with LOS of less than 7 days and 40.6% in those with LOS of 7 days or greater.

CRP Responders vs Nonresponders

Among the 324 patients who received corticosteroids, 131 (40.4%) were classified as responders, 92 (28.4%) were classified as nonresponders, and 101 (31.2%) were undetermined. Characteristics of CRP responders and CRP nonresponders are shown in Table 2 and Appendix Table 3. CRP responders were more likely to have dementia and higher median admission platelet count and fibrinogen level compared with CRP



Hospital day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No corticosteroids (n)	652	979	984	801	659	478	372	290	236	189	148	115	93	61	60
Received corticosteroids (n)	206	204	169	186	146	130	108	94	76	73	60	43	37	32	21



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
LOS ≥ 7	18.8	19.7	15.8	11.0	8.1	6.8	6.3	9.4	9.9	11.6	10.2	11.8	9.6	9.3	9.2
LOS < 7	19.7	19.0	14.8	10.5	8.3	9.0	7.1								

FIG 1. Trends in C-reactive Protein (CRP) Levels. (A) Percent change in CRP levels from presentation by hospital day. Corticosteroid treatment is associated with significant reduction in serum CRP levels within 72 hours of treatment (43% reduction in mean value; $P < .001$ at day 3). Error bars represent 95% confidence intervals as determined by the *t* statistics for the respective distributions. Hospital day 0 represents the day of presentation. The table shows the number of CRP lab values (n) averaged per hospital day. (B) Average CRP value by hospital day separated by length of stay (LOS) among patients who received corticosteroids. Upward trend in CRP level was observed after day 6 among patients treated with corticosteroids. This trend remained the same even while limiting analysis to those with LOS ≥7 days. The table shows mean CRP values (mg/dL).

TABLE 2. **Characteristics of CRP Nonresponders and Responders Among Patients Who Received Corticosteroids**

	CRP nonresponders (N = 92)	CRP responders (N = 131)	*P* Value
Age, median (IQR), y	64 (55-74)	66 (56-75)	.37
Female, No. (%)	41 (44.6)	61 (46.6)	.80
BMI, median (IQR), kg/m^2	29.4 (11.6)	28.7 (9.4)	.35
Full code, No. (%)	64 (69.6)	100 (76.3)	.26
Charlson Comorbidity Index, median (IQR)	2 (3)	3 (3)	.45
Hypertension, No. (%)	50 (54.4)	78 (59.5)	.44
Asthma/COPD, No. (%)	28 (30.4)	45 (34.4)	.54
Ever smoker, No. (%)	4 (4.4)	11 (8.4)	.24
Diabetes, No. (%)	32 (34.8)	52 (39.7)	.46
ESRD, No. (%)	5 (5.4)	3 (2.3)	.21
Initial WBC, median (IQR), k/μL	9.1 (6.6-14.5)	9.1 (6.8-12.2)	.91
Initial neutrophil count, median (IQR), k/μL	7.7 (4.9-12.1)	7.6 (5-10.5)	.81
Initial lymphocyte count, median (IQR), k/μL	0.9 (0.7-1.3)	0.9 (0.7-1.3)	.91
Initial creatinine, median (IQR), mg/dL	1.3 (0.9-2.3)	1 (0.8-1.6)	.07
Initial CRP, median (IQR), mg/dL	16.5 (8.7-22.9)	16.6 (11.7-24.9)	.22
Initial LDH, median (IQR), μg/L	512 (391-711)	521 (402-761)	.76
Initial ferritin, median (IQR), ng/mL	1,208 (637-2,105)	977 (614-1,737)	.25
Initial fibrinogen, median (IQR), mg/dL	655 (538-789)	716 (610-855)	.02
Initial D-dimer, median (IQR), μg/mL	2.0 (1.1-5.2)	2.7 (1.2-9.4)	.15
Initial procalcitonin, median (IQR), ng/mL	0.5 (0.2-2.3)	0.4 (0.2-2.0)	.86
Initial IL-6, median (IQR), pg/mL	50.6 (18.5-145.0)	18.1 (7.3-68.0)	<.001
Death, No. (%)	44 (47.8)	33 (25.2)	<.001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESRD, end-stage renal disease; IL-6, interleukin-6; IQR, interquartile range; LDH, lactate dehydrogenase; WBC, white blood cell.

TABLE 3. **Odds Ratio of Death Among CRP Responders Compared With CRP Nonresponders (Reference Group)**

	Odds ratio (95% CI)	*P* value
Crude OR	0.37 (0.21-0.65)	.001
Adjusted OR[a]	0.27 (0.14-0.54)	<.001

[a]Variables adjusted for in the model include age, Charlson Comorbidity Index, initial white blood cell count (categorical variable), initial CRP level (categorical variable), and initial fibrinogen level (categorical variable).
Abbreviations: CRP, C-reactive protein; OR, odds ratio.

nonresponders. Patients whose CRP response was undetermined were excluded from the analysis. Their characteristics are shown in Appendix Table 4.

The observed inpatient mortality rate was 25.2% among CRP responders and 47.8% among CRP nonresponders. This difference was also demonstrated in the Kaplan-Meier survival curve (Figure 2). The odds of inpatient mortality among CRP responders were strongly and significantly reduced compared with those among nonresponders in an unadjusted analysis (odds ratio [OR], 0.37; 95% CI, 0.21-0.65; $P = .001$) and after adjustment for demographic and clinical characteristics, including age, Charlson Comorbidity Index, initial WBC count, initial CRP

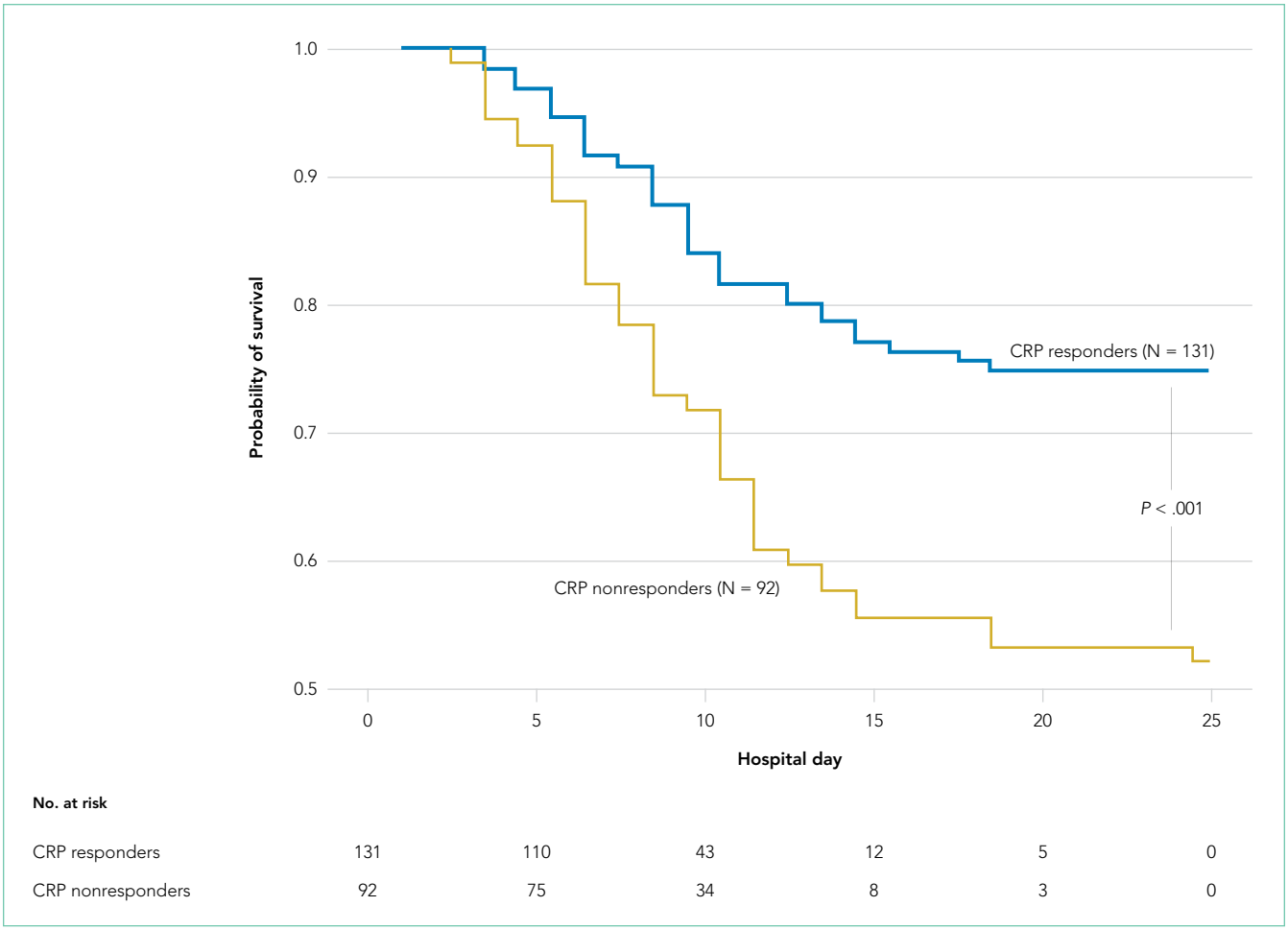


FIG 2. Kaplan-Meier survival plots in C-reactive protein (CRP) responders and nonresponders. A log-rank test of independence gives $P < .001$.

level, and initial fibrinogen level (OR, 0.27; 95% CI, 0.14-0.54; $P < .001$). Details on how variables were operationalized and information on missing data are shown in Appendix Table 1.

To explore whether this observed effect differed depending on severity of the respiratory illness, we examined the association between CRP response and mortality in subgroups stratified by intubation status. Within our cohort of 223 patients (92 CRP responders and 131 CRP nonresponders), 166 patients were never intubated, 50 patients were intubated in the first 48 hours, and 7 patients were intubated later on during the admission. The odds ratios for death among CRP responders vs nonresponders were 0.50 ($P = .07$) among patients never intubated and 0.46 ($P = .2$) among patients intubated within the initial 48 hours of admission.

DISCUSSION

In this retrospective study, we found that, on average, patients treated with corticosteroids had a swift and marked reduction in serum CRP. In addition, among patients treated with corticosteroids, those whose CRP level was reduced by 50% or more within 72 hours after treatment had a dramatically reduced risk of inpatient mortality compared with the risk among nonresponders. This study contributes to a growing body of evidence that suggests that corticosteroids may be an efficacious treatment to reduce adverse events in patients with COVID-19 who have evidence of high levels of inflammation as measured by CRP level.[3,4,12,13]

It remains unclear whether CRP is simply a biomarker of disease activity or whether it plays a role in mediating inflammation. While CRP is commonly understood to be an acute phase reactant, it has been suggested that, after undergoing proteolysis, it functions as a chemoattractant for monocytes.[14] In addition, it is now known that the inflammatory CD14+/CD16+ monocytes that express high levels of IL-6 are key drivers of the cytokine storm in COVID-19.[15] Therefore, it may be possible that the high level of circulating CRP in patients with cytokine storm recruits monocytes to the lungs, which leads to further lung injury.

Other mechanisms of immune dysregulation that may contribute to lung injury and respiratory failure in COVID-19, such as cytokine-induced T-cell suppression, have been proposed.[7,16] The related markers, such as levels of T cells or specific cytokines, may therefore represent different but related underlying immune mechanisms affecting the clinical course of COVID-19 that may respond to different therapeutic modalities, such as direct IL-6 blockade or chemokine receptor blockade, among others that are currently under investigation.[17,18]

Regardless of the underlying mechanism of immune regulation, our study shows that serial measurement of CRP may serve as an early indicator of response to corticosteroids that correlates with decreased mortality. The association between CRP response and reduced risk of mortality was present in both subgroups: those requiring mechanical ventilation and those who did not. The risk reduction was similar in magnitude to the overall effect but was not statistically significant in either group. Interestingly, our time series analysis demonstrated a rise in CRP around day 6 among patients treated with corticosteroids (notably, most patients were treated for 5 to 7 days). Our post hoc analysis suggests that this may represent a "rebound" in inflammation after discontinuation of corticosteroids. However, the clinical significance of this rebound and whether a longer course of steroids would improve outcomes is not known. Because corticosteroid therapy may be associated with adverse effects in some patients,[4] it is possible that CRP nonresponders represent a subset of patients in whom corticosteroids are not effective and for whom alternative therapies should be considered. In one study looking at the usefulness of IL-1 inhibition for severe COVID-19 infection, patients who received IL-1 inhibitor therapy had improved mortality and a significant decrease in CRP concentration as compared with the historical group.[19] Finally, it is worth noting that, in one large retrospective study, there was harm associated with corticosteroid therapy in patients with low levels of CRP, and in the RECOVERY trial there was a trend toward harm for patients with no oxygen requirement.[3,4] Serial measurement of CRP may further identify the subset of patients in whom corticosteroid therapy might be harmful.

This study has several limitations. First, the retrospective nature of this study is inherently prone to selection bias, and despite the large number of clinical variables accounted for, unmeasured confounders may still exist. This study was also conducted at a single clinical center operating under emergency circumstances at a time during which healthcare resources were limited. Overall in-hospital mortality was high but similar to mortality rates reported at other hospitals in the New York City area during the same months.[20] The strengths of this study include a large cohort of COVID-19 patients from New York City, an epicenter of COVID-19, who received corticosteroids.

CONCLUSION

We found that therapy with corticosteroids in patients with COVID-19 is associated with a substantial reduction in CRP levels within 72 hours of therapy, and for those patients in whom CRP levels decrease by 50% or more, there is a significantly lower risk of inpatient mortality. Future studies are needed to validate these findings in other cohorts and to determine whether markers other than CRP levels may be predictors of a therapeutic response or whether CRP nonresponders would benefit from other targeted therapies.

Disclosures: The authors have no conflicts of interest to disclose.

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