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RESEARCH

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Early C-reactive protein reduction predicts survival in COVID-19 severe pneumonia treated with glucocorticoids

Nicolò Reccardini[1,2*], Marco Confalonieri[1,2], Barbara Ruaro[1,2], Paola Confalonieri[1,2], Beatrice Da Re[2,3], Andrea Rocca[2] and Francesco Salton[1,2]

Abstract

Background prolonged, low-dose glucocorticoid treatment reduces systemic inflammation and mortality in patients with SARS-CoV-2-related pneumonia requiring respiratory support. Previous studies reported a significant C-reactive protein (CRP) reduction in the early days of treatment compared to placebo. While CRP is an independent predictor of severity in community-acquired pneumonia, there is no evidence on the correlation between CRP changes and mortality within a glucocorticoid-treated population.

Methods data from the MEDEAS randomized controlled trial were re-analyzed as a single cohort of patients with SARS-CoV-2-related pneumonia undergoing either dexamethasone 6 mg/day for 10 days or methylprednisolone 80 mg/day for ≥ 8 days from hospitalization. CRP relative decrease between treatment initiation and day 3 was calculated and tested to predict 28-day mortality. Additionally, clinically relevant CRP percentage changes by day 3 were calculated and tested to predict survival. A stratification was performed for baseline PaO_2:FiO_2, and a multivariable analysis was conducted to adjust for confounders.

Results 597 patients were included in the analysis. In multivariable logistic regression analysis, the relative decrease in CRP by day 3 was significantly associated with 28-day survival (OR 0.77; 95%CI 0.64–0.99; $p = 0.011$). Furthermore, a ≥ 5% CRP reduction was associated with a lower mortality compared to either < 5% reduction or any increase in CRP levels by day 3 (8.2% *versus* 18.5%; OR 0.40; 95%CI 0.23–0.69; $p = 0.001$) in the whole cohort. When stratifying for baseline PaO_2:FiO_2, a ≥ 5% CRP reduction resulted in a lower mortality (10.9% *versus* 28.3%; OR 0.31; 95%CI 0.16–0.61; p = < 0.001) in the more severe subgroup of patients presenting with a PaO_2:FiO_2 ≤200, while a ≥ 20% reduction was required to significantly impact on mortality among those presenting with a PaO_2:FiO_2 > 200 (3.7% *versus* 10.0%; OR 0.35; 95%CI 0.13–0.97; $p = 0.043$).

Conclusions in patients with COVID-19-related severe pneumonia receiving low-dose glucocorticoid treatment, even early reductions in CRP levels, together with other meaningful clinical traits, predict survival, representing a possible biomarker to guide personalized interventions.

*Correspondence:
Nicolò Reccardini
nico.recca@gmail.com

Full list of author information is available at the end of the article

Trial registration The MEDEAS randomized controlled trial was registered on ClinicalTrials.gov on 18 November 2020 (NCT04636671).

Keywords Covid-19, Pneumonia, Severe pneumonia, C-reactive protein, Glucocorticoids, Methylprednisolone, Dexamethasone

Background

Between January 2020 and April 2024, the World Health Organization (WHO) reported 7,046,320 deaths from COVID-19 globally [1]. Despite the heavy burden, the natural history of COVID-19 was significantly influenced by two main interventions: mass immunization, achieved through the prompt development of effective vaccines, and the former demonstration of the efficacy of glucocorticoids (GCs) in reducing mortality.

The biological activity of glucocorticoids (GCs) is well encoded in the literature, they exert their effect by binding to the glucocorticoid receptor alpha (GRα) and play a pivotal role in all phases of the immune response: from stimulating innate immunity to modulating pro-inflammatory transcription factors, ultimately facilitating disease resolution [2–5]. Nuclear factor-κB (NF-κB) is one of the central activators of innate immunity, targeting more than 1600 genes it stimulates a systemic inflammatory response, mainly through inflammatory cytokines and acute phase reactants [3]. The activated GC-GRα complex directly and indirectly interacts with NF-κB activity, leading to the transcriptional repression of major downstream proinflammatory factors, including the C-reactive protein (CRP) [3, 6–8].

The randomized controlled trial (RCT) RECOVERY first demonstrated the effectiveness of dexamethasone 6 mg once daily for a maximum of 10 days, showing a proportionally higher benefit in patients requiring a more intensive respiratory support [9]. Almost simultaneously, emerging evidence demonstrated the efficacy of other GC molecules administered with similar protocols, allowing to hypothesize a class effect [10–13]. Despite the proven efficacy of glucocorticoids, a subgroup of patients does not respond and actually experiences worse outcomes. It has been hypothesized that this may be due to a certain degree of resistance to GCs, but few studies have attempted to prove this on a pathobiological level, however, it has been suggested that the dose and duration of treatment customized according to clinical severity may lead to better outcomes [14]. Although current guidelines do not fully address which patient characteristics could guide individualized treatment, previous evidence has reported that CRP and pro-inflammatory cytokines levels are dramatically reduced within the first 72 hours of GC treatment and that CRP reduction is associated with a greater survival benefit among GC-treated community-acquired pneumonia patients compared to placebo [14–20]. Moreover, CRP is an independent predictor of severity in community-acquired pneumonia (CAP) [21].

These results are consistent with those more recently obtained using machine learning models, which highlighted CRP reduction as one of the most influential variables for the prediction of hospital mortality among GC-treated patients affected by SARS-CoV-2 pneumonia [22].

To date, it is not yet known what degree of CRP reduction can be considered a marker of response to treatment. We have therefore conducted a post-hoc analysis of data from the study *Prolonged higher dose methylprednisolone vs. conventional dexamethasone in COVID-19 pneumonia: a randomised controlled trial (MEDEAS)* to identify a cutoff in CRP reduction in the first 72 hours of treatment that may predict survival among hospitalized patients with COVID-19 pneumonia treated with GCs [23].

Methods

Study design and population

The MEDEAS study was a multicenter, open-label RCT (two parallel arms, allocation ratio 1:1) conducted in 26 Italian centers between April 2021 and May 2022, which analyzed treatment with low-dose GCs in patients with respiratory failure due to SARS-CoV-2 pneumonia. Of the 690 randomized patients, 677 (98.1%) received at least one study treatment (dexamethasone 6 mg/day for 10 days or methylprednisolone 80 mg/day for at least 8 days after admission). The primary endpoint was mortality proportion at day 28.

Data from the MEDEAS RCT were collectively reanalyzed as a single cohort of patients with SARS-CoV-2 related pneumonia requiring non-invasive respiratory support and undergoing either GC treatment protocol. The time of randomization was considered as the baseline of this study. The only exclusion criterion was missing CRP (mg/L) data at either baseline or day 3.

Aim of the study

This study aims at identifying the lowest percentage of CRP reduction between baseline and day 3 required to significantly correlate with a reduction in hospital mortality among GC-treated patients.

Study procedures

The percentage change in CRP between baseline and day 3 was calculated for each patient and correlated to 28-day all-cause mortality. Additionally, CRP percentage variation was used to define four subgroups according to clinically meaningful arbitrary cutoffs (reduction ≥ 5%, reduction ≥ 10%, reduction ≥ 15%, reduction ≥ 20%). The in-hospital mortality of each subgroup was compared to that of patients with a CRP increase or decrease below the individual cutoffs. The same analyses were conducted within strata defined according to the severity of the respiratory impairment at randomization as PaO_2:FiO_2 ≤200 and PaO_2:FiO_2 > 200 (moderate-severe versus mild hypoxemia), as well as according to the GC protocol (i.e. methylprednisolone-treated and dexamethasone-treated patients) [24]. After identification of the smallest variation in CRP required to significantly impact on mortality in the whole cohort, a multivariable logistic regression model was used to adjust for confounders.

Table 1 Demographics and baseline characteristics of the study population

	n **= 597**
Age, median (Q1;Q3)	65.0 (55.0;74.0)
Sex, No. (%)	
Male	421 (70.5)
Female	176 (29.5)
BMI, median (Q1;Q3)[#]	27.6 (24.8;30.7)
Ever smoker, No. (%)[¶]	262 (43.9)
Randomization group, No. (%)	
Dexamethasone	303 (50.8)
Methylprednisolone	294 (49.2)
Previous coexisting disease, No. (%)	
Any of the listed conditions	362 (60.6)
Diabetes[+]	102 (17.1)
Previous cancer	46 (7.7)
Arterial hypertension	284 (47.6)
Asthma	32 (5.4)
COPD	49 (8.2)
Bronchiectasis	7 (1.2)
Pulmonary embolism	12 (2.0)
Chronic kidney disease	29 (4.9)
Atrial fibrillation	41 (6.9)
Ischemic heart disease	46 (7.7)
Heart failure	42 (7.0)
Chronic liver disease	11 (1.8)
Vasculopathy	15 (2.5)
Anti-SARS-CoV-2 vaccination (at least one dose), No. (%)[§]	138 (23.1)
Use of glucocorticoids before enrollment, No. (%)[f]	289 (48.4)
No. of days of glucocorticoid use, median (Q1;Q3)[##]	3.0 (1.0;5.0)
Prednisone-equivalent cumulative dose (mg), median (Q1;Q3)[¶¶]	83.8 (37.5;150.0)
C-reactive protein (mg/L), median (Q1;Q3)	73.9 (37.0;124.0)
PaO_2:FiO_2 (mmHg), median (Q1;Q3)[++]	187.8 (126.0;257.1)
Respiratory support at randomization, No. (%)[§§]	
Low-flow oxygen	265 (44.4)
High-flow nasal cannula	110 (18.4)
Non-invasive mechanical ventilation	219 (36.7)
Concomitant use of remdesivir, No. (%)	129 (21.6)

Abbreviations: Q1, first quartile; Q3, third quartile; BMI, body mass index; COPD, chronic obstructive pulmonary disease. [#]47 missing data; [¶]41 missing data; [+]1 missing data; [§] [2]23 missing data; [f]21 missing data; [##]308 missing data; [¶¶]315 missing data; [++]2 missing data; [§§] [3] missing data.

Statistical analysis

Data were described using the mean (standard deviation [SD]) or median (first quartile; third quartile [Q1;Q3]) when continuous variables were involved, while categorical variables were described using absolute and relative frequencies (percentages). The normality of continuous variables was tested using the Shapiro–Wilk test. A univariable logistic regression model was used to test baseline variables. Between-group variations regarding categorical and dichotomous variables were assessed using the chi-square test; odds ratio and relative 95% confidence interval (95% CI) were calculated. To adjust for possible confounders, a multivariable logistic regression was conducted on all variables considered relevant, i.e. CRP percentage decrease by day 3, baseline CRP, baseline PaO_2:FiO_2, age, BMI, use of glucocorticoids before enrollment, anti-SARS-CoV-2 vaccination (at least one dose). The best model was chosen using the glmulti R package. An exhaustive screening was used to identify the best model without interactions and a genetic algorithm to identify the best model with interactions. The model comparison is based on corrected Akaike Information Criterion (AICC). A multivariable logistic regression model was also used to adjust the stratification of patients according to CRP for baseline demographics and population characteristics. A two-tailed p-value < 0.05 was considered statistically significant. The multivariable analysis was performed with R software (version 4.3.1), all other analyses were performed with JASP software (version 0.18.3).

Results

Of the 677 eligible patients in the MEDEAS RCT, 597 patients were included in this retrospective analysis, while 80 were excluded because CRP levels were missing at either baseline or day 3 (of these, 3 patients died between day 1 and day 3) (Fig. 3). At baseline, median [Q1;Q3] age was 65.0 [55.0;74.0] years and 421 (70%) patients were males. 303 (50.8%) patients were randomized to the dexamethasone group, while 294 (49.2%) to the methylprednisolone group. Median [Q1;Q3] CRP level was 73.9 [37.0;124.0] mg/L, and median [Q1;Q3] PaO_2:FiO_2 was 187.8 [126.0;257.1] (Table 1, Fig. 4).

In the entire study population, the median [Q1;Q3] relative change in CRP between day 1 and day 3 was −0.494 [−0.712;−0.124]. The CRP relative decrease did not show a statistically significant association with all-cause mortality at 28 days in the univariate logistic regression analysis ($p = 0.700$) and showed only modest predictivity of survival in the ROC curve analysis (AUC 0.674 [0.612–0.736]) (Fig. 1). A multivariable logistic regression model was used to adjust all-cause mortality at 28 days for possible confounders, showing that CRP relative decrease by day 3 after randomization (OR 0.77; 95%CI 0.64–0.99; $p = 0.011$), CRP at baseline (OR 1.01; 95%CI 1.00-1.01; $p = 0.006$), PaO_2:FiO_2 at baseline (OR 0.99; 95%CI 0.99-1.00; $p = 0.011$), and age at randomization (OR 1.12; 95%CI 1.08–1.17; p = < 0.001) have a significant impact on the outcome (Tables 2, 4).

When considering clinically relevant cutoffs, in the entire cohort a 5% or greater reduction in CRP levels between baseline and day 3 was associated with significantly lower all-cause mortality at 28 days than a < 5% reduction or increase (39 [8.2%] *versus* 23 [18.5%]; OR [odds ratio] 0.40; 95%CI 0.23–0.69; $p = 0.001$) (Table 3; Fig. 2). Similar results were obtained when comparing all other CRP reduction subgroups with either increase or reduction lower to the cutoff of the single subgroup (Table 3; Fig. 2).

After stratification for respiratory impairment, these results were only consistent in the more severe subgroup of patients presenting with a PaO_2:FiO_2 ≤200 at baseline. Indeed, among these patients, a 5% or greater reduction in CRP levels at day 3 resulted in a lower 28-day mortality compared to either increase or reduction < 5% (28 [10.9%] *versus* 17 [28.3%]; OR 0.31; 95%CI 0.16–0.61; p = < 0.001), the same result was observed when progressively higher percentage reductions in CRP levels were tested (Tables 3, 5, Fig. 5). Conversely, a reduction of at least 20% in CRP levels was required to have a significant impact on mortality among those presenting with a PaO_2:FiO_2 > 200 at randomization (7 [3.7%] *versus* 9 [10.0%]; OR 0.35; 95%CI 0.13–0.97; $p = 0.043$) (Tables 3, 5, Fig. 6).

Stratification according to randomization group showed no difference between the groups in all-cause mortality at 28 days (Table 6). Concomitant use of remdesivir did not have a significant impact on 28-day mortality in the whole population ($p = 0.079$), nor when a percentage reduction of CRP ≥ 5% by day 3 was considered ($p = 0.075$).

A multivariable logistic regression model was also used to compare the baseline characteristics between the group of patients with a CRP reduction ≥ 5% and those with a CRP reduction < 5% or any increase, showing that only CRP at baseline (OR 1.02; 95%CI 0.01–0.02; $p < 0.001$) has a significant impact on patient stratification based on CRP percentage variations (Tables 7, 8).

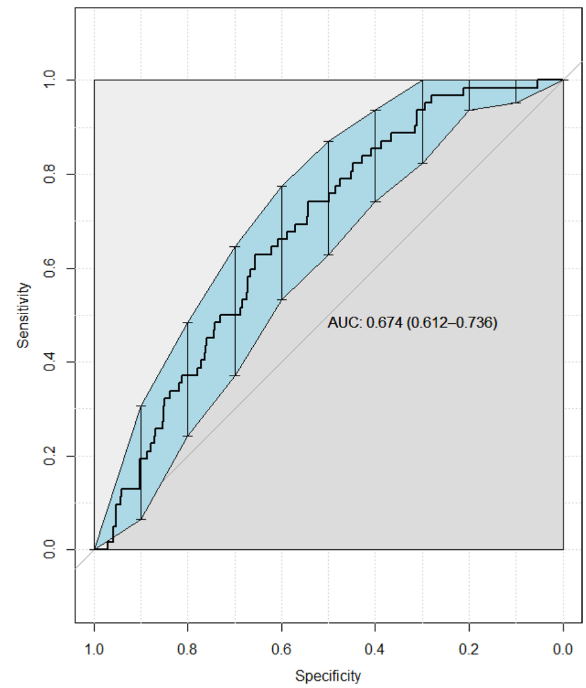

Fig. 1 ROC curve of the survival predictivity of the relative decrease in CRP by day 3 after randomization

Table 2. Multivariable logistic regression of 28-day all-cause mortality

	Odds ratio	95% CI	*p*-value
Prior glucocorticoids			
No			
Yes	1.85	0.84, 4.18	0.13
Anti-SARS-CoV-2 vaccination (at least one dose)			
No			
Yes	1.13	0.50, 2.56	0.8
Baseline C-reactive protein	1.01	1.00, 1.01	0.006
C-reactive protein relative decrease by day 3	0.77	0.64, 0.99	0.011
Baseline PaO_2:FiO_2	0.99	0.99, 1.00	0.011
Age	1.12	1.08, 1.17	< 0.001
BMI	0.98	0.90, 1.06	0.7

Abbreviations: CI, confidence interval; BMI, body mass index

Discussion

In a cohort of hospitalized patients with severe COVID-19 and treated with GCs, the relative decrease in CRP between day 1 and day 3 of treatment was significantly

Table 3 Odds of death at 28 days in the entire cohort and according to the CRP level and PaO2:FiO2 ratio at randomization

	CRP reduction ≥ cutoff	CRP reduction < cutoff or any increase	Odds ratio (95% CI)	*p*-value
Study population				
5%	39 (8.2)	23 (18.5)	0.40 (0.23–0.69)	0.001
10%	39 (8.6)	23 (16.3)	0.48 (0.28–0.84)	0.009
15%	35 (7.9)	27 (17.3)	0.41 (0.24–0.71)	0.001
20%	32 (7.6)	30 (17.2)	0.39 (0.23–0.67)	< 0.001
Baseline PaO_2:FiO_2 ≤200				
5%	28 (10.9)	17 (28.3)	0.31 (0.16–0.61)	< 0.001
10%	28 (11.2)	17 (25.0)	0.38 (0.19–0.75)	0.005
15%	26 (10.8)	19 (25.0)	0.36 (0.19–0.70)	0.003
20%	25 (10.7)	20 (24.1)	0.38 (0.20–0.72)	0.003
Baseline PaO_2:FiO_2 > 200				
5%	11 (5.1)	5 (7.9)	0.63 (0.21–1.87)	0.402
10%	11 (5.3)	5 (6.9)	0.76 (0.25–2.25)	0.616
15%	9 (4.5)	7 (8.9)	0.49 (0.17–1.36)	0.169
20%	7 (3.7)	9 (10.0)	0.35 (0.13–0.97)	0.043

Data are presented as No. (%), unless otherwise stated. Abbreviations: CRP, C-reactive protein; CI, confidence interval.

associated with 28-day survival, but only when other relevant patient characteristics were considered. Using potentially clinically meaningful cutoffs, a CRP reduction of just 5% by day 3 after the initiation of GC treatment was associated with a significantly lower 28-day mortality. Consistent results were obtained in the subgroup of patients with greater respiratory impairment who had a PaO_2:FiO_2 ≤200, whereas a reduction of at least 20% in CRP levels was required to have a significant impact on mortality among the milder patients presenting with a PaO_2:FiO_2 > 200.

The COVID-19 pandemic prompted the need for early identification of patients who deteriorate, to timely escalate the intensity of respiratory support. Therefore, a large body of literature focused on clinical and laboratory prognostic markers able to predict mortality or the need for intubation [25, 26]. Several studies correlated higher CRP values at admission with a worse outcome, while other studies demonstrated a reduction in CRP levels among GC-treated patients [18, 23]. In addition, CRP reduction had been previously correlated with response to GC therapy and disease resolution in severe CAP, ventilator-associated pneumonia, as well as in sepsis [27–29].

Although univariate logistic regression showed no significant correlation between CRP relative decrease and mortality, the relationship changes when adjusted for clinically relevant covariates. CRP alone is probably a suboptimal prognostic predictor, as also shown by the AUC; however, it should be noted that the original study was not designed with this aim. More realistically, the use of CRP as a biomarker should be considered within the clinical context and not as a stand-alone predictor of survival. Indeed, being located downstream of the inflammatory cascade, many factors may influence its kinetics, such as age, and at the same time, many other factors may influence survival beyond GC treatment [22, 30].

Nseir et al. evaluated the impact of CRP changes at 48 h after hospitalization on all-cause mortality at 30 days in a cohort of 111 patients with severe CAP [27]. The authors reported that a fractional decrease of less than 25% in CRP levels by day 2 is significantly associated with an unfavorable outcome. Despite the general agreement on the prognostic role of early CRP changes in severe CAP, in this study variations of less than 25% were not tested and, most importantly, the study protocol did not allow for the use of GCs.

More recently, Andersen et al. reported that both CRP absolute level and CRP relative decline by 50% after 3 days of hospitalization are predictors of 30-day mortality in a cohort of CAP patients [31]. On the contrary, Travlos et al. did not find any significant association between CRP variations at 96 h and survival, but only with hospital length of stay [32].

Previous evidence has shown that the benefit of GC therapy varies significantly depending on the level of respiratory support at the time of randomization, consistently with the results of our stratified analysis [9]. Indeed, among patients with greater respiratory

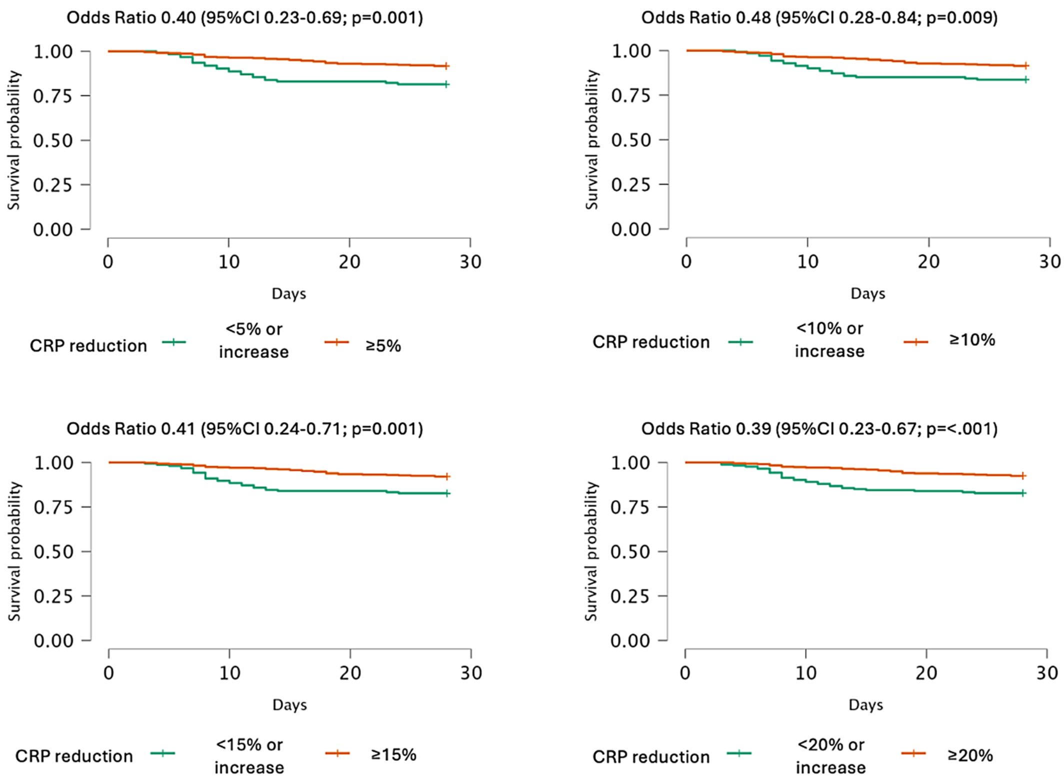

Fig. 2 Survival probability at 28 days in the entire study population. Abbreviations: CRP, C-reactive protein; CI, confidence interval

impairment, even a smaller relative change in CRP may reflect a positive response to treatment [9, 33]. In patients with severe COVID-19, the greater respiratory impairment is probably due, at least in part, to more severe systemic hyperinflammation; consequently, the clinical and laboratory response to GCs is greater. On the other hand, patients with a lower state of inflammatory activation also have less respiratory involvement, so the efficacy of GCs is not only reduced, but even potentially harmful. Finally, the multivariate logistic regression showed that also higher baseline CRP, lower baseline PaO_2:FiO_2 and older age are correlated with a higher mortality, consistently with recent literature data [10, 22].

Our study was the first to investigate the ability of CRP reductions to predict survival in patients affected by SARS-CoV-2 pneumonia treated with GCs.

One major limitation lies in its post-hoc nature; therefore, it might not be optimally powered. Additionally, CRP is a non-specific biomarker due to its downstream position in the inflammatory cascade and to the numerous factors that influence its kinetics beyond GC treatment. Furthermore, the study population underwent two different prolonged, low dose GC protocols, dealing with different molecules and equivalent dose. However, no differences between groups emerged in overall survival from the MEDEAS RCT, nor from the stratification performed in this study (Table 4) [23]. Finally, despite representing some cutoffs that can be easily implemented in clinical practice, arbitrary stratification according to percentage reduction in CRP could lead to a loss of information and the possible creation of spurious relationships.

Conclusions

In conclusion, in a population with severe COVID-19 pneumonia treated with low-dose GCs, even early (72-hour), reductions in CRP levels positively predict 28-day survival. Variations in CRP, together with the consideration of other relevant clinical traits, could therefore represent a possible biomarker to assess early response to GC treatment and guide a personalized therapeutic approach. However, further evidence is needed to corroborate our results and possibly to extend these results to CAP due to pathogens other than SARS-CoV-2.

Appendix

See Figs. 3, 4, 5, 6 and Tables 4, 5, 6, 7, 8.

Table 4 Logistic regression full models including all the variables deemed relevant

Characteristic	Full model 1			Full model 2			Full model 3		
	OR[a]	95% CI[a]	p-value	OR[a]	95% CI[a]	p-value	OR[a]	95% CI[a]	p-value
CRP decrease ≥ 5%									
0	–	–		–	–				
1	0.19	0.07, 0.46	< 0.001	0.15	0.05, 0.38	< 0.001			
CRP day 1	1.01	1.00, 1.01	0.003				1.01	1.00, 1.01	0.011
P/F ratio day 1	0.99	0.99, 1.00	0.017				0.99	0.99, 1.00	0.011
Sex									
F	–	–		–	–		–	–	
M	2.03	0.87, 5.03	0.11	2.39	1.01, 6.10	0.055	1.73	0.77, 4.12	0.2
Age	1.13	1.08, 1.19	< 0.001	1.14	1.09, 1.21	< 0.001	1.13	1.08, 1.18	< 0.001
BMI	0.99	0.91, 1.07	0.8	0.99	0.91, 1.07	0.8	0.99	0.91, 1.07	0.7
Prior glucocorticoids									
0	–	–		–	–		–	–	
1	1.57	0.70, 3.57	0.3	1.90	0.82, 4.57	0.14	1.88	0.86, 4.26	0.12
Covid vaccination									
0	–	–		–	–		–	–	
1	1.11	0.48, 2.56	0.8	1.12	0.47, 2.64	0.8	1.06	0.46, 2.40	0.9
CRP day 1 ≥ 100									
0				–	–				
1				4.55	1.90, 11.7	< 0.001			
P/F day 1 < 200									
0				–	–				
1				4.02	1.72, 10.2	0.002			
CRP % change							1.30	1.02, 1.58	0.010

[a]OR = Odds Ratio, CI = Confidence Interval

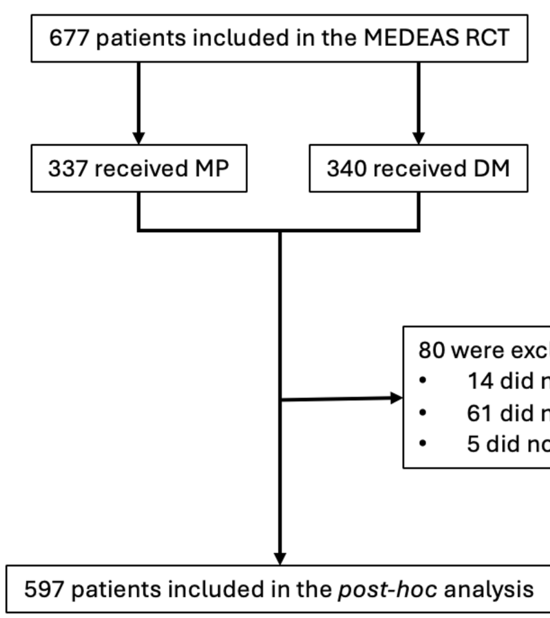

Fig. 3 Inclusion in the analysis

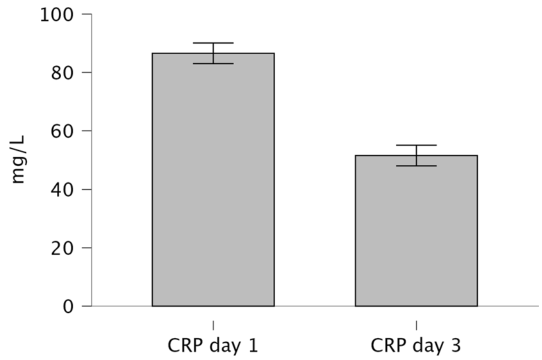

Fig. 4 Bar plots representing day 1 and day 3 CRP and relative 95% CI

Table 5 Between group differences according to baseline PaO2:FiO2

	≤200	>200
Baseline C-reactive protein, median (Q1;Q3)	83.0 (44.0;132.2)	56.7 (31.5;104.3)

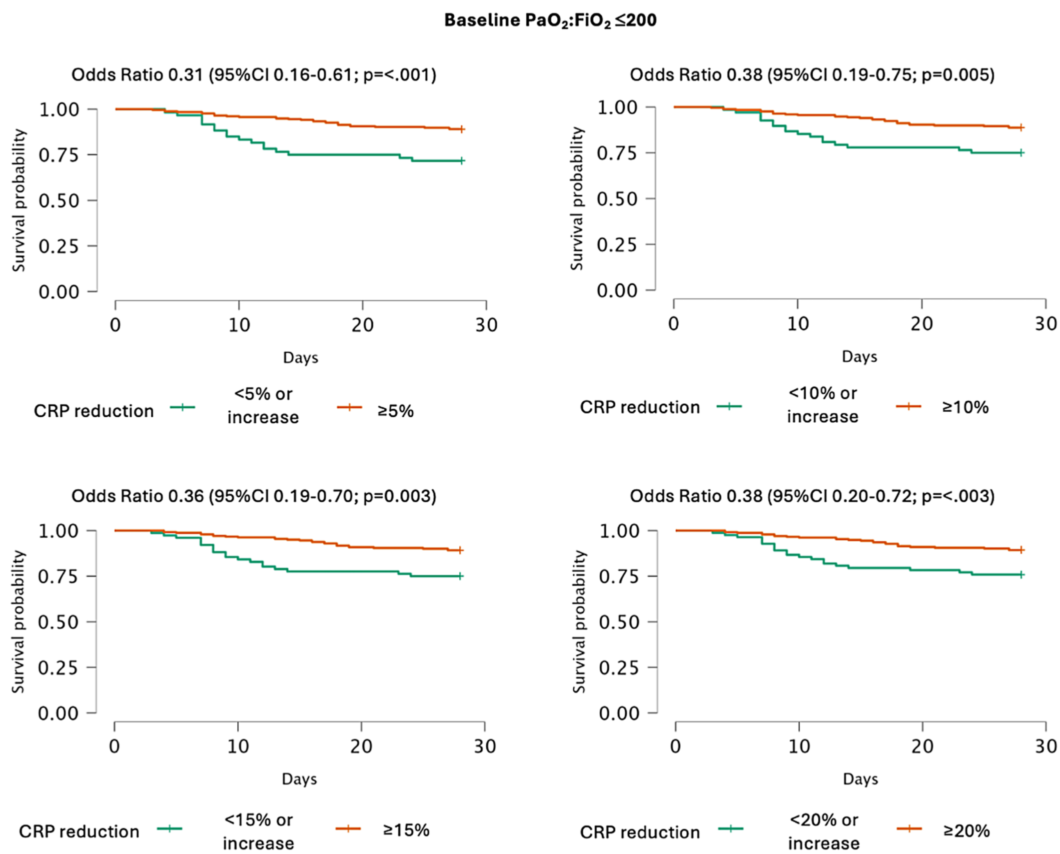

Fig. 5 Survival probability at 28 days in the subgroup presenting a PaO_2:FiO_2 ≤200 at randomization. Abbreviations: CRP, C-reactive protein; CI, confidence interval

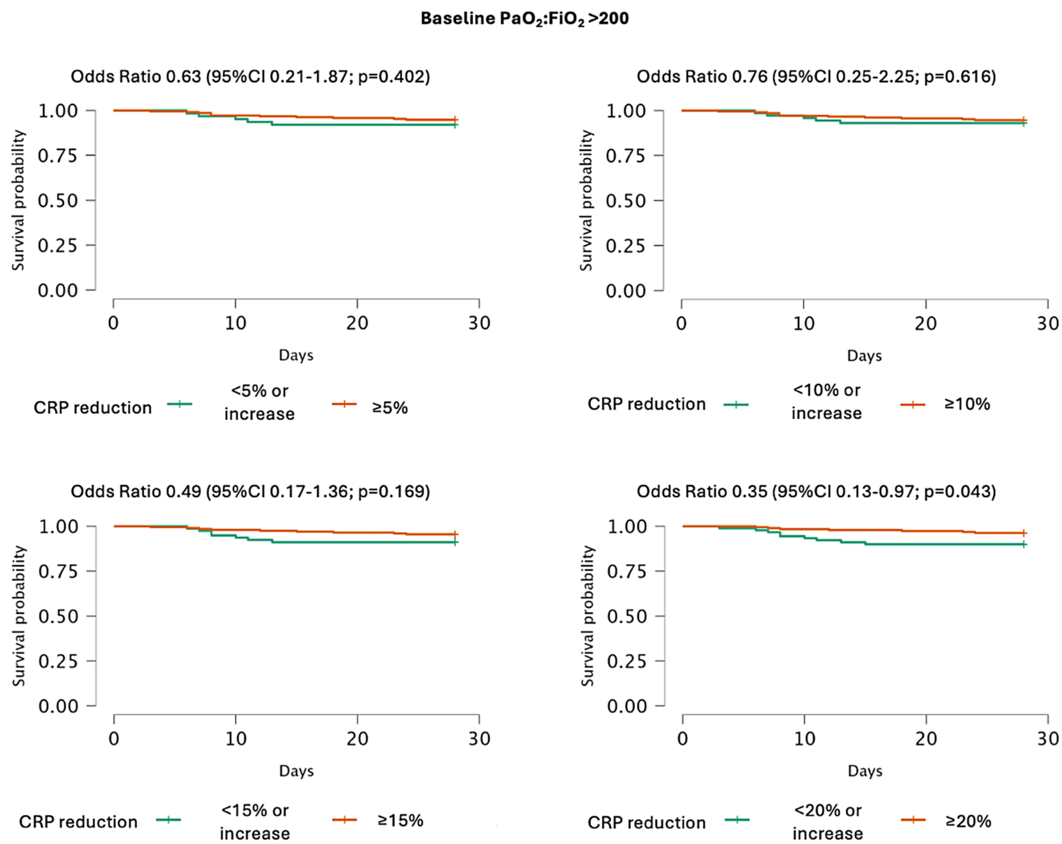

Fig. 6 Survival probability at 28 days in the subgroup presenting a PaO_2:FiO_2 > 200 at randomization. Abbreviations: CRP, C-reactive protein; CI, confidence interval

Table 6 Mortality at 28 days according to the randomization group and the relative decrease in CRP

Death at 28 days, No. (%)	Dexamethasone	Methylprednisolone	*p*-value
5% C-reactive protein reduction	20 (8.7)	19 (7.8)	0.729
10% C-reactive protein reduction	20 (9.1)	19 (8.1)	0.691
15% C-reactive protein reduction	18 (8.4)	17 (7.5)	0.720
20% C-reactive protein reduction	15 (7.4)	17 (7.7)	0.895

Table 7 Demographics and baseline characteristics of the study population according to CRP percentage reduction between day 1 and day 3

	CRP reduction ≥ 5%	CRP reduction < 5% or any increase	p-value
	n = 473	n = 124	
Age, median (Q1;Q3)	65.0 (54.0;74.0)	65.0 (56.0;73.0)	0.993
Sex, No. (%)			
Male	341.0 (57.1)	80.0 (13.4)	0.100
Female	132.0 (22.1)	44.0 (7.4)	
BMI, median (Q1;Q3)#	27.4 (24.7;30.7)	27.7 (25.2;30.7)	0.712
Ever smoker, No. (%)¶	202.0 (36.3)	60.0 (10.8)	0.468
Randomization group, No. (%)			
Dexamethasone	230.0 (38.5)	73.0 (12.2)	0.042
Methylprednisolone	243.0 (40.7)	51.1 (8.5)	
Previous coexisting disease, No. (%)			
Any of the listed conditions	290.0 (48.6)	72.0 (12.1)	0.510
Diabetes+	82.0 (13.8)	20.0 (3.4)	0.778
Previous cancer	38.0 (6.4)	8.0 (1.3)	0.556
Arterial hypertension	228.0 (38.2)	56.0 (9.4)	0.546
Asthma	26.0 (4.4)	6.0 (1.0)	0.772
COPD	36.0 (6.0)	13.0 (2.2)	0.300
Bronchiectasis	7.0 (1.2)	0.0 (0.0)	0.173
Pulmonary embolism	8.0 (1.3)	4.0 (0.7)	0.278
Chronic kidney disease	26.0 (4.4)	3.0 (0.5)	0.156
Atrial fibrillation	33.0 (5.5)	8.0 (1.3)	0.837
Ischemic heart disease	40.0 (6.7)	6.0 (1.0)	0.179
Heart failure	31.0 (5.2)	11.0 (1.8)	0.369
Chronic liver disease	10.0 (1.7)	1.0 (0.2)	0.335
Vasculopathy	11.0 (1.8)	4.0 (0.7)	0.569
Anti SARS-CoV-2 vaccination (at least one dose), No. (%)§	112.0 (29.9)	26.0 (7.0)	0.270
Use of glucocorticoids before enrollment, No. (%)ƒ	224.0 (38.9)	65.0 (11.3)	0.380
C-reactive protein (mg·L − 1), median (Q1;Q3)	82.0 (45.0;132.6)	36.0 (14.7;74.4)	< 0.001
PaO2:FiO2 (mmHg), median (Q1;Q3)++	185.8 (126.0;252.7)	205.7 (128.0;267.0)	0.403
Respiratory support at randomisation, No. (%)§§§			
Low-flow oxygen	211.0. (35.5)	54.0 (9.1)	0.868
High-flow nasal cannula	85.0 (14.3)	25.0 (4.2)	
Non-invasive mechanical ventilation	174.0 (29.3)	45.0 (7.6)	
Concomitant use of remdesivir, No. (%)	101.0 (16.9)	28.0 (4.7)	0.768

Table 8 Multivariable logistic regression of CRP reduction ≥ 5% between day 1 and day 3

	Odds radio	95% CI	*p*-value
Randomization group, No. (%)			
Dexamethasone			
Methylprednisolone	1.52	−0.003-0.837	0.052
Baseline C-reactive protein	1.02	0.011–0.021	< 0.001

Abbreviations: CI, confidence interval; CRP, C-reactive protein

Abbreviations

AICC Corrected Akaike Information Criterion
AUC Area under the curve
BMI Body mass index
CAP Community-acquired pneumonia
CI Confidence interval
COPD Chronic obstructive pulmonary disease
CRP C-reactive protein
GC Glucocorticoid
GRα Glucocorticoid receptor alpha
NF-κB Nuclear factor-κB
OR Odds ratio
Q1 First quartile
Q3 Third quartile
RCT Randomized controlled trial
ROC Receiver operating characteristic
SD Standard deviation
WHO World Health Organization

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not applicable.

Author contributions
N.R. and F.S.: conceptualization, investigation, data curation, formal analysis, writing– original draft, validation. M.C. and B.R.: conceptualization, writing– review and editing, validation. P.C. and B.D.R.: investigation, validation. A.R.: formal analysis, writing– review and editing, validation. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
this study is a post-hoc analysis of previously published data falling within the scopes of the MEDEAS randomised controlled trial, which was registered at ClinicalTrials.gov (NCT04636671) and approved by the Italian National Ethics Committee (2020-006054-43). The protocol and trial conduct complied with the Declaration of Helsinki, International Council for Harmonisation E6 Guideline for Good Clinical Practice and European regulations. Written informed consent was obtained from all subjects involved in the study.

Consent for publication
not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pulmonology, University Hospital of Cattinara, Trieste, Italy
[2]Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy
[3]Department of Pulmonology, Santa Maria degli Angeli Hospital, Pordenone, Italy

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