

Early Corticosteroids Decrease Mortality in Critically Ill Patients with COVID-19: A Cohort Study

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Research

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Abstract

Background: Critically ill patients with coronavirus disease 19 (COVID-19) have a high fatality rate likely due to a dysregulated immune response. Corticosteroids could attenuate this inappropriate response, although there are still some concerns regarding its use, timing, and dose.

Methods: This is a nationwide, prospective, multicenter, observational, cohort study in critically ill adult patients with COVID-19 admitted into Intensive Care Units (ICU) in Spain from March 12th to June 29th, 2020. Using a multivariable Cox model with inverse probability weighting, we compared relevant outcomes between patients treated with early corticosteroids (before or within the first 48h of ICU admission) with those who did not receive early corticosteroids or any corticosteroids at all. Primary endpoint was ICU mortality. Secondary endpoints included 7-day mortality, ventilator-free days, and complications.

Results: A total of 691 patients out of 882 (78.3%) received corticosteroid during their hospital stay. Patients treated with early-corticosteroids (n=485) had a lower ICU mortality (30.3% vs 40.6%, HR 0.71, 95% CI 0.57-0.89) and higher number of ventilator-free days (mean difference 2.5 days, 95% CI 1.3-3.8) compared to non-early treated patients. There were no differences in 7-day mortality (HR 0.76, 95% CI 0.48-1.2), medical complications (OR 2.18, 95% CI 0.91-5.25) or secondary infections (OR 0.88, 95% CI 0.67-1.15) between both groups. Of note, early use of moderate-to-high doses was associated with better outcomes than low dose regimens.

Conclusion: Early use of corticosteroids in critically ill patients with COVID-19 is associated with lower mortality (10.3% absolute risk reduction) and shorter duration of mechanical ventilation.

Background

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first recognized in Wuhan, China, in December 2019 [1]. The anti-viral immune response is crucial to eliminate the invading virus. However, an inappropriate response may cause a systemic hyperinflammatory state, producing complications such as acute respiratory distress syndrome (ARDS) and multisystem organ failure [2]. Early treatment of this hyperinflammation may be important for reducing mortality in COVID-19 patients.

Corticosteroids are used to treat several hyperinflammatory syndromes [3]. Early after the outbreak, the World Health Organization (WHO) recommended against the routine use of systemic corticosteroids for treating COVID-19 patients, due to their known side effects and a potential slowing of viral clearance [1]. However, the RECOVERY trial has shown improved outcomes in COVID-19 patients treated with corticosteroids [4]. Consequently, the US National Institutes of Health (NIH) is recommending now the use of dexamethasone to treat COVID-19 patients requiring supplemental oxygen [5].

Spain is one of the European countries most affected by the COVID-19 pandemic with a broad experience in the use of corticosteroids in Intensive Care Units (ICU) for patients with ARDS [6]. In a large COVID-19 registry of patients admitted into a network of ICUs, we examined whether early use of corticosteroids decreases all-cause mortality and improves clinically relevant outcomes.

Methods

Study design

This is a multicentre, observational study with retrospective analysis of prospectively collected data in consecutive critically ill COVID-19 patients admitted from March 12th to June 29th, 2020 into a network of ICUs in 36 hospitals from Spain and Andorra. The study was approved by a referral Ethics Committee (Ethics Committee of Euskadi, Spain) and by all participating hospitals.

Data source and study population

Following a standardized protocol, site investigators collected data from electronic medical records. We recorded pre-admission and daily data from ICU admission to ICU discharge. Before data analysis, two independent investigators and a statistician screened the database for errors against standardized ranges and contacted site investigators with queries.

All consecutive COVID-19 patients admitted to participating ICUs, were considered for study entry if they had: age ≥ 18 years and confirmed SARS-CoV-2 infection from a respiratory tract sample using RT-PCR assay. Exclusion criteria were non-confirmed SARS-CoV-2 infection, patients with no data at baseline, patients with do-not-resuscitate orders, and patients who did not meet the outcomes of death or ICU discharge by June 29th, 2020.

Variables, Exposures, and Endpoints

We recorded data on demographics and comorbidities according to established definitions (See Additional File), laboratory findings, vital signs, severity scores at ICU admission, supportive therapies, and relevant outcomes reported by June 29th, 2020. We collected pre-ICU-admission and full data set on the first day of ICU (baseline), and the “worst” values during ICU stay (maximum or minimum, depending on the parameter).

For this study, we established a post-hoc cut-off at 48 hours after ICU admission, and classified patients in two groups: (i) patients receiving corticosteroids within the first 48 hours (early-treated group); (ii) patients receiving corticosteroids after 48 hours or never (non-early group). Other exploratory exposures included the administration of corticosteroids at any time during hospital stay (ever-treated group = early plus delayed use) and no administration at all (never-treated group). We also examined patients receiving low dose of corticosteroids (defined as methylprednisolone < 1 mg/kg/d or dexamethasone < 0.12

mg/kg/d or prednisone < 0.5 mg/kg/d) or receiving moderate-to-high doses (any dose higher than low dose).

The primary endpoint was ICU mortality. We excluded from the analysis patients who died or were discharged within the first 48 hours. Secondary endpoints were medical and infectious complications, ventilator-free days, ICU length of stay (LOS), and 7-day mortality.

Statistical analysis

We aimed to enrol as many patients as possible, with no pre-defined sample size.

We report the values of variables as percentages, mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. To compare variables among groups, we used Student t-test or Mann-Whitney test and one-way ANOVA or Kruskal-Wallis test for numerical variables, and Chi-squared test or Fisher exact test for categorical variables.

To assess the relationship between corticosteroids treatment and endpoints, time-to-event curves were plotted using the Kaplan-Meier method and analysed with Cox regression analysis. For the Kaplan-Meier curves, patients with complementary outcomes were right-censored at the longest recorded LOS. We used inverse probability of treatment weighting (IPW) for baseline differences between treatment groups. We fitted logistic models using the following baseline variables: age, gender, comorbidities (diabetes mellitus and arterial hypertension), APACHE II and SOFA scores, and PaO₂/FiO₂ at admission. Weights were calculated following the methodology described elsewhere [7], and a pseudo-population (adjusted sample) was built subsequently. The 95% confidence intervals (CI) were the 2.5th and 97.5th percentiles of the distribution obtained from a nonparametric bootstrap with 1,000 samples. To test the robustness of results, we rerun the primary analysis under several assumptions and scenarios (See Additional File).

Missing data were not imputed. Analyses were performed in a complete case analysis basis. All tests were two-sided, and a p-value <0.05 was considered statistically significant. Analyses were performed using STATA version 16.

Results

From 1,102 consecutive patients with COVID-19, we analysed 882 patients (Fig. 1). Baseline characteristics are reported in Table 1. Acute hypoxemic respiratory failure was the main reason for ICU admission.

Table 1
Baseline Characteristics of Patients Receiving or Not Receiving Early Corticosteroids (in the first 48 hours of ICU admission)

	Whole cohort	Non-early	Early corticosteroids	p-value
Patients demographics and comorbidities				
N (%)	882	397 (45.01%)	485 (54.99%)	
Age, years	62.3 (11.4)/877	61.6 (12.4)/394	62.9 (10.6)/483	0.17
Female (%)	291/880 (33.1%)	138/395 (34.9%)	153/485 (31.5%)	0.31
Body mass index (kg/m ²)	29.2 (5.37)/550	29.1 (5.40)/258	29.2 (5.35)/292	0.93
Arterial Hypertension	420/882 (47.62%)	180/397 (45.34%)	240/485 (49.48%)	0.22
Diabetes Mellitus	201/882 (22.79%)	90/397 (22.67%)	111/485 (22.89%)	1.00
Chronic heart failure	13/882 (1.47%)	6/397 (1.51%)	7/485 (1.44%)	1.00
Chronic renal failure	52/882 (5.90%)	24/397 (6.05%)	28/485 (5.77%)	0.88
Asthma	24/882 (2.72%)	8/397 (2.02%)	16/485 (3.30%)	0.30
COPD	40/882 (4.54%)	16/397 (4.03%)	24/485 (4.95%)	0.62
Obese	299/792 (37.75%)	141/357 (39.50%)	158/435 (36.32%)	0.37
Dyslipidemia	132/882 (14.97%)	56/397 (14.11%)	76/485 (15.67%)	0.56
Cancer	27/882 (3.06%)	19/397 (4.79%)	8/485 (1.65%)	0.01
Laboratory findings				
Hematocrit (%)	39.2 (5.7)/602	39.0 (5.9)/289	39.4 (5.6)/313	0.35
Platelets, 1000/mm ³	236 (108)/672	227 (108)/305	243 (109)/367	0.05
Leukocytes, 10 ³ /μL	9.07 (5.81)/663	8.62 (5.37)/303	9.45 (6.14)/360	0.03
Lymphocytes, μL	0.82 (0.72)/658	0.79 (0.47)/297	0.84 (0.87)/361	0.51
CRP, mg/dL	74.5 (98.9)/623	81.5 (105.4)/274	69.0 (93.3)/349	0.02
Lactate, mmol/L	0.43 (0.94)/475	0.43 (1.01)/230	0.44 (0.88)/245	0.13

COPD: Chronic Obstructive Pulmonary Disease; CRP: C- Reactive Protein; LDH: Lactate dehydrogenase; AST: Aspartate Aminotransferase; NTProBNP: N-terminal pro-brain natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation; CURB65: Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older; SOFA: Sequential Organ Failure Assessment

	Whole cohort	Non-early	Early corticosteroids	p-value
Ferritin, ng/mL	1665 (1658)/285	1561 (1641)/106	1726 (1669)/179	0.26
D- Dimer, ng/mL	2026 (2339)/522	1825 (2094)/230	2185 (2507)/292	0.17
CRP/lymphocyte ratio	131 (234)/617	156 (295)/273	111 (169)/344	0.03
IL-6, pg/mL	253 (486)/87	163 (290)/25	289 (544)/62	0.47
LDH, U/L	484 (240)/595	485 (267)/265	484 (215)/330	0.27
Procalcitonin, ng/mL	1.36 (5.11)/454	1.64 (6.30)/194	1.15 (3.99)/260	0.27
Bilirubin, mg/dL	0.82 (1.16)/567	0.88 (1.62)/245	0.76 (0.61)/322	0.73
AST, U/L	58.3 (86.6)/650	59.7 (111.0)/291	57.2 (60.1)/359	0.40
Creatinine, mg/dL	1.05 (0.68)/658	1.07 (0.71)/297	1.03 (0.66)/361	0.70
Urea, mg/dL	46.5 (28.0)/462	46.3 (28.7)/197	46.6 (27.5)/265	0.75
NTProBNP, pg/mL	1880 (5166)/96	2068 (6380)/46	1707 (3780)/50	0.09
Vital signs				
Temperature, °C	36.9 (1.1)/654	37.1 (1.1)/309	36.7 (1.0)/345	< 0.001
Mean arterial pressure, mmHg	86.7 (15.3)/644	86.6 (14.7)/303	86.8 (15.8)/341	0.78
Heart rate, bpm	85.2 (18.8)/658	86.4 (18.6)/312	84.1 (18.9)/346	0.19
SpO ₂ , %	88.1 (9.2)/641	87.7 (10.5)/299	88.5 (7.8)/342	0.56
Respiratory rate, bpm	25.7 (7.3)/604	26.7 (8.0)/283	24.9 (6.6)/321	0.005
PaO ₂ /FiO ₂	150 (77)/559	149 (77)/254	151 (78)/305	0.76
Severity scores				
Apache II	13.51 (6.35)/600	13.14 (5.87)/252	13.77 (6.67)/348	0.54
CURB65	1.86 (1.22)/288	1.80 (1.20)/138	1.93 (1.23)/150	0.33
SOFA	5.64 (2.94)/474	5.70 (2.88)/208	5.58 (2.99)/266	0.42
COPD: Chronic Obstructive Pulmonary Disease; CRP: C- Reactive Protein; LDH: Lactate dehydrogenase; AST: Aspartate Aminotransferase; NTProBNP: N-terminal pro-brain natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation; CURB65: Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older; SOFA: Sequential Organ Failure Assessment				

Four-hundred and eighty-five patients (55.0%) were treated with early corticosteroids (See Supplementary Table S1). Corticosteroid exposure did not differ according to age, sex, body-mass index, severity scores, and main comorbidities (Table 1). During ICU stay, corticosteroid early-treated patients developed less organ dysfunction, had less requirement for renal replacement therapy (RRT), and less systemic inflammation than non-early treated patients (Table 2).

Table 2

Evolution of organ failure, vital signs, and laboratory findings during ICU stay according to the use of early corticosteroids in the first 48 h of ICU admission.

	Whole cohort	Non-early	Early corticosteroids	p-value
n (%)	882	397 (45.01%)	485 (54.99%)	
Mechanical ventilation, n (%)	722/882 (81.86%)	327/397 (82.37%)	395/485 (81.44%)	0.79
Vasopressor use, n (%)	639/882 (72.45%)	296/397 (74.56%)	343/485 (70.72%)	0.22
Renal replacement therapy, n (%)	96/867 (11.07%)	56/388 (14.43%)	40/479 (8.35%)	0.006
SOFA maximum	8.56 (3.66)/729	9.07 (3.88)/303	8.20 (3.46)/426	0.004
Vital Signs				
Temperature maximum, °C	37.87 (1.04)/869	38.05 (1.01)/388	37.73 (1.04)/481	< 0.001
Mean arterial pressure minimum, mmHg	68.77 (12.98)/868	68.42 (13.00)/388	69.06 (12.98)/480	0.22
Heart rate maximum, bpm	105.65 (20.91)/868	106.87 (20.93)/388	104.65 (20.87)/480	0.12
SpO ₂ , minimum, %	78.64 (16.20)/869	77.67 (17.46)/389	79.42 (15.09)/480	0.37
Respiratory rate, maximum, bpm	30.46 (7.04)/859	31.34 (7.42)/382	29.76 (6.64)/477	0.002
Respiratory rate, minimum, bpm	17.19 (4.44)/859	17.28 (4.51)/382	17.12 (4.38)/477	0.55
Arterial blood gas				
PaO ₂ /FiO ₂ minimum	98.3 (47.9)/833	100.4 (52.9)/367	96.6 (43.5)/466	0.40
PaCO ₂ maximum, mmHg	61.8 (19.3)/855	65.3 (20.2)/382	59.0 (18.0)/473	< 0.001
Laboratory findings				
Ferritin maximum, ng/mL	2305 (2257)/667	2293 (2269)/278	2315 (2252)/389	0.80
D-Dimer maximum, ng/mL	5124 (2983)/809	5058 (2954)/357	5176 (3009)/452	0.61

SOFA: Sequential Organ Failure Assessment; CRP: C- Reactive Protein; LDH: Lactate dehydrogenase; AST: Aspartate Aminotransferase; NTProBNP: N-terminal pro-brain natriuretic peptide

	Whole cohort	Non-early	Early corticosteroids	p-value
CRP maximum, mg/dL	121 (138)/845	134 (148)/373	111 (128)/472	0.003
Lymphocytes minimum, mL	0.45 (0.34)/848	0.49 (0.37)/377	0.42 (0.31)/471	0.002
CRP/ lymphocyte ratio maximum	273 (447)/843	308 (509)/372	246 (390)/471	0.11
IL-6 maximum, pg/mL	957 (1787)/314	1010 (1756)/96	933 (1804)/218	0.39
LDH maximum, U/L	648 (382)/828	633 (366)/361	660 (394)/467	0.16
Leukocytes maximum, 10 ³ /mL	15.46 (10.00)/843	14.58 (9.30)/376	16.17 (10.49)/467	0.01
Procalcitonin maximum, ng/mL	4.13 (9.92)/756	5.49 (12.49)/322	3.11 (7.32)/434	< 0.001
Platelets maximum, 1000/mm ³	387 (153)/852	399 (158)/379	377 (150)/473	0.01
Bilirubin, maximum, mg/dL	2.34 (3.66)/803	2.42 (3.93)/342	2.28 (3.45)/461	0.76
AST maximum, U/L	198 (372)/845	196 (402)/375	199 (346)/470	0.06
Creatinine maximum, mg/dL	1.84 (1.69)/851	2.00 (1.84)/378	1.71 (1.55)/473	0.14
Urea maximum, mg/dL	115 (161)/764	127 (228)/341	106 (69)/423	0.78
NTProBNP, maximum pg/mL	1996 (4816)/261	2430 (4970)/109	1685 (4694)/152	0.01
Hematocrit minimum, %	38.19 (5.98)/834	37.42 (6.07)/370	38.80 (5.85)/464	0.001
Lactate maximum, mmol/L	0.37 (0.81)/692	0.38 (0.90)/300	0.36 (0.74)/392	0.28
SOFA: Sequential Organ Failure Assessment; CRP: C- Reactive Protein; LDH: Lactate dehydrogenase; AST: Aspartate Aminotransferase; NTProBNP: N-terminal pro-brain natriuretic peptide				

Primary Outcome

Overall ICU mortality was 34.9% (n = 308), significantly lower in the early corticosteroids group (30.3%) than in non-early-treated group (40.6%) (HR 0.71, 95% CI 0.57–0.89) (Table 3, Fig. 2). A sensitivity analysis showed less mortality reduction with corticosteroids in women, patients < 60-year-old, with hypertension, cancer, or type 2 diabetes, CRP < 10 mg/dL, D-Dimer > 1500 ng/mL, ICU admission > 8 days after the onset of symptoms, corticosteroids within 7 days of symptom onset, PaFiO₂ > 200, or APACHE score > 14 at ICU admission (Table S2). The reduction in mortality with corticosteroids was independent of treatment with tocilizumab, initiation of steroids before ICU admission, need of invasive mechanical ventilation (MV), lymphocytes count, duration of corticosteroids treatment, or the admitting hospital (Table S2). This reduction in mortality was also observed when including the 149 patients not discharged from ICU or when including “missing” as a category in the IPW cohort.

Table 3

Outcomes according to early corticosteroids use in the first 48 h of ICU admission. IPW subcohort, n = 455

	Whole cohort	Non-early	Early corticosteroids	p-value
n (%)	882	397 (45.01%)	485 (54.99%)	
ICU mortality, cases/person-days	308 (34.9%)/57,589	161 (40.6%)/24,441	147 (30.3%)/33,148	
ICU mortality (hazard ratio)		1 (Ref.)	0.71 (0.57, 0.89)	0.003
ICU mortality (hazard ratio) IP-weighted*		1 (Ref.)	0.56 (0.39, 0.79)	0.002
7-day mortality, cases/person-days	72 (8.2%)/4230	37 (9.3%)/1874	35 (7.2%)/2356	
7-day mortality (hazard ratio)		1 (Ref.)	0.76 (0.48, 1.20)	0.23
7-day mortality (hazard ratio) IP-weighted*		1 (Ref.)	0.54 (0.20, 1.25)	0.11
ICU length of stay, days	17.8 (14.2)	19.7 (15.9)	16.4 (12.5)	
ICU length of stay (mean difference)		0 (Ref.)	-3.3 (-5.2, -1.4)	< 0.001
ICU length of stay (mean difference) IP-weighted*		0 (Ref.)	-4.6 (-8.4, -2.2)	0.002
ICU length of stay among survivors, days	18.1 (14.7)	20.2 (16.6)	16.6 (13.1)	
ICU length of stay among survivors (mean difference)		0 (Ref.)	-3.6 (-6.1, -1.2)	0.004
ICU length of stay among survivors (mean difference) IP-weighted*		0 (Ref.)	-4.3 (-9.5, -2.1)	0.01
Ventilatory-free days	8.4 (9.4)	7.0 (9.1)	9.6 (9.5)	
Ventilatory-free days (mean difference)		0 (Ref.)	2.5 (1.3, 3.8)	< 0.001
Ventilatory-free days (mean difference) IP-weighted*		0 (Ref.)	3.1 (1.9, 5.2)	< 0.001
Medical complications, n (%)	860 (97.5%)	383/397 (96.5%)	477/485 (98.4%)	
Medical complications (odds ratio)		1 (Ref.)	2.18 (0.91, 5.25)	0.08

	Whole cohort	Non-early	Early corticosteroids	p-value
Medical complications (odds ratio) IP-weighted*		1 (Ref.)	2.63 (0.45, 10.61)	0.12
Infectious complications, n (%)	509 (57.7%)	236/397 (59.5%)	273/485 (56.3%)	
Infectious complications (odds ratio)		1 (Ref.)	0.88 (0.67, 1.15)	0.34
Infectious complications (odds ratio) IP-weighted*		1 (Ref.)	0.76 (0.56, 1.25)	0.15

ICU mortality was lower when using moderate-to-high doses of corticosteroids (26.9% vs. 32.8%, (HR 0.58, 95% CI 0.45–0.75) (Table S3-S4, Figure S1).

Secondary outcomes

Patients treated with early corticosteroids had shorter ICU LOS (Table 3), lower rate of acute renal failure (HR 0.64; 95%CI, 0.48–0.84), higher rates of hyperglycaemia, and higher levels of aspartate transaminases. There were no differences in the rate of secondary infections between groups.

Regarding corticosteroids **doses**, early use of moderate-to-high doses, compared with low doses, was associated with a shorter ICU LOS, lower organ dysfunction, less requirement of MV or RRT, and no increase in medical or infectious complications (Table S3-S4).

Patients who **never** received corticosteroids were a less severe population: younger, with fewer signs of organ damage and inflammation, and lower requirement for MV. Nonetheless, compared with early-treated patients, they had higher ICU mortality (36.6% vs. 30.3%, HR 0.55, 95% CI 0.35–0.93) (Tables S5-6, Figure S2). In contrast, compared with ever-treated patients, they had no difference in ICU survival, but lower LOS, less requirement for mechanical ventilation and vasopressors, better disease progression, and a lower number of infectious complications (Tables S7-S8, Figure S3).

Discussion

The major findings of our study are that early use of corticosteroids in critically ill patients with COVID-19 was associated with: (i) lower ICU mortality when compared to delayed or no use of corticosteroids; (ii) shorter ICU LOS; (iii) decreased organ dysfunction, and (iv) fewer days on MV, with no increase in medical or infectious complications. These findings remained statistically significant after adjusting for age, gender, comorbidities, severity, and PaO₂/FiO₂ at admission.

To study the influence of corticosteroids on mortality in our cohort we set a cut-off point of 48 hours after admission to ICU. We consider this period long enough for an experienced clinician to assess patients' response to initial support and therapy and modify them accordingly. We have tried to solve the question

placed by many clinicians: shall I start corticosteroids in this patient? Like an intention-to-treat analysis, patients receiving corticosteroids after 48 h of ICU admission were not excluded because the decision to start therapy in this group was probably guided by other uncontrolled factors.

Two recent publications support the early and selective use of corticosteroids in symptomatic patients infected with SARS-CoV-2. The RECOVERY trial found a reduction in 28-day mortality in hospitalized COVID-19 patients treated with dexamethasone if they required oxygen or MV [4]. The study by Fadel et al. [8] found that an early short course of methylprednisolone in moderate-to-severe COVID-19 reduced escalation of ICU care, need for MV, and hospital mortality. Our study reinforces those results, especially in critically ill COVID-19 patients. Of note, these findings are in contrast with previous reports on corticosteroid therapy in past outbreaks of other coronaviruses (SARS-CoV, MERS-CoV), or other viral pneumonia (Influenza, Respiratory Syncytial Virus) [9–13].

Our sensitivity analysis showed that early use of corticosteroids was not as effective in women, in those with lower risk of death –younger patients with good oxygenation and less inflammation– and neither in those with greater risk or severity –cancer, diabetics, D-Dimer > 1500 ng/mL, APACHE score > 14–. These findings suggest that patient characteristics should be assessed before prescribing corticosteroids.

In clinical practice, corticosteroids are used in most critically ill patients [13]. The extensive use of corticosteroids in our cohort reflects the severity of our patients (almost 60% directly admitted to ICU upon arrival to the hospital, 81.9% with invasive mechanical ventilation in the first 48 hours after ICU admission, and with a mean $PaO_2/FiO_2 = 150$). Since observational studies are prone to selection bias, we used inverse probability of treatment weighting to tackle this problem. Corticosteroid therapy is further entangled by other factors that merit discussion, including timing, type of corticosteroids, duration of treatment, and dosing.

Our average time to corticosteroids administration was 12 days after symptom onset (Table S1), like the 13 days in the RECOVERY study for mechanically ventilated patients [4]. The decision to initiate corticosteroid therapy in our patients was guided when signs of hyperinflammation and severity of respiratory failure were evident. The delay or non-use of corticosteroids in 45% of our patients may reflect the controversy on their benefit/harm profile, WHO recommendations [1], or significant changes in clinical evolution. Ideally, we should start corticosteroid therapy in the initial phases of the hyperinflammatory state. Early use in the absence of hyperinflammation could be harmful, especially in the initial stage of viral replication [4, 14–15]. Similar to the RECOVERY trial, we have also found that corticosteroids were not associated with a reduction in mortality among those patients with symptoms duration under 7 days. One possible explanation is that corticosteroids may slow viral clearance in such an early phase. However, studies on viral clearance have yielded contradictory results [16–19]. Unfortunately, we did not collect time to viral clearance.

Interestingly, patients who never received corticosteroids had higher mortality than early-treated patients, a difference that was not observed when we compare them with ever-treated patients, that includes early plus delayed treatment. Delayed corticosteroids, when advanced organ damage already exists, might be

ineffective and even detrimental, as previously described in ARDS [20], with increased infectious complications and mortality, counteracting the positive effect of early treatment. The absence of benefit with too early use of corticosteroids (within 7 days of symptom onset), together with the beneficial effect of early use, and the worst results with delayed use, reveals a U-shaped time-outcome relationship. Although we do not know the optimal time to start corticosteroids, probably patients with elevated inflammatory markers after seven days of symptoms, requiring oxygen or ventilatory support may benefit the most, whereas those who have not received corticosteroids in early phases, probably will not benefit afterwards.

To the best of our knowledge, recommendations about dose and duration of corticosteroid treatment are empiric. With large doses and long treatments, the potential for adverse effects increases, and the possible benefit is lost [21]. The Italian National Institute for Infectious Diseases recommends a 10-day regimen: 5-days full dose of methylprednisolone 1 mg/Kg daily or dexamethasone 20 mg daily, and five days for tapering [22]. In general, most regimens for acute hyperinflammatory states recommend treatments shorter than two weeks [22, 23]. Most common dose regimens range between 0.5-2 mg/kg/day of methylprednisolone, equivalent to 0.1–0.4 mg/kg/day of dexamethasone, defined in our study as moderate-to-high doses. The cut-off points were defined before the publication of the RECOVERY trial that used a fixed dexamethasone dose (6 mg) lower than described in the literature for ARDS [6]. We observed a greater mortality reduction with a moderate-to-high dose regimen, similar to other studies [6, 24]. Although our classification is artificial, it favours a higher dose of corticosteroids. As a result of RECOVERY trial, the NIH recommend a low fixed dose of daily dexamethasone [4–5], but future comparative studies with higher doses are warranted [6]. Also, the beneficial effects of early corticosteroids in our patients expand beyond an absolute reduction in all-cause mortality, including a shorter ICU LOS, less organ dysfunction, and an increase in ventilator-free days.

This study has several strengths. First, this multicentre nationwide prospective data collection with over 1,000 patients from 36 ICUs provides a very detailed description of all gathered data from ICU admission to death or ICU discharge. Second, to the best of our knowledge, this is the first observational study that prospectively explores the association between different doses and timings of corticosteroid therapy in COVID-19 patients and ICU mortality. Third, we have used IPW to control for confounding with pre-specified demographic, comorbidities, and severity parameters. However, we acknowledge some limitations of our study. First, the observational nature of our study design. Although we adjusted for likely confounders, some unmeasured confounding is still possible. Second, we cannot exclude missing data for some variables and potential for inaccuracies in the electronic health records due to the burden of care experienced by participating clinicians during the pandemic. However, due to the nature of our registry, we consider that selection bias was not favoured, and our analyses are valid. Third, although moderate-to-high doses of dexamethasone were most effective, no firm conclusions can be drawn on the drug or the dose, as our hypothesis and the definition of variables in the protocol preclude to do so, and doses predefined as low are not completely equivalent and could be controversial. Finally, at the time of the analysis, 149 (13.5%) patients did not have a definitive outcome regarding status at ICU discharge and were not included in the main analysis, although included in the sensitivity analyses.

Conclusions

In conclusion, in critically ill COVID-19 patients with acute respiratory failure, the use of corticosteroids within the first 48 h of ICU admission was associated with a marked reduction in ICU mortality and ICU LOS. We also found a clear relationship between exposure and a beneficial effect on organ dysfunction. Further research is needed to characterize the optimal drug, onset, dose, and duration of corticosteroids therapy in this patient population.

Abbreviations

COVID-19: Coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ARDS: acute respiratory distress syndrome

WHO: World Health Organization

NIH: US National Institutes of Health

ICU: Intensive Care Unit

SD: standard deviation

IQR: interquartile range

LOS: length of stay

IPW: inverse probability of treatment weighting

APACHE: Acute Physiology and Chronic Health disease Classification System

SOFA: Sequential Organ Failure Assessment

CI: confidence interval

RRT: renal replacement therapy

HR: Hazard ratio

Declarations

Ethics approval: Approval was obtained from the referral Ethics Committee of Euskadi, Spain (by Nagore García Goitiandia. Secretaria del CEIm de Euskadi. Código interno: PI2020069. Versión del Protocolo:

VERSIÓN 5 -5 de mayo- 2020). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate: The need for written informed consent from participants was considered by each participating centre

Consent for publication: Not applicable

Availability of data and materials: After publication, data will be made available to other investigators on reasonable requests to the corresponding author. A proposal with a detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the corresponding author.

Competing interests: We declare no competing interests.

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Authors' contributions: PM, PC, ACT, MH, CF, and the COVID-19 Spanish ICU Network collected the clinical data. AG, EA, and CF performed the initial data analysis and interpretation. PM and PC summarised all data. ACT, AG, CF, PM, and JV drafted the manuscript. JV, MH, and PC contributed to data interpretation and revised the final manuscript. All authors contributed to critical revision of the manuscript for intellectual content, and all are responsible for the content of this paper.

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Ethics declarations

Conflicts of interest

None of the authors has any conflicts of interest to declare.

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Figures

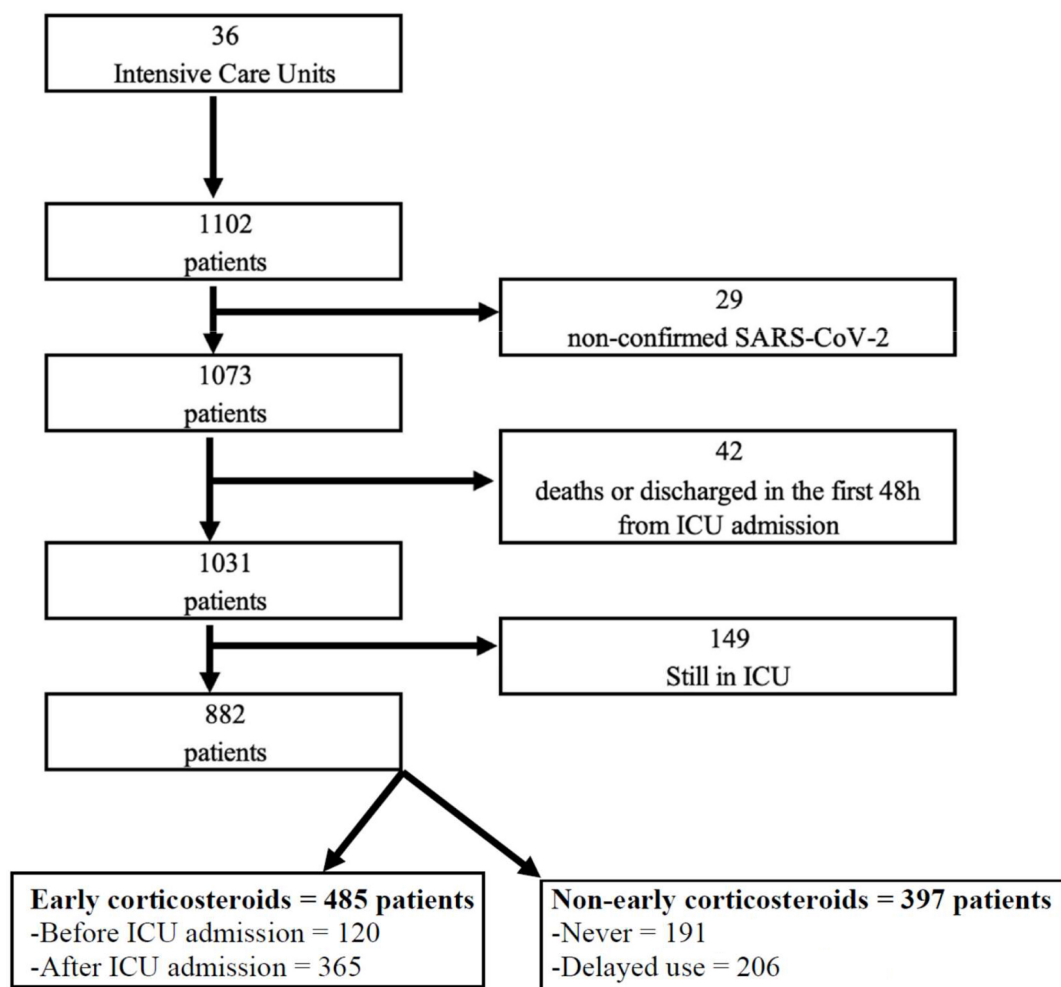


Figure 1

Flow chart of study participants. ICU= Intensive Care Unit.

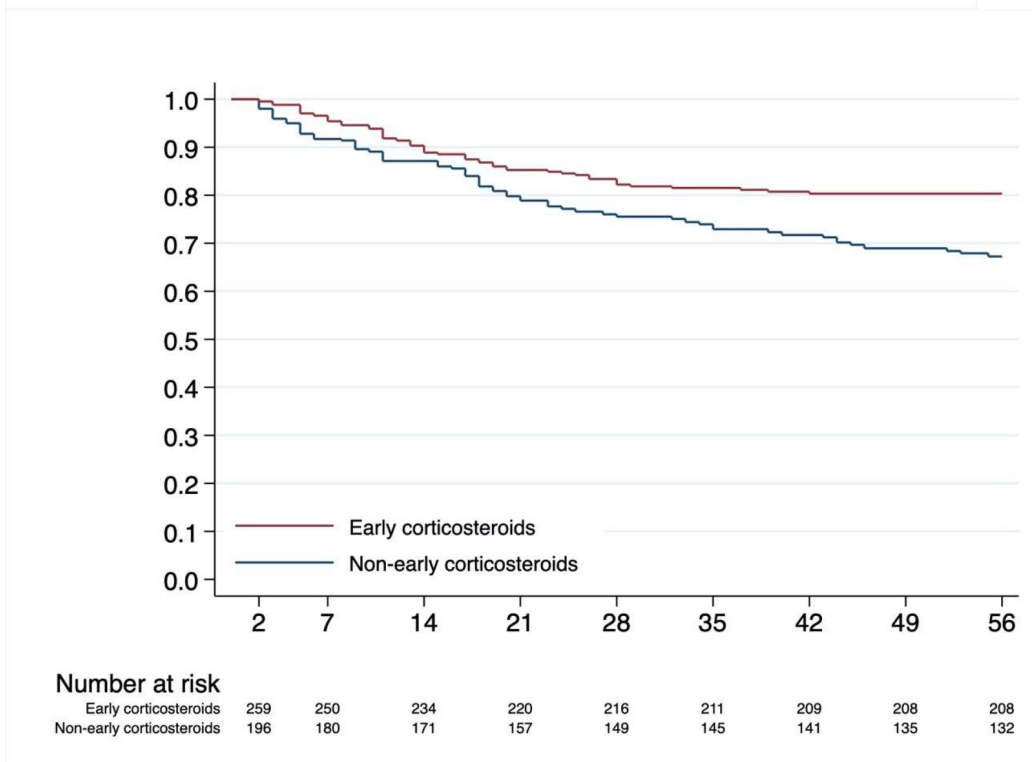
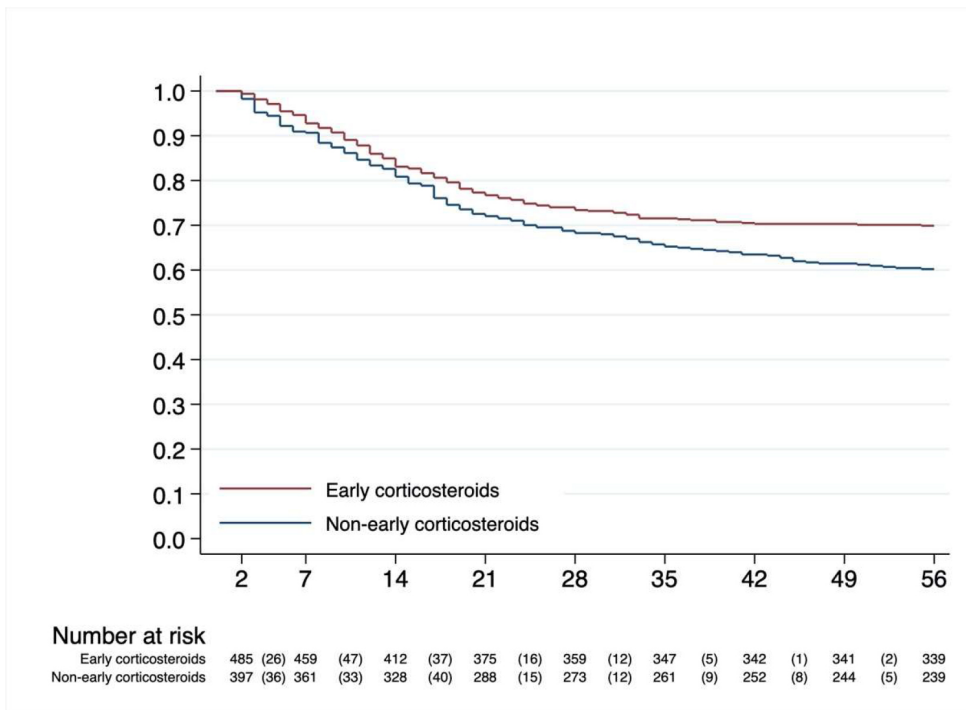


Figure 2

Kaplan-Meier estimates of mortality according to early use of corticosteroids during the first 48h of ICU stay. The upper graphs are crude estimates. The lower graphs are inverse probability weighted (IPW) estimates (N=455).

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