



**HAL**  
open science

## Corticosteroids in patients hospitalized for COVID-19 pneumonia who require oxygen: observational comparative study using routine care data

Viet-Thi Tran, Matthieu Mahévas, Firouze Bani-Sadr, Olivier Robineau, Thomas Perpoint, Elodie Perrodeau, Laure Gallay, Philippe Ravaud, François Goehringer, François-Xavier Lescure, et al.

### ► To cite this version:

Viet-Thi Tran, Matthieu Mahévas, Firouze Bani-Sadr, Olivier Robineau, Thomas Perpoint, et al.. Corticosteroids in patients hospitalized for COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. *Clinical Microbiology and Infection*, 2021, 27 (4), pp.603-610. 10.1016/j.cmi.2020.11.035 . hal-03687923

**HAL Id: hal-03687923**

**<https://hal.science/hal-03687923>**

Submitted on 24 Apr 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

## **Corticosteroids in patients hospitalised for COVID-19 pneumonia who require oxygen: observational comparative study using routine care data**

### **The COCORICO Collaborative Group**

**Writing committee:** Viet-Thi Tran<sup>1,2</sup>, Matthieu Mahévas<sup>3,4</sup>, Firouze Bani-Sadr<sup>5</sup>, Olivier Robineau<sup>6</sup>, Thomas Perpoint<sup>7</sup>, Elodie Perrodeau<sup>1,2</sup>, Laure Gallay<sup>8</sup>, Philippe Ravaud<sup>1,2</sup>, François Goehring<sup>9</sup>, François-Xavier Lescure<sup>10</sup>

<sup>1</sup> Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, 75004 Paris, France

<sup>2</sup> Université de Paris, CRESS, INSERM, INRA, F-75004 Paris, France

<sup>3</sup> Service de Médecine Interne, Hôpital Henri-Mondor, Assistance Publique-Hôpitaux de Paris, 75000 Paris France

<sup>4</sup> Université Paris-Est Créteil, 94000 Créteil, France

<sup>5</sup> Service de Médecine Interne, Centre Hospitalier Universitaire de Reims, 51100 Reims, France

<sup>6</sup> Service Universitaire des Maladies Infectieuses et du Voyageur, centre hospitalier, hôpital Guy Chatiliez, 59200 Tourcoing, France

<sup>7</sup> Service des maladies infectieuses et tropicales, Hospices Civils de Lyon, 69004 Lyon, France

<sup>8</sup> Service de Médecine Interne, Hôpital Edouard Herriot, Hospices Civils de Lyon, 69008 Lyon, France

<sup>9</sup> Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Régional Universitaire de Nancy, 54511 Vandoeuvre lès Nancy, France

<sup>10</sup> Service de maladies infectieuses et tropicales, Hôpital Bichat, Assistance Publique Hôpitaux de Paris, 75018 Paris, France

### **Corresponding author:**

Pr François-Xavier Lescure

Service de maladies infectieuses et tropicales, Hôpital Bichat, Assistance Publique Hôpitaux de Paris, 46 Rue Henri Huchard, 75018 Paris

Mail : [xavier.lescore@aphp.fr](mailto:xavier.lescore@aphp.fr)

Tel : 01 40 25 88 92

**Keywords:** COVID-19, Corticosteroids, therapeutic evaluation, observational study

**Word count:** 2614

# **Abstract**

## **Objective**

To assess the effectiveness of corticosteroids on outcomes of patients with COVID-19 pneumonia requiring oxygen without mechanical ventilation.

## **Methods**

We used routine care data from 51 hospitals in France and Luxembourg to assess the effectiveness of corticosteroids at 0.8 mg/kg/day eq. prednisone (CTC group) versus standard of care (no-CTC group) among adults 18 to 80 years old with confirmed COVID-19 pneumonia requiring oxygen without mechanical ventilation. The primary outcome was intubation or death by day 28. In our main analysis, characteristics of patients at baseline (i.e., time when patients met all inclusion criteria) were balanced by using propensity-score inverse probability of treatment weighting.

## **Results**

Among the 891 patients included in the analysis, 203 were assigned to the CTC group. Use of corticosteroids was not significantly associated with risk of intubation or death by day 28 (weighted hazard ratio [wHR] 0.92, 95% CI 0.61 to 1.39) or cumulative death rate (wHR 1.03, 95% CI 0.54 to 1.98). However, use of corticosteroids was associated with reduced risk of intubation or death by day 28 in the prespecified subgroups of patients requiring oxygen  $\geq$  3 L/min (wHR 0.50, 95% CI 0.30 to 0.85) or C-reactive protein level  $\geq$  100 mg/L (wHR 0.44, 95%CI 0.23 to 0.85). Number of hyperglycaemia events was higher for patients with than without corticosteroids, but number of infections was similar.

## **Conclusions**

We found no association between the use of corticosteroids and intubation or death in the broad population of patients 18 to 80 years old with COVID-19 hospitalized in non-intensive care unit settings. However, the treatment was associated with reduced risk of intubation or death for patients with  $\geq$  3 L/min oxygen or C-reactive protein level  $\geq$  100 mg/L at baseline. Further research need to confirm the right timing of corticosteroids for patients with COVID-19 requiring oxygen only.

## **Introduction**

Coronavirus disease 2019 (COVID-19) pneumonia is associated with a hyper-inflammatory phase, which is deemed responsible for the clinical worsening of many patients [1]. At the onset of the COVID-19 pandemic, guidance regarding corticosteroids for patients without acute respiratory distress syndrome was mixed [2]. Only evidence from small observational studies, with contrasting results, was available and practices varied widely across the world [3-8].

In July 2020, the RECOVERY trial showed that dexamethasone reduced 28-day mortality for patients receiving oxygen with and without invasive mechanical ventilation [9]. The efficacy of corticosteroids in critically ill patients was confirmed in subsequent trials and in a meta-analysis [10-12]. However, for patients with less severe disease, the trial highlighted a heterogeneity of the treatment effect, with a lower incidence of death among patients receiving oxygen but not among those without oxygen at randomization. We hypothesize that this relationship is a continuum and that the more severe the disease, the more effective the treatment. Differences in severity at baseline among the broad population of patients receiving oxygen only could explain the discordance between studies investigating the use of corticosteroids for COVID-19 [13-16].

Our aim was to bring additional data to better understand the effectiveness of corticosteroids in COVID-19 pneumonia, exploring a potential heterogeneity of the treatment effect in the broad population of patients with COVID-19 receiving oxygen without mechanical ventilation.

## **Methods**

We retrospectively used data collected from routine care to emulate a target trial aimed at assessing the efficacy and safety of corticosteroids in patients hospitalised with COVID-19, requiring oxygen and with an inflammatory syndrome [17].

### **Setting**

Our study involved the internal medicine or infectious disease wards from 51 hospitals in France and Luxembourg part of a network coordinated by REACTing (INSERM).

### **Study population**

Physicians performed a patient-by-patient screening of all patients hospitalised between March 1 and May 1, 2020. First, they identified all consecutive patients aged 18 to 80 years old who had PCR-confirmed SARS-CoV-2 infection. Second, they assessed whether these patients had an inflammatory syndrome with C-reactive protein (CRP) level  $\geq 40$  mg/L and required oxygen by mask or nasal prongs during hospitalization. Third, they excluded patients 1) discharged from the intensive care unit (ICU) to standard care or requiring immediate admission to the ICU (including patients requiring non-invasive ventilation); 2) with a contraindication to corticosteroids; 3) who received corticosteroids or anti-interleukin agents before baseline; 4) with severe comorbidities (body mass index  $<16$  kg/m<sup>2</sup>, renal diseases requiring dialysis, chronic heart failure New York Heart Association grade IV, liver cirrhosis Child grade C, or long-term oxygen therapy); 5) with decision to limit active treatments before baseline; and 6) included in the DISCOVERY trial (NCT04315948).

The study received approval by the IRB of the Henri-Mondor Hospital (AP-HP), France (no. 00011558) and by the national ethics committee of Luxembourg (no. 0620-101). The study was based on data from routine care already collected at the time of the study. All patients were informed that their hospital data would be used for research purposes and could refuse this use.

## **Treatment strategies**

We compared two treatment strategies: receiving at least one dose of corticosteroids at  $\geq 0.8$  mg/kg/day eq. prednisone or  $\geq 0.4$  mg/kg/day eq. prednisone if co-administered with lopinavir-ritonavir (CTC group) versus the standard of care (no-CTC group). These values were chosen to account for dose rounding by physician and for the drug–drug interaction between ritonavir and steroids (i.e., patients receiving lopinavir-ritonavir require a lower dose of corticosteroids to obtain an effect) [18]. Standard of care consisted of supportive therapy and treating the symptoms to prevent respiratory failure. No systematic antibiotic prophylaxis or antiviral agents were provided to patients in the study centres. Patients in the CTC group could start corticosteroids within a prespecified “grace period” of 5 days after baseline [17].

Our causal contrast of interest was the per-protocol effect; thus, patients receiving a lower dose of corticosteroids or starting corticosteroids after 5 days were dropped from the analysis. A specific sensitivity analysis mimicking an intention-to-treat analysis was performed in which all patients eligible for the study were analysed. For safety outcomes, all patients who received corticosteroids, whatever the dose and timing, were considered in the CTC group. The definition of group assignment based on patients’ observational data is reported in **Supplementary material 1**.

## **Start and end of follow-up**

The start of follow-up (baseline or time zero) for each individual was the time all eligibility criteria were checked. All patients were followed up from baseline until the occurrence of one of the following: 1) death, 2) loss to follow-up, or 3) end of follow-up, which occurred at least 28 days after baseline.

## **Outcomes**

The primary outcome was intubation or death by day 28. Secondary outcomes were death from any cause by day 28, weaning from oxygen on day 28, and discharge from hospital to

home/rehabilitation on day 28. All adverse events (e.g., infection, thromboembolic events, etc.) were abstracted from electronic health records in free text and independently re-coded by four physicians (XL, FG, TP and MM). In case of disagreement, consensus was obtained.

### **Statistical analysis**

A non-parsimonious multivariable logistic regression model was constructed to estimate the probability of receiving corticosteroids given baseline covariates (i.e., the propensity score [PS]). Variables of the PS model were pre-specified before any outcome analyses and are detailed in **Supplementary material 2**. Standardised differences were examined to assess balance, with a threshold of 10% to indicate clinically meaningful imbalance [19].

Inverse probability of treatment weighting (IPTW) was used to balance the two groups on potential confounders at baseline. Stabilized weights were used to reduce the variability of weights and standard errors of estimated treatment effects [20]. Cox proportional-hazards models were used to compute IPTW hazard ratios (wHRs) with 95% confidence intervals (CIs). IPTW estimates of the relative risk (wRR) were computed for binary outcomes.

Outcomes are presented for the total population and for predefined subgroups: those with  $\geq 3$  L/min oxygen at baseline [21], CRP level  $\geq 100$  mg/L at baseline [22], and a high dose of corticosteroids ( $\geq 120$  mg) at baseline [23]. We also performed two post-hoc subgroup analyses exploring the treatment effect by time since symptom onset  $\leq 7$  or  $> 7$  days [9] and among patients with both  $\geq 3$  L/min oxygen and CRP level  $\geq 100$  mg/L at baseline. In each subgroup, we recalculated the PS to balance the differences in baseline variables between treatment groups.

To account for immortal time bias, all patients in the no-CTC group who met the primary outcome (intubation or death) during the grace period were randomly assigned to one of the

two groups, given that their observational data were compatible with both groups at the time of the event [17] (**Supplementary material 3**).

We aimed for the maximal sample size achievable while accounting for logistical feasibility and costs. We supplemented our results with an “a posteriori” power calculation with an alpha risk of 0.05, based on the number of events observed in our data[24, 25].

Missing baseline and outcome variables were handled by multiple imputations by chained equations by using the other variables available. All statistical analyses were performed with R v3.6.1 or later (The R Foundation for Statistical Computing, <https://www.R-project.org/>).

## Results

### Patients and baseline characteristics

Among the 965 patients eligible for analysis, 194 received corticosteroids at  $\geq 0.8$  mg/kg/d eq. prednisone (or 0.4 mg/kg/d eq. prednisone if co-administered with lopinavir-ritonavir) within 5 days from baseline; 697 did not receive corticosteroids, 28 received corticosteroids at a lower dose, and 46 received corticosteroids after 5 days from baseline.

In all, 107 patients who did not receive corticosteroids met the primary outcome (intubation or death) during the grace period. To account for immortal time bias, we randomly assigned these 107 patients to the CTC or no-CTC group [17]. Thus, we compared 203 participants in the CTC group to 688 in the no-CTC group (**Figure 1 and supplementary material 3**).

The patients' median age was 63 years (interquartile range [IQR], 53 to 70), and 66.4% were men. The median time between symptom onset and baseline was 8 days (IQR, 6 to 10). Oxygen requirement was lower for patients in the no-CTC than CTC group: 22 (10.8%) and 130 (18.9%) received  $\leq 1$  L/min oxygen at baseline. Among the 194 patients who received corticosteroids, 53 (27.3%) received dexamethasone, 71 (36.6%) methylprednisolone, 21

(10.8%) prednisolone and 49 (25.3%) prednisone. At baseline, 85 (9.6%) patients also received hydroxychloroquine and 60 (6.7%) lopinavir-ritonavir (**Table 1, Supplementary material 4**). During follow-up, 146 patients additionally received hydroxychloroquine; 111 lopinavir-ritonavir; 14 remdesivir; and 19 interleukin-6 inhibitors (**Supplementary material 5**).

### **Propensity score model development**

Propensity scores ranged from 0.08 to 0.89 and from 0.04 to 0.83 in the CTC and no-CTC groups, with 93.2% in the region of common support [0.08–0.83] (**Supplementary material 6**). Among the 25 covariates in the planned PS, one (liver cirrhosis) was dropped from the final model because only one patient had liver cirrhosis in the CTC group. After applying IPTW, all 25 covariates (including liver cirrhosis) had weighted standardised differences < 10% (**Supplementary material 7**).

### **Follow-up and outcomes**

Among the 891 patients included in the main analysis, 78 had follow-up < 28 days (70 were discharged in good health status) and 63 died before day 28. Median follow-up for surviving patients was 80 days (IQR, 38 to 94).

In the unweighted sample, by day 28, 18.0% (n=36) and 19.4% (n=131) of patients in the CTC and no-CTC groups had been intubated or died (HR 0.89, 95% CI 0.62 to 1.28). In total, 8.5% (n=17) and 6.9% (n=46) of patients died in the CTC and no-CTC groups (HR 1.23, 95% CI 0.70 to 2.13). On day 28, 79.9% (n=148) and 83.6% (n=522) of patients, respectively, were weaned from oxygen (RR 0.96, 95% CI 0.88 to 1.03). Furthermore, 81.6% (n=151) and 84.4% (n=529), respectively, were discharged to home/rehabilitation (RR 0.97, 95% CI 0.90 to 1.04). From the number of events observed in our data, our sample allowed for 45% to 70% power to detect an HR of 0.7 to 0.6, consistent with results for patients  $\leq$  70 years old in the RECOVERY trial.

In the IPTW analyses, on day 28, 20.1% and 20.9% of patients in the CTC and no-CTC groups had been intubated or died (weighted HR [wHR] 0.92, 95% CI 0.61 to 1.39) (**Figure 2**) and 8.7% and 8.2% died, respectively (wHR 1.03, 95% CI 0.54 to 1.98) (**Figure 3**) (**Table 2**). The two groups did not differ in oxygen weaning (wRR 0.98, 95% CI 0.89 to 1.07) or discharge to home/rehabilitation (wRR 1.00, 95% CI 0.92 to 1.09) (**Table 2**).

Results for subgroups are presented in **Figure 4 and Supplementary material 8**. Corticosteroids reduced the risk of intubation or death by day 28 for patients with oxygen  $\geq 3$  L/min (outcome met for 15.1% of 120 patients in the CTC group vs. 26.5% of 277 patients in the no-CTC group [wHR 0.50, 95% CI 0.30 to 0.85]) and CRP level  $>100$  mg/L (11.5% of 120 patients in the CTC group vs. 24.2% of 326 patients in the no-CTC group [wHR 0.44, 95% CI 0.23 to 0.85]). Corticosteroids greatly reduced the risk of intubation or death for patients with both oxygen  $\geq 3$  L/min and CRP level  $>100$  mg/L at baseline (9% of 71 patients in the CTC group vs. 30.6% of 161 patients in the no-CTC group [wHR 0.26, 95% CI 0.12 to 0.55]). Finally, we did not find a significant effect of corticosteroids among patients with a time since symptom onset  $> 7$  days (13.7% of 111 patients in the CTC group vs. 13.7% of 361 patients in the no-CTC [wHR 0.96, 95% CI 0.46 to 1.99]).

We performed several sensitivity analyses, and all findings were consistent with the main analysis (**Supplementary material 9**). We found no significant centre effect (**Supplementary material 10**).

### **Safety**

Overall, 845 adverse events were extracted from patient records; 464 patients experienced at least one adverse event (150/283 [53.0%] and 314/682 (46.0%) among patients with and without corticosteroids) (**Table 3**). Differences involved mainly a higher number of hyperglycaemia events for patients with corticosteroids (64/283 [22.6%] vs 86/682 [12.6%]).

Rate of infection was not increased in patients with corticosteroids (50/283 [17.7%] vs 128/682 [18.8%]).

## **Discussion**

We report a multicentre study that used real-world data to emulate a target trial on the effectiveness of corticosteroids for patients with COVID-19 pneumonia in non-ICU settings.

We found no difference in risk of intubation or death for patients who received and did not receive corticosteroids, although the result was compatible with a 40% reduction in risk.

However, rate of intubation or death was lower for patients receiving corticosteroids with  $\geq 3$  L/min oxygen or with CRP level  $>100$  mg/L at baseline.

In all, our results are consistent with the hypothesis that that the more severe the disease (i.e., requiring higher oxygen flow and with a more severe inflammatory syndrome), the more effective the treatment. Difference in between our results and those from the RECOVERY trial may be due to the fact that we included a large number of patients who had limited requirements for oxygen (e.g., in the no-CTC group, 18% of patients received  $\leq 1$  L/min oxygen at baseline) and whose condition may be closer to the subgroup of patients who were not under oxygen at the time of randomization in the RECOVERY trial. Second, to maximize comparability between the two groups, we also chose to exclude patients with severe chronic conditions. This could explain the difference in death rates by 28 days in the no-CTC groups (8.2% in our study and 25% in the RECOVERY trial).

In all, our findings question the benefit/risk balance of corticosteroids in patients with the least severe disease. Indeed, although we found no increase in secondary infections, hyperglycaemia occurrence was higher in patients with than without corticosteroids.

### **Strengths and Limitations of study**

Our study is based on the analysis of a large number of consecutive patients and provides insight into the management of COVID-19 during the study period in France and

Luxembourg. Second, all safety data were reviewed in duplicate and independently by several clinicians, which strengthens our confidence in the absence of any warning signal for using corticosteroids in COVID-19 pneumonia in terms of secondary bacterial or fungal infection.

Our study has several limitations. First, despite the use of robust methods to draw causal inferences, our study is observational, and potential unmeasured confounders may bias our results [26]. Second, our study dealt with a heterogeneous prescription of corticosteroids in terms of drugs, time of start, dose, administration mode and duration. Third, we could not account for duration of corticoid prescription. Indeed, we may have observed only 3 days of corticosteroid treatment for a given patient because an event occurred on the fourth day. Only trials in which the dose and duration are specified before treatment, in “intent-to-treat”, can answer this question. Fourth, because we used data from a large number of hospitals, we could not standardize the process of identifying patients eligible to participate in the study. This situation may have led to missing some patients. Fifth, our sample was limited to the number of eligible patients available at the time of analysis and we cannot rule out that our findings are due to a lack of power

## **Conclusions**

We found no association of the use of corticosteroids and intubation or death in a broad sample of patients 18 to 80 years old hospitalised for COVID-19 pneumonia in non-ICU settings in France. However, use of corticosteroids was associated with reduced rate of intubation or death for patients receiving oxygen  $\geq 3$  L/min or CRP level  $\geq 100$  mg/L at baseline. These data support the hypothesis that that the more severe the disease, the more effective the treatment and call for discussing the treatment for patients requiring low oxygen flow.

**Funding:** No funding received for the present study.

**Ethical approval:** This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of the Henri-Mondor Hospital (AP-HP), France (no. 00011558) and by the National ethics committee of Luxembourg (no. 0620-101).

**Data sharing:** The data are available on request.

**Dissemination to related patient and public communities:** We plan to issue a press release on official publication of this manuscript and disseminate our findings through social media outlets, to ensure the results of the study have broad public outreach.

The lead author (X. Lescure) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Contributorship statement:** V-TT, EP, PR and F-XL conceived the study; MM, FB, OB, TP, LG, FG and F-XL participated in data collection; V-TT, EP and PR performed the statistical analyses; MM, OB, TP, FG and F-XL reviewed the data for the adverse events; MM, LG, and F-XL provided administrative and logistic support; V-TT, MM and F-XL wrote the first draft of the manuscript; All members of the writing committee contributed to the writing of the manuscript. All members of the writing committee meet the ICMJE criteria. All members of the writing committee agree with the manuscript results and conclusions. F-XL is the guarantor, had full access to the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All collaborators are listed in the supplementary appendix.

## References

1. Tay MZ, Poh CM, Rénia L et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; 20: 363-374.
2. Bhimraj A, Morgan RL, Shumaker AH et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020.
3. Fadel R, Morrison AR, Vahia A et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis* 2020.
4. Wu J, Huang J, Zhu G et al. Systemic Corticosteroids and Mortality in Severe and Critical COVID-19 Patients in Wuhan, China. *J Clin Endocrinol Metab* 2020; 105.
5. Bani-Sadr F, Hentzien M, Pascard M et al. Corticosteroid therapy for patients with COVID-19 pneumonia: a before-after study. *Int J Antimicrob Agents* 2020; 56: 106077.
6. Lu X, Chen T, Wang Y et al. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. *Crit Care* 2020; 24: 241.
7. Haberman R, Axelrad J, Chen A et al. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. *N Engl J Med* 2020; 383: 85-88.
8. Xu XW, Wu XX, Jiang XG et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *Bmj* 2020; 368: m606.

9. Horby P, Lim WS, Emberson JR et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020.
10. Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *Jama* 2020.
11. Angus DC, Derde L, Al-Beidh F et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *Jama* 2020.
12. Tomazini BM, Maia IS, Cavalcanti AB et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *Jama* 2020.
13. Jeronimo CMP, Farias MEL, Val FFA et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial. *Clin Infect Dis* 2020.
14. Bartoletti M, Marconi L, Scudeller L et al. Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicenter study. *Clin Microbiol Infect* 2020.
15. Corral L, Bahamonde A, Arnaiz delas Revillas F et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv* 2020; 2020.2006.2017.20133579.
16. Liu Z, Li X, Fan G et al. Low-to-moderate dose corticosteroids treatment in hospitalized adults with COVID-19. *Clin Microbiol Infect* 2020.
17. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016; 183: 758-764.
18. Josephson F. Drug-drug interactions in the treatment of HIV infection: focus on pharmacokinetic enhancement through CYP3A inhibition. *J Intern Med* 2010; 268: 530-539.
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083-3107.
20. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11: 550-560.
21. Hermine O, Mariette X, Tharaux PL et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2020.
22. Zeng Z, Yu H, Chen H et al. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. *Crit Care* 2020; 24: 525.
23. Buttgerit 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: 718-722.
24. Bacchetti P, McCulloch CE, Segal MR. Simple, defensible sample sizes based on cost efficiency. *Biometrics* 2008; 64: 577-585; discussion 586-594.
25. Bacchetti P. Current sample size conventions: flaws, harms, and alternatives. *BMC Med* 2010; 8: 17.
26. Hernán MA. The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data. *Am J Public Health* 2018; 108: 616-619.

## List of Tables

**Table 1: Demographic and clinical characteristics of the patients in the corticosteroids (CTC) and no-CTC groups at baseline.** The number in brackets in the first column corresponds to the actual quantity of data available for the corresponding variables before imputation of missing baseline data by multiple imputations by chained equations using the other variables available.

**Table 2: Primary and secondary outcomes at day 28.** IPTW estimates the average treatment effect on the whole population (ATE).

**Table 3: Adverse events.** Adverse events are counted in the safety population, without weighting.

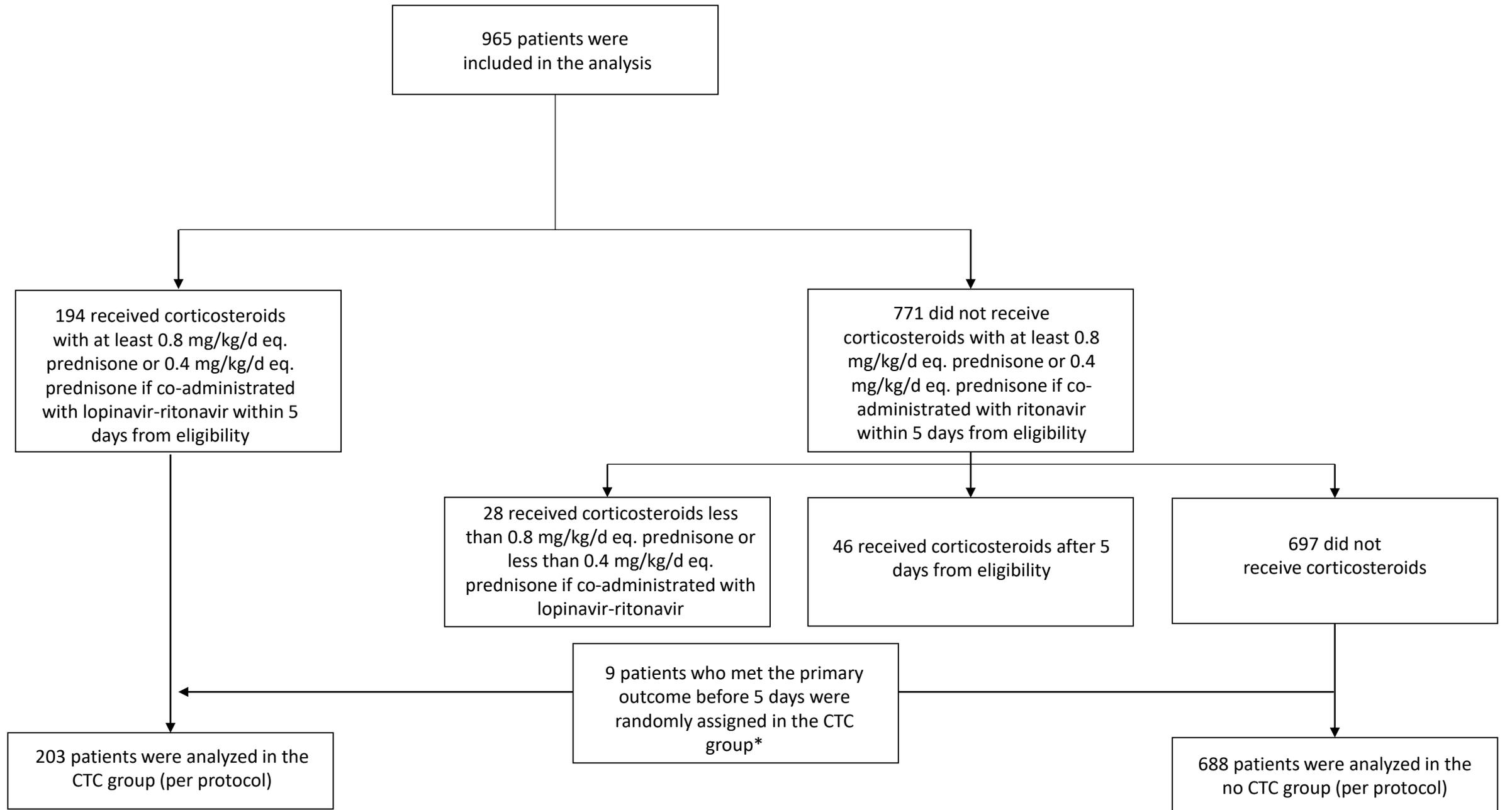
## List of figures

**Figure 1: Study flow chart.** \*To account for immortal time bias, we randomly assigned patients who met the primary outcome during the grace period between to the CTC or no-CTC group

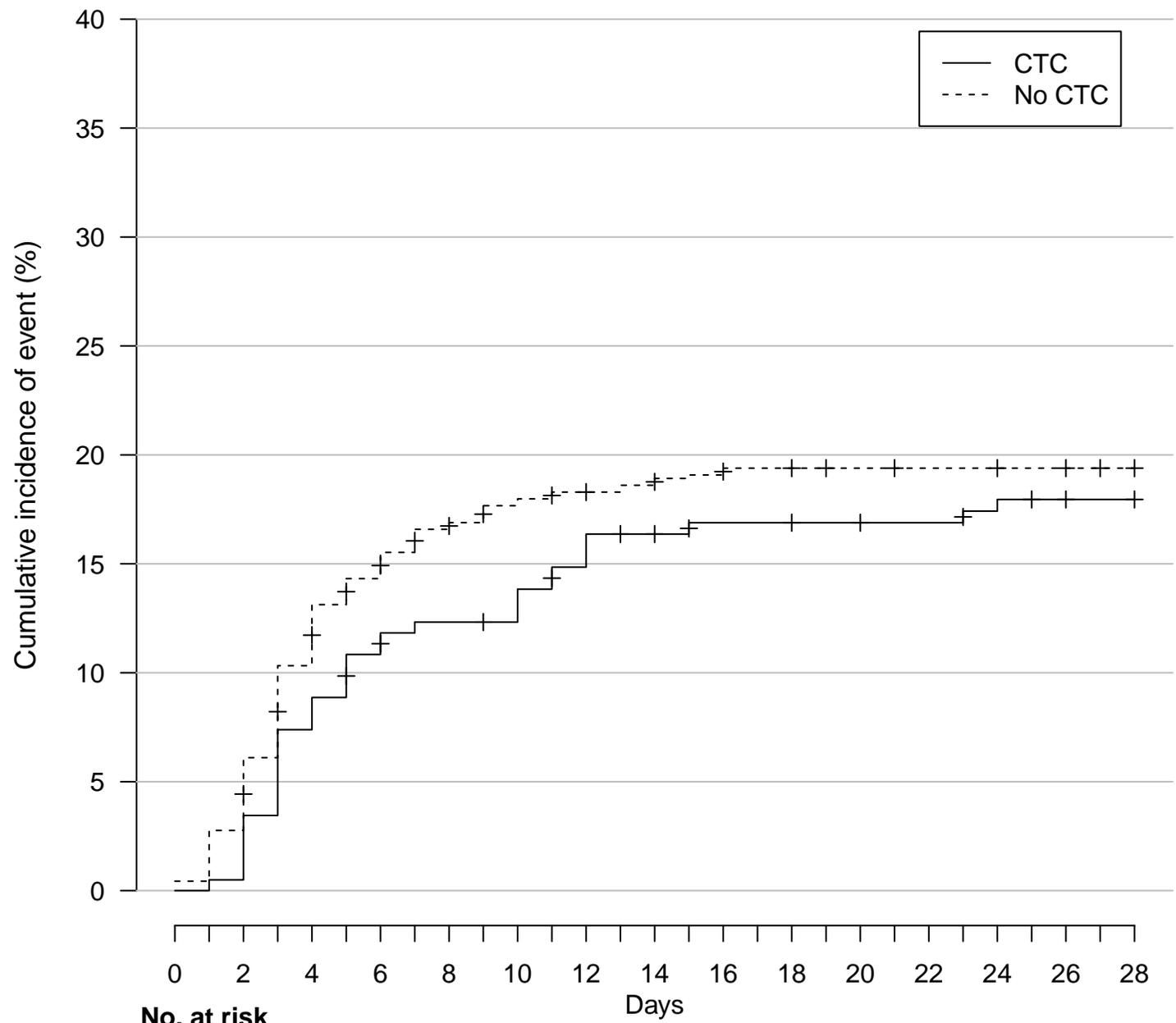
**Figure 2: Cumulative event curve for intubation or death** in the unweighted and IPTW sample.

**Figure 3: Cumulative event curve for death** in the unweighted and IPTW sample.

**Figure 4: Effect of corticosteroids on 28-day intubation or death in subgroups defined by oxygen requirement, C-reactive protein level and time since symptom onset, at baseline.** HR: hazard ratio; 95% CI: 95% confidence interval

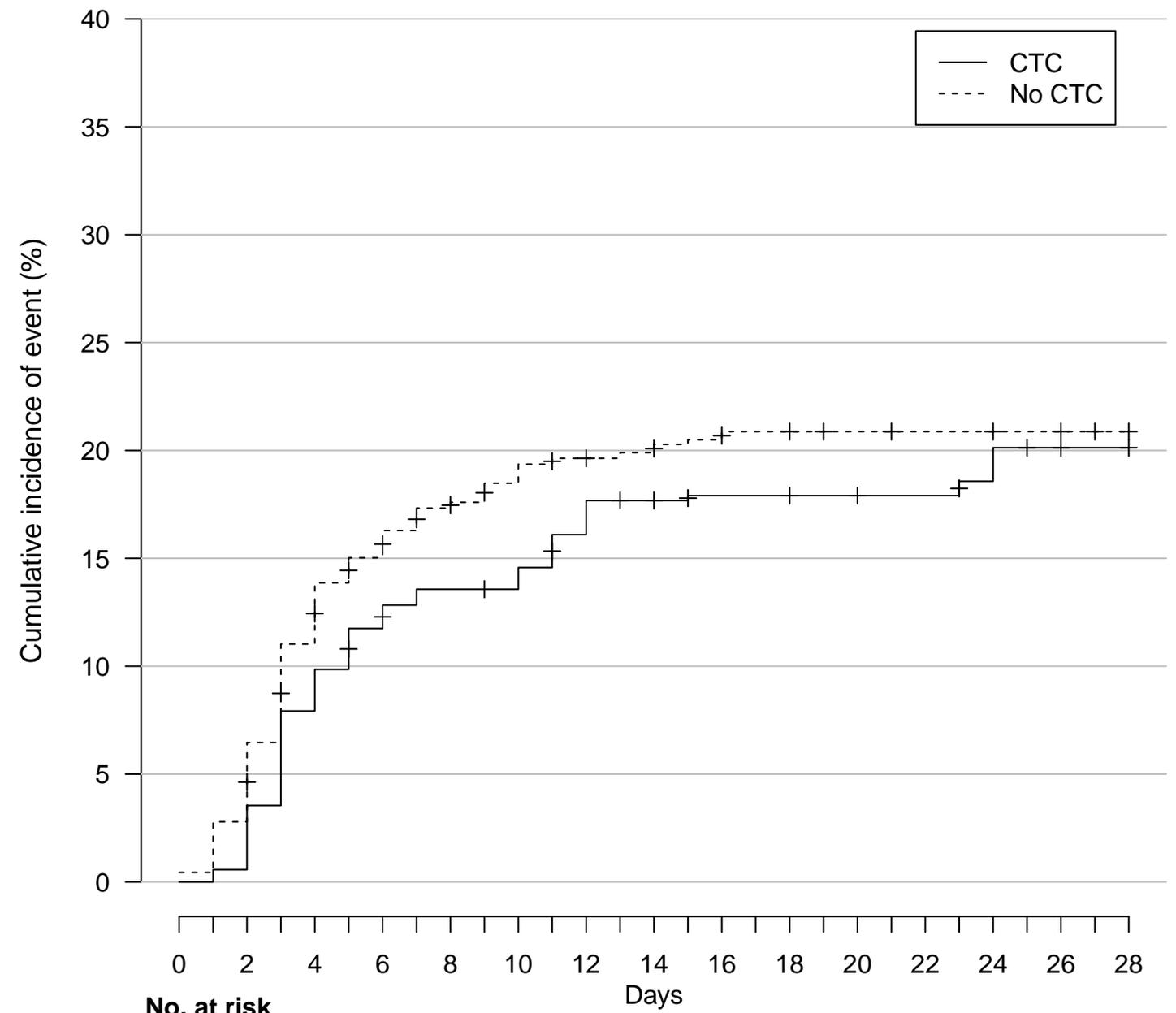


### Unweighted



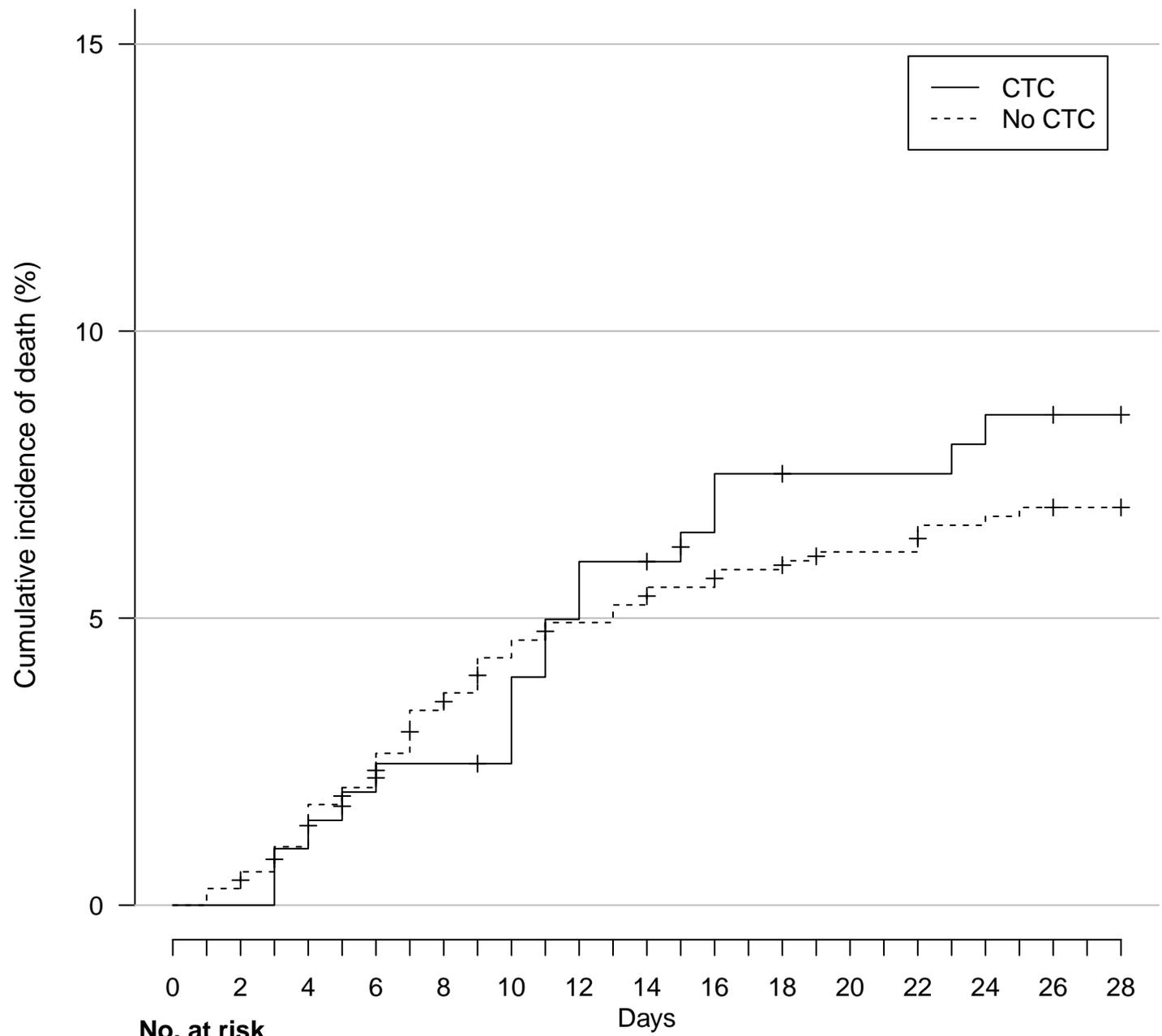
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
<b>No. at risk</b>															
CTC	203	202	188	180	176	174	168	164	158	158	157	156	154	152	150
No CTC	688	669	608	569	543	528	522	519	514	509	506	503	503	502	498

### IPTW (ATE weights)



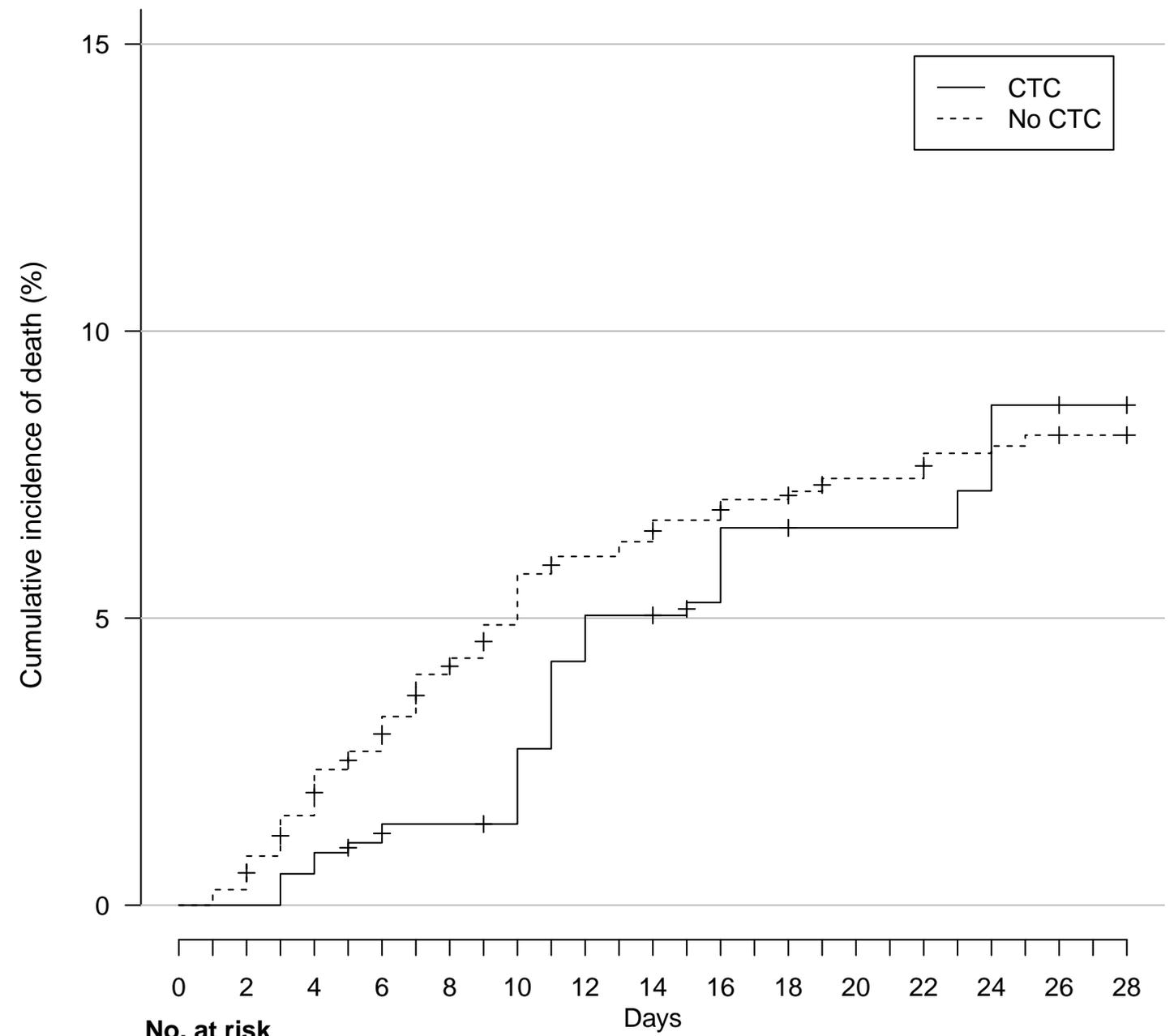
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
<b>No. at risk</b>															
CTC	203	201	186	177	172	169	163	159	155	155	154	154	151	148	146
No CTC	687	668	602	564	539	524	514	512	506	501	497	494	494	493	489

Unweighted



	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
<b>No. at risk</b>															
CTC	203	203	201	198	196	194	189	187	183	181	180	180	179	178	176
No CTC	688	686	673	657	638	624	619	617	614	611	606	606	602	600	598

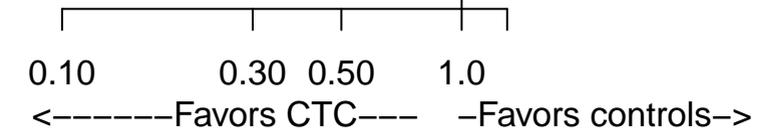
IPTW (ATE weights)



	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
<b>No. at risk</b>															
CTC	203	203	201	198	197	194	188	187	183	181	180	180	179	176	175
No CTC	687	685	668	652	634	620	611	610	606	603	597	597	593	591	589

### Hazard ratios

Analysis	n	CTC (wtd %)	n	No CTC (wtd %)	HR (95%CI)
<b>High dose corticosteroids</b>					
Yes	81	16.7	688	20.1	0.78 [0.35 ; 1.74]
No	113	13.0	688	20.3	0.58 [0.31 ; 1.08]
<b>Oxygen flow</b>					
< 3L	83	20.9	411	16.1	1.32 [0.72 ; 2.42]
>= 3L	120	15.1	277	26.5	0.50 [0.30 ; 0.85]
<b>C-reactive protein</b>					
< 100 mg/L	83	26.2	362	17.4	1.50 [0.87 ; 2.57]
>= 100 mg/L	120	11.5	326	24.3	0.44 [0.23 ; 0.85]
<b>Time from symptom onset</b>					
<= 7 days	92	23.0	323	28.9	0.74 [0.44 ; 1.25]
> 7 days	111	13.7	361	13.7	0.96 [0.46 ; 1.99]
<b>Oxygen flow and CRP</b>					
Oxygen flow >=3L and CRP >=100	71	9.0	161	30.6	0.26 [0.12 ; 0.55]
<b>All</b>	<b>203</b>	<b>20.1</b>	<b>688</b>	<b>20.9</b>	<b>0.92 [0.61 ; 1.39]</b>



**Table 1: Demographic and clinical characteristics of the patients in the corticosteroids (CTC) and no-CTC groups at baseline.** The number in brackets in the first column corresponds to the actual quantity of data available for the corresponding variables before imputation of missing baseline data by multiple imputations by chained equations using the other variables available.

Characteristic	Total (n=891)	CTC group (n=203)	No-CTC group (n=688)	P-value
<b>Demographic and clinical data</b>				
Age, median (IQR) – year	63 (53–70)	64 (56–72)	62 (52–70)	0.013
Male sex	66.4 (592)	71.4 (145)	65.0 (447)	0.09
<b>Comorbidities</b>				
Chronic respiratory disease (incl. asthma)	5.6 (50)	9.4 (19)	4.5 (31)	0.008
Chronic heart failure (NYHA I-III) (n=890)	3.5 (31)	3.9 (8)	3.3 (23)	0.69
Cardiovascular diseases (incl. hypertension)	44.7 (398)	48.3 (98)	43.6 (300)	0.24
Diabetes not requiring insulin (n=886)	17.6 (156)	18.2 (37)	17.4 (119)	0.79
Diabetes requiring insulin (n=889)	5.8 (52)	4.5 (9)	6.3 (43)	0.34
Chronic kidney failure	3.0 (27)	3.4 (7)	2.9 (20)	0.69
Liver cirrhosis	0.4 (4)	0.5 (1)	0.4 (3)	1
Immunosuppression (n=890)	5.4 (48)	6.9 (14)	4.9 (34)	0.28
BMI > 30 kg/m <sup>2</sup> (n=742)	32.3 (240)	27.8 (52)	33.9 (188)	0.12
Treatment with ACEIs or ARBs (n=888)	26.8 (238)	30.7 (62)	25.7 (176)	0.15
<b>COVID-19 data</b>				
Time from symptom onset to eligibility, median (IQR) – days (n=887)	8 (6–10)	8 (6–11)	8 (6–10)	0.25
Confusion at date of eligibility	7.9 (70)	10.3 (21)	7.1(49)	0.13
Dehydration at date of eligibility (n=888)	7.2 (64)	8.9 (18)	6.7 (46)	0.29
Respiratory rate, median (IQR) /min (n=739)	24 (20–28)	26 (21–30)	24 (20–28)	0.06
Oxygen saturation (without oxygen), median (IQR) (n=795)	93 (90–95)	92 (88–95)	93 (91–95)	<0.0001
Oxygen flow at admission, median (IQR) – L/min	2.0 (2.0–4.0)	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.0001
Systolic blood pressure, median (IQR) – mmHg (n=879)	129 (116–140)	129 (117–143)	129 (115–140)	0.90
Neutrophil count, median (IQR) – /mm <sup>3</sup> (n=851)	4790 (3435–6498)	5000 (3508–6900)	4750 (3400–6290)	0.06
Lymphocyte count, median (IQR) – /mm <sup>3</sup> (n=852)	900 (690–1201)	860 (642–1210)	920 (700–1200)	0.34
Platelet count, median (IQR) – x1000/mm <sup>3</sup> (n=878)	197 (157–254)	182 (146–254)	198 (159–253)	0.70

C-reactive protein median (IQR) – mg/L	100 (64–149)	111 (73–174)	95 (61–141)	0.001
Percentage of lung affected > 50% on CT scan (n=694*)	17.1 (119)	28.4 (50)	13.3 (69)	0.0001
<b>Treatment data</b>				
Corticosteroid**				
Dexamethasone	53 (27.3)	53 (27.3)	-	-
Methylprednisolone	71 (36.6)	71 (36.6)		
Prednisolone	21 (10.8)	21 (10.8)		
Prednisone	49 (25.3)	49 (25.3)		
High-dose corticosteroids (≥120 mg/day)	41.8 (81)	41.8 (81)	-	-
Corticosteroid treatment duration, median (IQR) – days (n=194)	7 (6–11)	7 (6–11)	-	-
Time from symptom onset to corticosteroids, median (IQR) – days	10 (8–13)	10 (8–13)	-	-
Treatment with lopinavir-ritonavir at baseline (n=890)	6.7 (60)	15.3 (31)	4.2 (29)	<0.0001
Treatment with hydroxychloroquine at baseline (n=889)	9.6 (85)	12.4 (25)	8.7 (60)	0.11

Results are presented as % (absolute number) unless stated otherwise.

Abbreviations: IQR, interquartile range; NYHA, New York Heart Association; BMI, body mass index; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

\* 127 patients did not have a CT scan at admission; \*\*Corresponds to the data for the 194 patients who received corticosteroids within 5 days of eligibility, with at least 0.8 mg/kg/day eq. prednisone or 0.4 mg/kg/day eq. prednisone if co-administered with lopinavir-ritonavir.

**Table 2: Primary and secondary outcomes at day 28.** IPTW estimates the average treatment effect on the whole population (ATE).

Outcomes	No. of events		Ratio (95% CI)	IPTW ratio* (95% CI)
	CTC group (n=203)	No-CTC group (n=688)		
Intubation or death	36	131	HR 0.89 (0.62–1.28)	wHR 0.92 (0.61–1.39)
Death	17	46	HR 1.23 (0.70–2.13)	wHR 1.03 (0.54–1.98)
Oxygen weaning	148/186*	522/625*	RR 0.96 (0.88–1.03)	wRR 0.98 (0.89–1.07)
Discharge from hospital to home or rehabilitation	151/186*	529/627*	RR 0.97 (0.90–1.04)	wRR 1.00 (0.92–1.09)

CTC: corticosteroids-receiving group. No CTC: standard of care, not receiving corticosteroids. IPTW: inverse probability of treatment weighting; ATE: average treatment effect; HR: hazard ratio; RR: relative risk; CI: confidence interval.

\*missing data were managed by using multiple imputations by chained equations.

**Table 3: Adverse events.** Adverse events are counted in the safety population, without weighting.

Adverse event	CTC group (n=283)	No-CTC group (n=682)	Difference (95% CI)
Any	53.0 (150)	46.0 (314)	7.0 (0.0 – 13.9)
<b>Expected with corticosteroids</b>			
Infection (incl. ventilator-associated pneumonia) *	17.7 (50)	18.8 (128)	-1.1 (-6.4 – 4.2)
Bacterial	7.1 (20)	7.5 (51)	0.4 (-4.0 – 3.2)
Viral	0.7 (2)	0.7 (5)	0 (-1.2 – 1.1)
Fungal	1.1 (3)	0.7 (5)	0.3 (-1.0 – 1.7)
Undocumented **	9.5 (27)	9.5 (77)	-1.7 (-5.9 – 2.4)
Ventilator-associated pneumonia	6.0 (17)	8.9 (61)	-2.9 (-6.4 – 0.6)
Hyperglycaemia	22.6 (64)	12.6 (86)	10.0 (4.5 – 15.5)
Hypertension	10.6 (30)	11.1 (76)	-0.5 (-4.8 – 3.8)
Confusion or psychiatric manifestation	1.4 (4)	1.9 (13)	-0.5 (-2.2 – 1.2)
Atrial fibrillation	4.6 (13)	3.8 (26)	0.8 (-2.0 – 3.6)
Hypokalaemia or fluid overload	1.1 (3)	1.3 (9)	-0.3 (-1.7 – 1.2)
<b>Other severe adverse events</b>			
Thromboembolic event (incl. pulmonary embolism)	2.8 (8)	3.5 (24)	-0.7 (-3.1 – 1.7)
Pulmonary embolism	2.1 (6)	2.6 (18)	-0.5 (-2.6 – 1.5)
Increased serum levels of aspartate aminotransferase	5.3 (15)	4.4 (30)	0.9 (-2.1 – 3.9)
Renal failure	2.5 (7)	2.6 (18)	-0.2 (-2.3 – 2.0)

Results are presented as % (absolute number). \*total number of infections differs from the sum of subcategories because a patient may have had multiple infectious adverse events of different nature. \*\*Undocumented infections refer to clinical and biological presentations suggestive of an infectious episode without formal identification of a specific pathogen.