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What is already known about this subject:
The RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial supports that dexamethasone administered at 6 mg once per day for ten days may be associated with reduced mortality only in patients with COVID-19 requiring respiratory support (i.e., oxygen or mechanical ventilation).

What this study adds:
In a multicenter observational study of patients hospitalized for COVID-19, we found that dexamethasone use administered either orally or by intravenous injection at a cumulative dose between 60 mg and 150 mg was associated with reduced mortality only in patients requiring respiratory support.

ABSTRACT

Aim: To examine the association between dexamethasone use and mortality among patients hospitalized for COVID-19.

Methods: We examined the association between dexamethasone use and mortality at AP-HP Greater Paris University hospitals. Study baseline was defined as the date of hospital admission. The primary endpoint was time to death. We compared this endpoint between patients who received dexamethasone and those who did not in time-to-event analyses adjusted for patient characteristics (such as age, sex, and comorbidity) and clinical and biological markers of clinical severity of COVID-19, and stratified by the need for respiratory support, i.e. mechanical ventilation or oxygen. The primary analysis was a multivariable Cox regression model.

Results: Of 12,217 adult patients hospitalized with a positive COVID-19 PT-PCR test, 171 (1.4%) received dexamethasone orally or by intravenous perfusion during the visit. Among patients who required respiratory support, the end-point occurred in 10/63 (15.9%) patients who received dexamethasone and 298/1,129 (26.4%) patients who did not. In this group, there was a significant association between dexamethasone use and reduced mortality in the primary analysis (HR, 0.46; 95%CI, 0.22 to 0.96, p=0.039). Among patients who did not require respiratory support, there was no significant association between dexamethasone use and the endpoint.

Conclusions: In this multicenter observational study, dexamethasone use administered either orally or by intravenous injection at a cumulative dose between 60 mg and 150 mg was associated with reduced mortality among patients with COVID-19 requiring respiratory support.

1. Introduction

Global spread of the novel coronavirus SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), has created an unprecedented infectious disease crisis worldwide [1–3].

The RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial, a randomized clinical trial examining a range of potential treatments for COVID-19, indicated that low-dose dexamethasone could reduce mortality in patients with COVID-19 requiring oxygen or mechanical ventilation support [4]. In that study, a total of 2,104 patients were randomized to receive dexamethasone 6 mg once per day for ten days, administered either orally or by intravenous injection, and were compared with 4,321 patients randomized to usual care alone. Dexamethasone was significantly associated with reduced 28-day mortality in ventilated patients (29.3% vs. 41.4%; rate ratio (RR), 0.64; 95% confidence interval CI, 0.51 to 0.81) and in patients receiving oxygen only (23.3% vs. 26.2%; RR, 0.82; 95% CI, 0.72 to 0.94). No benefit was observed among patients who did not require respiratory support (17.8% vs. 14.0%; RR, 1.19; 95% CI, 0.91 to 1.55).

These findings are of utmost importance and highlight that research into dexamethasone use in patients with COVID-19 is a priority [5].

In this report, we present results of a multicenter retrospective observational study of patients admitted for COVID-19 to 36 Greater Paris University hospitals. We examined whether oral or intravenous administration of dexamethasone to hospitalized adult patients with COVID-19 was associated with reduced mortality (i) among those who required respiratory support, i.e. mechanical ventilation or oxygen, and (ii) in those who did not. Following results of the RECOVERY trial [4], we hypothesized that dexamethasone

administration would be associated with reduced mortality in patients with COVID-19 who required respiratory support, and not in those who did not.

Although randomized controlled trials (RCTs) are considered the gold standard for clinical research, thus having a high impact on clinical guidelines and daily patients' care, observational studies are also important because they can bring important complementary information in the interpretation of the safety, efficacy, and effectiveness of a therapeutic option with greater external validity, i.e. in a population more closely resembling the target population, and in different subpopulations [6, 7]. Similar results from RCTs and observational studies can increase the confidence in the efficacy of a treatment [14, 15], as suggested by a prior study that found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials [8]. Specifically, if this observational study yielded similar results as those found in the RECOVERY trial, it would (i) increase the confidence in the efficacy of dexamethasone in patients with COVID-19 who require respiratory support, and (ii) support the usefulness of observational studies of patients with COVID-19 taking medications for other indications by showing that they could help decide which treatment should be prioritized for future randomized clinical trials and reduce the risk for patients of being exposed to potentially harmful and ineffective treatments in RCTs [9–12]. Finally, exploring the associations of different doses of dexamethasone with mortality in patients with COVID-19 could bring useful information to help guide design future RCTs of dexamethasone in patients with COVID-19 [12, 13].

2. Methods

2.1. Setting

We conducted this study in 36 Assistance Publique – Hôpitaux de Paris (AP-HP) hospitals. We included all adults aged 18 years or over who have been admitted with COVID-19 to these medical centers from the beginning of the epidemic in France, i.e. January 24th, until May 20th. For all patients, COVID-19 was ascertained by a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test from analysis of nasopharyngeal or oropharyngeal swab specimens. This observational study using routinely collected data received approval from the Institutional Review Board of the AP-HP clinical data warehouse (decision CSE-20-20_COVID19, IRB00011591). AP-HP clinical Data Warehouse initiative ensures patients' information and consent regarding the different approved studies through a transparency portal in accordance with European Regulation on data protection and authorization n°1980120 from National Commission for Information Technology and Civil Liberties (CNIL).

2.2. Data sources

We used data from the AP-HP Health Data Warehouse ('Entrepôt de Données de Santé (EDS)') [13]. This warehouse contains all the clinical data available on all inpatient visits for COVID-19 to Greater Paris University hospitals. The data obtained included patient demographic characteristics, vital signs, laboratory test and RT-PCR test results, medication administration data, current medication lists, current diagnoses, oxygen and ventilator use data, and death certificates.

2.3. Variables assessed

We obtained the following data for each patient at the time of hospital admission: sex, age [14], obesity, current smoking status, any medical condition associated with increased risk of severe COVID-19 [14, 15], and clinical and biological markers of severe COVID-19 [16, 17] at admission. These variables are detailed in **Supplementary Text 1**.

All medical notes and prescriptions are computerized in Greater Paris University hospitals. Medications and their mode of administration (i.e., dose, frequency, date, condition of intake) were identified from unstructured databases including medication administration data or scanned hand-written medical prescriptions through two deep learning models based on BERT contextual embeddings allowing for natural language processing [18], one for the medications and another for their mode of administration. The model was trained on the APmed corpus [19], a previously annotated dataset for this task. Extracted medications names were then normalized to the Anatomical Therapeutic Chemical (ATC) terminology using approximate string matching.

2.4. Endpoint

The endpoint was the time from study baseline to death. Patients without an end-point event had their data censored on May 20th, 2020.

2.5. Dexamethasone use

Study baseline was defined as the date of hospital admission. Dexamethasone use was defined as receiving this medication orally or by intravenous injection at any time during the follow-up period, from study baseline to the end of the index hospitalization or death.

2.6. Dexamethasone cumulative dose

Dexamethasone cumulative dose received was calculated and considered as a categorical variable with the following categories defined *a priori*: (i) 60 mg to 150 mg based on usual prescribing practice for acute respiratory distress syndrome (ARDS) in AP-HP hospitals (corresponding to 10 mg per day for 6 days, to 20 mg per day for 5 days followed by 10 mg per day for 5 days), (ii) other cumulative doses (i.e., more than 150 mg or less than 60 mg), and (iii) missing data.

2.7. Statistical analysis

All analyses were stratified by the need for respiratory support, i.e. oxygen or mechanical ventilation, at any time during the follow-up.

We calculated frequencies of each baseline characteristic described above in patients receiving and not receiving dexamethasone, and compared them using chi-square tests.

To examine the association of dexamethasone use with the endpoint, we performed Cox proportional-hazards regression models. To help account for the nonrandomized prescription of dexamethasone and reduce the effects of confounding, the primary analysis used a multivariable Cox regression model including as covariates sex, age, obesity, current smoking status, any medical condition associated with severe COVID-19, and clinical and biological markers of severe COVID-19 at admission. Weighted Cox regression models were used when the proportional hazards assumption was not met. Kaplan-Meier curves were performed and their pointwise 95% confidence intervals were estimated using the nonparametric bootstrap method [20].

As a sensitivity analysis, we performed a univariate Cox regression model in a matched analytic sample using a 1:10 ratio, based on the same variables used for the

multivariable Cox regression analysis. To reduce the effects of confounding, optimal matching was used in order to obtain the smallest average absolute distance across all clinical characteristics between exposed patient and non-exposed matched controls.

We performed additional analyses. First, we examined whether the cumulative dose of dexamethasone received during the visit was associated with the endpoint of death. Second, we performed multivariable Cox regression models including interaction terms to examine whether the association between dexamethasone use and the endpoint significantly differed across baseline characteristics.

For all associations, we performed residual analyses to assess the fit of the data, check assumptions, including proportional hazards assumptions, and examined the potential influence of outliers. To improve the quality of result reporting, we followed the recommendations of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative [21]. Statistical significance was fixed *a priori* at two-sided p-value<0.05. All analyses were conducted in R software version 2.4.3 (R Project for Statistical Computing).

3. Results

3.1. Characteristics of the cohort

Of the 16,170 with a positive COVID-19 RT-PCR test consecutively admitted to the 36 AP-HP hospitals from January 24th to May 20th, a total of 3,953 patients (24.4%) were excluded because of missing data or their age (i.e. less than 18 years old of age). Of the remaining 12,217 adult inpatients, 178 patients (1.46%) received dexamethasone. Of them, 7 (3.9%) were excluded because the route of administration was either ophthalmic, through aerosol, or unknown. Among the 171 remaining patients who received dexamethasone, 63

(36.8%) needed respiratory support (i.e. mechanical ventilation or oxygen), and 108 (63.2%) did not. Among the 12,039 patients who did not receive dexamethasone during the visit, 1,129 (9.4%) required respiratory support, and 10,910 (90.6%) did not (**Figure 1**). The mean cumulative dose administered was 107.8 mg (SD=63.5; median=100 mg; range: 10.0 mg to 320.0 mg) in those who required respiratory support and 101.8 mg (SD=89.8; median=90 mg; range: 10.0 mg to 600.0 mg) in those who did not. This treatment was administered orally in 97.1% of patients and by intravenous injection in 2.9% of them.

COVID-19 RT-PCR test results were obtained after a mean delay of 3.7 days (SD=8.4, median=0.9 days) from the date of hospital admission in patients who required respiratory support. This delay did not significantly differ between patients receiving or not receiving dexamethasone [mean delay in the exposed group=3.0 days (SD=6.2); mean delay in the non-exposed group=3.7 days (SD=8.5); Welch's t-test=0.79, p=0.430)]. In patients who did not require respiratory support, the mean delay was 4.7 days (SD=10.2, median=1.0 day), and this delay did not significantly differ between patients receiving or not receiving dexamethasone [mean delay in the exposed group=3.5 days (SD=8.9); mean delay in the non-exposed group=4.8 day (SD=10.2); Welch's t-test=1.5, p=0.163)].

Among patients who required respiratory support, the mean follow-up was 27.9 days (SD=20.4; median=21 days; range: 1 day to 106 days) and 308 patients (25.8%) had an end-point event at the time of data cutoff on May 20th. Among those who did not require respiratory support, the mean follow-up was 18.5 days (SD=24.6; median=6; range: 1 day to 117 days), and 1,100 (10.0%) patients had an end-point event at the time of data cutoff.

Associations between baseline characteristics and the endpoint are given in **Supplementary Table 1**. The distribution of the patient characteristics by dexamethasone use is shown in **Table 1**. Dexamethasone use significantly differed in clinical and biological

markers of severity at admission among patients who required respiratory support, and in sex, age, obesity and biological markers of severity at admission among those who did not. In the matched analytic samples, there were no significant differences in patient characteristics according to dexamethasone use (**Table 1**).

3.2. Study endpoint

Among patients with COVID-19 who required respiratory support, the end-point event of death occurred in 10/63 patients (15.9%) who received dexamethasone and 298/1,129 patients (26.4%) who did not (**Figure 2**). In this group of patients, we found a significant association between dexamethasone use and reduced mortality in both the crude, unadjusted analysis (hazard ratio (HR), 0.40; 95% CI, 0.18 to 0.87, p=0.021) and the primary multivariable Cox regression analysis (HR, 0.46; 95% CI, 0.22 to 0.96, p=0.039) (**Figure 2**; **Figure 3**). In the sensitivity analysis, the univariate Cox regression model in the matched analytic sample yielded a same tendency, albeit non-significant (HR, 0.31; 95% CI, 0.08 to 1.14, p=0.077) (**Figure 2; Figure 4**).

Among patients with COVID-19 who did not require respiratory support, the end-point event of death occurred in 14/108 patients (13.0%) who received dexamethasone and 131/1,086 patients (12.1%) who did not (**Figure 2**). In this group of patients, there was no significant association between dexamethasone use and the endpoint, neither in the crude, unadjusted analysis (HR, 0.73; 95% CI, 0.42 to 1.26, p=0.253) or in the primary multivariable Cox regression analysis (HR, 0.59; 95% CI, 0.30 to 1.16, p=0.126) (**Figure 2**; **Figure 3**). In the sensitivity analysis, the univariate Cox regression model in the matched analytic sample yielded a similar non-significant result (HR, 1.06; 95% CI, 0.45 to 2.49, p=0.894) (**Figure 2; Figure 4**).

A post-hoc analysis indicated that in the full sample of patients with respiratory support, we had 80% power to detect unadjusted hazard ratios for dexamethasone of at least 2.33/0.15 and of at least 2.37/0.14 in the matched analytic sample. In those without respiratory support, we had 80% power to detect unadjusted hazard ratios for dexamethasone of at least 1.99/0.30 in the full sample and 2.05/0.29 in the matched analytic sample using a 1:10 ratio.

When examining the association between the cumulative dose of dexamethasone received during the visit and the endpoint, we found that the administration of a cumulative dose between 60 mg to 150 mg among patients who required respiratory support was significantly associated with reduced mortality in the crude, unadjusted analysis (HR, 0.28; 95% CI, 0.08 to 0.87, p=0.028), the multivariable Cox regression analysis (HR, 0.24; 95% CI, 0.07 to 0.87, p=0.030), and in the univariate Cox regression model in the matched analytic sample using a 1:10 ratio (HR, 0.32; 95% CI, 0.07 – 0.95; p=0.048), whereas no significant association was observed with a different dose (**Supplementary Table 2, Supplementary Figure 1**). Among patients without respiratory support, there was no significant association between the cumulative dose of dexamethasone and the endpoint in the crude, unadjusted analysis (HR, 0.37; 95% CI, 0.12 to 1.16, p=0.089) and the adjusted multivariable analysis (HR, 0.47; 95% CI, 0.15 to 2.42, p=0.178). However, the administration of a cumulative dose between 60 mg to 150 mg was significantly associated with the endpoint in the univariate Cox regression model in the matched analytic sample (HR, 0.32; 95% CI, 0.15 to 0.99, p=0.049) (**Supplementary Table 2, Supplementary Figure 1**).

Finally, the association between dexamethasone use and the endpoint did not significantly differ across subgroups defined by baseline characteristics in both groups with and without respiratory support, except for patients with obesity who did not require respiratory support, for whose dexamethasone use was significantly associated with increased mortality compared

to obese patients without dexamethasone (HR, 3.90; 95% CI, 1.13 to 13.44, p=0.031) (**Supplementary Table 3**). However, none of the 16 patients with obesity who received a cumulative dose of 60 to 150 mg of dexamethasone died.

4. Discussion

In this multicenter retrospective observational study involving a large sample of patients hospitalized for COVID-19, we found that dexamethasone use, administered either orally or by intravenous injection at a cumulative dose between 60 mg and 150 mg, was significantly and substantially associated with reduced mortality among patients with COVID-19 requiring oxygen or mechanical ventilation support. This association did not significantly differ according to baseline clinical characteristics. No significant association between dexamethasone use and mortality was observed among patients with COVID-19 without respiratory support, except in the univariate Cox regression model in the matched analytic sample, whereas the administration of a cumulative dose between 60 mg to 150 mg was significantly associated with reduced mortality.

Although these findings should be interpreted with caution due to the observational design, they are in line with the results of the RECOVERY trial [4], which indicated that dexamethasone 6 mg once per day for ten days, administered either orally or by intravenous injection, was significantly associated with reduced 28-day mortality in ventilated patients and in patients receiving oxygen only.

The benefits of dexamethasone for patients with COVID-19 likely arise from its immunosuppressive properties. A prior study [22] suggests that low-dose dexamethasone treatment could complement endogenous cortisol activity to suppress COVID-19-associated immunopathology, while avoiding the adverse effects of high-dose glucocorticoid therapy

[22, 23]. Many immune-modulating effects of glucocorticoids reflect cell type-specific changes in the transcriptome [22], tempering the specialized activities of different immune cell types, such as B and T cells. Inhibitory interactions between glucocorticoid receptors and the transcription factors NF-κB and AP-1 may also be important modes of glucocorticoid anti-inflammatory action. An important observation from the RECOVERY trial and our observational study was that dexamethasone provided benefit only to severely ill patients with COVID-19, in whom acute respiratory distress syndrome, sepsis and, eventually, organ failure may reflect hyper-inflammatory state, a phase of COVID-19 where the immunomodulatory effects of glucocorticoids are likely beneficial, perhaps by breaking the inflammatory feedforward loop, at least in some patients.

Our findings, beyond increasing the confidence in the efficacy of dexamethasone in patients with COVID-19 who require respiratory support, also support the usefulness of observational studies of patients with COVID-19 taking medications for other indications, by showing that they can help decide which treatment should be prioritized for future randomized clinical trials and reduce the risk for patients of being exposed to potentially harmful and ineffective treatments in RCTs [9–12].

Our study has several limitations. First, there are two possible major inherent biases in observational studies: unmeasured confounding and confounding by indication. Some amount of unmeasured confounding may remain. However, our analyses adjusted for numerous potential confounders, including sex, age, obesity, current smoking status, any medical condition associated with severe COVID-19, and clinical and biological markers of severe COVID-19 at admission. Second, there are missing data for some variables and potential for inaccuracies in the electronic health records, such as the possible lack of documentation of illnesses or medications, or the misidentification of treatment mode of administration (e.g.,

dose, frequency), especially for hand-written medical prescriptions. Third, our study cannot establish causal relationships. Finally, despite the multicenter design, our results may not be generalizable to outpatients or other regions.

In this multicenter observational study, dexamethasone use administered either orally or by intravenous injection was associated with decreased mortality among adult patients hospitalized for COVID-19 requiring respiratory support.

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Conflicts of interest

Dr Hoertel has received personal fees and non-financial support from Lundbeck, outside the submitted work. Dr Limosin has received speaker and consulting fees from Janssen-Cilag outside the submitted work. Other authors declare no competing interests.

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Data Availability Statement

Data from the AP-HP Health Data Warehouse can be obtained with permission at https://eds.aphp.fr//.

Authors contribution

NH designed the study, contributed to statistical analyses, and wrote the first draft of the manuscript. MSR contributed to study design, performed statistical analyses and critically revised the manuscript. FL contributed to study design and critically revised the manuscript for scientific content. RV contributed to statistical analyses and critically revised the manuscript for scientific content. NB contributed to study design and critically revised the manuscript for scientific content. NB, ASJ, AN, NP, CD, AG, GL, MB, and AB contributed to database build process. AN, NP, CD, AG, GL, MB, ES, AB and JMA critically revised the manuscript for scientific content.

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Table 1. Characteristics of patients with or without respiratory support (oxygen or intubation) according to dexamethasone use.

	Exposed to dexamethasone	Not exposed to dexamethasone	Non-exposed matched group	Exposed to dexamethasone vs. Not exposed to dexamethasone (crude analysis)	Exposed to dexamethasone vs. Non-exposed matched group
	N (%)	N (%)	N (%)	Chi-square test	Chi-square test (p-value)
With respiratory support	63 (100%)	1,129 (100%)	630 (100%)		
Sex				<0.01 (>0.99)	0.09 (0.770)
Women	17 (27.0%)	308 (27.3%)	154 (24.4%)		
Men	46 (73.0%)	821 (72.7%)	476 (75.6%)		
Age				2.35 (0.309)	0.14 (0.931)
18 to 50 years	10 (15.9%)	239 (21.2%)	102 (16.2%)		
51 to 70 years	40 (63.5%)	606 (53.7%)	386 (61.3%)		
More than 70 years	13 (20.6%)	284 (25.2%)	142 (22.5%)		
Obesity [a]				0.25 (0.621)	<0.01 (0.946)
Yes	16 (25.4%)	329 (29.1%)	168 (26.7%)		
No	47 (74.6%)	800 (70.9%)	462 (73.3%)		
Smoking [b]				0.11 (0.736)	<0.01 (0.961)
Yes	11 (17.5%)	170 (15.1%)	103 (16.3%)		
No	52 (82.5%)	959 (84.9%)	527 (83.7%)		

Any medical condition [c]				2.20 (0.138)	1.83 (0.176)
Yes	36 (57.1%)	757 (67.1%)	419 (66.5%)		
No	27 (42.9%)	372 (32.9%)	211 (33.5%)		
Clinical severity of Covid-19 at admission [d]				12.71 (0.002*)	2.75 (0.253)
Yes	23 (36.5%)	529 (46.9%)	278 (44.1%)		
No	33 (52.4%)	354 (31.4%)	262 (41.6%)		
Missing	7 (11.1%)	246 (21.8%)	90 (14.3%)		
Biological severity of Covid-19 at admission [e]				9.59 (0.008*)	0.20 (0.906)
Yes	52 (82.5%)	716 (63.4%)	507 (80.5%)		
No	8 (12.7%)	279 (24.7%)	93 (14.8%)		
Missing	3 (4.76%)	134 (11.9%)	30 (4.76%)		
Without respiratory support	108 (100%)	10,910 (100%)	1,080 (100%)		
Sex				21.70 (<0.001*)	0.05 (0.820)
Women	32 (29.6%)	5738 (52.6%)	337 (31.2%)		
Men	76 (70.4%)	5172 (47.4%)	743 (68.8%)		
Age				28.86 (<0.001*)	0.17 (0.918)
18 to 50 years	16 (14.8%)	4153 (38.1%)	147 (13.6%)		
51 to 70 years	54 (50.0%)	3338 (30.6%)	559 (51.8%)		
More than 70 years	38 (35.2%)	3419 (31.3%)	374 (34.6%)		
Obesity [a]				6.87 (0.009*)	<0.01 (>0.99)
Yes	22 (20.4%)	1279 (11.7%)	220 (20.4%)		
No	86 (79.6%)	9631 (88.3%)	860 (79.6%)		
Smoking [b]				1.47 (0.225)	<0.01 (>0.99)
Yes	13 (12.0%)	908 (8.32%)	130 (12.0%)		

No	95 (88.0%)	10002 (91.7%)	950 (88.0%)		
Any medical condition [c]				1.76 (0.184)	<0.01 (0.992)
Yes	33 (30.6%)	2679 (24.6%)	336 (31.1%)		
No	75 (69.4%)	8231 (75.4%)	744 (68.9%)		
Clinical severity of Covid-19 at admission [d]				5.49 (0.064)	<0.01 (0.998)
Yes	17 (15.7%)	2022 (18.5%)	170 (15.7%)		
No	38 (35.2%)	2763 (25.3%)	377 (34.9%)		
Missing	53 (49.1%)	6125 (56.1%)	533 (49.4%)		
Biological severity of Covid-19 at admission [e]				61.83 (<0.001*)	0.01 (0.993)
Yes	69 (63.9%)	3254 (29.8%)	696 (64.4%)		
No	22 (20.4%)	2903 (26.6%)	216 (20.0%)		
Missing	17 (15.7%)	4753 (43.6%)	168 (15.6%)		

[a] Defined as having a body-mass index higher than 30 kg/m^2 or an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9).
[b] Current smoking status was self-reported.
[c] Assessed using ICD-10 diagnosis codes for diabetes mellitus (E11), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), neoplasms (C00-D49), and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D5-D8)
[d] Defined as having at least one of the following criteria: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90%, temperature > 40°C, or systolic blood pressure < 100 mm Hg.
[e] Defined as having at least one of the following criteria: high neutrophil-to-lymphocyte ratio, low lymphocyte-*to*-C-reactive protein (both variables were dichotomized at the median of the values observed in the full sample), and plasma lactate levels higher than 2 mmol/L.
* p-value is significant (p<0.05).

Figure 1. Study cohort.

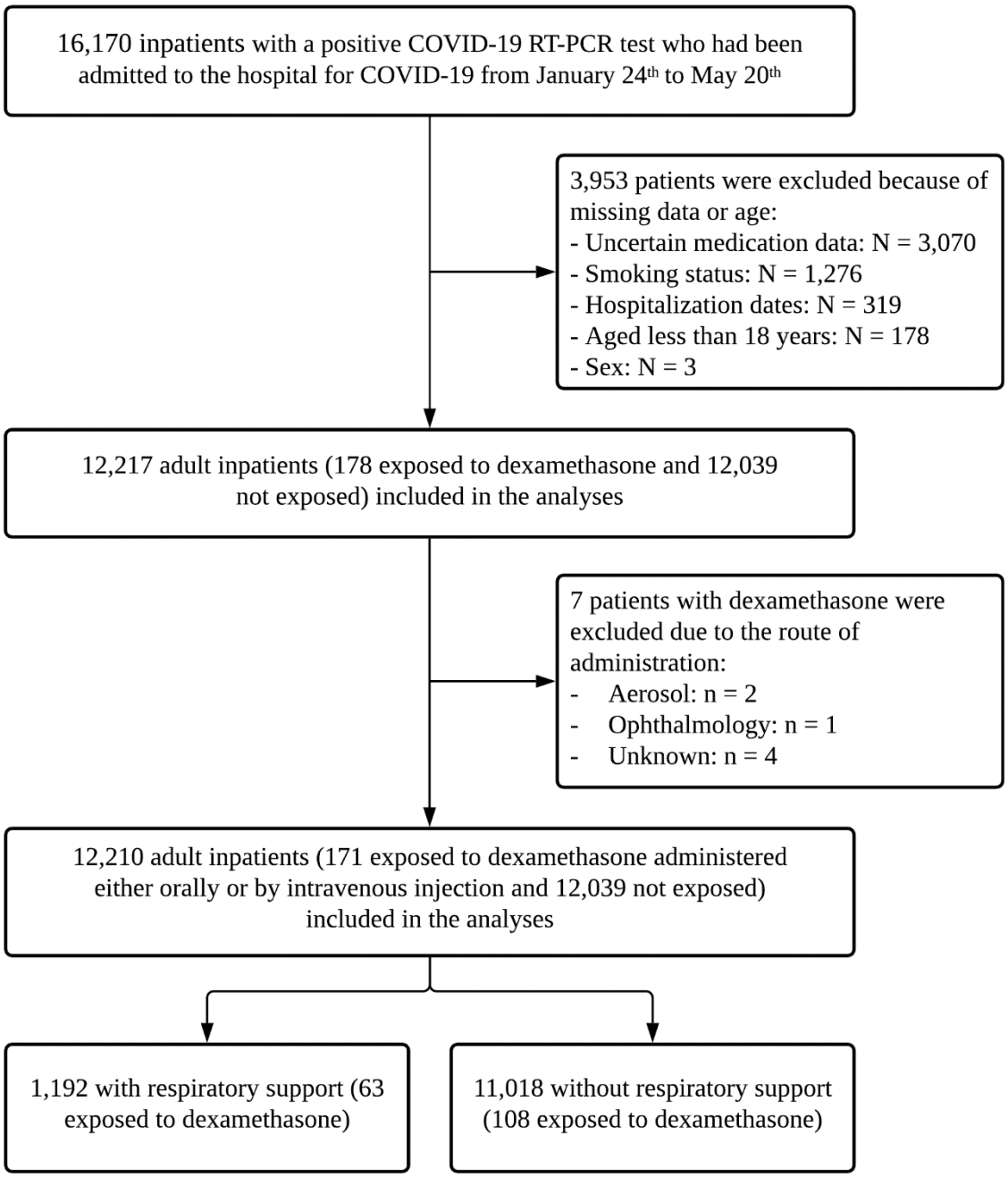
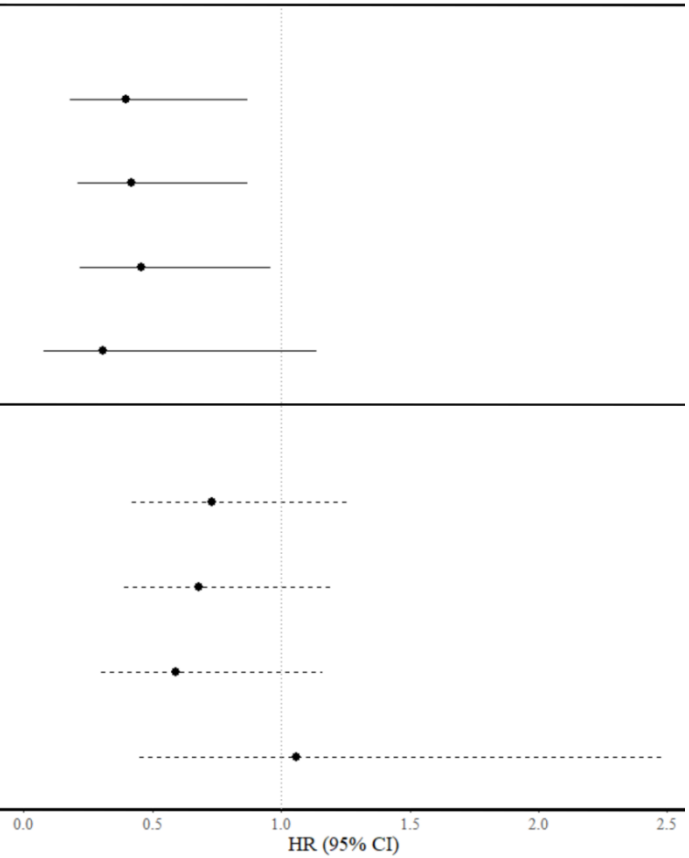


Figure 2. Association between dexamethasone use and time to death in the full sample and in the matched analytic sample.

	Dexamethasone	No dexamethasone	
	Events / Patients (%)	Events / Patients (%)	HR (95% CI; p-value)
With respiratory support			
Crude analysis	10 / 63 (15.9%)	298 / 1,129 (26.4%)	0.40 (0.18 – 0.87; 0.021*)
Cox regression adjusted for age and sex	10 / 63 (15.9%)	298 / 1,129 (26.4%)	0.42 (0.21 – 0.87; 0.020*)
Multivariable Cox regression analysis	10 / 63 (15.9%)	298 / 1,129 (26.4%)	0.46 (0.22 – 0.96; 0.039*)
Univariate Cox regression in a matched analytic sample	10 / 63 (15.9%)	150 / 630 (23.8%)	0.31 (0.08 – 1.14; 0.077)
Without respiratory support			
Crude analysis	14 / 108 (13.0%)	1,086 / 10,910 (10.0%)	0.73 (0.42 – 1.26; 0.253)
Cox regression adjusted for age and sex	14 / 108 (13.0%)	1,086 / 10,910 (10.0%)	0.68 (0.39 – 1.21; 0.189)
Multivariable Cox regression analysis	14 / 108 (13.0%)	1,086 / 10,910 (10.0%)	0.59 (0.30 – 1.16; 0.126)
Univariate Cox regression in a matched analytic sample	14 / 108 (13.0%)	131 / 1,080 (12.1%)	1.06 (0.45 – 2.49; 0.894)



* p-value is significant (p<0.05).
Abbreviations: HR, hazard ratio; CI, confidence interval

Figure 3. Kaplan-Meier curves for time to death in the full samples of patients hospitalized for COVID-19 who required respiratory support (i.e., mechanical ventilation or oxygen) (N=1,192) (A), and of those who did not (N=11,018) (B), according to dexamethasone use. The shaded areas represent pointwise 95% confidence intervals.

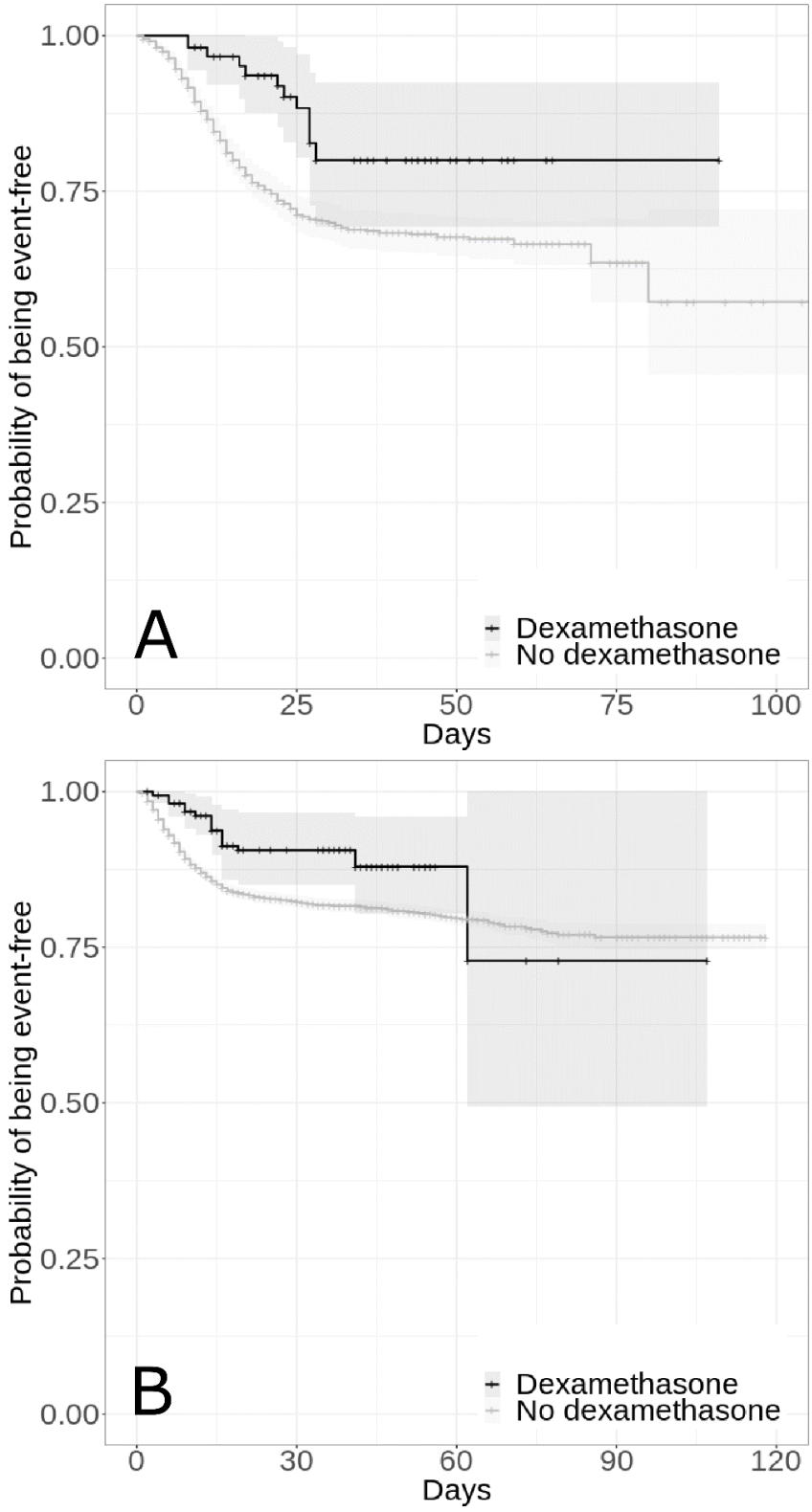
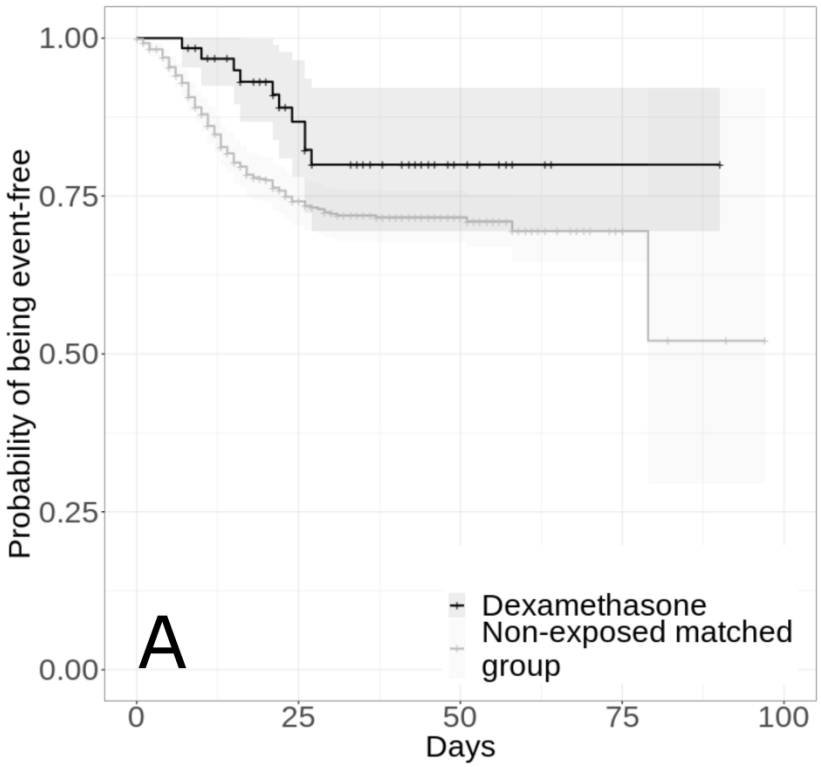
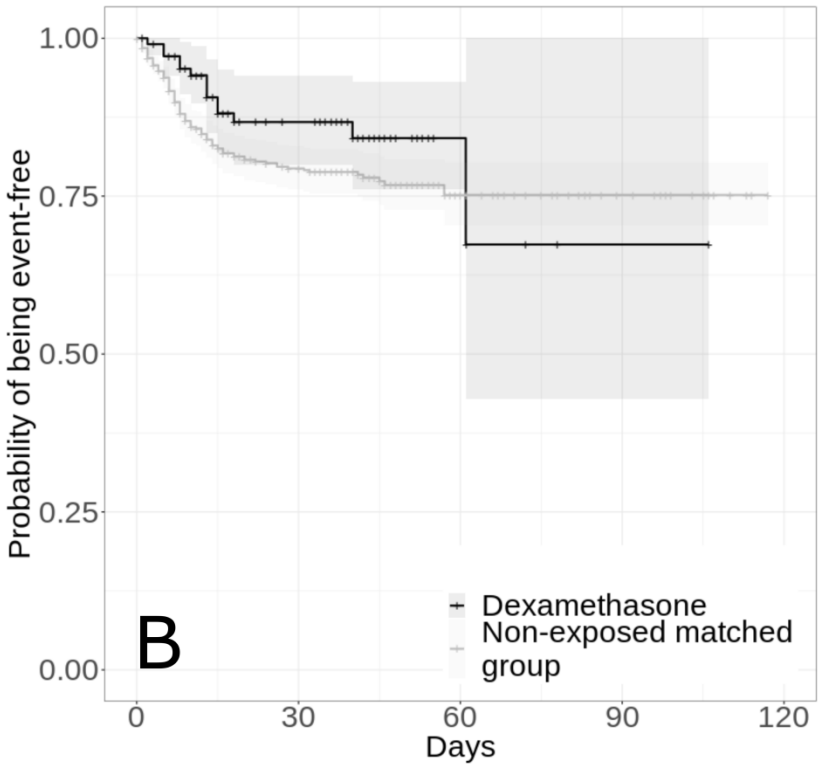


Figure 4. Kaplan-Meier curves for time to death in the matched analytic samples of patients hospitalized for COVID-19 who required respiratory support (i.e., mechanical ventilation or oxygen) (N=693) (A) and of those who did not (N=1,188) (B), according to dexamethasone use. The shaded areas represent pointwise 95% confidence intervals. For each exposed case, ten non-exposed controls were selected.



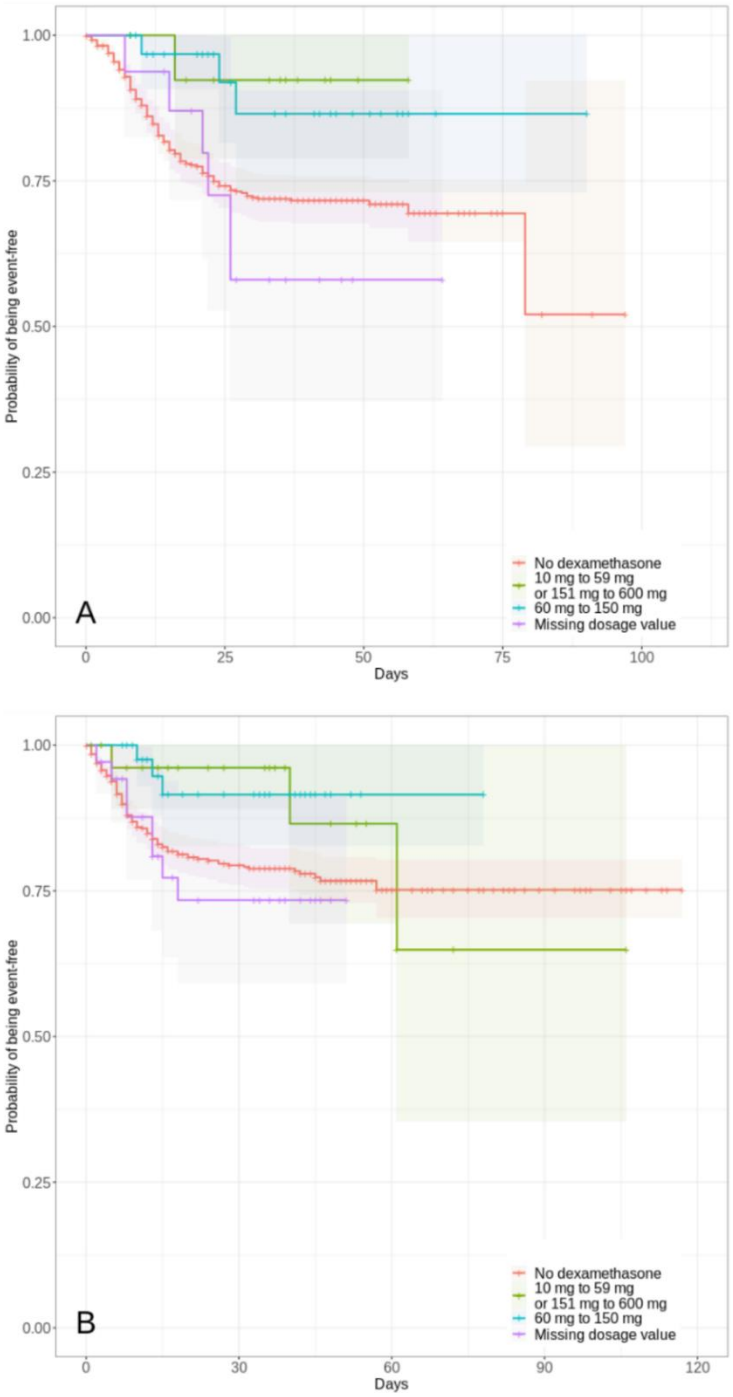


SUPPLEMENTARY MATERIAL

Supplementary Text 1

We obtained the following data for each patient at the time of the hospitalization: sex; age, which was categorized based on the OpenSAFELY study results [4] (i.e. 18-50, 51-70, 71+); obesity, defined as having a body-mass index higher than 30 kg/m^2 or an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9); self-reported current smoking status; any medical condition associated with increased risk of severe COVID-19 [4, 5] based on ICD-10 diagnosis codes, including diabetes mellitus (E11), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), neoplasms (C00-D49), and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D5-D8); clinical severity of COVID-19 at admission, defined as having at least one of the following criteria [5]: (i) respiratory rate > 24 breaths/min or < 12 breaths/min, (ii) resting peripheral capillary oxygen saturation in ambient air < 90% , (iii) temperature > 40°C, or (iv) systolic blood pressure < 100 mm Hg; and biological severity of COVID-19 at admission, defined as having at least one of the following criteria [5, 6]: (i) high neutrophil-to-lymphocyte ratio or (ii) low lymphocyte-to-C-reactive protein ratio (both variables were dichotomized at the median of the values observed in the full sample), or (iii) plasma lactate levels higher than 2 mmol/L.

Supplementary Figure 1. Kaplan-Meier curves for time to death in patients hospitalized for COVID-19 who required respiratory support (i.e., mechanical ventilation or oxygen) (N=1,192) (A) and in those who did not (N=11,008) (B), according to dexamethasone cumulative dose. The shaded areas represent pointwise 95% confidence intervals.



Supplementary Table 1. Associations of baseline clinical characteristics with the endpoint of death in patients with and without respiratory support (i.e., oxygen or intubation).

	Full population	With the end-point event	Without the end-point event	Crude analysis	Mutivariable analysis	
	N (%)	N (%)	N (%)	HR (SE) / p-value	HR (SE) / p-value	Collinearity diagnosis (VIF)
With respiratory support	1,192 (100%)	308 (25.8%)	884 (74.2%)			
Sex						1.02
Women	325 (27.3%)	78 (25.3%)	247 (27.9%)	Ref.	Ref.	
Men	867 (72.7%)	230 (74.7%)	637 (72.1%)	1.08 (0.13) / 0.563	1.23 (0.18) / 0.254	
Age						1.01
18 to 50 years	249 (20.9%)	32 (10.4%)	217 (24.5%)	Ref.	Ref.	
51 to 70 years	646 (54.2%)	149 (48.4%)	497 (56.2%)	1.73 (0.19) / 0.005*	1.03 (0.36) / 0.934	
More than 70 years	297 (24.9%)	127 (41.2%)	170 (19.2%)	3.79 (0.20) / <0.001*	2.92 (0.38) / 0.005*	
Obesity $^{\alpha}$						1.02
Yes	345 (28.9%)	92 (29.9%)	253 (28.6%)	1.04 (0.12) / 0.735	0.83 (0.21) / 0.379	
No	847 (71.1%)	216 (70.1%)	631 (71.4%)	Ref.	Ref.	
Smoking $^{\beta}$						1.01
Yes	181 (15.2%)	38 (12.3%)	143 (16.2%)	0.75 (0.17) / 0.095	0.60 (0.35) / 0.142	
No	1011 (84.8%)	270 (87.7%)	741 (83.8%)	Ref.	Ref.	
Any medical condition $^{\gamma}$						1.03
Yes	793 (66.5%)	257 (83.4%)	536 (60.6%)	3.47 (0.15) / <0.001*	4.35 (0.20) / <0.001*	
No	399 (33.5%)	51 (16.6%)	348 (39.4%)	Ref.	Ref.	

Clinical severity of Covid-19 at admission [μ]						1.02
Yes	552 (46.3%)	147 (47.7%)	405 (45.8%)	1.21 (0.13) / 0.157	1.53 (0.17) / 0.011*	
No	387 (32.5%)	89 (28.9%)	298 (33.7%)	Ref.	Ref.	
Missing	253 (21.2%)	72 (23.4%)	181 (20.5%)	1.38 (0.16) / 0.041*	1.92 (0.23) / 0.004*	
Biological severity of Covid-19 at admission [κ]						1.01
Yes	768 (64.4%)	193 (62.7%)	575 (65.0%)	0.89 (0.13) / 0.390	1.06 (0.20) / 0.778	
No	287 (24.1%)	79 (25.6%)	208 (23.5%)	Ref.	Ref.	
Missing	137 (11.5%)	36 (11.7%)	101 (11.4%)	1.00 (0.20) / 0.998	1.20 (0.37) / 0.654	
Without respiratory support	11,018 (100%)	1,100 (10.0%)	9,918 (90.0%)			
Sex						1.03
Women	5770 (52.4%)	450 (40.9%)	5320 (53.6%)	Ref.	Ref.	
Men	5248 (47.6%)	650 (59.1%)	4598 (46.4%)	1.50 (0.06) / <0.001*	1.14 (0.09) / 0.134	
Age						1.08
18 to 50 years	4169 (37.8%)	19 (1.73%)	4150 (41.8%)	Ref.	Ref.	
51 to 70 years	3392 (30.8%)	159 (14.5%)	3233 (32.6%)	8.18 (0.24) / <0.001*	4.46 (0.35) / <0.001*	
More than 70 years	3457 (31.4%)	922 (83.8%)	2535 (25.6%)	35.71 (0.23) / <0.001*	21.42 (0.34) / <0.001*	
Obesity [α]						1.02
Yes	1301 (11.8%)	200 (18.2%)	1101 (11.1%)	1.36 (0.08) / <0.001*	1.09 (0.10) / 0.403	
No	9717 (88.2%)	900 (81.8%)	8817 (88.9%)	Ref.	Ref.	
Smoking [β]						1.03
Yes	921 (8.36%)	166 (15.1%)	755 (7.61%)	1.48 (0.08) / <0.001*	0.93 (0.10) / 0.485	

No	10097 (91.6%)	934 (84.9%)	9163 (92.4%)	Ref.	Ref.	
Any medical condition [γ]						1.14
Yes	2712 (24.6%)	637 (57.9%)	2075 (20.9%)	4.66 (0.06) / <0.001*	3.19 (0.09) / <0.001*	
No	8306 (75.4%)	463 (42.1%)	7843 (79.1%)	Ref.	Ref.	
Clinical severity of Covid-19 at admission [μ]						1.13
Yes	2039 (18.5%)	480 (43.6%)	1559 (15.7%)	2.53 (0.08) / <0.001*	2.07 (0.11) / <0.001*	
No	2801 (25.4%)	260 (23.6%)	2541 (25.6%)	Ref.	Ref.	
Missing	6178 (56.1%)	360 (32.7%)	5818 (58.7%)	0.75 (0.08) / <0.001*	1.75 (0.13) / <0.001*	
Biological severity of Covid-19 at admission [κ]						1.14
Yes	3323 (30.2%)	670 (60.9%)	2653 (26.7%)	2.54 (0.08) / <0.001*	1.72 (0.10) / <0.001*	
No	2925 (26.5%)	243 (22.1%)	2682 (27.0%)	Ref.	Ref.	
Missing	4770 (43.3%)	187 (17.0%)	4583 (46.2%)	0.61 (0.10) / <0.001*	1.15 (0.14) / 0.321	

[α] Defined as having a body-mass index higher than 30 kg/m^2 or an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9).
[β] Current smoking status was self-reported.
[γ] Assessed using ICD-10 diagnosis codes for diabetes mellitus (E11), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), neoplasms (C00-D49), and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D5-D8)
[μ] Defined as having at least one of the following criteria: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90%, temperature > 40°C, or systolic blood pressure < 100 mm Hg.
[κ] Defined as having at least one of the following criteria: high neutrophil-to-lymphocyte ratio, low *lymphocyte-to-C-reactive protein* (both variables were dichotomized at the median of the values observed in the full sample), and plasma *lactate* levels *higher than 2 mmol/L*.
* p-value is significant (p<0.05).
Abbreviations: HR, hazard ratio; SE, standard error; VIF, variance inflation factor.

Supplementary Table 2. Associations between dexamethasone cumulative dose and the endpoint of death, in the full sample and in the matched analytic sample.

With oxygen or intubation					Without oxygen or intubation				
Dexamethasone total dosage	**Crude analysis**	**Cox regression adjusted for age and sex**	**Multivariable (Weighted) Cox regression analysis**	**Univariate Cox regression in the matched analytic samples**	**Dexamethasone total dosage**	**Crude analysis**	**Cox regression adjusted for age and sex**	**Multivariable (Weighted) Cox regression analysis**	**Univariate Cox regression in the matched analytic samples**
	HR (SE) / p-value	**HR (SE) / p-value**	**HR (SE) / p-value**	**HR (SE) / p-value**		**HR (SE) / p-value**	**HR (SE) / p-value**	**HR (SE) / p-value**	**HR (SE) / p-value**
No dexamethasone (n=1,129)	Ref.	Ref.	Ref.	Ref.	No dexamethasone (n=10,910)	Ref.	Ref.	Ref.	Ref.
Other dosage (n=14)	0.21 (0.03 – 1.47; 0.117)	0.21 (0.03 – 1.47; 0.115)	0.24 (0.03 – 1.83; 0.169)	0.24 (0.03 – 1.69; 0.150)	Other dosage (n=18)	0.60 (0.19 – 1.86; 0.376)	0.57 (0.18 – 1.77; 0.332)	0.23 (0.04 – 1.33; 0.101)	0.50 (0.15 – 1.52; 0.241)
60 mg to 150 mg (n=33)	0.28 (0.08 – 0.87; 0.028*)	0.28 (0.09 – 0.96; 0.027*)	0.24 (0.07 – 0.87; 0.030*)	0.32 (0.07 – 0.95; 0.048*)	60 mg to 150 mg (n=45)	0.37 (0.12 – 1.16; 0.089)	0.41 (0.13 – 1.27; 0.122)	0.47 (0.15 – 2.42; 0.178)	0.32 (0.15 – 0.99; 0.049*)
Missing values (n=16)	1.16 (0.51 – 2.60; 0.723)	1.22 (0.54 – 2.73; 0.636)	1.10 (0.41 – 2.96; 0.856)	1.32 (0.40 – 2.53; 0.507)	Missing values (n=35)	1.40 (0.69 – 2.78; 0.355)	1.19 (0.13 – 2.39; 0.618)	1.32 (0.72 – 2.42; 0.361)	1.19 (0.37 – 1.28; 0.634)

* p-value is significant ($p<0.05$).
Abbreviations: HR, hazard ratio; SE, standard error.

Supplementary Table 3. Interaction effect of baseline characteristics with dexamethasone use on the endpoint of death among adult inpatients with COVID-19.

	With respiratory support	Without respiratory support
	Multivariable Cox regression analysis	Multivariable Cox regression analysis
	HR (SE) / p-value	HR (SE) / p-value
Characteristics		
Sex		
Women	Ref.	Ref.
Men	1.86 (0.22 – 15.99; 0.573)	0.91 (0.18 – 4.57; 0.907)
Age		
18 to 50 years	Ref.	Ref.
51 to 70 years	0.64 (0.11 – 3.66; 0.619)	NA
More than 70 years	0.24 (0.03 – 1.84; 0.172)	NA
Obesity [α]		
Yes	2.54 (0.59 – 11.02; 0.213)	3.90 (1.13 – 13.44; 0.031*)
No	Ref.	Ref.
Smoking		
Yes	1.28 (0.12 – 13.51; 0.839)	0.22 (0.02 – 2.64; 0.233)
No	Ref.	Ref.
Any medical condition [β]		
Yes	0.35 (0.08 – 1.62; 0.181)	1.11 (0.28 – 4.34; 0.880)
No	Ref.	Ref.
Clinical severity of Covid-19 at admission [μ]		
Yes	1.35 (0.30 – 6.05; 0.694)	0.30 (0.04 – 2.55; 0.788)
No	Ref.	Ref.
Missing	NA	0.46 (0.12 – 1.78; 0.263)
Biological severity of Covid-19 at admission [κ]		
Yes	0.69 (0.10 – 4.70; 0.701)	0.31 (0.09 – 1.01; 0.052)
No	Ref.	Ref.
Missing	3.24 (0.30 – 35.00; 0.332)	0.35 (0.04 – 3.35; 0.362)

[α] Defined as having a body-mass index higher than 30 kg/m^2 or an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9).
[β] Assessed using ICD-10 codes for diabetes mellitus, diseases of the circulatory system, diseases of the respiratory system, neoplasms, and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism based on ICD-10 classification.
[μ] Defined as having at least one of the following criteria: respiratory rate > 24 breaths/min, oxygen saturation < 92%, temperature ≥ 40°C, and systolic blood pressure < 100 mm Hg.
[κ] Defined as having at least one of the following criteria: neutrophil-to-lymphocyte ratio higher than the median in the full sample, *lymphocyte-to-C-reactive protein ratio* lower than the median in the full sample, and plasma *lactate* level *higher than 2 mmol/L.*
* p-value is significant (p<0.05).