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Original Article

Effect of early dexamethasone on outcomes of COVID-19: A quasi-experimental study using propensity score matching

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KEYWORDS
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Abstract *Background:* The RECOVERY trial demonstrated that the use of dexamethasone is associated with a 36% lower 28-day mortality in hospitalized patients with COVID-19 on invasive mechanical ventilation. Nevertheless, the optimal timing to start dexamethasone remains uncertain.
Methods: We conducted a quasi-experimental study at National Taiwan University Hospital (Taipei, Taiwan) using propensity score matching to simulate a randomized controlled trial to receive or not to receive early dexamethasone (6 mg/day) during the first 7 days following the onset of symptoms. Treatment was standard protocol-based, except for the timing to start dexamethasone, which was left to physicians' decision. The primary outcome is 28-day mortality. Secondary outcomes include secondary infection within 60 days and fulfilling the criteria of de-isolation within 20 days.
Results: A total of 377 patients with COVID-19 were enrolled. Early dexamethasone did not decrease 28-day mortality in all patients (adjusted odds ratio [aOR], 1.03; 95% confidence interval [CI], 0.97—1.10) or in patients who required O2 for severe/critical disease at admission (aOR, 1.05; 95%CI, 0.94—1.18); but is associated with a 24% increase in superinfection in all patients (aOR, 1.24; 95% CI, 1.12—1.37) and a 23% increase in superinfection in patients of O2 for several/critical disease at admission (aOR, 1.23; 95% CI, 1.02—1.47). Moreover, early dexamethasone is associated with a 42% increase in likelihood of delayed clearance of SARS-CoV-2 virus (adjusted hazard ratio, 1.42; 95% CI, 1.01—1.98).
Conclusion: An early start of dexamethasone (within 7 days after the onset of symptoms) could be harmful to hospitalized patients with COVID-19.

Introduction

Despite the dramatical drop in risk of mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection after global rollout of highly effective vaccines in 2021, more than 1 million people died from coronavirus disease 2019 (COVID-19) during 2022.[1] Although remdesivir, nirmatrelvir/ritonavir, or molnupiravir are highly effective to prevent progression to severe COVID-19 when started within 5 days after symptom onset, no antiviral treatment has been shown to reduce mortality of critical COVID-19.[2]

Dexamethasone (6 mg/day, $\leq$10 days) is associated with a 36% lower 28-day mortality in hospitalized patients with critical COVID-19 who required invasive mechanical ventilation, probably via mitigating hyperinflammation-mediated acute respiratory distress syndrome.[3,4] However, whether early start of dexamethasone before patients become critically ill further improves the outcome remains uncertain given conflicting studies, although such practice has been common.[3—13]

A thought-provoking hypothesis to explain conflicting study findings is that the effect of dexamethasone depends on timing in the clinical course of SARS-CoV-2 infection — it could do more harm than good in the first 7 days when viral replication is extremely active but inflammation is minimal.[3,14] To date, the data from subgroup analysis of randomized controlled trials and retrospective real-world studies on the effects of early dexamethasone initiated in the first 7—10 days of clinical course remain statistically inconclusive.[3,8,9] Lack of high-quality evidence means uncertainty in the optimal timing to start dexamethasone for hospitalized patients with COVID-19.[13]

Taiwan successfully contained COVID-19 with combined interventions of testing-contact tracing and universal surgical mask-wearing in 2020, but experienced a community outbreak with approximately 14,000 confirmed cases in Taipei metropolitan area in May to July 2021 before the mass COVID-19 vaccination.[15—17] The National Taiwan University Hospital (NTUH) (Taipei, Taiwan) is a university medical center providing national protocol-based treatment for hospitalized patients with COVID-19.[18]

In this quasi-experimental study that simulates a randomized control trial, we aimed to compare the effect of early dexamethasone treatment on outcomes of

hospitalized patients with COVID-19 versus that of withholding dexamethasone during the first 7 days after the onset of symptoms.

Methods

Study design

This is a hospital-based cohort study that enrolled hospitalized patients with COVID-19. To simulate a randomized controlled trial that enrolled patients at the onset of symptoms and randomized them to receive or not to receive early dexamethasone during the first 7 days in the clinical course of SARS-CoV-2 infection, we used propensity score (PS) matching to select a non-early comparison group that was similar to the early dexamethasone group at the onset of symptoms but did not receive early dexamethasone.

Setting

The study period started from January 2020 through July 2021, before the mass COVID-19 vaccination in Taiwan. The majority (360 out of 377) of participants were enrolled after the preliminary report of the RECOVERY trial on June 16, 2020, which demonstrated the benefit of dexamethasone.[3] However, the potential influence of the RECOVERY trial on clinical practice was counterbalanced by the Taiwan national COVID-19 treatment guideline, which advised caution regarding early corticosteroid use.[18–21]

Participants

All hospitalized adult patients with laboratory confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) at the NTUH between January 2020 and July 2021 were eligible. We excluded patients who: (1) had known past SARS-CoV-2 infections; (2) had out-of-hospital cardiac arrest (OHCA) at arrival; or (3) were transferred elsewhere because of non-medical reasons.

Ethical statement

The study procedure was approved a priori by the Research Ethics Committee (REC) of NTUH (#202007056 RINC). As all participants received national guidelines-based standard treatment and medical care, the REC waived the requirement for informed consent.

Initial assessment

We prospectively obtained Information on age, sex, symptoms, date of symptom onset, as well as comorbidities from patients or medical records in a systematic format to facilitate public health contact tracing.[16,22]

Baseline covariates

We used the age-adjusted Charlson comorbidity index (CCI) scores to integrate age at hospitalization and comorbidities that are predictors for outcomes of hospitalized COVID-19 patients, including type 2 diabetes mellitus, solid organ malignancy, leukemia or lymphoma, rheumatological diseases, chronic liver diseases, chronic kidney diseases, chronic lung diseases, heart diseases (coronary artery diseases and congestive heart failure) and AIDS, into a single index for severity of comorbidities at the baseline.[23] Other baseline covariates included sex, obesity (defined as having a body mass index [BMI] $> 30\ kg/m^2$), hypertension, and HIV infection without AIDS.

Disease severity and O2 requirement at admission

Severity of COVID-19 at admission was categorized to mild, moderate, severe, or critical according to the National Institutes of Health (NIH) COVID-19 treatment guidelines.[24] Severe or critical COVID-19 disease requires oxygen therapy.[24]

Diagnostic evaluation during hospitalization

Diagnostic evaluations included the following: (1) hemogram, hepatic and renal profiles; (2) chest radiograph; (3) inflammatory biomarkers: C-reactive protein (CRP), procalcitonin, and ferritin; (4) serology on hepatitis B virus (HBV), hepatitis C virus (HCV); and human immunodeficiency virus (HIV); (5) co-infection cultures, including: blood culture, sputum cultures, urine pneumococcal and *Legionella* antigens, as well as serum mycoplasma and chlamydia IgM. SARS-CoV-2 RT-PCR was rechecked twice per week (Monday-Thursday, Tuesday-Friday, or Wednesday-Saturday/Sunday).

Treatment protocol

All patients were treated according to the latest COVID-19 treatment guidelines issued by Taiwan Centers for Disease Control (TCDC).[18] Indications for specific treatment were: (**1**) remdesivir (five days course) is recommended for those with moderate or severe disease[25]; (**2**) dexamethasone (6 mg daily up to 10 days, can be stepped down to oral prednisolone in equivalent dose if conditions improve) is recommended for those with critical disease who require invasive mechanical ventilation, and can be used in those with severe disease who require O2 (timing to start is up to physicians' decision);[3,18] (**3**) tocilizumab (or baricitinib) is also recommended for patients with severe or critical disease and a CRP level $>$7.5 mg/dL[26,27]; (**4**) bamlanivimab plus etesevimab and casirivimab plus imdevimab (available after June, 2021 in Taiwan) are recommended for those with mild disease and at risk for disease progression (old age or comorbidities) who were probably infected by susceptible variants[28,29]; (**5**) antimicrobial therapy for co-infections.

Isolation and de-isolation

CDC required that hospitalized patients with confirmed SARS-CoV-2 infection should be immediately placed in airborne infection isolation rooms until the patients are no longer shedding SARS-CoV-2 virus, defined as fulfilling both of two criteria (1) defervescence with symptoms improvement; and (2) negative results of two consecutive RT-PCR

(undetectable, or a serial cycle threshold [CT] value > 30).[30]

Early dexamethasone group vs. non-early group

We defined the early dexamethasone group as patients who received dexamethasone (6 mg/day) within the first 7 days following symptom onset. Conversely, the non-early group included patients who received dexamethasone after the first 7 days of illness or those who never received dexamethasone (or other corticosteroids).

Propensity score matching

We applied PS matching to control for the confounding from baseline covariates and the probability of receiving early dexamethasone treatment. Each patient who received early dexamethasone was matched to two control patients (who did not receive early dexamethasone) with the nearest neighbor matching within a caliper width of 0.2 of the standard deviation of the logit PS.[31] To estimate the effectiveness of PS matching, standardized differences and variance ratio before and after PS matching were calculated for each variable.[32,33] This study was designed to simulate a randomized controlled trial that enrolled patients at the onset of symptoms. Therefore, only baseline variables, including age (in years) and age-adjusted CCI scores, were used for PS matching. Inflammatory markers and disease severity at hospitalization were considered intermediate outcomes.[34] Controlling for these variables may introduce overadjustment bias.[34]

Patients required O2 for severe/critical disease at admission

To account for large differences in COVID-19 disease severity and oxygen requirement between the early and non-early groups, we conducted prespecified subgroup analyses of outcomes in high-risk patients who required oxygen for severe/critical COVID-19 disease at admission.

Outcome assessment

All patients were followed to 60 days after the date of admission. The primary outcome is all-cause mortality within 28 days from the hospital admission date. Secondary outcomes include: (1) mortality or developing respiratory failure that was still requiring mechanical ventilation by day 28; (2) superinfections (laboratory-confirmed bacterial or fungal infections >72 h after hospital admission by 60 days (to include late-onset fungal superinfections); and (3) viral clearance (as defined by fulfilling the criteria of de-isolation) within 20 day after the onset of symptom.

Statistical analysis

To estimate the effect of early dexamethasone on risk of developing primary outcome (death), respiratory failure that still requiring mechanical ventilation by day 28 and superinfections within 60 days after hospitalization, we applied a multivariable logistic regression with both average treatment effect (ATE) and average treatment effect on the treated (ATET) model after PS matching.

For analyzing viral clearance, we applied Cox proportional hazard regression to analyze time to de-isolation (counted from symptom onset). All patients were followed-for 20 days until fulfilling the criteria of de-isolation, mortality, or transfer to other hospitals, whichever took place first. We used stepwise Cox regression with removal threshold of $p = 0.1$ to select among covariates to be included into the multivariable model. CCI scores were used to summarize the effect of age and baseline comorbidities whose effect may or may not be statistically significant in univariable analysis. To show risk factors for delayed viral clearance, hazard ratio (HR) is presented as the reciprocal of HR estimated by Cox proportional hazard regression analysis on time (after the onset of symptoms) to viral clearance. The correlation between duration of corticosteroid (dexamethasone plus prednisolone) and time to viral clearance was analyzed by Pearson's correlation coefficient.

All statistical analyses were performed using STATA v17.0. (StataCorp, College Stations, TX, USA). Two-tailed p values < 0.05 are considered statistically significant.

Results

Of the 412 hospitalized patients with confirmed SARS-CoV-2 infection during the study period, 377 were eligible. Eighteen (4.8%) out of the 377 patients developed the primary outcome, with a total follow-up time of 5839 patient-days.

Seventy patients received early dexamethasone treatment within the first 7 days after symptom onset (early dexamethasone group); and 307 patients who did not (non-early group: including 100 patients who received dexamethasone for COVID-19 after the first 7 days) (Fig. 1). Table 1 shows the baseline characteristics of included patients. Patients of early dexamethasone group tended to have shorter time interval from symptom onset to admission (median: 2.5 days vs. 3 days, $p = 0.03$), while the proportion of patients with at least 1 dose COVID-19 vaccination 2 week before admission (1.5% vs. 3.9%, $p = 0.44$) between two groups was not significantly different. Table 2 shows the clinical features and laboratory data at admission, as well as treatment and outcomes.

Before PS matching, patients in early dexamethasone group are older (median age at admission: 69 vs. 55 years, $p < 0.001$) and to have more severe comorbidities (median age-adjusted CCI score: 5 vs 3). After PS matching, the bias toward unfavorable baseline age and severity of comorbidities in the early dexamethasone group was successfully eliminated, with standardized difference for age and age-adjusted CCI less than 0.1 (Table 3).

After PS matching, early dexamethasone treatment initiated within 7 days after the onset of symptoms did not demonstrate a benefit regarding all-cause 28-day mortality (adjusted odds ratio [aOR], 1.03; 95% confidence interval [CI], 0.97–1.10), or mortality or respiratory failure that still requiring mechanical ventilation by day 28 (aOR, 1.04; 95% CI, 0.96–1.12). However, early dexamethasone treatment is associated with a 24% increase in risk of developing superinfections (aOR, 1.24; 95% CI, 1.12–1.37). Prespecified

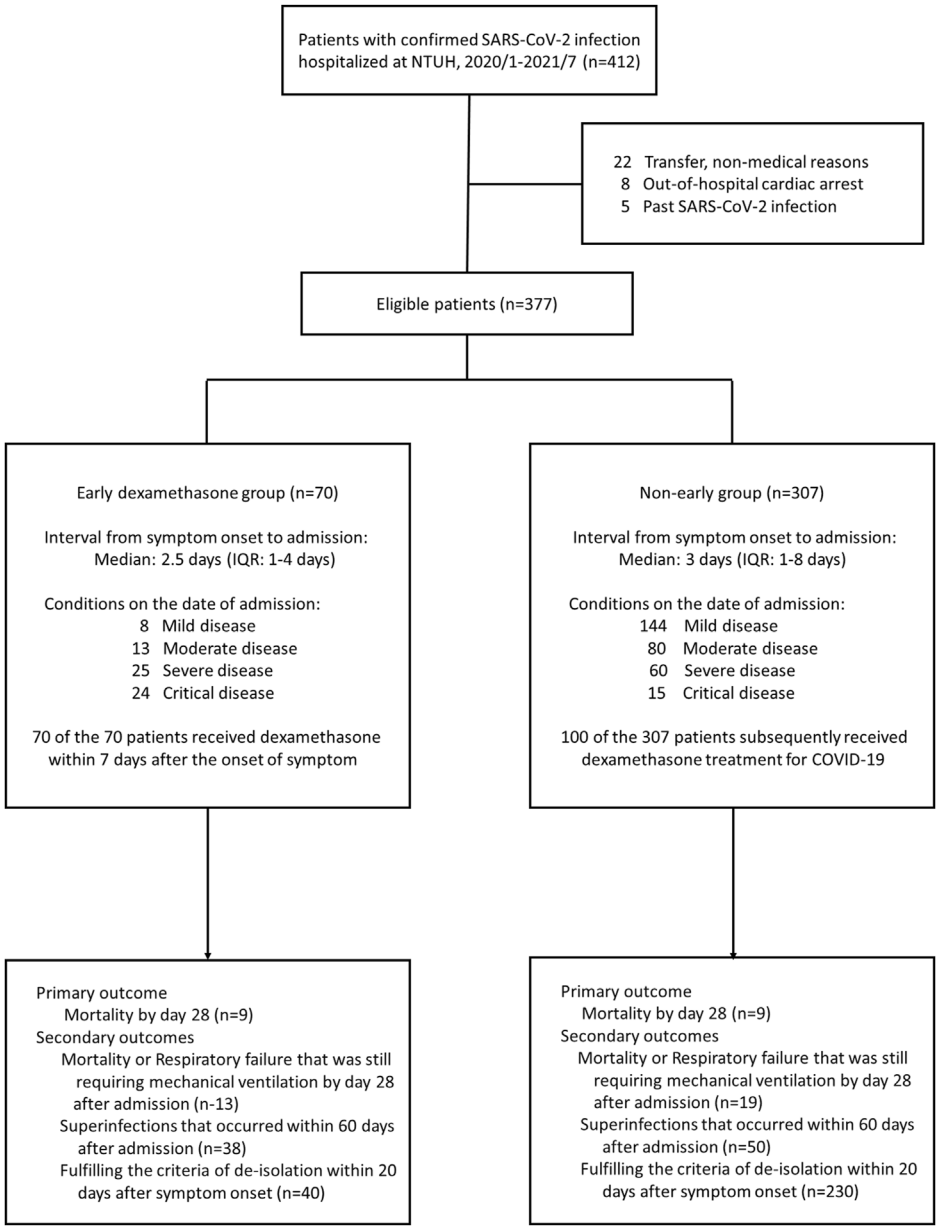

Figure 1. Study population.

analyses of the high-risk patients who required O2 for severe/critical disease at admission still show a lack of benefit for the primary outcome (aOR, 1.05; 95% CI, 0.94−1.18) and a 23% increase in risk of superinfection (aOR, 1.23; 95% CI, 1.02−1.47) (Table 4). Among the 88 patients who developed secondary infection, 20 (22.7%) developed bacteremia or fungemia, 40 (45.5%) developed hospital-acquired (HAP) or ventilator-associated pneumonia (VAP). Eleven (12.5%) patients developed probable invasive pulmonary aspergillosis with an increased serum galactomannan titer. The leading pathogen causing bloodstream infection were *Candida* species (n = 4), followed by *Staphylococcus aureus* (n = 2), *Klebsiella pneumoniae* (n = 2), and *Enterococcus faecium* (n = 2), while the leading pathogen causing HAP or VAP was *K. pneumoniae* (n = 9), followed by *Pseudomonas aeruginosa* (n = 8), and *Acinetobacter baumannii* complex (n = 7).

Early dexamethasone treatment is also associated with a 42% increase in the likelihood for delayed clearance of SARS-CoV-2 virus (p = 0.02, log rank test, Fig. 2; adjusted hazard ratio, 1.42; 95% CI, 1.01−1.98, Table 5) after adjusting for the effect of CCI. The duration of corticosteroid treatment (intravenous dexamethasone plus stepped down oral prednisolone) is strongly correlated with time (since symptom onset) to viral clearance (r = 0.38, p < 0.001) (Fig. 3).

Discussion

Our results show that early dexamethasone treatment, started during the first 7 days in clinical course, did not decrease 28-day mortality in all patients but is associated with a 24% increase in risk of superinfection. Prespecified

Table 1 Baseline characteristics.

(A) All included patients.

Characteristics	Early Dexamethasone Group (n = 70)	Non-Early Group (n = 307)	p value
Demographic			
Age (IQR), years	69 (57–75)	55 (41–66)	**<0.001**
Male sex	45 (64.3)	145 (47.2)	**0.01**
BMI >30 kg/m^2	10 (14.3)	21 (6.8)	**0.04**
Interval between symptoms onset to admission, days	2.5 (1–4)	3 (1–8)	**0.03**
Receive at least one COVID-19 vaccine 2 weeks before admission	1 (1.5)	12 (3.9)	0.44
Underlying disease			
Charlson comorbidity index >4	45 (64.3)	106 (34.5)	**<0.001**
Charlson comorbidity index	5 (4–7)	3 (2–6)	**<0.001**
Hypertension	37 (52.9)	91 (29.6)	**<0.001**
Dyslipidemia	14 (20.0)	39 (12.7)	0.11
Type 2 diabetes mellitus	27 (38.6)	53 (17.3)	**<0.001**
Heart disease	14 (20.0)	23 (7.5)	**<0.001**
Chronic lung disease	8 (11.4)	5 (1.6)	**0.001**
Chronic kidney disease	12 (17.1)	17 (5.5)	**0.001**
Dialysis	3 (4.3)	5 (1.6)	0.17
Chronic hepatitis B	6 (10.5)	30 (10.5)	0.72
Chronic hepatitis C	3 (4.3)	8 (2.6)	0.44
Cirrhosis	0 (0)	2 (0.7)	1.00
Solid organ malignancy	7 (10.0)	23 (7.5)	0.49
Hematologic malignancy	3 (4.3)	5 (1.6)	0.17
HIV infection	3 (4.3)	14 (4.6)	1.00
Rheumatology diseases	0 (0)	8 (2.6)	0.36

(B) High-risk patients who required oxygen for severe/critical disease at admission

Characteristics	Early Dexamethasone Group (n = 49)	Non-Early Group (n = 75)	p value
Baseline characteristics			
Age	70 (61–75)	68 (59–74)	0.47
Male sex	37 (75.5)	43 (57.3)	**0.04**
BMI >30 kg/m^2	5 (10.2)	8 (10.7)	0.93
Interval between symptoms onset to admission, days	3 (1–4)	8 (5–11)	**<0.001**
Receive at least one COVID-19 vaccine 2 weeks before admission	1 (2.0)	1 (1.3)	1.0
Charlson comorbidity index >4	33 (67.4)	54 (72.0)	0.58
Charlson comorbidity index	5 (4–7)	6 (4–8)	0.19

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range.
Note. Data are median (interquartile range, IQR) or percentage (%). High-risk population is defined as having a severe or critical disease that required oxygen supplement upon admission.

subgroup analysis on high-risk patients, who required O2 for severe/critical disease at admission, still shows the lack of benefit on 28-day mortality but a 23% increased risk of superinfection. Moreover, early dexamethasone is also associated with a 42% rise in the likelihood for delayed clearance of SARS-CoV-2 virus. To our knowledge, the present study is the first to supports the hypothesis that dexamethasone could do more harm than good in early stage of SARS-CoV-2 infection when viral replication is extremely active but inflammation is minimal.[3]

The RECOVERY randomized trial demonstrated that dexamethasone decreases 28-day mortality of patients with COVID-19 who were receiving invasive mechanical ventilation or those patients with symptoms for more than 7 days, thus provided strong evidence on the role of hyperinflammation in late stage of COVID-19; but the effects of dexamethasone in patients in early stage (symptom less than 7 days) remain statistically inconclusive although showing a trend toward harm (primary outcome: rate ratio (RR) of 28-day mortality 1.01, 95% CI: 0.87–1.17).[3] Our quasi-experimental data on early dexamethasone are consistent with this trend first identified by the RECOVERY trial, and further revealed the statistically significant increase in the risk of clinically highly relevant harm including superinfections and delayed virus clearance.

The strength of the present study is comprehensive information on date of symptoms onset and complete follow-up, with few missing data in contrast to the high rate of

Table 2 Clinical features at admission, treatments, and outcomes.

(A) All included patients.

Characteristics	Early Dexamethasone Group (n = 70)	Non-Early Group (n = 307)	p value
Clinical features			
Fever	49 (70.0)	194 (63.4)	0.30
Cough	49 (70.0)	191 (62.2)	0.22
Diarrhea	9 (12.9)	40 (13.0)	0.97
Rhinorrhea	1 (1.4)	25 (8.1)	0.06
Dysosmia	0 (0)	20 (6.5)	**0.03**
Dysgeusia	1 (1.4)	21 (6.8)	0.09
Lab data			
Hb (g/dL)	13.0 (11.6–14.7)	13.5 (12.4–14.7)	0.11
Platelet (K/μL)	196 (132–245)	209 (166–266)	**0.04**
WBC (K/μL)	7.25 (4.85–10.73)	5.47 (4.14–7.10)	**0.003**
Lymphocyte (K/μL)	0.85 (0.65–1.26)	1.08 (0.79–1.58)	**<0.001**
Neutrophil (K/μL)	5.73 (3.53–9.19)	3.76 (2.57–5.16)	**<0.001**
CRP (mg/dL)	6.6 (3.7–12.6)	0.7 (0.2–3.4)	**<0.001**
Procalcitonin (ng/mL)	0.13 (0.08–0.66)	0.06 (0.04–0.10)	**<0.001**
Ferritin (ng/mL)	964 (392–1782)	281 (121–723)	**<0.001**
Albumin (g/dL)	3.7 (3.4–3.9)	4.3 (3.9–4.6)	**<0.001**
ALT U/L)	24 (15–37)	19 (13–34)	0.06
LDH (U/L)	348 (286–539)	209 (173–282)	**<0.001**
BUN (mg/dL)	19.8 (13.6–38.6)	13.2 (10.3–17.5)	**<0.001**
Creatinine (mg/dL)	1.0 (0.8–1.5)	0.8 (0.6–1.0)	**<0.001**
CK (U/L)	127 (52–239)	73 (47–111)	**0.001**
Severity and O2 requirement on admission			
Mild, not on oxygen	8 (11.4)	144 (46.9)	**<0.001**
Moderate	13 (18.6)	88 (28.7)	0.09
Severe	25 (35.7)	60 (19.5)	**0.003**
Critical, invasive mechanical ventilation	24 (34.3)	15 (4.9)	**<0.001**
Treatment			
Remdesivir	50 (71.4)	76 (24.8)	**<0.001**
Corticosteroid	70 (100.0)	100 (32.6)	**<0.001**
Tocilizumab	32 (45.7)	37 (12.1)	**<0.001**
Baricitinib	1 (1.4)	4 (1.3)	1.0
Monoclonal antibody	3 (4.4)	15 (4.9)	1.0
Outcomes			
Mortality within 28 days after admission	9 (12.9)	9 (2.9)	**0.002**
Death or still required mechanical ventilation by 28 days after admission	13 (18.6)	19 (6.2)	**0.001**
Superinfection within 60 days after admission	38 (54.3)	50 (16.3)	**<0.001**
Fulfill the criteria of de-isolation within 20 days after admission	40 (65.6)	230 (78.0)	**0.04**

(B) High-risk patients who required oxygen for severe/critical disease at admission

Characteristics	Early Dexamethasone Group (n = 49)	Non-Early Group (n = 75)	p value
Treatment			
Remdesivir	35 (71.4)	43 (57.3)	0.11
Corticosteroid	49 (100)	63 (84.0)	**0.003**
Tocilizumab	27 (55.1)	27 (36.5)	**0.04**
Baricitinib	0 (0)	3 (4.0)	0.28
Outcomes			
Mortality within 28 days after admission	9 (18.4)	9 (12.0)	0.33
Death or still required mechanical ventilation 28 days after admission	12 (24.5)	19 (25.3)	0.91
Superinfection within 60 days after admission	36 (73.5)	34 (45.3)	**0.002**
Fulfill the criteria of de-isolation within 20 days after admission	24 (58.5)	31 (44.9)	0.17

Note. Data are median (interquartile range, IQR) or percentage (%).

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CRP, C-reactive protein; Hb, hemoglobin; IQR, interquartile range; LDH, Lactate dehydrogenase; WBC, white blood cell.

There was no enrolled patient receiving systemic corticosteroid therapy for pre-existing comorbidities within a month before admission.

Table 3 Patient characteristics before and after propensity score matching.

Characteristics	Before PS matching			After PS matching		
Early dexamethasone treatment (All included patients)	Yes	No	SD/VR	Yes	No	SD/VR
Age	69 (57—75)	55 (41—66)	0.89/0.61	69 (57—75)	69 (60—76)	0.07/0.78
Charlson comorbidity index	5 (4—7)	3 (2—6)	0.63/0.79	5 (4—7)	5 (4—7)	0.07/0.80
Early dexamethasone treatment (High risk patients who required oxygen for severe/critical disease at admission)						
Age	70 (61—75)	68 (59—74)	0.16/0.84	70 (61—75)	69 (64—74)	0.09/0.81
Charlson comorbidity index	5 (4—7)	6 (4—8)	−0.20/0.70	5 (4—7)	5 (3—7)	0.02/0.76

Abbreviations: NA, not applicable; PS, propensity score; SD, standardized difference; VR, variance ratio.
Note. Data are median (interquartile range, IQR) or percentage (%).

Table 4 Effect of early dexamethasone on primary and secondary outcomes.

Early dexamethasone treatment (Yes vs No) (All included patients)	Adjusted odds ratio (95% CI)[a]	p value[a]	Adjusted odds ratio (95% CI)[b]	p value[b]
Mortality by day 28	1.03 (0.97—1.10)	0.28	1.04 (0.95—1.15)	0.39
Mortality or was still requiring mechanical ventilation by day 28	1.04 (0.96—1.12)	0.30	1.05 (0.94—1.17)	0.36
Superinfections	**1.24 (1.12—1.37)**	**<0.001**	**1.32 (1.12—1.55)**	**0.001**
Early dexamethasone treatment (Yes vs No) (High-risk patients who required oxygen for severe/critical disease at admission)				
Mortality on day 28	1.05 (0.94—1.18)	0.38	1.07 (0.95—1.22)	0.26
Mortality or was still requiring mechanical ventilation by day 28	0.95 (0.83—1.09)	0.46	0.98 (0.83—1.16)	0.81
Superinfections	**1.23 (1.02—1.47)**	**0.03**	**1.25 (1.03—1.52)**	**0.03**

Abbreviations: CI: confidence interval.
Note: a. ATE model. B. ATET model.

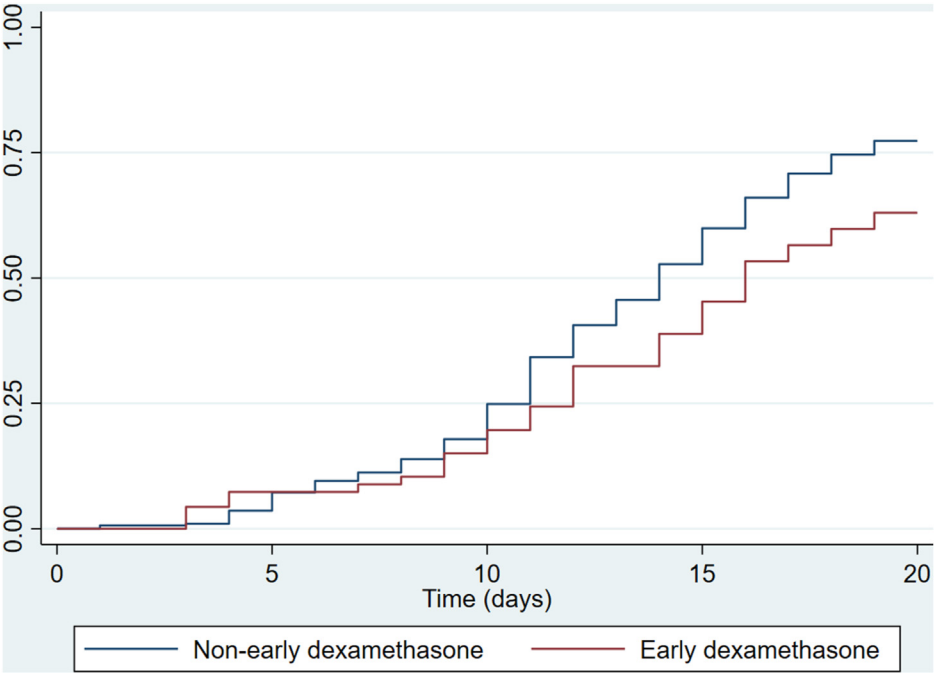

Figure 2. Kaplan-Meier analysis for time (after the onset of symptom) to viral clearance: early dexamethasone group versus non-early group (log-rank test, p = 0.02).

Table 5 Factors associated with not achieving viral clearance within 20 days after the onset of symptoms.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age >65 years	**1.63 (1.24–2.14)**	**0.001**	—	—
Male sex	1.25 (0.98–1.58)	0.07	—	—
Coronary artery disease	0.87 (0.59–1.28)	0.47	—	—
Chronic obstructive pulmonary disease	1.49 (0.70–3.15)	0.30	—	—
Chronic kidney disease (defined as eGFR <60 ml/min/1.73^2)	**2.03 (1.14–3.62)**	**0.02**	—	—
Type 2 diabetes mellitus	**1.81 (1.31–2.50)**	**<0.001**	—	—
Chronic liver disease (including chronic hepatitis B and liver cirrhosis)	1.33 (0.87–2.02)	0.18	—	—
Rheumatology diseases	2.80 (0.90–8.7)	0.08	—	—
Solid organ cancer	**2.10 (1.20–3.67)**	**0.009**	—	—
Hematologic malignancy	2.03 (0.65–6.34)	0.22	—	—
HIV infection	**0.38 (0.23–0.63)**	**<0.001**	—	—
Charlson comorbidity index, per 1 score increase	**1.11 (1.04–1.17)**	**0.001**	**1.10 (1.04–1.17)**	**0.002**
BMI>30 kg/m^2	0.95 (0.62–1.44)	0.79	—	—
Hypertension	1.28 (0.98–1.67)	0.07	—	—
Early dexamethasone treatment	**1.44 (1.03–2.02)**	**0.03**	**1.42 (1.01–1.98)**	**0.045**

Abbreviations: BMI, body mass index; HR, hazard ratio.
Note: To show risk factors for delayed viral clearance, HR is presented as the reciprocal of HR estimated by Cox proportional hazard regression analysis on time (after the onset of symptoms) to viral clearance.

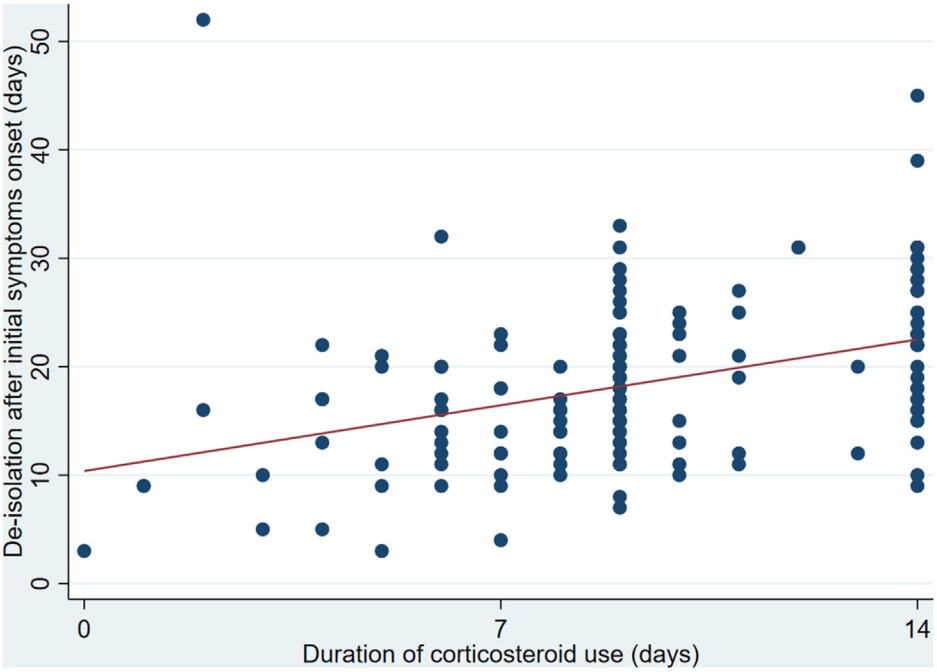

Figure 3. Correlation between duration of corticosteroid treatment (dexamethasone and stepped down oral prednisolone) and time (after the onset of symptom) to viral clearance ($r = 0.38$, $p < 0.001$). * The median duration (IQR) of dexamethasone or corticosteroid use of steroid users in early dexamethasone group and non-early dexamethasone group were 10 (8–13) and 10 (9–12) days, respectively.

missing information in two previous retrospective studies; as well as inclusion of all hospitalized patients with COVID-19, without excluding certain high-risk patients such as those received tocilizumab.[8,9] Moreover, unlike a previous study on timing of initiating corticosteroid which retrospectively included only patients who ever received corticosteroid in analyzing impact,[9] our study was designed to simulate the prospect of physicians who evaluate and treat new hospitalized patients with COVID-19. Therefore, our finding would be more informative and relevant to real-world practice.

High dose corticosteroid (dexamethasone 12 mg/day, equivalent to methylprednisolone 1 mg/kg/day, or higher dose) significantly prolongs SARS-CoV-2 viral shedding in

hospitalized patients with COVID-19, especially when started early in the course.[35—37] For lower-dose corticosteroid (dexamethasone 6 mg/day, equivalent to methylprednisolone 0.5 mg/kg/day), data on viral shedding are limited but conflicting, possibly because of lack of adjustment for baseline comorbidity.[35,36,38] Our data first showed that, after controlling covariates that affected viral shedding, lower-dose dexamethasone is associated with a 42% increase in the likelihood of delayed clearance of SARS-CoV-2 when administrated in the first 7 days after symptom onset. The negative impact on immunity to clear SARS-CoV-2 during stage of active viral replication is consistent with subsequent increase in the risk of bacterial and/or fungal superinfections.

Our findings provide new insight on optimizing treatment of COVID-19. In early stage when viral replication is extremely active and inflammation is minimal, antiviral treatment (remdesivir, nirmatrelvir/ritonavir, or molnupiravir) has the greatest benefit while dexamethasone (and other immunosuppressives) can be harmful and should be withheld.[3,5,8,9,11] On the other hand, in late stage when inflammation becomes the predominant pathophysiologic process and viral replication had declined, the start of dexamethasone can be life-saving for those need respiratory support, and therefore, should be initiated as soon as possible.[3,4,7,10] Similar therapeutic principles have been successfully applied in the treatment of SARS, the precedent for COVID-19.[19—21]

Our findings are subject to the following limitations. First, the treatment assignment is not randomized. Although we applied PS matching to adjust for both probability to receive dexamethasone and probability to develop outcome, we cannot exclude the possibility that some residual confounding may still exist. A large randomized controlled trials is required to balance all of potential confounding variables. Nevertheless, despite the warning regarding the potential harm of early dexamethasone administration within 7 days, as indicated by the RECOVERY trial investigators, most practitioners interpreted the statistically insignificant findings regarding the early use of dexamethasone as "no harm".[3] Consequently, they tend to err towards overusing dexamethasone during the first week of illness. As conducting new large randomized controlled trials to examine this important issue has now become increasingly challenging, our quasi-experimental study on the statistically significant harm of superinfection and delayed viral clearance associated with early dexamethasone represents the best available evidence regarding its early use. Second, all included patients received treatment in the same national COVID-19 treatment center and the sample size is modest. While the standardized diagnostic procedure and treatment protocol strengthens internal validity and statistical power of our study by minimizing variations in data collection and standard of medical care, generalizability to patients in other settings might be limited. Nevertheless, our study yielded estimates on the lack of impact of early dexamethasone on 28-day mortality (aOR: 1.03, 95% CI: 0.97 to 1.10) (Table 3) similar to the estimate reported in the large, multicenter RECOVERY trial ($\leq$7 day: aRR for 28-day mortality: 1.01, 95% CI: 0.87 to 1.17, Figure S1 in reference 3).[3] Therefore, our findings may still have a reasonably good external validity. Third, given the strict hospital infection control measures at NTUH,[39] our main analysis might underestimate the risk of early dexamethasone-associated bacterial or fungal superinfections and associated mortality. Fourth, since few of the enrolled patients received a full series of vaccines against SARS-CoV-2 and none were enrolled in the Omicron period, our data need to be interpreted cautiously for vaccinated patients in the current Omicron variant-predominant era. However, vaccinated people in Omicron era had a dramatically decreased risk of severe disease and death, which further argues against the rationale for early use of potentially harmful dexamethasone treatment.[40] Finally, individual variations exist in the clinical course of SARS-CoV-2 infection.[14] Even though the use of 7 days after symptom onset as the cut-off point to define early stage of SARS-CoV-2 infection is valid for hospitalized patients with COVID-19 in general, the 7-day rule may not be applied to the minority of patients who have persistent high-level viral replication (late start of dexamethasone could still be harmful for them) and patients whose clinical course rapidly progresses to hyperinflammation phase (early start of dexamethasone could still be life-saving for them). Therefore, it is imperative to exercise the clinical judgement for each patient on an individual basis. For patients who rapidly progress to respiratory failure in the first week, the use of corticosteroid needs to be cautious due to the risk of secondary infection. Our study highlights that, in such patients, the potential benefit of early dexamethasone treatment needs to be weighed against the risk of bacterial and fungal superinfection, including candidemia and pulmonary aspergillosis. Whether inflammatory biomarker helps to individualize the optimal timing to start dexamethasone treatment requires further clinical investigation.

In conclusion, the results of this quasi-experimental study among patients hospitalized to receive national protocol-based standard treatment for COVID-19 provide new evidence that early dexamethasone, started during the first 7 days after symptoms onset, did not decrease the risk of COVID-19-related mortality or disease progression requiring invasive mechanical ventilation but increase the risk of superinfection and delayed virus clearance. This finding strongly supports the new treatment paradigm that dexamethasone decreases hyperinflammation-mediated morbidity and mortality in late stage of COVID-19, but could do more harm than good in early stage of infection when viral replication is active and antiviral treatment has the greatest benefit.

Author contributions

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Conflicts of interest

All authors have no competing interest to disclose.

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