CADTH COVID-19 PANDEMIC

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Dexamethasone in the Treatment of Hospitalized Patients With COVID-19: A Critical Appraisal of the RECOVERY Trial

This report was published on July 24, 2020.

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ARDS	acute respiratory distress syndrome
CI	confidence interval
FCA	Focused Critical Appraisal
HR	hazard ratio
IDMC	independent data monitoring committee
NHS	National Health Service
RCT	randomized controlled trial
RR	risk ratio
Sars-COV-2	severe acute respiratory syndrome coronavirus 2

Table of Contents

Tables

Figure

The objective of a CADTH Focused Critical Appraisal (FCA) is to summarize and to evaluate the methodology, scientific rigour, and findings of a published study.

Background

Dexamethasone is a glucocorticoid that is has been used in Canada and worldwide for decades. The proposed mechanism of glucocorticoids in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — the virus that causes coronavirus disease 2019, or COVID-19 — involves the mitigation of an excessive immune response that can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure.[1] ARDS develops in approximately 20% of patients with COVID-19 and is linked to multi-organ failure through cytokine release syndrome.[1] Based on the possible mitigation of immune response through anti-inflammatory and immunosuppressive effects, there are several ongoing randomized controlled trials (RCTs) evaluating glucocorticoids to treat patients with severe COVID-19.[2]

In July 2020, the dexamethasone arm of the RECOVERY trial "A randomised trial of treatments to prevent death in patients hospitalised with COVID-19 (coronavirus)" was published.[3]

Trial Under Review

This FCA includes a summary with critical appraisal of the dexamethasone arm of the RECOVERY trial — RECOVERY Collective Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med*. 2020 Jul 17 [Epub ahead of print].[3]

Description of the Trial Under Review

Study Objective

The overall RECOVERY trial sought to investigate several different treatments for COVID-19 compared to usual standard of care for patients hospitalized with COVID-19 or suspected COVID-19 in the National Health Service (NHS) of the UK. The dexamethasone arm of the RECOVERY trial described in this FCA compared the effect of dexamethasone plus usual standard of care versus usual standard of care for the treatment of patients hospitalized with COVID-19.

Study Characteristics and Statistical Analysis

RECOVERY Study Design

The RECOVERY trial is an ongoing, open-label, randomized, multi-centre, adaptive platform trial with multiple active treatment arms being conducted in the UK and includes 176 sites in England, Scotland, Wales, and Northern Ireland.

The RECOVERY trial is adaptive, as treatment arms can be added or removed based on emerging evidence, and the randomization ratio is maintained as 2:1 for usual standard of care and each of the available active treatment arms in the main randomization. For example, if there were three active treatment arms, the trial would be randomized as 2:1:1:1

and if there were four active treatment arms, the trial would be randomized as 2:1:1:1:1; this ratio would change as the number of study arms changed. Additional substudies may be added.

The RECOVERY trial employed internet-based simple randomization, with allocation concealment. Randomization was not stratified.

The RECOVERY trial had three possible stages of randomization. Eligible patients hospitalized with COVID-19 or suspected COVID-19 (N = 9,355) were randomized (main randomization) 2:1 to receive usual standard of care or one of the active treatment arms, which included: lopinavir-ritonavir, dexamethasone (arms as of original protocol dated March 13, 2020), hydroxychloroquine (arm added March 23, 2020), or azithromycin (arm added April 7, 2020). There was a second randomization (1:1), added April 14, 2020, to either tocilizumab plus usual standard of care or usual standard of care for patients with hypoxia (oxygen saturation was less than 92%) and inflammation (C-reactive protein was 75 mg/dL or more). The main randomization was expanded to include another factorial 1:1 randomization (main randomization part b) to convalescent plasma plus usual standard of care or usual standard of care only (added May 14, 2020). Enrolment to the hydroxychloroquine and lopinavir-ritonavir arms stopped due to futility as of the time of publication of the dexamethasone arm results.

Patients, treating clinicians, and study staff were not blinded to treatment. The independent data monitoring committee (IDMC) reviewed unblinded study data approximately every two weeks and if the comparisons provided mortality evidence that was compelling and uncertainty narrow enough, the IDMC would inform the blinded steering committee and then make results available. The IDMC determined that stopping a treatment for benefit would require a 3 to 3.5 standard error reduction in mortality; however, there was no explicit stopping rule described a priori for futility. Unless the IDMC made results available, the steering committee, investigators, and all others involved in the trial would be blinded to the study results until 28 days after the last patient had been randomized to a particular arm.

Patients were followed up until hospital discharge, death, or 28 days post-randomization (whichever occurred first). There is a planned follow-up for six months post-randomization.

Funding for the RECOVERY trial was provided by a grant to:

> the University of Oxford from UK Research and Innovation and the National Institute for Health Research (NIHR); and by core funding provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, the NIHR Health Protection Unit in Emerging and Zoonotic Infections, and NIHR Clinical Trials Unit Support Funding.[3]

Inclusion and Exclusion Criteria — RECOVERY

Patients included in the RECOVERY trial were those admitted to hospital for laboratory-confirmed COVID-19 and with no medical conditions that might (in the opinion of the treating clinician) put the patient at significant risk from the trial. Specific medical conditions were not explicitly described. The protocol was modified April 9, 2020; inclusion criteria were expanded to include patients with suspected COVID-19. This was described as a clinical diagnosis based on the opinion of treating clinicians and defined as typical symptoms (influenza-like illness with fever and muscle pain or respiratory illness with cough and shortness of breath) and compatible chest X-ray findings (consolidation or ground-glass

shadowing, with alternate causes excluded or considered unlikely). Pregnant or breast-feeding patients were included and the protocol was modified on April 24, 2020 to include patients younger than 18 years of age. Patients provided informed consent, if possible; a legal representative provided consent otherwise.

A study arm would not be available to a patient if the hospital did not have access to the study drug or if the treating clinician felt that the study arm was definitely indicated or definitely contraindicated.

Specific contraindications to dexamethasone were not explicitly described in the study protocol.

Interventions RECOVERY Dexamethasone

Patients received dexamethasone plus usual standard of care or usual standard of care alone. Dexamethasone 6 mg was administered orally (via oral liquid or tablet) or IV once daily for 10 days, unless the patient was discharged from hospital, at which time the medication was discontinued. The route of administration was at the discretion of the treating clinician and explicit guidance around the route of administration was not provided. Usual standard of care was not defined in the study protocol or publication. Treating clinicians were responsible for prescribing the study drug and were free to modify or stop study treatments.

Outcome Assessment RECOVERY

The primary outcome was all-cause mortality within 28 days of randomization. Secondary outcomes included: time to hospital discharge; and for patients not receiving invasive mechanical ventilation at randomization, the composite outcome of subsequent invasive mechanical ventilation or death. Other pre-specified exploratory outcomes included: receipt and duration of invasive mechanical ventilation, receipt of hemodialysis or hemofiltration, cause-specific mortality, and major cardiac arrythmia (atrial flutter/fibrillation, supraventricular tachycardia, ventricular tachycardia including torsades de pointes). The primary outcome was changed from in-hospital mortality to 28-day all-cause mortality on April 7, 2020.

Outcomes data were collected via an online follow-up form that was completed once at the time of discharge, death, or 28 days post-randomization. Information collected included vital status, cause of death, receipt of assisted ventilation (type and duration), receipt of renal replacement therapy, duration of hospitalization, receipt of other study treatments, and adherence to allocated study treatment. Major cardiac arrhythmia data were also collected from May 12, 2020.[4]

Linkages to the NHS, registries, clinical audit, and other health records were also used to determine outcomes.

Time to discharge was defined as the number of days from randomization to discharge from an acute care hospital; the definitive source for the date of discharge was considered to be the linked hospital admissions data.[4]

Ventilation was categorized as invasive mechanical ventilation (including extra-corporeal membrane oxygenation) and non-invasive ventilation (including continuous positive airway pressure and high flow nasal oxygen).[4]

Statistical Analysis RECOVERY Dexamethasone

All analyses were conducted with the intention-to-treat population that included all randomized patients.

A Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) for patients who were randomized to dexamethasone compared to patients who were randomized to usual standard of care for the primary outcome of the 28-day mortality rate. Kaplan–Meier survival curves were also generated. A Cox proportional hazards regression analysis was used to estimate the HR for the comparison of time to hospital discharge. A log-binomial regression was used to estimate the risk ratio (RR) of the composite outcome of subsequent invasive mechanical ventilation or death for patients who were not receiving invasive ventilation at randomization.

Age adjustment (by age in the categories of younger than 70 years, 70 to 79 years of age, and 80 years or older) was incorporated into the statistical analysis plan after it was noted that the mean age was 1.1 years higher in the dexamethasone arm than the usual standard of care arm. This analysis was not pre-specified.

As of the data cut on July 6, 2020, a small number of patients (0.1%) who had not been followed for 28 days were censored; patients who had been discharged without information about 28-day mortality were assumed to be alive at 28 days.

Planned subgroup analyses were conducted for the primary outcome. The planned subgroups included: age (younger than 70 years; 70 years to 79 years of age, 80 years or older); sex; level of respiratory support at randomization (none, oxygen only, invasive mechanical ventilation); days since symptom onset (7 days or less, more than 7 days); and predicted 28-day mortality risk based on three risk groups, with an approximately equal number of deaths based on baseline characteristics. Ethnicity was also included as a pre-specified subgroup. Pre-specified subgroup analyses were conducted with regression models that included an interaction term between treatment assignment and the subgroup of interest.

The sample size for the RECOVERY trial was not calculated a priori. Sample size and recruitment were monitored by the blinded steering committee. As the trial progressed, the blinded steering committee determined that if 28-day mortality was 20%, then at least 2,000 patients allocated to active drug and 4,000 patients allocated to receive usual standard of care would provide at least 90% power at a two-sided P value of 0.01 to detect a clinically relevant difference of 20% (an absolute difference of 4%).

The unblinded IDMC informed the blinded steering committee if they determined that randomized comparisons demonstrated evidence on mortality strong enough to affect treatment strategies. The IDMC determined that stopping a treatment for benefit would require a 3 to 3.5 standard error reduction in mortality. There was no explicit stopping rule described a priori for futility. The IDMC reviewed dexamethasone data five times prior to determining that recruitment to the dexamethasone should be stopped; the alpha spent for these interim analyses was approximately 0.06%. Therefore, the alpha preserved for the final analysis was 4.94%.

Results RECOVERY Dexamethasone

Patient Disposition

Randomization occurred between March 19, 2020 (start of randomization for the overall RECOVERY trial) and June 8, 2020, when randomization to the dexamethasone arm of the RECOVERY trial ceased, as enrolment to the active treatment arm at this point exceeded 2,000 patients.

In the RECOVERY study, a total of 11,303 patients hospitalized with known or suspected COVID-19 were randomized into the trial, and 9,355 (82.7%) were eligible to be randomized to the dexamethasone arm (no compelling indication or contraindication to dexamethasone and the hospital had the available study drug). There were 1,948 (17.2%) patients who were not eligible to be randomized to dexamethasone (patients could have more than one reason); 357 of 11,303 (3.2%) were not in hospitals with available dexamethasone, and 1,701 of 11,303 (15.1%) were not considered to be suitable for randomization to dexamethasone, although further details were not reported. There were 6,425 out of 11,303 (56.8%) patients who were randomized to the dexamethasone arm. Of these, 2,104 were randomized to dexamethasone plus the usual standard of care and 4,321 were randomized to the usual standard of care alone. The remaining 2,930 of the 11,303 (25.9%) were randomized to other therapies. Complete 28-day follow-up form data were available for a total of 98.8% who were randomized to dexamethasone plus the usual standard of care and 99% in the usual standard of care alone group. Overall, follow-up information was available for 6,418 of the 6,425 (99.9%) randomized patients.

Details of the patient disposition are presented in Table 1.

Table 1: Patient Disposition

	Usual standard of care plus dexamethasone	Usual standard of care
Randomized to the RECOVERY trial, N	11,303	
Eligible to be randomized to dexamethasone, N (%)	9,355 (82.7%)	
Randomized to dexamethasone plus usual standard of care or usual standard of care alone	2,104	4,321
Follow-up forms received (28 day)	2,079 (98.8%)	4,278 (99.0%)
Received dexamethasone (treated), N (%)	1,975/2,079 (95.0%)	336/4,278 (7.8%)
Discontinued from study		
Reason for discontinuation, N (%)		
Consent withdrawn	1 (0.04%)	6 (0.14%)
Intention to treat, N	2,104	4,321

Baseline Characteristics

The mean age overall was 66.1 years and the mean age in the dexamethasone group was older than those in the usual care group (66.9 years versus 65.8 years, respectively). As a result of this discrepancy in age between the dexamethasone and the usual standard of care groups, age-adjusted results were reported. Patients receiving invasive mechanical ventilation were younger (mean age 59.1 years) than those receiving no oxygen (mean age 69.4 years) or oxygen only (mean age 66.7 years).

At randomization,16% were receiving invasive mechanical ventilation, 60% were receiving oxygen only (with or without non-invasive ventilation including continuous positive airway pressure and high flow nasal oxygen), and 24% were receiving no oxygen.

There were six pregnant women included in the trial, although the patients are not described further. There was the same proportion of males (64%) in each arm; however, there were more males (73%) in the group receiving invasive mechanical ventilation and fewer males in those receiving no oxygen (58%) relative to those receiving oxygen only (63%). The median time of symptom onset to randomization was similar in each group, and the median duration of hospitalization to randomization was two days in both groups. Overall, 56% of patients had at least one comorbidity, 24% had diabetes, 27% had heart disease, and 21% had chronic lung disease. There were slightly more patients receiving the usual standard of care than dexamethasone with the usual standard of care who had comorbid chronic lung disease (22% and 20%, respectively).

Overall, 89% of study patients had laboratory-confirmed SARS-COV-2 infection.

A total of 95% of usual standard of care plus dexamethasone and 8% of usual standard of care patients received dexamethasone. The most common concurrent therapy that was reported was azithromycin; 24% of usual standard of care plus dexamethasone patients and 25% of usual standard of care patients received azithromycin.

The median number of treatment days was seven, (interquartile range three to 10 days). Adherence to therapy was not reported. The distribution of oral versus IV dexamethasone was not reported.

Details of the baseline characteristics according to treatment group and the subgroups of respiratory support at randomization are reported in Table 2 and Table 3.

Table 2: Baseline Characteristics

Characteristic	Treatment group		Respiratory support		
	Usual standard of care plus dexamethasone N = 2,104	Usual standard of care N = 4,321	No oxygen N = 1,535	Oxygen only[a] N = 3,883	Invasive mechanical ventilation N = 1,007
Mean age (SD), years	66.9 (15.4)	65.8 (15.8)	69.4 (17.5)	66.7 (15.3)	59.1 (11.4)
Age group, N (%)					
< 70 years	1,141 (54)	2,504 (58)	659 (43)	2,148 (55)	838 (83)
70 years to 80 years	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥ 80 years	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Male, N (%)	1,338 (64)	2,749 (64)	891 (58)	2,462 (63)	734 (73)
Number of days since symptom onset, median (interquartile range)	8 (5 to 13)	9 (5 to 13)	6 (3 to 10)	9 (5 to 12)	13 (8 to 18)
Number of days since hospitalization, median (interquartile range)	2 (1 to 5)	2 (1 to 5)	2 (1 to 6)	2 (1 to 4)	5 (3 to 9)
Respiratory support, N (%)					
No oxygen	501 (24)	1,034 (24)	1,535 (100)	0 (0)	0 (0)
Oxygen only[a]	1,279 (61)	2,604 (60)	0 (0)	3,883 (100)	0 (0)
Invasive mechanical ventilation	324 (15)	683 (16)	0 (0)	0 (0)	1,007 (100)

Characteristic	Treatment group		Respiratory support		
Comorbidities, N (%)					
Diabetes	521 (25)	1,025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1,171 (27)	519 (34)	1,074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (< 1)	19 (< 1)	8 (1)	11 (< 1)	6 (1)
HIV	12 (1)	20 (< 1)	5 (< 1)	21 (1)	6 (1)
Severe liver disease[b]	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment[c]	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
Any aforementioned condition	1,174 (56)	2,417 (56)	911 (59)	2,175 (56)	505 (50)
SARS-Cov-2 test, N (%)					
Positive	1,850 (88)	3,848 (89)	1,333 (87)	3,416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Not yet known	7 (< 1)	20 (< 1)	9 (1)	15 (< 1)	3 (< 1)
Treatments given, n (%)					
Dexamethasone	1,975 (95)	336 (8)			
Lopinavir-ritonavir	2 (< 0.5)	4 (< 0.5)			
Hydroxychloroquine	17 (1)	22 (1)			
Azithromycin	499 (24)	1,082 (25)			
Tocilizumab or sarilumab	43 (2)	128 (3)			
Remdesivir	3 (< 0.5)	2 (< 0.5)			
Not recorded	7 (< 0.5)	12 (< 0.5)			

SD = standard deviation; Sars-COV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Oxygen-only group includes patients receiving non-invasive ventilation (continuous positive airway pressure and high flow nasal oxygen).

[b] Requires ongoing specialist care.

[c] Estimated glomerular filtration rate < 30 mL/min/1.82m^2.

Table 3: Baseline Characteristics By Respiratory Support

	No oxygen		Oxygen only[a]		Invasive mechanical ventilation	
	Usual standard of care plus dexamethasone N = 501	Usual standard of care N = 1,034	Usual standard of care plus dexamethasone N = 1,279	Usual standard of care N = 2,604	Usual standard of care plus dexamethasone N = 324	Usual standard of care N = 683
Mean age (SD), years	71.1 (16.3)	68.5 (18.0)	67.2 (15.2)	66.4 (15.3)	58.8 (11.3)	59.2 (11.5)
Age group, N (%)						
< 70 years	197 (39)	462 (45)	675 (53)	1,473 (57)	269 (83)	569 (83)
70 years to 80 years	114 (23)	224 (22)	306 (24)	531 (20)	49 (15)	104 (15)
≥ 80 years	190 (36)	348 (34)	298 (23)	600 (23)	6 (2)	10 (1)
Male, N (%)	286 (57)	605 (59)	819 (64)	1,643 (63)	233 (72)	501 (73)
Number of days since symptom onset, median (interquartile range)	6 (3 to 10)	7 (3 to 10)	8 (5 to 13)	9 (5 to 12)	13 (9 to 18)	13 (8 to 18)
Number of days since hospitalization, median (interquartile range)	2 (1 to 6)	2 (1 to 5)	2 (1 to 4)	2 (1 to 4)	5 (3 to 10)	5 (3 to 9)
Comorbidities, N (%)						
Diabetes	119 (24)	223 (22)	320 (25)	630 (24)	82 (25)	172 (25)
Heart disease	180 (36)	339 (33)	357 (28)	717 (28)	49 (15)	115 (17)
Chronic lung disease	121 (24)	230 (22)	259 (20)	624 (24)	35 (11)	77 (11)
Tuberculosis	2 (< 0.5)	6 (1)	1 (< 0.5)	10 (< 0.5)	3 (1)	3 (< 0.5)
HIV	2 (< 0.5)	3 (< 0.5)	9 (1)	12 (< 0.5)	1 (< 0.5)	5 (1)
Severe liver disease[b]	13 (3)	19 (2)	20 (2)	52 (2)	4 (1)	11 (2)
Severe kidney impairment[c]	28 (6)	91 (9)	85 (7)	168 (6)	53 (16)	99 (14)
Any aforementioned condition	313 (62)	598 (58)	702 (55)	1,473 (57)	159 (49)	346 (51)
SARS-Cov-2 test, N (%)						
Positive	425 (85)	908 (88)	1,123 (88)	2,293 (88)	302 (93)	647 (95)
Negative	74 (15)	119 (12)	152 (12)	300 (12)	21 (6)	34 (5)
Not yet known	2 (< 0.5)	7 (1)	4 (< 0.5)	11 (< 0.5)	1 (< 0.5)	2 (< 0.5)

SD = standard deviation; Sars-COV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Oxygen-only group includes patients receiving non-invasive ventilation (continuous positive airway pressure and high flow nasal oxygen).

[b] Requires ongoing specialist care.

[c] Estimated glomerular filtration rate < 30 mL/min/1.82m^2.

Efficacy

Primary outcome

The primary outcome of 28-day mortality occurred in 482 of 2,104 (22.9%) of the dexamethasone plus usual standard of care group and 1,110 of 4,321 (25.7%) of the usual standard of care group, an absolute difference of 2.8%. The age-adjusted HR was 0.83 (95% confidence interval [CI], 0.75 to 0.93; P < 0.001). The unadjusted HR was 0.87 (95% CI, 0.78 to 0.97; P = 0.009).

Secondary outcomes

The median duration of hospitalization was 12 days in the dexamethasone plus usual standard of care group and 13 days in the usual standard of care group alone. The percentage of patients discharged within 28 days was 1,413 of 2,104 (67.2%) in the dexamethasone plus usual care group and 2,745 of 4,321 (63.5%) in the usual care group; age-adjusted HR: 1.10 (95% CI, 1.03 to 1.17).

Receipt of invasive mechanical ventilation or death for those not ventilated at randomization occurred in 456 out of 1,780 (25.6%) of the dexamethasone plus usual standard of care group and 994 out of 3,638 (27.3%) of the usual standard of care group (age-adjusted RR, 0.92 [95% CI: 0.84 to 1.01]). The unadjusted analyses are not reported for secondary outcomes.

Exploratory outcomes

Of those who were not ventilated at randomization, the outcome of death occurred in 387 of 1,780 (21.7%) of the dexamethasone plus usual care group and in 827 of the 3,638 (22.7%) of the usual care group (age-adjusted RR, 0.93 [95%:CI: 0.84 to 1.03]). The second component of the composite outcome — receipt of invasive mechanical ventilation in patients who were not ventilated at randomization — occurred in in 102 of 1,780 (5.7%) of the dexamethasone plus usual standard of care group and 285 of 3,638 (7.8%) of the usual standard of care group (age-adjusted RR: 0.77 [95% CI, 0.62 to 0.95]). Other exploratory outcomes including cause-specific mortality, need for renal replacement, major cardiac arrythmia, and duration of ventilation are not reported.

Subgroup analyses

The results of the effect of primary outcome by subgroups are presented in Table 4 and in the included Figure 1 that follows.

Table 4: Effect of Dexamethasone on 28-Day All-Cause Mortality by Subgroups

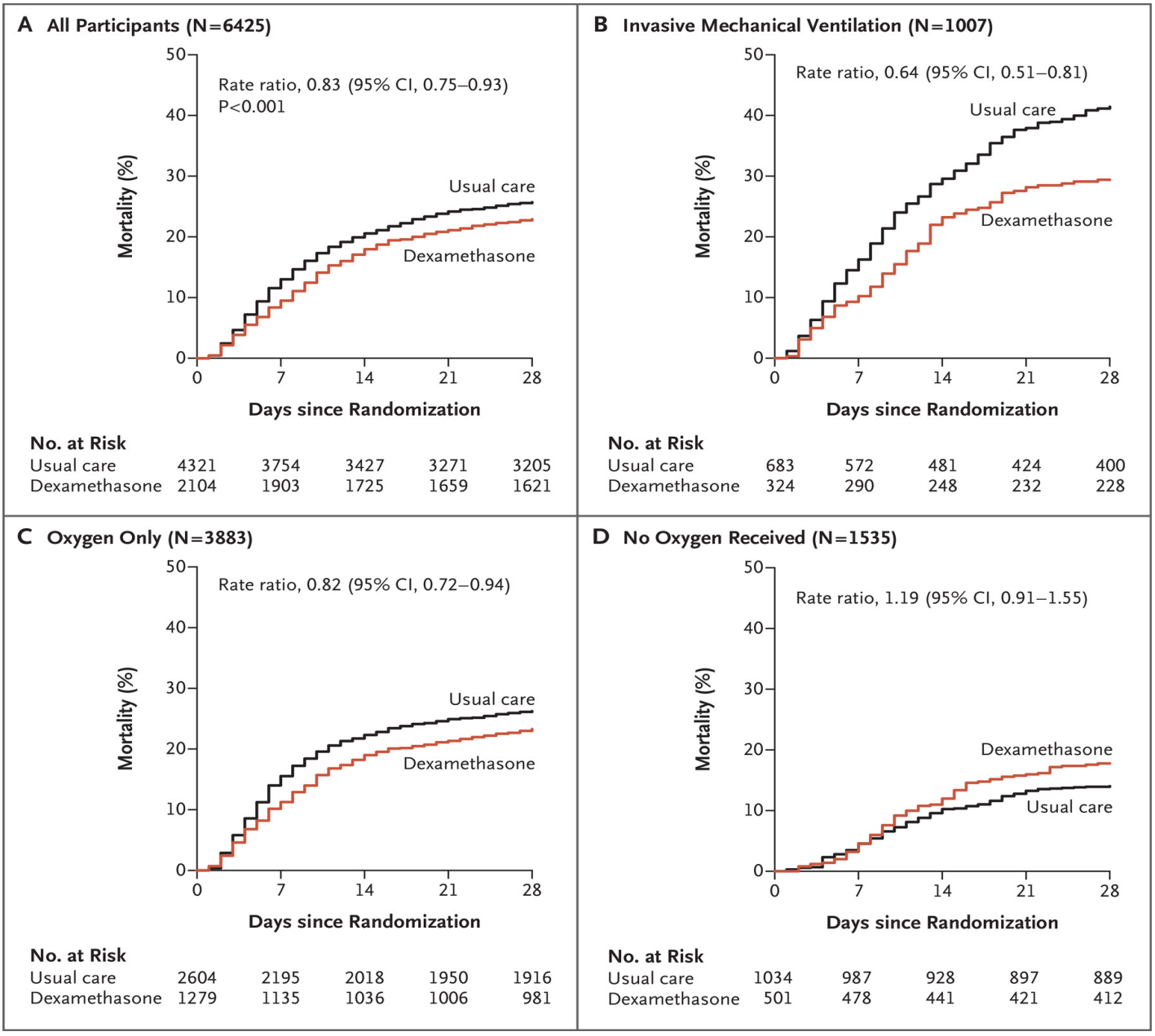
	Treatment allocation		Unadjusted Cox regression	Age-adjusted Cox regression
Subgroup	**Dexamethasone plus usual standard of care (N = 2,104)**	**Usual standard of care (N = 4,321)**	**HR (95% CI)**	**HR (95% CI)**
Respiratory support [a]				
No oxygen N = 1,535	89/501 (17.8)	145/1,034 (14.0)	1.30 (0.99 to 1.71)	1.19 (0.91 to 1.55)
Oxygen only[b] N = 3,883	298/1,279 (23.3)	685/2,604 (26.2)	0.86 (0.75 to 0.99)	0.82 (0.72 to 0.94)
Invasive mechanical ventilation N = 1,007	95/324 (29.3)	283/683 (41.4)	0.67 (0.54 to 0.84)	0.64 (0.51 to 0.81)
Age (chi-squared trend statistic = 4.9; P = 0.03)				
< 70	129/1,141 (11.3)	428/2,504 (17.1)		0.64 (0.53 to 0.78)
70 to 80	155/469 (33.0)	271/859 (31.5)		1.03 (0.84 to 1.25)
≥ 80	198/494 (40.1)	411/958 (42.9)		0.89 (0.75 to 1.05)
Sex (chi-squared trend statistic = 0.9; P = 0.33)				
Male	331/1,338 (24.7)	782/2,749 (28.4)		0.80 (0.71 to 0.91)
Female	151/766 (19.7)	328/1,572 (20.9)		0.90 (0.74 to 1.09)
Days since symptom onset to randomization (chi-squared test = 12.3; P < 0.001)				
≤ 7 days	269/916 (29.4)	500/1,801 (27.8)		1.01 (0.87 to 1.17)
> 7 days	212/1,184 (17.9)	604/2,507 (24.1)		0.69 (0.59 to 0.80)
Baseline risk (chi-squared trend statistic = 0.4, P = 0.51)				
< 30%	150/1,268 (11.8)	377/2,682 (14.1)	0.83 (0.69 to 1.00)	
≥ 30 < 45%	146/464 (31.5)	334/878 (38.0)	0.77 (0.63 to 0.94)	
≥ 45%	186/372 (50.0)	399/761 (52.4)	0.90 (0.76 to 1.07)	

HR = hazard ratio, 95% CI = 95% confidence interval.

[a] The chi-squared trend statistic is 13.1 (P = 0.0003 for) age-unadjusted analysis and the chi-squared trend statistic is 11.5 (P = 0.0007) for the age-adjusted analysis.

[b] The oxygen-only group includes patients receiving non-invasive ventilation (continuous positive airway pressure and high flow nasal oxygen).

Figure 1: Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization



Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

From the New England Journal of Medicine, RECOVERY Collaborative Group, Dexamethasone in hospitalized patients with Covid-19 – preliminary report. [3]

Safety

Adverse effects were not reported in the publication of the dexamethasone arm of the RECOVERY trial.[3]

Critical Appraisal

Internal Validity

The RECOVERY trial used accepted methods for randomization and allocation concealment.

There was an imbalance between the groups in terms of age; patients in the dexamethasone plus usual standard of care group were older (mean age 66.9 years) than the usual care alone group (mean age 65.8 years). This may bias the results in favour of usual care. As a result, the study results are adjusted for age. There was a slight imbalance between the groups in terms of chronic lung disease, with 20% in the dexamethasone plus usual standard of care group and 22% in the usual standard of care group. This may bias the results in favour of dexamethasone. There was a slight imbalance between the groups regarding the SARS-CoV-2 test result, with 12% in the dexamethasone plus usual standard of care group and 10% in the usual standard of care group with a negative SARS-CoV-2 test result. The impact of this imbalance on outcomes is not known. A description of ethnicity (although a planned subgroup analysis) was not reported.

There were no laboratory or quantitative clinical parameters reported as part of the RECOVERY trial; therefore, the balance of groups regarding oxygen saturation levels is not known. The NHS advice for usual oxygen target saturation for prescribed oxygen during the coronavirus pandemic was modified on April 9, 2020 to state that “oxygen prescribing targets for all adults treated in NHS hospitals should be adjusted from the current range (of oxygen saturation 94% - 98%) to oxygen saturation 92% - 96%” and that “a target range of 90% - 94% may be considered if clinically appropriate by hospitals according to prevailing oxygen flow demands.”[5] (Hospitals in Scotland did not specify a target oxygen target saturation.)[4] The impact of this change of practice on the balance of patients between the groups is unknown. An imbalance between the groups is possible based on local practice, available resources for initiation of oxygen therapy, or the evolving practice in treating COVID-19.

Although the receipt of other drugs recorded as part of the RECOVERY trial were balanced between study groups, other usual standard of care supportive medications including, for example, antibiotics or antithrombotic medications were not described. Other non-drug interventions such as prone positioning or other supportive care aspects of usual standard of care were not described. With so many sites in the RECOVERY trial, it is possible that there may have been variation in practice across sites. The impact of such variation in usual standard of care on balance between the groups is not known.

The RECOVERY trial was an open-label trial; thus, patients and the treating clinicians were aware if patients were receiving dexamethasone. The primary study outcome of 28-day all-cause mortality was objective, and knowledge of the treatment received is not expected to affect the results of the primary outcome. It is possible that the secondary outcome of initiation of mechanical ventilation may have been impacted by knowledge of the study treatment in the absence of study protocol criteria for the initiation of mechanical ventilation

and the large number of study sites that may increase practice heterogeneity. It is possible that treating clinicians may have had a lower threshold for initiation of mechanical ventilation for patients receiving usual standard of care alone; however, the likelihood that this outcome would be impacted, and the extent of this potential is unknown. In addition, usual care interventions may have been impacted by knowledge of the study drug administered, although the impact of these interventions on COVID-19 is not known.

The study intervention was 6 mg of dexamethasone given orally or IV. Given that the bioavailability of oral dexamethasone is approximately 80%,[6,7] it is likely that patients who received the oral drug did not receive the same overall exposure to dexamethasone as those who received it intravenously. The frequency of IV versus oral dexamethasone was not reported, so it is unclear whether the route of administration could have influenced the results.

A total of 8% of individuals in the usual standard of care alone group received dexamethasone (the dose was not reported), while 5% in the dexamethasone plus usual standard of care group did not receive dexamethasone. Although this involved only a small number of patients, receipt of dexamethasone outside the randomization may reduce the size of the treatment effect for the trial.

The primary outcome was changed through a protocol amendment from in-hospital mortality to 28-day mortality; however, both are objective outcomes that would not likely be impacted by the open-label nature of the trial design.

There were multiple treatment arms, three possible stages of randomization, and new treatment arms were added as the RECOVERY trial progressed; however, there was no control for type I error for the primary outcome. Additionally, there were multiple secondary outcomes and subgroup analyses; however, there was no control for type I error for these analyses. The statistically significant findings for secondary outcomes and subgroup analyses should be interpreted considering the inflated risk of type I error.

Although Cox proportional hazards models were used to compare the dexamethasone plus usual standard of care and the usual standard of care alone groups for 28-day mortality and duration of hospitalization, it is unclear if the proportional hazards assumption was tested and met, as this was not reported.

The study protocol describes that adverse events data will be collected; however, adverse events were not reported in the publication. Although the duration of therapy with dexamethasone was short and the dose was relatively low, given the age of the patient population and the presence of comorbidities, reporting of dexamethasone-related adverse events, such as hypertension, electrolyte abnormalities, hyperglycemia, neuropsychiatric conditions, venous thromboembolism, or secondary infections would be of interest.[8,9]

External Validity

The RECOVERY trial occurred within the context of the normal health services delivery setting for patients with COVID-19 in the UK, within the NHS.

The distribution of the UK population by ethnicity is not reported. Therefore, it is unclear if the results are generalizable to a Canadian population. There was no information about physiologic, laboratory, or virologic parameters; the impact of these factors on generalizability are unknown.

The RECOVERY trial did not report some baseline comorbidities that may impact the prognosis of COVID-19; for example, cancer, obesity, hypertension, or smoking.[10-15] While these factors may not have been realized at the initiation of the RECOVERY trial, the lack of information regarding these baseline comorbidities may impact the generalizability of the results.

The trial results included 89% of patients with laboratory-confirmed SARS-COV-2 infection. It is unclear if the results are generalizable to patient populations with greater numbers of suspected infection rates and this may vary across settings given availability and rapidity of testing.

Oxygen saturation was not reported in the RECOVERY trial. Available equipment for oxygen therapy may vary according to the size of the hospital or COVID-19 disease burden. There is a potential for some subjectivity around the initiation of oxygen therapy. Both factors may impact the generalizability of the study findings. If the patient disposition is different from what would be expected in Canada, this may limit generalizability to Canadian patients.

Patients receiving invasive mechanical ventilation were, on average, 10.3 years younger than those receiving no oxygen (mean age 59.1 years and 69.4 years, respectively) and, on average, 7.6 years younger than those receiving oxygen, only (mean age 66.7 years). Given the potential for some subjectivity related to the initiation of invasive mechanical ventilation and the potential for this to vary across many study centres,[16,17] it is unclear how this age difference would affect the generalizability of the study findings to countries or settings with different thresholds for invasive mechanical ventilation. In addition, only 2% of those receiving invasive mechanical ventilation were older than 80 years. This may limit the generalizability of findings to patients requiring invasive mechanical ventilation who are very elderly.

Dexamethasone is approved for use in Canada, and the dosing of dexamethasone in the RECOVERY trial is consistent with doses approved by Health Canada.

Details of the usual standard of care are not reported, which may impact generalizability. The impact of any differences in usual standard of care on generalizability to a Canadian setting is not known. As dexamethasone and remdesivir have not, to date, been studied together, the impact of the use of remdesivir on the generalizability of these results is unknown.

The outcome of all-cause mortality is relevant to clinical practice. The duration of follow-up appears to be adequate for an acute illness and 28-day mortality has been used as an outcome in large RCTs of treatments for COVID-19.[18] Longer-term follow-up data are of interest, as 4,158 of 6,425 (64.7%) patients were discharged from hospital within 28 days; the impact of dexamethasone on patients with longer, more complicated hospital stays is not known.

Summary and Conclusions

The RECOVERY trial — a large, open-label, adaptive randomized trial — found that hospitalized patients with COVID-19 in the UK who received dexamethasone experienced reduced 28-day mortality. This outcome was experienced by 482 out of 2,104 (22.9%) in the dexamethasone plus usual care group and 1,110 out of 4,321 (25.7%) in the usual care group (age-adjusted HR: 0.83; 95% CI, 0.75 to 0.93).

Limitations in the statistical analysis — particularly the lack of control for type I error for the analysis of the primary outcome in multiple treatment arms, secondary, and subgroup analyses — limit further interpretation of the RECOVERY trial. Other limitations include the open-label nature of the design and lack of description of the usual standard of care.

The RECOVERY trial is the first large randomized trial of a systemic glucocorticoid for COVID-19. Further RCTs examining systemic glucocorticoids for the treatment of COVID-19 are underway and may impact the interpretation or implementation of these results.

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