Rapid Translation of COVID-19 Preprint Data into Critical Care Practice

To the Editor:

The global coronavirus disease (COVID-19) pandemic has seen a significant increase in the use of preprint services to enable the widespread dissemination of research findings (1). However, whether such facilities influence practice change is currently unknown. Here, we describe the impact of the preprint release and eventual publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (2) on corticosteroid use in clinical practice in Australian ICUs. The RECOVERY trial tested the efficacy of dexamethasone (6 mg by mouth or intravenously for up to 10 d) in hospitalized patients with clinically suspected or confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and demonstrated a reduction in 28-day mortality, particularly in those receiving either mechanical ventilation or oxygen. Before these results, the Australian and New Zealand Intensive Care Society COVID-19 guidelines recommended against the routine use of corticosteroids (3).

SPRINT-SARI (Short Period Incidence Study of Severe Acute Respiratory Infection) Australia is a multicenter, prospective, observational database, with nearly complete coverage of all patients with laboratory-confirmed COVID-19 admitted to the ICU. Seventy-eight ($n = 78$) sites are participating, most of which are tertiary or metropolitan public hospitals, across all states and territories in Australia. Fifty-three ($n = 53$) contributed data to this analysis, including 15 sites with over 20 ICU beds.

A preprint of the RECOVERY trial results was released on June 22, 2020 (4). The final paper was published on July 17, 2020 (2), without any major changes. We compared corticosteroid use in adult patients in the SPRINT-SARI Australia database before preprint, after preprint, and after publication. The percentage of patients receiving corticosteroids per week was calculated as the number of patients receiving this therapy during their hospital stay (any dose or type and for any duration or indication) divided by the total number of patients with COVID-19 admitted to the ICU that week. Differences in proportions, with 95% confidence intervals (95% CIs), are provided. A Fisher exact test was used for comparisons across periods. All analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing).

A total of 461 patients with confirmed COVID-19 were included, from February 27 to November 11, 2020. Baseline characteristics, additional therapies, and clinical outcomes in each time period are shown in Table 1. Most of the patients were male, were overweight, and presented to the hospital with fever, cough, and shortness of breath. Just over half were 60 years of age or older. Mechanical ventilation was used in 37.7% of patients on Day 1 and in 55.3% of patients at any point during the ICU stay. Overall in-hospital mortality was 13.2%. Although illness severity at admission was similar across patients, those admitted in the period before the preprint release were older, more often males, and leaner; received high-flow nasal cannula treatment, noninvasive ventilation, or remdesevir less often; and received hydroxychloroquine more often. The duration of mechanical ventilation and ICU and hospital length of stay were longer in the preprint period, albeit ICU and hospital mortality were similar.

There was an increase in the cumulative number, and in the proportion, of patients receiving corticosteroids after the release of the preprint (Figure 1). For the period prior, corticosteroids were used in 29.5% of patients, which increased to 92.0% after the preprint release (absolute difference, 62.5% [95% CI, 51.3% to 73.6%]; $P < 0.001$). After formal publication of the trial results, 95.8% of patients received corticosteroids, a proportion similar to that observed in the preprint period (absolute difference, 3.8% [95% CI, −5.4% to 13.1%]; $P = 0.275$). Based on the degree of respiratory support at ICU admission, corticosteroid use increased from 4.0% to 66.7%, 7.7% to 100.0%, 35.9% to 100.0%, and 48.6% to 93.1% after the preprint release in those requiring no support, low-flow oxygen, high-flow nasal cannula administration or noninvasive ventilation, and mechanical ventilation, respectively. Corticosteroid use in the post-preprint period increased from 45.2% to 95.8% in centers with 10 or fewer ICU beds, from 28.9% to 88.9% in centers with 11 to 20 beds, and from 25.8% to 96.4% in centers with more than 20 beds.

To our knowledge, this is the first report to quantify the impact of a preprint release on clinical practice across an entire country. More specifically, the RECOVERY preprint findings were widely adopted by ICU clinicians in Australia, leading to significant practice change, with minimal further modification after eventual peer-reviewed publication. It is interesting to speculate whether this was in addition influenced by the widespread availability of this intervention, clinical familiarity, and minimal cost implications. Indeed, although corticosteroids have been extensively studied in critically ill populations (resulting in a well-established safety profile) (5), such rapid adoption of other higher-risk interventions remains a significant cause for concern (6).

It is important to emphasize that many factors are likely to have encouraged the rapid translation of the RECOVERY results into practice in Australia, beyond simply the preprint availability of the data. Indeed, the unique situation of a global viral pandemic, coupled with the eagerness of clinicians to use therapies for COVID-19 and the size and quality of the RECOVERY trial, are all likely to have hastened this process. To more thoroughly quantify the impact of preprint release, a more detailed assessment, including within other fields of research, is required, but this is beyond the scope of the current report.

We acknowledge the following limitations. First, the type, dose, and duration of corticosteroid therapy were not captured as part of SPRINT-SARI Australia. Second, a detailed description of corticosteroid use in other locations (e.g., the emergency department or general ward) is not possible, although the median duration of

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Table 1. Demographic, Illness Severity, Treatment, and Outcome Characteristics in SPRINT-SARI Australia before and after Preprint Release of the RECOVERY Trial

	Overall (*n* = *461*)	Before Preprint (*n* = *204*)	After Preprint* (*n* = *257*)	*P* Value†
Age, yr	61.0 (51.0–70.0)	63.5 (53.8–72.0)	58.0 (50.0–68.0)	0.002
<60	215 (46.6)	78 (38.2)	137 (53.3)	0.005
60–69	119 (25.8)	56 (27.5)	63 (24.5)	
70–79	105 (22.8)	60 (29.4)	45 (17.5)	
>80	22 (4.8)	10 (4.9)	12 (4.7)	
Sex, M, *n* (%)	295 (64.0)	141 (69.1)	154 (59.9)	0.052
APACHE II	14.0 (10.0–18.0)	14.0 (10.0–18.0)	14.0 (10.0–18.0)	0.970
Days between hospital and ICU admission	0.4 (0.1–2.0)	0.4 (0.1–2.6)	0.3 (0.1–1.5)	0.210
Days of symptoms at hospital admission	6.2 (3.7–9.2)	6.0 (3.4–9.0)	7.0 (4.1–9.3)	0.177
Body mass index, kg/m^2	29.7 (25.6–34.7)	28.8 (24.6–32.2)	30.5 (26.7–35.7)	0.001
Coexisting disorders, *n* (%)				
Diabetes	136 (30.8)	56 (27.5)	80 (33.6)	0.195
Obesity	119 (27.0)	51 (25.0)	68 (28.7)	0.445
Use of ACEi or ARB	91 (20.6)	51 (25.1)	40 (16.8)	0.042
Chronic cardiac failure	66 (14.9)	40 (19.6)	26 (10.9)	0.016
Asthma	60 (13.6)	22 (10.8)	38 (16.0)	0.148
Smoker	55 (12.5)	27 (13.2)	28 (11.9)	0.773
Chronic pulmonary disease‡	33 (7.5)	16 (7.8)	17 (7.1)	0.922
Symptoms, *n* (%)				
Fever	338 (78.2)	165 (85.1)	173 (72.7)	0.003
Cough	308 (71.3)	152 (78.4)	156 (65.5)	0.005
Shortness of breath	318 (73.6)	132 (68.0)	186 (78.2)	0.024
Respiratory support at ICU admission, *n* (%)				
No support	41 (9.8)	26 (14.1)	15 (6.4)	<0.001
Low-flow oxygen	68 (16.2)	39 (21.2)	29 (12.3)	
HFNC and/or NIV	152 (36.3)	39 (21.2)	113 (48.1)	
Invasive mechanical ventilation	158 (37.7)	80 (43.5)	78 (33.2)	
Interventions, *n* (%)				
Drugs				
Antibiotics	392 (91.2)	176 (91.2)	216 (91.1)	0.999
Steroids	288 (66.1)	57 (29.5)	231 (95.1)	<0.001
Hydroxychloroquine	37 (8.6)	35 (18.3)	2 (0.8)	<0.001
Oseltamivir	1 (0.2)	1 (0.5)	0 (0.0)	0.913
Lopinavir–ritonavir	13 (3.0)	9 (4.7)	4 (1.7)	0.125
Remdesevir	134 (29.1)	2 (1.0)	132 (51.4)	<0.001
Organ support§				
Mechanical ventilation	247 (55.3)	119 (58.3)	128 (52.7)	0.270
Inotropic or vasopressor	224 (52.6)	111 (57.2)	113 (48.7)	0.098
Neuromuscular blocking agent	169 (39.5)	86 (44.3)	83 (35.5)	0.077
HFNC	261 (60.7)	83 (42.8)	178 (75.4)	<0.001
Prone positioning	146 (34.2)	56 (28.9)	90 (38.6)	0.044
Renal replacement therapy	45 (10.5)	25 (12.9)	20 (8.6)	0.199
NIV	52 (12.2)	14 (7.2)	38 (16.4)	0.006
Other cardiac procedures	22 (5.1)	12 (6.2)	10 (4.3)	0.502
Tracheostomy	33 (7.7)	13 (6.7)	20 (8.6)	0.587
Inhaled nitric oxide	27 (6.3)	13 (6.7)	14 (6.0)	0.917
Extracorporeal membrane oxygenation	12 (2.8)	1 (0.5)	11 (4.7)	0.021
Clinical outcomes				
Duration of ventilation, d	10.0 (5.0–16.0)	12.0 (7.0–14.0)	8.0 (4.0–17.0)	0.020
ICU length of stay, d	6.7 (2.8–15.6)	8.0 (3.1–18.0)	6.0 (2.5–11.6)	0.006
Truncated at extraction, d	6.8 (2.8–15.8)	8.0 (3.1–18.0)	6.0 (2.6–12.7)	0.015
Hospital length of stay, d	15.1 (8.6–25.6)	17.2 (8.8–30.2)	14.3 (8.6–21.4)	0.029
Truncated at extraction, d	15.1 (8.9–26.7)	17.3 (8.9–30.5)	14.8 (8.9–23.1)	0.114
ICU mortality, *n* (%)	57 (12.4)	30 (14.7)	27 (10.5)	0.223
Hospital mortality, *n* (%)	61 (13.2)	30 (14.7)	31 (12.1)	0.488

Definition of abbreviations: ACEi = angiotensin-converting enzyme inhibitor; APACHE = Acute Physiology and Chronic Health Evaluation; ARB = angiotensin II receptor blocker; COVID-19 = coronavirus disease; HFNC = high-flow nasal cannula; NIV = noninvasive ventilation; RECOVERY = Randomised Evaluation of COVID-19 Therapy; SPRINT-SARI = Short Period Incidence Study of Severe Acute Respiratory Infection.
Data are shown as the median (quartile 25% to quartile 75%) or *n* (%). Percentages may not total 100 because of rounding.
*Including the period after final publication
†*P* values from Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables.
‡Not considering asthma.
§Assessed daily until ICU discharge.

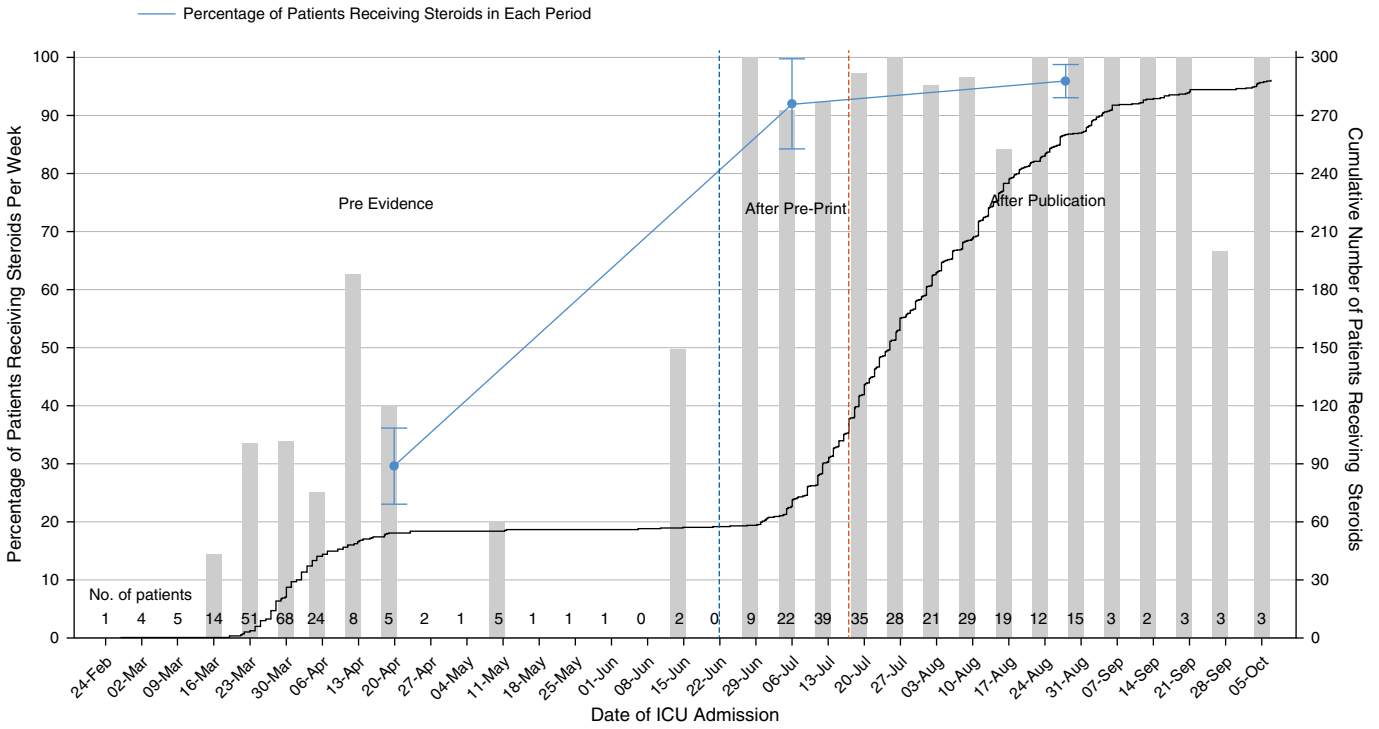

Figure 1. Patients receiving corticosteroids over time in Australian ICUs. The black line represents the cumulative number of patients receiving corticosteroids over time. The blue line represents the percentage (95% confidence interval) of patients receiving corticosteroids before any evidence was available (earlier than June 22, 2020), after the preprint release (between June 22, 2020, and July 17, 2020), and after the peer-reviewed publication (after July 17, 2020). The gray bars are the percentage of patients receiving corticosteroids per week. The number of patients with coronavirus disease (COVID-19) admitted to the ICU each week is reported along the *x*-axis. The total number of COVID-19 cases impacts the cumulative count in the post-preprint and postpublication time periods and should be taken into consideration when interpreting this figure. Pre = before preprint release.

hospitalization before ICU admission was 0.4 days (Table 1). Finally, the indication for corticosteroid therapy was not captured, and the subgroup receiving no respiratory support at ICU admission was small ($n = 15$, Table 1), which limits our ability to assess whether the RECOVERY findings were "overgeneralized."

In conclusion, preprint release of the RECOVERY trial findings led to an almost immediate dramatic change in corticosteroid use in critically ill patients with COVID-19 across Australia. Although the rapid translation of medical evidence is beneficial in cases in which the intervention is of proven benefit, preprint release of trial findings before peer review creates a risk of inappropriate global translation. Fortunately, in this scenario, independent findings from other research groups identified a similar result (7), and potentially thousands of critically ill patients with COVID-19 were advantaged globally through the rapid dissemination of these results. ■

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High Prevalence of Pulmonary Sequelae at 3 Months after Hospital Discharge in Mechanically Ventilated Survivors of COVID-19

To the Editor:

Severe coronavirus disease (COVID-19) is characterized by acute hypoxemic respiratory failure, usually with extensive consolidations and areas with ground glass on chest computed tomographic (CT) scans (1). Whether long-term respiratory sequelae persist in survivors of severe COVID-19 remains to be established. This report describes our findings of respiratory outcomes in mechanically ventilated survivors of COVID-19 at 3 months after hospital discharge.

Methods

We recorded clinical and follow-up data of all patients with COVID-19 treated at our ICU in the Maastricht Intensive Care COVID cohort (registered in the Netherlands Trial Register [NL8613]) (2). The institutional review board of Maastricht University Medical Center+ approved the study, and informed consent was obtained (METC2020–2287). During admission, ventilator strategies included lung-protective ventilation ($V_T \leq 6$ ml/kg) and positive end-expiratory pressure titration using electrical impedance tomography. Prone positioning was considered when the Pa_{O_2}/FI_{O_2} ratio was less than 112.5 mm Hg (15 kPa) and maintained for at least 12 hours.

At 3 months after hospital discharge, survivors were screened at a multidisciplinary post-ICU outpatient clinic for respiratory outcomes with pulmonary function testing (PFT), including spirometry, lung volumes, and diffusing capacity for carbon monoxide adjusted for Hb, chest high-resolution CT (HRCT) imaging, and 6-minute-walk test (6-MWT). Two experienced radiologists systematically scored chest HRCT scans for the presence of pulmonary abnormalities, including ground-glass opacifications, reticulation, consolidations, bronchiectasis, atelectasis, presence of new emphysema, cystic changes, air trapping, extent of lobe involvement, and total lung involvement. The extent of lobe involvement was visually scored on a 0–5 scale, as follows: 0 = no involvement, 1 = 1–5%, 2 = 6–25%, 3 = 26–50%, 4 = 51–75%, and 5 = >75% involvement (3). The CT Severity Score (CTSS) was calculated by adding the lobar scores. HRCT scans were compared with scans performed at presentation ($n = 33$) at the emergency department or during admission ($n = 5$), depending on availability. All data are presented as median (interquartile range [IQR]). Correlations between CTSS, PFT results, and 6-MWT were assessed using Spearman's rank correlation.

Results

During the first European pandemic wave between March and May 2020, the Maastricht Intensive Care COVID cohort included 94 patients. Fifty-two (55%) patients were alive 3 months after hospital discharge, and 48 of them (92%) participated in the follow-up clinic. The four missing patients attended follow-up elsewhere. Follow-up (IQR) occurred at a median of 120 (103–135) days after intubation and 90 (80–99) days after hospital discharge. Baseline characteristics are detailed in Table 1.

We found diminished TLC and diffusion capacity in 23 and 36 participants, respectively, but no airway obstruction on PFT (Table 1), whereas five participants had no abnormalities. The median 6-MWT result was 482 m (82% of predicted distance). Two participants were on home supplemental oxygen, and four participants experienced a significant saturation drop during this test (>4% drop).

Only two participants had no signs of COVID-19–related abnormalities at follow-up HRCT scan. HRCT scans showed ground-glass opacities in 89% ($n = 41$) of cases. Signs of reticulation, including course fibrous bands either with or without obvious parenchymal distortion, bronchiectasis, and bronchiolectasis, were seen in 67% ($n = 31$) of cases and were

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