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Temporal Improvements in COVID-19 Outcomes for Hospitalized Adults: A Post Hoc Observational Study of Remdesivir Group Participants in the Adaptive COVID-19 Treatment Trial

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Background: The COVID-19 standard of care (SOC) evolved rapidly during 2020 and 2021, but its cumulative effect over time is unclear.

Objective: To evaluate whether recovery and mortality improved as SOC evolved, using data from ACTT (Adaptive COVID-19 Treatment Trial).

Design: ACTT is a series of phase 3, randomized, double-blind, placebo-controlled trials that evaluated COVID-19 therapeutics from February 2020 through May 2021. ACTT-1 compared remdesivir plus SOC to placebo plus SOC, and in ACTT-2 and ACTT-3, remdesivir plus SOC was the control group. This post hoc analysis compared recovery and mortality between these comparable sequential cohorts of patients who received remdesivir plus SOC, adjusting for baseline characteristics with propensity score weighting. The analysis was repeated for participants in ACTT-3 and ACTT-4 who received remdesivir plus dexamethasone plus SOC. Trends in SOC that could explain outcome improvements were analyzed. (ClinicalTrials.gov: NCT04280705 [ACTT-1], NCT04401579 [ACTT-2], NCT04492475 [ACTT-3], and NCT04640168 [ACTT-4])

Setting: 94 hospitals in 10 countries (86% U.S. participants).

Participants: Adults hospitalized with COVID-19.

Intervention: SOC.

Measurements: 28-day mortality and recovery.

Results: Although outcomes were better in ACTT-2 than in ACTT-1, adjusted hazard ratios (HRs) were close to 1 (HR for recovery, 1.04 [95% CI, 0.92 to 1.17]; HR for mortality, 0.90 [CI, 0.56 to 1.40]). Comparable patients were less likely to be intubated in ACTT-2 than in ACTT-1 (odds ratio, 0.75 [CI, 0.53 to 0.97]), and hydroxychloroquine use decreased. Outcomes improved from ACTT-2 to ACTT-3 (HR for recovery, 1.43 [CI, 1.24 to 1.64]; HR for mortality, 0.45 [CI, 0.21 to 0.97]). Potential explanatory factors (SOC trends, case surges, and variant trends) were similar between ACTT-2 and ACTT-3, except for increased dexamethasone use (11% to 77%). Outcomes were similar in ACTT-3 and ACTT-4. Antibiotic use decreased gradually across all stages.

Limitation: Unmeasured confounding.

Conclusion: Changes in patient composition explained improved outcomes from ACTT-1 to ACTT-2 but not from ACTT-2 to ACTT-3, suggesting improved SOC. These results support excluding nonconcurrent controls from analysis of platform trials in rapidly changing therapeutic areas.

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The COVID-19 pandemic has caused more than 6 million deaths and half a billion cases globally (1). The standard of care (SOC) for patients hospitalized with COVID-19 has evolved rapidly during the pandemic and includes changes in oxygenation practices; airway management; use of prone positioning; anticoagulation practices; and use of antivirals, corticosteroids, and other immunomodulators (2–7). Some of these interventions were implemented after efficacy was determined by large clinical trials, whereas others were based on results of observational cohort studies or extrapolation from other disease states. These interventions have affected the morbidity and mortality of patients with COVID-19, but it is difficult to quantify their cumulative effect as the pandemic progresses.

In the United States, the in-hospital mortality rate for patients with COVID-19 peaked in March and April 2020, then decreased from approximately 20% to 10% by June 2020 (8). Recovery rates also improved during this period (9, 10). In-hospital mortality is associated with

See also:

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Supplement

patient characteristics and hospital factors (10, 11), but adjustment for these factors explains only some of the decrease in the mortality rate over time (10–13). Trends in COVID-19 SOC, including medication use and oxygen supplementation, may further explain the reduction in mortality rates (9).

We analyzed clinical outcome data from 3 sequential cohorts of hospitalized patients in the first 3 stages of ACTT (Adaptive COVID-19 Treatment Trial), which was conducted in multiple countries, with 86% of the participants from the United States (**Supplement Table 1**, available at Annals.org) (14–17). The first 3 stages of ACTT each included a remdesivir group; it was the treatment group in ACTT-1 and the control group in ACTT-2 and ACTT-3 (**Figure 1**). Instead of comparing treatment groups within each stage, we analyzed the 3 remdesivir-only groups from these 3 stages. We compared recovery and mortality between remdesivir cohorts, using trial stage as a proxy for SOC given during that period. Propensity scores were used to balance cohorts on baseline characteristics.

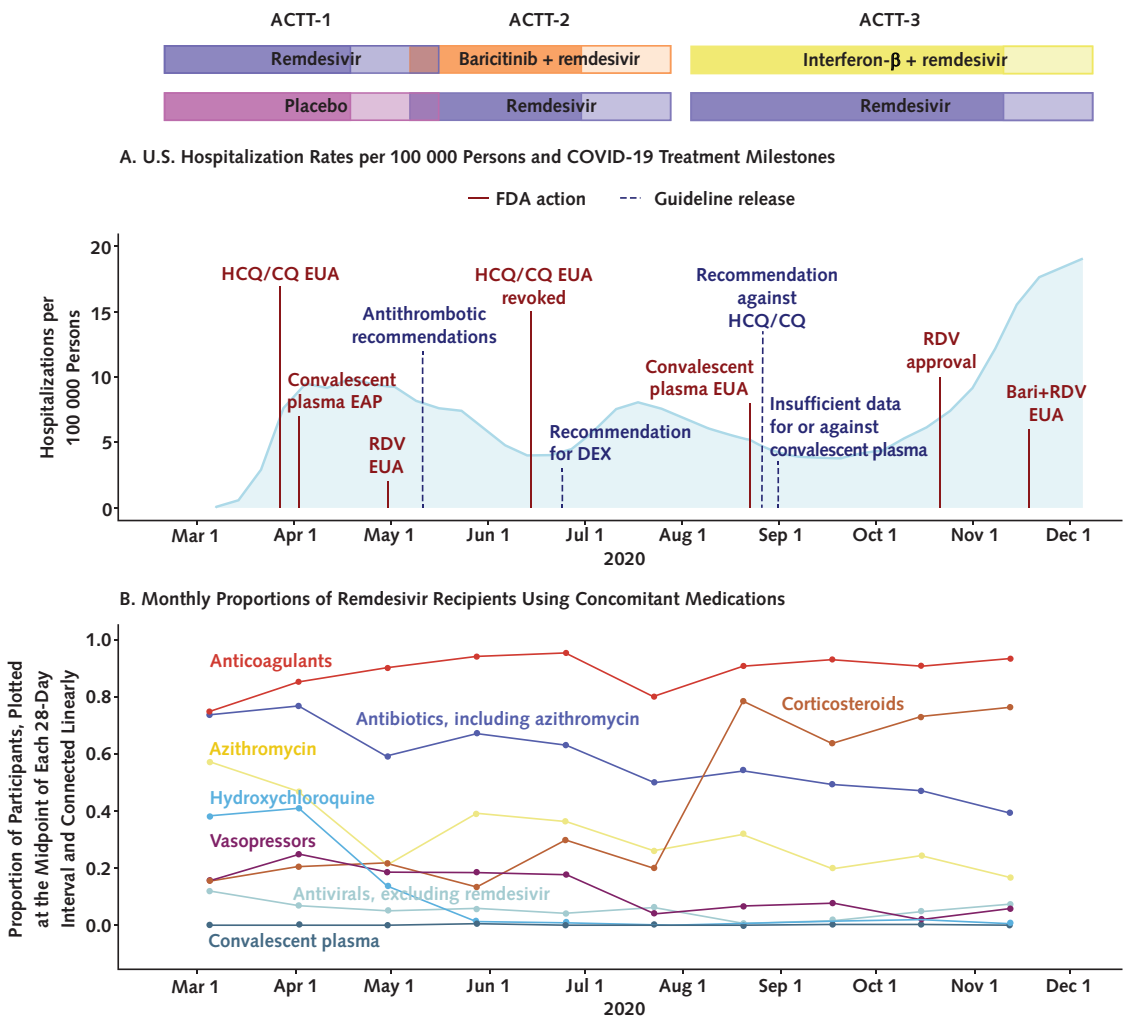
ACTT-4 did not include a remdesivir monotherapy group. A secondary analysis applied the same methods to compare outcomes between participants in the remdesivir-plus-dexamethasone group in ACTT-4 versus remdesivir recipients in ACTT-3 who also received dexamethasone.

METHODS

Data

The ACTT trials were sequential, double-blind, randomized, placebo-controlled trials that evaluated novel investigational therapeutics for the treatment of adults hospitalized with COVID-19. **Figure 1** shows enrollment and follow-up

Figure 1. U.S. hospitalization rates (8) and treatment milestones (*A*) and time trends of concomitant medication use (*B*) in ACTT-1, ACTT-2, and ACTT-3.



Treatment groups and periods of enrollment (*dark colors*) and follow-up after the last enrolled participant (*light colors*) are shown at the top of the figure. The colors of the bars correspond to the treatment groups. Treatment recommendations are from the National Institutes of Health COVID-19 Treatment Guidelines Panel (2). ACTT = Adaptive COVID-19 Treatment Trial; Bari = baricitinib; CQ = chloroquine; DEX = dexamethasone; EAP = Expanded Access Program; EUA = emergency use authorization; FDA = U.S. Food and Drug Administration; HCQ = hydroxychloroquine; RDV = remdesivir.

periods for ACTT-1, ACTT-2, and ACTT-3, whose consecutive remdesivir groups make up our primary analysis population. These stages enrolled approximately 500 people per group (**Supplement Figure 1**, available at Annals.org) and completed follow-up before COVID-19 vaccination began. ACTT-4 compared remdesivir plus baricitinib to remdesivir plus dexamethasone and was included in a secondary analysis (**Supplement Figure 2**, available at Annals.org). The ACTT protocol is available at Annals.org.

Data collected on demographic characteristics, laboratory parameters, baseline disease severity, comorbidities, and concomitant medication use were similar for the 4 stages of ACTT, with additional data added as understanding of COVID-19 evolved and based on the interventions studied in each stage. For example, beginning with ACTT-2, additional data were collected on baseline risk factors, such as history of deep venous thrombosis, pulmonary embolism, and coagulopathy, and more specific data were collected on dexamethasone use for COVID-19 before enrollment. Clinical assessments were performed daily from day 1 through day 29 while patients were hospitalized and at follow-up visits on days 15, 22, and 29 for those who were discharged from the hospital. Disease severity was measured with an 8-category ordinal scale (**Supplement Table 2**, available at Annals.org) and the National Early Warning Score (NEWS) (**Supplement Table 3**, available at Annals.org) (18). Categories of ordinal scale for hospitalized patients are based on oxygen delivery method (**Figure 2**), and a person's value on the scale is their "ordinal score" (OS). Our outcomes are 28-day mortality and 28-day recovery, defined as the day of discharge or the first day of continued hospitalization without a requirement for supplemental oxygen or medical care.

Statistical Analysis

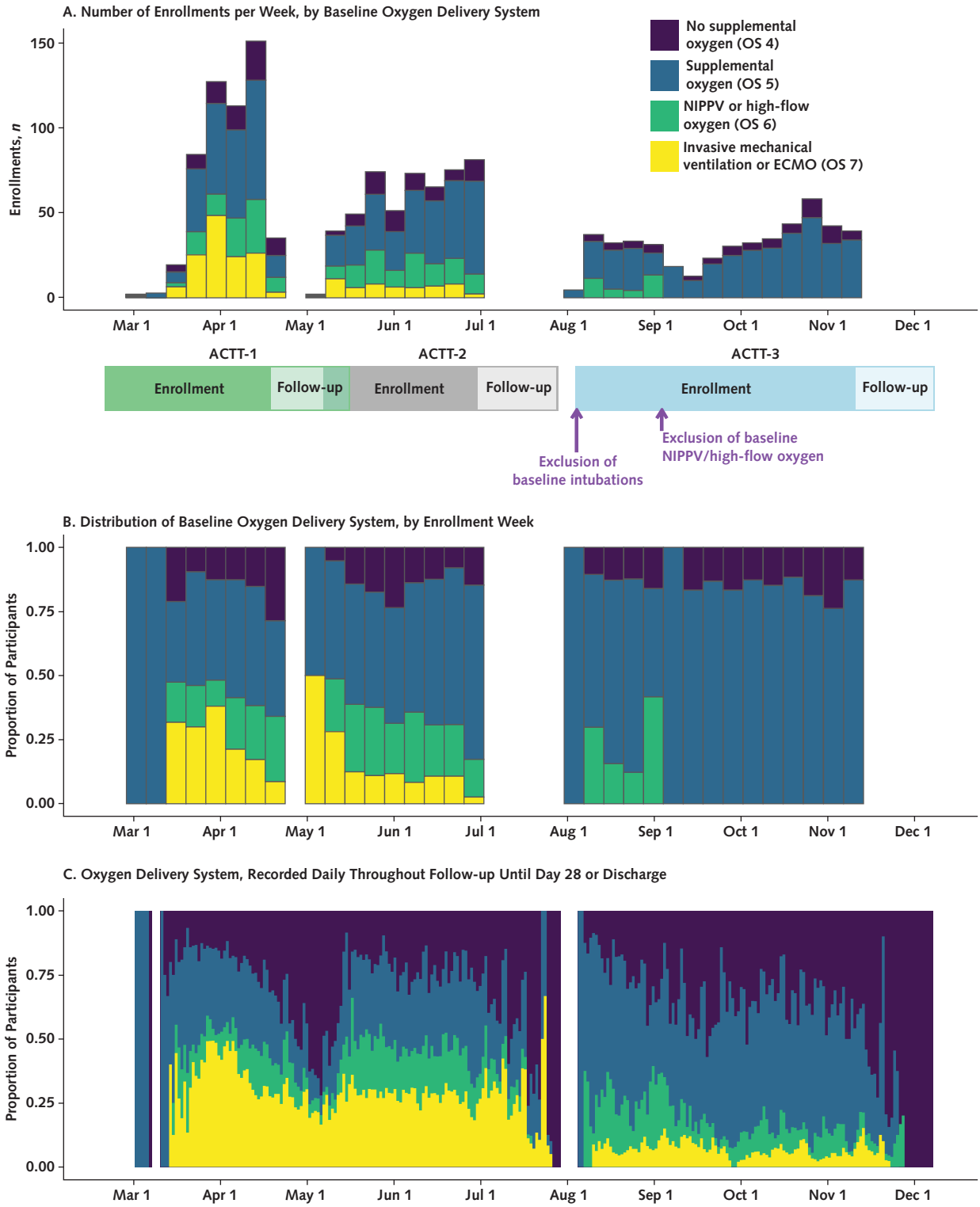
Our primary analysis included participants assigned to receive remdesivir plus SOC in ACTT-1, ACTT-2, and ACTT-3 (**Figure 1**). We used Cox regression to estimate recovery and mortality rates, with trial stage as a categorical predictor variable representing SOC given during that stage. Because we analyzed only remdesivir group participants, the data are effectively observational, as the randomization does not relate to our scientific question. Therefore, we analyzed the "as-treated" population and used propensity score weighting to balance baseline characteristics between cohorts. We followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for observational cohort studies (19). Although ACTT-4 did not include a remdesivir monotherapy group, a secondary analysis compared outcomes between those in the remdesivir-plus-dexamethasone group in ACTT-4 with the 77% of remdesivir recipients in ACTT-3 who also received dexamethasone as part of SOC.

The platform trial was designed to keep inclusion criteria relatively constant across stages, but exclusion criteria could be modified for study product safety considerations, including changes to laboratory thresholds and concomitant medication use. Modifications to stage-specific exclusion criteria were minor, and the proportions of patients who were excluded due to stage-specific exclusion criteria were 1.9% for ACTT-1, 1.6% for ACTT-2, 1.5% for ACTT-3, and 2.7% for ACTT-4 (**Supplement Tables 4** and **5**, available at Annals.org). Modifications to inclusion criteria were minor except for those relating to baseline OS (**Supplement Table 5**): ACTT-3 excluded patients with a baseline OS of 7 and also excluded those with a baseline OS of 6 after a mid-trial review by a data safety monitoring board (**Figure 2**). ACTT-4 included only participants with a baseline OS of 5 or 6. Causal inference with propensity scores requires all participants to have a nonzero probability of falling into any cohort (20). To ensure this, we omitted participants with a baseline OS of 7 when comparing ACTT-2 with ACTT-3 and included only those with an OS of 5 or 6 when comparing ACTT-3 with ACTT-4. We also excluded participants with chronic liver disease (an exclusion criterion for ACTT-3) from comparisons involving ACTT-3. Sensitivity analyses were planned to enforce identical laboratory exclusion criteria across stages (**Supplement Table 5**) and to include only sites participating in both stages for a given comparison.

Covariates were selected for inclusion in the propensity score model on the basis of clinical judgment and are summarized in **Table 1**. As measures of baseline disease severity, we included the NEWS and a modified 4C Mortality Score, a validated score that ranges from 0 to 21 and is based on age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C-reactive protein (CRP) level (**Supplement Tables 3** and **6,** available at Annals.org) (21–30). Because urea level was not recorded systematically in ACTT, our modified scale omits the urea point contributions (+1 for urea level of 7 to 14 mmol/L and +3 for urea level >14 mmol/L), but we included estimated glomerular filtration rate (eGFR) as a separate variable in the propensity score model to account for differences in kidney function. Although most covariates in the propensity score model were missing few data (0% to 2% of participants [**Supplement Table 7**, available at Annals.org]), CRP level was missing for 10% of participants (21% in ACTT-1, 3% in ACTT-2, 3% in ACTT-3, and 2% in ACTT-4). Multiple imputation was performed for missing CRP values. The **Supplement** (available at Annals.org) provides further details on the statistical analysis.

Evolving clinical understanding and external epidemiologic data suggest that intubation practices became more conservative between ACTT-1 and ACTT-2 (31, 32), but precise intubation protocols were not documented for ACTT sites. To estimate a change in intubation practice between ACTT-1 and ACTT-2, we fit a logistic regression model with baseline intubation as the outcome and trial stage as the predictor. The analysis included only patients with a baseline OS of 6 or 7 because we believe that few participants with an OS of 4 or 5 in ACTT-2 would have been intubated at baseline if they had instead contracted COVID-19 during ACTT-1 (**Supplement Figure 3**, available at Annals.org). Propensity scores were used to adjust for baseline characteristics. We modeled baseline intubations rather than time to intubation to prevent confounding from temporal improvements in SOC causing fewer patients to progress to severe illness in ACTT-2 than in ACTT-1. A small amount of confounding could have been introduced by care received between hospitalization and

Figure 2. Oxygen delivery system/OS by day and phase (ACTT-1, ACTT-2, and ACTT-3) for enrolled remdesivir recipients.



Panel A shows weekly enrollments by baseline oxygen delivery system, which corresponds to the OS of disease severity for hospitalized patients. Panel B shows proportions rather than counts to facilitate comparison of OS distributions between stages. Panels A and B show baseline distributions, whereas panel C includes all observations for each participant from enrollment until day 28 or discharge. ACTT = Adaptive COVID-19 Treatment Trial; ECMO = extracorporeal membrane oxygenation; NIPPV = noninvasive positive pressure ventilation; OS = ordinal score.

Table 1. Baseline Characteristics of Analyzed Remdesivir Recipients in ACTT-1 and ACTT-2

Characteristic	Unweighted		Propensity Score–Weighted	
	ACTT-1 (*n* = 492)	ACTT-2 (*n* = 496)	ACTT-1 (*n* = 493)	ACTT-2 (*n* = 497)
Demographic characteristics				
Male sex, *n (%)*	321 (65)	319 (64)	319 (65)	322 (65)
Race, *n (%)*				
American Indian or Alaska Native	3 (1)	8 (2)	4 (1)	8 (2)
Asian	77 (16)	50 (10)	63 (13)	63 (13)
Black or African American	99 (20)	75 (15)	85 (17)	86 (17)
Multiple	2 (0)	0 (0)	3 (1)	0 (0)
Native Hawaiian or other Pacific Islander	2 (0)	7 (1)	2 (0)	7 (1)
Unknown	62 (13)	120 (24)	91 (18)	87 (17)
White	247 (50)	236 (48)	244 (49)	246 (50)
Ethnicity, *n (%)*				
Hispanic or Latino	126 (26)	257 (52)	191 (39)	193 (39)
Not Hispanic or Latino	345 (70)	229 (46)	286 (58)	288 (58)
Not reported/unknown	21 (4)	10 (2)	16 (3)	16 (3)
Mean age (SD), *y*	58.4 (14.7)	55.4 (15.7)	57.5 (29.6)	57.6 (38.6)
Baseline disease severity and risk factors				
Ordinal score, *n (%)*				
4 (hospitalized and not requiring supplemental oxygen)	69 (14)	68 (14)	77 (16)	64 (13)
5 (hospitalized and requiring supplemental oxygen)	216 (44)	266 (54)	233 (47)	248 (50)
6 (hospitalized and requiring NIPPV or high-flow oxygen)	81 (16)	109 (22)	79 (16)	110 (22)
7 (hospitalized and receiving invasive mechanical ventilation or ECMO)	126 (26)	53 (11)	104 (21)	75 (15)
Mean NEWS (SD)	5.6 (3.2)	5.4 (2.8)	5.5 (3.8)	5.5 (4.8)
Mean symptom duration before enrollment (SD), *d*	9.6 (5.7)	8.6 (4.6)	9.2 (5.9)	9.2 (9.2)
Mean symptom duration before hospitalization (SD), *d*	6.9 (5.1)	6.8 (4.4)	6.7 (5.5)	6.7 (6.3)
Mean comorbidities (SD), *n**	1.9 (1.5)	1.8 (1.5)	1.9 (1.9)	1.9 (1.8)
Mean 4C Mortality Score (SD)	8.9 (3.2)	8.1 (3.2)	8.5 (4.6)	8.5 (6.8)
Vital signs				
Mean heart rate (SD), *beats/min*	84.7 (15.5)	83.8 (14.6)	84.1 (39.9)	84.1 (46.2)
Mean oxygen saturation (SD), *%*	93.7 (3.3)	94.2 (3)	94.0 (45)	94.0 (44.4)
Mean respiratory rate (SD), *breaths/min*	23.6 (5.7)	23 (5.7)	23.3 (11.3)	23.3 (14.4)
Mean systolic blood pressure (SD), *mm Hg*	122.7 (19.2)	123.9 (19.1)	123.3 (62.2)	123.3 (61.2)
Mean temperature (SD), *°C*	37.2 (0.8)	37.2 (0.8)	37.2 (17)	37.2 (18)
Geometric mean laboratory parameters (IQR)†				
Alanine aminotransferase, *U/L*	33.6 (20–53.2)	35.3 (23–55)	34.0 (21–53)	34.0 (22–54)
Aspartate aminotransferase, *U/L*	42.4 (29–59)	41.8 (29–57)	41.7 (29–59)	41.7 (29–57)
Bilirubin				
µmol/L	11.2 (6.8–13.7)	9.3 (6.8–12.7)	10.0 (6.8–12.0)	10.1 (6.8–13.7)
mg/dL	0.7 (0.4–0.8)	0.5 (0.4–0.7)	0.6 (0.4–0.7)	0.6 (0.4–0.8)
C-reactive protein, *mg/L*	103.3 (70.9–195.9)	100.1 (62.6–190)	101.6 (71.7–181.1)	101.8 (64.1–195)
eGFR, *mL/min/1.73 m^2*	88.6 (73–107)	90.1 (75–113.8)	89.1 (73–107.2)	89.0 (75–113)
Eosinophil count, *× 10^9/L*	0 (0–0.07)	0 (0–0.04)	0 (0–0.06)	0 (0–0.06)
Proportion of eosinophils among circulating leukocytes	0 (0–0.01)	0 (0–0.007)	0 (0–0.009)	0 (0–0.009)
Hemoglobin, *g/L*	122 (111–139)	128 (119–142)	124 (114–141)	124 (116–140)
Leukocyte count, *× 10^9/L*	6.6 (5.1–8.9)	6.7 (5.1–8.8)	6.7 (5.2–8.9)	6.7 (5.1–9)
Lymphocyte count, *× 10^9/L*	0.9 (0.7–1.3)	1 (0.7–1.4)	1 (0.8–1.4)	1 (0.7–1.4)
Proportion of lymphocytes among circulating leukocytes	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)
Neutrophil count, *× 10^9/L*	4.8 (3.5–7.1)	4.9 (3.4–7.1)	4.9 (3.5–7.1)	4.9 (3.4–7.3)
Proportion of neutrophils among circulating leukocytes	0.7 (0.7–0.8)	0.7 (0.7–0.8)	0.7 (0.7–0.8)	0.7 (0.7–0.8)
Platelet count, *× 10^9/L*	209 (160.8–287)	214.1 (168.8–278)	213 (161.9–289.8)	212.8 (170–278)

ACTT = Adaptive COVID-19 Treatment Trial; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; NEWS = National Early Warning Score; NIPPV = noninvasive positive pressure ventilation.
* Comorbidities include body mass index >30 kg/m^2, diabetes, chronic kidney disease, chronic liver disease, chronic respiratory disease, asthma, chronic oxygen requirement, coronary artery disease, hypertension, congestive heart failure, cancer, and immunodeficiency.
† Geometric means are shown for skewed variables and were log-transformed before balancing.

enrollment, so a sensitivity analysis repeated the model for only those enrolled within 2 days of hospitalization.

Institutional Review Board Approval

The trial protocol was approved by the institutional review board at each site or by a centralized institutional review board as appropriate.

Role of the Funding Source

The ACTT protocols were designed and written by the ACTT investigators and the study sponsor (National Institute of Allergy and Infectious Diseases [NIAID]), with input from the manufacturers of remdesivir (Gilead), baricitinib (Eli Lilly), and interferon-β1a (EMD Serono). Principal investigators and site staff gathered the data, which were

analyzed by statisticians at the statistical and data coordinating center (The Emmes Company) and NIAID. The funder (NIAID) participated in the writing of the manuscript and the decision to submit the manuscript for publication.

RESULTS

Figure 1 shows time trends in use of concomitant medications by remdesivir recipients in ACTT. Enrollment and follow-up periods are distinguished visually because periods with no new enrollments include more participants later in their disease trajectory who tended to have less severe disease. Hydroxychloroquine was used by about 40% of participants each month during ACTT-1, but very little was used in ACTT-2 and ACTT-3. Use of antibiotics in general and azithromycin in particular decreased across the 3 stages. Steroids were not recommended initially because of concerns about worsening viral replication from prior studies of severe acute respiratory syndrome (33). Use of corticosteroids, which were allowed for indications other than COVID-19, was about 20% in ACTT-1 and ACTT-2 and surged to about 70% in ACTT-3. Anticoagulant use (both prophylactic and therapeutic) was high during all 3 stages. Use of antivirals other than remdesivir was generally under 10% and decreased over time.

Table 1 shows unweighted and propensity score–weighted statistical summaries for remdesivir recipients analyzed in ACTT-1 and ACTT-2. Several variables, including age, race, OS distribution, modified 4C Mortality Score, and interval between symptom onset and enrollment, suggest that the ACTT-2 cohort was at lower risk for poor outcomes than the ACTT-1 cohort. ACTT-2 had substantially more Hispanic patients, whose risk profile may differ from that in non-Hispanic patients (34), than ACTT-1 (52% vs. 26%). A "Love plot" (Supplement Figure 4, available at Annals.org) (35) shows excellent balance after weighting. Figure 3 shows propensity score–weighted and unweighted survival curves with hazard ratio (HR) estimates and CIs. The unadjusted recovery rate for ACTT-2 participants was 1.23 times higher than for ACTT-1 participants (95% CI, 1.06 to 1.40). However, the adjusted HR was close to 1 (1.04 [CI, 0.92 to 1.17]), indicating that remdesivir recipients with comparable characteristics had similar recovery rates between ACTT-1 and ACTT-2. Similarly, although the unweighted 28-day mortality rate was estimated to be 0.69 times lower in ACTT-2 than ACTT-1 (CI, 0.45 to 1.04), the weighted HR was closer to the null value of 1 (0.90 [CI, 0.56 to 1.40]).

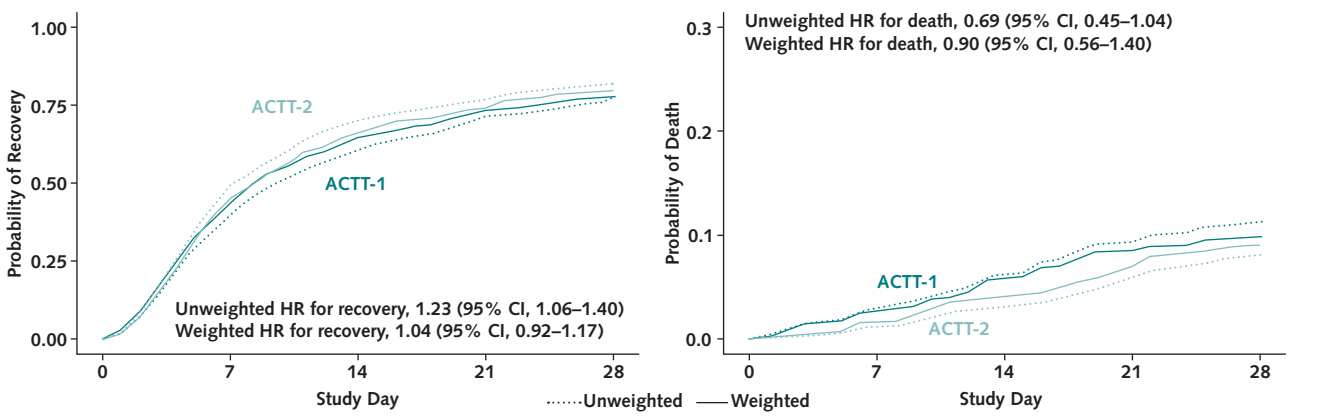
Figure 2 summarizes oxygen delivery systems by day and trial stage for remdesivir participants. For those with a baseline OS of 6 or 7, the unadjusted odds of intubation in ACTT-2 were 0.31 times lower than in ACTT-1 (CI, 0.20 to 0.48). The adjusted odds ratio was 0.75 (CI, 0.53 to 0.97), suggesting a change in practice between stages. Sensitivity analysis results were similar (Supplement Figure 5 and Supplement Table 9, available at Annals.org).

Table 2 shows unweighted and weighted statistical summaries for remdesivir recipients in ACTT-2 and ACTT-3. Although several variables (including race, ethnicity, OS, NEWS, and CRP level) suggest that the ACTT-3 population was at lower risk for poor outcomes, the ACTT-3 population was older (mean age, 59 vs. 55 years). The 2 cohorts were well balanced after weighting (Supplement Figure 6, available at Annals.org). Figure 4 shows survival curves with HR estimates. The adjusted HR for recovery indicates that the recovery rate was 1.43 times higher during the ACTT-3 period than the ACTT-2 period for people with comparable characteristics (CI, 1.24 to 1.64). The 28-day mortality rate in ACTT-3 was 0.45 times that in ACTT-2 for people with comparable characteristics (CI, 0.21 to 0.97).

Supplement Figure 7 and Supplement Table 10 (available at Annals.org) show results from 3 preplanned sensitivity analyses that 1) applied the same laboratory-based eligibility criteria across study stages, 2) included only sites that enrolled participants in both stages being compared, and 3) analyzed only patients with complete baseline data. Results of these analyses are similar to the main results.

Outcomes for recipients of remdesivir plus dexamethasone between ACTT-3 and ACTT-4 were similar (Supplement Figure 8, available at Annals.org). Recovery

Figure 3. Propensity score–weighted and unweighted survival curves for recovery and mortality in ACTT-1 and ACTT-2.



Note that the *y*-axis scale differs between panels. ACTT = Adaptive COVID-19 Treatment Trial; HR = hazard ratio.

Table 2. Baseline Characteristics of Remdesivir Recipients in ACTT-2 and ACTT-3, From an Analysis That Excluded Patients With Chronic Liver Disease and a Baseline Ordinal Score of 7 (Exclusion Criteria for ACTT-3)

Characteristic	Unweighted		Propensity Score–Weighted	
	ACTT-2 (*n* = 428)	ACTT-3 (*n* = 457)	ACTT-2 (*n* = 437)	ACTT-3 (*n* = 466)
Demographic characteristics				
Male sex, *n (%)*	276 (64)	251 (55)	264 (60)	282 (60)
Race, *n (%)*				
American Indian or Alaska Native	6 (1)	3 (1)	4 (1)	3 (1)
Asian	45 (11)	38 (8)	36 (8)	38 (8)
Black or African American	62 (14)	80 (18)	77 (18)	82 (18)
Multiple	0 (0)	3 (1)	0 (0)	2 (0)
Native Hawaiian or other Pacific Islander	5 (1)	5 (1)	5 (1)	6 (1)
Unknown	107 (25)	58 (13)	83 (19)	87 (19)
White	203 (47)	270 (59)	232 (53)	248 (53)
Ethnicity, *n (%)*				
Hispanic or Latino	225 (53)	151 (33)	180 (41)	193 (41)
Not Hispanic or Latino	195 (46)	300 (66)	250 (57)	267 (57)
Not reported/unknown	8 (2)	6 (1)	7 (2)	7 (1)
Mean age (SD), *y*	55 (16)	58.9 (16.1)	57.4 (60)	57.4 (57.8)
Baseline disease severity and risk factors				
Ordinal score, *n (%)*				
4 (hospitalized and not requiring supplemental oxygen)	65 (15)	66 (14)	71 (16)	72 (15)
5 (hospitalized and requiring supplemental oxygen)	260 (61)	361 (79)	302 (69)	325 (70)
6 (hospitalized and requiring NIPPV or high-flow oxygen)	103 (24)	30 (7)	64 (15)	69 (15)
Mean NEWS (SD)	4.8 (2.3)	4.4 (2.1)	4.6 (5)	4.6 (6.1)
Mean symptom duration before enrollment (SD), *d*	8.6 (4.5)	8.6 (4.3)	8.5 (9.2)	8.5 (9.7)
Mean symptom duration before hospitalization (SD), *d*	6.8 (4.4)	7.1 (4.3)	7.0 (8.6)	7.0 (8.3)
Mean comorbidities (SD), *n**	1.8 (1.5)	2.2 (1.6)	2.0 (3.3)	2.0 (2.2)
Mean 4C Mortality Score (SD)	7.7 (3.1)	8 (3)	7.9 (8)	7.9 (9)
Vital signs				
Mean heart rate (SD), *beats/min*	83.5 (14.2)	80 (13.7)	82.0 (68.5)	82.0 (84.9)
Mean oxygen saturation (SD), *%*	94.8 (2.8)	94.3 (2.6)	94.5 (78.2)	94.5 (90.5)
Mean respiratory rate (SD), *breaths/min*	22.1 (5.3)	20.9 (4.5)	21.5 (17.9)	21.5 (23.8)
Mean systolic blood pressure (SD), *mm Hg*	124.9 (18.9)	126.7 (17.7)	125.5 (112.4)	125.5 (117)
Mean temperature (SD), *°C*	37.1 (0.7)	36.8 (0.6)	37.0 (30.9)	37.0 (35.7)
Geometric mean laboratory parameters (IQR)†				
Alanine aminotransferase, *U/L*	35.2 (23–54)	33.3 (21–51)	33.6 (23–53.9)	33.6 (22–52)
Aspartate aminotransferase, *U/L*	41.2 (29–55)	37.9 (27–52)	39.7 (28–54)	39.7 (27.4–56.1)
Bilirubin				
µmol/L	8.9 (6.8–12.0)	8.5 (6.8–12.0)	8.9 (6.8–12.0)	8.9 (6.8–12.0)
mg/dL	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.7)
C-reactive protein, *mg/L*	93.9 (56.7–180.3)	66.9 (45.8–129.6)	75.9 (44.6–168.4)	75.9 (55.2–133.1)
eGFR, *mL/min/1.73 m^2*	92.2 (77–114.8)	85.2 (71–109)	87.6 (71–110)	87.6 (71.9–114)
Eosinophil count, *× 10^9/L*	0 (0–0.03)	0 (0–0.01)	0 (0–0.03)	0 (0–0.01)
Proportion of eosinophils among circulating leukocytes	0 (0–0.007)	0 (0–0.002)	0 (0–0.005)	0 (0–0.002)
Hemoglobin, *g/L*	130 (120–144)	130 (120–145)	130 (121–144)	130 (119–146)
Leukocyte count, *× 10^9/L*	6.4 (4.9–8.2)	6.6 (4.9–9.2)	6.6 (5.1–8.5)	6.6 (5.1–8.6)
Lymphocyte count, *× 10^9/L*	1.1 (0.8–1.4)	0.9 (0.6–1.3)	1 (0.7–1.3)	1 (0.7–1.4)
Proportion of lymphocytes among circulating leukocytes	0.2 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)
Neutrophil count, *× 10^9/L*	4.6 (3.3–6.5)	5 (3.4–7.2)	4.8 (3.5–6.7)	4.8 (3.4–6.8)
Proportion of neutrophils among circulating leukocytes	0.7 (0.7–0.8)	0.7 (0.7–0.8)	0.7 (0.7–0.8)	0.7 (0.7–0.8)
Platelet count, *× 10^9/L*	215.4 (168–276)	218.9 (171–279)	215 (168–275.9)	215 (171.4–273.1)

ACTT = Adaptive COVID-19 Treatment Trial; eGFR = estimated glomerular filtration rate; NEWS = National Early Warning Score; NIPPV = noninvasive positive pressure ventilation.

* Comorbidities include body mass index >30 kg/m^2, diabetes, chronic kidney disease, chronic liver disease, chronic respiratory disease, asthma, chronic oxygen requirement, coronary artery disease, hypertension, congestive heart failure, cancer, and immunodeficiency.

† Geometric means are shown for skewed variables and were log-transformed before balancing.

rates were nearly identical between stages for this group: The unweighted HR was 0.97 (CI, 0.84 to 1.11), and the weighted HR was 1.02 (CI, 0.89 to 1.19). The mortality rate was higher in ACTT-4 than in ACTT-3 (weighted HR, 1.75 [CI, 0.84 to 3.78]), but the CI was wide and these findings did not provide strong evidence of a difference in mortality rates between stages.

DISCUSSION

This study compared 28-day recovery and mortality between comparable cohorts of hospitalized adults with COVID-19 who participated in 4 sequential stages of ACTT spanning February 2020 to May 2021. Although our unadjusted HR estimates describe differences in outcomes between trial stages, the propensity score–weighted

HRs account for changes in patient composition over time and represent a "stage effect" attributed to the SOC received during different stages.

Remdesivir recipients in ACTT-2 (spanning May to July 2020) recovered faster and had numerically better mortality outcomes than those in ACTT-1 (February to May 2020). Observed SOC changes included a dramatic decrease in hydroxychloroquine use between ACTT-1 and ACTT-2 and a gradual decrease in empirical antibiotic use. We also found that the odds of baseline intubation in ACTT-2 were 25% lower than for comparable ACTT-1 participants. However, we did not find evidence that these changes affected 28-day recovery or mortality: Our adjusted HR estimates were close to 1, indicating that the better outcomes in ACTT-2 were due to differences in patient composition rather than improved SOC.

When comparing ACTT-3 (August to December 2020) with ACTT-2, the adjusted analyses showed improved 28-day recovery and mortality, suggesting improved SOC. Given that 77% of remdesivir recipients in ACTT-3 but only 11% in ACTT-2 received dexamethasone as SOC and the RECOVERY trial found a mortality benefit from dexamethasone, dexamethasone use is likely a key contributor to these improvements, although this observational analysis cannot confirm causality (36, 37). Another change in SOC between these stages was a gradual decrease in the use of antibiotics (including azithromycin). The large mortality reduction of 0.45 must be interpreted in the context of its wide CI (0.21 to 0.97), which is consistent with more moderate reductions. A detailed examination suggests low risk of bias from differences in stage-specific laboratory eligibility criteria (**Supplement Table 11**, available at Annals.org).

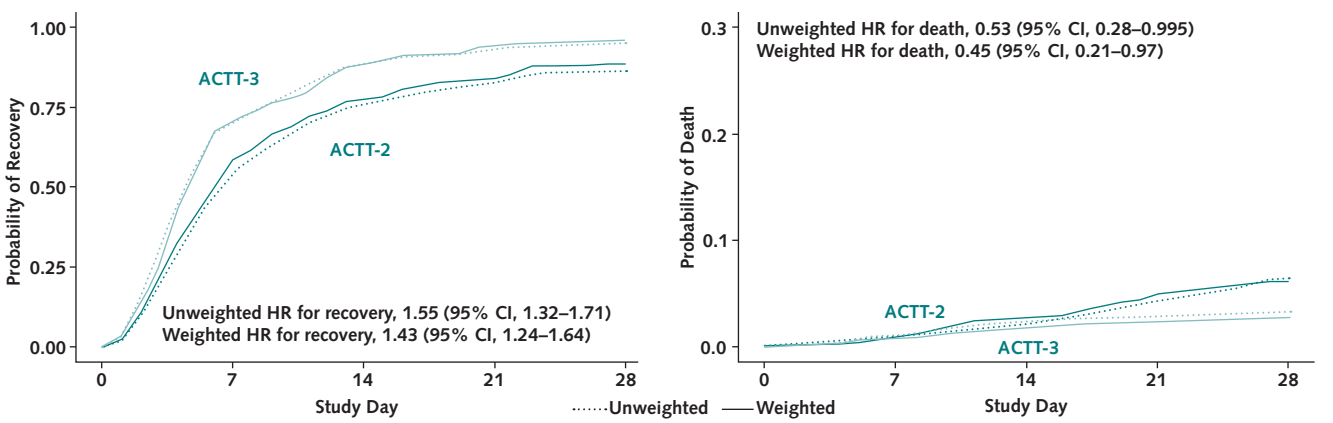
We did not find evidence for improved outcomes between ACTT-3 and ACTT-4 (December 2020 to May 2021) among people receiving remdesivir plus dexamethasone. This may be because concomitant medication use stayed fairly constant between these periods. The use of combination immunomodulatory therapy (dexamethasone plus a Janus kinase inhibitor or an interleukin-6 inhibitor) in patients with the most severe disease did not become part of SOC until March 2021 with the COV-BARRIER and RECOVERY baricitinib and tocilizumab trials (6, 7). Hospitalization rates were higher during ACTT-4 (**Supplement Figure 2**), and COVID-19 surges can stress the hospital system, increasing mortality (38), which could explain the numerically worse mortality outcomes in this stage. The appearance of the B.1.1.7 (Alpha) variant during ACTT-4 could also explain part of this mortality difference (39) (**Supplement Figure 9**, available at Annals.org). ACTT-4 spanned the initial availability of vaccines, but only 25 (0.5%) analyzed ACTT-4 participants were vaccinated, so bias from vaccination is probably low.

This study illustrates several issues related to the inclusion of nonconcurrent controls in analysis of data from platform trials (40–42). Even with similar eligibility criteria across stages, participant composition changed enough over time to substantially affect clinical outcomes. Early in a pandemic of a novel pathogen, patients may be more hesitant to present to a hospital, so those who do may tend to have more severe disease. Similarly, patients may be more hesitant to enroll in a trial of a novel therapeutic unless they are experiencing severe disease. We also found that SOC changed enough over time to substantially affect clinical outcomes for comparable patients.

These analyses also highlight issues related to outcome definitions. Although time to intubation and time to intubation or death have been used as outcome measures in clinical trials (43, 44), we found that intubation practices became more conservative over time. This could make outcomes appear worse for nonconcurrent controls, thus exaggerating the treatment effect. When contemporaneous controls are used, the temporal shift in the relationship between the outcome and the underlying disease severity affects treated and control participants simultaneously and equally.

Time to recovery is also not a purely objective outcome. ACTT participants were defined as having "recovered" when they were discharged from the hospital or if they remained hospitalized without requiring supplemental

Figure 4. Propensity score–weighted and unweighted survival curves for recovery and mortality for the comparison between ACTT-2 and ACTT-3.



This analysis excludes patients with chronic liver disease and a baseline ordinal score of 7, as these were exclusion criteria for ACTT-3. Note that the *y*-axis scale differs between panels. ACTT = Adaptive COVID-19 Treatment Trial; HR = hazard ratio.

oxygen or ongoing medical care. This definition is a proxy for a certain point in the underlying, unobserved, actual disease trajectory. The relationship between this proxy and the actual disease trajectory can vary. As the pandemic progressed, clinicians may have discharged patients earlier in their recovery trajectory, which could artificially inflate a treatment effect in a comparison with nonconcurrent controls. It could also explain part of the improvement in recovery outcomes between ACTT-2 and ACTT-3. Mortality is potentially more objective, although this can depend on varying protocols for withdrawal of care. Furthermore, low death rates mean that very large trials are needed for adequate power to detect a mortality reduction. In addition, treatments that reduce objectively measured symptoms are beneficial even if they do not affect mortality, and objective outcomes are needed to test such treatments.

This study has limitations. First, valid propensity score inference requires inclusion of all confounders in the analysis. Although we included many important confounders, some potential confounders were not measured. In particular, urea level was not recorded in ACTT, and this variable contributes either 1 or 3 points to the 21-point 4C Mortality Score. Our modified scale omitting urea level is therefore less predictive than the complete scale, although we included eGFR as a separate variable to account for differences in kidney function. D-dimer, interleukin-6, and interleukin-10 were not collected across ACTT stages. Another limitation is the restriction of mortality comparisons to a 28-day interval. It is possible that SOC changes between ACTT-2 and ACTT-3 delayed deaths past the 28-day time point without reducing the overall in-hospital mortality rate. However, more people in ACTT-2 were still intubated on day 28 than in ACTT-3 (4% vs. 1% weighted [**Supplement Table 12**, available at Annals.org]), making a reversal of the mortality HR after day 28 unlikely. Improved outcomes may have been influenced by unmeasured time-dependent factors, such as greater clinician bedside experience, although this may be more applicable to the comparison of ACTT-1 versus ACTT-2. COVID-19 surges can increase mortality, but hospitalization rates were higher in ACTT-3 than ACTT-2, which would tend to attenuate the estimated mortality improvement from SOC (average weekly rates were 8.5 and 6.3 per 100 000 persons in ACTT-3 and ACTT-2, respectively [**Figure 1**]). Circulating variants were generally unidentified during 2020 (**Supplement Figure 9**), and their effect on mortality was probably small. This trial mostly enrolled patients at academic research sites; results are generalizable to similar hospitals whose populations resemble the ACTT patient population.

This study analyzed time trends of mortality and recovery for comparable cohorts of hospitalized COVID-19 clinical trial participants and described evolving SOC practices. We found that intubation practice became more conservative between the period from February to May 2020 and the period from May to July 2020 and that improvements in recovery and mortality between these intervals were explained by differences in cohort composition. This contrasts with other studies examining U.S. in-hospital mortality, which found that mortality improvements persisted after patient characteristics were accounted for (10–13). Our mortality rates were lower: The unadjusted rate decreased from 11% to 7%, whereas other studies found a decrease from approximately 20% to 10% (10–13). The difference could be because the hospitals participating in ACTT may have more resources and experience and/or a different learning curve than other hospitals, followed protocol-specified care requirements, or drew a different patient population. We found improved recovery and mortality outcomes between the period from May to July 2020 and the period from August to December 2020, likely due to increased dexamethasone use. We did not find evidence for improvements in recovery or mortality between the period from August to December 2020 and the period from December 2020 to May 2021, possibly because SOC did not change substantially (the use of combination immunomodulatory treatment was implemented later). These findings support the exclusion of nonconcurrent controls when analyzing data from platform trials, particularly for COVID-19 treatments and vaccines.

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Data Sharing Statement: The following data will be made available with publication: deidentified participant data and data dictionary (https://accessclinicaldata.niaid.nih.gov). The following supporting documents will be made available with publication: statistical/analytical code (https://github.com/gepotter/actt1234). To access the data, a data access request (DAR) is required to be submitted to NIAID by the requester using the electronic DAR form as part of the process for requesting access found on the AccessClinicalData@NIAID data platform. The DAR will be reviewed by the NIAID Clinical Trials Data Access Committee. Upon approval of the DAR by NIAID and before accessing the data set, the primary requester and their institutional official will be notified and will be required to agree to and sign an NIAID Data Use Agreement. The agreement outlines the terms of use of the data and can be found on the AccessClinicalData@NIAID data platform.

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References

1. **Johns Hopkins University.** Johns Hopkins University Center for Systems Science and Engineering COVID-19 Dashboard. Accessed at https://coronavirus.jhu.edu on 17 June 2022.

2. **Kuriakose S, Singh K, Pau AK, et al; NIH COVID-19 Treatment Guidelines Panel.** Developing treatment guidelines during a pandemic health crisis: lessons learned from COVID-19. Ann Intern Med. 2021;174:1151-8. [PMID: 34125574] doi:10.7326/M21-1647
3. **Ghelichkhani P, Esmaeili M.** Prone position in management of COVID-19 patients; a commentary. Arch Acad Emerg Med. 2020;8: e48. [PMID: 32309812]
4. **Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators.** Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med. 2021;385:790-802. [PMID: 34351721] doi:10.1056/NEJMoa2105911
5. **Gordon AC, Mouncey PR, Al-Beidh F, et al; REMAP-CAP Investigators.** Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. 2021;384:1491-1502. [PMID: 33631065] doi:10.1056/NEJMoa2100433
6. **Marconi VC, Ramanan AV, de Bono S, et al; COV-BARRIER Study Group.** Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9:1407-18. [PMID: 34480861] doi:10.1016/S2213-2600(21)00331-3
7. **RECOVERY Collaborative Group.** Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637-45. [PMID: 33933206] doi:10.1016/S0140-6736(21)00676-0
8. **Centers for Disease Control and Prevention.** COVID Data Tracker. Accessed at https://covid.cdc.gov/covid-data-tracker/#hospitalizations-severity on 10 June 2022.
9. **Garg S, Patel K, Pham H, et al.** Clinical trends among U.S. adults hospitalized with COVID-19, March to December 2020: a cross-sectional study. Ann Intern Med. 2021;174:1409-19. [PMID: 34370517] doi:10.7326/M21-1991
10. **Roth GA, Emmons-Bell S, Alger HM, et al.** Trends in patient characteristics and COVID-19 in-hospital mortality in the United States during the COVID-19 pandemic. JAMA Netw Open. 2021;4:e218828. [PMID: 33938933] doi:10.1001/jamanetworkopen.2021.8828
11. **Asch DA, Sheils NE, Islam MN, et al.** Variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic. JAMA Intern Med. 2021;181:471-8. [PMID: 33351068] doi:10.1001/jamainternmed.2020.8193
12. **Horwitz LI, Jones SA, Cerfolio RJ, et al.** Trends in COVID-19 risk-adjusted mortality rates. J Hosp Med. 2021;16:90-92. [PMID: 33147129] doi:10.12788/jhm.3552
13. **Moon RC, Mackey RH, Cao Z, et al.** Is coronavirus disease 2019 (COVID-19) less deadly now? Trends in in-hospital mortality among hospitalized COVID-19 patients in the United States. Clin Infect Dis. 2022;74:2238-42. [PMID: 34534276] doi:10.1093/cid/ciab830
14. **Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members.** Remdesivir for the treatment of Covid-19 - final report. N Engl J Med. 2020;383:1813-26. [PMID: 32445440] doi:10.1056/NEJMoa2007764
15. **Kalil AC, Mehta AK, Patterson TF, et al; ACTT-3 study group members.** Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9:1365-76. [PMID: 34672949] doi:10.1016/S2213-2600(21)00384-2
16. **Kalil AC, Patterson TF, Mehta AK, et al; ACTT-2 Study Group Members.** Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384:795-807. [PMID: 33306283] doi:10.1056/NEJMoa2031994
17. **Wolfe CR, Tomashek KM, Patterson TF, et al; ACTT-4 Study Group.** Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. Lancet Respir Med. 2022;10:888-99. [PMID: 35617986] doi:10.1016/S2213-2600(22)00088-1
18. **Smith GB, Prytherch DR, Meredith P, et al.** The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013;84:465-70. [PMID: 23295778] doi:10.1016/j.resuscitation.2012.12.016
19. **von Elm E, Altman DG, Egger M, et al; STROBE Initiative.** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573-7. [PMID: 17938396]
20. **Rosenbaum PR, Rubin DB.** The central role of the propensity score in observational studies for causal effects. Biometrika. 1983; 70:41-55. doi:10.1093/biomet/70.1.41
21. **Wynants L, Van Calster B, Collins GS, et al.** Prediction models for diagnosis and prognosis of Covid-19: systematic review and critical appraisal. BMJ. 2020;369:m1328. [PMID: 32265220] doi:10.1136/bmj.m1328
22. **Miller JL, Tada M, Goto M, et al.** Prediction models for severe manifestations and mortality due to COVID-19: a systematic review. Acad Emerg Med. 2022;29:206-16. [PMID: 35064988] doi:10.1111/acem.14447
23. **van Dam PMEL, Zelis N, van Kuijk SMJ, et al.** Performance of prediction models for short-term outcome in COVID-19 patients in the emergency department: a retrospective study. Ann Med. 2021;53:402-9. [PMID: 33629918] doi:10.1080/07853890.2021.1891453
24. **Knight SR, Ho A, Pius R, et al; ISARIC4C investigators.** Risk stratification of patients admitted to hospital with Covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:m3339. [PMID: 32907855] doi:10.1136/bmj.m3339
25. **Yildiz H, Castanares-Zapatero D, Hannesse C, et al.** Prospective validation and comparison of COVID-GRAM, NEWS2, 4C Mortality Score, CURB-65 for the prediction of critical illness in COVID-19 patients [Letter]. Infect Dis (Lond). 2021;53:640-2. [PMID: 33691577] doi:10.1080/23744235.2021.1896777
26. **Jones A, Pitre T, Junek M, et al; COREG Investigators.** External validation of the 4C Mortality Score among COVID-19 patients admitted to hospital in Ontario, Canada: a retrospective study. Sci Rep. 2021;11:18638. [PMID: 34545103] doi:10.1038/s41598-021-97332-1
27. **Ocho K, Hagiya H, Hasegawa K, et al.** Clinical utility of 4C mortality scores among Japanese COVID-19 patients: a multicenter study. J Clin Med. 2022;11. [PMID: 35160272] doi:10.3390/jcm11030821
28. **Citu C, Gorun F, Motoc A, et al.** Evaluation and comparison of the predictive value of 4C Mortality Score, NEWS, and CURB-65 in poor outcomes in COVID-19 patients: a retrospective study from a single center in Romania. Diagnostics (Basel). 2022;12. [PMID: 35328256] doi:10.3390/diagnostics12030703
29. **Wirth A, Goetschi A, Held U, et al.** External validation of the modified 4C Deterioration Model and 4C Mortality Score for COVID-19 patients in a Swiss tertiary hospital. Diagnostics (Basel). 2022;12. [PMID: 35626285] doi:10.3390/diagnostics12051129
30. **Colombo CJ, Colombo RE, Maves RC, et al.** Performance analysis of the National Early Warning Score and Modified Early Warning Score in the Adaptive COVID-19 Treatment Trial cohort. Crit Care Explor. 2021;3: e0474. [PMID: 34278310] doi:10.1097/CCE.0000000000000474
31. **Sweeney DA, Malhotra A.** Coronavirus disease 2019 respiratory failure: what is the best supportive care for patients who require ICU admission. Curr Opin Crit Care. 2021;27:462-7. [PMID: 34310373] doi:10.1097/MCC.0000000000000863
32. **Doidge JC, Gould DW, Ferrando-Vivas P, et al.** Trends in intensive care for patients with COVID-19 in England, Wales, and Northern Ireland. Am J Respir Crit Care Med. 2021;203:565-74. [PMID: 33306946] doi:10.1164/rccm.202008-3212OC
33. **Hui DS.** Systemic corticosteroid therapy may delay viral clearance in patients with Middle East respiratory syndrome coronavirus infection [Editorial]. Am J Respir Crit Care Med. 2018;197:700-1. [PMID: 29227752] doi:10.1164/rccm.201712-2371ED

34. **Qeadan F, VanSant-Webb E, Tingey B, et al.** Racial disparities in COVID-19 outcomes exist despite comparable Elixhauser comorbidity indices between Blacks, Hispanics, Native Americans, and Whites. Sci Rep. 2021;11:8738. [PMID: 33888833] doi:10.1038/s41598-021-88308-2
35. **Ahmed A, Husain A, Love TE, et al.** Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J. 2006;27:1431-9. [PMID: 16709595]
36. **The RECOVERY Collaborative Group.** Dexamethasone in hospitalized patients with Covid-19 – preliminary report. N Engl J Med. 2020. doi:10.1056/NEJMoa2021436
37. **Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group.** Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704. [PMID: 32678530] doi:10.1056/NEJMoa2021436
38. **Kadri SS, Sun J, Lawandi A, et al.** Association between caseload surge and COVID-19 survival in 558 U.S. hospitals, March to August 2020. Ann Intern Med. 2021;174:1240-51. [PMID: 34224257] doi:10.7326/M21-1213
39. **Davies NG, Jarvis CI, Edmunds WJ, et al; CMMID COVID-19 Working Group.** Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021;593:270-4. [PMID: 33723411] doi:10.1038/s41586-021-03426-1
40. **Lee KM, Wason J.** Including non-concurrent control patients in the analysis of platform trials: is it worth it. BMC Med Res Methodol. 2020;20:165. [PMID: 32580702] doi:10.1186/s12874-020-01043-6
41. **Cohen DR, Todd S, Gregory WM, et al.** Adding a treatment arm to an ongoing clinical trial: a review of methodology and practice. Trials. 2015;16:179. [PMID: 25897686] doi:10.1186/s13063-015-0697-y
42. **Dodd LE, Freidlin B, Korn EL.** Platform trials - beware the non-comparable control group [Letter]. N Engl J Med. 2021;384:1572-3. [PMID: 33882210] doi:10.1056/NEJMc2102446
43. **WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.** A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:e192-e197. [PMID: 32539990] doi:10.1016/S1473-3099(20)30483-7
44. **Bégin P, Callum J, Jamula E, et al; CONCOR-1 Study Group.** Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021;27:2012-24. [PMID: 34504336] doi:10.1038/s41591-021-01488-2

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