Open Forum Infectious Diseases

MAJOR ARTICLE

Unraveling the Treatment Effect of Baricitinib on Clinical Progression and Resource Utilization in Hospitalized COVID-19 Patients: Secondary Analysis of the Adaptive COVID-19 Treatment Randomized Trial-2

Jonathan Fintzi,[1,a] Tyler Bonnett,[2,a] Pablo Tebas,[3] Vincent C. Marconi,[4] Corri B. Levine,[5] Hana M. El Sahly,[6] Susan L. F. McLellan,[5] Constance A. Benson,[7] Christina A. Rostad,[8] Anuradha Ganesan,[9] Nikhil Huprikar,[10] Maria G. Frank,[11] Richard A. Mularski,[12] Robert L. Atmar,[13] Pauline K. Park,[14] William R. Short,[15] John H. Beigel,[16] Aneesh K. Mehta,[17] and Daniel A. Sweeney[18]

[1]Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, Rockville, Maryland, USA, [2]Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA, [3]Division of Infectious Diseases/Clinical Trials Unit, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [4]Emory University School of Medicine and Rollins School of Public Health, Emory Vaccine Center, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia, USA, [5]Division of Infectious Disease, Department of Medicine, University of Texas Medical Branch, Galveston, Texas, USA, [6]Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas, USA, [7]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, La Jolla, California, USA, [8]Division of Infectious Diseases, Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Georgia, USA, [9]Division of Infectious Disease, Walter Reed National Military Medical Center, Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, USA, [10]Division of Pulmonary/Critical Care Medicine, Walter Reed National Military Medical Center, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, [11]Department of Medicine, Denver Health Hospital Authority, Associate Professor of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA, [12]The Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon, USA, [13]Department of Medicine, Baylor College of Medicine, Houston, Texas, USA, [14]Division of Acute Care Surgery, Department of Surgery, University of Michigan, Ann Arbor, Michigan, USA, [15]Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [16]Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, Rockville, Maryland, USA, [17]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA, and [18]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of California, San Diego, La Jolla, California, USA

Background. The Adaptive COVID Treatment Trial-2 (ACTT-2) found that baricitinib in combination with remdesivir therapy (BCT) sped recovery in hospitalized coronavirus disease 2019 (COVID-19) patients vs remdesivir monotherapy (RMT). We examined how BCT affected progression throughout hospitalization and utilization of intensive respiratory therapies.

Methods. We characterized the clinical trajectories of 891 ACTT-2 participants requiring supplemental oxygen or higher levels of respiratory support at enrollment. We estimated the effect of BCT on cumulative incidence of clinical improvement and deterioration using competing risks models. We developed multistate models to estimate the effect of BCT on clinical improvement and deterioration and on utilization of respiratory therapies.

Results. BCT resulted in more linear improvement and lower incidence of clinical deterioration compared with RMT (hazard ratio [HR], 0.74; 95% CI, 0.58 to 0.95). The benefit was pronounced among participants enrolled on high-flow oxygen or noninvasive positive-pressure ventilation. In this group, BCT sped clinical improvement (HR, 1.21; 95% CI, 0.99 to 1.51) while slowing clinical deterioration (HR, 0.71; 95% CI, 0.48 to 1.02), which reduced the expected days in ordinal score (OS) 6 per 100 patients by 74 days (95% CI, −8 to 154 days) and the expected days in OS 7 per 100 patients by 161 days (95% CI, 46 to 291 days) compared with RMT. BCT did not benefit participants who were mechanically ventilated at enrollment.

Conclusions. Compared with RMT, BCT reduces the clinical burden and utilization of intensive respiratory therapies for patients requiring low-flow oxygen or noninvasive positive-pressure ventilation compared with RMT and may thereby improve care for this patient population.

Keywords. clinical progression; COVID-19 therapy; critical care; multistate models; therapeutics.

The Adaptive COVID-19 Treatment Trials (ACTT) were designed in response to the urgent need to test therapeutics for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. ACTT-1 demonstrated that remdesivir shortened recovery time of patients hospitalized with coronavirus disease 2019 (COVID-19) [1]. Secondary analyses revealed that faster recovery was driven by a reduction in incidence of clinical deterioration, particularly among patients who did not require intensive care unit (ICU)–level therapies at baseline [1].

In ACTT-2, the Janus kinase (JAK) 1–2 inhibitor baricitinib in combination with remdesivir (baricitinib combination therapy [BCT]) reduced recovery time and increased the odds of

Received 28 February 2022; editorial decision 19 April 2022; accepted 22 April 2022; published online 27 April 2022

[a]J. F. and T. B. contributed equally to this work.

Correspondence: Jonathan Fintzi, PhD, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Room 4D23, Rockville, MD 20852 (jon.fintzi@nih.gov).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac219

improvement in clinical status at day 15 without increasing serious adverse events compared with treatment with remdesivir monotherapy (RMT) [2]. The decrease in recovery time was modest (a median time to recovery of 7 days for BCT compared with 8 days in the control group), with the largest effect observed in participants treated with high-flow oxygen or noninvasive positive-pressure ventilation (NIPPV) at baseline (median, 10 days for BCT compared with 18 days for control).

In this secondary analysis, we explore how BCT altered the clinical progression of ACTT-2 study participants through the ACTT-2 ordinal scale, which describes their therapy requirements and various demands on hospital resources, such as intensive care nursing and ventilation equipment. We apply a variety of statistical tools, including competing risks and multistate models, to analyze the full clinical trajectories of ACTT-2 study participants and further clarify the effect of BCT on clinical improvement and deterioration. Multistate analyses, in particular, incorporate data on intercurrent events and allow for a more detailed understanding of the dynamics of clinical progression. Our analysis may to help inform treatment guidelines and has implications for ICU resource utilization, which is an increasingly important consideration during periods of hospital strain as patient outcomes become interdependent due to resource constraints.

METHODS

Definitions

The ACTT-2 trial randomized COVID-19 patients at 67 trial sites across 8 countries to treatment with BCT or RMT [2]. This analysis is restricted to the 891 ACTT-2 participants who required any level of supplemental oxygen therapy at baseline (Supplementary Table 1). Participants in ACTT-2 were assessed daily throughout hospitalization using an 8-category ordinal score (OS) scale (Figure 1, with details in the Supplementary Methods). Individual patient trajectories through this scale are depicted in Supplementary Figures 1–3. A participant's score for a given day represented the worst clinical status for that participant during the preceding 24 hours. Participants who reached OS 1, 2, or 3 were considered recovered. To model clinical progression, we combined OS 4 and OS 5 into a single state encompassing standard nonintensive hospital therapy. Figure 1A depicts 2 possible patient trajectories through the ordinal scale used in our analyses.

Descriptive Analyses

We begin our descriptive analysis by graphically depicting the initial clinical progression and final outcomes of study participants as they transition through the ordinal scale, ignoring the timing of state transitions. We also tabulate the incidence of clinical improvement and deterioration relative to baseline, defined by a patient ever reaching an OS of lesser or greater severity than their status at randomization, regardless of their interim or subsequent progression. These events are not exclusive of one another or of eventual recovery or death. As a further descriptive analysis, we summarize the total clinical burden for each patient by the sum of their daily OS levels throughout the study period, assigning a daily value of 1 to OS 1–3, 2 to OS 4–5, 3 to OS 6, 4 to OS 7, and 5 to OS 8, and assess via Wilcoxon-Mann-Whitney U tests whether participants treated with BCT tended to have a lower total burden over the study period [3]. Differences in expected burden are assessed using the Mann-Whitney parameter (MWP)—the probability that a randomly selected participant treated with BCT will have a higher total burden than a randomly selected participant treated with RMT [2]. Additional details of this test are provided in the Supplementary Methods, and sensitivity results from alternative formulations of the total clinical burden score are provided in Supplementary Table 2.

Competing Risks Models

We used competing risk models to estimate the treatment effect on the cumulative incidence of patients who improved or worsened relative to baseline. We assessed the effect of BCT on recovery, death, clinical improvement relative to baseline, and clinical deterioration relative to baseline using Fine-Gray proportional subdistribution hazard models [4]. These models relate the cumulative incidence of each event to the hazard among patients who have not yet experienced that event [5]. We report subdistribution hazard ratios from models fit separately to each baseline OS group, as well as overall estimates from stratified models that allow for separate baseline hazards in each group. Unlike the multistate Markov models (MSMs) described in the next subsection, which consider all observed state transitions, each patient only contributes a single time-to-event observation to each competing risks model. Additional technical details and model diagnostics are provided in the Supplementary Data (Supplementary Figures 4–7).

Multistate Models

We used the modified ACTT ordinal scale and time-inhomogeneous MSMs fit to data from each participant's clinical course to describe the effect of BCT on changes in clinical status leading to improvement and deterioration throughout hospitalization. A key advantage of the MSM approach compared with traditional methods is the ability to incorporate patients' full clinical trajectories, including intercurrent events, which allows for a more detailed understanding of the dynamics of progression. The model structure (Figure 1B) dictates the states between which a patient may directly transition and reflects clinical practices at the time ACTT-2 was conducted. For example, a patient receiving high-flow oxygen would not be discharged without first receiving nonintensive therapy. We only consider data from each participant's initial course

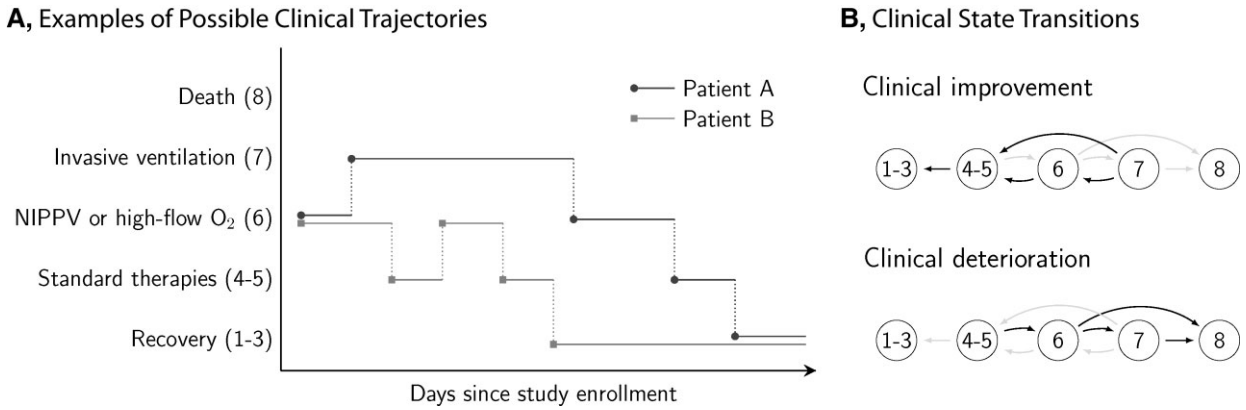

Figure 1. Multistate model for clinical progression in ACTT-2. A, Examples of possible paths through the ACTT-2 OS scale. Both patients A and B are on NIPPV or high-flow oxygen (OS 6) at baseline. A standard time-to-event analysis assesses whether treatment with baricitinib shortens the expected time until the patients enter the recovered state (OS 1–3). The multistate analysis assesses whether treatment with baricitinib alters the dynamics of how patients travel throughout the ordinal scale over the course of the study. B, Multistate model diagrams. Arrows indicate the states between which a patient may transition without first passing through another intermediate state. Note that the data are daily snapshots and that multiple transitions are possible within the same day. The 2 panels correspond to clinical pathways for the treatment effect of baricitinib—clinical improvement and deterioration. The hazard ratios for the treatment effect are assumed to be common to all transitions within each transition group and, hence, describe the overall effects on clinical improvement and clinical deterioration in each baseline ordinal score group. Abbreviations: ACTT-2, Adaptive COVID Treatment Trial-2; NIPPV, noninvasive positive-pressure ventilation; OS, ordinal score.

of hospitalization; hence discharge and death are both absorbing states. The model was fit separately for participants in each baseline OS group. For each group, we report common hazard ratios representing the overall treatment effects on transitions leading to either clinical improvement or deterioration, corresponding to the two groups of transitions highlighted in Figure 1B. We also use our MSMs to estimate the expected days of ICU-level respiratory support over the study period per 100 patients in each baseline OS group. Uncertainty about the treatment effects and expected ICU resource utilization is quantified using bootstrap confidence intervals, with *P* values computed using a rerandomization procedure. Technical details of the model specification and estimation procedures are provided in the Supplementary Data along with model diagnostics (Supplementary Figures 8–11) and sensitivity analyses (Supplementary Figures 12–14).

RESULTS

Participants Receiving Low-Flow Oxygen Therapy at Enrollment – OS 5

The clinical courses of participants receiving low-flow oxygen at baseline (OS 5; n = 564) were consistent with a more direct path to recovery and lower total clinical burden among patients treated with BCT than RMT (MWP, 0.46; 95% CI, 0.41 to 0.51) (Table 1). Incidence of clinical deterioration was lower among patients given BCT (BCT, 22.9% vs RMT, 30.1%; hazard ratio [HR], 0.75; 95% CI, 0.54 to 1.02). Though the majority of participants in baseline OS 5 eventually recovered in both arms (505 of 564), the initial change in clinical status was more often in a positive direction in the BCT arm. More patients receiving BCT exhibited linear improvement (75.0% vs 67.4%), and fewer patients transiently worsened before recovery (Figure 2A; Supplementary Table 3A and B). Our MSM suggests that BCT slowed transitions, resulting in clinical deterioration (HR, 0.78; 95% CI, 0.59 to 1.03) (Figure 2C), albeit the effect was not statistically significant, but BCT had no effect on transitions leading to clinical improvement (HR, 1.06; 95% CI, 0.91 to 1.24). The daily proportion of baseline OS 5 participants on mechanical ventilation appears to be lower throughout the study period (Figure 2B). We estimate that BCT reduced the expected days of high-flow oxygen/NIPPV therapy per 100 patients over the study period by 20 days (95% CI, −2 to 39 days) (Figure 2D; Supplementary Table 3C) compared with RMT and reduced the expected days of mechanical ventilation per 100 patients by 39 days (95% CI, −1 to 84 days).

Participants Receiving High-Flow Oxygen Therapy or NIPPV at Enrollment – OS 6

Participants enrolled on high-flow oxygen or NIPPV (OS 6; n = 216) who received BCT also experienced a more direct path to recovery and had lower total clinical burden compared with participants who received RMT (MWP, 0.40; 95% CI, 0.33 to 0.48). The majority of baseline OS 6 participants recovered (152 of 216). However, participants treated with BCT had lower incidence of clinical deterioration to mechanical ventilation or death (BCT, 30.1%, vs RMT, 41.6%; HR, 0.68; 95% CI, 0.43 to 1.06) (Table 1). Participants treated with BCT were more likely to initially improve as their first transition and less likely to regress after an initial improvement (Supplementary Table 4A and B). Direct recovery and improvement in respiratory

Table 1. Dynamics of Clinical Progression

	Overall		Supplemental Oxygen (5)		Noninvasive Ventilation/High-Flow Oxygen (6)		Invasive Ventilation (7)	
	BCT (n = 445)	RMT (n = 446)	BCT (n = 288)	RMT (n = 276)	BCT (n = 103)	RMT (n = 113)	BCT (n = 54)	RMT (n = 57)
Probability total burden higher for BCT participant								
MWP estimate (95% CI)	0.44 (0.41–0.48)		0.46 (0.41–0.51)		0.40 (0.33–0.48)		0.44 (0.37–0.55)	
Recovery								
No. recovered (%)	365 (82.0)	335 (75.1)	262 (91.0)	243 (88.0)	81 (78.6)	71 (62.8)	22 (40.7)	21 (36.8)
Subdistribution hazard ratio (95% CI)	1.27 (1.10–1.46)		1.21 (1.02–1.43)		1.55 (1.13–2.11)		1.09 (0.60–1.97)	
De-escalation of oxygen therapy or recovery								
No. ever de-escalated relative to baseline (%)	393 (88.3)	363 (81.4)	263 (91.3)	244 (88.4)	91 (88.3)	86 (76.1)	39 (72.2)	33 (57.9)
Subdistribution hazard ratio (95% CI)	1.24 (1.08–1.43)		1.18 (1.00–1.41)		1.41 (1.06–1.88)		1.27 (0.80–2.01)	
Escalation of oxygen therapy or death								
No. ever escalated relative to baseline (%)	109 (24.5)	142 (31.8)	66 (22.9)	83 (30.1)	31 (30.1)	47 (41.6)	Equivalent to death	
Subdistribution hazard ratio (95% CI)	0.74 (0.58–0.95)		0.75 (0.54–1.02)		0.68 (0.43–1.06)			
Death								
No. died (%)	23 (5.2)	36 (8.1)	4 (1.4)	11 (4.0)	7 (6.8)	13 (11.5)	12 (22.2)	12 (21.1)
Subdistribution hazard ratio (95% CI)	0.64 (0.38–1.06)		0.35 (0.11–1.09)		0.54 (0.22–1.34)		1.00 (0.45–2.23)	

Abbreviations: BCT, baricitinib combination therapy; MWP, Mann-Whitney parameter (the probability that a randomly selected participant treated with BCT will have a higher total burden than a randomly selected participant treated with RMT); RMT, remdesivir monotherapy.

therapy requirements followed by recovery accounted for 58.3% of baseline OS 6 participants treated with BCT vs 42.5% of patients given RMT (Figure 3A). The third most common clinical course among baseline OS 6 patients—deterioration to mechanical ventilation with no subsequent change in clinical status over the study period—was more common among patients treated with RMT vs BCT (n = 12, 10.6%, vs n = 5, 4.9%). There was more heterogeneity in clinical trajectories among participants in OS 6 at baseline than those in OS 5, as the 3 most common paths accounted for only 63.2% of participants in the BCT arm and 53.1% of participants given RMT. Our MSM estimated that BCT slowed clinical deterioration (HR, 0.71; 95% CI, 0.48 to 1.02) (Figure 3C) and sped improvement (HR, 1.21; 95% CI, 0.99 to 1.51). The daily proportion of baseline OS 6 participants receiving ICU-level therapies throughout the study period was lower among BCT participants compared with RMT participants (Figure 3B). Based on our MSM, we estimate that BCT reduced the expected days of high-flow oxygen/NIPPV therapy per 100 patients over the study period compared with RMT by 74 days (95% CI, −8 to 154 days) (Figure 3D; Supplementary Table 4C) and the expected days of mechanical ventilation per 100 patients by 161 days (95% CI, 46 to 291 days).

Participants on Invasive Mechanical Ventilation at Enrollment – OS 7

Participants enrolled in OS 7 and treated with BCT did not tend to have lower total burden than baseline OS 7 participants treated with RMT (MWP, 0.44; 95% CI, 0.37 to 0.55). We also did not find evidence that BCT increased incidence of extubation (HR, 1.27; 95% CI, 0.80 to 2.01). Although the proportions of BCT and RMT participants who were initially extubated were comparable, BCT patients regressed less frequently following an initial improvement (Supplementary Table 5A and B). The most common clinical path for participants who were mechanically ventilated at baseline was to remain in OS 7 for the duration of the study (RMT: n = 15, 26.3%; BCT: n = 7, 13%) (Figure 4A). Though the second and third most common paths were both consistent with a linear improvement and eventual recovery, a higher fraction of the BCT participants followed the shorter path of extubation to non-ICU respiratory therapy followed by recovery (BCT: n = 11, 20.4%; RMT: n = 4, 7.0%). The proportion of patients recovered or requiring non-ICU-level therapies at the end of follow-up was only modestly better compared with patients receiving RMT (BCT: n = 30, 56%; RMT: n = 24, 42%) (Figure 4B). In our MSM, BCT was not shown to speed clinical improvement (HR, 1.05; 95% CI, 0.76 to 1.49) or slow clinical deterioration (HR, 0.89; 95% CI, 0.46 to 1.66) among participants in baseline OS 7 (Figure 4C). Correspondingly, we estimate that BCT does not alter expected ICU resource utilization in this group of participants over the study period (Figure 4D; Supplementary Table 5C).

DISCUSSION

In addition to the clinical benefit of baricitinib demonstrated in ACTT-2, treatment with baricitinib in addition to standard of care led to decreased mortality of participants in 3 other trials, COV-BARRIER [6], COV-BARRIER OS7 [7], and RECOVERY [8]. Nonetheless, there is value in further

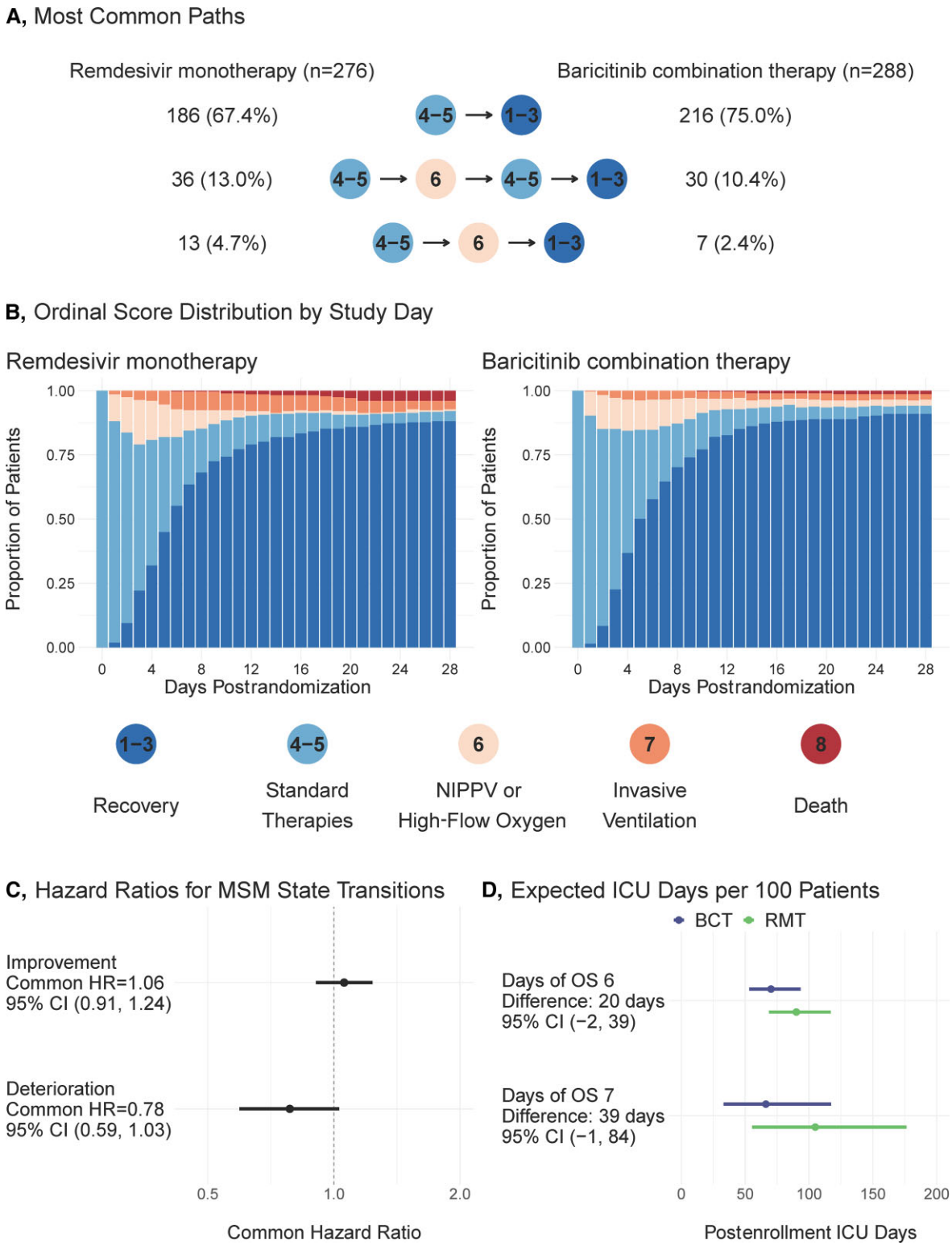

Figure 2. Dynamics of clinical progression – baseline supplemental oxygen (OS 5). A, The per-arm proportions of patients who followed 1 of the 3 most common clinical paths in either arm, considering only the observed sequence of ordinal scores without regard for timing of transitions. B, Stacked proportions of patients in each ordinal score by treatment arm at each day postrandomization. The combined area of bars representing ICU therapies has a direct correspondence to the expected days of ICU therapies required per 100 patients on each arm. C, Common hazard ratios for the overall treatment effect on clinical improvement and deterioration estimated from a multistate model. D, Multistate model estimates of expected utilization of ICU-level respiratory therapies (OS 6 and OS 7) per 100 patients over the study period. Abbreviations: BCT, baricitinib combination therapy; HR, hazard ratio; ICU, intensive care unit; MSM, multistate model; NIPPV, noninvasive positive-pressure ventilation; OS, ordinal score; RMT, remdesivir monotherapy.

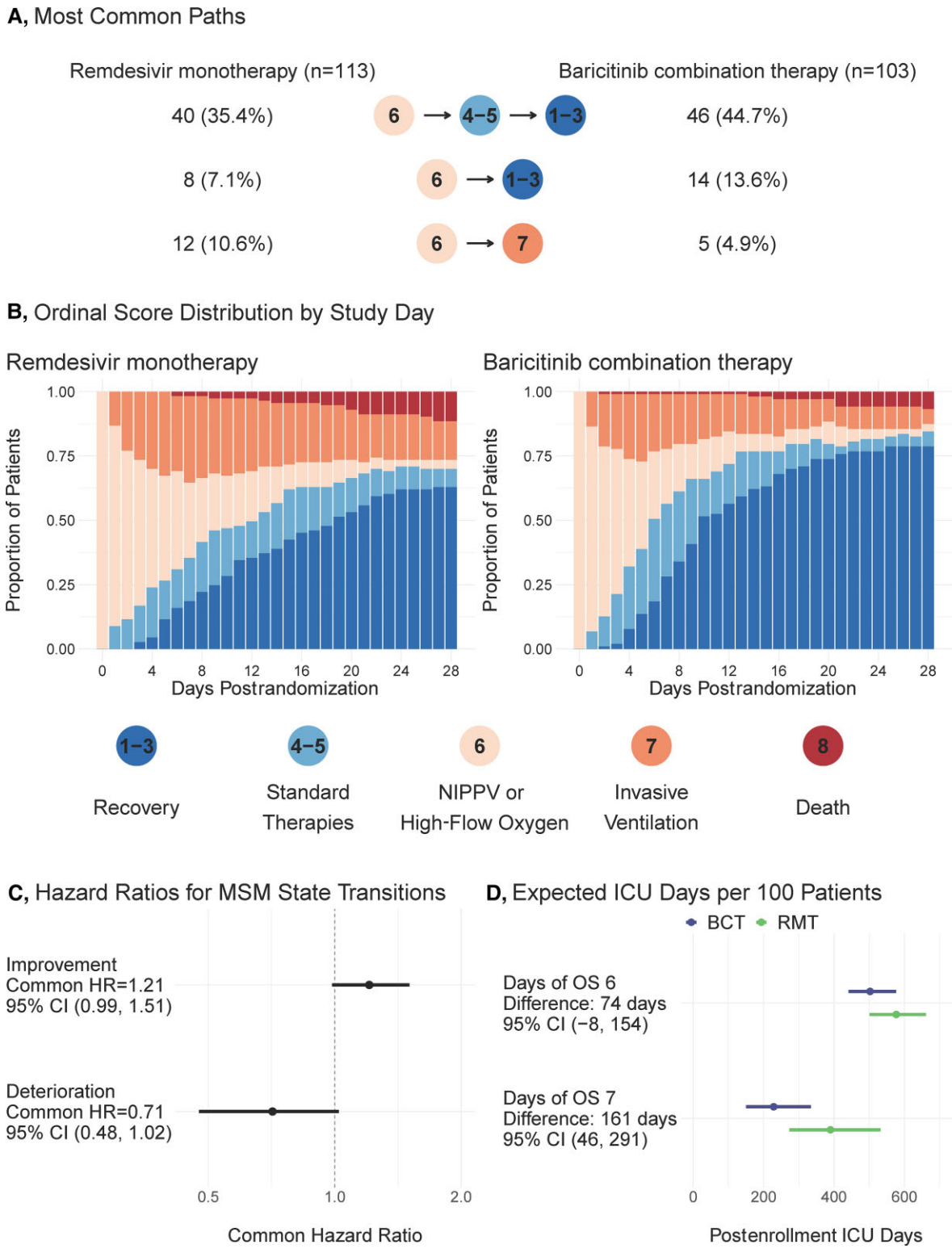

Figure 3. Dynamics of clinical progression – baseline NIPPV or high-flow oxygen (OS 6). A, The per-arm proportions of patients who followed 1 of the 3 most common clinical paths in either arm, considering only the observed sequence of ordinal scores without regard for timing of transitions. B, Stacked proportions of patients in each ordinal score by treatment arm at each day postrandomization. The combined area of bars representing ICU therapies has a direct correspondence to the expected days of ICU therapies required per 100 patients on each arm. C, Common hazard ratios for the overall treatment effect on clinical improvement and deterioration estimated f-rom a multistate model. D, Multistate model estimates of expected utilization of ICU-level respiratory therapies (OS 6 and OS 7) per 100 patients over the study period. Abbreviations: BCT, baricitinib combination therapy; HR, hazard ratio; ICU, intensive care unit; MSM, multistate model; NIPPV, noninvasive positive-pressure ventilation; OS, ordinal score; RMT, remdesivir monotherapy.

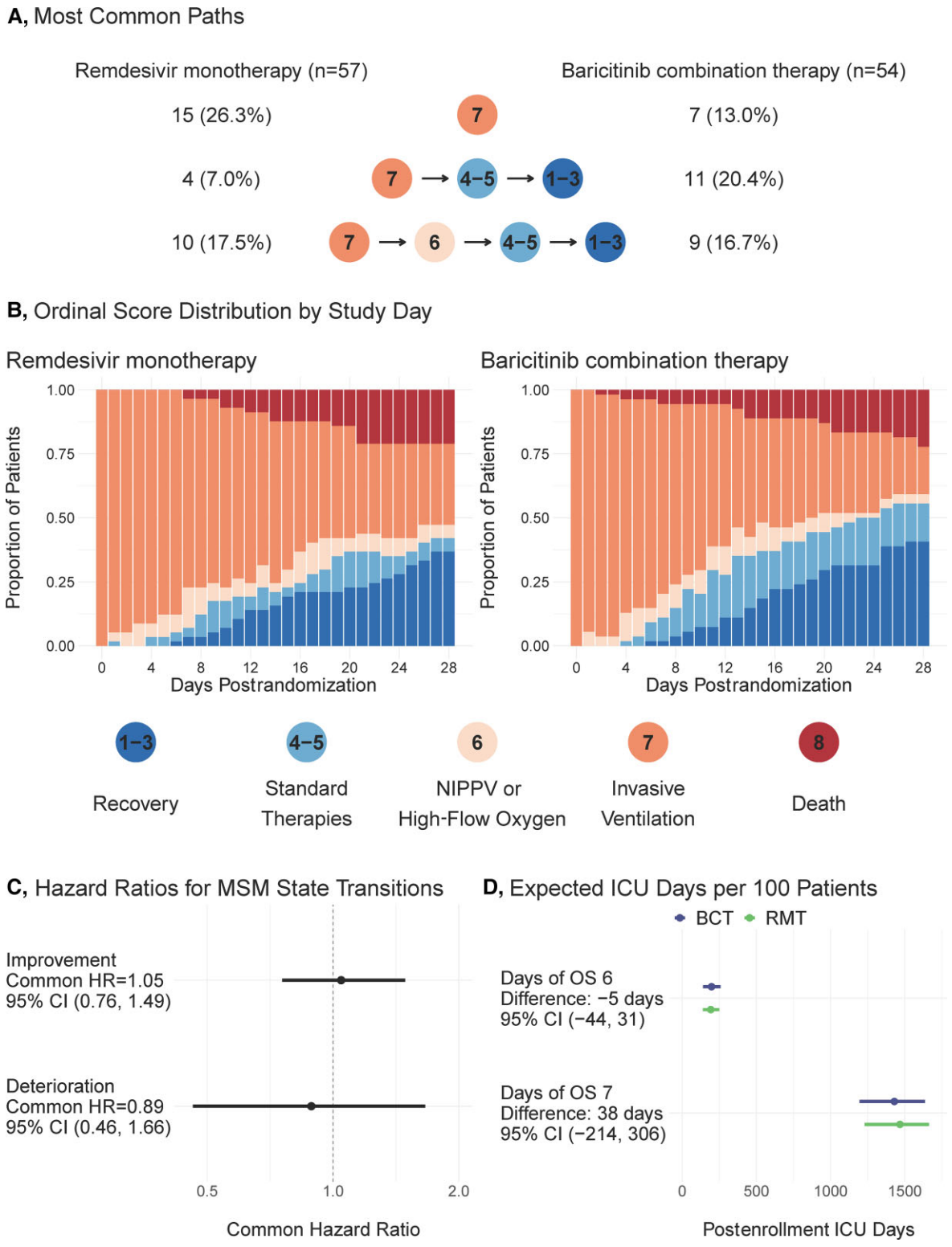

Figure 4. Dynamics of clinical progression – baseline invasive mechanical ventilation (OS 7). A, The per-arm proportions of patients who followed 1 of the 3 most common clinical paths in either arm, considering only the observed sequence of ordinal scores without regard for timing of transitions. B, Stacked proportions of patients in each ordinal score by treatment arm at each day postrandomization. The combined area of bars representing ICU therapies has a direct correspondence to the expected days of ICU therapies required per 100 patients on each arm. C, Common hazard ratios for the overall treatment effect on clinical improvement and deterioration estimated from a multistate model. D, Multistate model estimates of expected utilization of ICU-level respiratory therapies (OS 6 and OS 7) per 100 patients over the study period. Abbreviations: BCT, baricitinib combination therapy; HR, hazard ratio; ICU, intensive care unit; MSM, multistate model; NIPPV, noninvasive positive-pressure ventilation; OS, ordinal score; RMT, remdesivir monotherapy.

understanding how this therapy alters the clinical course of hospitalized patients and health care resource utilization. We deployed a variety of statistical approaches to understand how BCT altered clinical progression of ACTT-2 study participants. Descriptive analyses and competing risk models revealed a consistent trend toward a more linear path to recovery among BCT participants who were in OS 5 or OS 6 at baseline, though we did not find evidence that patients on mechanical ventilation at enrollment benefited from BCT. Baseline OS 6 participants experienced the greatest benefit from BCT, and MSMs revealed that BCT had a multifaceted benefit in both speeding clinical improvement and impeding clinical deterioration in this group. Baseline OS 6 participants treated with BCT had a lower total clinical burden and significantly lower expected use of critical care–level respiratory therapy. We conclude that BCT use in OS 5 and OS 6 patients has the potential to reduce utilization of ICU-level therapies and alleviate inpatient capacity strain.

Hospital capacity strain, particularly on ICU resources, has been shown to worsen clinical outcomes [9]. A similar pattern emerged during the SARS-CoV-2 pandemic, with increased mortality among critically ill COVID-19 patients admitted during periods of increased ICU demand [1, 10, 11]. The prospect of patient outcomes being adversely affected by resource constraints is especially harrowing as demand for ICU beds has exceeded capacity throughout the SARS-CoV-2 pandemic. For example, ∼1 in 4 US hospitals with ICUs reported that at least 95% of their ICU beds were full in the midst of the SARS-CoV-2 Delta wave of the summer of 2021, and this phenomenon has occurred at multiple times throughout the pandemic [12]. The most straightforward manner of reducing hospital strain is to provide a therapy that prevents hospitalization or results in shorter inpatient stays. The ACTT-1 study showed that remdesivir reduced the recovery time for hospitalized patients with COVID-19 by 5 days compared with placebo [13]. Secondary analyses of ACTT-1 have shown that remdesivir reduced utilization of ICU-level respiratory therapies for patients with COVID-19 [1]. ACTT-2 demonstrated that the addition of baricitinib to remdesivir therapy further curtailed the recovery time of hospitalized patients with COVID-19 by an additional day [14]. BCT may further improve the care delivered to this patient population by easing demand for scarce ICU-level resources among certain hospitalized patients with COVID-19.

The biological mechanisms by which BCT led to a more linear path to recovery and inhibited clinical deterioration among baseline OS 5 and OS 6 participants are not elucidated by this secondary analysis and merit further investigation. In randomized clinical trials, Jak inhibitors have been shown to reduce multiple inflammatory cytokines across a diverse range of disease states [15, 16]. These cytokines, which include interleukin-6, interferon-γ, and Granulocyte-macrophage colony-stimulating factor (GM-CSF), have been implicated in the pathogenesis of progression to severe and critical COVID-19 [17, 18]. Moreover, a direct-acting antiviral effect has been proposed for baricitinib, in addition to the anti-inflammatory benefits [19]. Most patients hospitalized with COVID-19 who require minimal to no oxygen support will not progress to severe disease because viral replication is interrupted before the host proceeds to the accelerated cytokine phase. We speculate that baricitinib would have its greatest effect when applied to individuals who have begun this process or some time after the process has started, which likely correlates with patients in OS 5 and OS 6 at baseline. Stopping disease progression short of intubation could reduce the risks of known ICU- and ventilation-associated complications, including nosocomial infections, and might also reduce complications following acute COVID [20].

It is important to acknowledge that standards of care for hospitalized patients with COVID-19 and hospital resource management have shifted over the course of the SARS-CoV-2 pandemic and that some of the choices we made in our analysis reflect clinical practice at the time ACTT-2 was conducted [16]. For example, we refer to high-flow oxygen therapy as an ICU-based treatment, which may not be universally true today. Similarly, most participants in ACTT-2 were not treated with dexamethasone, as this was not part of the standard of care until the final weeks of study enrollment. Results from the STOP-COVID trial suggest that tofacitinib, another Jak inhibitor, could be administered effectively in combination with steroids to reduce the incidence of clinical deterioration to mechanical ventilation among hospitalized patients [17]. Further investigation of co-administering immunomodulatory drugs and steroids, specifically baricitinib and dexamethasone, could have significant implications for the clinical course of hospitalized patients with COVID-19.

The decision to deploy a new therapy is based first and foremost on whether the therapy is convincingly shown to be effective at treating an individual patient. We argue that an important secondary benefit of effective COVID-19 therapies is the conservation of limited medical resources as patient outcomes can be highly interdependent during times when health care systems are stressed. We conducted a variety of analyses to evaluate how BCT altered the trajectories of respiratory therapy requirements compared with RMT and quantified the aggregate impact of BCT on utilization of critical care resources. We conclude that the addition of baricitinib therapy for the treatment of hospitalized patients presenting in OS 5 and OS 6 could decrease requirements for expensive critical care support and help alleviate ICU strain.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the

posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The authors would like to thank Lori Dodd, PhD, Gail Potter, PhD, Jason Liang, PhD, Dean Follmann, PhD, and Kevin Rubenstein, MS, for thoughtful discussions that helped to improve the analysis, Sophia Charuhas, MA, and Stacy Kopka, MS, for help in preparing the manuscript for submission, and Jonathan Marchand for administrative support.

Financial support. This analysis used data from the Adaptive Covid-19 Treatment Trial (ACTT-2) trial (DOI: 10.1056/NEJMoa2031994). The ACTT-2 trial was sponsored and primarily funded by the National Institute of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH), Bethesda, Maryland. This trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, under contract HHSN261200800001E 75N910D00024, task order number 75N91019F00130/75N91020F00010, and by the Department of Defense, Defense Health Program. This trial has been supported in part by the NIAID of the NIH (M1AI148684, UM1AI148576, UM1AI148573, UM1AI148575, UM1AI148452, UM1AI148685, UM1AI148450, UM169432, and UM1AI148689) and by the NIH Stimulating Access to Research in Residency grant (grant number 5R38AI140299-02). The trial has also been funded in part by the governments of Japan, Mexico, Denmark, and Singapore. The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council (MRC_UU_12023/23). V.C.M. received support from the Emory CFAR (grant number P30AI050409). Collaborating investigators involved with collection of data during the ACTT-2 trial are noted in the Supplementary Data.

Disclaimer. The views expressed are those of the authors and do not reflect the official views of the Uniformed Services University of the Health Sciences, the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the National Institutes of Health, the Department of Health and Human Services, Walter Reed National Military Medical Center, the Department of Defense, or the Departments of the Army, Navy, or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government. This work utilized the computational resources of the NIH HPC Biowulf computing cluster (http://hpc.nih.gov).

Potential conflicts of interest. V.C.M. has received investigator-initiated research grants (to the institution) and consultation fees from Eli Lilly, Bayer, Gilead Sciences, and ViiV. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. The ACTT-2 trial protocol was reviewed and approved by an institutional review board at each study site and monitored by an independent data safety and monitoring committee. Written informed consent was provided by each study participant, or by their legally authorized representative in the event that the patient could not provide consent. Full details of the ACTT-2 design, conduct, and oversight are available in the ACTT-2 protocol, which is available with the primary manuscript disseminating the study results [2].

References

1. Fintzi J, Bonnett T, Sweeney DA, et al. Deconstructing the treatment effect of remdesivir in the adaptive coronavirus disease 2019 (COVID-19) treatment trial-1: implications for critical care resource utilization. Clin Infect Dis. **2021**.
2. Fay MP, Malinovsky Y. Confidence intervals of the Mann-Whitney parameter that are compatible with the Wilcoxon-Mann-Whitney test. Stat Med **2018;** 37: 3991–4006.
3. Kawaguchi A, Koch GG. sanon: an R package for stratified analysis with nonparametric covariable adjustment. J Stat Softw **2015;** 67:1–37.
4. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc **1999;** 94:496–509.
5. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med **2017;** 36:4391–400.
6. Marconi VC, Ramanan AV, de Bono S, et al. 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.
7. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med **2022;** 10:327–336.
8. Horby PW, Emberson JR, Mafham M, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. medRxiv 2022.03.02.22271623 [Preprint]. 3 March **2022**. Available at: https://doi.org/10.1101/2022.03.02.22271623. Accessed April 12, 2022.
9. Eriksson CO, Stoner RC, Eden KB, Newgard CD, Guise J-M. The association between hospital capacity strain and inpatient outcomes in highly developed countries: a systematic review. J Gen Intern Med **2017;** 32:686–96.
10. Bravata DM, Perkins AJ, Myers LJ, et al. Association of intensive care unit patient load and demand with mortality rates in US department of Veterans Affairs hospitals during the COVID-19 pandemic. JAMA Netw Open **2021;** 4:e2034266.
11. French G, Hulse M, Nguyen D, et al. Impact of hospital strain on excess deaths during the COVID-19 pandemic—United States, July 2020–July 2021. MMWR Morb Mortal Wkly Rep **2021;** 70:1613–6.
12. United States Department of Health and Human Services. Hospital utilization. Available at: https://protect-public.hhs.gov/pages/hospital-utilization. Accessed 6 April 2022.
13. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med **2020;** 383:1813–26.
14. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med **2020;** 384:795–807.
15. Jorgensen SCJ, Tse CLY, Burry L, Dresser LD. Baricitinib: a review of pharmacology, safety, and emerging clinical experience in COVID-19. Pharmacotherapy **2020;** 40:843–56.
16. Yeleswaram S, Smith P, Burn T, et al. Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment. Clin Immunol **2020;** 218:108517.
17. Zhang X, Zhang Y, Qiao W, Zhang J, Qi Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol **2020;** 86:106749.
18. Sims JT, Krishnan V, Chang CY, et al. Characterization of the cytokine storm reflects hyperinflammatory endothelial dysfunction in COVID-19. J Allergy Clin Immunol **2021;** 147:107–11.
19. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet **2020;** 395:e30–31.
20. Centers for Disease Control and Prevention. Post-COVID conditions: information for healthcare providers. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html. Accessed 7 April 2022.