Supplemental Material*

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Supplemental Methods

Supplemental Statistical Methods

The analysis of the treatment effect of in the ACTT-2 trial of baricitinib+remdesivir compared to placebo+remdesivir focused on three clinical outcomes: 28-day recovery, 28-day mortality, and 28-day progression to invasive mechanical ventilation (IMV) or death. Each outcome was handled using a competing risks framework which recognizes that certain events necessarily preclude others (e.g., recovery is necessarily unobservable for participants who die before achieving recovery). It has been widely reported that failure to account for the presence of competing risks can lead to biased estimates of the relative hazard faced by different groups [1]. In the analysis of 28-day recovery, the competing event is death. In the analyses of 28-day mortality and 28-day progression to IMV or death, the competing event is recovery.

The competing risks coding is identical to the coding used for the originally published result [2]. In a traditional competing risks setting, the competing events are mutually exclusive. Note, however, that although it was rare in the ACTT studies it was possible to recover within 28 days of randomization and still go on to require IMV or die. This required the models for 28-day recovery and 28-day mortality to be fit separately, which is atypical of a competing risks analysis (in which, for example, the usual formulation would specify one Fine-Gray subdistribution hazards model for recovery and death from which the subdistribution hazard ratios for both competing events are estimated simultaneously). To handle the observed data for cases where both the primary event and competing event occurred, the primary event was given precedence. That is, participants who recovered and later died within 28 days were coded as having recovered in the 28-day recovery model but were coded as having died in the 28- day mortality model (there were N=2 cases where this occurred). For the 28-day progression to IMV or death outcome, where recovery is treated as a competing event, any recoveries which were observed prior to IMV or death were ignored (N=3).

The estimate of interest in the Fine-Gray subdistribution hazard model is a subdistribution hazard ratio (SHR) and is distinct from a hazard ratio estimated using a Cox model. The SHR relates the relative rates of the occurrence of the primary model event in subjects who have not yet experienced an event of that type (including those who have already experience the competing event). As such, the subdistribution hazard model estimates the effect of covariates on the cumulative incidence function for the primary event, which takes into account the presence of competing risks.

We implemented each of the above-described subdistribution hazard models 4 times using the ACTT-2 data: once for each quartile of the ACTT risk profile. Subdistribution hazard ratios for each quartile-outcome combination are presented in Figure 1. Note that there were no deaths observed in the "Least risk" quartile, leading to an undefined subdistribution hazard ratio for the 28-day mortality outcome.

PATH guidelines for assessing heterogeneity of treatment effect

We followed the PATH guidelines for assessing heterogeneity of treatment effect [3, 4]. The recommendations are copied below.

The below two lists indicate PATH criteria for when risk modeling is likely to be valuable and for recommendations for risk modeling. The guidelines are in black, while blue text describes how they were satisfied for this paper. PATH guidelines for caveats before moving to clinical practices and for effect modeling as not applicable as we are not recommending a change in clinical practice and we performed risk modeling rather than effect modeling.

PATH criteria: when is a risk-modeling approach to RCT analysis likely to be most valuable?

This list includes seven criteria. In general, not all criteria will be met for a single analysis. Criteria 1, 5, 6, 7 were met for this paper.

1) When an overall treatment effect is well established

   The primary analysis showed that baricitinib + remdesivir improved time to recovery compared to remdesivir alone [5].

   In the exploratory analysis of change in laboratory parameters from baseline to Day 5, we established overall effects for ANC, ALC, and CRP. These are the same parameters that differed significantly between treatment groups in the high-risk quartile.

2) When the benefits and harms/burdens of a given intervention are finely balanced (i.e., of similar magnitude on average), increasing the sensitivity of the treatment decision to risk prediction
   The treatment was not associated with harm [5]

3) When treatments are associated with a nontrivial amount of serious harm or burden, increasing the importance of careful patient selection
   The treatment was not associated with harm [5]

4) When several large, well-conducted RCTs of contemporary interventions are available and appropriate for pooling in individual patient meta-analysis, to provide improved statistical power and broader variation in baseline outcome risk
   We analyzed a single trial.

5) When substantial, identifiable heterogeneity of risk in the trial population is anticipated
   a) When there are validated risk models and well-established risk factors

We used a risk profile developed and validated on the ACTT-1 data [2], and we also validated it on the ACTT-2 data. ACTT-2 participants showed heterogeneity by this risk profile.

b) When case mix heterogeneity is substantial in the trial population

6) When there is strong preliminary evidence that a prediction model is clinically useful for treatment selection, or when models are in current use for treatment selection (i.e., validation is a high priority)
In previous work, the risk profile identified a group of patients that benefitted the most from remdesivir treatment in ACTT-1 [2].

7) When the clinical variables in the proposed models are routinely available in clinical care
The risk profile variables are routinely available (ALC, ANC, platelets, and oxygen support level).

PATH guidance on risk-modeling approaches to identify HTE

General

1. Reporting RCT results stratified by a risk model is encouraged when overall trial results are positive to better understand the distribution of effects across the trial population.
   We reported results stratified on risk profile quartile.
2. Predictive approaches to HTE require close integration of clinical and statistical reasoning and expertise.
   The development of the original risk profile and its application in this work were both collaborative efforts by clinicians and statisticians.

Identify or develop a model

3. When available, apply a high-quality, externally developed, compatible risk model to stratify trial results.
   We applied a risk profile externally developed on the ACTT-1 data set to stratify the ACTT-2 data.

4. When a high-quality, externally developed model is unavailable, consider developing a model using the entire trial population to stratify trial results; avoid modeling on the control group only. N/A
5. When developing new risk models or updating externally developed risk models, specify the analytic plan before examining trial data and follow guidance for best practices for prediction model development. N/A

Apply the model and report results

6. Report metrics for model performance for outcome prediction on the RCT, including measures of discrimination and calibration (when appropriate).
   We reported ROC curves and AUROC for the risk profile in each ACTT-2 treatment group for three outcomes (recovery, mortality, and invasive mechanical ventilation and/or death) and included the Hosmer–Lemeshow C-statistics p-values to assess calibration.

7. Report distribution of predicted risk (or the risk score) in each group of the trial and in the overall study population.
   We included dot plots overlaid with violin plots of risk score distributions within each treatment group and overall.

8. Report outcome rates and both relative and absolute risk reduction across risk strata.

   The paper expanding and elaborating upon the PATH guideline states that this recommendation can also be met by reporting hazard ratios within a clinically meaningful window [4]. We opted for hazard ratios

instead of risk ratios as this was the prespecified analysis approach in the clinical trial [5] and was also used in the paper that developed the risk profile on the ACTT-1 data [2]. The PATH guidance for time-to-event analysis includes visualization of cumulative incidence curves, which we included for the high-risk cohort, and also states that "Relative treatment effect estimates can be summarized by hazard ratios over a clinically meaningful time horizon (or several such horizons). Absolute treatment effect estimates can be summarized by cumulative incidences at a clinically meaningful time point (or several such points)." [4] We summarized 28-day hazard ratios of outcomes (recovery, mortality, and invasive mechanical ventilation and/or death) and also included absolute treatment effect estimates quantified as differences in 28-day cumulative incidences of outcomes between treatment arms within each of the four risk quartiles.

9. When there are important treatment-related harms, these harms should be reported in each risk stratum to support stratum-specific evaluation of benefit–harm tradeoffs.

   Important treatment-related harms were not found in ACTT-2. The primary analysis found that "patients receiving baricitinib plus remdesivir had a significantly lower incidence of adverse events, adverse events leading to discontinuation of the trial drug, serious adverse events, serious adverse events with a fatal outcome, and infection-related adverse events than patients who received remdesivir alone." [5]

10. To test the consistency of the relative treatment effect across prognostic risk, a continuous measure of risk (e.g., the logit of risk) may be used in an interaction term with treatment group indicator.

    For consistency with the previous analysis and with our primary analysis (which used risk quartiles), we included categorical risk quartile indicators in the model instead of a continuous risk profile variable. The high-risk quartile was omitted as the reference category. For time to recovery, we found a significant difference in treatment effect between high and least risk quartiles. For mortality and IMV/death, no significant differences were found.

Supplemental Laboratory Methods

C-reactive protein (CRP) measurement: Frozen serum samples from participants were stored at -80 until use. All serum CRP measurements from individual participants was performed at National Laboratory for Cancer Research, Frederick, MD, USA for assay standardization. CRP levels were measured by an electrochemiluminescence assay (Meso Scale Discovery) per manufacturer protocol. Individual patient CRP measurements at a given timepoint were obtained in duplicate and averaged.

Quantification of Upper respiratory SARS-CoV-2 RNA (Viral Load (VL): Either oropharyngeal or nasopharyngeal swabs were collected from participants at baseline and study day 5 per trial protocol [2]. Swabs were preserved in viral transport media and at -70°C until analysis. Baseline and day 5 swabs from a subset of participants were analyzed. Swab viral loads were assayed by the Roche cobas SARS- CoV-2 RT-PCR assay on the Roche cobas 6800 system. Exogenous standards and calibrations were performed with the SeraCare AccuPlex SARS-CoV-2 verification panel. Measurement validations were performed with spike-in of clinical materials, as well as with use of reconstituted calibrators or standards. Quantitative calculations below the assay limit of quantification (LOQ) of 1.79 log10 copies/mL, values were imputed to half the LOQ when RNA was detectable but below the LOQ (1.49 log10 copies/mL or 31 copies/mL) and one quarter the LOQ (1.19 log10 copies/mL or 15.5 copies/mL) when RNA was undetectable.

Absolute lymphocyte count (ALC), Absolute neutrophil count (ANC), and Platelet count measurements: Standard complete blood count collections were performed at each study site. ALC, ANC and Platelet count were determined within the participants hospital clinical lab and recorded at baseline prior to treatment, and at day 5 of study treatment.

Statistical Analysis of Laboratory Parameters

As described in the main text, temporal trends of ACTT risk profile laboratory parameters (ALC, ANC, and Platelet count) were compared between treatment arms with t-tests on differences in the log-transformed values from baseline to study day 5. We performed linear regression of the change in log-transformed values from baseline to day 5 on treatment, risk quartile, and treatment- by- risk- quartile-interaction to evaluate differential treatment effects on ALC, ANC, and platelet count between ACTT risk quartiles. These analyses were repeated for CRP and VL. The log transformation was chosen because the distributions are skewed and because a multiplicative change was considered more clinically relevant than an additive change. For each laboratory parameter, participants with missing day-5 measurements were excluded from this analysis.

A separate analysis examined the baricitinib+remdesivir arm only. We compared ALC, ANC, and platelet trajectories between risk quartiles within the baricitinib+remdesivir arm alone with t-tests on the log-transformed ratio changes.

Supplemental Tables and Figures

Supplement Table 1. Definition of the 8-category ordinal scale of disease severity based on oxygen delivery method and clinical status.

Ordinal score (OS) value	Definition
1	Not hospitalized and no limitations of activities
2	Not hospitalized, with limitation of activities, home oxygen requirement, or both
3	Hospitalized, not requiring supplemental oxygen or ongoing medical care
4	Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
5	Hospitalized, requiring any supplemental oxygen
6	Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices
7	Hospitalized, receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)
8	Death

Recovery is defined as OS 1, 2, or 3.

Supplement Table 2: Hazard ratio coefficients for the ACTT-1 derived risk score for invasive mechanical ventilation (IMV) and/or death.

Predictor variable	Hazard ratio	95% confidence interval
Ordinal score (OS)	0.91	[0.71; 1.15]
Log-transformed absolute neutrophil count (ANC)	1.93	[1.16; 3.20]
Log-transformed platelet count	0.63	[0.38; 1.04]
Log-transformed absolute lymphocyte count (ALC)	0.58	[0.40; 0.83]

The ACTT risk score is based on the following estimated linear predictor in the hazard function: Linear predictor = log(0.91) x OS + log(1.93) x log(ANC) + log(0.63) x log(platelets) + log(0.58) x log(ALC). The ACTT risk score quantifies the risk of IMV/death (so lies between zero and one) and was calculated by applying the predictRisk function in the riskRegression package to the competing risks model object. Coefficients were estimated in [2].

Supplement Table 3: Number of participants included in different analyses by treatment arm

	Baricitinib + Remdesivir	Placebo + Remdesivir	Overall
Enrolled and randomized	515	518	1033
As-treated population	508	509	1017
Included in ACTT risk profile analysis	494	505	999
Included in analysis of change in ALC (Day 1 to 5)	404	401	805
Included in analysis of change in ANC (Day 1 to 5)	404	401	805
Included in analysis of change in platelet count (Day 1 to 5)	404	406	810

Abbreviations: ALC (Absolute lymphocyte count), ANC (Absolute neutrophil count)

Supplement Table 3 shows numbers of participants included in various analyses. All analyses stratified by ACTT risk profile included 999 participants in the as-treated population who had non-missing risk profile components. These comprised 98% of the as-treated population. Supplement Table 4 summarizes number and % of participants in the as-treated population missing variables that we analyzed.

Supplement Table 4: Number and % of participants in the as-treated population missing values of variables analyzed at baseline

	Baricitinib + Remdesivir n (%)	Placebo + Remdesivir n (%)
Age	0 (0)	0 (0)
Sex	0 (0)	0 (0)
Race group	0 (0)	0 (0)
Ethnicity	0 (0)	0 (0)
BMI (kg/m2)	13 (2.6)	17 (3.3)
CRP (mg/L)	21 (4.1)	16 (3.1)
Viral Load (log10)	175 (34)	174 (34)
Time from symptom onset to enrollment	0 (0)	2 (0.4)
Immunodeficiency (Yes)	0 (0)	0 (0)
Baseline Ordinal Score	0 (0)	0 (0)
Platelet count	4 (0.8)	1 (0.2)
Absolute Neutrophil Count	14 (2.8)	3 (0.6)
Absolute Lymphocyte Count	13 (2.6)	3 (0.6)
ACTT risk score	14 (2.8)	4 (0.8)

Abbreviations BMI: Body mass index, CRP: C-reactive protein

Supplement Table 5: ACTT-2, Quartiles of ACTT risk profile vs. treatment assignment

	Assignment		
	Placebo +RDV	Baricitinib + RDV	Total
ACTT risk profile quartile			
Least risk	139 (28%)	132 (27%)	271 (27%)
Lower risk	133 (26%)	103 (21%)	236 (24%)
Moderate risk	105 (21%)	116 (23%)	221 (22%)
High risk	128 (25%)	143 (29%)	271 (27%)
Total	505 (100%)	494 (100%)	999 (100%)

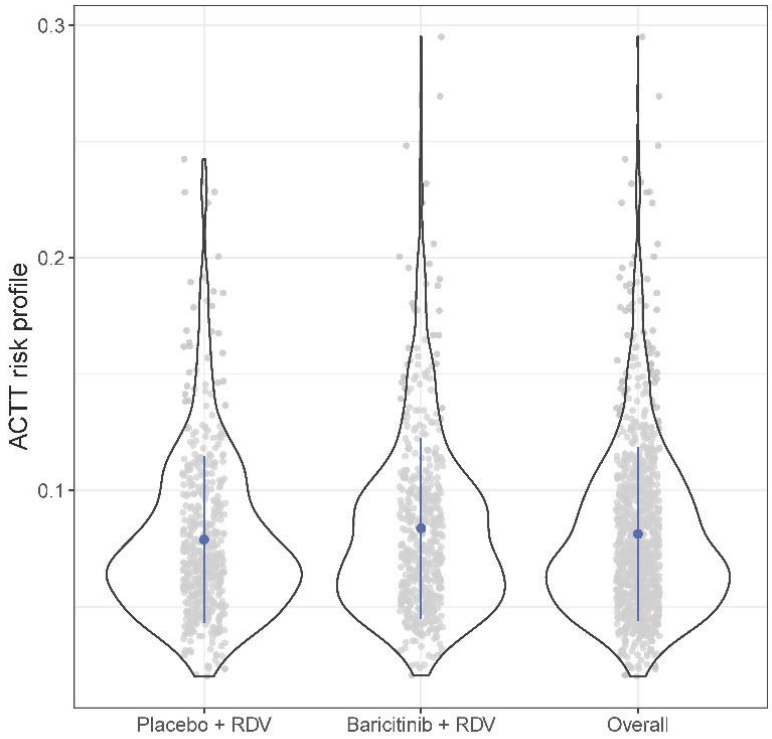
NOTE: Analysis includes 999 people who received the assigned treatment and had non-missing ACTT risk profile components (Supplement Table 3). RDV = Remdesivir

Supplement Table 6: Baseline characteristics of ACTT-1 participants by quartiles of the ACTT risk profile

Risk quartiles were derived based on ACTT-1 and ACTT-2 participants combined. BMI: Body mass index; CRP: C-reactive protein; IQR: Interquartile range.

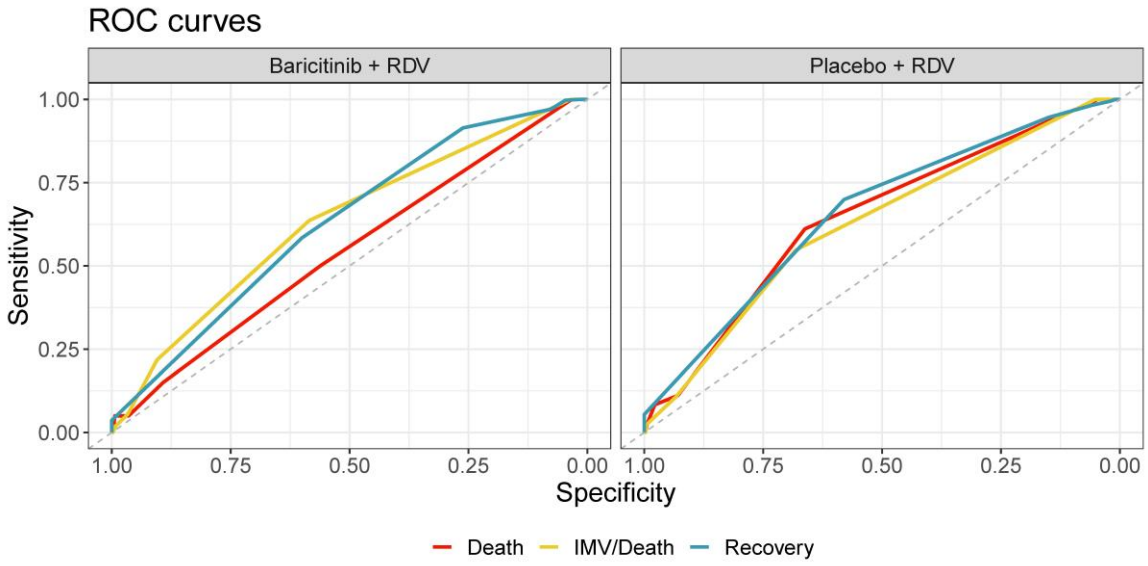
	Least risk[a] N = 242	**Lower risk N = 277**	**Moderate risk N = 291**	**High risk N = 241**	**Overall, N = 1,051**
Age - median [IQR]	57 (45-65)	59 (48-69)	60 (50-71)	62 (52-71)	59 (49-70)
Sex - Male – N (%)	129(53)	172(62)	197(68)	180(75)	678(65)
Race group - N (%)					
American Indian or Alaska Native	0(0)	1(0.4)	2(0.7)	4(1.7)	7(0.7)
Asian	25(10)	38(14)	42(14)	30(12)	135(13)
Black or African American	50(21)	62(22)	56(19)	51(21)	219(21)
White	145(60)	142(51)	151(52)	124(51)	562(53)
Ethnicity					
Hispanic or Latino - N (%)	60(25)	60(22)	65(22)	63(26)	248(24)
BMI kg/m^2- median (IQR)	29.6 (26.6-34.6)	29.3 (25.7-33.3)	29.4 (25.5-34.2)	28.4 (24.7-33.7)	29.0 (25.6-34.0)
Baseline CRP mg/L – (mg/L) median [IQR]	79.2 (39.8-125.0)	120.5 (74.8-180.2)	150.6 (89.1-228.1)	171.3 (106.6-263.3)	126.6 (71.3-204.8)
Baseline Viral Load (log10), - median (IQR)	3.2 (2.3-4.2)	3.3 (2.4-4.4)	3.7 (2.9-4.7)	3.6 (2.8-5.0)	3.4 (2.5-4.6)
N (%) with viral load data (Collection was planned only for a subset of participants.)	180(74)	207(75)	202(69)	176(73)	765(73)
Time from symptom onset to enrollment (days) – median (IQR)	9 (7-12)	9 (6-12)	9 (7-12)	9 (6-13)	9 (6-12)
Immunodeficiency - N (%)	13(5.4)	20(7.2)	19(6.5)	21(8.7)	73(6.9)

Supplement Figure 1: ACTT risk profile distribution by treatment arm and overall in ACTT-2



This figure shows the distribution of the predicted risk scores (ACTT risk profile) within each treatment arm and as a whole. The risk score for an individual is interpreted as the predicted risk of IMV/death. The mean for each treatment arm and the overall mean are denoted by blue dots, while blue bars indicate mean plus/minus one standard deviation. An extreme value with a risk profile of 0.989 in the placebo+RDV arm was excluded from the visualization. Because risk profile was analyzed by quartiles, this outlier does not exert undue influence. RDV=remdesivir

Supplement Figure 2: Receiver Operating Characteristic (ROC) curves for death, IMV/death, and recovery for the ACTT risk profile



RDV= Remdesivir, IMV= Invasive Mechanical Ventilation

Supplement Table 7: AUROC values with 95% confidence intervals for death, IMV/death, and recovery for the ACTT risk profile.

Treatment group	Death	IMV/Death	Recovery
Baricitinib+RDV	0.557 95%CI (0.439~0.675)	0.664 95%CI (0.593~0.734)	0.655 95%CI (0.583~0.726)
Placebo+ RDV	0.725 95%CI (0.657~0.792)	0.674 95%CI (0.615~0.733)	0.689 95%CI (0.632~0.746)

RDV= Remdesivir, CI= Confidence Interval, IMV= Invasive Mechanical Ventilation, AUROC = Area Under the Receiver Operating Characteristics.

Supplement Table 8: Hosmer Lemeshow calibration test statistics for the ACTT risk profile.

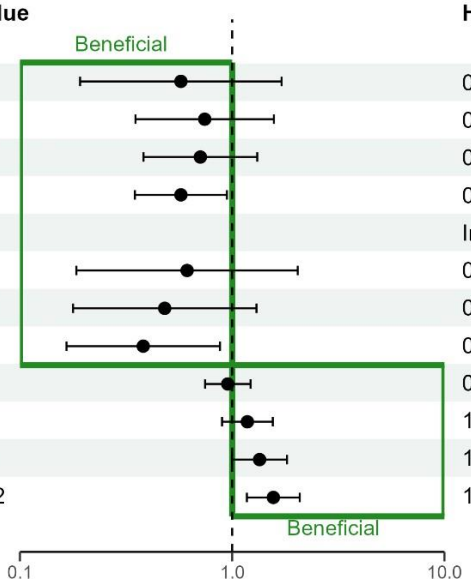
This table is included as part of PATH guidelines and shows chi-square test statistics and associated p-values derived from Hosmer-Lemeshow (H-L) tests, aiming to assess the calibration performance of prognostic models for each of the three endpoints by treatment arms. A large chi-square value indicates insufficient calibration. Smaller grouping numbers were used in H-L tests for "Death" to ensure that each group had at least 5 events (2 and 4 groups were selected for RDV (remdesivir) and Baricitinib+RDV model, respectively.) The default 10 groups were used for the other two endpoints. The results suggest that the ACTT risk profile is reasonably calibrated in the baricitinib + remdesivir arm for the endpoints of death and recovery, but not for IMV/death; also, is not sufficiently calibrated in the placebo + remdesivir arm for all the three endpoints.

Endpoint	Treatment arm	Test statistic	P-value
IMV/death	Placebo + RDV	83	<0.001
	Baricitinib + RDV	16.9	0.03
Death	Placebo + RDV	10.3	<0.001
	Baricitinib + RDV	1.7	0.42
Recovery	Placebo + RDV	20.2	0.01
	Baricitinib + RDV	5.4	0.71

RDV= Remdesivir, IMV= Invasive Mechanical Ventilation

Supplement Figure 3: Hazard ratios from Cox regression for the effect of baricitinib+remdesivir vs. placebo+remdesivir for risk groups defined by the ACTT risk profile.

Item	Number in Placebo + RDV group	Number in Baricitinib + RDV group	P-value	HR (95%CI)
IMV/Death, Least risk	139	132	0.32	0.57 (0.19~1.71)
IMV/Death, Lower risk	133	103	0.43	0.74 (0.35~1.57)
IMV/Death, Moderate risk	105	116	0.27	0.71 (0.38~1.31)
IMV/Death, High risk	128	143	0.03	0.57 (0.35~0.94)
Death, Least risk	139	132		Inf (NA)
Death, Lower risk	133	103	0.42	0.61 (0.18~2.04)
Death, Moderate risk	105	116	0.15	0.48 (0.18~1.30)
Death, High risk	128	143	0.02	0.38 (0.17~0.88)
Recovery, Least risk	139	132	0.70	0.95 (0.74~1.22)
Recovery, Lower risk	133	103	0.24	1.18 (0.89~1.55)
Recovery, Moderate risk	105	116	0.05	1.35 (1.00~1.81)
Recovery, High risk	128	143	0.002	1.56 (1.17~2.08)



RDV=Remdesivir, CI=confidence interval, HR= Hazard Ratio, IMV= Invasive Mechanical Ventilation

Supplement Table 9 shows that baseline covariates are generally balanced between arms in the high-risk quartile, while [5] shows that they were balanced overall between treatment arms. Supplement Figure 4 summarizes treatment effect estimates from Fine-Gray competing risks models incorporating the following covariates: treatment assignment, age, sex, log transformed C-reactive protein, baseline ordinal score (categorized into levels 4,5,6, and 7), and the presence of coexisting conditions (none, one, and two or more). The adjusted analysis supports the primary finding of benefit on all three outcomes in the high-risk quartile.

Supplement Table 9: Baseline characteristics of ACTT-2 participants in high-risk group by treatment arm

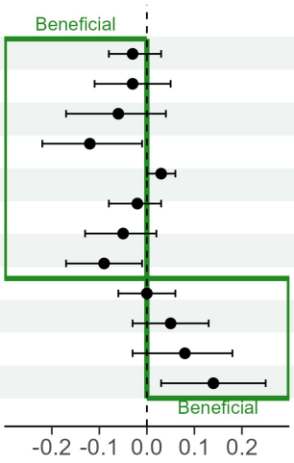
	Overall, N=271	**Baricitinib + RDV, N=143**	**Placebo + RDV, N=128**
Age - median (IQR)	59.0 (47.0-69.0)	59.0 (45.0-67.5)	59.0 (49.0-69.3)
Sex - Male – N (%)	193(71)	94(66)	99(77)
Race group - N (%)			
American Indian or Alaska Native	1(0.4)	0(0)	1(0.8)
Asian	26(9.6)	15(10)	11(8.6)
Black or African American	32(12)	17(12)	15(12)
White	132(49)	66(46)	66(52)
Ethnicity			
Hispanic or Latino - N (%)	156(58)	87(61)	69(54)
BMI (kg/m^2) **-** median (IQR)	29.4 (25.6-33.8)	30.0 (25.9-34.0)	28.4 (25.5-33.6)
Baseline CRP (mg/L)- median (IQR)	174.2 (108.4-245.3)	175.0 (115.8-238.1)	173.3 (99.4-259.5)
Baseline VL (log10) - median (IQR)	4.5 (2.9-5.8)	4.8 (1.7-6.2)	4.4 (3.1-5.6)
N (%) with viral load data (Collection was planned only for a subset of participants.)	171(63)	87(61)	84(66)
Time from symptom onset to enrollment (days) – median (IQR)	8.0 (5.0-10.0)	8.0 (6.0-10.0)	8.0 (5.0-10.0)
Baseline Absolute Lymphocyte Count (ALC) ($10^9/L$) - median (IQR)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.8)
Baseline Absolute Neutrophil Count (ANC) ($10^9/L$) - median (IQR)	7.8 (5.8-11.0)	8.2 (5.9-11.3)	7.6 (5.8-10.4)
Baseline Platelet count ($10^9/L$) – median (IQR)	207.0 (158.5-256.5)	211.0 (168.5-264.0)	200.0 (151.0-250.0)
Baseline Ordinal Score - N (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	24(8.9)	12(8.4)	12(9.4)
5. Hospitalized, requiring supplemental oxygen	138(51)	79(55)	59(46)
6. Hospitalized, receiving noninvasive ventilation or high flow oxygen devices	65(24)	34(24)	31(24)
7. Hospitalized, receiving IMV or ECMO	44(16)	18(13)	26(20)
Coexisting conditions – N/total no. (%)			
None	50(18)	23(16)	27(21)
One	67(25)	41(29)	26(20)

Two or more	146(54)	75(52)	71(55)
Immunodeficiency - N (%)	6(2.2)	3(2.1)	3(2.3)
Hypertension - N (%)	146(54)	75(52)	71(55)
Cancer - N (%)	10(3.7)	4(2.8)	6(4.7)
Type I Diabetes - N (%)	1(0.4)	0(0)	1(0.8)
Type II Diabetes - N (%)	102(38)	61(43)	41(32)
Chronic kidney disease - N (%)	18(6.6)	6(4.2)	12(9.4)
Chronic liver disease - N (%)	9(3.3)	3(2.1)	6(4.7)
Chronic respiratory disease - N (%)	19(7.0)	12(8.4)	7(5.5)
Asthma - N (%)	23(8.5)	12(8.4)	11(8.6)
Coronary artery disease - N (%)	35(13)	17(12)	18(14)
Congestive heart failure - N (%)	18(6.6)	8(5.6)	10(7.8)
Chronic oxygen requirement - N (%)	8(3.0)	5(3.5)	3(2.3)
Obesity - N (%)	127(47)	73(51)	54(42)
Cardiac valvular disease - N (%)	11(4.1)	3(2.1)	8(6.3)
Coagulopathy - N (%)	2(0.7)	0(0)	2(1.6)
Current or prior DVT or PE - N (%)	6(2.2)	1(0.7)	5(3.9)
Risk profile (continuous scale) – median (IQR)	0.7 (0.5-1.3)	0.8 (0.5-1.4)	0.7 (0.5-1.3)

Supplement Table 9: All variables are balanced between the two treatment arms except for sex.
BMI: Body mass index; VL: Viral load, CRP: C-reactive protein IMV: Invasive Mechanical Ventilation; ECMO: Extracorporeal membrane oxygenation, DVT: Deep Venous Thrombosis, PE: Pulmonary embolism, IQR: *Interquartile range.*

Supplement Figure 4: Estimated difference in cumulative incidence of IMV/death, death, and recovery between baricitinib+remdesivir and placebo+remdesivir for risk groups defined by the ACTT risk profile.

Item	Number in Placebo + RDV group	Number in Baricitinib + RDV group	Cumulative incidence RDV group	Cumulative incidence Baricitinib + RDV group	Cumulative incidence difference (95%CI)
IMV/Death, Least risk	139	132	0.07	0.04	-0.03(-0.08~0.03)
IMV/Death, Lower risk	133	103	0.14	0.11	-0.03(-0.11~0.05)
IMV/Death, Moderate risk	105	116	0.22	0.16	-0.06(-0.17~0.04)
IMV/Death, High risk	128	143	0.30	0.19	-0.12(-0.22~-0.01)
Death, Least risk	139	132	0.00	0.03	0.03(0.00~0.06)
Death, Lower risk	133	103	0.06	0.04	-0.02(-0.08~0.03)
Death, Moderate risk	105	116	0.11	0.05	-0.05(-0.13~0.02)
Death, High risk	128	143	0.15	0.06	-0.09(-0.17~-0.01)
Recovery, Least risk	139	132	0.94	0.94	0.00(-0.06~0.06)
Recovery, Lower risk	133	103	0.86	0.91	0.05(-0.03~0.13)
Recovery, Moderate risk	105	116	0.77	0.84	0.08(-0.03~0.18)
Recovery, High risk	128	143	0.67	0.80	0.14(0.03~0.25)

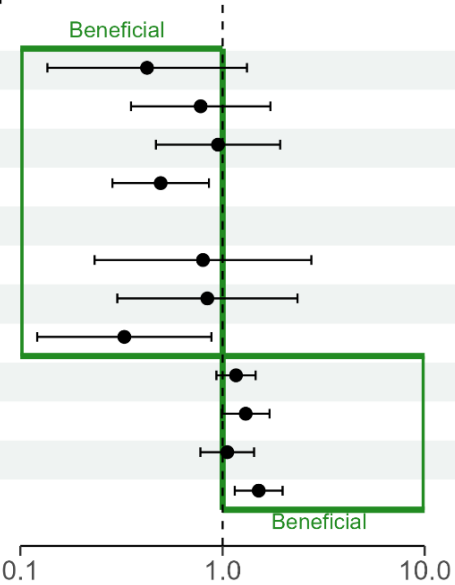


Supplement Figure 4 summarizes treatment effect estimates from Fine-Gray competing risks models incorporating the following covariates: treatment assignment, age, sex, log transformed C-reactive protein, baseline ordinal score (categorized into levels 4,5,6, and 7), and the presence of coexisting conditions (none, one, and two or more). The adjusted analysis supports the primary finding of benefit on all three outcomes in the high-risk quartile.

In the high-risk quartile, the 28-day cumulative incidence of invasive mechanical ventilation and/or death was 30% among placebo+remdesivir recipients and 19% among baricitinib+remdesivir recipients, a decrease of approximately 12 percentage points (cumulative incidence difference = -0.12). In the high-risk quartile, the 28-day cumulative incidence of death was 15% in placebo+remdesivir recipients and 6% among recipients of baricitinib+remdesivir, while that for recovery was 67% in placebo+remdesivir recipients and 80% in recipients of baricitinib+remdesivir. Abbreviations: RDV: remdesivir, IMV: Invasive mechanical ventilation

Supplement Figure 5: Hazard ratios from adjusted Fine-Gray competing risks models for the effect of baricitinib+remdesivir vs. placebo+remdesivir for risk groups defined by the ACTT risk profile.

Item	Number in Placebo + RDV group	Number in Baricitinib + RDV group	HR (95%CI)
IMV/Death, Least risk	139	132	0.42 (0.14~1.32)
IMV/Death, Lower risk	133	103	0.78 (0.35~1.72)
IMV/Death, Moderate risk	105	116	0.95 (0.47~1.93)
IMV/Death, High risk	128	143	0.49 (0.28~0.85)
Death, Least risk	139	132	Inf (NA)
Death, Lower risk	133	103	0.80 (0.23~2.75)
Death, Moderate risk	105	116	0.84 (0.30~2.35)
Death, High risk	128	143	0.33 (0.12~0.88)
Recovery, Least risk	139	132	1.16 (0.93~1.46)
Recovery, Lower risk	133	103	1.30 (0.99~1.71)
Recovery, Moderate risk	105	116	1.05 (0.78~1.43)
Recovery, High risk	128	143	1.51 (1.15~1.98)



IMV: Invasive mechanical ventilation, RDV=Remdesivir, CI=confidence interval, HR= Hazard Ratio.

Supplement Table 10: Coefficient estimates from a Fine-Gray competing risk model assessing the interaction between treatment group and ACTT risk profile quartile among ACTT-2 participants on time to recovery.

Bari=baricitinib, RDV=remdesivir.

		Hazard Ratio	95% Lower	95% Upper	P-value
Time to Recovery					
Treatment (Bari+RDV vs. Placebo+RDV)		1.524	1.160	2.002	0.003
Risk quartile indicators	Moderate vs. High	1.271	0.954	1.695	0.10
	Lower vs. High	1.847	1.408	2.424	<0.001
	Least vs. High	2.888	2.191	3.807	<0.001
Treatment by risk quartile interactions	(Moderate vs. High) × treatment	0.854	0.582	1.252	0.42
	(Lower vs. High) × treatment	0.764	0.526	1.110	0.16
	(Least vs. High) × treatment	0.625	0.431	0.907	0.01
Time to IMV/death					
Treatment (Bari+RDV vs. Placebo+RDV)		0.569	0.348	0.929	0.02
Risk quartile indicators	Moderate vs. High	0.685	0.413	1.136	0.14
	Lower vs. High	0.414	0.238	0.721	0.002
	Least vs. High	0.192	0.093	0.397	<0.001
Treatment by risk quartile interactions	(Moderate vs. High) × treatment	1.240	0.566	2.715	0.59
	(Lower vs. High) × treatment	1.337	0.550	3.251	0.52
	(Least vs. High) × treatment	1.006	0.303	3.338	0.99
Time to Death*					
Treatment (Bari+RDV vs. Placebo+RDV)		0.374	0.163	0.857	0.02
Risk quartile indicators	Moderate vs. High	0.692	0.328	1.460	0.33
	Lower vs. High	0.396	0.173	0.905	0.03
Treatment by risk interactions	(Moderate vs. High) × treatment	1.293	0.355	4.706	0.70
	(Lower vs. High) × treatment	1.700	0.396	7.296	0.48

Supplement Table 10 shows results from a Fine-Gray model including treatment effects, risk quartile indicator variables, and treatment by risk interaction terms. The high-risk quartile was used as the reference category, so the subdistribution hazard ratio (HR) of 1.524 represents the HR for the treatment effect within the high- risk quartile. The significant interaction coefficient of 0.625 means that the HR for the treatment effect in the least-risk quartile is 0.625 times that for the high-risk quartile. Equivalently, the treatment effect for the high-risk quartile is 1/0.625 =1.60 times that for the least-risk quartile, with 95% CI from 1/0.907 to 1/0.431 (i.e., 1.10 to 2.32). Although a multiplicity adjustment was not planned for these exploratory analyses, the p-value of 0.01 for this interaction coefficient retains significance after a Bonferroni correction adjusting for the three interaction tests. Other interactions comparing treatment effects on recovery between moderate and high- risk groups, and between lower-risk and high-risk groups, were not significant, nor were any of the treatment by risk quartile interaction terms for the outcomes of IMV/death and death. The model for time to death excludes the least risk group because cell counts in this category were too low (0 and 4 in control and treated arms) to obtain an estimable HR when this group was included.

Supplement Table 11: Linear regression assessing the interaction effect between treatment group and ACTT risk profile quartile among ACTT- 2 participants on the difference in log(Absolute Lymphocyte Count) from baseline to Day 5.

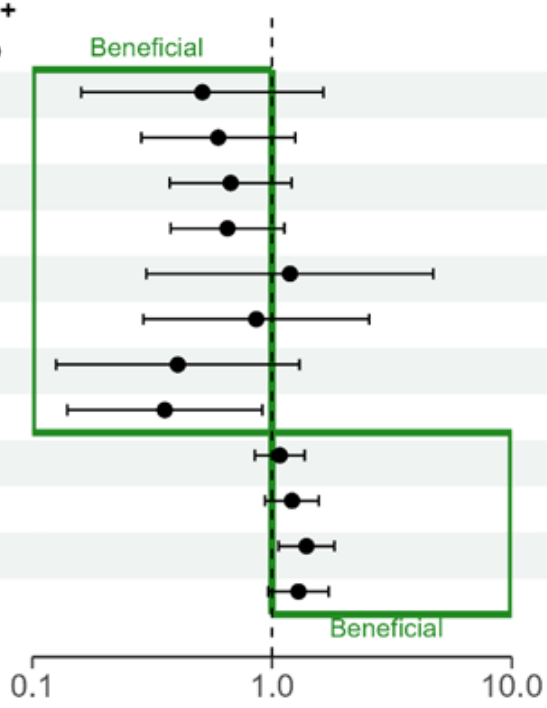
		Coefficient	Standard Error	P-value
Intercept		0.130	0.047	0.005
Treatment (Bari+RDV vs. Placebo+RDV)		0.411	0.066	<0.001
Risk quartile indicators	Moderate vs. High	0.022	0.070	0.755
	Lower vs. High	-0.122	0.068	0.072
	Least vs. High	-0.0003	0.071	0.997
Risk quartile by treatment interaction terms	(Moderate vs. High) × treatment	-0.287	0.098	0.003
	(Lower vs. High) × treatment	-0.040	0.098	0.687
	(Least vs. High) × treatment	-0.204	0.099	0.039

Supplement Table 11 shows results from a linear regression model of log-transformed ratio of Day 5 to baseline Absolute Lymphocyte Count (ALC) (i.e., log(Day 5 ALC / Baseline ALC) = log(Day 5 ALC) – log (baseline ALC) on treatment, risk quartile, and treatment by risk quartile interaction. The high-risk quartile was used as the reference category, so the treatment effect of 0.411 means that in the high-risk quartile, baricitinib+remdesivir increased the geometric mean ALC ratio change by a factor of exp(0.411) = 1.508 compared to placebo+remdesivir. The significant interaction term for the moderate-risk quartile means that the increase in geometric mean ALC ratio change due to baricitinib in the moderate-risk quartile was exp(-0.287)=0.75 times that in the high-risk quartile (i.e., the treatment effect was 1.508×0.75 = 1.13 in the moderate-risk quartile, which was significantly different from the effect of 1.508 in the high-risk quartile, p=0.003). The significant interaction term for the least-risk quartile means that the increase in geometric mean ALC ratio change due to baricitinib in the least-risk quartile was exp(-0.204)=0.815 times that in the high-risk quartile. In other words, the treatment effect was 1.508×0.815 = 1.23 in the least risk quartile, which was significantly different from the estimated effect of 1.508 in the high-risk quartile, p=0.039).

Analogous models were fit for the log-transformed changes in ANC, platelets, CRP, and viral load, but the interaction terms were not significant in those models, so results are not displayed. Bari=baricitinib, RDV=remdesivir.

Supplement Figure 6. Fine-Gray subdistribution hazard ratios (HR) for the effect of baricitinib+remdesivir vs. placebo+remdesivir by risk quartiles defined by baseline C-reactive protein (CRP) levels instead of by the ACTT risk profile.

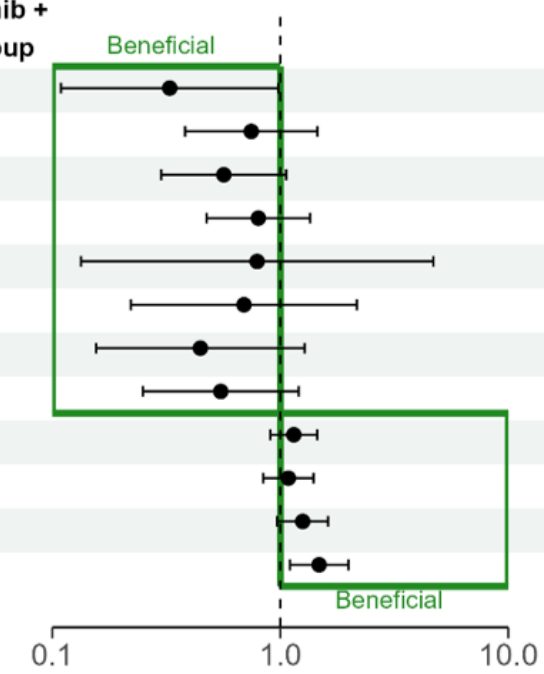
Item	Number in Placebo + RDV group	Number in Baricitinib + RDV group	HR (95%CI)
IMV/Death, Least risk	131	110	0.51 (0.16~1.64)
IMV/Death, Lower risk	122	119	0.60 (0.28~1.25)
IMV/Death, Moderate risk	116	125	0.67 (0.37~1.21)
IMV/Death, High risk	120	120	0.65 (0.38~1.13)
Death, Least risk	131	110	1.19 (0.30~4.72)
Death, Lower risk	122	119	0.86 (0.29~2.55)
Death, Moderate risk	116	125	0.40 (0.13~1.30)
Death, High risk	120	120	0.36 (0.14~0.91)
Recovery, Least risk	131	110	1.08 (0.85~1.37)
Recovery, Lower risk	122	119	1.21 (0.94~1.57)
Recovery, Moderate risk	116	125	1.39 (1.07~1.82)
Recovery, High risk	120	120	1.29 (0.96~1.73)



Supplement Figure 6 shows treatment effect estimates by CRP risk quartiles rather than ACTT risk profile quartiles. These show a similar pattern to Figure 1 in the main text. While the ACTT risk profile shows a significant treatment benefit on all three outcomes from baricitinib+remdesivir compared to placebo+remdesivir, CRP shows a significant benefit for mortality in the high-risk category, a significant benefit for recovery in the moderate-risk category, and no other significant treatment effects. RDV=remdesivir, CI=confidence interval, HR= Hazard Ratio.

Supplement Figure 7. Fine-Gray subdistribution hazard ratios (HR) for the effect of baricitinib+remdesivir vs. placebo+remdesivir by baseline absolute neutrophil count (ANC) quartiles instead of by ACTT risk profile quartiles.

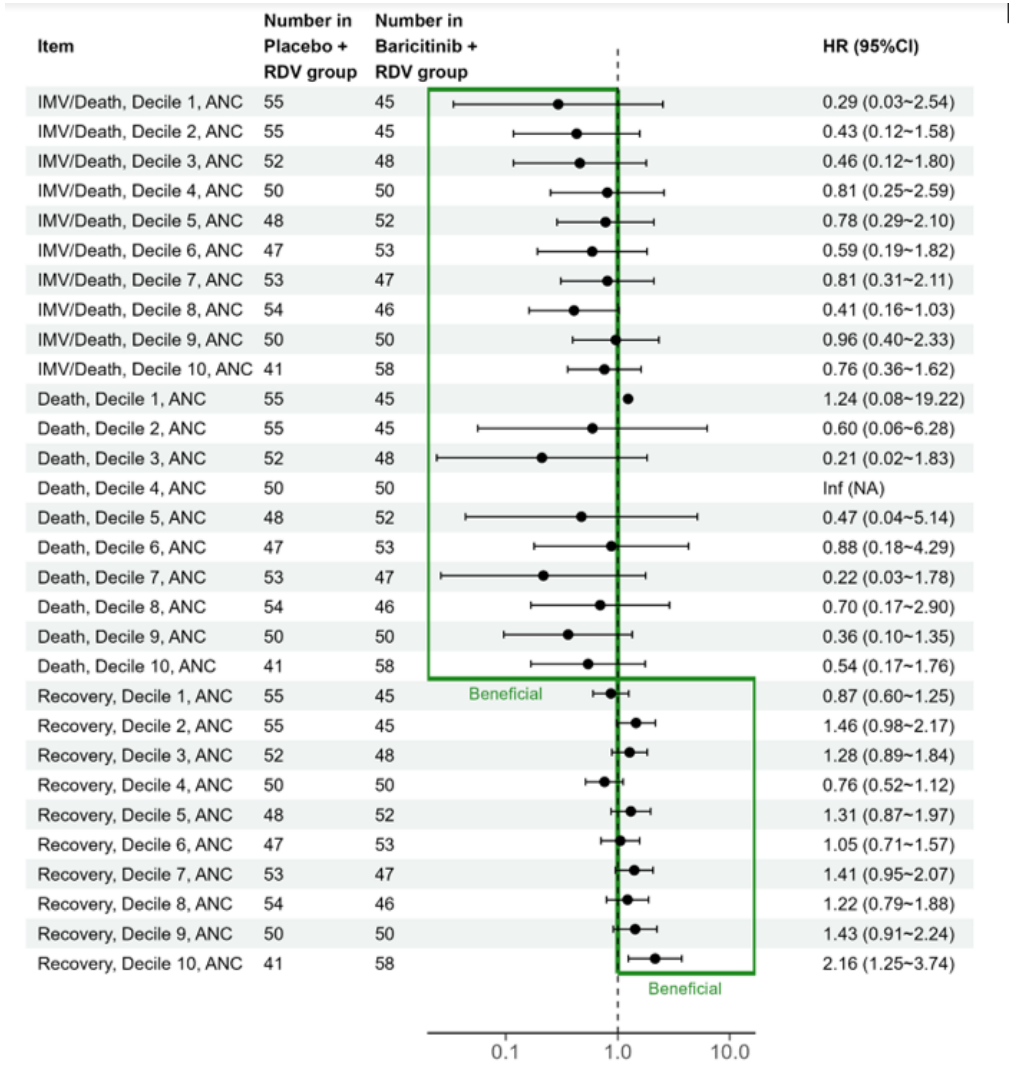
Item	Number in Placebo + RDV group	Number in Baricitinib + RDV group	HR (95%CI)
IMV/Death, Quartile 1, ANC	137	113	0.33 (0.11~0.98)
IMV/Death, Quartile 2, ANC	123	127	0.75 (0.38~1.46)
IMV/Death, Quartile 3, ANC	126	124	0.57 (0.30~1.06)
IMV/Death, Quartile 4, ANC	119	130	0.80 (0.48~1.35)
Death, Quartile 1, ANC	137	113	0.79 (0.13~4.68)
Death, Quartile 2, ANC	123	127	0.69 (0.22~2.17)
Death, Quartile 3, ANC	126	124	0.45 (0.16~1.28)
Death, Quartile 4, ANC	119	130	0.55 (0.25~1.20)
Recovery, Quartile 1, ANC	137	113	1.15 (0.90~1.45)
Recovery, Quartile 2, ANC	123	127	1.08 (0.84~1.40)
Recovery, Quartile 3, ANC	126	124	1.25 (0.97~1.62)
Recovery, Quartile 4, ANC	119	130	1.48 (1.10~1.99)



RDV=remdesivir, CI=confidence interval, IMV: Invasive Mechanical Ventilation

Supplement Figure 7 shows treatment effect estimates by ANC risk quartiles rather than ACTT risk profile quartiles. Baricitinib + remdesivir improved recovery time in the highest quartile of ANC, but did not experience a treatment effect for IMV/death or death alone.

Supplement Figure 8. Fine-Gray subdistribution hazard ratios (HR) for the effect of baricitinib+remdesivir vs. placebo+remdesivir by baseline absolute neutrophil count (ANC) deciles.

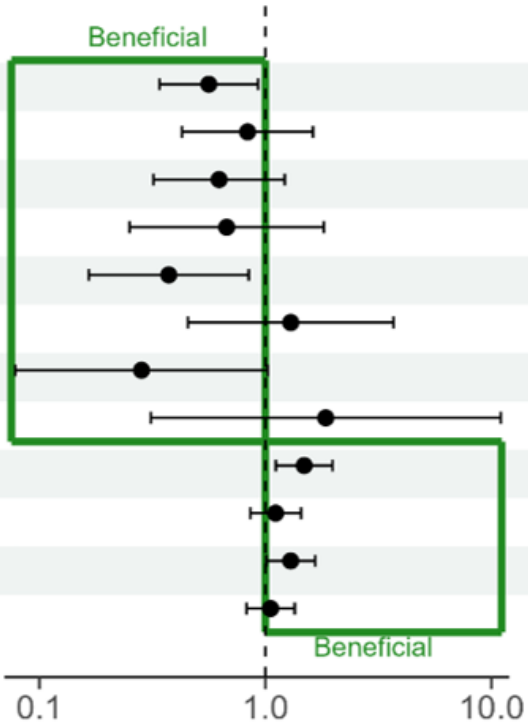


Supplement Figure 8 shows an analysis by ANC deciles, which also does not provide evidence for a threshold defining a subgroup that benefits most.

IMV: Invasive Mechanical Ventilation, RDV: remdesivir

Supplement Figure 9. Fine-Gray subdistribution hazard ratios (HR) for the effect of baricitinib+remdesivir vs. placebo+remdesivir by absolute lymphocyte count (ALC) quartiles instead of ACTT risk profile quartiles

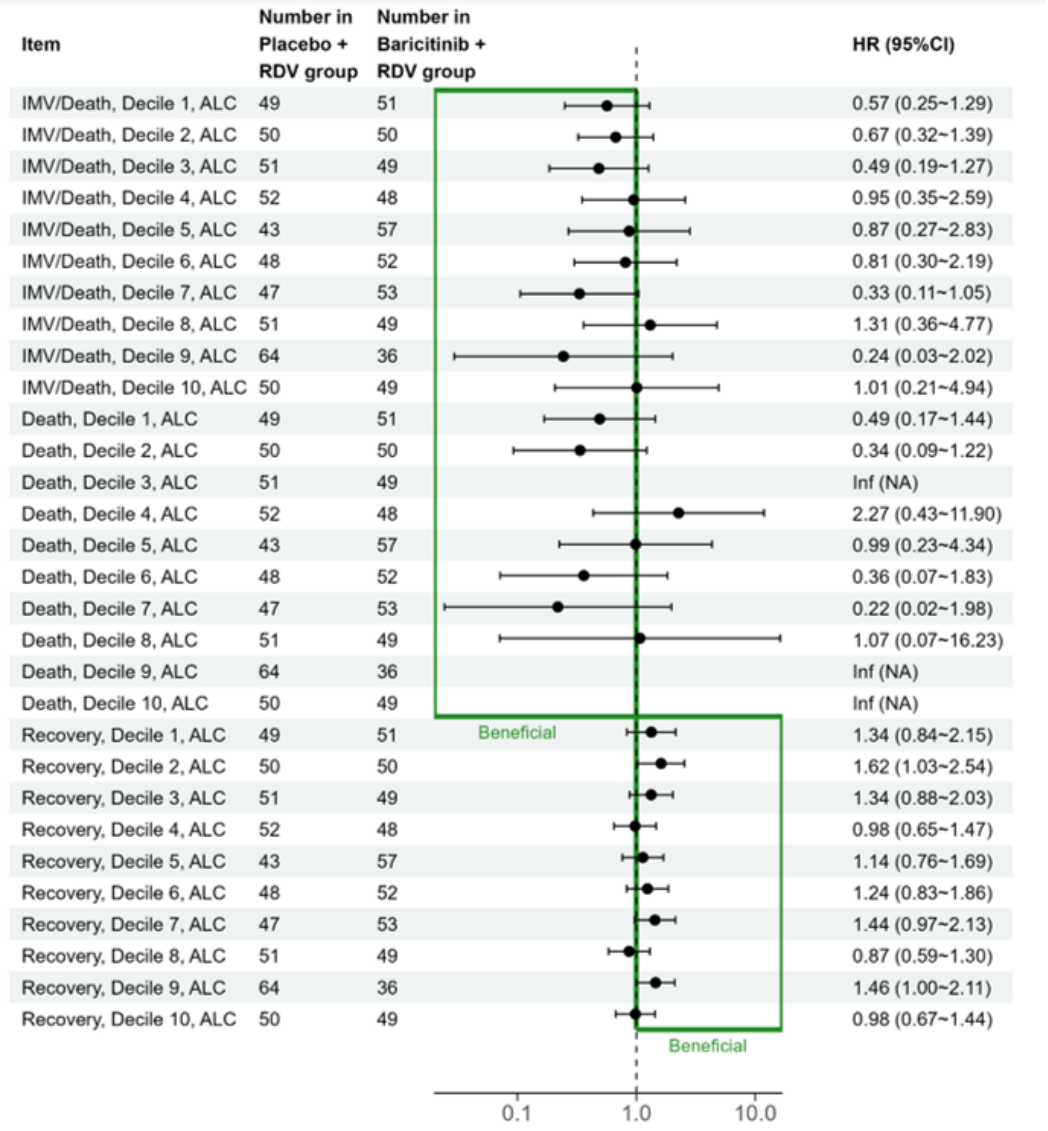
Item	Number in Placebo + RDV group	Number in Baricitinib + RDV group	HR (95%CI)
IMV/Death, Quartile 1, ALC	123	127	0.56 (0.34~0.93)
IMV/Death, Quartile 2, ALC	122	128	0.83 (0.43~1.63)
IMV/Death, Quartile 3, ALC	122	128	0.62 (0.32~1.22)
IMV/Death, Quartile 4, ALC	138	111	0.67 (0.25~1.81)
Death, Quartile 1, ALC	123	127	0.37 (0.17~0.84)
Death, Quartile 2, ALC	122	128	1.29 (0.45~3.70)
Death, Quartile 3, ALC	122	128	0.28 (0.08~1.03)
Death, Quartile 4, ALC	138	111	1.85 (0.31~11.02)
Recovery, Quartile 1, ALC	123	127	1.48 (1.11~1.98)
Recovery, Quartile 2, ALC	122	128	1.11 (0.86~1.44)
Recovery, Quartile 3, ALC	122	128	1.29 (1.01~1.66)
Recovery, Quartile 4, ALC	138	111	1.05 (0.82~1.35)



RDV=remdesivir, CI=confidence interval, HR= Hazard Ratio

Supplement Figure 9 shows treatment effect estimates by ALC risk quartiles rather than ACTT risk profile quartiles. The lowest ALC quartile (defined by ALC < 0.74 10^9/L) benefits most from baricitinib+remdesivir for all outcomes analyzed, but the treatment effects in the other three quartiles do not show a pattern. The median ALC was 1.0, so a threshold of 1.0 would combine the first and second quartiles. Since treatment effects for the second quartile are much closer to the null value, combining these groups would dilute the treatment effect in the subgroup, so a threshold ALC of 1.0 would be less informative than 0.74.

Supplement Figure 10. Fine-Gray subdistribution hazard ratios (HR) for the effect of baricitinib+remdesivir vs. placebo+remdesivir by baseline absolute lymphocyte count (ALC) deciles.



Supplement Figure 10 shows the same analysis by deciles of ALC to identify a more precise threshold for defining a group benefitting most. The treatment effect estimates in the lower three deciles are similar and do not provide evidence of an alternate numeric threshold for ALC.

RDV: remdesivir, CI: confidence interval, IMV: invasive mechanical ventilation

Supplement Table 12: Fractions and percentages of ACTT-2 participants receiving steroids prior to enrollment by ACTT risk profile quartile and treatment arm.

Fraction indicates the number of participants per quartile per treatment arm. Parenthesis value indicates percentage of participants per quartile per treatment arm

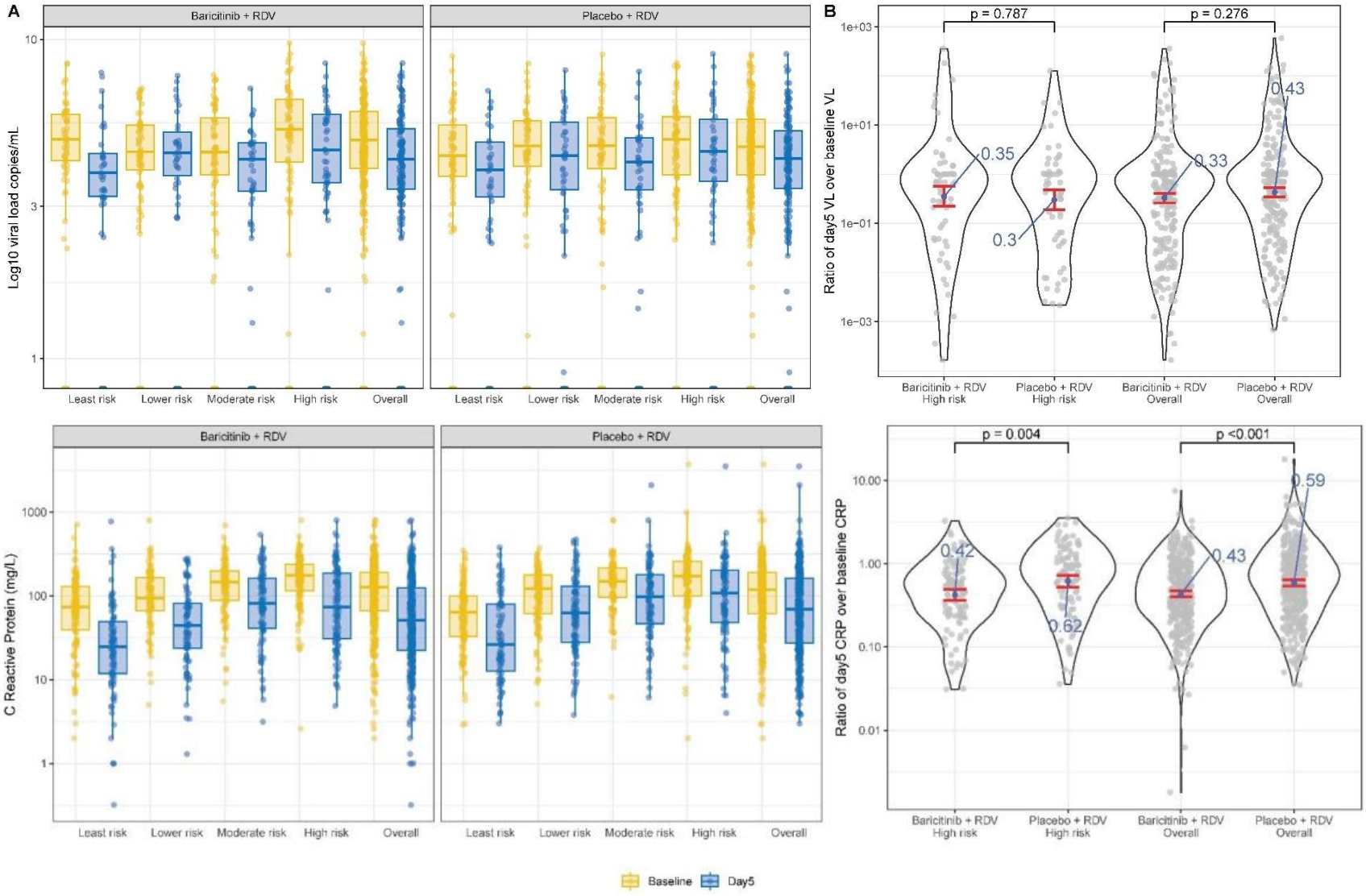
Arms	Least risk†	Lower risk	Moderate risk	High risk	Total
Steroid use					
Placebo + remdesivir	3/139(2.2)	2/133(1.5)	2/105(1.9)	5/128(3.9)	12/505(2.4)
Baricitinib + remdesivir	3/132(2.3)	4/103(3.9)	1/116(0.9)	1/143(0.7)	9/494(1.8)
Dexamethasone use					
Placebo + remdesivir	1/139(0.7)	0/133(0)	2/105(1.9)	1/128(0.8)	4/505(0.8)
Baricitinib + remdesivir	0/132(0)	1/103(1.0)	1/116(0.9)	0/143(0)	2/494(0.4)

Supplement Table 13: Fractions and percentages of ACTT-1 and ACTT-2 participants receiving steroids at any point during the study period by ACTT risk profile quartile and treatment arm.

Study	Arms	Least risk	Lower risk	Moderate risk	High risk	Total
ACTT-1	Placebo	23/121 (19%)	22/132 (17%)	42/141 (30%)	39/124 (31%)	126/518 (24%)
	Remdesivir	26/121 (21%)	26/145 (18%)	32/150 (21%)	31/117 (26%)	115/533 (22%)
ACTT-2	Placebo+ Remdesivir	18/139 (13%)	31/133 (23%)	29/105 (28%)	39/128 (30%)	117/505(23%)
	Baricitinib+ Remdesivir	18/132 (14%)	19/103 (18%)	27 /116 (23%)	39/143 (27%)	103/494(21%)

Fraction indicates the number of participants per quartile per treatment arm. Parenthesis value indicates percentage of participants per quartile per treatment arm.

Supplement Figure 11: Changes in log_{10} viral load (upper panels) or C-reactive protein (CRP) (lower panels) after initiation of treatment with baricitinib+ remdesivir vs. placebo+remdesivir, by ACTT risk quartile.



Supplement Figure 11 (continued, from page 33): Changes in log_{10} viral load (upper panels) or C-reactive protein (CRP) (lower panels) after initiation of treatment with baricitinib+remdesivir vs. placebo+remdesivir, by ACTT risk quartile. Panel A represents the distribution of log_{10}viral load and CRP measurements in individual participants, by quartile, at baseline (yellow) and at day 5 (blue). Panel B presents the distributions of ratio change log_{10}viral load and CRP measurements from baseline to Day 5 in the high-risk quartile, and in the study population overall, by treatment arm. The center of the ratio change distribution is quantified by the geometric mean of the ratio change with 95% CI. P-values are from t-tests on the log-transformed ratio changes. Participants with missing Day 5 measurements were excluded from this figure. VL: viral load, RDV: remdesivir

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