Viral and host factors are associated with mortality in hospitalized COVID-19 patients

ACTIV-3/TICO Study Group*

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Summary: COVID-19 mortality risk of virus, host factors

Abstract

Background: Persistent mortality in adults hospitalized due to acute COVID-19 justifies pursuit of disease mechanisms and potential therapies.

Objective: To evaluate which virus and host response factors associate with mortality risk among participants in Therapeutics for Inpatients with COVID-19 (TICO/ACTIV-3) trials.

Design: A secondary analysis of 2625 participants randomized to one of five antiviral products or matched placebo.

Setting: 114 centers on four continents

Participants: Adults hospitalized for acute SARS-CoV-2 infection

Measurements: Uniform, site-level collection of participant baseline clinical variables. Research laboratories assayed baseline upper respiratory swabs for SARS-CoV-2 viral RNA and plasma for anti-SARS-CoV-2 antibodies, SARS-CoV-2 nucleocapsid antigen (viral Ag), and interleukin-6 (IL-6). Associations between factors and time to mortality by 90 days were assessed using univariate and multivariable Cox proportional hazards models.

Results: Viral Ag ≥4500 ng/L (vs <200 ng/L, aHR 2.07, 1.29--3.34), viral RNA (<35,000 copies/mL (aHR 2.42, 1.09-5.34), ≥35,000 copies/mL (aHR 2.84, 1.29-6.28), vs. below detection), respiratory support (<4L O_2 (aHR 1.84 (1.06-3.22), ≥4L O_2 (aHR 4.41, 2.63-7.39), or non-invasive ventilation / high-flow nasal cannula (aHR 11.30, 6.46-19.75) vs. no oxygen)), renal impairment (aHR 1.77, 1.29-2.42), and IL-6 >5.8 ng/L (aHR 2.54, 1.74-3.70, vs ≤5.8 ng/L) were significantly associated with mortality risk in final adjusted analyses.

Limitations: Viral Ag, viral RNA, and IL-6 were not measured in real-time.

Conclusions: Baseline viral-specific, clinical, and biological variables are strongly associated with mortality risk within 90 days, revealing potential pathogen and host response therapeutic targets for acute COVID-19 disease.

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Keywords: acute COVID-19, viral factors, host response

Introduction

Mortality in adults hospitalized with COVID-19 is unacceptably high, ranging from 5-15% during delta, early omicron, and later omicron variant periods,(1) justifying continued assessment of clinical variable and biomarker assocations with relevant outcomes. By leveraging clinical trials that enroll patients with standardized data and biospecimen collection, secondary analyses of trial data provide a resource to better understand predictors of clinical outcomes, and may also identify higher risk subpopulations defined by biological variables for whom mechanism-based interventions may be considered in future studies.

COVID-19 risk prediction models have utilized patient demographic variables including older age, male sex, and comorbid conditions including diabetes mellitus, hypertension, chronic lung disease, and cardiovascular disease that are associated with worse COVID-19 outcomes.(2-4) Integration of electronic health record (EHR)-based clinical and laboratory data,(5, 6) and blood-based host biomarkers that reveal inflammatory status, improves model prediction,(7-9) and can prospectively identify COVID-19 trial eligiblity.(10, 11) However, biomarkers of host tissue injury or pathogen burden that require measurement outside of clinical laboratories have not been broadly reported for COVID-19 mortality risk prediction.

SARS-CoV-2 viral burden quantified by viral RNA or antigen levels in the upper respiratory tract has shown inconsistent association with clinical outcomes and little relation to systemic markers.(12-14) In contrast, serum SARS-CoV-2 RNA levels are generally associated with markers of clinical COVID-19 disease progression, including mortality.(15) More recent work has also demonstrated the importance of plasma viral antigen as an independent predictor of in-hospital outcomes.(16, 17)

Adding plasma-based viral markers plus inflammatory and tissue damage biomarkers to clinical data may reveal pathogen-host COVID-19 disease mechanisms and help identify precision-based therapies appropriate for higher risk disease populations.(18, 19) The aim of this work was to evaluate the association of baseline variables with risk of mortality by integrating viral-specific, host-related, and clinical factors among participants enrolled in Therapeutics for Inpatients with COVID-19 (TICO/ACTIV-3) randomized clinical trials.

Methods

Participants

We report secondary analyses of 2625 adults aged 18 years and older hospitalized for acute COVID-19 whom were enrolled in the IRB-approved TICO platform trial (NCT04501978) from August 2020 – November 2021 across 114 sites on four continents.(20-25) Participants were required to have an attributable symptom onset ≤12 days prior to enrollment, with additional trial-specific criteria included in the supplement (**Supplement, p.2-5**). For the modified intention-to-treat population (n=2625), participants were randomly assigned to receive one of five antiviral products (bamlanivimab, sotrovimab, amubarvimab–romlusevimab, tixagevimab–cilgavimab, and ensovibep) or matched placebo and received all or part of the assigned study product. Following informed consent, baseline clinical data and biospecimens were collected 0-24 hours prior to randomization and evaluted in this study. Pulmonary status was re-assessed immediately prior to randomization.

Central Laboratory Measurements

Baseline plasma samples were used to measure interleukin-6 (IL-6) via electrochemiluminescence (Meso Scale Discovery), anti-spike (S) neutralizing antibody using a surrogate viral neutralization test (GenScript cPass**, Supplement, p.6)**, anti-nucleocapsid (N)–binding antibodies (Bio-Rad Platelia SARS-CoV-2 Total Antibody Test, **Supplement, p.6**), and quantitative plasma SARS-CoV-2 nucleocapsid antigen (viral Ag) by microbead-based immunoassay (Quanterix).(17) SARS-CoV-2 viral RNA levels were measured from a mid-turbinate nasal (upper respiratory) swab collected concurrent with the plasma sample,(16, 26) quantified and assessed for Delta variant using reverse transcriptase PCR (RT-PCR) assay (**Supplement, p.6-7).** Subsequent sequencing analyses revealed 99.6% concordance with the RT-PCR assay for the Delta variant.

Clinical Data

Common case report forms collected baseline data on each TICO trial participant including demographic characteristics, geographic location, infection time period, pre-COVID comorbidities , SARS-CoV-2 vaccination status , days since COVID-19 symptom onset, concomitant medications, COVID clinical severity including pulmonary status, modified Borg dyspnea scale, National Early Warning Score (NEWS),(27) and clinical laboratory measurements; a full list of all variables under each category is available (**Supplement, p.7-8**).

Statistical Analysis

Baseline factors associated with mortality through Day 90 were identified using univariate and multivariable Cox proportional hazards models. All multivariable models presented included

adjustment for age, sex, race/ethnicity, residence, geographical region, infection time period, active or placebo treatment group, and baseline pulmonary status. Informed by prior COVID-19 studies, three models were constructed to test for associations with time to mortality: one examining predisease participant characteristics (demographics, BMI, and comorbid conditions),(2-4) one examining disease incident characteristics, and one combining the significant results of the other two models (excluding comorbid conditions observed in less than 5% of participants). The multivariable model for disease incident characteristic included symptom duration, vaccination, viral RNA, viral Ag, anti-S Ab , anti-N Ab, measures of clinical severity, C-reactive protein, absolute lymphocyte count, estimated glomerular filtration rate, and interleukin-6.(7-11) Adjusted hazard ratios (aHR, 95% CI) with significance ($P<0.05$) are reported; aHR > 1 signified worse mortality.

Participants were followed until day 90, death, or lost to follow-up, and for the primary analysis were censored at the date last known to be alive.. Some baseline values of IL-6 and viral Ag were missing (5.7% and 3.1% respectively), so multiple imputation was used to assess the sensitivity of the complete case analysis to missingness of these variables (**Supplement, p.9-10**).

The presence of interactions between viral Ag and other baseline variables was assessed by including an interaction term in the adjusted Cox proportional hazards model. For the final adjusted model, we tested the proportional hazards assumption and subsequently conducted an analysis stratified by geographical region. The relationship between viral Ag as a continuous variable and mortality HR was plotted using a restricted cubic spline. While the significance

level has been controlled at the conventional level of 5%, due to the large number of hypothesis tests presented here, the results should be interpreted carefully.

Two additional sensitivity analyses were performed. The first limited the cohort to only participants randomized to placebo to exclude any treatment effect. A second cohort excluded participants randomized to the tixagevimab–cilgavimab trial that enrolled the most participants and a greater proportion of higher respiratory support, helping assess validity with lower respiratory illness severity.(23) All analyses were done using SAS, version 9.4 (SAS Institute), or R, version 4.0 (R Foundation). Further details on statistical methods are provided (**Supplement, pp.2-10**).

Role of the Funding Source

Investigators from the National Institutes of Health were directly involved in all aspects of this study, including study design, data collection, analysis, and interpretation, as well as report writing.

Results

Baseline Clinical and Viral-Specific Cohort Characteristics

Between August 2020 and November 2021, 2694 adults hospitalized for acute SARS-CoV-2 infection were enrolled in five TICO randomized controlled trials. We report on baselinevariables as risk factors for mortality for 2625 participants in the mITT population (**Table 1**). The median age was 57 years (IQR 46, 68), 58% were male, and 42% Black or Hispanic, and 78% of participants were enrolled in the United States.

Median (IQR) time from symptom onset to randomization was eight days (6,10), and 10% of participants had previously received two vaccine doses. The overall median (IQR) baseline plasma viral Ag was 1445 ng/L (234, 4731), and 57% of participants had a viral Ag ≥1000 ng/L.(16) Forty-three percent had viral RNA levels of 35,000 or more copies/mL, 52% were positive for anti-S and 62% were positive for anti-N SARS-CoV-2 antibodies. Baseline COVID-19 therapies included: corticosteroids (68%), remdesivir (61%, first dose median 1 day (IQR 1, 2) prior to randomization). A full set of baseline variables with associated percent survival and death are presented in the supplement (**Table S1**). Timing from symptom onset, most recent positive test, and hospitalization to randomization are described by TICO trial (**Table S2**).

Clinical variables to assess COVID-19 severity are also reported in Table 1. At baseline, most participants required no or low levels of oxygen support. Twenty percent reported "severe-maximal" dyspnea (score 5-10) on the Borg dyspnea scale. Other clinical biomarkers of inflammation or organ damage were also frequently abnormal, including an absolute lymphocyte count (ALC) <0.9 x10^9/L (55%) and C-reactive protein (CRP) >75 mg/L (43%).

<u>Association of Participant Clinical and Viral-Specific Variables with Mortality Risk</u>

We assessed demographic variables and pre-existing comorbidities for association with time to mortality by day 90 (**Table 2**). A Kaplan-Meier curve for mortality was constructed (**Supp. Figure 1**), with 84 (3.2%) participants censored prior to day 90. Compared with the US, participants enrolled in Europe had lower mortality (aHR-0.33, 0.20-0.57), and participants enrolled in Africa had higher mortality (aHR-3.88, 2.34-6.43).

We also assessed medications administered prior to randomization for their association with mortality (**Table S3**), including remdesivir (aHR 0.65, 0.48-0.86), corticosteroids (aHR 0.94, 0.68-1.29), prophylactic dose heparin (aHR 1.14, 0.86-1.51), and intermediate/therapeutic dose heparin (aHR 1.47, 0.97-2.24).

Among COVID-19 characteristics (**Table 3**), symptom duration and vaccination were not significantly associated with time to mortality in adjusted models. Higher plasma antigenemia was significantly associated with increased mortality as a binary factor (aHR 2.24, CI 1.66, 3.02, viral Ag ≥1000 ng/L), or by quartiles (aHR-2.99, CI 2.02-4.43, for viral Ag ≥4500 ng/L versus Ag<200 ng/L). Viral RNA <35,000 (aHR-2.50, CI 1.25-4.99) and ≥35,000 (aHR-3.94, CI 2.00-7.76) copies/mL were associated with increased mortality (versus viral RNA below limit of detection). Presence of either anti-SARS-CoV-2 Ab was associated with reduced mortality. To better characterize the association of effective vaccination with mortality risk, we evaluated the impact of having received two vaccine doses with a positive anti-S Ab (n=181), a group that had a comparative mortality risk aHR of 0.66 (CI 0.41-1.07, p=0.09).

For clinical measures of COVID severity (**Table 3**), compared with participants requiring no oxygen, we observed significant and increasing mortality risk for higher baseline respiratory support requirements. A severe to maximal Borg scale score versus nothing to slight was associated with increased mortality risk (aHR-1.46, 1.04-2.05), even after adjusting for level of respiratory support. In addition, clinical and laboratory variables that are markers for systemic inflammation (CRP, IL-6) or organ-level damage (ALC, serum creatinine, eGFR) were also individually significantly associated with mortality in adjusted analyses.

Association Between Participant Variables and Impact on Mortality Risk

A model that further examined the impact of plasma viral Ag by also adjusting for anti-S by anti-N Ab status demonstrated that mortality risk was primarily derived from viral Ag level (**Table S4**), as the highest aHR was only partially reduced in the presence of one or both Abs **(Supp. Figure 2**). Models that examined the impact of either anti-SARS-CoV-2 Ab in conjunction with log10 viral Ag revealed that neither Ab was a significant predictor of mortality given the effect of viral Ag and other covariates (**Table S4**). Additionally, when we assessed viral antigen adjusted for demographic variables, treatment arm, and respiratory severity, the aHR for mortality appeared to increase for increasing viral Ag levels ($p<0.001$) (**Supp. Figure 3**).

We also evaluated the relationship between plasma viral Ag and upper respiratory viral RNA and their association with mortality. Most participants with viral Ag >200 ng/L had quantifiable viral RNA (1720/1876, 91.7%), and in participants with quantifiable viral RNA, the aHR for mortality was significantly increased when viral Ag ≥4500 ng/L (**Table S5**). Participants without quantifiable viral RNA and viral Ag <200 ng/L had a significantly lower mortality risk than those with quantifiable viral RNA and viral Ag <200 ng/L, with cumulative data suggesting these factors were additive (**Supp. Figure 4**).

To better understand the relationship between viral Ag level and specific clinical variables and their association with mortality, we first evaluated viral Ag level and baseline pulmonary status (**Figure 1, Table S6**). There was an additive impact of higher viral Ag levels on the hazard for mortality amongst participants requiring NIV or HFNC, maximally with viral Ag >4500 ng/L (aHR-40.4, 14.0-116.4). The impact of viral Ag and other clinical variables including Borg dyspnea scale, NEWS score, CRP, IL-6, ALC, and eGFR on mortality were assessed (**Supp.**

Figures 5-10). Mortality risk appeared additive among participants with elevated inflammatory markers CRP (>75 mg/L) (**Supp. Figure 7**) or IL-6 (>5.8 ng/L) (**Supp. Figure 8**), or reduced ALC (<0.9 x 10^9 / L) (**Supp. Figure 9**) in the presence of higher viral Ag levels.

We also assessed the relationship of CRP and IL-6, systemic markers of inflammation, with viral Ag. CRP >75 mg/L (aHR-1.40, 1.03-1.91, vs. CRP <50 mg/L) or IL-6 >5.8 ng/L (aHR-2.59, 1.83-3.66 vs. IL-6 ≤5.8 ng/L) were significantly associated with increased mortality risk even after adjusting for log10 viral Ag (**Table S7, S8**); viral Ag remained significantly associated with mortality risk after adjusting for CRP (aHR-3.03, 2.02-4.53) or IL-6 (aHR-2.31, 1.53-3.48) for Ag ≥4500 vs. <200 ng/L, with minimal impact due to collinearity between CRP and IL-6 (**Table S9**).

A multivariable model that included key viral and clinical factors demonstrated significant associations with mortality risk for viral Ag, viral RNA, pulmonary status, IL-6, and eGFR, along with demographic variables age, region, and infection period (**Table 4**). Visualization of adjusted survival curves by plasma viral Ag (**Supp. Figure 11**), upper respiratory viral RNA (**Supp. Figure 12**), or IL-6 (**Supp. Figure 13**) support the model results in Table 4. For this model, the proportional hazards assumption was violated (p=0.004), with region a significant variable when tested individually (p<0.001). Because the effect of region could differ over time during the COVID-19 pandemic, we re-ran the model with region as a stratification variable, and observed similar results for other co-variates (**Table S10**)with a valid proportional hazards assumption (p=0.26). An association between missingness of IL-6 and viral Ag and mortality was observed, and the association between viral Ag and mortality was not accounted for by other relevant predictors (**Table S11**). To account for variable missingness, the final model fit using multiple imputation revealed consistent results (**Table S12**).

In an analysis limited to participants randomized to placebo, significant associations with mortality risk for viral Ag, higher levels of respiratory support, and clinical laboratory markers remained (**Table S13**). When excluding participants from the tixagevimab–cilgavimab TICO trial, viral Ag, O_2 ≥4L/min or NIV/HFNC respiratory support levels, as well as several clinical laboratory markers retained significance with similar point estimates as the primary model (**Table S14)**.

Discussion

In a secondary analysis of data from 2625 participants enrolled in five placebo-controlled clinical trials conducted under the TICO master protocol, we observed that several virus-specific and host biomarkers had a strong association with mortality risk by day 90. Importantly, biomarkers assayed in research laboratories, including plasma viral Ag, upper respiratory viral RNA, and IL-6, were among the most strongly associated with mortality risk, adding potential biological insights to the robust literature on COVID-19 prognosis and prediction factors that has typically relied on clinically obtained data.(28-30) Our results support emerging data for plasma viral antigen as an important predictor of clinical outcomes following SARS-CoV-2 infection,(16, 17) but also reveal the importance of upper respiratory viral RNA. These results also suggest additive mortality risk for individuals with higher viral Ag or viral RNA levels and abnormal biomarker values that reflect systemic inflammation or organ damage. Our findings support continued assessment of therapies that reduce plasma viral replication or target pathways of tissue injury to attempt to limit organ damage and related clinical outcomes.

When we assessed the relationship of virus-specific variables with each other and to mortality, SARS-CoV-2 plasma viral antigen and upper respiratory viral RNA, as opposed to anti-SARS-CoV-2 antibodies, emerged as key risk factors, yet the impact of antiviral therapy on these viral measures and subsequent clinical outcomes is not known. Notably, because vaccination rates were low during our study, it may be important to evaluate novel antiviral therapies in the current state of increased vaccination rates and bivalent SARS-CoV-2 vaccine availability, yet reports of waning primary series vaccine effectiveness against Omicron.(31)

Prior COVID-19 trials demonstrated steroid or anti-IL-6/IL-6 receptor therapeutic benefit,(10, 32, 33) as well as steroid-induced CRP reduction.(34) However, our final adjusted model suggests IL-6 but not CRP is associated with mortality, thus it may be important to further evaluate anti-inflammatory therapies in combination with anti-viral therapies that effectively reduce plasma viral Ag and viral RNA levels. Absence of real-time assays for viral antigen, RNA or IL-6 currently limits deploying this type of adaptive, precision-based therapeutic approach.

In addition to confirming prior COVID-19 studies that identify the degree of baseline respiratory support as a strong predictor of mortality risk,(33) our analyses show additive risk for mortality amongst participants with higher levels of virus who require NIV or HFNC levels of respiratory support. Interestingly, greater respiratory distress quantified on the Borg dyspnea scale was also associated with increased mortality risk even after adjusting for baseline respiratory support requirements, and may suggest a potential relationship between increased dyspnea and higher viral antigen burden or other clinical markers of inflammation and multiorgan injury.

Limitations

There are a few noteworthy limitations in our findings. One, our cohort was predominantly not vaccinated (~80%), therefore some results may be harder to interpret as we consider current COVID-19 disease interventions.. Two, we observed noteworthy regional differences in aHR for mortality. Median time from symptom onset to randomization was similar across regions, and the number of trial participants on room air at baseline per region was not proportional to observed morality hazard ratios), suggesting that illness duration or severity at baseline may not be major contributors to regional differences in mortality risk. Variability in trial accrual by site and region, along with uncertainty around directive COVID-19 related care and post-hospitalization resources preclude full evaluation of the validity of apparent regional differences in mortality risk. Three, COVID-19 therapies including vaccines, remdesivir, or corticosteroids for COVID-19 may be subject to confounding by indication and impact clinical trajectory in unmeasured ways not accounted for in adjusted analyses using only baseline data.

Conclusions

In a large, diverse cohort comprising TICO clinical trial participants, several virus-related and clinical variables measured early during hospitalization for COVID-19 were significantly associated with risk of mortality within 90 days. With its levels strongly associated with increased mortality, high viral antigen and viral RNA may represent ongoing viral replication and possible systemic spread that could warrant augmentation of anti-viral therapy. Furthermore, host biomarkers measured at early time points, including eGFR and IL-6, were

strongly associated with mortality. As such, it is critical to study how abnormal biomarkers reflect the host viral response at the organ and tissue levels and to identify and prioritize potential precision-based therapeutic targets, particularly as additional real-time biomarker assays become available.

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408 **Table 1. Baseline Characteristics**

	Did not Die (n=2364)		Died (n=261)		% in Subgroup* (n=2625)
	N	%	N	%	
Demographics					
Age - med. (IQR) years	56 (45 - 67)		67 (57 - 76)		
18-39 years	347	97.2	10	2.8	13.6
40-49 years	457	94.8	25	5.2	18.4
50-59 years	585	93.3	42	6.7	23.9
60-69 years	502	87.3	73	12.7	21.9
70-79 years	344	84.7	62	15.3	15.5
≥ 80 years	129	72.5	49	27.5	6.8
Sex					
Male	1355	89.5	159	10.5	57.7
Female	1009	90.8	102	9.2	42.3
Race/ethnicity					
Asian	112	92.6	9	7.4	4.6
Black	558	88.9	70	11.1	23.9
Hispanic	430	89.0	53	11.0	18.4
White	1178	90.4	125	9.6	49.6
Other	86	95.6	4	4.4	3.4
Region					
Africa	100	76.3	31	23.7	5.0
Asia	38	90.5	4	9.5	1.6
Europe	378	96.2	15	3.8	15.0
United States	1848	89.8	211	10.2	78.4
Residence					
Independent, w/o assistance	2233	90.4	237	9.6	94.1
Other	131	84.5	24	15.5	5.9
Infection time period					
Pre 2021	377	93.3	27	6.7	15.4
Jan-Jun 2021	983	92.8	76	7.2	40.3
Jul-Nov 2021	1004	86.4	158	13.6	44.3
Treatment group					
Active	1345	91.0	133	9.0	56.3
Placebo	1147	88.8	128	11.2	43.7
COVID Characteristics					
Symptom duration- med. (IQR) days	8 (6 - 10)		8 (5 - 9)		
< 5	359	90.2	39	9.8	15.2
5 - 7	686	89.7	79	10.3	29.1
8 - 10	985	90.4	104	9.6	41.5
> 10	334	89.5	39	10.5	14.2
# vaccine doses					
0	1949	90.7	201	9.3	82.6
1	166	90.2	18	9.8	7.1

2	228	85.1	40	14.9	10.3
Plasma viral Ag - med. (IQR) ng/L	1296 (199 - 4152)		4775 (1038 - 11702)		
1000+	1270	87.3	185	12.7	57.2
< 1000	1030	94.7	58	5.3	42.8
Upper resp. viral RNA					
Negative	325	97.3	9	2.7	13.3
< 35,000 copies/mL	1007	92.6	80	7.4	43.3
35,000+ copies/mL	930	85.2	161	14.8	43.4
Anti-S Ab					
Positive	1200	91.5	112	8.5	51.6
Negative	1100	89.4	131	10.6	48.4
Anti-N Ab					
Positive	1442	90.9	144	9.1	62.3
Negative	859	89.7	99	10.3	37.7
Variant					
Delta	729	84.1	138	15.9	48.6
Not Delta	844	92.0	73	8.0	51.4
Comorbid Conditions					
Diabetes					
Yes	651	88.0	89	12.0	28.2
No	1713	90.9	172	9.1	71.8
Hypertension					
Yes	1057	88.0	144	12.0	45.8
No	1307	91.8	117	8.2	54.2
Renal impairment					
Yes	217	83.5	43	16.5	9.9
No	2147	90.8	218	9.2	90.1
BMI - med. (IQR)	31 (26 - 36)		28 (25 - 35)		
< 18.5 (underweight)	39	81.3	9	18.8	1.8
18.5-24.9 (healthy)	382	88.6	49	11.4	16.5
25-29.9 (overweight)	671	88.2	90	11.8	29.1
30-39.9 (obese)	914	92.0	80	8.0	38.0
≥ 40 (morbidly obese)	350	91.6	32	8.4	14.6
Concomitant Medications Prior to Randomization					
Immunomodulators					
Yes	134	79.3	35	20.7	6.4
No	2230	90.8	226	9.2	93.6
Corticosteroids					
Yes	1584	88.7	202	11.3	68.0
No	780	93.0	59	7.0	32.0
Remdesivir					
Yes	1457	90.5	153	9.5	61.3
No	907	89.4	108	10.6	38.7
COVID Severity					

Pulmonary status					
No O_2	636	96.5	23	3.5	25.1
O_2 < 4 L/min	906	95.3	45	4.7	36.2
O_2 ≥ 4 L/min	623	85.5	106	14.5	27.8
Non-invasive vent./HFNC	199	69.6	87	30.4	10.9
Borg Dyspnea Scale					
0-2 (nothing to slight)	1071	92.8	83	7.2	47.8
3-4 (mod-somewhat severe)	706	89.8	80	10.2	32.5
5-10 (severe-maximal)	406	85.5	69	14.5	19.7
NEWS					
< 2	306	96.8	10	3.2	12.1
2-3	796	93.6	54	6.4	32.5
4-5	755	90.5	79	9.5	31.9
≥ 6	495	80.9	117	19.1	23.4
Lymphocytes - med. (IQR) **$x10^9/L$**	0.85 (0.59 - 1.24)			0.61 (0.37 - 0.90)	
< 0.9	1235	86.6	191	13.4	55.3
0.9-1.5	750	94.2	46	5.8	30.9
> 1.5	337	94.4	20	5.6	13.8
Serum creatinine - med. (IQR) **umol/L (mg/dL)**	74.3 (61.9–96.4) (0.84 (0.70-1.09))			88.4 (66.3–125.6) (1.00 (0.75-1.42))	
< 97.3 (1.1)	1783	92.3	149	7.7	73.7
97.3-132.6 (1.1-1.5)	356	86.6	55	13.4	15.7
> 132.6 (1.5)	220	79.4	57	20.6	10.6
eGFR - med. (IQR) **$mL/min/1.73m^2$**	92 (71 - 108)			73 (46 - 97)	
< 60	406	80.2	100	19.8	19.3
≥ 60	1953	92.4	161	7.6	80.7
CRP - med. (IQR) **mg/L**	60 (26 - 112)			93 (51 - 161)	
< 50	995	94.0	63	6.0	40.9
50-75	378	91.7	34	8.3	15.9
> 75	956	85.8	158	14.2	43.1
IL-6 - med. (IQR) **ng/L**	5 (2 - 13)			15 (8 - 35)	
≤ 5.8	1189	96.4	44	3.6	49.8
> 5.8	1047	84.3	195	15.7	50.2

*Column percent

Med.=Median, IQR=interquartile range, w/o=without, Ag=antigen, Ab=antibody, Anti-S=anti-spike, Anti-N=anti-nucleocaspid, BMI=body mass index, O_2=supplemental oxygen, vent.=ventilation, HFNC=high flow nasal canula, resp=respiratory, NEWS=national early warning score, eGFR=estimated glomerular filtration rate, CRP=C-reactive protein, IL-6=interleukin 6

Table 2. Predictors of 90 Day Mortality – Demographics and Comorbidities

		Unadjusted	Adjusted*	
	N Pts.	HR (95% CI)	HR (95% CI)	p-value
Demographics				
Age (per 10 years older)	2625	1.55 (1.42 – 1.69)	1.70 (1.55 – 1.87)	<0.001
18-39 years	357	(ref.)	(ref.)	
40-49 years	482	1.85 (0.89 - 3.86)	2.05 (0.98 - 4.29)	0.055
50-59 years	627	2.39 (1.20 - 4.76)	2.72 (1.36 - 5.45)	0.005
60-69 years	575	4.72 (2.44 - 9.14)	5.29 (2.71 - 10.33)	<0.001
70-79 years	406	5.76 (2.95 - 11.23)	7.83 (3.97 - 15.45)	<0.001
≥ 80 years	178	11.29 (5.72 - 22.29)	16.81 (8.37 - 33.78)	<0.001
Race/Ethnicity				
Asian	121	0.77 (0.39 - 1.52)	0.87 (0.36 - 2.13)	0.77
Black	628	1.19 (0.89 - 1.59)	0.77 (0.53 - 1.10)	0.153
Hispanic	483	1.14 (0.82 - 1.57)	1.23 (0.88 - 1.72)	0.23
White	1303	(ref.)	(ref.)	
Other	90	0.46 (0.17 - 1.23)	0.48 (0.18 - 1.30)	0.147
Sex				
Male	1514	(ref.)	(ref.)	
Female	1111	0.87 (0.68 - 1.11)	0.89 (0.69 - 1.14)	0.34
Residence				
Independent w/o assistance	2470	0.60 (0.39 - 0.91)	0.84 (0.54 - 1.30)	0.43
All other	155	(ref.)	(ref.)	
Region				
Africa	131	2.63 (1.81 - 3.84)	3.88 (2.34 - 6.43)	<0.001
Asia	42	0.90 (0.33 - 2.41)	0.98 (0.26 - 3.70)	0.98
Europe	393	0.36 (0.21 - 0.61)	0.33 (0.20 - 0.57)	<0.001
United States	2059	(ref.)	(ref.)	
Infection time period				
Pre 2021	404	0.47 (0.31 - 0.70)	0.54 (0.35 - 0.82)	0.004
Jan-Jun 2021	1059	0.51 (0.39 - 0.67)	1.05 (0.76 - 1.44)	0.77
Jul-Nov 2021	1162	(ref.)	(ref.)	
Treatment group				
Active	1478	0.79 (0.62 - 1.01)	0.81 (0.64 - 1.04)	0.095
Placebo	1147	(ref.)	(ref.)	
Comorbid Conditions				
BMI				
< 18.5 (underweight)	48	1.67 (0.82 - 3.40)	0.93 (0.45 - 1.93)	0.85
18.5-24.9 (healthy)	431	(ref.)	(ref.)	
25-29.9 (overweight)	761	1.03 (0.73 - 1.45)	1.02 (0.71 - 1.47)	0.90
30-39.9 (obese)	994	0.69 (0.48 - 0.98)	0.80 (0.55 - 1.17)	0.25
≥ 40 (morbidly obese)	382	0.73 (0.47 - 1.14)	1.13 (0.70 - 1.83)	0.62
Asthma				

Yes	260	0.83 (0.54 - 1.29)	1.01 (0.65 - 1.57)	0.97
No	2365			
COPD				
Yes	167	1.09 (0.67 - 1.75)	0.81 (0.49 - 1.32)	0.39
No	2458			
Diabetes mellitus				
Yes	740	1.33 (1.03 - 1.72)	1.09 (0.84 - 1.42)	0.50
No	1885			
Heart failure				
Yes	116	1.77 (1.11 - 2.82)	1.28 (0.78 - 2.09)	0.33
No	2509			
Hypertension				
Yes	1201	1.49 (1.17 - 1.90)	1.14 (0.88 - 1.48)	0.31
No	1424			
Renal impairment				
Yes	260	1.89 (1.36 - 2.62)	1.49 (1.06 - 2.10)	0.022
No	2365			
HIV				
Yes	42	1.52 (0.68 - 3.42)	1.61 (0.71 - 3.65)	0.25
No	2583			
Other immune suppression				
Yes	82	2.00 (1.19 - 3.36)	1.97 (1.16 - 3.36)	0.012
No	2543			
Malignancy				
Yes	106	2.79 (1.86 - 4.18)	2.30 (1.51 - 3.50)	<0.001
No	2519			
Number of comorbidities†				
0	952	(ref.)	(ref.)	
1	790	1.45 (1.04 - 2.01)	1.13 (0.80 - 1.58)	0.49
2+	573	1.68 (1.19 - 2.37)	1.28 (0.89 - 1.85)	0.182

* Adjusted for age, sex, race/ethnicity, residence, geographical region, infection time period, treatment group, and baseline pulmonary status

† Including asthma, COPD, diabetes, heart failure, hypertension, renal impairment, HIV, other immune suppression, and malignancy

HR=hazard ratio, ref=reference group, w/o=without, BMI=body mass index, COPD=chronic obstructive pulmonary disease, HIV=human immunodeficiency virus

Table 3. Predictors for 90 Day Mortality – COVID Characteristics and Clinical Severity

	N Pts.	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	p-value
COVID Characteristics				
Symptom duration (days)				
< 5	398	(ref.)	(ref.)	
5 - 7	765	1.06 (0.73 - 1.56)	1.01 (0.68 - 1.50)	0.95
8 - 10	1089	0.97 (0.67 - 1.41)	0.99 (0.67 - 1.45)	0.96
> 10	373	1.07 (0.69 - 1.67)	1.05 (0.65 - 1.68)	0.85
Number of vaccine doses				
0	2150	(ref.)	(ref.)	
1	184	1.05 (0.65 - 1.70)	0.90 (0.55 - 1.47)	0.67
2	268	1.64 (1.17 - 2.31)	0.98 (0.67 - 1.44)	0.92
Anti-S Ab status				
Positive	1312	0.80 (0.62 - 1.03)	0.59 (0.46 - 0.77)	<0.001
Negative	1231	(ref.)	(ref.)	
Anti-N Ab status				
Positive	1586	0.88 (0.68 - 1.14)	0.74 (0.57 - 0.97)	0.031
Negative	958	(ref.)	(ref.)	
Anti-S x Anti-N Ab				
Anti-S +, Anti-N +	1058	0.77 (0.57 – 1.04)	0.54 (0.39 – 0.73)	<0.001
Anti-S +, Anti-N -	254	0.57 (0.38 – 0.96)	0.37 (0.22 – 0.64)	<0.001
Anti-S -, Anti-N +	527	0.80 (0.56 – 1.14)	0.69 (0.48 – 0.99)	0.043
Anti-S -, Anti-N -	704	(ref.)	(ref.)	
Plasma viral Ag ng/L				
< 200	609	(ref.)	(ref.)	
200 - 1499	680	1.06 (0.67 - 1.68)	0.97 (0.61 - 1.54)	0.89
1500 - 4499	595	1.45 (0.93 - 2.27)	1.38 (0.88 - 2.16)	0.162
≥ 4500	659	3.78 (2.58 - 5.55)	2.99 (2.02 - 4.43)	<0.001
1000+	1455	2.49 (1.85 - 3.34)	2.24 (1.66 - 3.02)	<0.001
< 1000	1088	(ref.)	(ref.)	
Upper resp. viral RNA				
Negative	334	(ref.)	(ref.)	
< 35,000 copies/mL	1087	2.79 (1.40 - 5.55)	2.50 (1.25 - 4.99)	0.009
35,000+ copies/mL	1091	5.79 (2.96 - 11.32)	3.94 (2.00 – 7.76)	<0.001
Clinical Severity				
Pulmonary status				
No O_2	659	(ref.)	(ref.)	
O_2 < 4 L/min	951	1.36 (0.82 - 2.25)	1.75 (1.05 - 2.90)	0.032
O_2 ≥ 4 L/min	729	4.44 (2.83 - 6.97)	5.16 (3.27 - 8.16)	<0.001

Non-invasive vent./HFNC	286	10.12 (6.39 - 16.02)	15.37 (9.29 - 25.44)	<0.001
Borg Dyspnea Scale				
0-2 (nothing to slight)	1154	(ref.)	(ref.)	
3-4 (mod-somewhat severe)	786	1.44 (1.06 - 1.96)	1.09 (0.79 - 1.50)	0.60
5-10 (severe-maximal)	475	2.07 (1.50 - 2.85)	1.46 (1.04 - 2.05)	0.029
NEWS				
< 2	316	(ref.)	(ref.)	
2-3	850	2.05 (1.04 - 4.03)	0.98 (0.44 - 2.17)	0.96
4-5	834	3.11 (1.61 - 6.00)	1.00 (0.44 - 2.26)	1.00
≥ 6	612	6.66 (3.49 - 12.70)	1.60 (0.70 - 3.63)	0.26
Lymphocytes x10⁹/L				
< 0.9	1426	(ref.)	(ref.)	
0.9-1.5	796	0.42 (0.30 - 0.57)	0.50 (0.36 - 0.70)	<0.001
> 1.5	357	0.41 (0.26 - 0.65)	0.50 (0.31 - 0.81)	0.005
Serum creatinine umol/L (mg/dL)				
< 1.1	1932	(ref.)	(ref.)	
1.1-1.5	411	1.80 (1.32 - 2.45)	1.67 (1.21 - 2.32)	0.002
> 1.5	277	2.92 (2.15 - 3.96)	2.77 (1.98 - 3.87)	<.001
eGFR mL/min/1.73m²				
< 60	506	2.82 (2.20 - 3.62)	2.29 (1.74 - 3.03)	<.001
≥ 60	2114	(ref.)	(ref.)	
CRP mg/L				
< 50	1058	(ref.)	(ref.)	
50-75	412	1.40 (0.92 - 2.12)	1.21 (0.80 - 1.84)	0.37
> 75	1114	2.46 (1.84 - 3.30)	1.71 (1.27 - 2.31)	<0.001
IL-6 ng/L				
≤ 5.8	1233	(ref.)	(ref.)	
> 5.8	1242	4.74 (3.42 - 6.58)	3.20 (2.28 - 4.47)	<0.001

* Adjusted for age, sex, race/ethnicity, residence, geographical region, infection time period, treatment group, and baseline pulmonary status

HR=Hazard ratio, ref.=reference group, Ag=antigen, Ab=antibody, Anti-S=anti-spike, Anti-N=anti-nucleocaspid, O_2=supplemental oxygen, resp=respiratory NEWS=national early warning score, eGFR=estimated glomerular filtration rate, CRP=C-reactive protein, IL-6=interleukin 6

Table 4. Predictors of Mortality – Multivariable Model Adjusted for Relevant Viral and Clinical Factors

	N Pts.*	HR (95% CI)†	p-value
Age			
18-39 years	323	(ref.)	
40-49 years	436	1.94 (0.90 - 4.20)	0.093
50-59 years	559	1.91 (0.91 - 4.01)	0.088
60-69 years	497	3.55 (1.73 - 7.29)	<0.001
70-79 years	359	4.29 (2.07 - 8.89)	<0.001
≥ 80 years	156	8.00 (3.72 - 17.22)	<0.001
Race/Ethnicity			
Asian	118	0.97 (0.39 - 2.42)	0.95
Black	559	0.66 (0.44 - 1.00)	0.052
Hispanic	426	1.27 (0.87 - 1.84)	0.21
White	1143	(ref.)	
Other	84	0.39 (0.12 - 1.25)	0.113
Sex			
Male	1347	(ref.)	
Female	983	0.88 (0.66 - 1.16)	0.36
Residence			
Independent w/o assistance	2194	0.72 (0.44 - 1.18)	0.19
All other	136	(ref.)	
Region			
Africa	129	5.45 (3.10 - 9.58)	<0.001
Asia	42	0.88 (0.23 - 3.34)	0.85
Europe	369	0.34 (0.19 - 0.60)	<0.001
United States	1790	(ref.)	
Infection time period			
Pre 2021	374	0.56 (0.36 - 0.89)	0.013
Jan-Jun 2021	923	0.97 (0.68 - 1.37)	0.86
Jul-Nov 2021	1033	(ref.)	
Treatment group			
Active	1318	0.84 (0.64 - 1.10)	0.21
Placebo	1012	(ref.)	
Pulmonary status			
No O_2	584	(ref.)	
O_2 < 4 L/min	852	1.84 (1.06 - 3.22)	0.032
O_2 ≥ 4 L/min	650	4.41 (2.63 - 7.39)	<0.001
Non-invasive vent./HFNC	244	11.30 (6.46 - 19.75)	<0.001
Plasma viral Ag ng/L			
< 200	549	(ref.)	
200 - 1499	616	1.03 (0.61 - 1.75)	0.90
1500 - 4499	553	1.24 (0.74 - 2.09)	0.41

≥ 4500	612	2.07 (1.29 - 3.34)	0.003
Upper resp. viral RNA			
Negative	305	(ref.)	
< 35,000 copies/mL	1024	2.42 (1.09 - 5.34)	0.029
35,000+ copies/mL	1001	2.84 (1.29 - 6.28)	0.010
Lymphocytes x10⁹/L			
≤ 1.5	2007	(ref.)	
> 1.5	323	0.77 (0.45 - 1.31)	0.34
eGFR mL/min/1.73m²			
< 60	439	1.77 (1.29 - 2.42)	<0.001
≥ 60	1891	(ref.)	
CRP‡ mg/L			
< 50	958	(ref.)	
50-75	368	0.96 (0.60 - 1.52)	0.85
> 75	1004	1.10 (0.78 - 1.55)	0.58
IL-6 ng/L			
≤ 5.8	1141	(ref.)	
> 5.8	1189	2.54 (1.74 - 3.70)	<0.001

* Number of participants in subgroup with all variables in multivariate model available (N=2330)
† Adjusted for all variables in the table
‡Also adjusted as a binary variable (≤ 75, >75), with adjusted HR 0.89 (0.67, 1.20), p=0.45 (not shown)
HR=hazard ratio, ref.=reference group, w/o=without, O_2=supplemental oxygen, resp=respiratory, Ag=antigen, eGFR=estimated glomerular filtration rate, CRP=C-reactive protein, IL-6=interleukin-6

Figure Legend

Figure 1: Day 90 Mortality by Baseline Pulmonary and Plasma Viral Antigen Status – Adjusted for age, sex, race/ethnicity, residence, geographical region, infection period, and treatment group

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