Optimal timing of remdesivir initiation in hospitalized COVID-19 patients administered with dexamethasone

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Summary: Initiation of remdesivir prior to or simultaneously with dexamethasone was associated with significantly shorter time to clinical improvement and positive IgG antibody, lower risk of death, in addition to a shorter length of hospital stay in patients with moderate COVID-19.

Abstract

Background: Evidence is lacking about any additional benefits of introducing remdesivir on top of dexamethasone, and the optimal timing of initiation.

Methods: In a territory-wide cohort of 10,445 COVID-19 patients from Hong Kong who were hospitalized between 21st January 2020 and 31st January 2021, 1544 patients had received dexamethasone during hospitalization. Exposure group consisted of patients who had initiated remdesivir prior to dexamethasone (n=93), or co-initiated the two drugs simultaneously (n=373); whereas non-exposure group included patients who were given remdesivir after dexamethasone (n=149), or those without remdesivir use (n=929). Multiple imputation and inverse probability of treatment weighting for propensity score were applied and hazard ratios (HR) of event outcomes were estimated using Cox regression models.

Results: Time to clinical improvement (HR=1.23, 95%CI 1.02-1.49, p=0.032) and positive IgG antibody (HR=1.22, 95%CI 1.02-1.46, p=0.029) were significantly shorter in the exposure group than that of non-exposure. The exposure group had a shorter hospital length of stay by 2.65 days among survivors, lower WHO clinical progression scale scores from five days of follow-up onwards, lower risks of in-hospital death (HR=0.59, 95%CI 0.36-0.98, p=0.042) and composite outcomes; and without experiencing an increased risk of ARDS. Differences in the cumulative direct medical costs between groups were no longer significant from 17 days of follow-up onwards.

Conclusions: Initiation of remdesivir prior to or simultaneously with dexamethasone was associated with significantly shorter time to clinical improvement and positive IgG antibody, lower risk of in-hospital death, in addition to shorter length of hospital stay in patients with moderate COVID-19.

Keywords: COVID-19, remdesivir, dexamethasone, time to clinical improvement, length of hospital stay

Introduction

In respond to the Coronavirus Disease 2019 (COVID-19) pandemic, a number of pharmaceutical agents have been repurposed for managing hospitalized patients with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection,[1, 2] where remdesivir and dexamethasone are two potential drugs under consideration.[3, 4] International guidelines generally recommend remdesivir for hospitalized COVID-19 patients requiring supplemental oxygen but not mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and dexamethasone among those requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO.[5-8]

For patients requiring supplemental oxygen but not invasive mechanical ventilation or ECMO, some guidelines suggest the combination of remdesivir and dexamethasone as a therapeutic option; yet combining an antiviral with an anti-inflammatory corticosteroid has been proposed from the theoretical perspective, where its safety and efficacy remain to be determined.[5, 7] To our knowledge, only one cohort study has specifically examined the effects of remdesivir and dexamethasone combination on COVID-19 patients so far, concluding that this drug combination on top of standard care was associated with significantly lower 30-day mortality and the need for mechanical ventilation compared to standard care alone.[9] However, this before-and-after study poses some inherent limitations that may have influenced the interpretation of findings, such as possible differences in standard care between the two time periods, and a substantially higher proportion of patients receiving supplemental oxygen in the intervention group at baseline.[9]

Accordingly, clinical evidence on the combined use of remdesivir and dexamethasone is urgently needed, namely longer-term clinical outcomes stratified by patient subgroups, viral clearance, and the optimal dose, timing and duration of respective therapy.[1, 8, 10-15] Therefore, this observational cohort study aims to conduct a propensity score (PS) analysis of hospitalized COVID-19 patients who had initiated remdesivir prior to or simultaneously with dexamethasone versus those who had initiated remdesivir after that of dexamethasone or who were not given remdesivir at all. With respect to the timing of remdesivir administration, it is hypothesized that clinical benefits would be observed with early or co-initiation of the antiviral relative to dexamethasone, compared to delayed introduction or non-users.

Methods

Data source and study population

A territory-wide retrospective cohort of all COVID-19 patients who were consecutively admitted with positive reverse transcription polymerase chain reaction (RT-PCR) results to public hospitals in the Hong Kong Special Administrative Region, China was reviewed for the period from 21st January 2020 to 31st January 2021. Electronic medical records of COVID-19 patients were retrieved from the Hospital Authority. Our cohort comprised cases of mild disease to critically ill, which was fully representative of the hospitalized COVID-19 patient population in the local region. Data cutoff date was 30th April 2021.

Both remdesivir and dexamethasone were treatment options for hospitalized COVID-19 patients in Hong Kong since July 2020.[16] Oral or intravenous dexamethasone of 6mg once daily for up to 10 days was recommended for hospitalized patients with pneumonia, and those who required supplemental oxygen or invasive mechanical ventilation.[16] A 5-day regimen of intravenous remdesivir of 200mg on the first day and 100mg once daily on subsequent days was recommended for hospitalized patients with pneumonia, who were breathing ambient air or requiring supplemental oxygen; and a 10-day regimen for those on invasive mechanical ventilation or ECMO.[16]

'New-user' design [17] was applied to include hospitalized COVID-19 patients who had initiated oral or intravenous dexamethasone during admission, in an effort to mitigate the selection and immortal time biases. Patients who were discharged alive or those deceased on or before the initial dispensing day of dexamethasone were excluded. The baseline date was defined as that of dexamethasone initiation.

Treatment exposure and follow-up period

Patients who had initiated remdesivir intravenously prior to dexamethasone, or co-initiated remdesivir and dexamethasone on the same day during hospitalization were categorized as the exposure (or denoted as remdesivir-dexamethasone) group. Patients who had received their first dose of remdesivir after dexamethasone initiation, or who were not administered with remdesivir at all were classified as the non-exposure (or denoted as dexamethasone) group. The distribution of timing of dexamethasone initiation following hospital admission is

shown in Supplementary Figure 1. Patients were followed up until in-hospital death, hospital discharge, or the data cutoff date, whichever came first.

Baseline covariates

Baseline covariates of patients included details on dexamethasone and remdesivir use, age, sex, time period of hospitalization, pre-existing comorbidities, use of long-term medications (within three years before baseline), admission via emergency department, in-hospital pharmacological and non-pharmacological treatments, laboratory parameters (taken from the closest measurement before baseline during hospitalization), and clinical severity determined by the WHO clinical progression scale (CPS) (Table 1).[18] Acute respiratory distress syndrome (ARDS) diagnosed on or before baseline was also identified.

Outcomes

The primary outcome was time to clinical improvement, defined as a reduction on the WHO CPS [18] by at least one score. Secondary outcomes were time to hospital discharge; recovery without the need for oxygen therapy; viral clearance (first negative PCR results); low viral load (Ct value ≥35 cycles); positive antibody against COVID-19 (first positive IgG antibody); ARDS; composite outcome of in-hospital death or invasive mechanical ventilation; composite outcome of in-hospital death, invasive mechanical ventilation, or intensive care unit (ICU) admission; and in-hospital death.

Other study outcomes included hospital length of stay (LOS) for discharged survivors; mean changes in laboratory parameters from baseline to the last available measurement during hospitalization; mean changes in the WHO CPS score, clinical status as indicated by the WHO CPS, and cumulative direct medical costs incurred from baseline to 90-day follow-up. Components of the direct medical costs are listed in Supplementary Table 1, where the reference costs were obtained from a public website [19] and the Hospital Authority.[20]

Statistical analyses

A PS model with treatment group as the outcome variable conditional on the aforementioned baseline covariates in a logistic regression model was constructed, and the propensity of receiving remdesivir prior to dexamethasone versus not receiving remdesivir was estimated.

Inverse probability of treatment weighting (IPTW) using the PS was performed. Weight truncation at the 1st and 99th percentile of the observed PS weighting distribution was applied to address extreme weights.[21] Multiple imputation by chained equation was implemented to impute missing laboratory parameters (Supplementary Table 2) included in the PS model using the observed baseline covariates without any missing information. Rubin's rules were applied to pool the treatment effects estimated from the 20 independent imputed datasets.[22] Balance of each baseline covariate before and after PS weighting was assessed using standardized mean difference (SMD), with SMD >0.2 indicating covariate imbalance.[23]

Cox regression models weighted by the IPTW were fitted to estimate the treatment effects on primary and secondary outcomes, expressed in terms of hazard ratio (HR) and 95% confidence interval (CI). Linear regression models using the IPTW were applied to estimate the treatments effects on other outcomes in continuous form.

Several sensitivity analyses were performed, namely to extend the follow-up beyond hospital discharge; limit the observation period to at most 90 days; and adopt the complete-case approach using IPTW. Besides, subgroup analyses were performed with the re-calculation of PS and IPTW within each of the following subgroups: age; sex; timing of dexamethasone initiation; exclusion of non-remdesivir users or patients who had initiated remdesivir after that of dexamethasone; with or without concomitant use of other systemic steroids (including hydrocortisone, prednisolone, or methylprednisolone); oral or intravenous administration of dexamethasone; dosage of dexamethasone; early or co-initiation of remdesivir relative to dexamethasone; with or without the need for invasive mechanical ventilation or ECMO, and ICU admission.

All statistical analyses were performed using STATA Version 16 (StataCorp LP, College Station, TX). All significance tests were two- tailed, where p<0.05 was considered statistically significant.

Results

Among 10,445 patients admitted to hospital with COVID-19 between 21st January 2020 and 31st January 2021, 1,544 patients were administered dexamethasone orally or intravenously during hospitalization (Supplementary Figure 2). In this cohort, 615 (39.8%) patients had

ever received remdesivir, of whom 93 (15.1%) were given remdesivir prior to dexamethasone initiation, 373 (60.7%) had co-initiated remdesivir and dexamethasone on the same day, and 149 (24.2%) were given remdesivir after dexamethasone initiation (Supplementary Table 3). The median of delay of remdesivir initiation following dexamethasone was 2 (interquartile range: 1-4) days. Exposure group consisted of 466 patients with remdesivir use prior to or co-initiated with dexamethasone; whereas the non-exposure group included 1,078 patients who had initiated remdesivir after dexamethasone, or those who were never treated with remdesivir. The median follow-up period of patients in exposure and non-exposure groups were 13 (interquartile range: 8-24) and 13 (9-23) days, respectively (Supplementary Table 4).

Baseline characteristics of patients in the exposure and non-exposure groups before and after PS weighting are listed in Table 1. After multiple imputation and weighting, PS distribution between the two groups highly overlapped (Supplementary Figure 3). Clinical severity of COVID-19, pre-existing comorbidities, long-term medication use, treatments received during hospitalization, and laboratory parameters were comparable between groups. Overall, baseline characteristics were well balanced with all SMDs <0.2.

Time to clinical improvement (median 12 vs 13 days; HR=1.23, 95%CI 1.02-1.49, p=0.032) and positive IgG antibody (median 5 vs 6 days; HR=1.22, 95%CI 1.02-1.46, p=0.029) were significantly shorter in the exposure group than that of non-exposure (Table 2 and Figure 1). Although the time to hospital discharge and recovery were not significantly shorter for the exposure group, survivors had a shorter hospital LOS by 2.65 days (95%CI 1.01-4.29, p=0.002) than their non-exposure counterparts. Trends towards faster viral clearance and low viral load were demonstrated in the exposure group compared to non-exposure. Furthermore, exposure group was associated with significantly lower risks of in-hospital death (HR=0.59, 95%CI 0.36-0.98, p=0.042) and composite outcomes (in-hospital death or invasive mechanical ventilation: HR=0.67, 95%CI 0.46-0.96, p=0.031; in-hospital death, invasive mechanical ventilation or ICU admission: HR=0.64, 95%CI 0.43-0.97, p=0.034) than the non-exposure group. Meanwhile, no significant differences in the risk of ARDS were identified between the two groups.

Results of various sensitivity and subgroup analyses showed similar trends and were generally comparable to those of main analysis (Supplementary Tables 5 and 6). In addition to significantly shorter time to clinical improvement and hospital discharge, faster recovery

could be observed in the subgroup of patients initiating remdesivir prior to that of dexamethasone (excluding patients with co-initiation of the two drugs) compared to late introduction or no remdesivir use at all; and achieving positive IgG antibody faster, with significantly lower risks of composite outcomes and ARDS among those initiating remdesivir prior to or simultaneously with that of dexamethasone compared to late introduction (initiating remdesivir after dexamethasone).

As illustrated in Figure 2 and Supplementary Table 7, the proportion of patients with in-hospital death or on mechanical ventilation on 90-day was significantly lower in the exposure group (7% vs 13%, p<0.001), and lower WHO CPS scores were observed among patients of the exposure group compared to their non-exposure counterparts from five days of follow-up onwards. Mean WHO CPS scores in the exposure group were significantly lower on 30-day (1.27 vs 1.90, p<0.001), 60-day (0.88 vs 1.49, p<0.001), and 90-day (0.79 vs 1.38, p<0.001). Mean cumulative direct medical costs incurred by patients of the two groups from baseline to 90-day follow-up revealed that the differences converged to non-significance from 17 days onwards.

Changes in laboratory parameters from baseline to the last available measurement were estimated within each group and by differences between groups (Supplementary Table 8 and Supplementary Figure 4). A significantly larger increase in mean platelet count (135.3 vs 120.4 x10^9/L, p<0.001) was observed in the exposure group compared to that of non-exposure. Notably, both baseline and last measurements of the two groups were within the normal range. In contrast, patients in the exposure group had significantly smaller increases in mean alkaline phosphatase (ALP) (5.3 vs 8.8 U/L, p=0.048) and alanine transaminase (ALT) (12.5 vs 35.7 U/L, p=0.002), yet a significantly smaller decrease in mean hemoglobin (-0.6 vs -0.9 g/dL, p<0.001) than their non-exposure counterparts.

Discussion

Among patients with mainly moderate COVID-19 who were treated with dexamethasone during hospitalization, initiating remdesivir prior to or simultaneously with the corticosteroid was associated with significantly shorter time to clinical improvement and positive IgG antibody, lower risks of in-hospital death and composite outcomes, and a shorter LOS.

Trends towards faster hospital discharge and viral clearance were also evident in the exposure group compared to non-exposure, without imposing any significant risk of ARDS.

In a retrospective cohort study with the majority of COVID-19 patients requiring low-flow oxygen therapy at baseline, no significant reduction of mortality was found with the combination of dexamethasone and remdesivir compared to remdesivir treatment alone, where a longer time to clinical improvement (hospital discharge or reduction in the WHO severity score by at least two points) was even observed with the combined use of remdesivir with corticosteroids; however, the authors noted that patients on the drug combination might have been more severely ill.[24] Meanwhile, our study design was unique in considering the timing of remdesivir initiation, revealing that remdesivir might confer additional benefits in promoting clinical improvement among dexamethasone users when it was initiated prior to or simultaneously with dexamethasone compared to late introduction or no remdesivir use, in a patient population with mainly moderate COVID-19 that would have benefited from this antiviral.[25-27]

In line with previous findings, early use of remdesivir was associated with a shorter hospital LOS, and it could potentially facilitate recovery and hospital discharge of COVID-19 patients.[3, 28-31] While remdesivir has not been consistently shown to reduce the risk of mortality compared to placebo or standard care, such discrepancy could be dependent on the severity of COVID-19 and level of respiratory support required.[24-26, 28, 30, 32] Consistent with the before-and-after study suggesting reduced mortality and the need for mechanical ventilation with remdesivir and dexamethasone combination versus standard care alone,[9] our results have further demonstrated that early or co-initiation of remdesivir with dexamethasone was associated with lower risks of these negative outcomes compared to late introduction or not using the antiviral at all. Overall, our study has provided preliminary evidence to support the notion that combining dexamethasone with remdesivir would be more beneficial to using the corticosteroid alone, in addition to the preferred timing of antiviral initiation relative to anti-inflammatory agents,[1] as evidenced by the potential clinical benefits and the absence of any significant harms in this patient population with mainly moderate COVID-19.

In response to whether the timing or sequence of drug initiation would have an impact on patient outcomes, our subgroup analyses further demonstrated that initiating remdesivir prior

to dexamethasone was associated with better clinical outcomes than late introduction of remdesivir after the corticosteroid or not using the antiviral at all; and results might even be more prominent when remdesivir was administered prior to or simultaneously with dexamethasone compared to late introduction of the antiviral. These observations were justifiable based on the theoretical understanding of the progression of a viral infection, where early introduction of antivirals might help to inhibit viral replication and possibly prevent the 'cytokine storm', followed by the addition of anti-inflammatory agents (such as corticosteroids) to suppress the hyper-inflammation should it develop.[1, 11, 14, 33]

Meanwhile, as corticosteroids are immunosuppressive, they could potentially delay viral clearance by hampering the host antiviral immune response, especially when they are administered early with uncontrolled viral replication, given at high doses, or to patients with non-severe COVID-19.[13, 14, 33-37] Based on our results, initiation of remdesivir prior to or simultaneously with dexamethasone was associated with a trend towards faster viral clearance, compared to initiating the antiviral after dexamethasone or not using remdesivir at all; in addition to a significantly shorter time to positive IgG antibody, which has been associated with faster viral clearance in itself [38]. Therefore, our study supported the idea of introducing remdesivir prior to dexamethasone in low doses [1] for moderate COVID-19.

In terms of changes in laboratory parameters, the exposure group had significantly smaller increases in ALP and ALT, and a smaller decrease in hemoglobin compared to non-exposure group. These observations were in favor of patients with early or co-initiation of remdesivir with dexamethasone, as elevated liver enzymes, and the presence of anemia, have been observed to associate with severe COVID-19 or even an increased risk of mortality.[39-41]

Utilizing electronic medical records available from the public healthcare service provider, this retrospective cohort study offered a real-life picture of the clinical management of hospitalized COVID-19 patients. In addition to reporting various clinical outcomes and changes in virologic measures, our study had compared the results over 90 days of follow-up. Our findings have also provided insights into the preferred timing of remdesivir initiation relative to dexamethasone. Nevertheless, several limitations of this study should be acknowledged. Firstly, owing its observational nature, unmeasured or residual confounding is possible, despite our attempt to balance the baseline covariates with multiple imputation and weighting. While observational studies using PS weighting cannot substitute randomized

controlled trials, we have accounted for all possible pretreatment variables in PS estimation in order to adjust for confounding by indication.[42] Secondly, as the majority of our cohort did not require supplemental oxygen or mechanical ventilation, and were treated with interferon therapy at baseline, our results would not be generalizable to other patient populations or subgroups. Thirdly, our findings might not apply to other antivirals or corticosteroids, as their safety and efficacy could differ by drug type, dosage, and duration of therapy. Lastly, effects of the remdesivir and dexamethasone combination with other concomitant drugs for COVID-19 were not explored, such as tocilizumab and baricitinib, as their use was very limited in our cohort. Results of the ACTT-4 trial are pending, which will compare the outcomes of baricitinib plus remdesivir versus dexamethasone plus remdesivir in hospitalized COVID-19 patients.[43]

Among hospitalized patients with mainly moderate COVID-19 who were treated with dexamethasone, initiating remdesivir prior to or simultaneously with the corticosteroid was potentially associated with shorter time to clinical improvement and achieving positive IgG antibody, lower risks of in-hospital death and composite outcomes, in addition to a shorter LOS, compared to late introduction of remdesivir after dexamethasone or not using the antiviral at all. This study provided preliminary evidence to support early or co-initiation of remdesivir with dexamethasone, and emphasized the need for further research on this drug combination with other potential therapeutics targeting immune dysregulation.[7, 10, 11]

NOTES

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Figure Legends

Figure 1. Kaplan-Meier survival curves for at least 1-point clinical improvement on WHO clinical progression scale, hospital discharge, recovery, low viral load, IgG antibody, and in-hospital death

Shown are Kaplan-Meier survival curves for at least 1-point clinical improvement on the WHO clinical progression scale, hospital discharge, recovery, low viral load, IgG antibody, and in-hospital death. Shaded areas indicate 95% confidence intervals. Estimates of the hazard ratio and 95% confidence intervals were derived from Cox regression models weighted by the IPTW.

Figure 2. Comparisons of (a) clinical status measured by WHO Clinical Progression Scale score, (b) WHO Clinical Progression Scale score, and (c) cumulative direct medical costs by days from baseline to 90-day among patients between remdesivir-dexamethasone and dexamethasone group

Figure 2a shows the changes from baseline in clinical status (in-hospital death, levels of respiratory support, and hospital discharge) on 7, 15, 30, 60, and 90 days of follow-up for the remdesivir-dexamethasone and dexamethasone groups. Figures 2b and 2c show the mean WHO clinical progression scale scores and mean cumulative direct medical costs incurred from baseline to 90-day follow-up by treatment groups.

Table 1. Baseline characteristics of patients hospitalized with COVID-19 in the two treatment groups before and after multiple imputation and propensity score weighting

Baseline characteristics	Before weighting					After weighting				
	Remdesivir-Dexamethasone (n=466)		Dexamethasone (n=1,078)		SMD	Remdesivir-Dexamethasone (n=466)		Dexamethasone (n=1,078)		SMD
	N / Mean	% / SD	N / Mean	% / SD		% / Mean	% / SD	N / Mean	% / SD	
Age, years †	64.8	12.5	64.3	14.4	0.03	64.0	11.8	64.5	14.4	0.04
≤65	226	(48.5%)	577	(53.5%)	0.10	(51.3%)		(53.4%)		0.04
>65	240	(51.5%)	501	(46.5%)		(48.7%)		(46.6%)		0.05
Sex					0.03					0.19
Male	264	(56.7%)	628	(58.3%)		(48.1%)		(57.7%)		
Female	202	(43.3%)	450	(41.7%)		(51.9%)		(42.3%)		
Period					1.28					0.03
21st January 2020 - 30th November 2020	64	(13.7%)	717	(66.5%)		(48.6%)		(50.1%)		
1st December 2020 - 31st January 2021	402	(86.3%)	361	(33.5%)		(51.4%)		(49.9%)		
Pre-existing comorbidities										
Charlson Comorbidity Index †‡	4.7	2.0	4.9	2.2	0.08	4.8	2.0	4.8	2.2	0.01
1-4	237	(50.9%)	523	(48.6%)	0.13	(51.0%)		(50.1%)		0.03
5-6	156	(33.5%)	332	(30.8%)		(30.0%)		(31.3%)		
7-14	73	(15.7%)	222	(20.6%)		(19.0%)		(18.7%)		
Diabetes mellitus	194	(41.6%)	401	(37.2%)	0.09	(38.3%)		(37.2%)		0.02
Hypertension	295	(63.3%)	615	(57.1%)	0.13	(61.3%)		(55.8%)		0.11
Liver disease	56	(12.0%)	134	(12.4%)	0.01	(12.4%)		(11.1%)		0.04
Chronic lung disease	57	(12.2%)	126	(11.7%)	0.02	(9.5%)		(10.9%)		0.04
Chronic heart disease	60	(12.9%)	200	(18.6%)	0.16	(12.8%)		(16.5%)		0.10
Chronic kidney disease	46	(9.9%)	209	(19.4%)	0.27	(13.5%)		(18.7%)		0.14
Malignancy	11	(2.4%)	32	(3.0%)	0.04	(6.7%)		(2.9%)		0.18
Long-term medications										
ACEI/ARB	143	(30.7%)	284	(26.3%)	0.10	(28.2%)		(24.8%)		0.08
Anticoagulant	256	(54.9%)	471	(43.7%)	0.23	(55.0%)		(48.9%)		0.12
Antiplatelet	78	(16.7%)	200	(18.6%)	0.05	(13.5%)		(16.8%)		0.09
Lipid-lowering agent	171	(36.7%)	351	(32.6%)	0.09	(39.0%)		(31.0%)		0.17
NSAID	89	(19.1%)	244	(22.6%)	0.09	(15.4%)		(21.2%)		0.15
Time from admission to remdesivir initiation, days †	3.6	3.2	6.0	3.7	0.73	4.1	3.3	5.5	3.6	0.40

Cumulative dosage of remdesivir, mg †	595.9	235.7	604.7	219.1	0.04	599.1	228.0	608.4	210.1	0.04
Duration of use of remdesivir, days †	4.3	2.1	4.5	1.9	0.12	4.3	2.0	4.4	1.9	0.07
Time from admission to dexamethasone initiation, days †	4.1	3.5	4.5	4.1	0.11	4.7	3.4	4.3	3.9	0.10
Administration route of dexamethasone										
Oral	64	(13.7%)	283	(26.3%)	0.32	(19.3%)		(27.3%)		0.19
Intravenous injection	402	(86.3%)	795	(73.7%)		(80.7%)		(72.7%)		
Dosage of dexamethasone										
Up to 6mg daily	185	(39.7%)	518	(48.1%)	0.17	(46.4%)		(46.9%)		0.01
More than 6mg daily	281	(60.3%)	560	(51.9%)		(53.6%)		(53.1%)		
Cumulative dosage of dexamethasone, mg †	51.5	68.5	53.0	51.8	0.03	52.8	79.6	55.2	55.1	0.04
Duration of use of dexamethasone, days †	7.3	10.1	8.3	8.2	0.11	7.7	11.7	8.3	8.0	0.07
Drug initiation sequence					NA					NA
Remdesivir followed by dexamethasone	93	(20.0%)	NA	NA		(22.0%)		NA		
Co-initiation of remdesivir and dexamethasone	373	(80.0%)	NA	NA		(78.0%)		NA		
Treatment performed prior to dexamethasone initiation										
Remdesivir	466	(100.0%)	0	(0.0%)	NA	(100.0%)		(0.0%)		NA
Interferon-β-1b	255	(54.7%)	879	(81.5%)	0.60	(68.4%)		(72.1%)		0.08
Ribavirin	139	(29.8%)	443	(41.1%)	0.24	(45.8%)		(38.3%)		0.15
Tocilizumab	2	(0.4%)	25	(2.3%)	0.16	(0.8%)		(2.1%)		0.10
Baricitinib	5	(1.1%)	4	(0.4%)	0.08	(0.8%)		(0.8%)		0.00
Other systemic steroids	12	(2.6%)	45	(4.2%)	0.09	(2.2%)		(3.6%)		0.08
ECMO	1	(0.2%)	2	(0.2%)	0.01	(0.1%)		(0.3%)		0.04
Ventilation	63	(13.5%)	129	(12.0%)	0.05	(11.9%)		(11.4%)		0.02
Invasive mechanical ventilation	63	(13.5%)	128	(11.9%)	0.05	(11.9%)		(11.3%)		0.02
Non-invasive mechanical ventilation	13	(2.8%)	32	(3.0%)	0.01	(2.6%)		(3.0%)		0.02
Dialysis	4	(0.9%)	11	(1.0%)	0.02	(0.4%)		(0.8%)		0.05
ICU admission	112	(24.0%)	212	(19.7%)	0.11	(22.4%)		(19.7%)		0.07
Admission via emergency department	196	(42.1%)	670	(62.2%)	0.41	(54.1%)		(56.9%)		0.06
WHO Clinical Progression Scale Score (range 0-10) †	4.7	1.1	4.6	1.0	0.09	4.6	1.1	4.6	1.0	0.03
ARDS	25	(5.4%)	38	(3.5%)	0.09	(4.1%)		(4.1%)		0.00
Laboratory parameters [normal range] †										
White blood cell, $\times 10^9$/L [3.7-9.2 $\times 10^9$/L]	5.7	2.4	5.7	2.5	0.00	5.5	2.2	5.7	2.5	0.09
Neutrophil, $\times 10^9$/L [1.7-5.8 $\times 10^9$/L]	4.3	2.4	4.2	2.4	0.04	3.9	2.1	4.2	2.4	0.10
Lymphocyte, $\times 10^9$/L [1.0-3.1 $\times 10^9$/L]	1.0	0.5	1.0	0.4	0.08	1.0	0.5	1.0	0.4	0.01

Parameter										
Platelet, ×10^9/L [145-370 ×109/L]	181.7	61.1	185.6	72.9	0.06	176.4	63.3	183.9	72.3	0.11
Lactate dehydrogenase, U/L [110-210 U/L]	334.1	138.6	319.0	142.0	0.11	320.6	127.7	324.2	145.7	0.03
Creatine kinase, U/L [26-192 U/L]	273.2	461.1	253.7	516.4	0.04	269.0	481.5	258.8	508.7	0.02
Total bilirubin, μmol/L [5-27 μmol/L]	9.5	6.7	10.0	7.1	0.07	9.3	6.0	9.9	6.8	0.08
C-reactive protein, mg/L [<5 mg/L]	63.2	54.2	58.9	55.5	0.08	56.8	48.7	60.1	57.8	0.06
Cycle threshold value, cycle	23.1	5.0	24.6	5.5	0.28	24.9	6.0	24.1	5.6	0.13
eGFR, ml/min/1.73m^2 [>90 ml/min/1.73m^2]	104.6	59.4	103.1	64.5	0.02	104.9	44.8	106.7	80.3	0.03
ALP, U/L [30-120 U/L]	68.9	32.6	73.8	56.3	0.10	67.9	33.8	72.3	49.4	0.10
ALT, U/L [<46.5 U/L]	37.3	25.4	39.1	40.7	0.05	36.0	24.4	38.4	39.2	0.07
Hemoglobin, g/dL [13.4-17.1 g/dL]	13.3	1.6	13.2	1.8	0.05	13.3	1.4	13.2	1.8	0.03

Notes:

ACEI = angiotensin converting enzyme inhibitor; ALP = alkaline phosphatase; ALT = alanine transaminase; ARB = angiotensin receptor blocker; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation; SMD = standardized mean difference

† Age, Charlson Comorbidity Index, clinical severity, cumulative dosage, duration of use of dosage, time from admission to dexamethasone initiation, and laboratory parameters on admission are presented in mean ± SD

‡ The calculation of Charlson Comorbidity Index does not include Acquired Immune Deficiency Syndrome (AIDS)

¶ SMD of <0.2 indicates covariate balance between remdesivir-dexamethasone and dexamethasone groups

Table 2. Comparison of time to clinical improvement, hospital discharge, recovery, changes in virologic measures, and risks of in-hospital death, composite outcomes, and acute respiratory distress syndrome between the two treatment groups

	Before weighting		After weighting		
	Remdesivir-dexamethasone	Dexamethasone	Remdesivir-dexamethasone vs Dexamethasone		
Outcomes	% (N)	% (N)	HR†	95% CI	P-value
Clinical improvement on WHO clinical progression scale by ≥ 1 score	92.1% (466)	88.1% (1,078)	1.23	(1.02, 1.49)	0.032
Hospital discharge	90.6% (466)	87.1% (1,078)	1.18	(0.97, 1.43)	0.090
Recovery (score ≤ 4)	79.2% (154)	74.5% (341)	0.94	(0.72, 1.23)	0.663
Viral clearance (first negative PCR result)	32.7% (456)	31.6% (1,043)	1.29	(0.93, 1.79)	0.126
Low viral load (Ct value ≥ 35)	31.3% (457)	31.2% (1,033)	1.25	(0.91, 1.72)	0.177
IgG antibody	97.1% (339)	91.7% (806)	1.22	(1.02, 1.46)	0.029
Outcomes	% (N)	% (N)	HR‡	95% CI	P-value
In-hospital death or invasive mechanical ventilation (score ≥ 7)	14.5% (448)	18.8% (1,059)	0.67	(0.46, 0.96)	0.031
In-hospital death or invasive mechanical ventilation (score ≥ 7) or intensive care unit admission	11.3% (417)	17.4% (1,016)	0.64	(0.43, 0.97)	0.034
In-hospital death	7.7% (466)	11.6% (1,078)	0.59	(0.36, 0.98)	0.042
ARDS	10.7% (441)	8.2% (1,040)	0.99	(0.59, 1.66)	0.965

Notes:

ARDS = acute respiratory distress syndrome; CI = confidence interval; Ct = cycle threshold; HR = hazard ratio; IgG = immunoglobulin G; PCR = polymerase chain reaction

† HR >1 (or <1) indicates remdesivir-dexamethasone group was associated with better (worse) clinical improvement, early (late) hospital discharge, recovery, or achieving virologic measures compared to the dexamethasone group;

‡ HR >1 (or <1) indicates remdesivir-dexamethasone group was associated with higher (lower) risk of in-hospital death, composite outcomes, or ARDS compared to the dexamethasone group.
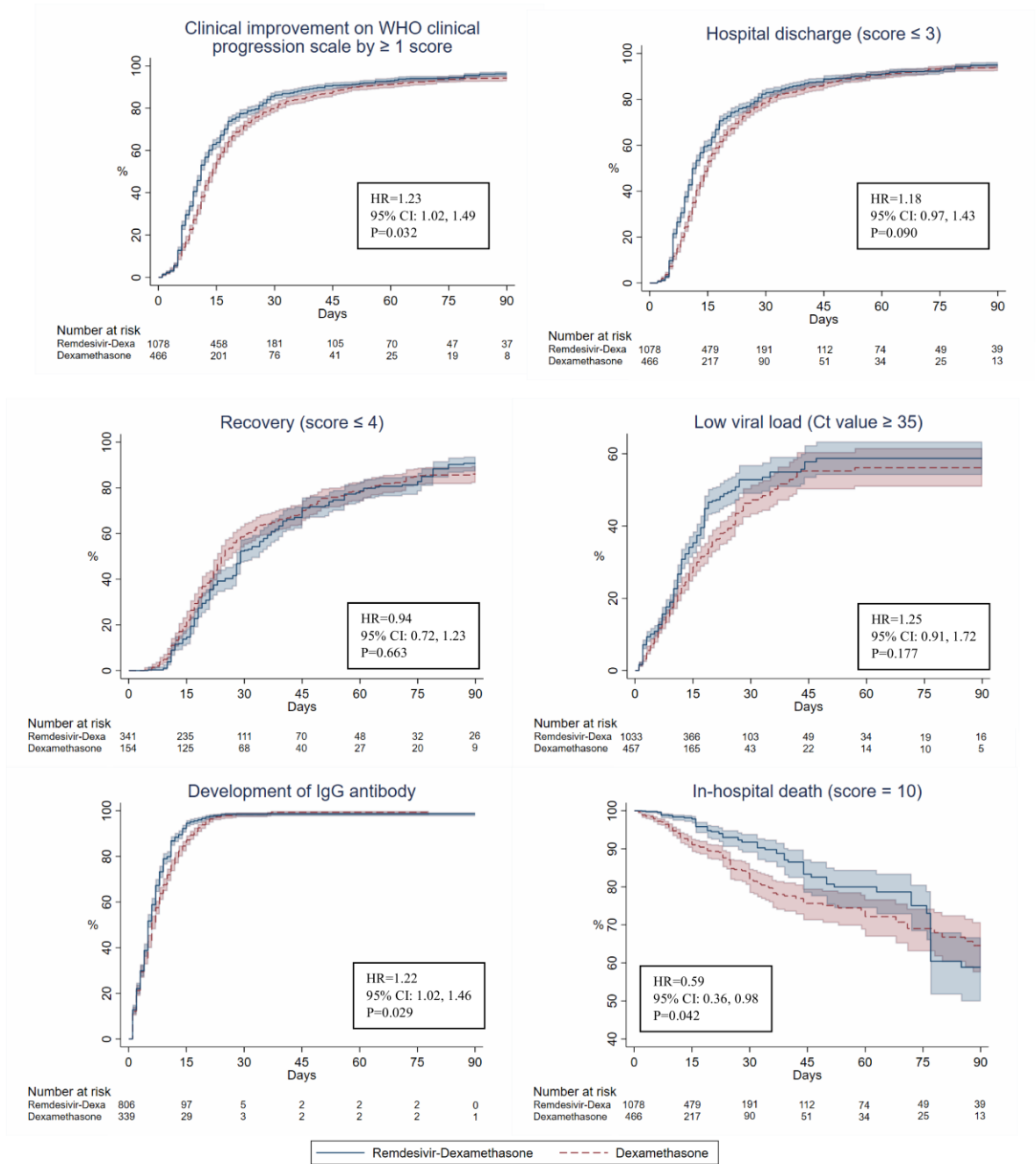
Figure 1

Figure 2

	Rem-Dexa	Dexa	Rem-Dexa	Dexa	Rem-Dexa	Dexa	Rem-Dexa	Dexa	Rem-Dexa	Dexa	Rem-Dexa	Dexa
■ In-hospital death	0%	0%	1%	3%	2%	7%	3%	10%	5%	11%	6%	11%
▟ Mechanical ventilation	4%	2%	6%	5%	4%	3%	4%	3%	1%	2%	1%	1%
‖ Supplemental oxygen without ventilation	23%	31%	29%	37%	25%	27%	10%	10%	6%	4%	1%	2%
▥ No oxygen therapy	72%	67%	38%	41%	11%	13%	2%	5%	1%	1%	1%	1%
▟ Discharge	0%	0%	26%	15%	59%	51%	81%	73%	88%	82%	91%	85%
	0		7		15		30		60		90	

Days from baseline

WHO Clinical Progression Scale

Breakeven day: 5th day

Cumulative direct medical costs (US$)

Breakeven day: 17th day

Days from baseline

Days from baseline

—— Remdesivir-Dexamethasone   - - - - Dexamethasone