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The association of remdesivir and in-hospital outcomes for COVID-19 patients treated with steroids

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Background: Remdesivir has been shown to decrease SARS-CoV-2 viral loads and the duration of COVID-19 symptoms. However, current evidence regarding the association between remdesivir and in-hospital mortality for patients with COVID-19 steroid treatments is limited. We aimed to investigate whether remdesivir reduces in-hospital mortality among patients with COVID-19 treated with steroids.

Methods: In this retrospective multicentre study, we reviewed the medical records of 3372 patients discharged between 1 March 2020 and 30 March 2021, with laboratory confirmed COVID-19 in the Mount Sinai Health System and treated with steroids. We evaluated the effect of remdesivir on the outcomes using propensity score analyses. Subgroup analyses were conducted by stratification of patients by endotracheal intubation and COVID-19 antibody status. Acute kidney injury (AKI) was defined as an absolute serum creatinine increase of 0.3 mg/dL or a relative increase of 50%.

Results: Of the 3372 eligible patients, 1336 (39.6%) received remdesivir. After 1:1 propensity score matching ($N = 999$ pairs), in-hospital mortality was similar between those with and without remdesivir (21.4% versus 21.6%, respectively, $P = 0.96$). Remdesivir was not significantly associated with in-hospital mortality regardless of endotracheal intubation or COVID-19 antibody status. However, there was a signal that remdesivir was associated with a reduced risk of AKI in the propensity matched analysis (17.5% versus 23.4%, respectively, $P = 0.001$).

Conclusions: Remdesivir was not associated with reduced risk of in-hospital mortality in patients with COVID-19 treated with steroids but potentially associated with decreased risk of AKI. These findings should be confirmed in prospective studies focusing on COVID-19 patients treated with steroids.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread all around the world since the first reported case in December 2019.[1] The WHO declared COVID-19 to be a pandemic on 11 March 2020 and, as of 22 April 2020, New York City became the epicentre.[2–4] On 11 January 2021, the number of deaths due to the COVID-19 pandemic has almost exceeded 2.5 million, and the number of COVID-19 cases reached 114 million globally;[4] 28 million of which were from the USA alone where total deaths exceeded 0.5 million.

The options of treatments have dramatically changed since the beginning of the pandemic. Initially, hydroxychloroquine and azithromycin were used. However, no efficacy was proven.[5] To tackle inflammation and cytokine storm associated with COVID-19, steroids became the preferred treatment for critically ill patients with COVID-19.[6,7] Meanwhile, remdesivir, a nucleotide analogue prodrug that inhibits viral RNA, was also expected to be effective against SARS-CoV-2, and US FDA approved remdesivir as the treatment of COVID-19 on 22 October 2020.[8] However, while it is known that remdesivir decreases the duration of symptoms, it is still questionable if remdesivir reduces the mortality of patients infected with COVID-19, especially treated with steroids.[8–12]

Therefore, we aimed to investigate whether remdesivir reduced in-hospital mortality among patients with COVID-19 on steroids in a diverse population of New York City. We also investigated the effectiveness of remdesivir in subgroups stratified by endotracheal intubation and COVID-19 antibody status.

Methods

Data source

This retrospective study was conducted by review of the medical records of 9965 hospitalized patients who were discharged between 1 March 2020 and 30 March 2021, with laboratory confirmed COVID-19 in the Mount Sinai Health System.[13–15] Identification of COVID-19 was based on a nasopharyngeal swab, which was tested using a PCR. For the purpose of this study (examine the effectiveness of remdesivir among patients on steroids), we limited our cohort to patients who were treated with steroids within 2 days of admission ($n = 3984$). Steroids were defined as treatment with systemic betamethasone, dexamethasone, hydrocortisone, prednisone, prednisolone and methylprednisolone. Patients younger than 18 years of age were excluded ($n = 9$). In addition, we excluded patients who were transferred to another facility ($n = 86$). Finally, we excluded 517 patients who were discharged within 2 days of admission (dead or alive) to mitigate the selection bias or immortal time bias. The final cohort included 3372 COVID-19 patients treated with steroids. Then, we divided them into two groups: with and without remdesivir treatment.

This study was approved by the institutional review boards of Icahn School of Medicine at Mount Sinai (#2000495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review boards.

We reviewed patients' electronic medical records and extracted demographics, comorbidities, vital signs, laboratory data and clinical outcomes. Patients were stratified into two groups: those with and those without remdesivir. The standardized Mount Sinai Health System protocol of treatment by remdesivir is as follows: 200 mg on Day 1, then followed by 100 mg daily for a total of 5 or up to 10 days. Generally, remdesivir is discontinued if ALT is more than 5 times the upper normal limits or until hospital discharge.

Outcomes

The primary outcome of interest was in-hospital mortality. Secondary outcomes were acute kidney injury (AKI) and liver injury. AKI was defined according to kidney disease improving global outcomes (KDIGOs) criteria stratified by creatinine level: Stage 1, 1.5–1.9 times baseline or $\geq$0.3 mg/dL increase; Stage 2, 2.0–2.9 times baseline; Stage 3, 3 times or creatinine >4.0 mg/dL.[16,17] Liver injury was defined as ALT more than 5 times the upper normal limit (46 U/L).

Covariates

Comorbidities were characterized based on the ICD 10 codes. All vital signs and blood tests were recorded at the time of admission. Further, we controlled for relevant treatments, including therapeutic anticoagulation, prophylactic anticoagulation, convalescent plasma and tocilizumab. Therapeutic anticoagulation was defined as apixaban, dabigatran, rivaroxaban (excluding 2.5 mg as prevention of atherosclerotic cardiovascular events),[18] edoxaban, warfarin and enoxaparin (as therapeutic dose), IV continuous unfractionated heparin, and argatroban. Prophylactic anticoagulation was defined as subcutaneous heparin or enoxaparin in prophylactic dose.

Statistical analysis

Continuous variables are presented as mean ± SD or median [IQR] depending on the data distribution, and categorical variables are expressed as percentages. Differences in baseline characteristics between groups were evaluated, using the χ^2 test for categorical variables and *t*-test or Wilcoxon test for continuous variables.

A propensity score analysis was performed to adjust for the difference in baseline characteristics between those with remdesivir and those without remdesivir treatment. We performed 1:1 match using the nearest neighbour with a calliper equal to 0.2 of the SD of the logit of the propensity score.[19] The following variables were used to estimate propensity score: age, sex, race, asthma, COPD, obstructive sleep apnoea, obesity, hypertension, diabetes mellitus, HIV, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate (eGFR), blood urea nitrogen, WBC count and haemoglobin, AST, ALT, vital signs, therapeutic anticoagulation, prophylactic anticoagulation, steroids, tocilizumab and treatment with convalescent plasma.[14,20,21] The Modification of Diet in Renal Disease equation was used to estimate eGFR.[16] We compared the in-hospital mortality and incidence of secondary outcomes between the patients with and without remdesivir treatment. In addition, as a sensitivity analysis, we performed inverse probability treatment weighted (IPTW) analysis to estimate the effect of remdesivir for in-hospital mortality. There were 4.0% ($n = 136$) of missing C-reactive protein and 9.9% ($n = 316$) of missing D-dimer data. We imputed missing data using mice package (R software) and repeated propensity score matched and IPTW analysis.

We compared the in-hospital mortality between the propensity score matched patients with and without remdesivir in the following subgroups: (i) patients on endotracheal intubation or patients not on endotracheal intubation; (ii) patients with COVID-19 antibody or those without COVID-19 antibody (only patients who had COVID-19 antibody tests were included, $N = 1893$); and (iii) patients who were discharged between 18 February 2021 and 30 March 2021. Patients were matched by re-estimated propensity score in each subgroup.

In addition, we performed the following analyses: (i) sensitivity analysis excluding patients with liver injury or severe renal impairment at admission (ALT >5 times at baseline or eGFR <30 mL/min/1.73 m^2) because these patients were not usually recommended to use remdesivir; and (ii) comparison of patients who were given remdesivir within 24 h and those who were given remdesivir between 24 and 72 h to estimate the effect of early administration of remdesivir on outcomes.

All statistical analyses were performed using R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria). *P* values <0.05 were considered to be statistically significant.

Results

Of the eligible 3372 COVID-19 patients treated with steroids, 1336 (39.6%) received remdesivir. Median time from admission to the time when remdesivir was given was 23.0 h [IQR 16.1, 35.8]. Among patients on remdesivir, remdesivir course was: 1–4 days, $n = 343$ (25.7%); 5 days, $n = 973$ (72.8%); and 6–10 days, $n = 20$ (1.5%).

Baseline characteristics, vital signs and laboratory data for patients with and without remdesivir are reported in Table 1. Patients with remdesivir were less likely to have comorbidities including asthma, COPD, hypertension, diabetes mellitus, atrial fibrillation, heart failure, coronary artery disease and alcoholic/non-alcoholic liver disease (all $P < 0.05$). Patients with remdesivir had lower oxygen saturation at admission. They also had lower WBC count, D-dimer, blood urea nitrogen and C-reactive protein, and higher haemoglobin and eGFR compared with those without remdesivir. During hospitalization, patients on remdesivir were more likely to receive prophylactic anticoagulation and convalescent plasma, and less likely to receive tocilizumab (Table 1).

Table 2 shows crude in-hospital outcomes. Patients on remdesivir had lower in-hospital mortality compared with those who were not treated with remdesivir. They also experienced lower AKI and liver injury (Table 2).

Table 1. Baseline characteristics of patients admitted with COVID 19 stratified by remdesivir treatment

	Before propensity score matching				After propensity score matching		
	patients without remdesivir, *N* = 2036	patients with remdesivir, *N* = 1336	*P* value	SMD	patients without remdesivir, *N* = 999	patients with remdesivir, *N* = 999	SMD
Age (years), mean (SD)	66.5 (15.7)	65.7 (15.9)	0.15	0.05	65.4 (16.1)	65.9 (15.8)	0.025
Male, *n* (%)	1141 (56.0)	764 (57.2)	0.54	0.023	570 (57.1)	569 (57.0)	0.002
Race, *n* (%)			<0.001	0.299			0.012
white	564 (27.7)	468 (35.0)			334 (33.4)	335 (33.5)	
African American	421 (20.7)	195 (14.6)			151 (15.1)	150 (15.0)	
Hispanic	569 (27.9)	263 (19.7)			215 (21.5)	213 (21.3)	
Asian	119 (5.8)	119 (8.9)			81 (8.1)	84 (8.4)	
other	363 (17.8)	291 (21.8)			218 (21.8)	217 (21.7)	
Comorbidities							
asthma, *n* (%)	166 (8.2)	69 (5.2)	0.001	0.12	55 (5.5)	59 (5.9)	0.017
COPD, *n* (%)	156 (7.7)	58 (4.3)	<0.001	0.14	50 (5.0)	50 (5.0)	<0.001
hypertension, *n* (%)	810 (39.8)	412 (30.8)	<0.001	0.19	332 (33.2)	313 (31.3)	0.041
diabetes mellitus, *n* (%)	483 (23.7)	272 (20.4)	0.024	0.081	203 (20.3)	207 (20.7)	0.01
obstructive sleep apnoea, *n* (%)	59 (2.9)	36 (2.7)	0.81	0.012	26 (2.6)	27 (2.7)	0.006
BMI (kg/m^2), median [IQR]	27.8 [27.4, 32.7]	28.5 [24.7, 33.2]	0.003	0.040	27.8 [24.1, 32.3]	28.5 [24.7, 33.2]	0.046
HIV, *n* (%)	36 (1.8)	17 (1.3)	0.32	0.041	17 (1.7)	14 (1.4)	0.024
cancer, *n* (%)	183 (9.0)	94 (7.0)	0.051	0.072	68 (6.8)	69 (6.9)	0.004
atrial fibrillation, *n* (%)	179 (8.8)	84 (6.3)	0.01	0.095	72 (7.2)	66 (6.6)	0.024
heart failure, *n* (%)	208 (10.2)	65 (4.9)	<0.001	0.20	52 (5.2)	55 (5.5)	0.013
coronary artery disease, *n* (%)	333 (16.4)	141 (10.6)	<0.001	0.17	72 (7.2)	66 (6.6)	0.024
peripheral artery disease, *n* (%)	100 (4.9)	49 (3.7)	0.10	0.061	41 (4.1)	40 (4.0)	0.005
chronic viral hepatitis, *n* (%)	23 (1.1)	9 (0.7)	0.25	0.048	5 (0.5)	7 (0.7)	0.026
alcoholic/non-alcoholic liver disease, *n* (%)	67 (3.3)	22 (1.6)	0.005	0.11	22 (2.2)	19 (1.9)	0.021
Vital signs							
temperature, median [IQR]	37.9 [37.4, 38.8]	37.9 [37.3, 38.8]	0.28	0.019	38.0 [37.4, 38.8]	37.9 [37.3, 38.7]	0.023
heart rate (/min), median [IQR]	95.0 [82.0, 109.0]	94.0 [83.0, 107.0]	0.47	0.047	95.0 [83.0, 109.0]	94.0 [83.0, 107.0]	0.073
respiratory rate (/min), median [IQR]	20.0 [18.0, 24.0]	20.0 [18.0, 22.0]	<0.001	0.14	20.0 [18.0, 22.0]	20.0 [18.0, 22.0]	0.013
systolic blood pressure (mmHg), median [IQR]	130.0 [116.0, 146.0]	130.0 [117.0, 145.0]	0.77	0.009	130.0 [116.0, 144.5]	130.0 [117.0, 145.0]	0.009
diastolic blood pressure (mmHg), median [IQR]	75.0 [66.0, 85.0]	74.0 [67.0, 84.0]	0.94	0.013	75.0 [67.0, 84.0]	74.0 [66.0, 84.0]	0.033
O_2 saturation (%), median [IQR]	89.0 [79.0, 92.0]	88.0 [81.0, 91.0]	<0.001	0.012	90.0 [82.0, 92.0]	88.0 [81.0, 91.0]	0.028
Blood tests							
WBC (K/μL), median [IQR]	7.5 [5.5, 10.8]	6.6 [5.0, 9.0]	<0.001	0.16	7.0 [5.2, 10.1]	6.70 [5.10, 9.20]	0.019
haemoglobin (g/dL), median [IQR]	13.0 [11.4, 14.4]	13.6 [12.3, 14.7]	<0.001	0.33	13.5 [12.2, 14.7]	13.5 [12.3, 14.6]	0.006
eGFR (mL/min/1.73 m^2), median [IQR]	65.6 [35.4, 92.8]	76.0 [56.7, 95.2]	<0.001	0.28	74.5 [52.8, 96.2]	74.3 [55.0, 93.8]	0.002

Continued

Table 1. *Continued*

	Before propensity score matching				After propensity score matching		
	patients without remdesivir, *N* = 2036	patients with remdesivir, *N* = 1336	*P* value	SMD	patients without remdesivir, *N* = 999	patients with remdesivir, *N* = 999	SMD
blood urea nitrogen (mg/dL), median [IQR]	20.0 [13.0, 36.0]	17.0 [12.0, 24.0]	<0.001	0.48	17.0 [12.0, 24.0]	17.0 [12.00, 25.00]	<0.001
AST (U/L), median [IQR]	42.0 [27.0, 68.0]	43.0 [30.0, 63.0]	0.67	0.11	41.0 [28.0, 62.0]	43.0 [30.0, 64.0]	0.027
ALT (U/L), median [IQR]	30.0 [19.0, 53.0]	31.0 [20.0, 49.0]	0.39	0.11	30.0 [19.0, 49.0]	31.0 [20.0, 51.0]	0.031
C-reactive protein (mg/L), median [IQR]	102.0 [43.4, 187.0]	86.8 [48.7, 144.5]	<0.001	0.20	92.0 [37.8, 175.4]	87.5 [48.9, 144.4]	0.094
D-dimer (μg/mL), median [IQR]	1.45 [0.79, 2.71]	1.07 [0.66, 1.79]	<0.001	0.22	1.16 [0.68, 2.08]	1.11 [0.66, 1.85]	0.009
Treatment							
therapeutic anticoagulation, *n* (%)	869 (42.7)	426 (31.9)	<0.001	0.23	328 (32.8)	327 (32.7)	0.002
prophylactic anticoagulation, *n* (%)	1120 (55.0)	898 (67.2)	<0.001	0.25	657 (65.8)	660 (66.1)	0.006
use of tocilizumab, *n* (%)	84 (4.1)	42 (3.1)	0.17	0.052	33 (3.3)	33 (3.3)	<0.001
convalescent plasma, *n* (%)	295 (14.5)	473 (35.4)	<0.001	0.50	233 (23.3)	288 (28.8)	0.13

IL-6, interleukin-6; SMD, standardized mean difference.

Table 2. Treatment by remdesivir and in-hospital outcomes

	Before propensity score matching			After propensity score matching		
	patients without remdesivir, *N* = 2036	patients with remdesivir, *N* = 1336	*P* value	patients without remdesivir, *N* = 999	patients with remdesivir, *N* = 999	*P* value
In-hospital mortality	573 (28.1)	285 (21.3)	<0.001	216 (21.6)	214 (21.4)	0.96
ICU admission	576 (28.3)	363 (27.2)	0.50	222 (22.2)	260 (26.0)	0.053
Endotracheal intubation	375 (18.4)	196 (14.7)	0.005	140 (14.0)	140 (14.0)	>0.999
AKI			<0.001			0.001
no AKI	1335 (65.6)	1096 (82.0)		765 (76.6)	824 (82.5)	
Stage 1	200 (9.8)	102 (7.6)		81 (8.1)	72 (7.2)	
Stage 2	86 (4.2)	43 (3.2)		36 (3.6)	35 (3.5)	
Stage 3	413 (20.3)	95 (7.1)		117 (11.7)	68 (6.8)	
Liver injury	375 (18.4)	196 (14.7)	0.005	140 (14.0)	140 (14.0)	>0.999

Data are given as *n* (%).

In propensity score matched analysis, 999 patients in each group were matched. Baseline characteristics and in-hospital treatments were well balanced, with standardized differences of <0.10 (Table 1). The mortality was similar for patients with remdesivir compared with those without remdesivir (21.4% versus 21.6%, respectively, $P = 0.96$, OR [95% CI] 0.98 [0.80–1.22]). Similarly, remdesivir was not significantly associated with in-hospital mortality (OR [95% CI] 0.93 [0.74–1.16], $P = 0.20$) after multiple imputation. The IPTW analysis also showed the similar results (OR [95% CI] 0.87 [0.71–1.06], $P = 0.17$). In the analysis using IPTW with multiple imputation, OR [95% CI] was 0.92 [0.74–1.14], $P = 0.46$.

The incidence of AKI was significantly lower in patients with remdesivir compared with those without after propensity score matching (17.5% versus 23.4%, respectively, $P = 0.001$, Table 2). IPTW analysis showed the similar result (OR [95% CI] 0.60 [0.48–0.76], $P < 0.001$).

Subgroup analyses are shown in Table 3. Patients with remdesivir did not have significantly different in-hospital mortality compared with those without in the subgroup of patients with or without endotracheal intubation, with or without COVID-19 antibody, and the subgroup limited to the latest data (Table 3).

In the sensitivity analysis after exclusion of patients with ALT >5 times the upper limit and eGFR <30 mL/min/1.73 m^2 ($N = 2828$), in-hospital mortality was not significantly different between patients with remdesivir and those without (20.7% versus 21.3%, respectively, $P = 0.78$) among propensity matched cohorts (951 pairs). Finally, the in-hospital mortality was not different among patients who were given remdesivir within 24 h ($n = 705$) and those who were given remdesivir between 24 and 72 h ($n = 516$) after matching patients by propensity score (439 pairs: 19.8% versus 21.6%, respectively, $P = 0.56$).

Discussion

The salient of our findings is the following: (i) remdesivir was not associated with the reduced risk of in-hospital mortality among patients treated with steroids; (ii) remdesivir was associated with the reduced risk of AKI without increased risk of liver injury; and (iii) remdesivir was not associated with reduced risk of in-hospital mortality regardless of endotracheal intubation or antibody status.

As of 2 March 2021, remdesivir is the only FDA-approved antiviral medication for the treatment of COVID-19. Remdesivir is considered to be effective by reducing the viral load and pulmonary damage with early administration.[9,22] However, our data revealed that median time from hospitalization to start of remdesivir treatment was almost 1 day. There are several reasons to be considered. First, it takes time to diagnose COVID-19 given the high volume of tests needed and the shortage of the machines for testing. Second, use of remdesivir requires approval by infectious disease physicians as per the protocol in our study cohort, which might delay the administration of this drug. Nonetheless, our data revealed no difference in mortality between patients with remdesivir administration within 24 h versus 24–72 h, which validates the current protocol of treatment by remdesivir.

The current study suggests that remdesivir is not associated with reduced risk of in-hospital mortality among patients treated

Table 3. In-hospital mortality for subgroups of patients stratified by endotracheal intubation, antibody and study period

	Before propensity score matching in each subgroup			After matching by propensity score in each subgroup		
	patients without remdesivir, *N* (%)	patients with remdesivir, *N* (%)	*P* value	patients without remdesivir, *N* (%)	patients with remdesivir, *N* (%)	*P* value
Patients without endotracheal intubation	$N = 1661, 292$ (17.6)	$N = 1140, 121$ (10.6)	<0.001	$N = 862, 110$ (12.8)	$N = 862, 94$ (10.9)	0.26
Patients with endotracheal intubation	$N = 375, 281$ (74.9)	$N = 196, 164$ (83.7)	0.022	$N = 130, 108$ (83.1)	$N = 130, 108$ (83.1)	>0.999
Patients with COVID-19 antibody-positive	$N = 515, 123$ (23.9)	$N = 660, 162$ (24.5)	0.85	$N = 377, 79$ (21.0)	$N = 377, 89$ (23.6)	0.43
Patients with COVID-19 antibody-negative	$N = 472, 103$ (21.8)	$N = 246, 40$ (16.3)	0.094	$N = 223, 42$ (18.8)	$N = 223, 36$ (16.1)	0.53
Patients who were discharged after 17 February 2021	$N = 673, 148$ (22.0)	$N = 648, 160$ (24.7)	0.27	$N = 425, 81$ (19.1)	$N = 425, 98$ (23.1)	0.18

with steroids. While steroid treatment is considered to reduce cytokine storm due to COVID-19,[23] reducing viral load and viral activity may not be enough to reduce mortality due to COVID-19. These results were consistent with a previous randomized controlled trial and a meta-analysis, which did not reveal a mortality benefit of remdesivir.[10,24] Additionally, we also demonstrated that remdesivir was not associated with reduced risk of death for patients requiring endotracheal intubation, which was compatible with the previous study.[8] As cytokine storm due to COVID-19 is considered to be the cause of high mortality rates, we might suspect that patients have mainly cytokine storm and inflammation, and not viral load and activity, which could explain why remdesivir was not associated with a reduced risk of death.[25,26] Moreover, we elucidated that the results were unchanged regardless of antibody status. As it is expected that the number of people with positive antibody against COVID-19 is increasing according to the progress of vaccination globally, our data also suggest that the use of remdesivir may also be reconsidered among patients who have received vaccination but are infected in the near future.

The current study also suggested that treatment with remdesivir may be associated with a reduced risk of AKI. Although AKI due to COVID-19 leads to in-hospital mortality,[27] little is known about the management and treatment of AKI due to COVID-19.[28] Our data may indicate that treatment with remdesivir could prevent AKI caused by COVID-19, even if this did not result in mortality benefit. Although little is known about AKI after hospitalization due to COVID-19 and how residual kidney damage due to COVID-19 will remain, we might expect that remdesivir is potentially effective for the prevention of kidney damage among COVID-19 patients. Long-term follow-up is needed to investigate how AKI will affect the residual damage of the kidney after discharge, and whether potential prevention of AKI by the use of remdesivir during hospitalization could affect patients' kidney function in the long term.

Our study is not without limitations. First, this was a retrospective observational study. Despite rigorous adjustments including multiple imputation for missing data and propensity score analyses, we could not exclude unmeasured confounders. We adjusted for treatments such as anticoagulation, tocilizumab and convalescent plasma and we assessed the outcomes using the well-balanced cohorts. Second, we do not have radiological information such as pneumonia of our cohorts, which could be the unmeasured confounder.

In conclusion, remdesivir was not associated with reduced risk of in-hospital mortality in patients with COVID-19 treated with steroids but was potentially associated with a decreased risk of AKI. These findings should be confirmed in prospective studies focusing on COVID-19 treated with steroids.

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This work was carried out as part of our routine work.

Transparency declarations

None to declare.

Author contributions

Data curation, full access to all of the data in the study and responsibility taken for the integrity of the data and the accuracy of the data analysis: T.K., M.T. and N.N.E. Study concept and design, and drafting of the manuscript: T.K. Statistical analysis: T.K. and M.T. Administrative, technical, or material support, and study supervision: N.N.E. Acquisition, analysis, or interpretation of data, and critical revision of the manuscript for important intellectual content: all authors.

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