Open Forum Infectious Diseases

MAJOR ARTICLE

Remdesivir Use in Patients Requiring Mechanical Ventilation due to COVID-19

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Background. Remdesivir has been associated with accelerated recovery of severe coronavirus disease 2019 (COVID-19). However, whether it is also beneficial in patients requiring mechanical ventilation is uncertain.

Methods. All consecutive intensive care unit (ICU) patients requiring mechanical ventilation due to COVID-19 were enrolled. Univariate and multivariable Cox models were used to explore the possible association between in-hospital death or hospital discharge, considered competing-risk events, and baseline or treatment-related factors, including the use of remdesivir. The rate of extubation and the number of ventilator-free days were also calculated and compared between treatment groups.

Results. One hundred thirteen patients requiring mechanical ventilation were observed for a median of 31 days of follow-up; 32% died, 69% were extubated, and 66% were discharged alive from the hospital. Among 33 treated with remdesivir (RDV), lower mortality (15.2% vs 38.8%) and higher rates of extubation (88% vs 60%), ventilator-free days (median [interquartile range], 11 [0–16] vs 5 [0–14.5]), and hospital discharge (85% vs 59%) were observed. Using multivariable analysis, RDV was significantly associated with hospital discharge (hazard ratio [HR], 2.25; 95% CI, 1.27–3.97; $P = .005$) and with a nonsignificantly lower mortality (HR, 0.73; 95% CI, 0.26–2.1; $P = .560$). RDV was also independently associated with extubation (HR, 2.10; 95% CI, 1.19–3.73; $P = .011$), which was considered a competing risk to death in the ICU in an additional survival model.

Conclusions. In our cohort of mechanically ventilated patients, RDV was not associated with a significant reduction of mortality, but it was consistently associated with shorter duration of mechanical ventilation and higher probability of hospital discharge, independent of other risk factors.

Keywords. antiviral treatment; coronavirus; COVID-19; critically ill patients; intensive care unit; remdesivir; SARS-CoV-2.

The coronavirus disease 2019 (COVID-19) pandemic hit Northern Italy particularly hard, stressing the health care system to an unprecedented level. The lack of effective antiviral treatments and the shortage of intensive care unit (ICU) beds contributed to high mortality [1]. Under the pressure of the rising tide of the epidemic, several molecules of uncertain clinical efficacy have been used to treat patients in different stages of the disease, including those requiring invasive mechanical ventilation (IMV). The most promising drug so far has been remdesivir (RDV), which has shown antiviral efficacy in vitro [2] and potential efficacy in primate models [3]. Data on the clinical efficacy of RDV in humans are, however, somewhat contradictory. A randomized clinical trial, prematurely halted due to difficulty with patient recruitment, did not show any clear benefit of RDV over supportive standard of care [4]. Conversely, a preliminary data analysis from a US-led trial suggested that patients treated with RDV recovered more quickly than those treated with placebo [5]. Of note, no apparent benefit was observed in the subset of patients receiving IMV. It is therefore still an open question whether RDV is beneficial in critically ill patients.

The aim of our study was to assess the possible survival benefit of RDV and other purposed antiviral candidates in a real-world cohort of patients admitted to the ICU who required IMV for severe COVID-19.

METHODS

Study Population

All consecutive patients admitted to the ICUs of the San Gerardo Hospital of Monza who required IMV because of COVID-19 pneumonia (polymerase chain reaction–proven) between March 1 and 31, 2020, were evaluated. This convenience time interval was chosen because it coincided with the peak of the epidemic and provided the opportunity to observe all patients through death or hospital discharge.

Received 18 August 2020; editorial decision 2 October 2020; accepted 6 October 2020.

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DOI: 10.1093/ofid/ofaa481

The following variables at ICU admission were collected: age, gender, date of symptom onset, comorbidities, Simplified Acute Physiology Score 2 (SAPS-2), lymphocyte count, levels of d-dimer, lactate-de-hydrogenase (LDH), C-reactive protein, creatinine, and arterial lactate.

Data were collected within the STORM trial, an observational cohort study enrolling patients hospitalized at San Gerardo Hospital due to COVID-19. The study was approved by the national ethical review board for the COVID-19 emergency.

Treatment Regimens

Use of RDV, hydroxychloroquine (HCQ), and lopinavir/ritonavir (LPV/r) was evaluated. We considered patients exposed to each drug since the date of the first administration, regardless of the actual duration of the treatment. Remdesivir was provided by the manufacturer through the compassionate use program, whose inclusion criteria have been described elsewhere [6]; in brief, they required the patient to be hemodynamically stable with no need for inotropes or pressors and to have an estimated glomerular filtration rate (eGFR) >30 mL/min and transaminase levels <5 times the upper limit of normality. The prescribed treatment schedule for RDV was 200 mg intravenously on the first day, followed by 100 mg for the next 9 days. Patients who were taking LPV/r had to discontinue it >12 hours before the first dose of RDV.

Hydroxychloroquine and LPV/r were used by oral route through a nasogastric tube (crushed tablets or oral formulation, where available), as authorized by the Italian Drug Agency [7]. The dose of HCQ was 200 mg twice daily, and that of LPV/r was 400/100 mg twice daily. Treatment durations were not prespecified.

Outcome Measures

The main end point was the time between intubation and 2 competing events: all-cause in-hospital mortality and hospital discharge. The secondary end point was extubation, measured as the time to extubation with no need of reintubation for >48 hours (competing with death in the ICU) and as the number of ventilator-free days in the first 28 days of follow-up since intubation.

Statistical Analysis

Crude incidence curves of each competing event (in-hospital death and hospital discharge as primary end points) were calculated using the Aalen-Johansen estimator on the overall sample, on subgroups defined by baseline factors (cutoffs for continuous factors were determined using receiver operating characteristics curve methodology), and by administered treatment. The Gray test was used to compare incidence curves. Univariate Cox models were used to assess the impact of different drugs on the primary end points. Since treatments could have been administered to patients after intubation, we modeled exposure to each treatment as time-depending covariates.

Multivariable Cox regression models were applied to estimate the cause-specific hazard of death or discharge by treatment administered, after adjusting for baseline covariates associated with the outcome at univariate analysis or deemed to be clinically relevant. As RDV use was preceded in almost all instances by LPV/r and LPV/r was discontinued before RDV introduction, in order to disentangle their possible effects, we modeled a time-varying treatment covariate with 3 levels (use of LPV/r alone, use of RDV after LPV/r, and lack of use of both drugs).

In addition, as few patients received RDV in the first week of observation due to the long sequential workflow needed to obtain it through the compassionate use program, we performed additional sensitivity analyses. First, survival analyses conditional on a landmark time at 7 days after intubation were performed. This implied the exclusion of patients who had died before day 7, thus limiting the possible selection bias caused by inclusion in the treated group of patients who survived long enough to receive the drug (immortal time bias). Moreover, the landmark was essential to estimate the crude cumulative incidence by time-dependent RDV to ensure an adequate number of patients at risk in the treated group. Second, we compared patients treated with RDV with a control group of untreated patients who were matched 1:1 for age, gender, SAPS-2, and d-dimer level at the time of intubation and who were alive and free from acute kidney injury (ie, eGFR <30 mL/min; grade ≥3 transaminase elevation and hemondynamic instability requiring pressors at the time of RDV introduction in the matched case).

Eventually, we calculated the number of ventilator-free days as the number of days successfully liberated from IMV in the first 28 days of follow-up, assigning 0 ventilator-free days to deceased patients. Four patients whose observation was censored before 28 days of follow-up were excluded from this analysis. The association of baseline characteristics and treatments with the number of ventilator-free days was evaluated using the Wilcoxon rank-sum test. As treatments could not be handled as time-dependent covariates, they were considered to have been initiated on the day of intubation.

All statistical analyses were performed using R software, version 3.6.2. P values are 2-sided, and the significance level was defined as $P < .05$.

RESULTS

Patient Characteristics and Outcomes

One hundred nineteen individuals were admitted to 1 of the 5 ICUs dedicated to patients with COVID-19. We excluded 2 patients who were discharged without need for intubation and 4 patients whose data were not available (the enrollment flowchart is shown in Supplementary Figure 1). The characteristics of the remaining 113 patients are listed in Table 1.

Table 1. Characteristics of 113 Patients Admitted to ICU Wards Between March 1 and 31 who Required Mechanical Ventilation for COVID-19

Characteristic	
Male gender, No. (%)	90 (79.6)
Age, median (IQR), y	61 (56–67)
BMI,[a] median (IQR), kg/m^2	29.4 (25.9–32.6)
Comorbidities, No. (%)	
Hypertension	53 (46.9)
Diabetes	20 (17.7)
History of ischemic cardiopathy	6 (5.3)
History of cerebrovascular disease	4 (3.5)
History of neoplasms	11 (9.7)
Chronic obstructive pulmonary disease	5 (4.4)
Immunodepression	5 (4.4)
SAPS-2 score, median (IQR)	28 (24–34)
D-dimer, median (IQR), ng/mL	1765 (693–6243)
Lymphocyte count, median (IQR), $\times 10^3/\mu L$	0.69 (0.55–0.95)
LDH, median (IQR), IU/L	450 (363–582)
C-reactive protein, median (IQR), mg/dL	18.24 (8.4–27.6)
Creatinine, median (IQR), mg/dL	0.9 (0.7–1.2)
Arterial lactate, median (IQR), mmol/L	1.5 (1.1–1.9)
Drug treatment, No. (%)	
Remdesivir	33 (29.2)
Hydroxychloroquine	95 (85.6)
Lopinavir/ritonavir	64 (57.7)
Time from symptom onset to intubation, median (IQR), d	11 (8–14)

Abbreviations: BMI, body mass index; IQR, interquartile range; LDH, lactate dehydrogenase; SAPS-2, Simplified Acute Physiology Score 2.

[a]BMI missing for 36 patients.

Most patients (80%) were male, with a median age (interquartile range [IQR]) of 61 (56–67) years. The median time between the onset of symptoms and intubation (IQR) was 11 (8.75–14) days. The median SAPS-2 score at intubation (IQR) was 28 (24–34). Remdesivir, HCQ, and LPV/r were used in 29%, 86%, and 58% of the patients, respectively.

Over a median (IQR) of 31 (19–41) days of follow-up, 36 fatalities were observed. Seventy-eight (69%) patients were extubated after a median (IQR) of 15 (11–23) days of IMV. Among these, 75 were discharged alive from the hospital.

At 28 days of follow-up, the estimated cumulative incidence rates of in-hospital mortality and discharge (IQR) were 24% (16.1%–31.8%) and 18.9% (11.7%–26.2%); 20.5% of patients were still intubated, while 36.6% had been extubated and moved to a medical ward. Supplementary Figure 2 shows the incidence of in-hospital mortality and hospital discharge, as estimated by the Aalen-Johansen estimator.

Baseline Predictors

Table 2 shows the proportion of deaths, hospital discharge, extubations, and ventilator-free days according to patients' characteristics. Higher proportions of deaths and lower rates of extubation and hospital discharge were observed in older patients, in those with hypertension or cardiovascular comorbidities, and in those with higher SAPS-2 or d-dimer levels at intubation. Consistently, these patients spent less time free from ventilation.

Table 3 shows the estimated hazard ratios of mortality and hospital discharge, according to univariate Cox models. Age >60 years (hazard ratio [HR], 3.2; 95% CI, 1.5–6.9), hypertension (HR, 2.3; 95% CI, 0.7–7.7), diabetes (HR, 2.2; 95% CI, 1.06–4.4), history of ischemic cardiopathy (HR, 3; 95% CI, 1.05–8.5), history of cerebrovascular disease (HR, 2; 95% CI, 1.03–3.99), SAPS-2 >28 (HR, 3.4; 95% CI, 1.6–7.1), and selected laboratory abnormalities (levels of d-dimer, LDH, and arterial lactate) were associated with increased mortality. In addition, a shorter time between symptom onset and intubation was also associated with a significantly higher risk of death (per day of delay; HR, 0.93; 95% CI, 0.86–1).

Additional analyses exploring the factors associated with ventilator-free days confirmed that a higher number of ventilator-free days was associated with younger age (≤60 vs 60 years; median [IQR], 11 [0–16] vs 0 [0–14.5] days; $P = .051$), lower SAPS-2 (≤28 vs 28; median [IQR], 11.5 [0–17] vs 0 [0–11]; $P = .002$), and lower d-dimer (≤3.5 vs >3.5 $\log_{10}$ ng/mL; median [IQR], 11 [0–16] vs 0 [0–7]; $P = .005$).

Drug Effect on Patient Course

Remdesivir was used in 33 patients after a median (IQR) of 7 (4–11) days since intubation. The patients treated with RDV were similar to the others in terms of demographic characteristics, comorbidities, and disease severity (median SAPS-2, 29 vs 27; $P = .726$), although they had significantly lower d-dimer (966 vs 2052 ng/mL; $P = .001$) and statistically (but not clinically) significantly lower levels of arterial lactates (1.6 vs 1.1 mmol/L; $P < .001$). The full comparison is shown in Supplementary Table 1.

As shown in Table 3, we observed fewer deaths among patients treated with RDV (5/33, 15.2%) than in those never exposed to RDV (31/80, 38.8%). Moreover, patients treated with RDV were more likely to be extubated (88% vs 60%) and to be discharged alive (85% vs 59%) than the others. When exposure to RDV was modeled as a time-varying covariate in Cox models, it was associated with a not significantly lower in-hospital mortality (HR, 0.74; 95% CI, 0.28–1.98; $P = .552$) and with a significantly higher hazard of being discharged alive (HR, 1.76; 95% CI, 1.08–2.86; $P = .022$). Importantly enough, the effect of RDV on these outcomes was influenced by its timing. When the models were adjusted for the interaction term between RDV use and the time elapsed between intubation and RDV use, the association between RDV and hospital discharge became more evident (HR, 3.44; 95% CI, 1.52–7.79; $P = .003$), suggesting that patients who received it earlier obtained larger benefits. After this adjustment, in-hospital mortality also appeared to be lower among patients treated with RDV (HR, 0.46; 95% CI, 0.08–2.46; $P = .361$), although the association was not statistically significant. Moreover, patients treated with RDV

Table 2. Observed Mortality, Extubation Rate, and Hospital Discharge by Patient Characteristics

Characteristics	Death, No. (%)	Extubation, No. (%)	Hospital Discharge, No. (%)	Ventilator-Free Days, Median (IQR)
All patients (n = 113)	36 (31.9)	78 (69)	75 (66.4)	13 (5.25–17)
Age				
≤60 y (n = 54)	9 (16.7)	46 (85.2)	44 (81.5)	11 (0–16)
>60 y (n = 59)	27 (45.8)	32 (54.2)	31 (52.5)	0 (0–14.5)
Gender				
Male (n = 90)	29 (32.2)	62 (68.9)	59 (65.6)	6 (0–15)
Female (n = 23)	7 (30.4)	16 (69.6)	16 (69.9)	0 (0–16.5)
Hypertension/CV disease				
No (n = 54)	12 (22.2)	43 (79.6)	41 (75.9)	7 (0–15)
Yes (n = 59)	24 (40.7)	35 (59.3)	34 (57.6)	0 (0–16)
SAPS-2				
≤28 (n = 60)	10 (16.7)	50 (83.3)	48 (80)	11.5 (0–17)
>28 (n = 53)	26 (49.1)	28 (52.8)	27 (50.9)	0 (0–12)
Date of intubation				
≤ Mar 20, 2020 (n = 60)	21 (34.4)	42 (68.9)	40 (65.6)	6 (0–15)
> Mar 20, 2020 (n = 53)	15 (28.8)	36 (69.2)	35 (67.3)	6.5 (0–16.5)
D-dimer, $\log_{10}$				
≤3.5 (n = 76)	18 (23.7)	59 (77.6)	56 (73.7)	11 (0–16)
>3.5 (n = 37)	18 (48.6)	19 (51.4)	19 (51.4)	0 (0–7)
Use of remdesivir				
Yes (n = 33)	5 (15.2)	29 (87.9)	28 (84.8)	11 (0–16)
No (n = 80)	31 (38.8)	49 (61.3)	47 (58.8)	5 (0–14.5)
Use of lopinavir/ritonavir				
Yes (n = 64)	16 (25)	49 (76.6)	47 (73.4)	11 (0–17)
No (n = 47)	18 (38.3)	29 (61.7)	28 (59.6)	0 (0–13)
Use of hydroxychloroquine				
Yes (n = 95)	28 (29.5)	67 (70.5)	65 (68.4)	7 (0–16)
No (n = 16)	6 (37.5)	11 (68.8)	10 (62.5)	6 (0–16)

Abbreviations: CV, cardiovascular; IQR, interquartile range; SAPS-2, Simplified Acute Physiology Score 2.

spent slightly more ventilator-free days than the others (median [IQR], 11 [0–16] vs 5 [0–14.5] days; $P = .236$). Consistent with this finding, in the survival model exploring extubation and death in the ICU as a competing-risk events, RDV was associated with significantly higher extubation rates (HR, 1.97; 95% CI, 1.19–3.25; $P = .008$).

As RDV was rarely administered during the first week after intubation, we conducted a sensitivity analysis with a "landmark" (ie, a shift of the observation) of 7 days after intubation. This led to the exclusion of 14 patients who had died within the first week of IMV (and 7 patients who had been extubated within <7 days). In this analysis, as shown in Figure 1, RDV was still significantly associated with hospital discharge (HR, 1.76; 95% CI, 1.08–2.86; $P = .022$), while no differences were present in terms of mortality.

Hydroxychloroquine and LPV/r were used in 95 and 64 patients, respectively. In almost half of the cases (42% for HCQ and 47% for LPV/r), the drug was started before ICU admission. The proportions of patients treated with HCQ or LPV/r who were later switched to RDV were 34% and 47%, respectively.

Use of HCQ was not associated with in-hospital death (HR, 1.2; 95% CI, 0.46–3.18; $P = .708$) or hospital discharge (HR, 1.18; 95% CI, 0.6–2.29; $P = .636$). Similarly, no association was found between HCQ and the number of ventilator-free days. Adjustment for timing of HCQ introduction or other covariates did not change the results to a significant extent. Conversely, LPV/r was not associated with risk of death (HR, 0.92; 95% CI, 0.46–1.86; $P = .823$), but it appeared to be associated with hospital discharge (HR, 2.02; 95% CI, 1.25–3.24; $P = .004$). Thus, the effect of LPV/r, along with that of RDV, was further explored in multivariable analyses, as shown in the last section.

In order to assess whether the associations between RDV and LPV/r use and the outcome measures were independent from other possible confounders, we ran multivariate analyses adjusted for exposure to these drugs (as time-varying covariates) and for other baseline characteristics. Table 4 shows the final multivariable model, in which use of RDV was significantly associated with higher probability of hospital discharge (HR, 2.25; 95% CI, 1.27–3.97) and with a nonsignificantly lower probability of in-hospital death (HR, 0.73; 95% CI, 0.26–2.1). Conversely, the association of LPV/r with hospital discharge, detected in univariate analysis, became only marginally significant. These results were confirmed when the analyses were repeated using a landmark of

Table 3. Association of Baseline Factors With In-Hospital Deaths or Hospital Discharge (Univariate Competing-Risk Cox Regression Models)

	Event: In-Hospital Death		Event: Discharge	
Factors	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Male gender	1.05 (0.46–2.41)	.902	0.89 (0.51–1.54)	.668
Age (>60 y vs ≤60 y)	3.25 (1.52–6.95)	.002	0.95 (0.60–1.51)	.839
BMI (<30 kg/m^2 vs ≥30 kg/m^2)	0.65 (0.25–1.65)	.360	0.63 (0.31–1.26)	.190
Comorbidities (yes vs no)				
Hypertension	2.35 (0.72–7.69)	.159	1.19 (0.75–1.89)	.470
Diabetes	2.16 (1.06–4.40)	.035	0.70 (0.35–1.40)	.309
Ischemic cardiopathy	3.00 (1.05–8.51)	.040	0.57 (0.14–2.32)	.431
Cerebrovascular disease	2.03 (1.03–3.99)	.041	1.14 (0.72–1.82)	.569
Neoplasms	1.67 (0.65–4.32)	.287	1.11 (0.48–2.57)	.809
COPD	1.82 (0.43–7.64)	.413	1.32 (0.41–4.24)	.638
Immunodepression	2.35 (0.72–7.69)	.159	0.53 (0.07–3.82)	.528
SAPS-2, per unit	1.04 (1.01–1.07)	.007	0.99 (0.96–1.02)	.438
SAPS-2 (>28 vs ≤28)	3.42 (1.64–7.13)	.001	0.85 (0.53–1.36)	.491
D-dimer, per $\log_{10}$ ng/mL	2.30 (1.35–3.94)	.002	0.53 (0.34–0.83)	.006
Log_{10} d-dimer (>3.5 vs ≤3.5)	2.47 (1.27–4.81)	.008	0.68 (0.40–1.15)	.150
Lymphocytes, per 10^3 cells/μL	1.09 (0.44–2.68)	.855	1.41 (0.74–2.66)	.297
LDH, per 100 IU/mL	1.42 (1.19–1.70)	<.001	0.85 (0.74–0.98)	.023
CRP, per mg/dL	1.01 (0.98–1.03)	.717	0.98 (0.97–1.00)	.096
Creatinine, per 0.1 mg/dL	1.06 (1.00–1.11)	.048	0.96 (0.91–1.01)	.099
Arterial lactate, per mmol/L	1.85 (1.29–2.65)	<.001	0.48 (0.30–0.78)	.002
Time from onset of symptoms to intubation, per day	0.93 (0.86–1.00)	.042	1.06 (1.02–1.10)	.006
Date of intubation (< or ≥ Mar 20)	1.52 (0.77–3.00)	.229	1.57 (0.98–2.52)	.060

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HR, hazard ratio; LDH, lactate dehydrogenase; SAPS-2, Simplified Acute Physiology Score 2.

7 days in order to correct for the delay in RDV use (death HR, 0.9; 95% CI, 0.3–2.7; $P = .85$; discharge HR, 2.25; 95% CI, 1.27–3.97; $P = .005$). Similarly, time-updated RDV use remained associated with a significantly higher hazard of extubation (HR, 2.1; 95% CI, 1.19–3.73; $P = .011$) in multivariable models using extubation and death in the ICU as competing-risk events.

In the last sensitivity analysis, we compared 33 patients treated with RDV with a control group of 33 untreated patients, extracted from our cohort, by matching each treated case with 1 untreated individual with the same selected baseline characteristics and who was still alive and free from acute kidney injury, transaminase elevation, and hemodynamic instability at the time of RDV introduction in the corresponding treated case.

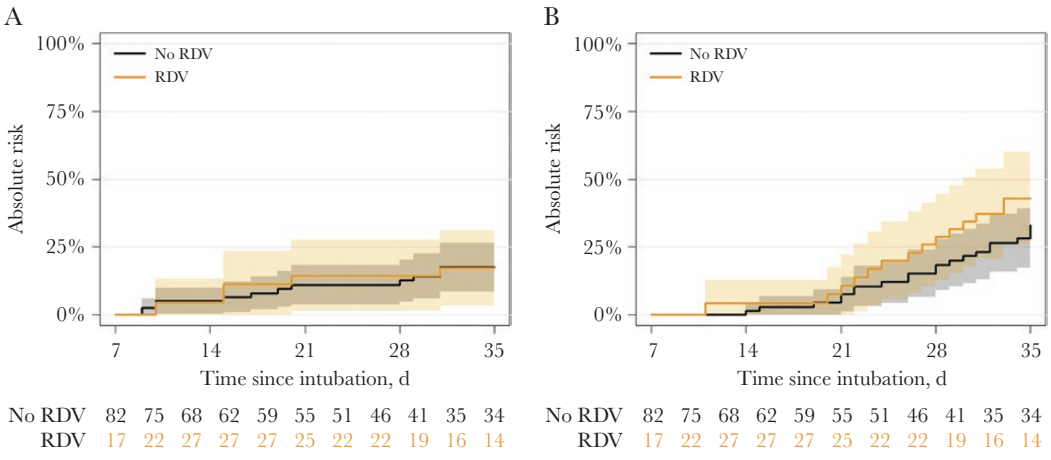

Figure 1. Aalen-Johansen crude incidence curves showing the association between exposure to remdesivir (modeled as time-varying variable) and in-hospital death (A) or discharge from the hospital (B). A landmark of 7 days was applied. Abbreviation: RDV, remdesivir.

Table 4. Results From Multivariable Competing-Risk Regression Models Assessing In-Hospital Mortality and Hospital Discharge as Competing Risks

	Event: In-Hospital Death		Event: Discharge	
Factors	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Drug exposure (RDV or LPV/r)				
None	1	-	1	-
RDV (after LPV/r)	0.73 (0.26–2.09)	.560	2.25 (1.27–3.97)	.005
LPV/r (w/o RDV)	1.40 (0.62–3.17)	.426	1.73 (0.90–3.34)	.102
Age (≥60 y vs <60 y)	1.70 (0.69–4.20)	.247	1.30 (0.74–2.30)	.364
Hypertension or CV disease	1.87 (0.88–3.97)	.103	0.74 (0.45–1.22)	.238
SAPS-2 >28	2.36 (0.99–5.61)	.053	0.88 (0.47–1.64)	.678
D-dimer >3.5 $\log_{10}$ ng/mL	2.19 (1.07–4.49)	.033	0.62 (0.36–1.07)	.085

All variables shown in the tables are adjusted for each other.

Abbreviations: CV, cardiovascular; HR, hazard ratio; LPV/r, lopinavir/ritonavir; RDV, remdesivir; SAPS-2, Simplified Acute Physiology Score 2.

The characteristics of the 2 groups of patients are presented in Supplementary Table 2. Also in this analysis, those who had received RDV had a lower risk of death (HR, 0.53; 95% CI, 0.18–1.57; $P = .251$) and a higher probability of being discharged (HR, 1.48; 95% CI, 0.83–2.64; $P = .181$), although the difference was no longer statistically significant, possibly because of the reduced power of this analysis.

DISCUSSION

We reported the outcomes of a large and well-documented case series of patients sequentially admitted to our ICUs who required IMV due to severe COVID-19 during the peak of the epidemic.

After 28 days of follow-up, 24% of the patients had died, while more than half had improved their condition and had been discharged from the ICU. Several studies have recently reported death rates of patients with COVID-19 requiring IMV. However, different analytical approaches and inconsistent follow-up lengths have led to significant differences in the reported death rates, ranging from 23% to 60% [8–14]. Thanks to a prolonged and homogeneous follow-up, we were able to reliably assess patients' survival rates. This estimate is important, particularly because the efficacy of several treatment interventions for COVID-19 is often being explored in single-arm studies or in comparison with historical groups [6, 15, 16]. When it comes to patients in the ICU, having a reliable yardstick is of the utmost importance, given the limited number of randomized clinical trials actively enrolling patients under IMV.

We also were able to explore the possible impact of RDV on the outcomes. In particular, testing whether RDV was beneficial in critically ill patients was of extreme interest. Although RDV has been the first drug to get Food and Drug Administration authorization as potential treatment for severe COVID-19, it is still under investigation due to conflicting data from trials [4, 5]. In our cohort, the use of RDV was not associated with a significant reduction of mortality, but it was associated with shorter duration of IMV and higher probability of hospital discharge, independent of other risk factors. In addition, we cannot exclude that the effect on survival may have been hampered by delayed access to the drug.

Our results are in contrast with the preliminary report of a randomized trial, in which RDV was associated with accelerated recovery among patients requiring oxygen supplementation but not among those requiring IMV [5]. Patients requiring IMV, however, need a longer time to fully recover. A short follow-up duration may have limited the ability of the trial to detect any difference. Pending definitive results that are able to prove RDV efficacy incontrovertibly, our data suggest that critically ill patients requiring IMV may benefit from RDV.

The use of HCQ was not associated with a significant clinical benefit in our cohort. This result was consistent in all the analyses performed. The lack of clinical effect, despite early use of the drug after hospitalization, is discouraging and suggests that the prognosis of patients on IMV is not influenced by HCQ. Notably, the use of HCQ for COVID-19 has been promoted so far on undemonstrated premises, and several observational studies now question its overall efficacy [17–20].

Using univariate analysis, LPV/r was apparently associated with a shorter duration of hospitalization and IMV. However, LPV/r was generally initiated before ICU admission and discontinued early after intubation (in particular, right before RDV introduction). When LPV/r and RDV were modeled together, the effect of LPV/r waned, while that of RDV was confirmed. Although we cannot completely rule out an effect of LPV/r in patients on IMV, our results suggest it to be unlikely. A previous randomized clinical trial, prematurely halted due to insufficient patient recruitment, failed to demonstrate a significant benefit of LPV/r [21]. More recently, released but as yet unpublished results from the Recovery trial suggest that LPV/r is not associated with a meaningful mortality benefit in hospitalized patients, though the study did not enroll a sufficient number of patients on IMV to make conclusions about them.

In our work, we confirmed that some baseline factors, already identified as predictors of severe COVID-19, were associated with increased mortality in patients on IMV. In particular, older age,

hypertension, and cardiovascular diseases were confirmed as important predictors of an unfavorable outcome [13, 22, 23]. Higher SAPS-2, a validated measure of severity of disease in ICUs, was associated with higher mortality and longer duration of IMV. However, it is worth noting that the actual mortality of our population exceeded that predicted based solely on the SAPS-2 and that the interpatient variability of the score was narrow (80% of the patients had scores between 19 and 39). In this respect, prognostic scores based on multi-organ functions, such as the SAPS-2, may have reduced power to stratify the risk of a disease like COVID-19, which manifests itself, especially at early stages, with little impairment of organ functions other than respiratory. Levels of d-dimer, LDH, and alteration of inflammation markers were, in our study and in others, significantly associated with survival and duration of IMV [9, 24, 25]. Whether these markers can be used in scores specifically designed for the prognostic stratification of patients with COVID-19 in ICUs merits investigation.

Our study has limitations that need to be acknowledged. First, the study was observational in nature, as it lacked a randomized design. Patients treated with RDV may be inherently different from the others, and this may have influenced our results. Nonetheless, we performed a series of analyses aimed at correcting the unbalance between treatment arms, including multivariable analyses, an analysis using a landmark of 7 days (thus excluding early mortality), and a sensitivity analysis comparing patients treated with RDV with a set of patients not treated with RDV and extracted from our cohort by matching each treated case with 1 untreated individual, with the same selected baseline characteristics and who was still alive and free from conditions contraindicating RDV at the time of RDV introduction in the corresponding case. The fact that RDV remained constantly associated with lower mortality and higher probability of hospital discharge in all analyses reassured us about the solidity of this result. Second, the timing of drug introductions was different, and the drugs were used in various combinations. It can therefore be difficult to assess their individual effect. Third, this was a single-center study, which could limit to some extent its generalizability.

In conclusion, our study provides solid estimates on the outcome of patients with COVID-19 requiring IMV. In addition, it provides important insight into predictors of survival and suggests that RDV has a favorable effect in shortening the duration of IMV and accelerating recovery.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We would like to kindly thank Prof. Miriam Giorgio for the language revision of the paper.

Remdesivir-Ria study group. Alessandra Gambaro, Anna Spolti, Ilaria Beretta (study coordinators), Luca Bisi, Anna Cappelletti, Elisabetta Chiesa, Viola Cogliandro, Paola Columpsi, Sergio Foresti, Giulia Gustinetti, Francesca Iannuzzi, Ester Pollastri, Marianna Rossi, Francesca Sabbatini, Nicola Squillace, Daniela Ferlicca, Fabrizia Mauri, Marco Giani, Matteo Pozzi, Vincenzo Russotto (Clinicians).

Potential conflicts of interest. The authors do not have any association that might pose a conflict of interest for the present work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. Data were collected within the STORM trial, an observational cohort-study including all patients hospitalized in the "San Gerardo" Hospital due to COVID-19. The design of the work was approved by the National Ethical Committee for the COVID-19 emergency. Given the nature of the study, written informed consent was not required.

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