Remdesivir use and risks of acute kidney injury and acute liver injury among patients hospitalized with COVID-19: a self-controlled case series study

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Abstract

Aim: to investigate and quantify the risks of AKI and ALI associated with remdesivir use, given the underlying diseases of SARS-CoV-2 infection.

Methods: This self-controlled case series (SCCS) study was conducted using electronic hospital records between 23rd January 2020 and 31st January 2021 as retrieved from the Hong Kong Hospital Authority which manages all laboratory-confirmed COVID-19 cases in Hong Kong. Outcomes of AKI and ALI were defined using the KDIGO Guideline and Asia Pacific Association of Study of Liver consensus guidelines. Incidence rate ratios (IRR) for AKI and ALI following the administration of remdesivir (exposure) in comparison to a non-exposure period were estimated using the conditional Poisson regression models.

Results: Of 860 COVID-19 patients administered remdesivir during hospitalization, 334 (38.8%) and 137 (15.9%) had incident ALI and AKI, respectively. Compared with the baseline period, both ALI and AKI risks were increased significantly during the pre-exposure period (ALI: IRR=6.169, 95%CI=4.549-8.365; AKI: IRR=7.074, 95%CI=3.763-13.298) and remained elevated during remdesivir treatment. Compared to the pre-exposure period, risks of ALI and AKI were not significantly higher in the first two days of remdesivir initiation (ALI: IRR=1.261, 95%CI=0.915-1.737; AKI: IRR=1.261, 95%CI=0.889-1.789) and between days 2-5 of remdesivir treatment (ALI: IRR=1.087, 95%CI=0.793-1.489; AKI: IRR=1.152, 95%CI=0.821-1.616).

Conclusion: The increased risks of AKI and ALI associated with intravenous remdesivir treatment for COVID-19 may be due to the underlying SARS-CoV-2 infection. The risks of AKI and ALI were elevated in the pre-exposure period, yet no such increased risks were observed following remdesivir initiation when compared to the pre-exposure period.

Keywords: COVID-19; remdesivir; acute liver injury; acute kidney injury; case series

Manuscript Text

Introduction

Coronavirus disease 2019 (COVID-19) has posed an unprecedented challenge to nearly all governments worldwide, which are trying desperately to control the infection and mortality rate by means of vaccination and a variety of treatments. The pathogenesis of SARS-CoV-2 infection has been well-described(1). Spike protein of coronaviruses binds with the receptor angiotensin-converting enzyme 2 (ACE2) expressed in alveolar cells, thereby promoting viral entry and utilizing host cell machinery for replication with viral RNA-dependent RNA polymerase (RdRp)(2, 3). Meanwhile, podocytes and proximal tubular cells in the kidney also express high levels of ACE2, which may contribute to the development of acute kidney injury (AKI) upon SARS-CoV-2 infection(3). While a remarkable drop in kidney function indicates the onset of acute tubular injury, the situation is often mild(4). Another possible injury mechanism involves the immune system that triggers inflammation and immune cell infiltration, which play a critical role in tubular injury and thrombi(4). A similar mechanism mediated by immune response and thrombosis could also be responsible for hepatocytes injury(5). Meanwhile, hepatic injury is also noticed alongside elevated levels of liver enzymes, such as aspartate transaminase (AST) and alanine transaminase (ALT) (6). In addition, ACE2 is expression at highest level in cholangiocytes, followed by hepatocytes based on RNA sequencing data(7). Therefore, hepatotoxicity is directly linked to viral infection despite variation in expression level(8).

Remdesivir is an effective pharmaceutical option targeting the infection pathway and subsequent immune responses. It is a board-spectrum antiviral monophosphoramidate prodrug that is metabolized in the liver to form remdesivir triphosphate; the metabolite is a nucleotide analogue that competes with ATP and interferes with RdRp activity, so viral RNA replication ceases to operate(9-11). In this regard, this drug could trigger mitochondrial injury as it inhibits mammalian DNA and RNA polymerases(9, 11-15). This may lead to increased aminotransferase level in liver and mitochondrial injury in renal tubular cells, although action in the kidney may only occur with long-term treatment(9, 12, 15). In addition, CYP3A4, which metabolizes remdesivir in the liver, and hepatocytes transporters are susceptible to drug interactions with other agents, thus potentially causing liver damage(11). Product label from FDA and EMA include increased transaminase level, bilirubin and creatinine as clinical implications, while increase in liver enzymes is highlighted by

FDA as a possible adverse side effect(16, 17). Despite these possible injurious mechanisms, previous usage of remdesivir treating MER and EVD demonstrates a safe profile without significant renal adverse events(9, 18). Although cases of AKI and increased aminotransferase level have been reported for treating COVID-19, even among healthy volunteers, many randomized controlled studies have demonstrated limited adverse events with an acceptable safety profile(9, 11-15, 19-21).

In brief, kidney and liver injury are reported shortly after remdesivir initiation in case studies(9, 22-24), but the exact injury mechanisms remain to be defined and investigated. Controlled trials may find remdesivir to be generally tolerable(25-27), yet its safety data on acute kidney injury (AKI) and acute liver injury (ALI) in the post-marketing real-world setting have not been published so far. With patients serving as their own control, this self-controlled case series (SCCS) study aims to estimate the risks of AKI and ALI with reference to remdesivir initiation among hospitalized COVID-19 patients who also had incident acute kidney injury or acute liver injury.

Methods

Data source and study population

We analyzed all patients with COVID-19 diagnosis, defined by positive polymerase chain reaction (PCR) test for SARS-CoV-2 infection, in the Hong Kong Special Administrative Region, China for the study period between 23rd January 2020 and 31st January 2021 using self-controlled case series method. According to local government policies, all patients with laboratory-confirmed COVID-19 would be admitted to public hospitals for clinical management and isolation purposes, regardless of their disease severity. Electronic medical records of patients hospitalized with COVID-19 were retrieved from the Hong Kong Hospital Authority, a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong. Data from the Hospital Authority has been validated and utilized for drug safety (28) and pharmaco-epidemiological studies of drug treatments for COVID-19.(29, 30)

Exposure and study outcomes

Patients who had initiated remdesivir during their hospitalization for COVID-19 were included in the current analysis if they had incident ALI or AKI. Remdesivir is one of the treatment options for patients hospitalized with COVID-19 in Hong Kong(31). The recommended dosage is 200mg once for the first day, and 100mg once daily for the next four days or until hospital discharge(32). Remdesivir is suggested to be used for COVID-19 patients with severe but non-critical disease (oxygen saturation <94% on room air); and against routine use in critical cases such as admission to an intensive care unit (ICU), requiring the initiation of high-flow nasal oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)(31).

ALI was defined as satisfying at least one of the following conditions(33): (i) increase in ALT was over two times the upper limit of normal (ULN); (ii) increase in AST was over two times the ULN; (iii) increase in total bilirubin was over two times the ULN; or (iv) the international normalized ratio (INR) was over 1.7. According to the Asia Pacific Association of Study of Liver consensus guidelines(34), the ULN of ALT, AST, and total bilirubin were defined as 40 U/L, 40 U/L, and 19 μmol/L, respectively. AKI was defined as satisfying at least one of the following conditions: (i) increase in serum creatinine (SCr) by 0.3 mg/dL within 48 hours; (ii) increase in SCr to 1.5 times of baseline, which was known or presumed to have occurred within the week prior, according to the KDIGO Clinical Practice Guideline for Acute Kidney Injury(35). Definition of ALI and AKI referred to serum abnormality at any point during the observation period.

Self-controlled case series (SCCS)

The SCCS was used to investigate the association of remdesivir use for COVID-19 treatment and the risk of ALI or AKI. The SCCS study design relies on comparisons within individuals who have experienced both the outcome and exposure of interest, with participants serving as their own control(36). Incidence rate ratios (IRRs) are derived by comparing the rate of events during periods of medication exposure with the rate during all other observed time periods (ie, without medication). The major advantage of SCCS lies in its ability to control for the fixed confounders and time-invariant confounding that possibly vary between individuals (namely socioeconomic factors, and genetic factors)(37).

Study assumptions

In SCCS, there were three key assumptions such that the study would provide valid and unbiased estimates(37). First, recurrent events of ALI and AKI among remdesivir users were assumed to be independent. If the events were dependent, it would be possible for the first event to increase the risk of a future event(37), so only first incident event was studied. Second, the occurrence of an event must not alter the probability of subsequent exposure. Therefore, pre-exposure period was included to resolve the problem that occurrence of ALI and AKI may temporarily alter the probability of remdesivir initiation. Third, there must be no censoring by the outcome of interest. It is inadmissible for SCCS analyses to censor exposure by the outcome, since the exposure history would then be event-dependent and violate another SCCS assumption. This would produce bias in an unpredictable direction. When a risk period is censored by patient's death, the incidence rate would be estimated to be higher. If death occurs during baseline period, IRR would be biased downwards. On the other hand, death during exposed period would bias IRR upwards. This is a case of event-dependent observation periods (Supplementary Figure 1), which violates the assumption of SCCS, and requires an extended version of SCCS which adjusted for censoring by applying a weighting according to the duration from the event to end of observation(38).

Exposure and risk periods

Study exposure was the initiation of remdesivir treatment in patients hospitalized with COVID-19. Patients were censored on the following dates: date of hospital discharge, death, or the end of the observation period (30th April 2021), whichever occurred the earliest. The risk periods were patient time divided into six mutually exclusive risk windows: (i) the baseline period covered that from hospital admission to 3 days before treatment initiation, and more than 5 days after treatment to the end of observation period, which would be used as reference for comparison; and the exposure-related risk periods were defined as (ii) pre-exposure period (1-2 days before treatment initiation), (iii) first 2 days (days 0-1) on remdesivir initiation, (iv) days 2-5 on treatment, (v) more than 5 days on drug use to the end of treatment (applicable to patients on an extended treatment course only), and (vi) wash-out period (within 5 days after treatment). The pre-exposure period, which was designed to evaluate any increased incidences of ALI or AKI before the initiation of remdesivir, would help prevent any temporary changes of probability of exposure(37). Figure 1 illustrates the schema of SCCS, and describes the six risk periods in this observational study.

Statistical analysis

Baseline characteristics of remdesivir users who had incident ALI or AKI during the observation period were described in this SCCS study. The association between remdesivir use and ALI or AKI during different risk periods were estimated by comparing the rates of event occurrence. Incidence rates, in term of events per 10,000 person-days, of ALI and AKI over the remdesivir treatment period were calculated. Incidence rate ratios (IRRs) and their corresponding 95% confidence intervals (CIs) of events for different risk periods compared with the baseline period were estimated using conditional Poisson regression model with an offset for the length of the risk period. Age is not adjusted for in the analysis given the short hospitalization period of each COVID-19 patient.

To test the credibility and robustness of the main results, sensitivity analyses were conducted to compare the IRRs between different risk periods of (i) removing patients who died during hospitalization, as death cases within hospitalization could raise an issue where the exposure that might have otherwise occurred after the event would never be known(37); (ii) patients with at least five days use of remdesivir; (iii) extending the observation period to 30th April 2021 for discharged cases; (iv) removing those with events at the day of remdesivir initiation; (v) removing those re-initiating remdesivir after discontinuation; and varying definitions of ALI: (vi) ALT or AST >5 x ULN or alkaline phosphatase (ALP) >2 x ULN confirmed on at least 2 consecutive blood draws in patients with previously normal values; (vii) any elevation of ALT, ALP, or AST, associated with (a) increased total bilirubin [≥ 2.5 mg/dL], in absence of prior diagnosis of liver disease, Gilbert's syndrome, or evidence of hemolysis or (b) coagulopathy with INR > 1.5 in absence of coumadin therapy or known vitamin K deficiency, (viii) add ALP to define ALI using Drug-Induced Liver Injury Network definition(39).

To determine the effects in different scenarios, eight subgroup analyses were also performed in this study. Patients were allocated into the following subgroups: (i) age ≤ 60 years; (ii) age > 60 years; (iii) those who presented with WHO Clinical Progression Scale score ≤ 4 on remdesivir initiation; (iv) those who presented with WHO Clinical Progression Scale score ≥ 5 on remdesivir initiation; (v) those who had remdesivir discontinued; (vi) those who had interferon-β-1b; (vii) those who had ribavirin; and (vii) those who had dexamethasone.

All statistical analyses were performed with the STATA version SE 17.0 (StataCorp LLC) and R, and the R code was adapted in a SCCS approach in this study(40). A two-sided significance level of 5% was used in all statistical analyses.

Results

Among 10,412 patients hospitalized with COVID-19 between 23rd January 2020 and 31st January 2021, 860 of them were administered intravenous remdesivir as in-patient treatment (Figure 2). There were 334 (38.8%) remdesivir users who had incident ALI (Grade 3: 61; Grade 4: 7), and 137 (15.9%) who had incident AKI during hospitalization. Incidence rates of ALI and AKI among hospitalized COVID-19 patients were 154 and 39 per 10,000 person-days respectively. Distributions of timing of remdesivir initiation, and that of incident and recurrent outcomes by the day since remdesivir initiation are plotted in Supplementary Figures 2 and 3, respectively. Baseline characteristics of remdesivir users who had incident ALI or AKI are listed in Table 1. Among remdesivir users with ALI and AKI, there were 34 (10.2%) and 46 (33.6%) deaths during observation period, including 27 and 36 deaths occurred during the baseline period, respectively. 93 (27.8%) and 18 (13.1%) patients required the discontinuation of remdesivir due to incident ALI and AKI, respectively.

Table 2 shows the incidence rates of remdesivir users who had ALI and AKI in different observation periods, and the IRRs of ALI and AKI in each risk period compared to the baseline period and pre-exposure period, respectively. Mean durations of observation period were 30.7 days and 40.0 days for remdesivir users with ALI and AKI. Patients with ALI had a mean of 4.5 days for remdesivir treatment, while that for patients with AKI was 4.7 days. Compared with the baseline period, ALI risk increased significantly during the pre-exposure period (IRR=6.169, 95%CI=4.549-8.365), remained elevated during first two days of remdesivir treatment (IRR=7.778, 95%CI=5.973-10.130), 2-5 days of treatment (IRR=6.702, 95%CI=5.193-8.650), and >5 days after remdesivir initiation (IRR=4.902, 95%CI=2.353-10.214). Compared to the pre-exposure period, risk of ALI was not significantly higher during remdesivir treatment periods. Similarly, there was an increased risk of AKI during pre-exposure period (IRR=7.074, 95%CI=3.763-13.298) compared with that of the baseline period. Such elevated risk sustained during first two days of remdesivir treatment

(IRR=8.227, 95%CI=5.064-13.364), subsequent days 2-5 (IRR=5.922, 95%CI=3.705-9.467) and >5 days of remdesivir treatment (IRR=6.185, 95%CI=2.483-15.408). When compared to the pre-exposure period, AKI risk was not significantly higher during remdesivir treatment periods.

Similar results were found in the sensitivity (Supplementary Table 1) and subgroup (Supplementary Table 2) analyses. Results of the subgroup analyses were generally comparable to those of the main analysis, where increased risks of ALI and AKI were consistently observed during the pre-exposure period and remdesivir treatment, and not significantly higher during remdesivir treatment when compared with the pre-exposure period.

Discussion

This current study investigates the safety of remdesivir treatment initiation of hospitalized COVID-19 patients in terms of AKI and ALI. The result does not suggest significant association of remdesivir initiation with the risk of AKI and ALI. The increased risks of ALI and AKI after intravenous remdesivir treatment for COVID-19 may be due the underlying SARS-CoV-2 infection. The risks of ALI and AKI were elevated in the pre-exposure and treatment periods compared with baseline, yet no such increased risks were observed following remdesivir initiation when compared to the pre-exposure period.

Approximately 7% of the remdesivir recipients developed AKI, which was the most common adverse event for drug discontinuation(41), but this incidence rate was not significant. Meanwhile, no severe nephrotoxicity was found in a retrospective review of 5-day remdesivir treatment with 15 days follow-up period, but 10.5% of the patients still showed at least 10 mL/min/1.73m^2 decrease in eGFR, which was comparable to data reported in the randomized controlled trial(15). Similarly, remdesivir did not lead to significant AKI risk at the end of treatment or two days after treatment completion even in patients with impaired eGFR of less than 30 mL/min/1.73m^2(42). These results were consistent with our finding that remdesivir initiation was not associated with an increased risk of AKI when compared to pre-exposure period. Meanwhile, based on the pharmacokinetics of remdesivir and its short administration duration, remdesivir was considered safe for patients with impaired renal function, and benefits of its use may outweigh the risk(9). Remdesivir was also generally tolerated in kidney transplant patients as AKI was reported in 27% of them where half of

them have been diagnosed AKI before administration, at which the peak of serum creatinine was detected, and they retained baseline function three days after initiation towards at the end of treatment(43). Therefore, remdesivir was not responsible for the injury, although randomized controlled trials were necessary to compare the incidence of AKI especially under the challenge presented by similar renal complication of COVID-19 and remdesivir(43). This study was also consistent with our finding of insignificant risk of AKI after remdesivir initiation compared to pre-exposure. Similar finding was reported in solid-organ transplant recipients whose elevation in GFR or hepatic enzyme was insignificant compared with other antiviral drugs(44). However, analysis of WHO Safety database with other pharmaceutical treatments highlighted a 20-fold increased risk of acute renal failure, suggesting a disproportionality signal of remdesivir nephrotoxicity(14). This elevated risk could be caused by the concurring SARS-CoV-2 infection while our result illustrated an insignificant increased risk on AKI and ALI compared to pre-exposure period. While some illustrated a direct cause of remdesivir initiation to AKI, most believed that AKI was multifactorial, with drug-induced AKI being one of the contributors(9, 14, 15, 45). The literature demonstrated an elevated risk of AKI after remdesivir treatment for COVID-19 patients, but the risk had no significant difference compared with AKI risk before COVID-19 hospitalization.

Meanwhile, 25% and 33% of patients had elevated AST and ALT level respectively; patients generally suffered from different degrees of elevation in liver enzymes, but only a maximum of 6% of the population would have grade 3 elevation or above(15). Similar finding was reported when comparing remdesivir with other treatments of COVID-19: serum AST and ALT levels were significantly higher in remdesivir group and the risk of hepatic impairment increased(46, 47). Some case studies suggested causality of hepatotoxicity as AST and ALT levels were elevated or peaked immediately after the initiation of remdesivir, but situation ameliorated afterwards (22, 48, 49). In addition, the disproportionately high reporting of aminotransferase elevation compared with other COVID-19 treatment options suggested drug-induced liver injury(50). Nonetheless, some studies did not associate remdesivir with liver injury as the difference of clinical measurements was insignificant between treatment and placebo groups(51). Most patients with kidney transplants also showed no significant hepatoxicity with stable liver function throughout the study period, despite its small sample size(43). Successful disease management with remdesivir was also reported in liver transplants patients as the bilirubin and aminotransferase levels did not elevate during the period, or such elevation was insignificant(44, 52). A case of remdesivir initiation immediately post-liver transplant showed near complete recovery after 3 months, but it is unclear if remdesivir directly

caused the elevated liver enzymes following the transplant(53). The patient had increased CT value only when the remdesivir was initiated and had negative PCR result within a month(53). These studies demonstrated an inconsistent result regarding the risk of hepatotoxicity after remdesivir initiation, but mild transient elevation of liver enzymes was still described (51, 54). SARS-CoV-2 infection *per se* could lead to raised AST and ALT levels, through a variety of mechanisms including cytokine storm, hypoxic injury, and vascular thrombosis(5, 6, 8). Therefore, the elevation of liver enzymes during the course of COVID-19 was not solely attributable to the administration of remdesivir. If the potential benefits of remdesivir initiation would outweigh the risks, this antiviral treatment should not be precluded(53, 55).

Using a population-based cohort of COVID-19 patients, this study has evaluated the safety of remdesivir treatment during hospitalization. Although our results did not suggest treatment toxicity in terms of AKI and ALI, several key limitations have to be addressed. First, unmeasured or residual confounding could remain and influence the findings due to the observational nature of this study, although any fixed confounders were controlled for in the SCCS study design. Second, majority of the admitted patients were on long-term anticoagulant medication, likely being prescribed under pre-existing conditions, and were treated with interferon-β-1b at baseline as part of the effective triple combination therapy for COVID-19(56), hence our results would not be applicable to other patient populations. Lastly, any combined or synergistic effects of remdesivir with other concomitant medications such as baricitnib and tocilizumab were not explored given their limited use in this patient cohort. However, concomitant medications were unlikely to affect the results because of the within-patient comparison nature of SCCS.

Remdesivir initiation in treating COVID-19 did not significantly increase the risks of AKI and ALI when compared to the pre-exposure period. Although most adverse events were mild and severe adverse events were rare, cautious use of remdesivir was still recommended with close monitoring of kidney and liver functions. The challenge of assessing the safety of remdesivir lay in its similar laboratory measures with COVID-19. Therefore, impaired kidney and liver functions should not be solely evaluated as a contraindication to remdesivir use(15). Our findings would also suggest that the increased risks of AKI and ALI were attributed to the persisting manifestation of SARS-CoV-2 infection. However, should the clinical condition worsen or an acute liver or kidney injury develop

after remdesivir initiation, discontinuation of remdesivir may be necessary and other treatment options should be explored.

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Ethics approval and informed consent

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (Reference No. UW 20-493). Given the extraordinary nature of the COVID-19 pandemic, individual patient informed consent was not required for this retrospective cohort study using anonymized data.

Data sharing statement

The data that support the findings of this study were provided by the Hong Kong Hospital Authority. Restrictions apply to the availability of these data, which were used under license for this study.

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Conflicts of interest

B.J.C consults for Roche, Sanofi Pasteur, GSK and Moderna. The authors report no other potential conflicts of interest.

Authors' contributions

C.K.H.W. reviewed the literature, designed statistical analysis, conducted analyses, and wrote the manuscript. C.H.A. and W.Y.C. reviewed the literature, contributed to the interpretation of the analysis, and wrote the manuscript. C.H.A. conducted analyses. Y.L.M. and S.L.L. contributed to the clinical input, and interpretation of the analysis. X.X., E.H.Y.L. and B.J.C. contributed to the interpretation of the analysis. M.C. wrote the manuscript. K.K.C.M. and K.T.K.L. contributed to the interpretation of the analysis, critically reviewed and revised the manuscript. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figure 1. Study schema and definitions of treatment periods. The study was divided into 6 separate periods: pre-exposure period, first 2 days on treatment, day 2-5 on treatment, more than 5 days on drug use to the end of treatment, wash-out period, and more than 5 days after treatment to the end of observation period.

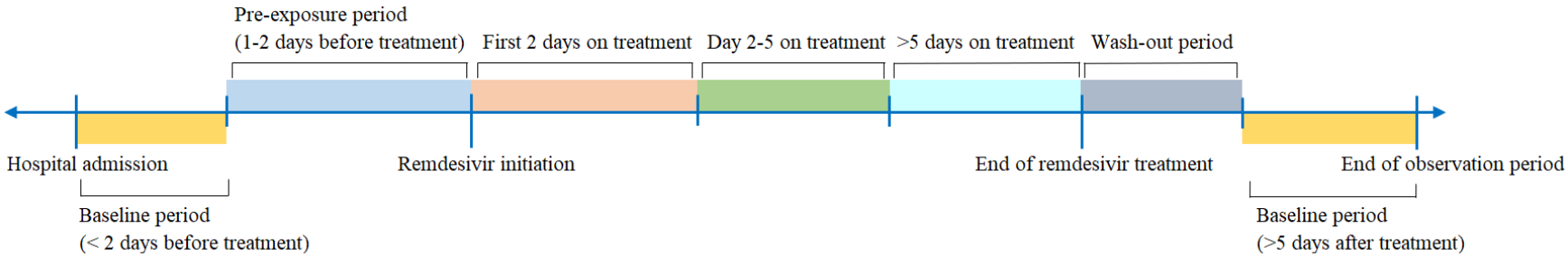


Figure 2. Flowchart of inclusion and exclusion of hospitalized COVID-19 patients administering remdesivir between 23rd January 2020 and 31st January 2021 in Hong Kong SAR, China.

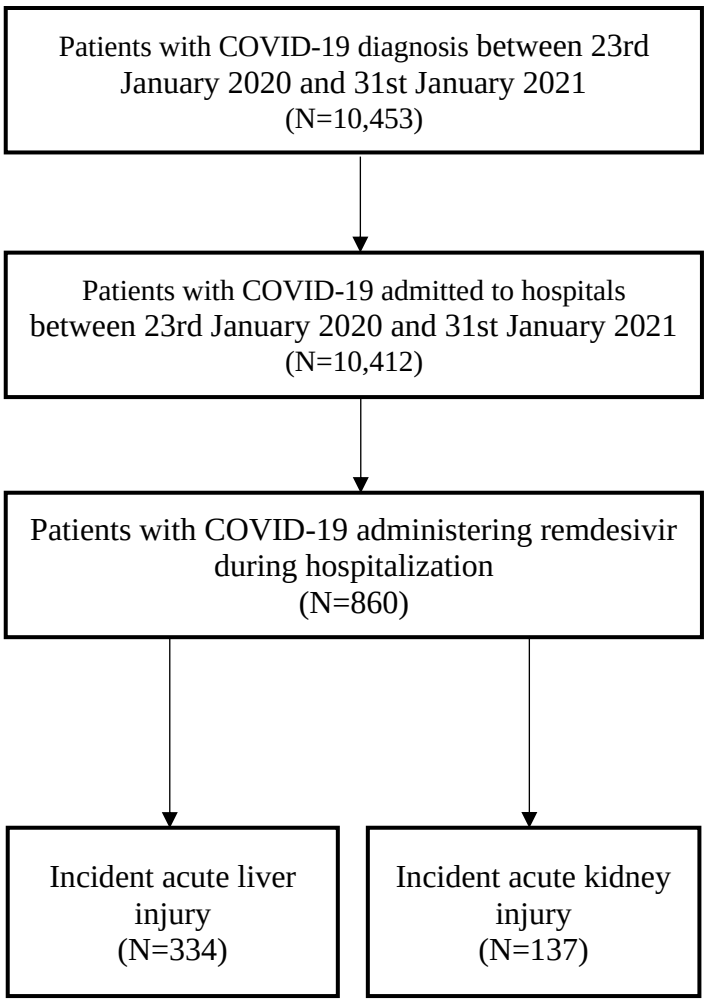


Table 1. Baseline characteristics of hospitalized patients with COVID-19 initiating remdesivir users who had incident acute liver injury or acute kidney injury

Baseline characteristics	Remdesivir users			
	Acute liver injury (n=334)		Acute kidney injury (n=137)	
	N / Mean	% / SD	N / Mean	% / SD
Age, years †	61.5	14.4	69.4	12.8
≤65	198	(59.3%)	44	(32.1%)
>65	136	(40.7%)	93	(67.9%)
Sex				
Male	216	(64.7%)	85	(62.0%)
Female	118	(35.3%)	52	(38.0%)
Pre-existing comorbidities				
Charlson's Index †‡	3.9	2.3	6.1	2.4
0-4	221	(66.2%)	33	(24.1%)
5-6	74	(22.2%)	49	(35.8%)
7-15	39	(11.7%)	55	(40.2%)
Chronic heart disease	35	(10.5%)	35	(25.5%)
Chronic kidney disease	39	(11.7%)	62	(45.3%)
Chronic lung disease	47	(14.1%)	24	(17.5%)
Diabetes mellitus	137	(41.0%)	104	(75.9%)
Hypertension	197	(59.0%)	124	(90.5%)
Chronic liver disease	48	(14.4%)	24	(17.5%)
Hepatitis	2	(0.6%)	0	(0.0%)
Cirrhosis	3	(0.9%)	1	(0.7%)
Hepatocellular carcinoma	0	(0.0%)	1	(0.7%)
Malignancy	7	(2.1%)	6	(4.4%)
Vitamin D deficiency	16	(4.8%)	14	(10.2%)
Long-term medications				
ACEI/ARB	82	(24.6%)	66	(48.2%)
Anticoagulant	197	(59.0%)	111	(81.0%)
Antiplatelet	44	(13.2%)	44	(32.1%)
Lipid-lowering agent	118	(35.3%)	86	(62.8%)
NSAID	56	(16.8%)	52	(38.0%)
Treatment performed prior to baseline				
Remdesivir	334	(100.0%)	137	(100.0%)
Time from admission to remdesivir initiation, days †	4.2	3.4	4.1	4.1
Cumulative dosage of remdesivir, mg †	598.5	238.2	632.1	280.2
Duration of use of remdesivir, days †	4.4	2	4.8	2.2
Other antimicrobials	237	(71.0%)	112	(81.8%)
Antivirals	160	(47.9%)	67	(48.9%)
Ribavirin	128	(38.3%)	45	(32.8%)
Lopinavir-ritonavir	46	(13.8%)	27	(19.7%)

Antibiotics	184	(55.1%)	100	(73.0%)
Immunomodulators	305	(91.3%)	127	(92.7%)
Dexamethasone	240	(71.9%)	111	(81.0%)
Time from admission to dexamethasone initiation, days †	4.0	3.6	3.3	3.8
Administration route of dexamethasone				
Oral	50	(18.1%)	25	(20.0%)
Intravenous injection	226	(81.9%)	100	(80.0%)
Dosage of dexamethasone				
Up to 6mg daily	106	(38.4%)	40	(32.0%)
More than 6mg daily	170	(61.6%)	85	(68.0%)
Cumulative dosage of dexamethasone, mg †	70.1	88.5	92.3	112.5
Duration of use of dexamethasone, days †	10.1	12.9	13.5	16.4
Other systemic steroid	11	(3.3%)	11	(8.0%)
Interferon-β-1b	228	(68.3%)	92	(67.2%)
Baricitinib	5	(1.5%)	2	(1.5%)
Tocilizumab	18	(5.4%)	10	(7.3%)
Paracetamol	309	(92.5%)	121	(88.3%)
ECMO	2	(0.6%)	2	(1.5%)
Dialysis	4	(1.2%)	5	(3.6%)
ICU admission	101	(30.2%)	81	(59.1%)
Admission via emergency department	154	(46.1%)	81	(59.1%)
Clinical severity by WHO Clinical Progression Scale				
WHO Clinical Progression Scale Score (range 0-10) †	4.9	1.2	5.6	1.3
No oxygen therapy (Score 4)	200	(59.9%)	46	(33.6%)
Supplemental oxygen without ventilation (Score 5-6)	110	(32.9%)	72	(52.6%)
Mechanical ventilation (Score 7-9)	24	(7.2%)	19	(13.9%)
Laboratory parameters [normal range] †				
White blood cell, $\times 10^9$/L [3.7-9.2 $\times 10^9$/L]	5.8	2.7	6.8	3.7
Neutrophil, $\times 10^9$/L [1.7-5.8 $\times 10^9$/L]	4.3	2.6	5.3	3.5
Lymphocyte, $\times 10^9$/L [1.0-3.1 $\times 10^9$/L]	1.0	0.5	0.9	0.6
Platelet, $\times 10^9$/L [145-370 ×109/L]	178.5	61.5	184.0	71.7
Lactate dehydrogenase, U/L [110-210 U/L]	353.5	160.9	372.9	182.3
Creatine kinase, U/L [26-192 U/L]	329.0	629.0	345.8	637.0
Total bilirubin, μmol/L [5-27 μmol/L]	10.2	8.1	10.2	9.4
C-reactive protein, mg/L [<5 mg/L]	61.6	56.3	72.7	64.9
Cycle threshold value, cycle	22.5	5.2	20.8	4.7
eGFR, ml/min/1.73m^2 [>90 ml/min/1.73m^2]	103.6	58.4	91.1	88.6
ALT, U/L [<46.5 U/L]	51.3	36.0	35.1	23.1
AST, U/L	73.0	119.4	43.0	117.7
ALP, U/L [30-120 U/L]	70.7	32.2	73.0	32.2

R score	2.1	1.7	1.3	4.2
INR [< 1.1]	1.1	0.4	1.1	0.6
Hemoglobin, g/dL [13.4-17.1 g/dL]	13.5	1.7	12.9	2.0

Notes: ACEI = Angiotensin converting enzyme inhibitor; ALP = Alkaline phosphatase; ALT = Alanine transaminase; ARB = Angiotensin receptor blockers; AST = Aspartate transaminase; ECMO = Extracorporeal membrane oxygenation; eGFR= Estimated glomerular filtration rate; ICU = Intensive Care Unit; INR = International normalized ratio; NSAID = Nonsteroidal anti-inflammatory drugs; R score = (ALT/ULN)/(ALP/ULN); SD = Standard deviation; ULN = Upper limit of normal

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

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

Table 2. Comparison of risks of acute liver injury and acute kidney injury between different risk periods

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	Baseline period as reference			Pre-exposure period as reference		
						IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=334)											
Baseline period	183	40.1%	642	(552, 742)	2,850		(reference)		0.162	(0.120, 0.220)	<0.001
Pre-exposure period	67	22.0%	1,370	(1,062, 1,740)	489	6.169	(4.549, 8.365)	<0.001		(reference)	
Day 0-1 on drug initiation	103	30.8%	1,829	(1,493, 2,219)	563	7.778	(5.973, 10.130)	<0.001	1.261	(0.915, 1.737)	0.156
Day 2-5 on drug treatment	121	41.9%	1,909	(1,584, 2,280)	634	6.702	(5.193, 8.650)	<0.001	1.087	(0.793, 1.489)	0.606
Day >5 on drug treatment	9	25.0%	882	(403, 1,675)	102	4.902	(2.353, 10.214)	<0.001	0.795	(0.370, 1.707)	0.556
Wash-out period	186	55.7%	1,670	(1,438, 1,928)	1,114	3.134	(2.497, 3.932)	<0.001	0.508	(0.380, 0.679)	<0.001
Acute kidney injury (N=137)											
Baseline period	85	45.9%	445	(356, 551)	1,909		(reference)		0.180	(0.130, 0.249)	<0.001
Pre-exposure period	13	11.5%	714	(380, 1,221)	182	7.074	(3.763, 13.298)	<0.001		(reference)	
Day 0-1 on drug initiation	27	19.7%	1,080	(712, 1,571)	250	8.227	(5.064, 13.364)	<0.001	1.261	(0.889, 1.789)	0.194
Day 2-5 on drug treatment	30	24.8%	1,038	(700, 1,482)	289	5.922	(3.705, 9.467)	<0.001	1.152	(0.821, 1.616)	0.412
Day >5 on drug treatment	6	28.6%	938	(344, 2,041)	64	6.185	(2.483, 15.408)	<0.001	0.843	(0.405, 1.758)	0.649
Wash-out period	45	32.8%	794	(579, 1,062)	567	2.904	(1.927, 4.377)	<0.001	0.548	(0.400, 0.750)	<0.001

Notes: CI = Confidence interval; IRR = Incidence rate ratio

Supplementary Table 1. Sensitivity analyses on the outcomes

	Removing patients who died during hospitalization										
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=297)											
Baseline period	156	38.0%	638	(542, 747)	2,444		(reference)		0.176	(0.128, 0.242)	<0.001
Pre-exposure period	62	22.7%	1,403	(1,075, 1,798)	442	5.680	(4.130, 7.812)	<0.001		(reference)	
Day 0-1 on drug initiation	91	30.6%	1,816	(1,462, 2,230)	501	7.117	(5.378, 9.418)	<0.001	1.253	(0.896, 1.752)	0.188
Day 2-5 on drug treatment	110	43.0%	1,982	(1,629, 2,389)	555	6.369	(4.862, 8.343)	<0.001	1.121	(0.807, 1.557)	0.495
Day >5 on drug treatment	8	30.8%	1,159	(501, 2,285)	69	5.631	(2.554, 12.416)	<0.001	0.991	(0.437, 2.250)	0.983
Wash-out period	171	57.6%	1,752	(1,499, 2,035)	976	3.006	(2.366, 3.818)	<0.001	0.529	(0.392, 0.715)	<0.001
Acute kidney injury (N=87)											
Baseline period	48	38.7%	329	(243, 436)	1,459		(reference)		0.139	(0.064, 0.303)	<0.001
Pre-exposure period	9	12.7%	789	(361, 1,499)	114	7.196	(3.305, 15.669)	<0.001		(reference)	
Day 0-1 on drug initiation	15	17.2%	938	(525, 1,546)	160	7.396	(3.963, 13.803)	<0.001	1.028	(0.436, 2.423)	0.950
Day 2-5 on drug treatment	18	23.4%	994	(589, 1,572)	181	6.044	(3.324, 10.989)	<0.001	0.840	(0.361, 1.952)	0.685
Day >5 on drug treatment	4	40.0%	1,333	(363, 3,414)	30	7.117	(2.280, 22.216)	<0.001	0.989	(0.265, 3.685)	0.987
Wash-out period	24	27.6%	643	(412, 957)	373	2.448	(1.411, 4.246)	0.001	0.340	(0.152, 0.761)	0.009

	At least 5 days use of remdesivir										
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=125)											
Baseline period	70	40.5%	530	(413, 669)	1,322		(reference)		0.189	(0.109, 0.326)	<0.001
Pre-exposure period	19	17.4%	1,080	(650, 1,686)	176	5.304	(3.066, 9.174)	<0.001		(reference)	
Day 0-1 on drug initiation	32	25.6%	1,435	(982, 2,026)	223	5.392	(3.426, 8.486)	<0.001	1.017	(0.569, 1.816)	0.956
Day 2-5 on drug treatment	52	42.3%	1,562	(1,166, 2,048)	333	3.971	(2.672, 5.901)	<0.001	0.749	(0.437, 1.284)	0.293
Day >5 on drug treatment	9	25.0%	882	(403, 1,675)	102	3.721	(1.751, 7.904)	<0.001	0.702	(0.298, 1.650)	0.417
Wash-out period	51	40.8%	1,094	(815, 1,439)	466	2.355	(1.584, 3.500)	<0.001	0.444	(0.259, 0.762)	0.003
Acute kidney injury (N=62)											

Baseline period	36	45.0%	490	(344, 679)	734		(reference)		0.104	(0.023, 0.466)	0.003
Pre-exposure period	2	4.3%	270	(33, 976)	74	9.589	(2.146, 42.846)	0.003		(reference)	
Day 0-1 on drug initiation	13	21.0%	1,130	(602, 1,933)	115	28.414	(13.478, 59.900)	<0.001	2.963	(0.652, 13.460)	0.159
Day 2-5 on drug treatment	20	33.3%	1,163	(710, 1,796)	172	18.882	(9.686, 36.809)	<0.001	1.969	(0.447, 8.674)	0.370
Day >5 on drug treatment	6	28.6%	938	(344, 2,041)	64	20.383	(7.724, 53.784)	<0.001	2.126	(0.397, 11.396)	0.379
Wash-out period	21	33.9%	840	(520, 1,284)	250	8.453	(4.115, 17.365)	<0.001	0.882	(0.197, 3.954)	0.869

Extending the observation period to 30th April 2021

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=340)											
Baseline period	188	35.7%	76	(66, 88)	24,578		(reference)		0.009	(0.007, 0.013)	<0.001
Pre-exposure period	68	21.9%	1,360	(1,056, 1,724)	500	106.983	(78.828, 145.195)	<0.001		(reference)	
Day 0-1 on drug initiation	104	30.6%	1,809	(1,478, 2,192)	575	131.357	(100.427, 171.814)	<0.001	1.228	(0.892, 1.690)	0.208
Day 2-5 on drug treatment	122	41.5%	1,880	(1,561, 2,245)	649	116.863	(89.956, 151.819)	<0.001	1.092	(0.797, 1.497)	0.582
Day >5 on drug treatment	9	25.0%	882	(403, 1,675)	102	90.703	(42.356, 194.234)	<0.001	0.848	(0.388, 1.854)	0.679
Wash-out period	188	55.3%	1,651	(1,423, 1,904)	1,139	49.597	(39.386, 62.454)	<0.001	0.464	(0.347, 0.619)	<0.001
Acute kidney injury (N=144)											
Baseline period	92	45.3%	120	(97, 147)	7,650		(reference)		0.038	(0.020, 0.071)	<0.001
Pre-exposure period	14	11.7%	718	(393, 1,205)	195	26.417	(14.168, 49.258)	<0.001		(reference)	
Day 0-1 on drug initiation	29	20.1%	1,107	(741, 1,590)	262	27.997	(17.370, 45.127)	<0.001	1.060	(0.535, 2.101)	0.868
Day 2-5 on drug treatment	32	25.2%	1,060	(725, 1,496)	302	20.190	(12.713, 32.066)	<0.001	0.764	(0.386, 1.514)	0.441
Day >5 on drug treatment	6	28.6%	938	(344, 2,041)	64	17.959	(7.218, 44.686)	<0.001	0.680	(0.237, 1.950)	0.473
Wash-out period	48	33.3%	807	(595, 1,070)	595	10.161	(6.795, 15.193)	<0.001	0.385	(0.202, 0.733)	0.004

Removing event outcome on day of remdesivir initiation

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=334)											
Baseline period	183	40.1%	642	(552, 742)	2,850		(reference)		0.162	(0.120, 0.220)	<0.001

Pre-exposure period	67	22.0%	1,370	(1,062, 1,740)	489	6.169	(4.549, 8.365)	<0.001		(reference)	
Day 0-1 on drug initiation	103	30.8%	1,829	(1,493, 2,219)	563	7.778	(5.973, 10.130)	<0.001	1.261	(0.915, 1.737)	0.156
Day 2-5 on drug treatment	121	41.9%	1,909	(1,584, 2,280)	634	6.702	(5.193, 8.650)	<0.001	1.086	(0.793, 1.489)	0.606
Day >5 on drug treatment	9	25.0%	882	(403, 1,675)	102	4.902	(2.353, 10.214)	<0.001	0.795	(0.370, 1.706)	0.556
Wash-out period	186	55.7%	1,670	(1,438, 1,928)	1,114	3.134	(2.497, 3.932)	<0.001	0.508	(0.380, 0.679)	<0.001
Acute kidney injury (N=137)											
Baseline period	85	45.9%	445	(356, 551)	1,909		(reference)		0.141	(0.075, 0.266)	<0.001
Pre-exposure period	13	11.5%	714	(380, 1,221)	182	7.074	(3.763, 13.298)	<0.001		(reference)	
Day 0-1 on drug initiation	27	19.7%	1,080	(712, 1,571)	250	8.227	(5.064, 13.364)	<0.001	1.163	(0.585, 2.313)	0.667
Day 2-5 on drug treatment	30	24.8%	1,038	(700, 1,482)	289	5.922	(3.705, 9.467)	<0.001	0.837	(0.422, 1.659)	0.611
Day >5 on drug treatment	6	28.6%	938	(344, 2,041)	64	6.185	(2.483, 15.408)	<0.001	0.874	(0.302, 2.527)	0.804
Wash-out period	45	32.8%	794	(579, 1,062)	567	2.904	(1.927, 4.377)	<0.001	0.411	(0.216, 0.782)	0.007

Removing patients with repeated remdesivir treatment

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=329)											
Baseline period	183	40.3%	643	(553, 743)	2,845		(reference)		0.165	(0.122, 0.224)	<0.001
Pre-exposure period	66	22.0%	1,364	(1,055, 1,735)	484	6.061	(4.463, 8.230)	<0.001		(reference)	
Day 0-1 on drug initiation	102	31.0%	1,835	(1,496, 2,227)	556	7.791	(5.979, 10.151)	<0.001	1.285	(0.931, 1.774)	0.126
Day 2-5 on drug treatment	120	42.0%	1,914	(1,587, 2,289)	627	6.703	(5.191, 8.655)	<0.001	1.106	(0.805, 1.519)	0.534
Day >5 on drug treatment	9	25.0%	882	(403, 1,675)	102	4.894	(2.349, 10.198)	<0.001	0.808	(0.376, 1.735)	0.584
Wash-out period	185	56.2%	1,693	(1,457, 1,955)	1,093	3.142	(2.503, 3.942)	<0.001	0.518	(0.387, 0.694)	<0.001
Acute kidney injury (N=131)											
Baseline period	85	46.2%	446	(356, 552)	1,905		(reference)		0.149	(0.079, 0.280)	<0.001
Pre-exposure period	13	11.9%	730	(389, 1,249)	178	6.717	(3.575, 12.621)	<0.001		(reference)	
Day 0-1 on drug initiation	26	19.8%	1,083	(708, 1,587)	240	7.734	(4.735, 12.634)	<0.001	1.151	(0.577, 2.298)	0.689
Day 2-5 on drug treatment	29	24.8%	1,032	(691, 1,482)	281	5.586	(3.478, 8.974)	<0.001	0.832	(0.418, 1.653)	0.599
Day >5 on drug treatment	6	28.6%	938	(344, 2,041)	64	5.934	(2.380, 14.793)	<0.001	0.883	(0.306, 2.553)	0.819
Wash-out period	43	32.8%	795	(575, 1,071)	541	2.903	(1.928, 4.371)	<0.001	0.432	(0.227, 0.823)	0.011

	ALT or AST >5 x ULN or ALP >2 x ULN confirmed on at least 2 consecutive blood draws in patients with previously normal values									
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=45)											
Baseline period	25	37.3%	269	(174, 397)	929		(reference)		0.133	(0.046, 0.386)	<0.001
Pre-exposure period	5	12.5%	769	(250, 1,795)	65	7.513	(2.593, 21.770)	<0.001		(reference)	
Day 0-1 on drug initiation	9	20.0%	1,111	(508, 2,109)	81	9.276	(3.914, 21.982)	<0.001	1.235	(0.399, 3.824)	0.715
Day 2-5 on drug treatment	5	12.2%	472	(153, 1,101)	106	3.186	(1.105, 9.189)	0.032	0.424	(0.117, 1.535)	0.191
Day >5 on drug treatment	0	0.0%	0	NA	42	NA	NA	NA	NA	NA	NA
Wash-out period	12	26.7%	615	(318, 1,075)	195	2.617	(1.189, 5.758)	0.017	0.348	(0.119, 1.023)	0.055

	Any elevation of ALT, ALP, or AST, associated with (a) increased total bilirubin [≥ 2.5 mg/dL], in absence of prior diagnosis of liver disease, Gilbert's syndrome, or evidence of hemolysis or (b) coagulopathy with INR > 1.5 in absence of coumadin therapy or known vitamin K deficiency									
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=40)											
Baseline period	14	26.9%	171	(93, 286)	820		(reference)		NA	NA	NA
Pre-exposure period	2	6.3%	392	(47, 1,417)	51	NA	NA	NA		(reference)	
Day 0-1 on drug initiation	4	10.0%	533	(145, 1,366)	75	NA	NA	NA	NA	NA	NA
Day 2-5 on drug treatment	7	19.4%	729	(293, 1,502)	96	NA	NA	NA	NA	NA	NA
Day >5 on drug treatment	5	45.5%	1,786	(580, 4,167)	28	NA	NA	NA	NA	NA	NA
Wash-out period	18	45.0%	1,233	(731, 1,948)	146	NA	NA	NA	NA	NA	NA

	Add ALP to define acute liver injury using the Drug-Induced Liver Injury Network definition									
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=342)											
Baseline period	185	39.4%	634	(546, 732)	2,917		(reference)		0.156	(0.116, 0.210)	<0.001

Pre-exposure period	71	22.8%	1,420	(1,109, 1,791)	500	6.405	(4.754, 8.630)	<0.001		(reference)	
Day 0-1 on drug initiation	109	31.9%	1,896	(1,557, 2,287)	575	8.062	(6.222, 10.445)	<0.001	1.259	(0.922, 1.718)	0.148
Day 2-5 on drug treatment	125	42.1%	1,929	(1,606, 2,298)	648	6.736	(5.235, 8.668)	<0.001	1.052	(0.773, 1.431)	0.749
Day >5 on drug treatment	9	23.7%	783	(358, 1,486)	115	4.093	(1.962, 8.538)	<0.001	0.639	(0.298, 1.369)	0.249
Wash-out period	187	54.7%	1,626	(1,401, 1,877)	1,150	3.082	(2.460, 3.862)	<0.001	0.481	(0.362, 0.639)	<0.001

Notes: ALP = Alkaline phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase; CI = Confidence interval; INR = International normalized ratio; IRR = Incidence rate ratio; ULN = upper limit of normal

Supplementary Table 2. Subgroup analyses on the outcomes

	Age ≤ 60 years										
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=145)											
Baseline period	74	38.1%	853	(669, 1,070)	868		(reference)		0.205	(0.139, 0.301)	<0.001
Pre-exposure period	35	26.1%	1,620	(1,129, 2,254)	216	4.884	(3.326, 7.173)	<0.001		(reference)	
Day 0-1 on drug initiation	52	35.9%	2,241	(1,674, 2,939)	232	7.335	(5.260, 10.230)	<0.001	1.502	(1.005, 2.244)	0.047
Day 2-5 on drug treatment	59	50.4%	2,458	(1,871, 3,171)	240	7.128	(5.192, 9.784)	<0.001	1.459	(0.988, 2.155)	0.057
Day >5 on drug treatment	4	33.3%	1,538	(419, 3,939)	26	5.283	(1.985, 14.058)	<0.001	1.082	(0.392, 2.986)	0.880
Wash-out period	99	68.3%	2,255	(1,833, 2,746)	439	2.868	(2.155, 3.816)	<0.001	0.587	(0.410, 0.841)	0.004
Acute kidney injury (N=27)											
Baseline period	14	36.8%	327	(179, 549)	428		(reference)		0.078	(0.031, 0.199)	<0.001
Pre-exposure period	4	18.2%	1,176	(321, 3,012)	34	12.748	(5.023, 32.356)	<0.001		(reference)	
Day 0-1 on drug initiation	6	22.2%	1,277	(468, 2,779)	47	10.009	(4.421, 22.660)	<0.001	0.785	(0.279, 2.211)	0.647
Day 2-5 on drug treatment	7	29.2%	1,148	(461, 2,364)	61	7.670	(3.603, 16.327)	<0.001	0.602	(0.222, 1.632)	0.318
Day >5 on drug treatment	4	57.1%	2,500	(681, 6,401)	16	11.189	(3.444, 36.351)	<0.001	0.878	(0.218, 3.534)	0.854
Wash-out period	11	40.7%	1,009	(504, 1,806)	109	3.556	(1.760, 7.184)	<0.001	0.279	(0.109, 0.712)	0.008
	Age > 60 years										
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=189)											
Baseline period	109	41.6%	550	(452, 663)	1,982		(reference)		0.143	(0.093, 0.219)	<0.001
Pre-exposure period	32	18.8%	1,172	(802, 1,655)	273	6.996	(4.561, 10.731)	<0.001		(reference)	
Day 0-1 on drug initiation	51	27.0%	1,541	(1,147, 2,026)	331	7.637	(5.310, 10.983)	<0.001	1.092	(0.693, 1.720)	0.705
Day 2-5 on drug treatment	62	36.0%	1,574	(1,206, 2,017)	394	6.721	(4.764, 9.481)	<0.001	0.961	(0.615, 1.500)	0.860
Day >5 on drug treatment	5	20.8%	658	(214, 1,535)	76	3.816	(1.450, 10.044)	0.007	0.546	(0.197, 1.509)	0.243
Wash-out period	87	46.0%	1,289	(1,032, 1,590)	675	3.284	(2.403, 4.489)	<0.001	0.470	(0.308, 0.716)	<0.001
Acute kidney injury (N=110)											

Baseline period	71	48.3%	479	(374, 605)	1,481		(reference)		0.163	(0.078, 0.344)	<0.001
Pre-exposure period	9	9.9%	608	(278, 1,154)	148	6.124	(2.907, 12.898)	<0.001		(reference)	
Day 0-1 on drug initiation	21	19.1%	1,034	(640, 1,581)	203	7.955	(4.567, 13.856)	<0.001	1.299	(0.578, 2.917)	0.526
Day 2-5 on drug treatment	23	23.7%	1,009	(639, 1,514)	228	6.227	(3.659, 10.598)	<0.001	1.017	(0.456, 2.267)	0.967
Day >5 on drug treatment	2	14.3%	417	(50, 1,505)	48	3.000	(0.673, 13.365)	0.150	0.490	(0.096, 2.490)	0.390
Wash-out period	34	30.9%	742	(514, 1,037)	458	2.661	(1.660, 4.266)	<0.001	0.435	(0.202, 0.935)	0.033

WHO Clinical Progression Scale score ≤ 4

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=200)											
Baseline period	99	37.4%	783	(637, 954)	1,264		(reference)		0.270	(0.186, 0.390)	<0.001
Pre-exposure period	47	25.0%	1,531	(1,125, 2,036)	307	3.709	(2.564, 5.366)	<0.001		(reference)	
Day 0-1 on drug initiation	56	28.0%	1,667	(1,259, 2,164)	336	4.236	(2.980, 6.022)	<0.001	1.142	(0.764, 1.708)	0.518
Day 2-5 on drug treatment	69	41.3%	1,933	(1,504, 2,446)	357	3.983	(2.844, 5.580)	<0.001	1.074	(0.726, 1.588)	0.721
Day >5 on drug treatment	2	20.0%	625	(76, 2,258)	32	1.821	(0.408, 8.136)	0.432	0.491	(0.108, 2.238)	0.358
Wash-out period	116	58.0%	1,750	(1,446, 2,099)	663	1.967	(1.472, 2.629)	<0.001	0.530	(0.374, 0.752)	<0.001
Acute kidney injury (N=46)											
Baseline period	25	40.3%	463	(300, 683)	540		(reference)		0.239	(0.074, 0.777)	0.017
Pre-exposure period	4	9.3%	563	(154, 1,442)	71	4.181	(1.287, 13.584)	0.017		(reference)	
Day 0-1 on drug initiation	6	13.0%	732	(269, 1,593)	82	5.598	(2.020, 15.508)	<0.001	1.339	(0.361, 4.958)	0.662
Day 2-5 on drug treatment	7	17.9%	814	(327, 1,677)	86	5.084	(1.890, 13.677)	0.001	1.216	(0.334, 4.426)	0.767
Day >5 on drug treatment	0	0.0%	0	NA	5	0.000	NA	0.998	0.000	NA	0.997
Wash-out period	12	26.1%	609	(315, 1,064)	197	1.633	(0.677, 3.936)	0.275	0.391	(0.116, 1.310)	0.128

WHO Clinical Progression Scale score ≥ 5

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=134)											
Baseline period	84	44.0%	530	(422, 656)	1,586		(reference)		0.082	(0.049, 0.137)	<0.001

Pre-exposure period	20	17.2%	1,099	(671, 1,697)	182	12.255	(7.307, 20.553)	<0.001		(reference)	
Day 0-1 on drug initiation	47	35.1%	2,070	(1,521, 2,753)	227	15.774	(10.728, 23.194)	<0.001	1.287	(0.750, 2.209)	0.359
Day 2-5 on drug treatment	52	42.6%	1,877	(1,402, 2,462)	277	11.947	(8.184, 17.440)	<0.001	0.975	(0.569, 1.670)	0.926
Day >5 on drug treatment	7	26.9%	1,000	(402, 2,060)	70	9.847	(4.215, 23.007)	<0.001	0.804	(0.315, 2.050)	0.647
Wash-out period	70	52.2%	1,552	(1,210, 1,961)	451	5.344	(3.783, 7.548)	<0.001	0.436	(0.260, 0.733)	0.002
Acute kidney injury (N=91)											
Baseline period	60	48.8%	438	(334, 564)	1,369		(reference)		0.098	(0.046, 0.209)	<0.001
Pre-exposure period	9	12.9%	811	(371, 1,539)	111	10.191	(4.795, 21.660)	<0.001		(reference)	
Day 0-1 on drug initiation	21	23.1%	1,250	(774, 1,911)	168	11.277	(6.461, 19.681)	<0.001	1.107	(0.492, 2.490)	0.807
Day 2-5 on drug treatment	23	28.0%	1,133	(718, 1,700)	203	7.556	(4.399, 12.980)	<0.001	0.741	(0.330, 1.667)	0.469
Day >5 on drug treatment	6	30.0%	1,017	(373, 2,213)	59	7.898	(3.136, 19.891)	<0.001	0.775	(0.251, 2.392)	0.658
Wash-out period	33	36.3%	892	(614, 1,253)	370	4.015	(2.497, 6.455)	<0.001	0.394	(0.182, 0.851)	0.018

Patients who had remdesivir discontinued

Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=125)											
Baseline period	70	40.5%	530	(413, 669)	1,322		(reference)		0.189	(0.109, 0.326)	<0.001
Pre-exposure period	19	17.4%	1,080	(650, 1,686)	176	5.304	(3.066, 9.174)	<0.001		(reference)	
Day 0-1 on drug initiation	32	25.6%	1,435	(982, 2,026)	223	5.392	(3.426, 8.486)	<0.001	1.017	(0.569, 1.816)	0.956
Day 2-5 on drug treatment	52	42.3%	1,562	(1,166, 2,048)	333	3.971	(2.672, 5.901)	<0.001	0.749	(0.437, 1.284)	0.293
Day >5 on drug treatment	9	25.0%	882	(403, 1,675)	102	3.721	(1.751, 7.904)	<0.001	0.702	(0.298, 1.650)	0.417
Wash-out period	51	40.8%	1,094	(815, 1,439)	466	2.355	(1.584, 3.500)	<0.001	0.444	(0.259, 0.762)	0.003
Acute kidney injury (N=62)											
Baseline period	36	45.0%	490	(344, 679)	734		(reference)		0.104	(0.023, 0.466)	0.003
Pre-exposure period	2	4.3%	270	(33, 976)	74	9.589	(2.146, 42.846)	0.003		(reference)	
Day 0-1 on drug initiation	13	21.0%	1,130	(602, 1,933)	115	28.414	(13.478, 59.900)	<0.001	2.963	(0.652, 13.460)	0.159
Day 2-5 on drug treatment	20	33.3%	1,163	(710, 1,796)	172	18.882	(9.686, 36.809)	<0.001	1.969	(0.447, 8.674)	0.370
Day >5 on drug treatment	6	28.6%	938	(344, 2,041)	64	20.383	(7.725, 53.784)	<0.001	2.126	(0.397, 11.396)	0.379
Wash-out period	21	33.9%	840	(520, 1,284)	250	8.453	(4.115, 17.365)	<0.001	0.882	(0.197, 3.954)	0.869

						With use of interferon-β-1b					
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=217)											
Baseline period	138	40.8%	667	(560, 788)	2,069		(reference)		0.148	(0.104, 0.212)	<0.001
Pre-exposure period	47	21.7%	1,335	(981, 1,776)	352	6.737	(4.707, 9.641)	<0.001		(reference)	
Day 0-1 on drug initiation	66	28.0%	1,646	(1,273, 2,094)	401	7.733	(5.631, 10.619)	<0.001	1.148	(0.779, 1.692)	0.486
Day 2-5 on drug treatment	96	47.1%	2,172	(1,759, 2,652)	442	7.925	(5.926, 10.598)	<0.001	1.176	(0.815, 1.698)	0.386
Day >5 on drug treatment	6	25.0%	882	(324, 1,921)	68	4.819	(1.967, 11.805)	<0.001	0.715	(0.283, 1.810)	0.479
Wash-out period	140	59.3%	1,867	(1,570, 2,203)	750	3.615	(2.784, 4.695)	<0.001	0.537	(0.381, 0.755)	<0.001
Acute kidney injury (N=99)											
Baseline period	62	44.6%	443	(340, 569)	1,398		(reference)		0.114	(0.057, 0.230)	<0.001
Pre-exposure period	11	12.9%	797	(398, 1,426)	138	8.743	(4.348, 17.580)	<0.001		(reference)	
Day 0-1 on drug initiation	22	22.2%	1,196	(749, 1,810)	184	9.843	(5.675, 17.072)	<0.001	1.126	(0.531, 2.387)	0.757
Day 2-5 on drug treatment	21	23.1%	968	(599, 1,479)	217	6.043	(3.453, 10.574)	<0.001	0.691	(0.321, 1.487)	0.344
Day >5 on drug treatment	3	23.1%	769	(159, 2,248)	39	5.576	(1.576, 19.724)	0.008	0.638	(0.159, 2.555)	0.525
Wash-out period	35	35.4%	862	(600, 1,199)	406	3.604	(2.261, 5.744)	<0.001	0.412	(0.204, 0.832)	0.013
						With use of ribavirin					
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=125)											
Baseline period	77	37.4%	590	(466, 737)	1,305		(reference)		0.164	(0.106, 0.256)	<0.001
Pre-exposure period	31	24.8%	1,442	(980, 2,047)	215	6.080	(3.908, 9.460)	<0.001		(reference)	
Day 0-1 on drug initiation	36	27.9%	1,593	(1,116, 2,205)	226	6.106	(4.012, 9.293)	<0.001	1.004	(0.618, 1.633)	0.986
Day 2-5 on drug treatment	56	45.9%	2,090	(1,578, 2,713)	268	6.561	(4.494, 9.580)	<0.001	1.079	(0.688, 1.693)	0.741
Day >5 on drug treatment	6	42.9%	1,667	(612, 3,628)	36	7.078	(2.709, 18.491)	<0.001	1.164	(0.429, 3.161)	0.766
Wash-out period	65	50.4%	1,522	(1,175, 1,940)	427	2.944	(2.065, 4.197)	<0.001	0.484	(0.313, 0.748)	0.001
Acute kidney injury (N=46)											

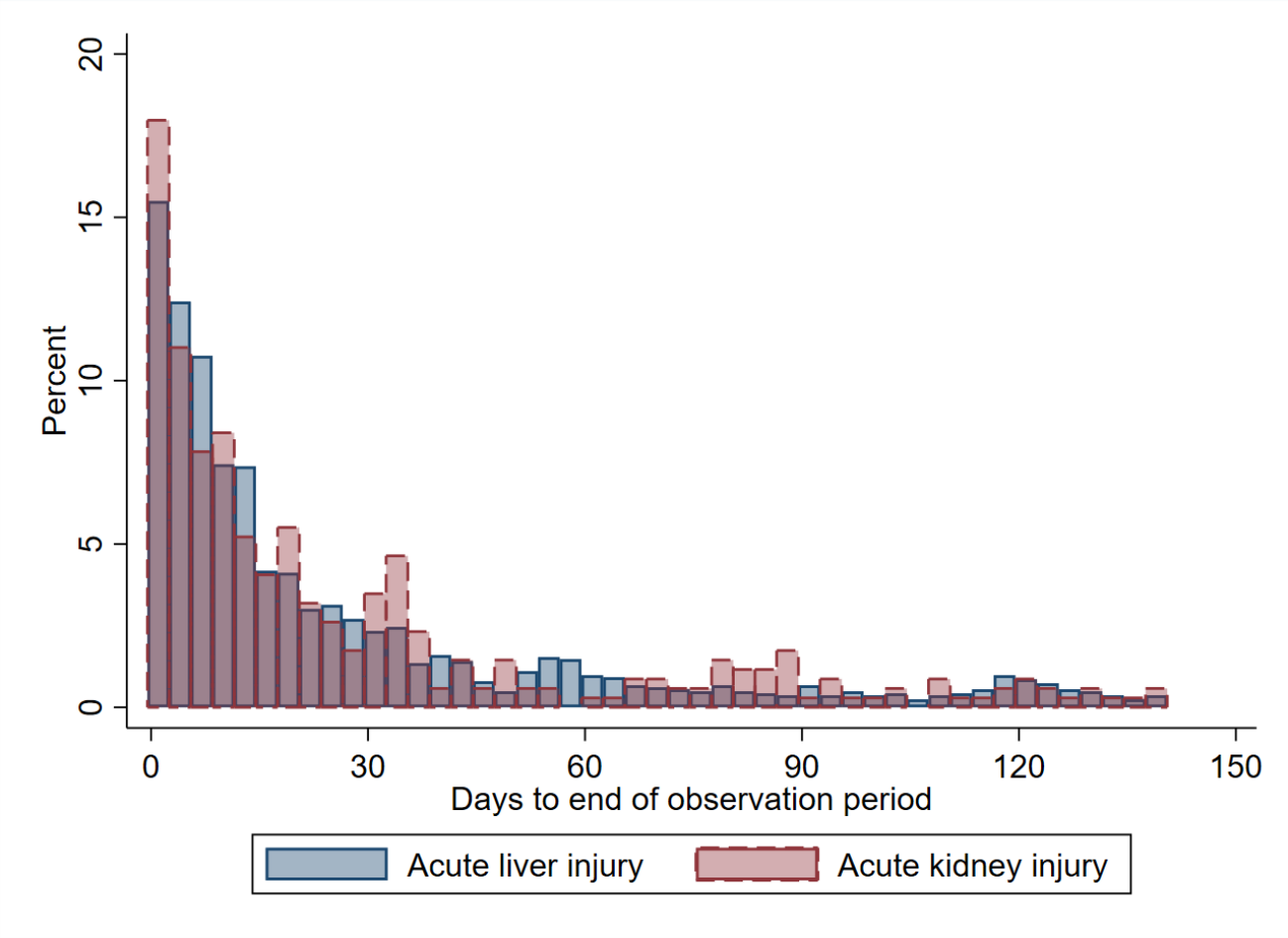
Baseline period	31	43.7%	503	(342, 714)	616		(reference)		0.294	(0.084, 1.027)	0.055
Pre-exposure period	3	7.0%	390	(80, 1,139)	77	3.405	(0.974, 11.905)	0.055		(reference)	
Day 0-1 on drug initiation	11	23.9%	1,279	(639, 2,289)	86	9.804	(4.538, 21.179)	<0.001	2.879	(0.801, 10.354)	0.105
Day 2-5 on drug treatment	11	25.0%	1,100	(549, 1,968)	100	6.804	(3.155, 14.674)	<0.001	1.998	(0.547, 7.302)	0.295
Day >5 on drug treatment	1	25.0%	833	(21, 4,643)	12	10.665	(1.018, 111.736)	0.048	3.132	(0.233, 42.181)	0.390
Wash-out period	14	30.4%	729	(399, 1,223)	192	3.000	(1.479, 6.087)	0.002	0.881	(0.248, 3.124)	0.844

With use of dexamethasone

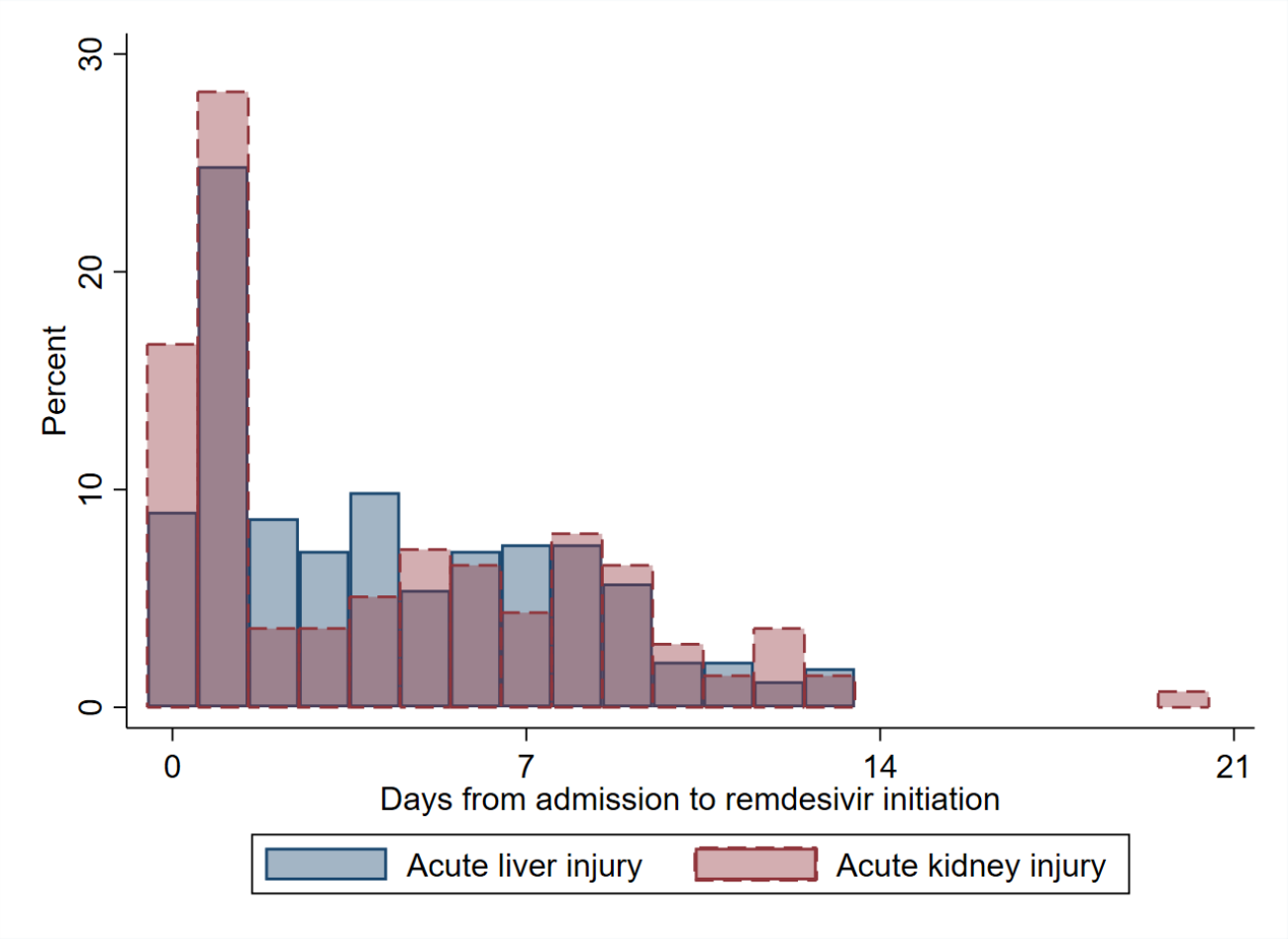
Outcomes	Events	Rate	Incidence rate (Events/10,000 person-days)	95% CI	Person-days	IRR	95% CI	P-value	IRR	95% CI	P-value
Acute liver injury (N=249)											
Baseline period	154	39.9%	615	(522, 720)	2,505		(reference)		0.166	(0.117, 0.236)	<0.001
Pre-exposure period	47	18.9%	1,155	(848, 1,536)	407	6.018	(4.232, 8.556)	<0.001		(reference)	
Day 0-1 on drug initiation	84	30.4%	1,787	(1,426, 2,213)	470	8.648	(6.475, 11.551)	<0.001	1.437	(0.992, 2.081)	0.055
Day 2-5 on drug treatment	102	42.0%	1,903	(1,552, 2,310)	536	7.645	(5.794, 10.087)	<0.001	1.270	(0.883, 1.828)	0.198
Day >5 on drug treatment	7	21.2%	729	(293, 1,502)	96	4.390	(1.931, 9.983)	<0.001	0.730	(0.309, 1.724)	0.472
Wash-out period	157	56.9%	1,727	(1,468, 2,019)	909	3.666	(2.866, 4.690)	<0.001	0.609	(0.435, 0.853)	0.004
Acute kidney injury (N=125)											
Baseline period	79	46.2%	434	(344, 541)	1,819		(reference)		0.124	(0.064, 0.240)	<0.001
Pre-exposure period	12	11.8%	727	(376, 1,270)	165	8.049	(4.173, 15.525)	<0.001		(reference)	
Day 0-1 on drug initiation	26	20.8%	1,121	(732, 1,642)	232	9.063	(5.512, 14.900)	<0.001	1.126	(0.553, 2.293)	0.744
Day 2-5 on drug treatment	26	22.6%	945	(618, 1,385)	275	5.853	(3.563, 9.616)	<0.001	0.727	(0.354, 1.493)	0.386
Day >5 on drug treatment	6	30.0%	984	(361, 2,141)	61	7.344	(2.921, 18.461)	<0.001	0.912	(0.308, 2.703)	0.869
Wash-out period	39	31.2%	744	(529, 1,017)	524	3.111	(2.024, 4.784)	<0.001	0.387	(0.197, 0.758)	0.006

Notes: CI = Confidence interval; IRR = Incidence rate ratio

Supplementary Figure 1. Frequency of time from event outcomes to the end of observation period



Supplementary Figure 2. Distributions of days from admission to remdesivir initiation among remdesivir users who had incident (a) acute liver injury (N=334) and (b) with acute kidney injury (N=137)



Supplementary Figure 3. Distributions of acute liver injury and acute kidney injury events by time of remdesivir initiation