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

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Summary

Background and 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 23 January 2020 and 31 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 hospitalisation, 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 2 days of remdesivir initiation (ALI: IRR = 1.261, 95% CI = 0.915–1.737; AKI:

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IRR = 1.261, 95% CI = 0.889–1.789) and between days 2 and 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.

1 | 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 utilising 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 smay 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 expressed at the 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 broad-spectrum antiviral monophosphoramidate prodrug that is metabolised 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 metabolises 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 the increase in liver enzymes is highlighted by FDA as a possible adverse side effect.[16,17] Despite these possible injurious mechanisms, the 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 randomised 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 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 hospitalised COVID-19 patients who also had incident AKI or ALI.

2 | METHODS

2.1 | Data source and study population

We analysed 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 23 January 2020 and 31 January 2021 using SCCS 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 hospitalised 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 utilised for drug safety[28] and pharmacoepidemiological studies of drug treatments for COVID-19.[29,30]

2.2 | Exposure and study outcomes

Patients who had initiated remdesivir during their hospitalisation 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 hospitalised with COVID-19 in Hong Kong.[31] The recommended

dosage is 200 mg once for the first day, and 100 mg once daily for the next 4 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 normalised 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 h; (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 AKI.[35] Definition of ALI and AKI referred to serum abnormality at any point during the observation period.

2.3 | Self-controlled case series

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]

2.4 | 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 the 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 the 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 the baseline period, IRR would be biassed downwards. On the other hand, death during the exposed period would bias IRR upwards. This is a case of event-dependent observation periods (Figure S1), which violates the assumption of SCCS, and requires an extended version of SCCS which is adjusted for censoring by applying a weighting according to the duration from the event to the end of observation.[38]

2.5 | Exposure and risk periods

Study exposure was the initiation of remdesivir treatment in patients hospitalised with COVID-19. Patients were censored on the following dates: date of hospital discharge, death or the end of the observation period (30 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 the 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 in probability of exposure.[37] Figure 1 illustrates the schema of SCCS and describes the six risk periods in this observational study.

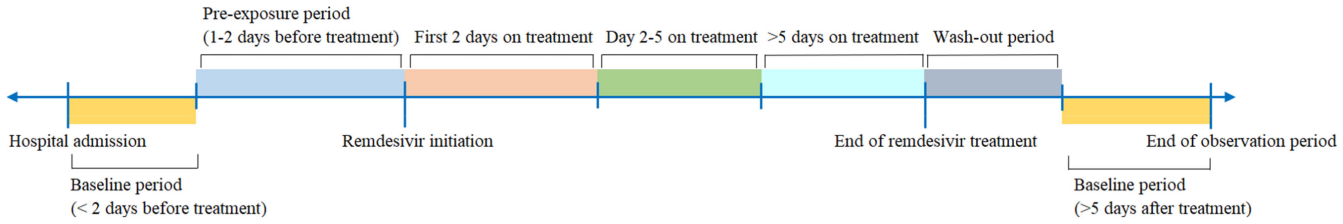

FIGURE 1 Study schema and definitions of treatment periods. The study was divided into six separate periods: Pre-exposure period, first 2 days on treatment, day 2–5 on treatment, more than 5 days on drug use to the end of treatment, wash-out period and more than 5 days after treatment to the end of the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

2.6 | 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 terms 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 a 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 hospitalisation 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 hospitalisation, as death cases within hospitalisation 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 5 days use of remdesivir; (iii) extending the observation period to 30 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× ULN or alkaline phosphatase (ALP) >2× 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 an SCCS approach in this study.[40] A two-sided significance level of 5% was used in all statistical analyses.

3 | RESULTS

Among 10,412 patients hospitalised with COVID-19 between 23 January 2020 and 31 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

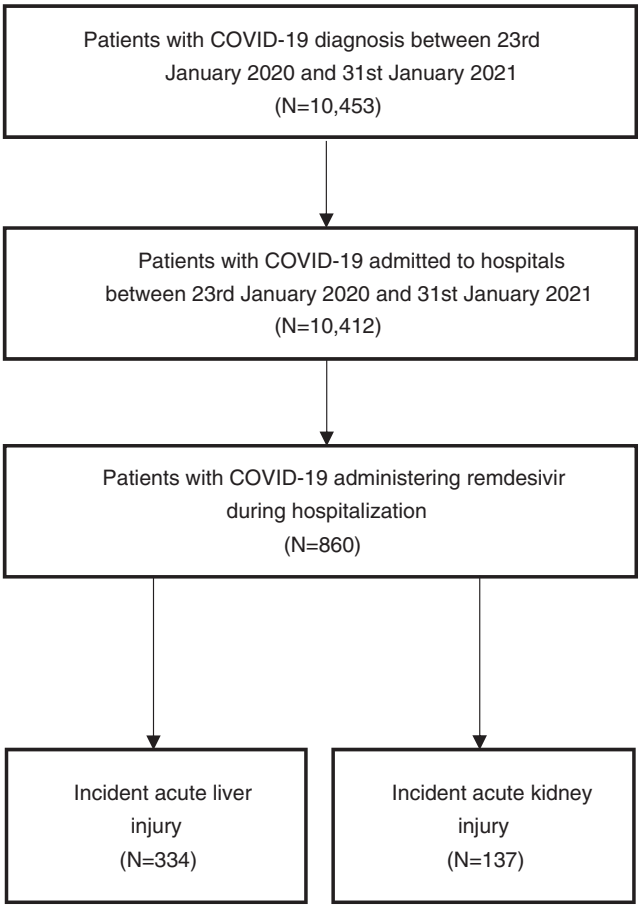

FIGURE 2 Flowchart of inclusion and exclusion of hospitalised COVID-19 patients administering remdesivir between 23 January 2020 and 31 January 2021 in Hong Kong SAR, China. Patients with COVID-19 were admitted to hospitals between 23 January 2020 and 31 January 2021 (N = 10,412). Patients with COVID-19 were administered with remdesivir during hospitalisation (N = 860)

during hospitalisation. Incidence rates of ALI and AKI among hospitalised COVID-19 patients were 154 and 39 per 10,000 person-days respectively. Distributions of the timing of remdesivir initiation, and that of the incident and recurrent outcomes by the day since remdesivir initiation are plotted in Figures S2 and S3, 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 the observation period, including 27 and 36 deaths that 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. The mean duration of the observation period was 30.7 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,

TABLE 1 Baseline characteristics of hospitalised patients with COVID-19 initiating remdesivir users who had an incident acute liver injury or acute kidney injury

	Remdesivir users			
	Acute liver injury (n = 334)		Acute kidney injury (n = 137)	
Baseline characteristics	***N*/Mean**	**%/SD**	***N*/Mean**	**%/SD**
Age (years)[a]	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[a,b]	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)[a]	4.2	3.4	4.1	4.1
Cumulative dosage of remdesivir (mg)[a]	598.5	238.2	632.1	280.2
Duration of use of remdesivir (days)[a]	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[a]	4.0	3.6	3.3	3.8

(Continues)

TABLE 1 (Continued)

Baseline characteristics	Remdesivir users			
	Acute liver injury (n = 334)		Acute kidney injury (n = 137)	
	N/Mean	%/SD	N/Mean	%/SD
Administration route of dexamethasone				
Oral	50	18.1%	25	20.0%
Intravenous injection	226	81.9%	100	80.0%
Dosage of dexamethasone				
Up to 6 mg daily	106	38.4%	40	32.0%
More than 6 mg daily	170	61.6%	85	68.0%
Cumulative dosage of dexamethasone (mg)[a]	70.1	88.5	92.3	112.5
Duration of use of dexamethasone (days)[a]	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)[a]	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][a]				
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 $\times$ 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
Haemoglobin g/dL [13.4–17.1 g/dL]	13.5	1.7	12.9	2.0

Abbreviations: 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 normalised ratio; NSAID, nonsteroidal anti-inflammatory drugs; R score, (ALT/ULN)/(ALP/ULN); SD, standard deviation; ULN, upper limit of normal.

[a]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.

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

95% CI = 4.549–8.365), remained elevated during first 2 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, the 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 2 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 the remdesivir treatment periods.

Similar results were found in the sensitivity (Table S1) and subgroup (Table S2) 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.

4 | DISCUSSION

This current study investigates the safety of remdesivir treatment initiation of hospitalised COVID-19 patients in terms of AKI and ALI. The result does not suggest a 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 to 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 randomised controlled trial.[15] Similarly, remdesivir did not lead to significant AKI risk at the end of treatment or 2 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 the 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 3 days after initiation towards at the end of treatment.[43] Therefore, remdesivir was not responsible for the injury, although randomised controlled trials were necessary to compare the incidence of AKI, especially under the challenge presented by the similar renal complications 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. A 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 the 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 the 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 hospitalisation.

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] A similar finding was reported when comparing remdesivir with other treatments of COVID-19: serum AST and ALT levels were significantly higher in the 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 the 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,

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	2850	Reference			0.162	0.120, 0.220	<0.001
Pre-exposure period	67	22.0%	1370	1062, 1740	489	6.169	4.549, 8.365	<0.001	Reference		
Day 0–1 on drug initiation	103	30.8%	1829	1493, 2219	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%	1909	1584, 2280	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, 1675	102	4.902	2.353, 10.214	<0.001	0.795	0.370, 1.707	0.556
Wash-out period	186	55.7%	1670	1438, 1928	1114	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	1909	Reference			0.180	0.130, 0.249	<0.001
Pre-exposure period	13	11.5%	714	380, 1221	182	7.074	3.763, 13.298	<0.001	Reference		
Day 0–1 on drug initiation	27	19.7%	1080	712, 1571	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%	1038	700, 1482	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, 2041	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, 1062	567	2.904	1.927, 4.377	<0.001	0.548	0.400, 0.750	<0.001

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

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 hospitalisation. 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, the 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 baricitinib 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, the 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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AUTHORSHIP

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Author 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.

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.

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.

DATA AVAILABILITY 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.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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