Journal of Microbiology, Immunology and Infection 57 (2024) 76—84

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Safety and effectiveness of remdesivir for the treatment of COVID-19 patients with end-stage renal disease: A retrospective cohort study

Yan-Bo Huang [a], Chip-Jin Ng [a,1], Cheng-Hsun Chiu [b], Chung-Hsien Chaou [a], Shi-Ying Gao [a], Shou-Yen Chen [a,*,1]

[a] *Department of Emergency Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan 333, Taiwan*
[b] *Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan 333, Taiwan*

Received 5 September 2023; received in revised form 26 October 2023; accepted 7 December 2023
Available online 15 December 2023

KEYWORDS
COVID-19;
End-stage renal disease;
Remdesivir;
Side effects

Abstract *Background:* Remdesivir has been used to treat severe coronavirus 2019 (COVID-19); however, its safety and effectiveness in patients remain unclear. This study aimed to investigate the safety and effectiveness of remdesivir in patients with COVID-19 with end-stage renal disease (ESRD).
Methods: This retrospective study used the Chang Gung Research Database (CGRD) and extracted data from 21,621 adult patients with COVID-19 diagnosed between April 2021 and September 2022. The patients were divided into groups based on their remdesivir use and the presence of ESRD. The adverse effects of remdesivir and their outcomes were analyzed after propensity score matching.
Results: To compare the adverse effects of remdesivir, propensity scores were used for one-to-one matching between patients with and without ESRD treated with remdesivir (N = 110). There were no statistically significant differences in heart rates, blood glucose levels, variations in hemoglobin levels before and after remdesivir use, or liver function between the two groups after remdesivir use. A comparison was made between patients with ESRD using remdesivir and those not using remdesivir after propensity score matching (N = 44). Although a shorter length of stay (LOS), lower intensive care unit (ICU) admission rate, and lower intubation rate were noted in the ESRD group treated with remdesivir, the difference was not statistically significant.

* Corresponding author. Department of Emergency Medicine, Chang Gung Memorial Hospital. No. 5 Fushing St., Gueishan Shiang, Taoyuan, Taiwan.
E-mail addresses: allendream0621@yahoo.com.tw, allendream0621@gmail.com (S.-Y. Chen).
[1] Shou-Yen Chen and Chip-Jin Ng contribute to the article equal as corresponding author

https://doi.org/10.1016/j.jmii.2023.12.003

Conclusion: Remdesivir is safe for use in patients with COVID-19 and ESRD; no increased adverse effects were noted compared with patients without ESRD. However, the effectiveness of remdesivir use in patients with COVID-19 and ESRD remains uncertain.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also referred to as coronavirus 2019 (COVID-19), rapidly spread worldwide and lead to a global pandemic by the end of 2019. Most individuals infected with the virus experience mild-to-moderate respiratory illnesses and recover without requiring specific treatment.[1] However, older adults and individuals with underlying conditions such as cardiovascular disease, diabetes, chronic respiratory diseases, kidney disease, or cancer are more susceptible to severe illness with COVID-19.[2,3] Based on data from the World Health Organization (WHO), as of June 7, 2023, over 6.9 million individuals have died from COVID-19 worldwide.[4]

Remdesivir is an RNA-dependent polymerase inhibitor, and previous studies have demonstrated its effectiveness in reducing recovery time and lowering respiratory tract symptoms in patients with COVID-19.[5—7] Guidelines established by the Infectious Diseases Society of America (IDSA) and the National Institutes of Health (NIH) also recommend the use of remdesivir in patients with severe COVID-19.[8,9] Although remdesivir has been shown to be effective in treating COVID-19, it is known to have side effects, including nausea, vomiting, elevated transaminase levels, anemia, hyperglycemia, and in some cases, bradycardia.[2,5,6]

For patients with end-stage renal disease (ESRD), severe COVID-19 is more common and the mortality rate can be as high as 25—30 %.[10,11] Remdesivir may play a role in the treatment of patients with COVID-19 and ESRD; however, there are limited data regarding the effectiveness and safety of remdesivir use in patients with ESRD. Our study aimed to investigate the safety of remdesivir use in patients with COVID-19 and ESRD by determining the occurrence of side effects. We also aimed to determine the effectiveness of remdesivir treatment in patients with COVID-19 with ESRD.

Methods

Study design

This retrospective study used the data from the Chang Gung Research Database (CGRD). The CGRD is a de-identified database derived from the medical records of Chang Gung Memorial Hospital (CGMH). Established in 1976, the CGMH is currently the largest healthcare system in Taiwan, comprising seven medical institutions distributed across the northeastern and southern regions. Collectively, they provide 10,070 beds and treat more than 280,000 patients annually.[12] The study was approved by the institutional review board of the Chang-Gung Memorial Hospital, Taiwan (IRB no. 202201848B0).

Study setting and population

In Taiwan, due to the reimbursement conditions set by the National Health Insurance, the use of remdesivir is limited to patients with severe COVID-19, including those requiring oxygen therapy or with evidence of pneumonia on chest X-rays.[13] The recommended treatment regimen is a 5-d course of remdesivir, and it is advised to be used in combination with dexamethasone.

Data of patients who visited the emergency department (ED) and were diagnosed with COVID-19 between April 2021 and September 2022 were retrieved from the CGRD. Patients aged <18 years and those who did not require hospitalization were excluded. Basic demographic data of the patients, including age, sex, initial vital signs, laboratory data, and underlying diseases, were collected. Data on treatment course and prognosis, including length of stay (LOS), mortality, intubation, and intensive care unit (ICU) admission, were also retrieved. The severity and risk of the patients were assessed by using WHO ordinal scale and inflammation risk categories.[14,15] The patients were also classified as different outbreak periods of virus variants including alpha, delta, and omicron. The alpha, delta, and omicron variant outbreak were defined as the time period before June 30, 2021, the period between July 1, 2021 to December 31, 2021, and the period after January 1, 2022 separately according to reports of virus sequencing by Taiwan centers of Disease Control (CDC).

The patients were divided into four groups based on whether they received renal replacement therapy (RRT) or were treated with remdesivir.

Outcome assessment

To analyze the safety of remdesivir in patients with ESRD, we compared common side effects of remdesivir, including bradycardia, anemia, and elevated liver function.[2,5,6] Primary outcomes after remdesivir use, including variations in heart rate, glucose level, hemoglobin level, and liver function, were compared between patients with and without ESRD.

For the analysis of therapeutic effects of remdesivir in patients with ESRD, the patients with a "do not resuscitate (DNR)" order were excluded since the prognosis could be affected if the patient or family did not receive resuscitation including intubation, inotropic agents, or other invasive treatment. According to the treatment guideline and criteria of using remdesivir in COVID-19 patients, the proportion of oxygen and steroid use could be different

between patients receiving remdesivir or not, so the covariates including oxygen and dexamethasone use were adjusted during the analysis of therapeutic effects of remdesivir. The outcome was assessed by comparing the treatment course, intubation rate, ICU admission, and mortality between patients with ESRD who received remdesivir and those who did not.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA). To minimize bias caused by individual differences, we conducted one-to-one matching using propensity scores. To compare the side effects of remdesivir, we matched patients with and without ESRD who received remdesivir. To compare the effectiveness of remdesivir in patients with ESRD, we matched patients with ESRD who received remdesivir with patients with ESRD who did not receive remdesivir. The covariates included in the logistic regression model were age, sex, and the Charlson Comorbidity Index (CCI). The collected patient data were compared using the Student's t-test and Welch's t-test for continuous variables and Pearson's chi-square test for categorical variables. Statistical significance was set at $p < 0.05$.

Results

A total of 98,763 patients with COVID-19 confirmed between April 2021 and September 2022 were included in the CGRD database (Fig. 1). After excluding patients aged <18 years and those who did not require hospitalization, 21,621 adult patients with COVID-19 were admitted to hospitals. Patients were categorized into four groups based on the use of remdesivir, with or without ESRD: (1) patients without ESRD with remdesivir use (N = 937), (2) patients without ESRD without remdesivir use (N = 18,513), (3) patients with ESRD with remdesivir use (N = 110), and (4) patients with ESRD without remdesivir use (N = 2061).

Table 1 presents the data of patients with and without ESRD treated with remdesivir. Patients with ESRD had a higher rate of underlying diseases, including cardiovascular disease (17.27 % vs. 5.66 %, p < 0.001), hypertension (90 % vs. 60.51 %, p < 0.001), congestive heart failure (42.73 % vs. 16.65 %, p < 0.001), chronic liver disease (24.55 % vs. 12.59 %, p = 0.001), and diabetes (63.64 % vs. 39.49 %, p < 0.001). Patients with ESRD were younger (71.15 vs. 74.63 years, p = 0.252) and had lower hemoglobin levels (10.01 vs. 12.06 g/dL, p < 0.001), higher C-reactive protein (CRP) levels (93.48 vs. 68.27 mg/L, p = 0.023), longer LOS (13.31 vs. 10.2 d, p = 0.015), and higher mortality rates (20 % vs. 10.67 %, p = 0.006). The WHO ordinal scale was similar in both groups (4 vs. 4, p = 0.807), but the patients with ESRD had higher proportion of high inflammation risk (62.73 % vs. 42.69 %, p < 0.001). Most patients of both groups were admitted during outbreak of omicron variant.

To compare the side effects of remdesivir, propensity scores were used for one-to-one matching between patients with and without ESRD treated with remdesivir (N = 110) (Table 2). There were no statistically significant differences in heart rates (84.39 vs. 85.87, beats/min, p = 0.561) or blood glucose levels (163.86 vs. 88.75 mg/dL, p = 0.083) between the two groups after remdesivir use. Patients with ESRD had lower initial hemoglobin levels (10.01 vs. 11.58 g/dL, p < 0.001), but no statistically significant difference was found in variation of hemoglobin levels before and after remdesivir use (−0.3 vs. 0.05, p = 0.323). For liver function, no significant difference was observed between the two groups (0.43 vs. 0.86 mg/dL, 0.294); however, lower alanine transaminase (ALT) levels were noted in patients with ESRD after remdesivir use (19.08 vs. 51.71 U/L, p = 0.038).

The effectiveness of remdesivir in patients with ESRD and COVID-19 was analyzed after excluding patients with a "do not resuscitate (DNR)" order (Table 3). The ESRD group treated with remdesivir had a higher proportion of patients receiving dexamethasone (62 vs. 3.88 %, p < 0.001) and oxygen therapy (70 vs. 41.29 %, p = 0.001). Comparisons were performed between patients with ESRD using remdesivir and those not receiving remdesivir after propensity score matching based on sex, age, vital signs, oxygen use, and dexamethasone use (N = 44) (Table 4). Among the matched patients, shorter LOS (12.49 vs. 15.15 d, p = 0.266), lower ICU admission rate (13.64 vs. 29.55 %, p = 0.120), and lower intubation rate (15.91 vs. 31.82 %, p = 0.134) was observed in the patient group using remdesivir; however, no significant difference was found. There was also no significant difference in mortality between the two groups (p = 0.5).

Discussion

Although data from randomized trials have not consistently shown the clinical benefits of remdesivir in patients with COVID-19, some multinational clinical trials reported benefits in specific subgroups, such as shorter recovery time, reduced need for mechanical ventilation, and decreased mortality rates.[16] The Adaptive COVID-19 Treatment Trial (ACTT-1) indicated that patients with severe COVID-19 treated with remdesivir had a shorter recovery time, leading to emergency-use authorization (EUA) by the U.S. Food and Drug Administration (FDA) on May 1, 2020.[5] In the subsequent WHO-sponsored multinational SOLIDARITY trial, there was a minimal and statistically insignificant difference in the overall 28-d mortality rate. However, remdesivir reduced the need for intubation in patients not receiving mechanical ventilation.[17] Similar results were observed in the DisCoVeRy trial, in which remdesivir significantly delayed the need for new mechanical ventilation or extracorporeal membrane oxygenation (ECMO) in a subset of randomly assigned participants without mechanical ventilation or ECMO support.[18] Currently, the guidelines from the National Institutes of Health (NIH) recommend the use of remdesivir for treating patients with severe COVID-19.[8,9] Although remdesivir has become an important therapy for COVID-19, there is insufficient evidence regarding its use in patients with renal insufficiency, especially those with ESRD. Our study provides real-world data on the use of remdesivir in patients with ESRD.

In previous studies, the common adverse effects associated with remdesivir treatment included fever, anemia, hyperglycemia, and abnormal liver function.[5] Case reports

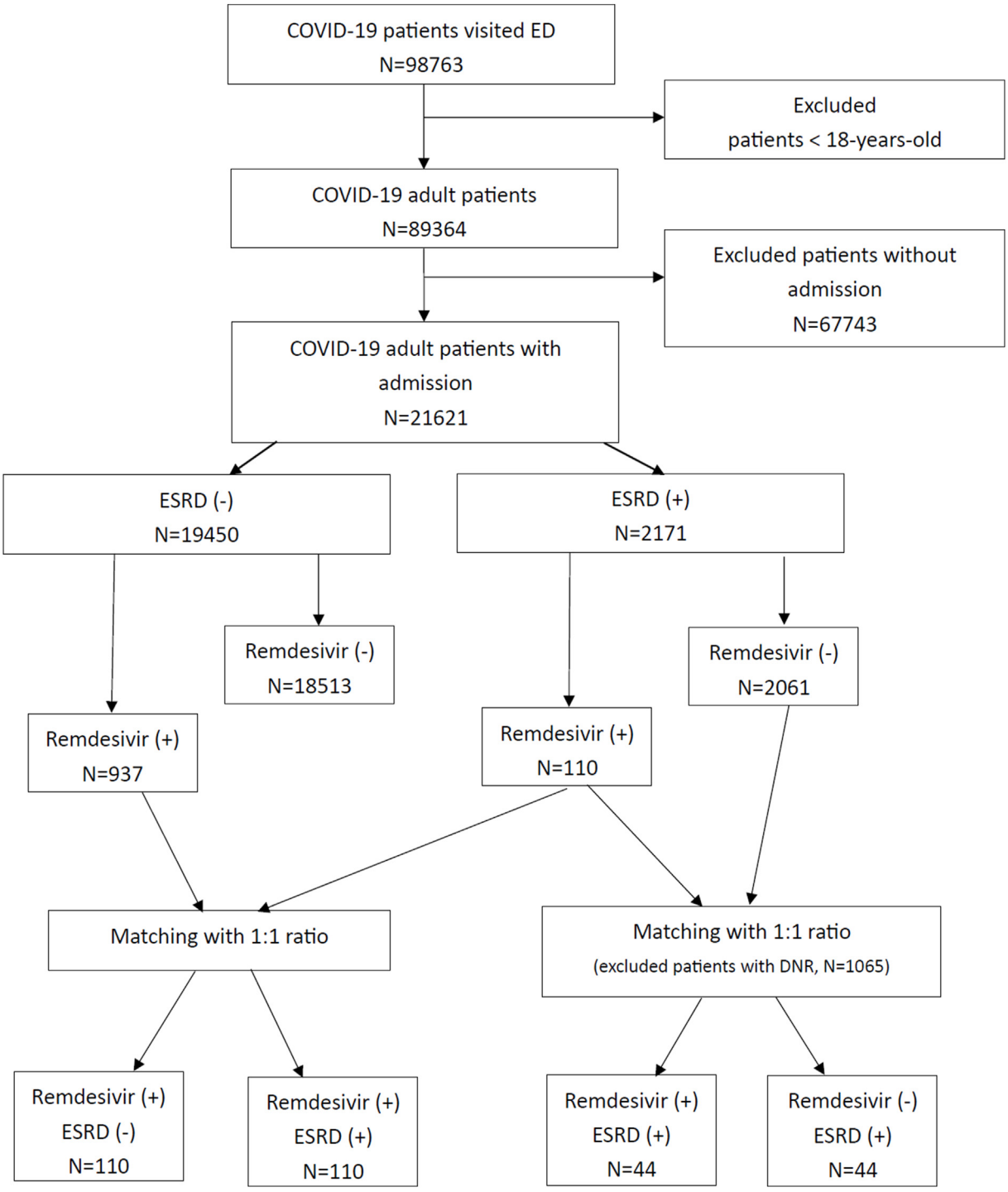

Figure 1. Flow diagram of patient selection.

have also reported bradycardia following the use of remdesivir.[2,19] Our study revealed that patients with ESRD did not experience more adverse effects to remdesivir than did patients without ESRD after a 5-d treatment course. No significant differences were observed in heart rate or blood sugar levels between patients with and without ESRD. Patients with ESRD are more prone to anemia due to decreased erythropoietin production in the kidneys and shortened red blood cell lifespan.[20] The initial and 5-d hemoglobin levels were lower in the ESRD group, but no significant difference was noted in the variation in hemoglobin levels after remdesivir use. Regarding liver function, patients with ESRD did not exhibit higher ALT or bilirubin levels than patients without ESRD after 5-d remdesivir use. The assumed source of drug toxicity is the accumulation of remdesivir and its excipient sulfobutylether-beta cyclodextrin (SBECD) in the body, which can accumulate in the blood of patients with impaired renal function.[21,22] A study

Table 1 Comparison between ESRD and non-ESRD patients of COVID-19 infection using remdesivir.

	Non-ESRD (N = 937)	ESRD (N = 110)	*p*-value
Age, years, mean (SD)	74.63 (15.6)	71.15 (13.97)	0.025*
Gender, male, N (%)	535 (57.1)	58 (52.73)	0.439
Initial vital signs			
BT, °C mean (SD)	37.55 (1.15)	37.2 (1.37)	0.011*
SBP, mmHg, mean (SD)	132.04 (32.33)	139.39 (39.31)	0.078
DBP, mmHg, mean (SD)	73.58 (19.2)	75.05 (24.02)	0.560
RR, breaths per minute, mean (SD)	20.84 (5)	21.15 (4.79)	0.541
HR, bpm, mean (SD)	98.55 (22.47)	98.15 (21.27)	0.862
HR after 5 days, bpm, mean (SD)	85.49 (18.14)	84.39 (18.6)	0.568
SpO2, %, mean (SD)	92.48 (7.21)	91.97 (8.9)	0.576
Initial laboratory data			
WBC, 1000/uL, mean (SD)	8.97 (6.27)	9.47 (5.27)	0.382
Hb, g/dL, mean (SD)	12.06 (2.32)	10.01 (2.04)	<0.001*
Hb after 5 days, g/dL, mean (SD)	11.77 (2.28)	9.09 (1.52)	<0.001*
Creatinine, mg/dL, mean (SD)	1.24 (0.96)	6.55 (3.84)	<0.001*
ALT, U/L, mean (SD)	35.76 (103.23)	29.28 (38.97)	0.241
ALT after 5 days, U/L, mean (SD)	51.44 (71.14)	19.08 (21.72)	0.001*
Bilirubin, mg/dL, mean (SD)	1.04 (2.35)	0.98 (2.33)	0.882
Bilirubin after 5 days, mg/dL, mean (SD)	0.6 (0.82)	0.43 (0.23)	0.160
CRP, mg/L, mean (SD)	68.27 (77.5)	93.48 (96.01)	0.023*
Sugar, mg/dL, mean (SD)	147.53 (73.29)	182.75 (139.44)	0.081
Sugar after 5 days, mg/dL, mean (SD)	166.43 (111.1)	163.86 (95.33)	0.954
Na, mEq/L, mean (SD)	134.17 (8.87)	134.32 (4.54)	0.785
K, mEq/L, mean (SD)	3.95 (0.63)	4.38 (0.93)	<0.001*
Troponin I, ng/mL, mean (SD)	0.39 (2.83)	0.49 (1.41)	0.768
D-dimer, ng/mL, mean (SD)	2963.74 (3542.22)	3521.18 (3842.97)	0.759
Ferritin, ng/mL, mean (SD)	1251 (866.91)	848.5 (777.11)	0.673
WHO Ordinal Scale and Inflammation Risk Categories			
WHO Ordinal Scale			
Median (IQR)	4 (4—4)	4 (3—4)	0.807
Inflammation Risk Categories			<0.001*
High, N (%)	400 (42.69)	69 (62.73)	
Intermediate, N (%)	257 (27.43)	15 (13.64)	
Low, N (%)	280 (29.88)	26 (23.64)	
Outbreak period			0.051
Alpha variant, N (%)	75 (8)	4 (3.64)	
Delta variant, N (%)	<3	<3	
Omicron variant, N (%)	861 (91.89)	105 (95.45)	
Prognosis			
LOS, days, mean (SD)	10.2 (8.01)	13.31 (12.66)	0.015*
Intubation, N (%)	45 (4.8)	10 (9.09)	0.093
ICU admission, N (%)	112 (11.95)	20 (18.118)	0.087
ICU LOS, days, mean (SD)	7.17 (8)	9.26 (12.61)	0.096
Mortality, N (%)	100 (10.67)	22 (20)	0.006*
Underlying diseases			
Cardiovascular disease, N (%)	53 (5.66)	19 (17.27)	<0.001*
Hypertension, N (%)	567 (60.51)	99 (90)	<0.001*
Congestive heart failure, N (%)	156 (16.65)	47 (42.73)	<0.001*
Cerebrovascular disease, N (%)	249 (26.57)	28 (25.45)	0.891
Chronic pulmonary disease, N (%)	271 (28.92)	23 (20.91)	0.098
Chronic liver disease, N (%)	118 (12.59)	27 (24.55)	0.001*
Diabetes mellitus, N (%)	370 (39.49)	70 (63.64)	<0.001*
Malignancy, N (%)	198 (1.13)	25 (22.73)	0.792

*$p < 0.05$.

ESRD: end stage renal disease; BT: body temperature; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR: respiratory rate; HR: heart rate; bpm: beats per minute; WBC white blood cell; Hb: hemoglobin; ALT: alanine transaminase; WHO: World Health Organization; IQR: interquartile range; LOS: length of stay; ICU: intensive care unit.

Table 2 Comparison of adverse effects of remdesivir between COVID-19 patients with ESRD and non-ESRD after propensity score matching.

	Non-ESRD (N = 110)	ESRD (N = 110)	*p*-value
Adverse effects of remdesivir			
Bradycardia			
HR, bpm, mean (SD)	99.9 (22.24)	98.15 (21.27)	0.563
HR after 5 days, bpm, mean (SD)	85.87 (18.08)	84.39 (18.6)	0.561
Anemia			
Hb, g/dL, mean (SD)	11.58 (2.5)	10.01 (2.04)	<0.001*
Hb after 5 days, g/dL, mean (SD)	10.99 (2.2)	9.09 (1.52)	<0.001*
Hb variation, mean (SD)	0.05 (1.66)	−0.3 (1.79)	0.323
Elevated liver function			
ALT, U/L, mean (SD)	28.89 (25.46)	29.28 (38.97)	0.937
ALT after 5 days, U/L, mean (SD)	51.71 (62.29)	19.08 (21.72)	0.038*
Bilirubin, mg/dL, mean (SD)	1.49 (4.24)	0.98 (2.33)	0.541
Bilirubin after 5 days, mg/dL, mean (SD)	0.86 (1.48)	0.43 (0.23)	0.294
Increase glucose level			
Sugar, mg/dL, mean (SD)	159.08 (81.6)	182.75 (139.44)	0.288
Sugar after 5 days, mg/dL, mean (SD)	88.75 (11.32)	163.86 (95.33)	0.083
Sugar variation, mean (SD)	−29.75 (39.79)	42.5 (57.27)	0.084

*$p < 0.05$.
ESRD: end stage renal disease; HR: heart rate; bpm: beats per minute; Hb: hemoglobin; ALT: alanine transaminase.

Table 3 Comparison between usage and non-usage of remdesivir in COVID-19 patients with ESRD.

	No remdesivir use (N = 1056)	remdesivir use (N = 50)	*p*-value
Age, years, mean (SD)	65.99 (14.49)	67.34 (14.95)	0.520
Gender, male, N (%)	576 (54.55)	25 (50)	0.628
Dexamethasone use, N (%)	41 (3.88)	31 (62)	<0.001*
Oxygen use, N (%)	436 (41.29)	35 (70)	<0.001*
Initial vital signs			
BT, °C mean (SD)	36.52 (1.05)	37.21 (1.23)	<0.001*
SBP, mmHg, mean (SD)	150.62 (37.93)	149.78 (40.16)	0.884
DBP, mmHg, mean (SD)	78.32 (19.46)	79.22 (22.45)	0.762
RR, breaths per minute, mean (SD)	18.17 (4.06)	20.85 (5.27)	0.001*
HR, bpm, mean (SD)	90.04 (19.96)	98.83 (18.86)	0.003*
HR after 5 days, bpm, mean (SD)	82.48 (15.86)	83.82 (16.8)	0.584
SpO2, %, mean (SD)	95.23 (6.82)	92.9 (7.13)	0.021*
Initial laboratory data			
WBC, 1000/uL, mean (SD)	9.62 (5.24)	8.45 (4.74)	0.147
Hb, g/dL, mean (SD)	9.77 (1.96)	9.68 (1.67)	0.738
Hb after 5 days, g/dL, mean (SD)	9.16 (1.35)	8.77 (1.11)	0.187
ALT, U/L, mean (SD)	42.04 (140.99)	31.17 (31.75)	0.118
ALT after 5 days, U/L, mean (SD)	98.4 (418.08)	28.25 (20.89)	0.021*
Bilirubin, mg/dL mean (SD)	1.01 (1.76)	0.55 (0.6)	0.012*
Bilirubin after 5 days, mg/dL, mean (SD)	0.87 (3.02)	0.58 (0.83)	0.253
CRP, mg/L, mean (SD)	64.77 (77.84)	69.69 (84.87)	0.705
Sugar, mg/dL, mean (SD)	181.26 (136.67)	218.25 (181.31)	0.245
Sugar after 5 days, mean (SD)	155.23 (114.49)	116.5 (13.44)	0.637
Na, mEq/L, mean (SD)	133.72 (7.74)	133.6 (4.17)	0.872
K, mEq/L, mean (SD)	4.36 (1.08)	4.54 (1.09)	0.274
Troponin I, ng/mL, mean (SD)	0.94 (4.46)	0.2 (0.32)	0.002*
D-dimer, ng/mL, mean (SD)	2877.08 (3268.94)	3495.47 (4436.98)	0.726
Ferritin, ng/mL, mean (SD)	927.17 (991.08)	848.5 (777.11)	0.923

(*continued on next page*)

Table 3 (*continued*)

	No remdesivir use (N = 1056)	remdesivir use (N = 50)	*p*-value
WHO Ordinal Scale and Inflammation Risk Categories			
WHO Ordinal Scale			
Median (IQR)	3 (3—4)	4 (3—4)	<0.001*
Inflammation Risk Categories			0.039*
High, N (%)	441 (41.76)	30 (60)	
Intermediate, N (%)	268 (25.38)	9 (18)	
Low, N (%)	347 (32.86)	11 (22)	
Outbreak period			<0.001*
Alpha variant, N (%)	11 (1.04)	<3	
Delta variant, N (%)	561 (53.13)	<3	
Omicron variant, N (%)	484 (45.83)	48 (96)	
Prognosis			
LOS, days, mean (SD)	11.31 (11.16)	12.02 (7.6)	0.538
Intubation, N (%)	105 (9.94)	8 (16)	0.253
ICU admission, N (%)	125 (11.84)	7 (14)	0.812
ICU LOS, days, mean (SD)	7.79 (10.29)	7.43 (6.68)	0.723
Mortality, N (%)	13 (1.23)	4 (8)	0.006*
Underlying diseases			
Cardiovascular disease, N (%)	170 (16.1)	6 (12)	0.564
Hypertension, N (%)	942 (89.2)	43 (86)	0.633
Congestive heart failure, N (%)	351 (33.24)	20 (40)	0.403
Cerebrovascular disease, N (%)	265 (25.09)	12 (24)	0.994
Chronic pulmonary disease, N (%)	192 (18.18)	13 (26)	0.229
Chronic liver disease, N (%)	271 (25.66)	9 (18)	0.293
Diabetes mellitus, N (%)	649 (61.46)	34 (68)	0.435
Malignancy, N (%)	214 (20.27)	11 (22)	0.906

*$p < 0.05$.
ESRD: end stage renal disease; BT: body temperature; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR: respiratory rate; HR: heart rate; bpm: beats per minute; WBC white blood cell; Hb: hemoglobin; ALT: alanine transaminase; WHO: World Health Organization; IQR: interquartile range; LOS: length of stay; ICU: intensive care unit.

Table 4 Comparison between usage and non-usage of remdesivir in COVID-19 patients with ESRD after propensity score matching.

	No remdesivir use (N = 44)	remdesivir use (N = 44)	*p*-value
LOS, days, mean (SD)	15.15 (13.13)	12.49 (7.79)	0.266
Intubation, N (%)	14 (31.82)	7 (15.91)	0.134
ICU admission, N (%)	13 (29.55)	6 (13.64)	0.120
ICU LOS, days, mean (SD)	11.51 (12.98)	8.16 (6.72)	0.146
Mortality, N (%)	<3 (<6.82)[a]	3 (6.82)	0.500

[a] The number less than 3 cannot be showed for avoiding identification according to the rules of the dataset.
ESRD: end stage renal disease; LOS: length of stay; ICU: intensive care unit.

by Luke et al. demonstrated that the half-life of SBECD in patients with impaired renal function was higher, and dialysis can shorten this half-life.[23] A case report by Lê et al. indicated that a single 4-h session of hemodialysis can reduce the concentration of remdesivir metabolites by 59 %.[24] This may explain why patients with ESRD treated with remdesivir do not experience more liver function abnormalities.

Patients with ESRD are highly susceptible to COVID-19 because of repeated exposure to healthcare facilities for dialysis, compromised immune systems, and the presence of various comorbidities. Although the mortality rate of COVID-19 in the general population is approximately 2—3%, it can be as high as 25—30 % in patients with chronic kidney disease.[10,11,25] Therefore, the effective treatment of COVID-19 is important for patients with COVID-19 and ESRD. In a small prospective observational study conducted in India, administering remdesivir to patients with ESRD within 48 h of hospitalization reduced oxygen requirements and shortened recovery time.[26] Another study conducted in Pakistan involving 83 patients with COVID-19 and ESRD suggested that the use of remdesivir may reduce recovery time.[27] Our study showed that patients with ESRD and COVID-19 receiving remdesivir had a lower intubation rate,

fewer ICU admissions, and shorter LOS; however, no statistically significant difference was noted. This may be attributed to the inadequate number of cases in our study, because several patients with ESRD with DNR orders were excluded from the analysis of outcome measures. Although the benefits of remdesivir have been shown in previous reports, its effectiveness in treating patients with COVID-19 with ESRD requires further study.

Limitations

Our study had some limitations. First, it was a single-country, multicenter study, which may introduce a selection bias and limit the generalizability of the results to other regions or countries. Second, data on the blood concentration of remdesivir and the timing of its administration relative to dialysis was lacking, making it difficult to determine the effect of dialysis on the concentration of remdesivir in the blood and its association with outcomes and adverse effects. Third, some data related to severity or outcome evaluation including clinical symptoms, image data of lung, and cycle threshold value (CT value) of polymerase chain reaction (PCR) were not available from our database. This could impact the thoroughness of our outcome evaluation. Lastly, some patients with ESRD were excluded because of DNR; therefore, the number of cases in the analysis of the effectiveness of remdesivir decreased, which may have affected the results.

Conclusions

Our study demonstrates the safety of remdesivir in patients with ESRD and COVID-19. Common adverse effects of remdesivir, including anemia, hyperglycemia, abnormal liver function, and bradycardia, were not higher in patients with ESRD than in patients without ESRD. Although remdesivir use in patients with COVID-19 and ESRD appears to improve some clinical conditions, its effectiveness remains uncertain and could not be proved in our study. Further studies are required to explore the effects of remdesivir in the treatment of patients with COVID-19 and ESRD.

Conflicts of interest

None for all authors.

Funding

This study received no funding.

Acknowledgments

This study was supported by the Chang Gung Memorial Hospital. The authors thank all colleagues who provided expertise that substantially assisted with the research, although they may not necessarily agree with all the interpretations presented in this paper.

References

1. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**(24):759—65.
2. Devgun JM, Zhang R, Brent J, Wax P, Burkhart K, Meyn A, et al. Identification of bradycardia following remdesivir administration through the US food and drug administration American college of medical toxicology COVID-19 toxic pharmacovigilance project. *JAMA Netw Open* 2023;**6**(2):e2255815.
3. Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet* 2022;**400**(10360):1305—20.
4. Organization. WH. *WHO coronavirus (COVID-19) dashboard*. 2023. Available from: https://covid19.who.int/.
5. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 - final report. *N Engl J Med* 2020;**383**(19):1813—26.
6. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;**395**(10236):1569—78.
7. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe covid-19. *N Engl J Med* 2020;**382**(24):2327—36.
8. (NIH). NIoH. *COVID-19 treatment guidelines*. 2023. Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/hospitalized-adults-therapeutic-management/.
9. (IDSA). IDSoA. *IDSA guidelines on the treatment and management of patients with COVID-19*. 2023. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#Recommendations15-17:Remdesivir.
10. Goicoechea M, Sánchez Cámara LA, Macías N, Muñoz de Morales A, Rojas Á G, Bascuñana A, et al. COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. *Kidney Int* 2020;**98**(1):27—34.
11. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. *Kidney Int* 2020;**98**(1):20—6.
12. Tsai MS, Lin MH, Lee CP, Yang YH, Chen WC, Chang GH, et al. Chang Gung Research Database: a multi-institutional database consisting of original medical records. *Biomed J* 2017;**40**(5):263—9.
13. Control. TCfD. 新型冠狀病毒*(SARS-CoV-2)*感染臨床處置指引 *2023*. Available from: https://www.cdc.gov.tw/Category/Page/xCSwc5oznwcqunujPc-qmQ.
14. Rubio-Rivas M, Mora-Luján JM, Formiga F, Arévalo-Cañas C, Lebrón Ramos JM, Villalba García MV, et al. WHO ordinal scale and inflammation risk categories in COVID-19. Comparative study of the severity scales. *J Gen Intern Med* 2022;**37**(8):1980—7.
15. Rubio-Rivas M, Corbella X, Formiga F, Menéndez Fernández E, Martín Escalante MD, Baños Fernández I, et al. Risk categories in COVID-19 based on degrees of inflammation: data on more than 17,000 patients from the Spanish SEMI-COVID-19 registry. *J Clin Med* 2021;**10**(10).
16. Siemieniuk RA, Bartoszko JJ, Zeraatkar D, Kum E, Qasim A, Martinez JPD, et al. Drug treatments for covid-19: living

systematic review and network meta-analysis. *BMJ* 2020;**370**: m2980.
17. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for covid-19 - interim WHO solidarity trial results. *N Engl J Med* 2021;**384**(6):497—511.
18. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis* 2022;**22**(2):209—21.
19. Touafchia A, Bagheri H, Carrié D, Durrieu G, Sommet A, Chouchana L, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. *Clin Microbiol Infect* 2021;**27**(5):791.e5—8.
20. Eschbach JW. Erythropoietin 1991–an overview. *Am J Kidney Dis* 1991;**18**(4 Suppl 1):3—9.
21. website. EMA. *Summary on compassionate use*. 2020. Available from: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.
22. Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). *J Pharmaceut Sci* 2010;**99**(8):3291—301.
23. Luke DR, Wood ND, Tomaszewski KE, Damle B. Pharmacokinetics of sulfobutylether-β-cyclodextrin (SBECD) in subjects on hemodialysis. *Nephrol Dial Transplant* 2012;**27**(3): 1207—12.
24. Lê MP, Le Hingrat Q, Jaquet P, Wicky PH, Bunel V, Massias L, et al. Removal of remdesivir's metabolite GS-441524 by hemodialysis in a double lung transplant recipient with COVID-19. *Antimicrob Agents Chemother* 2020;**64**(11).
25. Corbett RW, Blakey S, Nitsch D, Loucaidou M, McLean A, Duncan N, et al. Epidemiology of COVID-19 in an urban dialysis center. *J Am Soc Nephrol* 2020;**31**(8):1815—23.
26. Aiswarya D, Arumugam V, Dineshkumar T, Gopalakrishnan N, Lamech TM, Nithya G, et al. Use of remdesivir in patients with COVID-19 on hemodialysis: a study of safety and tolerance. *Kidney Int Rep* 2021;**6**(3):586—93.
27. Butt B, Hussain T, Jarrar M, Khalid K, Albaker W, Ambreen A, et al. Efficacy and safety of remdesivir in COVID-19 positive dialysis patients. *Antibiotics* 2022;**11**(2).