



A Valid Warning or Clinical Lore: an Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort

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ABSTRACT Per prescribing guidance, remdesivir is not recommended for SARS-CoV-2 in patients with renal disease given the absence of safety data in this patient population. This study was a multicenter, retrospective chart review of hospitalized patients with SARS-CoV-2 who received remdesivir. Safety outcomes were compared between patients with an estimated creatinine clearance (eCrCl) of <30 ml/min and an eCrCl of ≥30 ml/min. The primary endpoint was acute kidney injury (AKI) at the end of treatment (EOT). Of 359 patients who received remdesivir, 347 met inclusion criteria. Patients with an eCrCl of <30 ml/min were older {median, 80 years (interquartile range [IQR], 63.8 to 89) versus 62 (IQR, 54 to 74); $P < 0.001$ }, were more likely to be on vasopressors on the day of remdesivir administration (30% versus 12.7%; $P = 0.003$), and were more likely to be mechanically ventilated during remdesivir therapy (27.5% versus 12.4%; $P = 0.01$) than those with an eCrCl of ≥30 ml/min. Despite these confounders, there was no significant difference in the frequency of EOT AKI (5% versus 2.3%; $P = 0.283$) or early discontinuation due to abnormal liver function tests (LFTs) (0% versus 3.9%; $P = 0.374$). Of the 5% of patients who developed EOT AKI on remdesivir with an eCrCl <30 ml/min, no cases were attributable to remdesivir administration per the treating physician. Comparable safety outcomes were observed when 1:1 nearest neighbor matching was applied to account for baseline confounders. In conclusion, remdesivir administration was not significantly associated with increased EOT AKI in patients with an eCrCl of <30 ml/min compared to patients with an eCrCl of ≥30 ml/min.

KEYWORDS COVID, SARS-CoV-2, SBECD, chronic kidney disease, remdesivir, renal failure

The novel coronavirus 2019 (SARS-CoV-2) has been recognized as a human pathogen associated with potentially severe respiratory infections. Since its identification in December 2019, the virus has led to nearly 45 million infections and over 1.3 million deaths worldwide (<https://coronavirus.jhu.edu/map.html>). Of those infected, approximately 15% of patients will develop severe pneumonia, and 5% will develop respiratory or multiorgan failure (1). Given the high morbidity and mortality associated with this disease, the development of an effective and safe treatment is a public health priority.

Remdesivir is a nucleotide analog with *in vitro* activity against multiple coronaviruses, including SARS-CoV, MERS-CoV, and, more recently, SARS-CoV-2 through inhibition of viral RNA-dependent RNA polymerase (2). More importantly, a randomized trial found that remdesivir was superior to placebo in shortening the time to recovery in

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patients with SARS-CoV-2 (3). Combined data from an observational study and randomized trial have even demonstrated a mortality benefit compared to standard care in the treatment of SARS-CoV-2 (4). However, available data are conflicting, and the findings of an early clinical trial failed to show that remdesivir was associated with any statistically significant clinical benefits compared to placebo in patients with SARS-CoV-2 (5). Nevertheless, given the severity of the SARS-CoV-2 pandemic and the limited armamentarium of available treatment options, remdesivir has been granted approval by the Food and Drug Administration (FDA) for the treatment of patients hospitalized with SARS-CoV-2 (2).

Although there is a paucity of data evaluating remdesivir's pharmacokinetic parameters, a study in healthy volunteers without SARS-CoV-2 who received remdesivir detected 10% of the dose to be excreted in urine. However, in these same volunteers, 49% of GS-441524, remdesivir's prodrug, was detected in the urine (2). GS-441524 has also been observed to be elevated in both patients with mild renal dysfunction and patients requiring intermittent hemodialysis (6–9). However, it has been suggested that GS-704277, a transient prodrug of remdesivir prior to further hydrolysis to GS-441524, is accumulated in renal disease and is, in turn, responsible for the elevated serum concentrations of GS-441524 in the population (10). Regardless, no dose adjustments are recommended for patients with renal dysfunction at this time. Routine monitoring of liver function tests (LFTs) is recommended in patients receiving remdesivir, with guidance to discontinue the drug in patients with alanine aminotransferase (ALT) of ≥ 10 times the upper limit of normal (ULN) (2). Therefore, it is unclear if the potential accumulation of either GS-441524 or GS-704277 in patients with renal disease receiving remdesivir would increase the risk of adverse effects.

Given the limited solubility of remdesivir, sulfobutylether-beta-cyclodextrin sodium (SBECD) is required for intravenous (i.v.) administration (11). Although nephrotoxicity has been associated with the administration of first-generation β -cyclodextrins by way of accumulation into renal epithelial cells, SBECD has been designed not to accumulate in renal epithelial cells (12). Despite this, i.v. remdesivir was shown to be nephrotoxic at doses of 5 mg/kg/day for 7 days in rhesus monkeys and at doses of ≥ 3 mg/kg/day for up to 4 weeks in rats (2). However, these respective doses are 3.5-fold and 2.1-fold higher than the daily doses used for the treatment of SARS-CoV-2 infections in humans (2). It is encouraging that in clinical practice, a total of four cases of acute kidney injury (AKI) in patients receiving remdesivir have been reported to a national French pharmacovigilance database, and no cases were considered causal (13). Occurrence of AKI in patients with SARS-CoV-2 who received remdesivir in clinical trials has also been observed, albeit at low rates comparable to placebo (3, 5, 14).

Regardless, in the absence of definitive clinical data, prescribing guidance recommends against use of remdesivir in patients with an estimated glomerular filtration rate (eGFR) of < 30 ml/min unless the benefit outweighs the risk (2). Although eGFR has traditionally been calculated using the modification of diet in renal disease equation, remdesivir's original fact sheet for health care providers under the Emergency Use Authorization (EUA) recommended using the Cockcroft-Gault equation (15). Guidance from the European Medicines Agency is even more restrictive and currently states that remdesivir is contraindicated in severe renal impairment (16).

Given that AKI has been reported to occur in over one-fourth of hospitalized patients with SARS-CoV-2, there is an unmet clinical need to identify if remdesivir therapy is safe in patients with an estimated creatinine clearance (eCrCl) of < 30 ml/min (17). Often, the benefit of remdesivir outweighs the theoretical risk of SBECD and GS-441524 accumulation considering the high mortality rate associated with hospitalization due to SARS-CoV-2. Therefore, the purpose of this study was to compare the risk of safety outcomes between hospitalized SARS-CoV-2 patients with an eCrCl of < 30 ml/min and an eCrCl of ≥ 30 ml/min who required remdesivir administration.

RESULTS

Of 359 patients who received remdesivir, 347 met inclusion criteria. Twelve patients were excluded because they required renal replacement therapy prior to remdesivir initiation. Of the patients who met inclusion criteria, there were 40 patients with an eCrCl of <30 ml/min and 307 patients with an eCrCl of \geq 30 ml/min.

Patients with an eCrCl of <30 ml/min were older (median, 80 years [interquartile range [IQR], 63.8 to 89] versus 62 [IQR, 54 to 74]; $P < 0.001$), were more likely to be on vasopressors on the day of remdesivir initiation (30% versus 12.7%; $P = 0.003$), and were more likely to be mechanically ventilated on the day of remdesivir initiation (27.5% versus 12.4%; $P = 0.01$) than those with an eCrCl of \geq 30 ml/min (Table 1). Despite these confounders, there was no significant difference in the frequency of end-of-treatment (EOT) AKI (5% versus 2.3%; $P = 0.283$) or early discontinuation due to abnormal LFTs (0% versus 3.9%; $P = 0.374$). However, patients with an eCrCl of <30 ml/min calculated on the first day of administration of remdesivir had a higher 30-day mortality rate than those with an eCrCl of \geq 30 ml/min (50% versus 16.2%; $P < 0.001$). Of the two patients who developed EOT AKI on remdesivir with an eCrCl <30 ml/min, no cases were attributable to remdesivir administration per the treating physician. One patient was deemed to have developed AKI due to hypotension, and the other patient's nephrologist deemed AKI to be secondary to either tacrolimus toxicity or contrast-induced nephropathy.

A subset analysis of patients without AKI on the day of remdesivir initiation did not identify an eCrCl of <30 ml/min to be associated with either EOT AKI (4.2% versus 2%; $P = 0.425$) or early discontinuation due to abnormal LFTs (0% versus 4%; $P > 0.999$); however, patients within this subset with an eCrCl of <30 ml/min also had a higher 30-day mortality rate than those with an eCrCl of \geq 30 ml/min (55% versus 16.5%; $P < 0.001$) (Table 2).

When nearest neighbor matching was applied, there was no significant difference in age (median, 80 years [IQR, 63.8 to 89] versus 84 [IQR, 70.8 to 87.5]; $P = 0.554$), use of vasopressors on the day of remdesivir initiation (30% versus 20%; $P = 0.302$), or use of mechanical ventilation on the day of remdesivir initiation (27.5% versus 20%; $P = 0.431$) in patients with an eCrCl of <30 ml/min compared to those with an eCrCl of \geq 30 ml/min (Table 3). However, baseline presence of heart failure, diabetes mellitus, and AKI on the day of remdesivir initiation remained significantly more common in patients with an eCrCl of <30 ml/min. Regardless, there was no significant difference in the frequency of EOT AKI (5% versus 2.5%; $P > 0.999$) or early discontinuation due to abnormal LFTs (0% versus 5%; $P = 0.494$).

DISCUSSION

To our knowledge, this is the first study to evaluate the risk of nephrotoxicity of remdesivir in patients with an eCrCl of <30 ml/min. All randomized trials published to date which have evaluated the use of remdesivir in patients with SARS-CoV-2 have excluded patients with renal disease (3, 5, 14). Therefore, in addition to our evaluation of the risk of AKI in patients who receive remdesivir, our analysis also revealed no increased risk of LFT abnormalities in patients with SARS-CoV-2 who receive remdesivir in the setting of renal disease.

There was a relatively low frequency of EOT AKI in our cohort, which is consistent with previously reported literature. In clinical trials, the frequency of AKI among hospitalized patients treated with remdesivir for SARS-CoV-2 has ranged from 1% to 4.7% (3, 5, 14). In addition, these same clinical trials report the frequency of ALT elevations attributable to remdesivir to have occurred in 1% to 6.5% of patients, which is also consistent with our findings (3, 5, 14).

The administration of remdesivir for SARS-CoV-2 has been advocated without regard to eCrCl, as many clinicians have extrapolated safety data from i.v. voriconazole, which is formulated with SBECD (7). Each 100-mg dose of lyophilized remdesivir powder is formulated with 3 g of SBECD, which is comparable to a standard formulation of 200 mg of i.v. voriconazole, which contains 3.2 g of SBECD (2, 19). Therefore, it is

TABLE 1 Full bivariate analysis

Characteristic ^d	Patients with an eCrCl of:		P value ^e
	<30 ml/min (n = 40)	≥30 ml/min (n = 307)	
Baseline demographics and treatment information			
Age (median [IQR] [yrs])	80 (63.8–89)	62 (54–74)	<0.001 ^a
Female gender (no. [%])	23 (57.5)	146 (47.6)	0.237 ^b
Body mass index of >30 kg/m ² (no. [%])	14 (35)	149 (48.5)	0.117 ^b
Cirrhosis (no. [%])	2 (5)	4 (1.3)	0.114 ^c
Diabetes mellitus (no. [%])	24 (60)	95 (30.9)	<0.001 ^b
Heart failure (no. [%])	18 (45)	33 (10.7)	<0.001 ^b
Hypertension (no. [%])	34 (85)	176 (57.3)	<0.001 ^b
Renal transplant (no. [%])	1 (2.5)	3 (1)	0.389 ^c
Baseline SCr (median [IQR] [mg/dl])	1.2 (1–2.1)	0.85 (0.7–1)	<0.001 ^a
SCr on the day of remdesivir administration (median [IQR] [mg/dl])	2.8 (1.6–4.2)	0.87 (0.7–1.1)	<0.001 ^a
CrCl (ml/min) on the day of remdesivir administration by C-G (median [IQR])	20.3 (15.3–26.3)	82.5 (57.8–108.6)	<0.001 ^a
eGFR (ml/min/1.73 m ²) on the day of remdesivir administration by MDRD (median [IQR])	21 (15.2–34.1)	89.4 (63.8–111.7)	<0.001 ^a
ALT > 5 × ULN on the first day of remdesivir administration			0.638 ^c
Total no.	40	304	
No. (%)	2 (5)	10 (3.3)	
In AKI on the day of remdesivir administration (no. [%])	16 (40)	8 (2.6)	<0.001 ^b
Vasopressor or inotrope use during remdesivir (no. [%])	12 (30)	39 (12.7)	0.003^b
Mechanical ventilation during remdesivir (no. [%])	11 (27.5)	38 (12.4)	0.01^b
Concomitant nephrotoxic drug (no. [%])			
Vancomycin	5 (12.5)	52 (16.9)	0.65 ^c
Aminoglycoside	1 (2.5)	0 (0)	0.115 ^c
i.v. acyclovir	1 (2.5)	0 (0)	0.115 ^c
TMP-SMX	0 (0)	4 (1.3)	>0.999 ^c
Amphotericin B	0 (0)	0 (0)	>0.999 ^c
ACE/ARB	8 (20)	50 (16.3)	0.554 ^b
Loop/thiazide diuretics	24 (60)	106 (34.5)	0.002^b
Tacrolimus/cyclosporine	1 (2.5)	3 (1)	0.389 ^c
i.v. contrast	3 (7.5)	41 (13.4)	0.447 ^c
NSAIDS	0 (0)	7 (2.3)	>0.999 ^c
Days of remdesivir treatment (median [IQR])	5 (4–5)	5 (5–5)	0.002^a
Safety outcomes			
AKI using EOT SCr			0.283 ^c
Total no.	40	303	
No. (%)	2 (5)	7 (2.3)	
AKI using peak SCr (no. [%])	2 (5)	11 (3.6)	0.652 ^c
AKI 48 h posttreatment			0.212 ^c
Total no.	21	173	
No. (%)	3 (14.3)	12 (6.9)	
ALT > 5 × ULN on last day of remdesivir			0.145 ^c
Total no.	38	294	
No. (%)	0 (0)	19 (6.5)	
Remdesivir discontinued early due to abnormal LFTs (no. [%])	0 (0)	12 (3.9)	0.374 ^c
30-day mortality			<0.001 ^b
Total no.	34	232	
No. (%)	19 (55.9)	38 (16.4)	

^aMann-Whitney U test.^bChi-square test.^cFisher's exact test.^dC-G, Cockcroft-Gault equation; MDRD, modification of diet in renal disease; TMP-SMX, trimethoprim-sulfamethoxazole; ACE/ARB, angiotensin-converting enzyme/angiotensin receptor blocker; NSAIDS, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine; LFTs, liver function tests.^eBolded values are *P* < 0.05.

reassuring that the majority of studies evaluating i.v. voriconazole in patients with underlying renal disease have found no risk of nephrotoxicity (20, 21).

The only study which identified possible nephrotoxicity associated with i.v. voriconazole used a cumulative dose of ≥400 mg/kg (22). Achieving this cumulative dose would require at least 50 days of voriconazole therapy assuming a standard maintenance dose of 4 mg/kg every 12 h. Only two patients in our cohort received 10 days of remdesivir therapy, and we

TABLE 2 Subgroup analysis of patients without AKI on the day of remdesivir administration

Characteristic ^d	Patients with an eCrCl of:		P value ^e
	<30 ml/min (n = 24)	≥30 ml/min (n = 299)	
AKI using EOT SCr			0.425 ^c
Total no.	24	295	
No. (%)	1 (4.2)	6 (2)	
AKI using peak SCr			0.578 ^c
Total no.	24	299	
No. (%)	1 (4.2)	10 (3.3)	
ALT > 5 × ULN on last day of remdesivir			0.378 ^d
Total no.	24	286	
No. (%)	0 (0)	18 (6.3)	
Remdesivir discontinued early due to abnormal LFTs (no. [%])	0 (0)	12 (4)	>0.999 ^c
30-day mortality			<0.001^b
Total no.	20	224	
No. (%)	11 (55)	37 (16.5)	

^aMann-Whitney U test.^bChi-square test.^cFisher's exact test.^dSCr, serum creatinine; LFTs, liver function tests.^eBolded values are $P < 0.05$.

suspect the majority of patients would routinely receive a 5-day course in light of a randomized controlled trial which failed to show a significant benefit between a 5-day course versus a 10-day course of remdesivir in patients with severe SARS-CoV-2 (14).

However, the potential from renal toxicity from the accumulation of remdesivir's active metabolites remains to be fully elucidated. An anecdotal report of a double lung transplant patient with normal renal function at baseline who received remdesivir for the treatment of SARS-CoV-2 experienced renal failure 3 days after the drug was initiated (18). The patient demonstrated elevated serum levels of GS-441524 despite undetectable remdesivir concentrations while in renal failure, which suggests that while remdesivir itself may not be nephrotoxic, GS-441524 accumulation may be responsible for renal injury. Ultimately, the patient's clinicians deemed the cause of acute kidney injury to be multifactorial (13).

Studies in mice have demonstrated that GS-441524 does not cause nephrotoxicity, but GS-704277, a transient prodrug of remdesivir prior to further hydrolysis to GS-441524, does. On the other hand, the mechanism of renal toxicity of GS-704277 in mice is mediated through organic ion transporters (OAT), and active transport of GS-704277 has never been detected in humans (13).

Although this study did not identify a significantly increased risk of AKI or LFT abnormalities in patients who received remdesivir with an eCrCl of <30 ml/min, there was a significantly higher mortality rate in this population. We suspect that the higher mortality rate in patients with an eCrCl of <30 ml/min is attributable to the older age, more comorbidities, more frequent use of vasopressors or inotropes, and more frequent use of mechanical ventilation. However, it is noteworthy that a cohort of over 17 million patients has identified renal disease to be a predictor of SARS-CoV-2-related mortality (23). It should also be recognized that over one-fourth of patients with an eCrCl of <30 ml/min required mechanical ventilation, and to date, there is no evidence of efficacy of remdesivir for SARS-CoV-2 in this patient population. Although the aim of our report was not to assess the efficacy of remdesivir, it is noteworthy that in a randomized controlled trial of hospitalized patients due to SARS-CoV-2, the administration of remdesivir failed to impact the time to recover compared to placebo in a subset of 285 patients receiving mechanical ventilation or extracorporeal membrane oxygenation (3). The overall efficacy of the drug continues to undergo scrutiny, given the unpublished interim results of the SOLIDARITY trial suggest

TABLE 3 Matched bivariate analysis

Characteristic ^d	Patients with an eCrCL of:		P value ^e
	<30 ml/min (n = 40)	≥30 ml/min (n = 40)	
Baseline demographics and treatment information			
Age (median [IQR] [yrs])	80 (63.8–89)	84 (70.8–87.5)	0.554 ^a
Female gender (no. [%])	23 (57.5)	18 (45)	0.263 ^b
Body mass index of >30 kg/m ² (no. [%])	14 (35)	16 (40)	0.644 ^b
Cirrhosis (no. [%])	2 (5)	0 (0)	0.494 ^c
Diabetes mellitus (no. [%])	24 (60)	12 (30)	0.007^b
Heart failure (no. [%])	18 (45)	6 (15)	0.003^b
Hypertension (no. [%])	34 (85)	29 (72.5)	0.172 ^c
Renal transplant (no. [%])	1 (2.5)	0 (0)	>0.999 ^c
Baseline SCr (median [IQR] [mg/dl])	1.2 (1–2.1)	0.85 (0.7–1)	<0.001^a
SCr (mg/dl) on the day of remdesivir administration (median [IQR])	2.8 (1.6–4.2)	0.9 (0.8–1.3)	<0.001^a
CrCl (ml/min) on the day of remdesivir administration by C-G (median [IQR])	20.3 (15.3–26.3)	51.3 (38.3–66.6)	<0.001^a
eGFR (ml/min/1.73 m ²) on the day of remdesivir administration by MDRD (median [IQR])	21 (15.2–34.1)	73.6 (53.8–93.9)	<0.001^a
ALT > 5 × ULN on the first day of remdesivir administration			0.494 ^c
Total no.	40	39	
No. (%)	2 (5)	0 (0)	
In AKI on the day of remdesivir administration (no. [%])	16 (40)	6 (15)	0.012^b
Vasopressor or inotrope use during remdesivir (no. [%])	12 (30)	8 (20)	0.302 ^a
Mechanical ventilation during remdesivir (no. [%])	11 (27.5)	8 (20)	0.431 ^b
Concomitant nephrotoxic drug (no. [%])			
Vancomycin	5 (12.5)	9 (22.5)	0.239 ^c
Aminoglycoside	1 (2.5)	0 (0)	>0.999 ^c
i.v. acyclovir	1 (2.5)	0 (0)	>0.999 ^c
TMP-SMX	0 (0)	0 (0)	>0.999 ^c
Amphotericin B	0 (0)	0 (0)	>0.999 ^c
ACE/ARB	8 (20)	8 (20)	>0.999 ^c
Loop/thiazide diuretics	24 (60)	15 (37.5)	0.04^b
Tacrolimus/cyclosporine	1 (2.5)	0 (0)	>0.999 ^c
i.v. contrast	3 (7.5)	7 (17.5)	0.311 ^c
NSAIDS	0 (0)	1 (2.5)	>0.999 ^c
Days of remdesivir treatment (median [IQR])	5 (4–5)	5 (4–5)	0.782 ^a
Safety outcomes			
AKI using EOT SCr (no. [%])	2 (5)	1 (2.5)	>0.999 ^c
AKI using peak SCr (no. [%])	2 (5)	1 (2.5)	>0.999 ^c
ALT > 5 × ULN on last day of remdesivir			0.49 ^c
Total no.	38	38	
No. (%)	0 (0)	2 (5.3)	
Remdesivir discontinued early due to abnormal LFTs (no. [%])	0 (0)	2 (5)	0.494 ^c
30-day mortality			0.029^b
Total no.	34	31	
No. (%)	19 (55.9)	9 (29)	

^aMann-Whitney U test.^bChi-square test.^cFisher's exact test.^dC-G, Cockcroft-Gault equation; MDRD, modification of diet in renal disease; TMP-SMX, trimethoprim-sulfamethoxazole; ACE/ARB, angiotensin-converting enzyme/angiotensin receptor blocker; NSAIDS, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine; LFTs, liver function tests.^eBolded values are $P < 0.05$.

remdesivir does not prevent mortality or initiation of ventilation or reduce the duration of hospital stay in patients with SARS-CoV-2 (24).

The strengths of this study include its multicenter, real-world use, and its novelty. Within our health system, we have encountered clinicians who have not administered remdesivir for patients with symptomatic SARS-CoV-2 due to the risk of both SBEDD and GS-441524 accumulation, which emphasizes the need for the presented data. However, several limitations also exist with this study. First, given the observational nature of the study, there are baseline confounders despite an attempt to balance groups through nearest neighbor matching, which may have been attributable to the small sample size of these variables in the full cohort. However, nearly all of these baseline confounders were captured to evaluate the risk of AKI, and, while these risk factors

were significantly more common in patients with an eCrCl of <30 ml/min, there was no significant association with endpoints evaluating renal toxicity. Second, this analysis is limited by the small number of patients with an eCrCl of <30 ml/min. Despite the fact that this was a multicenter study in five institutions, we were only able to include 40 patients with an eCrCl of <30 ml/min. Therefore, evaluation of remdesivir in a larger cohort of patients with renal disease may be difficult given many clinicians may be hesitant to administer the drug in this population. Nevertheless, further safety evaluation of remdesivir in patients with an eCrCl of <30 ml/min is warranted. Third, it is noteworthy that all patients in this study received remdesivir as a lyophilized powder, which contains less SBECD than remdesivir as an injectable solution (3 g versus 6 g); therefore, caution is warranted when extrapolating the results from the study (2). Finally, therapeutic drug monitoring of neither remdesivir, GS-441524, GS-704277, nor SBECD was performed given that these assays are not commercially available. While it is noteworthy that plasma concentrations of GS-441524 can be elevated in patients with acute kidney injury, our data would argue against any nephrotoxic consequences or LFT abnormalities from this metabolite (6).

In conclusion, remdesivir administration was not significantly associated with increased EOT AKI in patients with an eCrCl of <30 ml/min compared to patients with an eCrCl of ≥ 30 ml/min. Based on our findings, remdesivir could be considered therapy for severe infections due to SARS-CoV-2 in this patient population. However, further study is warranted.

MATERIALS AND METHODS

This study was a multicenter, retrospective chart review of adult patients with SARS-CoV-2 admitted to one of five hospitals within the Yale New Haven Health System who received remdesivir lyophilized powder between 11 May 2020 and 18 October 2020. This study was deemed exempt by the institutional review board given that criteria were met as a quality improvement study. Patients were excluded if they were on renal replacement therapy prior to remdesivir administration. Patients who met inclusion criteria had an eCrCl that was calculated using the Cockcroft-Gault formula at the time of remdesivir administration given the prescribing guidance under the FDA's Emergency Use Authorization (25). Baseline serum creatinine (SCr) was defined using the most recent SCr available prior to hospitalization prior to SARS-CoV-2. Patients with an SCr on the day of remdesivir administration that was 1.5 times the baseline SCr were considered to be in AKI at the time of remdesivir administration (26).

Safety outcomes were compared between patients with an eCrCl of <30 ml/min and an eCrCl of ≥ 30 ml/min on the day of remdesivir administration. The primary endpoint was AKI at the EOT, defined as an SCr on the final day of remdesivir administration greater than 1.5 times the SCr used on the first day of remdesivir. Secondary endpoints included AKI defined by peak SCr during remdesivir therapy, AKI 48 hours after completion of remdesivir, discontinuation of remdesivir due to abnormal LFTs, ALT of ≥ 5 times the ULN on the last day of remdesivir, and all-cause 30-day mortality. ALT normal values were in concordance with recommendations from the American College of Gastroenterology (27). Patients with an ALT of ≥ 5 times the ULN on the first day of remdesivir administration or who did not have an ALT obtained on the last day of remdesivir administration were excluded from the secondary endpoint evaluating the frequency of ALT of ≥ 5 times the ULN on the last day of remdesivir. Patients without an available outcome at 30 days were excluded from the secondary endpoint evaluating 30-day mortality. A subset analysis was performed for patients without AKI at the time of remdesivir initiation.

Categorical variables were compared by a chi-square test or Fisher's exact test. Fisher's exact test was performed on samples with an expected frequency of less than or equal to 5, while the chi-square test was performed on samples with an expected frequency of greater than 5. Continuous variables were compared using a Mann-Whitney U test. Categorical and continuous variables were deemed statistically significant if they possessed a *P* value of <0.05 . Matching was performed using a 1:1 nearest neighbor method by the following factors: age, mechanical ventilation during remdesivir, vasopressor or inotrope use during remdesivir, days of remdesivir treatment, AKI on the day of remdesivir treatment, diabetes mellitus, and heart failure. Statistical analyses were performed with the software R with the installed Commander and Matchit packages (28).

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This study was carried out as part of our routine work.
We have no conflicts of interest to declare.

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