RESEARCH LETTER

Remdesivir and Kidney and Cardiovascular Outcomes in COVID-19 Patients With Reduced GFR

To the Editor:

Acute and chronic kidney disease are important risk factors for hospitalization and death from coronavirus disease 2019 (COVID-19).[1] In addition to acute complications of COVID-19, survivors may experience a wide range of persistent symptoms, collectively referred to as "long COVID," and are at an increased risk of cardiovascular and kidney post-acute sequelae, including myocardial infarction, heart failure, thromboembolic disease, and kidney failure.[2,3] It is important to understand whether treatments approved to treat COVID-19 can mitigate the morbidity and mortality of long COVID in high-risk populations.

Remdesivir was the first antiviral therapy approved for treatment of COVID-19. A recent meta-analysis of randomized clinical trial data showed that remdesivir reduced mortality in patients hospitalized with COVID-19 who did not require mechanical ventilation (adjusted odds ratio, 0.80; 95% confidence interval, 0.70-0.93).[4] Patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 were excluded from the initial registrational trials of remdesivir; however, the US Food and Drug Administration label was expanded to include all levels of kidney function in July 2023. To determine if the use of remdesivir is associated with differences in long-term cardiovascular and kidney outcomes among patients with reduced eGFR, we designed a propensity score-matched study to compare the risk of major adverse cardiovascular events (MACEs) or major adverse kidney disease and decline in eGFR among hospitalized patients who received remdesivir versus historical comparators with COVID-19 (Item S1).

There were 200 individuals with admission eGFR <60 mL/min/1.73 m^2 or kidney failure receiving kidney replacement therapy who received remdesivir within 72 hours of admission and 555 potential historical comparators who met inclusion criteria (Fig 1). A sufficiently close match was found for 198 of the 200 (99%) remdesivir-treated patients, who were variably matched to 335 historical comparators. Among the matched cohorts, 162 (81.8%) remdesivir-treated and 250 (74.6%) historical comparators survived >30 days; pairs with both a matched remdesivir-treated patient and at least one historical comparator who survived >30 days (148 remdesivir-treated patients and 209 historical controls) were considered the primary cohort for analysis (Table S1). The mean age was 71 years (SD 13); 56.6% were men; and 53.2% were White non-Hispanic, 17.6% were Black, 16.8% were Hispanic, and 12.3% were Asian. Comorbid conditions were common; 215 (60.2%) patients had diabetes, 289 (80.9%) had hypertension, and 236 (66.1%) had coronary artery disease. The rate of MACEs between 30 days and 18 months was high (2.54 events per 100 patient-months), whereas major adverse kidney disease occurred less commonly (0.74 events per 100 patient-months). There was no significant difference in MACEs or major adverse kidney disease between remdesivir-treated patients and historical comparators followed for 18 months (Fig S1, Table S2). However, remdesivir use was associated with a significant attenuation of eGFR decline between 30 days and 18 months among survivors without kidney failure at baseline (−2.11 mL/min/year [95% confidence interval, −4.12

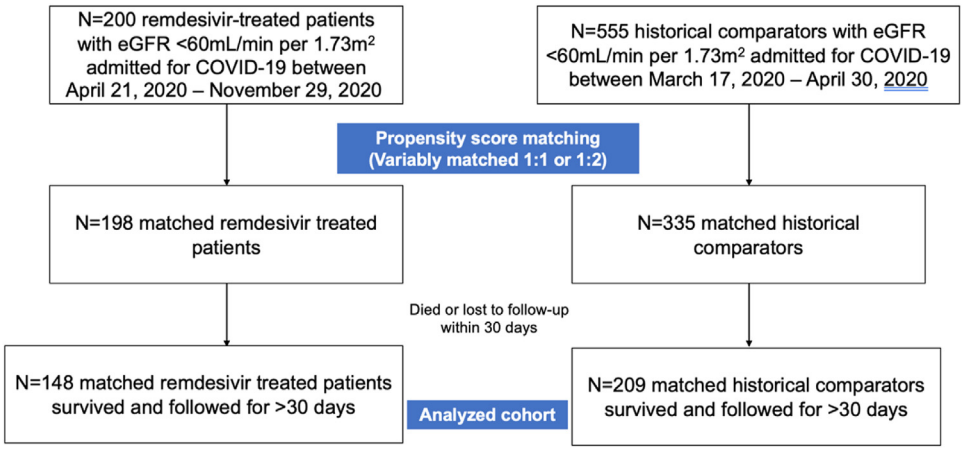

Figure 1. We matched patients across independent variables associated with remdesivir administration, including age, sex, race, sequential organ failure assessment score at admission, mechanical ventilation within 72 hours, presenting creatinine, history of diabetes, hypertension, cardiovascular disease, congestive heart failure, kidney failure status, prior solid organ transplantation, number of hospitalizations, and total encounters within 1 year before admission. We performed nearest-neighbor matching without replacement with a caliper of 0.1 standard deviation of the propensity score. COVID-19, coronavirus 2019; eGFR, estimated glomerular filtration rate.

Table 1. Slope of eGFR Decline From 30 Days to 18 Months

	Unadjusted eGFR Slope (95% CI) (mL/min/1.73 m^2 per Year Decline)	P[a]	Adjusted eGFR Slope (95% CI) (mL/min/1.73 m^2 per Year Decline)	P[a]
Paired patients without kidney failure who survived ≥30 d (n = 336)				
Comparators	−6.52 (−8.05 to −5.00)		−6.45 (−7.97 to −4.93)	
Remdesivir	−2.10 (−4.12 to −0.08)	<0.001	−2.11 (−4.12 to −0.10)	<0.001
All patients without kidney failure who survived ≥30 d (n = 384)				
Comparators	−6.07 (−7.42 to −4.73)		−6.02 (−7.36 to −4.68)	
Remdesivir	−3.60 (−5.39 to −1.82)	0.03	−3.63 (−5.41 to −1.86)	0.04

Note: The analysis of eGFR slope includes the 336 patients without baseline kidney failure in which at least one matched paired patient survived >30 days. The median and interquartile range (IQR) of number of eGFR per person in follow-up is 7 (IQR, 3-19), the median time between eGFR measurements is 38 (IQR, 16-121) days. Sensitivity analysis of all the 384 patients who did not have kidney failure at baseline and survived >30 days revealed similar findings**.** The multivariable linear mixed-effects models are adjusted for age, sex, Black race, diabetes, hypertension, coronary artery disease, congestive heart failure, solid organ transplant, requiring mechanical ventilation within 72 hours, SOFA score, admission serum creatinine, and frequency of overall and inpatient encounters in the year before admission for COVID-19.

Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval; COVID-19, coronavirus disease 2019; SOFA, sequential organ failure assessment.

[a]Comparing eGFR slopes between remdesivir-treated patients and historical comparators.

to −0.10] versus −6.45 mL/min/year decline [95% confidence interval, −7.97 to −4.93] in historical comparators) (Table 1). Sensitivity analysis using all surviving patients demonstrated similar attenuation of eGFR decline in remdesivir-treated patients compared with historical comparators.

Our study is in line with prior studies showing that the rate of MACEs is high in patients with COVID-19. Bowe et al[5] found that compared with control groups without COVID-19, patients who survived COVID-19 exhibited an increased burden of cardiovascular conditions and that repeat episodes of COVID-19 contributed to the burden of long COVID.[2] Additionally, adverse kidney outcomes were more common in patients with COVID-19; 30-day survivors of COVID-19 exhibited higher risk of acute kidney injury, 50% eGFR decline, and kidney failure.[3] Furthermore, COVID-19 can trigger collapsing glomerulopathy in patients with high-risk *APOL1* genotype and has poor long-term outcomes.[6] Understanding whether treatments for COVID-19 reduce long COVID-19 is an important unmet need.

Our study has limitations. First, we chose historical comparators from the first wave of COVID-19 before the emergency use authorization of remdesivir to avoid confounding by indication and minimize selection bias. We performed detailed chart review to ensure accurate information on disease severity and other baseline covariates and achieved good balance between the remdesivir-treated patients and matched untreated comparators after propensity score matching. Given the study period (March-November 2020), treated and untreated patients were exposed to the same variant (wild type), the vast majority were first infections, and all patients were unvaccinated. However, standard of care differed throughout the study period; all historical comparators were admitted before routine use of dexamethasone at our center, which may have affected the long-term outcomes.[7] Second, patients may have been hospitalized outside our health care network and not captured in "Care Everywhere" documentation. To minimize the risk of bias, we matched patients based on the number of inpatient and total encounters in our health care network in the 1 year before COVID-19. Finally, our study evaluated patients who received remdesivir at the time of hospital admission; deploying antiviral strategies earlier in the disease course may more effectively reduce the high rates of MACEs. Future studies are needed to test whether early antiviral therapies can more effectively decrease the risk of long COVID.

In conclusion, use of remdesivir in hospitalized patients with COVID-19 and reduced eGFR was not associated with a decreased risk of MACEs or major adverse kidney disease but was associated with a less steep slope of eGFR decline among survivors followed up to 18 months.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Supplementary Methods

Figure S1: Association between remdesivir use and MACE and MAKE between 30 days and 18 months after hospitalization for COVID-19.

Table S1: Patient Characteristics Pre- and Post-propensity Score Matching.

Table S2: Association Between Remdesivir Use and Adverse Cardiovascular and Kidney Outcomes at Multiple Timepoints.

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Authors' Contributions: Research idea and study design: MES; data acquisition: JED, QW, DC, RS, JCL, IS, MES; data analysis/interpretation: JED, QW, SZ, MES; supervision: MES. Each author contributed important intellectual content during manuscript drafting and revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This work was funded through an investigator-initiated grant to Dr Sise from Gilead.

Financial Disclosure: Dr Sise has received research funding from Gilead, Novartis, Cabaletta, Merck, Abbvie, Angion, Otsuka, and EMD-Serono. Dr Sise has served as a paid consultant for scientific advisory boards for Travere, Calliditas, Novartis, Mallinckrodt, and Vera and as a paid Data Monitoring Committee member for Alpine Immunosciences.

Prior Presentation: A subset of patients included in this analysis of long-term outcomes have been previously reported in published reports describing short-term kidney outcomes (PMID 36848366, 35373125).

Peer Review: Received September 15, 2023. Evaluated by 1 external peer reviewer, with direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form January 26, 2024.

 Published online May 3, 2024 with doi 10.1016/j.xkme.2024.100835

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