Patients with chronic kidney disease (CKD), especially those with end-stage renal disease (ESRD), are susceptible to the development of severe coronavirus disease 2019 (COVID-19), which is associated with high mortality. Apart from respiratory support depending upon the severity of the respiratory involvement, management of COVID-19 is largely supportive. Remdesivir is a nucleotide analog that inhibits viral RNA-dependent RNA polymerase (RdRp) and that was issued an emergency use authorization by the U.S. Food and Drug Administration in May 2020. The active metabolite of remdesivir is eliminated by the kidneys and can accumulate in patients with reduced estimated glomerular filtration rate (eGFR); moreover, the sulfobutylether-β-cyclodextrin (SBECD) carrier is known to accumulate in these patients. The largest clinical trial evaluating the use of this agent in COVID-19 excluded patients with stage 4 CKD or those requiring dialysis (i.e., eGFR <30 ml/min/1.73 m²). We aimed to report our single-center experience using remdesivir in patients with COVID-19 who had acute kidney injury (AKI) and CKD.

RESULTS

One hundred fifty-seven patients with COVID-19 who were admitted to the intensive care unit or our nephrology high dependency unit between July 7 and September 22, 2020 had either AKI or CKD. Forty-six of 157 (29.3%) cases were treated with remdesivir. The median age of these patients was 53.1 years (range 15–84 years) and 30 (65.2%) were male. Renal diagnoses were ESRD in 16 (34.7%) and AKI in 30 (65.2%) patients. Eight (17.4%) of 46 patients were recipients of live donor kidney transplants. Of 30 patients with AKI, 3 (6.5%), 2 (4.3%), and 25 (83.3%) patients had Kidney Disease: Improving Global Outcomes AKI stages 1, 2, and 3, respectively. Notably, all patients with stage 1 and 2 AKI were kidney transplant recipients. Table 1 shows the baseline characteristics of these cases. Comorbidities included hypertension in 35 (76%) patients, diabetes in 26 (56.5%) patients, coronary artery disease in 4 (8.7%) patients, nephrolithiasis in 3 (6.5%) patients, and HIV in 1 (2.2%) patient. Twelve (26%) patients were treated in the intensive care unit. At the time of initiation of remdesivir, oxygen requirements were as follows: noninvasive ventilation (n = 7), high flow nasal canula (n = 1), nonrebreathing mask (n = 11), face mask (n = 15), and nasal prongs (n = 12). Further in the course of illness, 9 (19.5%) patients required invasive mechanical ventilation.

Remdesivir (COVIFOR, Hetero Labs Limited [Hyderabad, India], under license from Gilead Sciences, Inc [Foster City, CA]) was administered as a total dose of 600 mg (200 mg on day 1, followed by 100 mg/day), which was extended in 2 patients to 1200 mg because satisfactory clinical improvement was not observed. The median number of days from hospital admission to starting remdesivir was 5 days (range 1–26 days).
Table 1. Baseline characteristics and patient response to remdesivir therapy

| Case no. | Age/sex | Kidney disease (if AKI- KDIGO staging) | Co-morbidities | Duration of symptoms before remdesivir, days | O2 need before starting remdesivir | Before starting remdesivir | Peak (if present)/within 48 hrs of cessation of therapy | Serum AST/ALT, IU/L | Dose of remdesivir, mg | Patient outcome if still admitted (WHO ordinal score change) |
|----------|---------|----------------------------------------|----------------|---------------------------------------------|-----------------------------------|---------------------------|------------------------------------------------|------------------|-----------------------|-------------------------------------------------------------|
| 1        | 56/M    | ESRD                                   | HTN, DM        | 11                                          | NRBM, 6 L/min                     | 118/81                    | 26/25 (improved)                                      |                   | 600                   | Died                                                        |
| 2        | 65/M    | ESRD                                   | HTN, DM        | 1                                           | HFNC                            | 24/14                     | 20/10                                           |                   | 600                   | Died                                                        |
| 3        | 62/F    | AKI 3                                  | HTN, DM, CKD, nephrolithiasis | 3                                          | NIV                             | 13/16                     | Death                                             |                   | 500                   | Died                                                        |
| 4        | 42/M    | AKI 3                                  | HTN, CKD       | 10                                          | NRBM, 6 L/min                     | 39/14                     | Day 5: 57/33, day 9: 19/21 (grade 1 AST elevation) |                   | 600                   | Discharged                                                  |
| 5        | 55/M    | ESRD                                   | HTN            | 4                                           | FM, 4 L/min                      | 20/20                     | 23/16                                           |                   | 1200                  | Discharged                                                  |
| 6        | 50/F    | AKI 3                                  | HTN, DM        | 4                                           | FM, 8 L/min                      | 133/101                   | 14/30 (improved)                                    |                   | 600                   | Discharged                                                  |
| 7        | 68/M    | AKI 3                                  | HTN, DM, CAD, CKD | 2                                          | NRBM, 6 L/min                     | 76/56                     | 43/36 (improved)                                    |                   | 500                   | Died                                                        |
| 8        | 50/F    | AKI 3                                  | HTN, DM, CKD   | 2                                           | FM, 10 L/min                     | 41/27                     | 36/23                                           |                   | 200                   | Died                                                        |
| 9        | 50/M    | ESRD                                   | DM             | 3                                           | NRBM, 8 L/min                     | 69/67                     | 41/62 (persistent grade 1 ALT elevation)            |                   | 400                   | Died                                                        |
| 10       | 52/M    | AKI 3                                  | None           | 7                                           | NIV                             | 101/66                    | 25/31 (improved)                                    |                   | 300                   | Died                                                        |
| 11       | 27/M    | AKI 3                                  | KTR, HTN, Beta thalassemia trait | 12                                          | NP, 4 L/min                      | 40/27                     | Day 5: 39/57, day 9: 15/30 (grade 1 ALT elevation, improved at day 9) |                   | 600                   | Discharged                                                  |
| 12       | 38/M    | AKI 3                                  | None           | 4                                           | NIV                             | 35/41                     | 20/9                                            |                   | 600                   | Discharged                                                  |
| 13       | 49/M    | ESRD                                   | HTN, DM, CAD   | 5                                           | FM, 4 L/min                      | 33/22                     | 30/20                                           |                   | 600                   | Discharged                                                  |
| 14       | 44/F    | AKI 3                                  | HTN, CKD       | 8                                           | NRBM, 6 L/min                     | 28/14                     | 27/11                                           |                   | 600                   | Discharged                                                  |
| 15       | 65/M    | AKI 3                                  | HTN, DM, CKD   | 10                                          | NRBM 12 L/min                    | 20/12                     | Day 3: 65/18 (grade 1 AST elevation), death        |                   | 600                   | Died                                                        |
| 16       | 50/M    | AKI 3                                  | KTR, DM        | 7                                           | NP, 4 L/min                      | 20/11                     | 32/8                                            |                   | 600                   | Discharged                                                  |
| 17       | 75/F    | ESRD                                   | HTN, DM        | 10                                          | NP, 6 L/min                      | 21/9                      | 27/9                                            |                   | 600                   | Admitted (4 to 3)                                           |
| 18       | 50/F    | AKI 2                                  | KTR, beta thalassemia trait | 10                                          | NP, 2 L/min                      | 21/9                      | 48/39                                           |                   | 600                   | Discharged                                                  |
| 19       | 39/M    | AKI 3                                  | KTR, HTN, DM   | 8                                           | NP, 2 L/min                      | 24/9                      | 20/11                                           |                   | 600                   | Discharged                                                  |
| 20       | 43/F    | AKI 3                                  | HTN, CKD       | 7                                           | NP, 4 L/min                      | 16/11                     | 20/13                                           |                   | 600                   | Discharged                                                  |
| 21       | 52/F    | ESRD                                   | HIV, PTB       | 4                                           | FM, 4 L/min                      | 116/77                    | 44/39 (improved)                                    |                   | 600                   | Discharged                                                  |
| 22       | 48/F    | AKI 1                                  | KTR            | 3                                           | NRBM, 8 L/min                     | 23/13                     | 34/17                                           |                   | 1100                  | Discharged                                                  |
| 23       | 60/M    | AKI 3                                  | HTN, DM, CKD   | 8                                           | NIV                             | 34/23                     | 44/20                                           |                   | 600                   | Died                                                        |
| 24       | 15/F    | AKI 3                                  | OKD            | 15                                          | NRBM, 8 L/min                     | 164/219                   | 49/113 (improved)                                   |                   | 500                   | Discharged                                                  |
| 25       | 38/F    | ESRD                                   | HTN, CKD, PTB  | 2                                           | FM, 4 L/min                      | 105/27                    | 59/19 (improved)                                    |                   | 600                   | Discharged                                                  |
| 26       | 46/F    | AKI 1                                  | KTR, HTN, DM   | 8                                           | NP, 2 L/min                      | 27/33                     | 24/16                                           |                   | 600                   | Discharged                                                  |
| 27       | 84/M    | AKI 3                                  | HTN, DM, CKD   | 15                                          | NP, 4 L/min                      | 22/31                     | 25/28                                           |                   | 600                   | Discharged                                                  |
| 28       | 53/M    | ESRD                                   | HTN, DM        | 1                                           | NIV                             | 56/62                     | 22/15 (improved)                                    |                   | 600                   | Discharged                                                  |
| 29       | 68/M    | ESRD                                   | HTN, DM, CAD   | 7                                           | NP, 4 L/min                      | 22/10                     | 23/18                                           |                   | 600                   | Discharged                                                  |
| 30       | 36/F    | AKI 3                                  | HTN, CKD, PTB  | 6                                           | FM, 6 L/min                      | 36/17                     | 19/8                                            |                   | 600                   | Discharged                                                  |
| 31       | 48/M    | ESRD                                   | HTN, CAD       | 4                                           | NRBM 8 L/min                     | 96/40                     | 37/25 (improved)                                    |                   | 600                   | Died                                                        |
| 32       | 58/M    | AKI 2                                  | HTN, DM, KTR   | 4                                           | FM, 4 L/min                      | 49/22                     | 25/24                                           |                   | 600                   | Discharged                                                  |
| 33       | 50/M    | AKI 3                                  | HTN, DM, PTB   | 4                                           | FM, 6 L/min                      | 27/25                     | 19/18                                           |                   | 600                   | Died                                                        |

(Continued on following page)
median duration of follow-up was 15.5 days (range 6–81 days). Thirty-six (78.2%) patients were on dialysis (ESRD \( n = 16 \) and AKI \( n = 20 \)) at the time of initiation of therapy. Therapy could not be completed in 6 patients who died. Remdesivir was discontinued early because of clinical improvement in 2 patients, and therapy is ongoing in 2 patients.

Most patients tolerated the infusion well except for patient 43 who had an infusion reaction with hypertension, breathlessness, and a drop in oxygen saturation, and the patient responded immediately to steroids and antihistamine treatment. Transient behavioral changes were noted in 5 cases and acute gout was observed in 1 patient while they were undergoing therapy (World Health Organization–Uppsala Monitoring Center causality category: possible) (Supplementary Methods). Baseline liver function test abnormalities (elevated aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels) were noted in 14 (30.4%) cases before starting remdesivir—grade 1 elevation in 13 patients (AST in 4, ALT in 1, and both AST and ALT in 8) and grade 2 elevation in 1 patient, which improved by the end of therapy in 12 cases. Liver function remained stable in 28 (60.9%) cases. Three (6.5%) patients were found to have newly occurring grade 1 elevations of AST/ALT during therapy. No patient had a severe rise in AST/ALT >5 times the upper limit of normal, therefore therapy was not required to be discontinued for this reason in any of the patients. No renal function abnormalities attributable to drug were observed (Table 2). Fourteen (30.4%) patients died, 24 (52.2%) patients were discharged from the hospital after recovery, and 8 (17.3%) cases are still admitted, of which 2 are still undergoing treatment.

**DISCUSSION**

We observed no clinically significant ALT elevations and no patients needed early discontinuation of therapy because of side effects. Twenty-four treated patients were discharged from the hospital. No significant abnormalities of renal function attributable to the drug were noted in any of the patients.

Apart from dexamethasone, remdesivir is the only other pharmaceutical agent approved for use in COVID-19. Trials evaluating this agent have excluded patients with impaired kidney function, so there are no data on its efficacy and safety in renal failure. The national clinical management protocol\(^4\) states that the use of remdesivir is contraindicated in patients with eGFR <30 ml/min/1.73 m\(^2\) or when there is a need for hemodialysis. A policy of withholding its use in patients with kidney diseases because of lack of safety data can deprive these patients of one of the only
available therapeutic options. Although remdesivir has not been shown to reduce mortality, its use decreased the time to recovery in patients with moderate and severe COVID-19. It has been suggested that remdesivir can be used with close monitoring in patients with renal impairment.\(^5\)

Unmodified alpha- and beta-cyclodextrins are typically reabsorbed and concentrated in renal tubules and interact with cellular structures affecting cell integrity. SBECED was designed to address this problem; it remains in an ionized state after glomerular filtration and does not undergo significant tubular reabsorption. Although SBECED accumulates in patients with decreased eGFR, elevation in the serum creatinine did not correlate with SBECED levels.\(^6\) Moreover, SBECED carrier is effectively removed by dialysis; a 4-hour session removes almost half of the accumulated SBECED.\(^7\)

This is the first report of the use of remdesivir in patients with severely reduced kidney function, and our findings suggest that it is tolerated well. Mild derangement in the liver function tests at baseline improved post-treatment. Although it is not possible to attribute such improvement to drug use, it suggests that mild elevations in transaminases should not be considered as a contraindication.

Our study has several limitations. Most of our patients were on hemodialysis, so we cannot comment on its safety in patients with severe renal impairment but not yet on dialysis. We did not measure serum concentration of the SBECD, so the extent of its accumulation in our patients is not known. However, accumulation of SBECD does not correlate with rise in creatinine. We used the aqueous formulation of remdesivir which has double (6 g vs. 3 g) the concentration of SBECD than powdered form, which can be preferentially used in patients with renal impairment. Although our patients tolerated the drug well, the safety and efficacy of remdesivir cannot be determined without control subjects.

In conclusion, remdesivir was well tolerated in patients with AKI and CKD including those on hemodialysis. Larger, well-controlled studies evaluating its safety and efficacy in patients with kidney diseases are needed.

DISCLOSURE
All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary Methods.

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Table 2. Renal function during remdesivir therapy in patients with AKI

| Case | Serum creatinine at admission, mg/dl | Serum creatinine before initiation of remdesivir, mg/dl | Peak serum creatinine on remdesivir therapy, mg/dl | Serum creatinine at completion/within 48 hrs of therapy, mg/dl |
|------|-------------------------------------|------------------------------------------------------|-------------------------------------------------|----------------------------------------------------------|
| 3    | 6.6                                 | On dialysis                                          | On dialysis                                     | Death                                                   |
| 4    | 15.6                                | On dialysis                                          | On dialysis                                     | On dialysis                                             |
| 6    | 7.7                                 | On dialysis                                          | On dialysis                                     | On dialysis                                             |
| 7    | 8.0                                 | On dialysis                                          | On dialysis                                     | On dialysis                                             |
| 8    | 7.9                                 | On dialysis                                          | Death                                           | Death                                                   |
| 10   | 6.1                                 | On dialysis                                          | Death                                           | Death                                                   |
| 11   | 3.5                                 | 4.5                                                  | 3.7                                             | 2                                                       |
| 12   | 7.3                                 | 2.9                                                  | 2.7                                             | 2.5                                                     |
| 14   | 5.5                                 | 4                                                    | 3.7                                             | 3.2                                                     |
| 15   | 8.2                                 | On dialysis                                          | On dialysis                                     | Death                                                   |
| 16   | 5.7                                 | 5.9                                                  | 5.5                                             | 4                                                       |
| 18   | 2.1                                 | 2.3                                                  | 2.1                                             | 1.7                                                     |
| 19   | 4.72                                | 6.0                                                  | 4                                               | 2.2                                                     |
| 20   | 7.0                                 | 3                                                    | On dialysis                                     | Death                                                   |
| 22   | 2.32                                | 1                                                    | 2.2                                             | 2.3                                                     |
| 23   | 11.8                                | On dialysis                                          | On dialysis                                     | Death                                                   |
| 24   | 6.7                                 | On dialysis                                          | On dialysis                                     | On dialysis                                             |
| 26   | 1.6                                 | 1.6                                                  | 1.6                                             | 1.4                                                     |
| 27   | 9.0                                 | On dialysis                                          | On dialysis                                     | On dialysis                                             |
| 30   | 8.7                                 | On dialysis                                          | On dialysis                                     | On dialysis                                             |
| 32   | 2.0                                 | 2.0                                                  | 1.7                                             | 1.4                                                     |
| 33   | 6.0                                 | 3                                                    | On dialysis                                     | On dialysis                                             |
| 34   | 9.8                                 | 3                                                    | On dialysis                                     | On dialysis                                             |
| 35   | 4.1                                 | 6.8\(^b\)                                            | 6.6                                             | 6.1                                                     |
| 38   | 11.0                                | 3                                                    | On dialysis                                     | On dialysis                                             |
| 39   | 9.6                                 | 3                                                    | On dialysis                                     | On dialysis                                             |
| 41   | 7.3                                 | 3                                                    | On dialysis                                     | On dialysis                                             |
| 42   | 1.4                                 | 1.79                                                 | 1.9                                             | 1.5                                                     |
| 44   | 4.7                                 | 3                                                    | On dialysis                                     | On dialysis                                             |
| 45   | 11.5                                | 3                                                    | On dialysis                                     | On dialysis                                             |

AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes. All patients with end-stage renal disease were receiving hemodialysis or slow, low efficacy dialysis as a modality of renal replacement.\(^a\)

*Serum creatinine values not available.

\(^b\)Patient 6 achieved dialysis independence 5 days after the completion of therapy (creatinine at discharge 2.5 mg/dl). Patient 35 received 2 sessions of dialysis before remdesivir therapy, after which creatinine showed a dropping trend.

\(^c\)Patient 15 received 1 session of hemodialysis followed by peritoneal dialysis for 28 hrs. All other patients requiring dialysis were undergoing hemodialysis.

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CKD of Unknown Origin in Supebeda, Chhattisgarh, India

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Chronic kidney disease (CKD) is predominantly caused by diabetes, hypertension, and glomerular diseases. Nephrotoxic drugs, herbal medications, toxins, and infection are other causes of CKD in developing countries.

A clustered increase in prevalence of CKD has been observed in select geographic areas in several countries over the past 2 decades.1 The etiology of CKD cannot be attributed to the known or traditional risk factors or causes, and the term chronic kidney disease of unknown etiology (CKDu) has been used to describe this entity.2 Young males belonging to agricultural communities comprise the most common affected demographic. In India, this condition has been described from coastal villages of Srikakulam district in Andhra Pradesh and parts of Odisha.3,5 A variety of hypotheses including prolonged dehydration leading to heat stress, heavy metal toxicity, pesticide exposure, snake bite and genetics have been proposed.1

Recent media reports have highlighted an unusually high number of the deaths due to kidney disease in the tribal village of Supebeda in the Indian state of Chhattisgarh (Supplementary Figure S1).4 Twelve patients from this village with kidney dysfunction were referred to 2 hospitals in Raipur between November 2019 and March 2020. In this report, we describe the clinical presentation of these patients and present results of select toxicological analyses (Supplementary Methods).

CASE SERIES

The 12 patients in this series (Table 1) came from 9 families (Figure 1), and 8 (66.7%) were males. The median age was 46 (interquartile range: 16.5) years. A majority presented with weakness, body aches, and decreased appetite. None gave a history of edema, hypertension, diabetes, snakebite, or acute kidney injury. All the patients were or had been farmworkers and regularly used pesticides and fertilizers without protective equipment. Six (50%) were regular consumers of locally brewed alcohol, and 7 (58.8%) were tobacco users. All had used herbal and ayurvedic medications. Most patients were poor and uneducated. The predominant cereal used by these patients was rice, and the primary source of drinking water was communal shallow wells and hand pumps. The blood pressure was <140/90 mm Hg in 11 (91.7%) patients.