

# Remdesivir, Renal Function and Short-Term Clinical Outcomes in Elderly COVID-19 Pneumonia Patients: A Single-Centre Study

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**Background:** Remdesivir, an antiviral agent able to reduce inflammatory cascade accompanying severe, life-threatening pneumonia, became the first drug approved by the Food and Drug Administration for the treatment of hospitalized patients with coronavirus 2 related severe acute respiratory syndrome (SARS CoV2). As from its previously known clinical indications, the use of remdesivir in the presence of severe renal impairment is contraindicated; however, the impact of remdesivir on renal function in aging patients has not been elucidated.

**Subjects and Methods:** This retrospective observational study involved 109 individuals consecutively admitted in internal medicine section, Azienda Ospedaliero Universitaria Pisana hospital, in November–December 2020 due to a confirmed diagnosis of SARS CoV2 and receiving remdesivir according to international inclusion criteria. Biochemical variables at admission were evaluated, together with slopes of estimated glomerular filtration rate (eGFR) built during remdesivir treatment. Participants were followed until discharge or exitus.

**Results:** Patients were stratified according to age (80 formed the study cohort and 29 served as controls); CKD stage III was present in 46% of them. No patients showed any sign of deteriorated renal function during remdesivir. Fourteen patients in the elderly cohort deceased; their eGFR at baseline was significantly lower. Recovered patients were characterized by a relevant eGFR gaining during remdesivir treatment.

**Conclusion:** We show here for the first time as remdesivir does not influence eGFR in a cohort of elderly people hospitalized for SARS CoV2, and that eGFR gain during such treatment is coupled with a better prognosis.

**Keywords:** remdesivir, SARS CoV2, glomerular filtration rate, aging, chronic kidney disease

## Introduction

Coronavirus Disease 2019 (COVID-19) is an ongoing global pandemic causing significant increases in morbidity and mortality, whose clinical impact is particularly severe for older individuals.<sup>1,2</sup> Approximately 25% of deaths due to COVID-19 have been registered in people over the age of seventy, whose frequent serious comorbidities act as relevant predisposing factors for a more severe COVID-19 clinical course and consequent death.<sup>3,4</sup> Such high mortality is prominently due to severe acute respiratory syndrome, able to quickly spread to vulnerable populations such as comorbid elderly individuals with aging-related disorders. The current

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ongoing pandemic of COVID-19, together with a huge effort to discover new drugs or vaccines able to stop the virus spreading, requires repurposing of existing drugs as safe and effective alternative potentially able to fight the disease. Among these, remdesivir, an ATP-analogue nucleotide with a broad-spectrum of antiviral activity against Ebola, Nipah, respiratory syncytial virus family and a diverse category of coronaviruses including severe acute respiratory syndrome coronavirus 2 (SARS CoV2),<sup>5–7</sup> is currently utilized. It should be able to inhibit the viral RNA synthesis by a specific mechanism of delayed chain termination; however, its use against COVID-19 has been, so far, characterized by alternate fortune.

The impact of antiviral therapies on the prognosis of SARS CoV2 patients is debated.<sup>8</sup> Mortality rate, clinical improvement, and discharge have been better among patients receiving remdesivir compared to placebo or standard of care;<sup>9</sup> however, a recent meta-analysis including five randomized clinical trials resulted in little to no reduction in mortality, and in a small reduction in the proportion of patients receiving mechanical ventilation, although a 5-day course seems to reduce mortality, need for ventilation, and serious adverse events, while increasing the percentage of patients who recovered or clinically improved.<sup>10</sup> Matter of fact, based on encouraging actions documented in *in vitro* settings and animal models,<sup>11–13</sup> along with the promising, although not univocal results of a few randomized clinical trials,<sup>14,15</sup> it has been authorized for the treatment of SARS CoV2 patients in several countries.<sup>16</sup> Among the limitations to its use, an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m<sup>2</sup> has been applied in the clinical practice, according to a 74% renal elimination of remdesivir and its active metabolite, and to the potential accumulation of its vector sulphobutylether- $\beta$ -cyclodextrin (SBE- $\beta$ -CD).<sup>17,18</sup> However, no information is so far available on the true impact of remdesivir on renal function in aging subjects; the widespread use of this antiviral treatment in the attempt to fight SARS CoV2 should be accompanied by further knowledge on its short-term impact on the kidney, and which could be, if any, the relationship between renal function and COVID-19-related clinical outcomes.

Aim of the present study was to evaluate the impact of remdesivir on renal function and clinical outcome in a cohort of elderly individuals hospitalized for SARS CoV2 and deserving treatment with remdesivir according

to the internationally standardized clinical indications for its use.

## Subjects and Methods

### Study Design

This single-centre, observational, retrospective study was performed in the sections of internal medicine of the University Hospital in Pisa, Italy during the second phase of the current pandemic; patients admitted between November 1st, 2020 and December 20th, 2020 and matching inclusion criteria were included in the analysis. Inclusion criteria were age >65 years, CT scan-confirmed diagnosis of interstitial pneumonia SARS CoV2 related, admission in intermediate intensity-care setting, eligible to treatment with remdesivir according to local infectious disease consortium and international guidelines (positive PCR testing on nasopharyngeal swab; symptom onset < 10 days; respiratory failure or need of O<sub>2</sub> supply and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (P/F) >200≤300 at blood gas analysis; eGFR >30 mL/min/1.73m<sup>2</sup>; serum liver enzymes <5-fold upper limit). In each subject, medical history, clinical characteristics, presence of chronic comorbidities and ongoing therapies were registered; biochemistry and arterial blood gas analysis at admission were performed on venous and arterial blood samples. In all patients some inflammatory parameters (fibrinogen, ferritin, C reactive protein (CRP)) were also monitored every two days, together with IL-6, measured by ELISA.

All patients received the same therapeutic protocol, regularly updated according to the scientific literature and described in detail elsewhere;<sup>19</sup> briefly, dexamethasone 6 mg iv for 10 days and enoxaparin 4000–6000 IU once daily.

Remdesivir was administered applying the five-day EMA protocol:<sup>20</sup> 200 mg iv the first day and 100 mg iv in days 2–5. During the 5-day treatment, serum creatinine was measured daily and eGFR slopes were built according to the CKD-EPI formula. Episodes of acute kidney injury (AKI), defined as an increase in serum creatinine by  $\geq$  0.3 mg/dl within 48 hours (2012 KDIGO guidelines), were also registered. Delta ( $\Delta$ ) eGFR was calculated as percent of variation of mean eGFR registered at day 4 and 5 of remdesivir treatment, with respect to the value at admission in hospital.

Patients were followed until death or release from the hospital (discharged when matching all the following

standardized criteria: no fever in the last 48 hours, satO<sub>2</sub> >94% in ambient air (AA) or P/F >300 in AA since the last 48 hours, respiratory rate <22/min in resting condition, no other clinical acute conditions).

For some analyses, data were compared with those obtained in a group of patients exactly matching the same inclusion criteria, admitted in the same hospital division during the same period and following the same therapeutic protocol (including remdesivir), but aging <60 years, who served as controls.

## Approvals

This retrospective, observational study was conducted according to the principles stated in the Declaration of Helsinki, and it conforms to standards currently applied in our country. Ethical approval was obtained from the local institutional review board (Comitato Etico Area Vasta Nord Ovest, Internal Review Board).

## Statistics

Statistical analysis was performed using IBM SPSS Software. Shapiro–Wilk normality test was performed on all continuous variables. Normally distributed variables were presented as mean ± standard deviation (SD), whereas variables with skewed distribution were presented as median and interquartile range (IR). Categorical data were presented as percentage. Comparative statistics for continuous variables were performed using the independent samples Student's *t*-test or the corresponding non-parametrical Wilcoxon/Kruskal–Wallis Test, as appropriate. Inter-group differences among categorical variables were tested using Pearson's chi-square test with Fisher's exact test, as appropriate. Correlation analyses were conducted using Spearman's rank-order correlation test and regression analysis was conducted where appropriate.

To investigate predictors of the outcome univariate logistic regression was first performed, statistically significant variables ( $p < 0.05$ ) were then included in a multivariable logistic regression analysis to identify independent outcome predictors. All statistical analyses were considered significant with a two-tailed  $p$ -value  $< 0.05$ .

## Results

### Clinical Characteristics of the Study Cohort

The study cohort was formed of 80 individuals whose clinical characteristics are shown in [Table 1](#). Mean age was 79

years; 27.5% of them had type 2 diabetes (T2D) and 46% had CKD stage III according with the NKF criteria. Half the population was already treated at home with antithrombotic and RAS-active drugs. As expected, all patients showed laboratory signs of a powerful inflammatory state, shown by high fibrinogen and IL-6 levels. Besides age, the main difference with younger individuals was prevalence of some comorbidities (hypertension and atrial fibrillation) and higher HS troponin and brain natriuretic peptide (BNP); as expected mean eGFR at admission was significantly higher in controls. Blood gas analysis parameters at admission did not differ between the two groups.

Stratifying the aging cohort by sex ([Suppl Table A](#)), the only different parameters at baseline were serum creatinine at admission, BNP and ferritin, all significantly higher in males; a gender-related difference in ferritin levels has been reported already during SARS CoV2.<sup>21</sup>

As reported in [Suppl Table B](#), patients with T2D did not differ from non-diabetic individuals except for higher random and fasting plasma glucose values and for a higher prevalence of hypertension and heart failure; serum potassium was slightly higher and arterial pH was lower, even within the normal range.

## Outcomes

Over the permanence in the hospital, 66 patients (82.5%) recovered and were discharged (mean staying: 14 days), while 14 deceased. [Table 2](#) shows clinical and biochemical parameters at in-hospital admission; deceased subjects were older, with a significantly lower eGFR at baseline and higher fibrinogen levels; interestingly, P/F at admission did not differ between the two groups. Only 4.9% of the patients participating in the study developed an AKI episode during the observational follow-up.

When we performed such comparison in the subset of twenty-two T2D patients, deceased patients ( $n=4$ ) were characterized by worse respiratory parameters and, similarly to that observed in the whole study cohort, by a worse baseline renal function at admission ([Suppl Table C](#)). Both fasting and random plasma glucose, although not significantly different, tended to be higher in dead patients.

[Table 3](#) shows linear correlations between baseline variables in recovered and deceased aging patients. Inflammatory markers were related one to each other in discharged patients, while in deceased the most significant linear correlations emerged in the subset of T2D patients, with HbA1c relating with inflammatory markers and P/F. eGFR at admission was significantly and inversely correlated with CRP levels in

**Table 1** Clinical Characteristics of the Study Cohort and Control Group at Hospital Admission

	Study Cohort n = 80	Controls n = 29	p value
Age (years)	79 [73, 85]	56 [50, 60]	< 0.0001
Male (n, %)	42, 52.5	24, 82.7	0.0043
Type 2 diabetes (n, %)	22, 27.5	6, 20.7	0.4721
Hypertension (n, %)	46, 57.5	10, 34.5	0.0336
Heart failure (n, %)	9; 11.2	0	0.0593
Atrial fibrillation (n, %)	16, 20.0	0	0.0091
ASCVD (n, %)	19, 23.7	4, 13.8	0.2602
ACEi/ARB (n, %)	40, 50.0	9, 31.0	0.0786
Statins (n, %)	21, 26.2	6, 20.7	0.5523
Antithrombotic therapy (n, %)	41, 51.2	5, 17.2	0.0015
eGFR <60 mL/min/1.73m <sup>2</sup> (n, %)	37, 46.2	5, 17.2	0.0060
Random plasma glucose (mg/dl)	128 [113, 170]	156 [130, 194]	0.0137
Serum creatinine (mg/dl)	1.0 [0.8, 1.3]	1.0 [0.8, 1.2]	0.5606
eGFR (mL/min/1.73m <sup>2</sup> )	60.2 ± 18.8	81.2 ± 20.4	< 0.0001
Serum Na <sup>2+</sup> (mEq/l)	137 [135, 140]	136 [134, 139]	0.1088
Serum K <sup>+</sup> (mEq/l)	4.1 ± 0.5	4.0 ± 0.6	0.7600
BUN (mmol/l)	23 [18, 32]	18 [15, 21]	0.0009
CRP (mg/dl)	6.4 [2.3, 12.5]	6.1 [2.1, 10.0]	0.5432
IL-6 (pg/mL)	19.6 [6.8, 30.0]	20.7 [13.4, 31.6]	0.5595
Ferritin (µg/l)	513 [226, 816]	731 [304, 1089]	0.1317
Fibrinogen (mg/dl)	503 ± 143	485 ± 150	0.7154
D-dimer (mg/l)	0.4 [0.3, 0.9]	0.3 [0.2, 0.4]	0.0020
HS Troponine (ng/l)	20 [10, 35]	7 [7, 12]	<0.0001
BNP (pg/mL)	62 [37, 187]	18 [10, 44]	<0.0001
pH	7.46 [7.44, 7.49]	7.47 [7.45, 7.50]	0.5394
PaO <sub>2</sub> (mmHg)	61 [53, 72]	61 [54, 72]	0.8158
PaCO <sub>2</sub> (mmHg)	34 [31, 38]	32 [30, 36]	0.3019
HCO <sub>3</sub> <sup>-</sup> (mmol/l)	25.1 ± 3.2	25.0 ± 2.5	0.7704
PaO <sub>2</sub> /FiO <sub>2</sub> (P/F) (mmHg)	278 [237, 316]	283 [250, 330]	0.4346

Notes: Wilcoxon/Kruskal–Wallis Tests (Rank Sums). Statistically significant differences are in bold.

deceased patients ( $r = -0.545$ ,  $p < 0.05$ ) and with HS Troponin levels in discharged patients ( $r = -0.368$ ,  $p < 0.05$ ). Regression analysis showed a linear relationship between baseline eGFR and CRP levels in deceased patients ( $\beta = -0.256$ , CI 95%  $-0.492$ ,  $-0.02$ ,  $p < 0.05$ ) (Suppl Figure A).

### eGFR During Remdesivir

We then built the slopes of eGFR during remdesivir treatment, dividing patients according to the clinical outcome. Figure 1 shows as in both subgroups, remdesivir use was associated with a clinically relevant eGFR gaining, which

**Table 2** Clinical and Biochemical Characteristics of the Study Cohort According to Clinical Outcome

	Discharged n = 66	Deceased n = 14	p value
Age (years)	78 [72, 84]	82 [78, 90]	<b>0.0218</b>
Male (n, %)	32, 48.5	10, 71.4	0.1184
Type 2 diabetes (n, %)	18, 27.2	4, 28.5	0.9213
Hypertension (n, %)	39, 59.0	7, 50.0	0.5320
Heart failure (n, %)	8, 12.1	1, 7.1	0.5923
Atrial fibrillation (n, %)	11, 16.6	5, 35.7	0.1056
ASCVD (n, %)	15, 22.7	4, 28.5	0.6407
ACEi/ARB (n, %)	33, 50.0	7, 50.0	1.000
Statins (n, %)	17, 25.6	4, 28.5	0.8279
Antithrombotic therapy (n, %)	32, 48.5	9, 64.3	0.2827
eGFR <60 mL/min/1.73m <sup>2</sup> (n, %)	27, 41.0	10, 71.4	<b>0.0375</b>
Random plasma glucose (mg/dl)	124 [107, 171]	138 [126, 180]	0.1246
Serum creatinine (mg/dl)	1.0 [0.8, 1.2]	1.2 [1.0, 1.5]	<b>0.0250</b>
eGFR (mL/min/1.73m <sup>2</sup> )	62.3 ± 18.2	50.3 ± 19.3	<b>0.0299</b>
Serum Na <sup>2+</sup> (mEq/l)	138 [135, 140]	137 [134, 143]	0.9554
Serum K <sup>+</sup> (mEq/l)	4.0 ± 0.5	4.2 ± 0.5	0.4809
BUN (mmol/l)	22 [18, 27]	31 [18, 39]	0.0886
CRP (mg/dl)	5.5 [2.1, 12.3]	9.2 [5.0, 17.0]	0.0530
IL-6 (pg/mL)	19.6 [6.8, 29.6]	18.6 [7.4, 32.5]	0.8098
Ferritin (µg/l)	439 [210, 816]	690 [335, 1188]	0.2594
Fibrinogen (mg/dl)	487 ± 142	581 ± 126	<b>0.0249</b>
D-dimer (mg/l)	0.5 [0.3, 0.9]	0.4 [0.3, 1.3]	0.6239
HS Troponine (ng/l)	25.1 ± 23.1	31.2 ± 17.8	0.4027
BNP (pg/mL)	173 ± 276	149 ± 137	0.7671
pH	7.46 ± 0.05	7.46 ± 0.03	0.9832
PaO <sub>2</sub> (mmHg)	69.7 ± 22.4	67.5 ± 37.7	0.2274
PaCO <sub>2</sub> (mmHg)	34.6 ± 5.0	33.2 ± 7.4	0.3194
HCO <sub>3</sub> <sup>-</sup> (mmol/l)	25.4 ± 3.0	23.4 ± 3.4	<b>0.0400</b>
PaO <sub>2</sub> /FiO <sub>2</sub> (P/F) (mmHg)	281 [240, 329]	252 [201, 290]	0.0623

**Notes:** Wilcoxon/Kruskal–Wallis Tests (Rank Sums). Statistically significant differences are in bold.

was almost two-fold higher than those observed in deceased patients (mean  $\Delta$ eGFR day 4-day 1: +20.9% vs +11.4%); however, while patients encountering a favourable outcome were characterized by a rather stable eGFR during remdesivir administration, deceased subjects

displayed a more fluctuating trend of the slope, with a larger variability of absolute eGFR values (Figure 1).

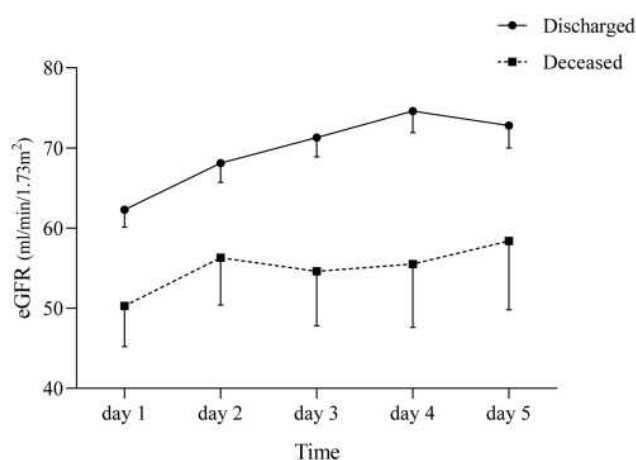
Suppl Figure B shows eGFR slopes in the subset of aging patients with CKD at baseline: the two subgroups started from a similar eGFR (44.6±9.2 in survivors and

**Table 3** Matrix of Univariate Correlations Between Variables of Interest in Elderly Discharged (A) and Deceased (B) Patients

(A)	Age	RPG	HbA1c	eGFR	CRP	IL-6	Fibr	HS TnT
P/F	-0.028	<b>-0.375</b>	0.001	0.113	<b>-0.333</b>	0.175	-0.141	0.118
HS TnT	<b>0.429</b>	-0.001	-0.384	<b>-0.368</b>	0.164	<b>0.334</b>	0.233	-
Fibrinogen	0.032	<b>0.372</b>	-0.019	-0.128	<b>0.600</b>	<b>0.426</b>	-	-
IL-6	-0.025	0.125	0.243	-0.231	0.306	-	-	-
CRP	0.104	<b>0.333</b>	-0.153	-0.156	-	-	-	-
eGFR	<b>-0.339</b>	-0.248	-0.103	-	-	-	-	-
HbA1c	<b>-0.471</b>	<b>0.549</b>	-	-	-	-	-	-
RPG	0.205	-	-	-	-	-	-	-
(B)	Age	RPG	HbA1c	eGFR	CRP	IL-6	Fibr	HS TnT
P/F	-0.063	-0.149	<b>-0.379</b>	-0.008	-0.036	0.482	-0.347	0.038
HS TnT	0.475	0.084	<b>0.974</b>	-0.234	0.081	0.079	0.211	-
Fibrinogen	0.042	0.308	<b>-0.683</b>	-0.255	0.348	-0.223	-	-
IL-6	0.067	-0.452	<b>-1.000</b>	-0.252	0.205	-	-	-
CRP	0.146	0.201	<b>0.696</b>	<b>-0.545</b>	-	-	-	-
eGFR	<b>-0.517</b>	-0.269	<b>-0.869</b>	-	-	-	-	-
HbA1c	<b>-0.666</b>	<b>0.990</b>	-	-	-	-	-	-
RPG	-0.188	-	-	-	-	-	-	-

Notes: HbA1c available only in T2D individuals (n=22).  $\rho$  values with  $p < 0.05$  are shown in bold.

41.0±9.7 mL/min/1.73m<sup>2</sup>) in deceased, but these ones, differently from survivors, did not show any relevant eGFR improvement during remdesivir treatment (mean  $\Delta$ eGFR: +30±41% vs +9±40%,  $p=0.245$ ).



**Figure 1** Glomerular function of the study cohort of elderly patients in relation to clinical outcome. Data are shown as mean±SE.

## Predictors of Outcome

By univariate analysis, age, fibrinogen, CRP and baseline eGFR were predictors of mortality (Table 4); however, when grouped together in a multivariable model, none such variables remained as significant independent predictors of mortality, even after testing for interactions with age and sex. This was true also in the subset of T2D patients, in which none of the explored variables was able to predict the main outcome (data not shown).

In the group of younger patients serving as controls, three individuals out of twenty-nine (10.3%) deceased. eGFR at baseline was 81.0±7.4 and 87.8±6.6 mL/min/1.73m<sup>2</sup> in discharged and deceased, respectively ( $p=ns$ ). [Suppl Figure C Upper Panel](#) shows eGFR slopes in such group according to the prognosis: discharged were clearly characterized by a relevant eGFR increase during remdesivir treatment (+18.5±15.2 mL/min/1.73m<sup>2</sup>). [Suppl Figure C Lower Panel](#) compares eGFR slopes of discharged individuals: in both groups, although starting

**Table 4** Univariate and Multivariate Analysis in the Whole Cohort of Elderly Patients (n=80)

Variable	Univariate			Multivariate		
	OR	CI	p	OR	CI	p
<b>Age</b>	<b>1.102</b>	<b>1.015–1.196</b>	<b>0.021</b>			
Sex	2.656	0.756–9.327	0.127			
Hospital stay	0.939	0.864–1.019	0.131			
Hypertension	0.692	0.218–2.202	0.533			
Heart failure	0.558	0.064–4.856	0.597			
ASCVD	1.360	0.373–4.963	0.642			
Atrial fibrillation	2.778	0.780–9.896	0.115			
Type 2 diabetes	1.067	0.297–3.836	0.921			
CKD ≥stage 3	1.870	0.584–5.985	0.292			
PaO <sub>2</sub> /FiO <sub>2</sub> (P/F)	0.990	0.980–1.000	0.061			
BNP	1.000	0.997–1.002	0.763			
HS Troponine	1.011	0.985–1.037	0.403			
Ferritin	1.001	0.999–1.002	0.323			
<b>CRP</b>	<b>1.099</b>	<b>1.013–1.193</b>	<b>0.024</b>	1.038	0.938–1.149	0.471
IL-6	1.002	0.944–1.063	0.960			
<b>Fibrinogen</b>	<b>1.005</b>	<b>1.000–1.010</b>	<b>0.030</b>	1.003	0.998–1.009	0.230
D-dimer	1.045	0.824–1.326	0.715			
Serum Na <sup>2+</sup>	0.967	0.918–1.019	0.212			
Serum K <sup>+</sup>	1.924	0.711–5.207	0.198			
Random plasma glucose	1.003	0.994–1.012	0.473			
<b>eGFR at admission</b>	<b>0.963</b>	<b>0.929–0.998</b>	<b>0.036</b>	0.971	0.934–1.009	0.139
ΔeGFR	10.266	0.019–3.707	0.324			

**Note:** Statistically significant differences are in bold.

from a significantly different eGFR, regained renal function was evident, with a similar trend over time.

## Discussion

During the first months of the pandemic, the promising inhibition properties of remdesivir toward SARS-CoV-2 have been identified, and, based on encouraging results obtained in a few placebo-controlled human studies showing a better recovery of COVID-19 positive hospitalized patients,<sup>22,23</sup> these observations have been rapidly translated into a clinical use of this molecule in fighting the most serious symptoms and signs of SARS CoV2 in adults; however, the behavior of renal function during such treatment in elderly people has not been detailed.

This single-center observational study shows, for the first time, as remdesivir: i) does not worsen renal function in elderly individuals with and without CKD; ii) intriguingly, several patients show a relevant eGFR improvement during remdesivir administration; such trend seems to be

coupled with an increased probability of recovering from SARS CoV2 and a better prognosis.

Impaired renal function is a proven major determinant of all-cause and cardiovascular mortality in the general population and in patients carrying several acute and chronic comorbidities<sup>24–26</sup> and marks an unfavorable prognosis in bacterial and viral infections.<sup>27,28</sup> In our cohort of elderly individuals hospitalized for SARS CoV2, common indicators of renal function at the admission and, to some extent, recovery of kidney function during hospitalization, influenced their prognosis, even in the presence of a disease whose main target organ is, apparently, the lung. This confirms that the kidney is primarily involved in SARS CoV2 infection,<sup>29,30</sup> likely via the high affinity of SARS CoV2 virus for ACE2,<sup>31</sup> and reinforces the importance of preserved renal function as a major prognostic determinant in patients hospitalized for SARS CoV2 pneumonia.

In deceased elderly subjects, a reduced renal function at admission was inversely related with CRP, the most

widely used indicator of inflammation, able to predict disease severity in COVID-19 patients.<sup>32</sup> This confirms a possible role the systemic inflammatory condition as determinant of impaired renal function<sup>33–35</sup> or, possibly, reflects the effects on the kidney of a more severe viral infection, determining a multiorgan failure.

The eGFR slopes during remdesivir administration deserve to be commented on. The first observation regards the renal safety of remdesivir, which did not induce any eGFR loss, and this was true irrespective of the presence of CKD stage III. Even more, both survivors and patients who died during hospitalization quite rapidly increased their eGFR while receiving remdesivir, although the phenomenon was more evident in the former group. This could be simply ascribed to their better eGFR at baseline, already described as determinant of renal function improvement after antiretroviral therapies;<sup>36</sup> alternatively, this ameliorated kidney function might reflect a better response to therapies, with an improved function of several organs and tissues.

The subgroup of CKD patients ([Suppl Figure B](#)) displays a quite peculiar difference in eGFR trend over remdesivir treatment: constant and progressive increase over time in discharged vs small oscillations characterizing the slope of deceased ones. This might suggest that the improvement in glomerular function during recovery, together with eGFR at admission, influence the clinical outcome in severely ill SARS CoV2 patients with chronically impaired renal function. Of note, individuals with type 2 diabetes did not differ from non-diabetic ones in terms of eGFR slope or performance of prognostic markers (data not shown), again suggesting a main role played by the kidney, rather than other comorbidities, in influencing clinical course, and even prognosis, of these individuals.

Despite the described association between SARS CoV2 and acute renal damage,<sup>37</sup> and although the study cohort included a considerable proportion of patients with CKD, only a very small percentage developed AKI during the first days of hospitalization, concomitant to remdesivir treatment. This aspect deserves particular attention. Before the pandemic, the clinical experience with remdesivir, developed to fight RNA viruses with global pandemic potential, including SARS and MERS coronaviruses and in particular Ebola, was rather limited. We show here, by a real-life observation in elderly, frail people, as remdesivir is safe on the kidney and its use is not coupled with any sign of acute deterioration of renal function; even more, as already pointed out, some patients

encountered an eGFR rise during the treatment. This finding might reflect a possible nephroprotective action of remdesivir that has not yet been described; we might only speculate that remdesivir might promptly counteract SARS CoV2-mediated direct, acute damage in the proximal tubular epithelium and of podocytes detachment from the glomerular basement membrane, together with the role played by the attenuation of systemic inflammation. Another possibility, that unfortunately we have been unable to test in patients participating in this survey, could be a decrease in ACE2 activity.<sup>38,39</sup>

Matter of fact, in such cohort of patients with severe pneumonia and respiratory failure, no variable among those routinely checked was able to independently predict their short-term prognosis, and this was also true for the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, an established indicator of respiratory failure severity in people carrying SARS CoV2, underlying the complexity of the disease, with systemic involvement of multiple tissues and organs.

The main strength of this study resides in the detailed and repeated eGFR monitoring performed during the treatment, with no missing data due to the strict daily monitoring of several biochemical variables, the nature of the study cohort, with casual high prevalence of CKD, standardized conditions of the observation with strict rules for receiving the drug. We should however acknowledge several limitations, including the retrospective nature of the study, the relatively small number of subjects, the existence of pre-defined clinical indications to remdesivir treatment that cannot allow to generalize the possible clinical meaning of this observation.

## Conclusions

Taken together these observations reassure on the safe use of remdesivir with respect to renal function in SARS CoV2 elderly patients, pointing out as the evaluation of eGFR slope during the antiviral treatment could integrate respiratory parameters and inflammation markers, providing a better prognostic phenotype of such frail patients.

## Abbreviations

AA, ambient air; AKI, acute kidney injury; BNP, brain natriuretic peptide; CKD, chronic kidney disease; COVID-19, Coronavirus Disease 2019; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HS, Troponin: high sensitivity troponin; IL-6, interleukin 6; P/F, PaO<sub>2</sub>/FiO<sub>2</sub> ratio; RAS, renin angiotensin system; SARS CoV2, severe acute respiratory syndrome coronavirus 2; T2D, type 2 diabetes.



## Data Sharing Statement

The datasets used and/or analysed during the current study are not publicly available due to privacy concerns. They are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

Ethical approval was obtained from the local institutional review board (Comitato Etico Area Vasta Nord Ovest, Internal Review Board). All patients provided consent for the anonymous use of data from their clinical records for scientific purposes.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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