Phase-3 Randomized Controlled Trials on Exclusion of Participants With Kidney Disease in COVID-19

Api Chewcharat[1], Yuan-Ting Chang[2], Meghan E. Sise[3], Roby P. Bhattacharyya[4], Megan B. Murray[5,6] and Sagar U. Nigwekar[3]

[1]Department of Medicine, Mount Auburn Hospital, Harvard Medical School, Cambridge, Massachusetts, USA; [2]Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, United Kingdom; [3]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [4]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [5]Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA; and [6]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Correspondence: Sagar U. Nigwekar, Department of Medicine, Division of Nephrology, Massachusetts General Hospital, 165 Cambridge Street, Suite 302, Boston, Massachusetts, USA 02114. E-mail: snigwekar@mgh.harvard.edu

Received 18 June 2020; revised 28 September 2020; accepted 13 October 2020; published online 21 October 2020

Kidney Int Rep (2021) **6,** 196–199; https://doi.org/10.1016/j.ekir.2020.10.010

Severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 (COVID-19), has a range of presentations and outcomes from asymptomatic carriage to acute respiratory distress syndrome and death.[1] The incidence of acute kidney injury (AKI) is high among patients with COVID-19.[2,3] Moreover, patients with chronic kidney disease (CKD), who make up more than 10% of the global population,[4] are at high risk for severe COVID-19.[5] Patients with end-stage renal disease who make frequent visits to in-center hemodialysis facilities are at high risk for exposure to and infection with severe acute respiratory syndrome coronavirus 2 and are at high risk of developing disease once exposed because of their older average age and multiple comorbidities.[6]

Remarkably, nearly 250 phase-3 randomized controlled trials have been planned to identify safe and effective interventions to prevent or treat COVID-19. To inform practitioners and researchers whether and how findings from these trials can be applied to patients with kidney disease (AKI, CKD, or end-stage renal disease), we conducted a systematic review of registered trials and quantified the proportion of potential subjects with kidney disease who are excluded from enrollment. Variables predicting trials with exclusion criteria regarding kidney disease were also explored using multiple logistic regression (Supplementary Methods).

A total of 248 trials were identified, of which 55 trials did not meet the inclusion criteria (13 trials were for unrelated topics, 4 trials were nonrandomized single-arm interventions, and 38 trials included fewer than 100 participants). Of the remaining 193 trials (representing 258,794 participants), 83 trials (43.0%) (representing 149,294 participants [57.7%]) excluded patients with kidney disease. Criteria to exclude patients with kidney disease included abnormal estimated glomerular filtration rate (eGFR) or renal replacement therapy (n = 57 trials), abnormal serum creatinine (n = 6 trials), history of kidney stone (n = 1 trial), history of nephrotic syndrome (n = 1 trial), or renal impairment, not further specified (n = 18 trials). The eGFR thresholds provided as exclusion cutoffs are summarized in Figure 1.

The exclusion of patients with kidney disease occurred across the spectra of trials with varying sample sizes, funding sources, and outpatient/inpatient settings (Table 1). Details on the exclusion criteria thresholds applied to each trial for each intervention are shown in Table 2. The corresponding appropriate thresholds at which each intervention was contraindicated are represented in Supplementary Table S1. It appears that exclusion criteria regarding kidney disease are generally applied regardless of number of enrollments *(100–499, 500–999, >1,000)*, participant settings *(outpatient, inpatient, health care workers, and not specified)*, locations *(North America, South America, Africa, Asia/Australia, Europe, and multiple locations)*, and funding sources *(academic/government, industry, and not specified)*, as none of these factors were

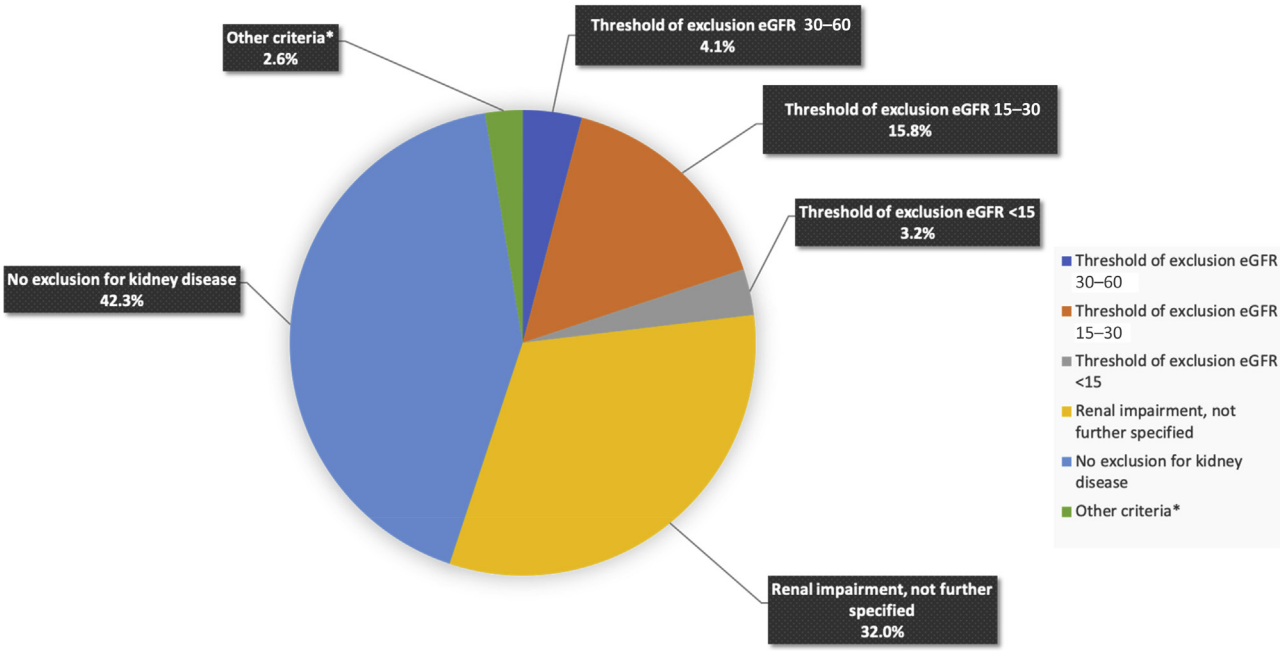

Figure 1. Percentage of participants in trials with each indicated exclusion criterion (n = 258,794 participants). *Other criteria include history of nephrotic syndrome (0.2%), history of kidney stone (0.3%), and various serum creatinine cutoffs (2.1%).

significantly different across various exclusion criteria regarding kidney disease, as shown in Supplementary Table S2. Moreover, none of these factors significantly predict whether or not trials have exclusion criteria regarding kidney disease. (Supplementary Table S3)

Almost all studies of humanized monoclonal antibodies, such as tocilizumab or sarilumab, convalescent plasma, and nonpharmacologic treatment, such as hyperbaric oxygen therapy, in which renal clearance is minimal or irrelevant, included participants with kidney disease. However, 2 trials (14%) with 410 participants (10%) among humanized monoclonal antibody trials excluded patients with kidney impairment. On the contrary, most bacille Calmette-Guerin vaccine trials did not exclude patients with kidney disease. Nonetheless, 2 trials (22%) with 1380 participants (7%) excluded patients with CKD or dialysis patients. The rationale for excluding patients with kidney impairment among bacille Calmette-Guerin vaccination trials might be explained by the fact that patients with renal impairment were considered as immunocompromised hosts. They might be at risk of disseminated or severe tuberculosis infection. However, according to the manufacturer's labeling, there is no contraindication or dose adjustment for this particular population.

By contrast, more than 50% of studies of small molecule antivirals, such as remdesivir or favipiravir, and antimalarials, such as hydroxychloroquine or chloroquine, excluded such participants. Regarding hydroxychloroquine/chloroquine, 20 trials (61%) with 41,229 participants (78%) excluded patients with renal impairment although there is no requirement for dose adjustment for short-term use including treating patients with COVID-19. All remdesivir trials excluded participants with kidney disease (2 trials excluded participants with eGFR $<$50 ml/min per 1.73 m^2 and 1 trial excluded participants with eGFR $<$30 ml/min per 1.73 m^2), as discussed in Adamsick *et al.*[7] Although there is a contraindication among patients with eGFR $<$30 ml/min per 1.73 m^2, some trials excluded participants at eGFR 50 ml/min per 1.73 m^2.

Interestingly, some trials excluded patients with renal diagnoses not further specified kidney function. One trial excluded patients with a history of kidney stones, as the experimental arm was vitamin C supplementation, which is associated with higher risk of kidney stones. Another trial excluded patients with a history of nephrotic syndrome, because the proposed intervention was discontinuation of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, which should not be discontinued among patients with nephrotic syndrome. Their rationales appear to be appropriate.

Most interventions, including humanized monoclonal antibodies, hydroxychloroquine/chloroquine, lopinavir/ritonavir, convalescent plasma, vaccination, and hyperbaric oxygen, are not contraindicated in patients with renal impairment; however, renal dose for these interventions might be required. Many ongoing trials use strict criteria excluding patients with renal impairment without considering dose adjustment.

Table 1. Characteristics of COVID-19 trials

Characteristics	Trials, n	Participants, n	Percentage of trials with exclusion of kidney disease, n (%)	Percentage of participants with exclusion of kidney disease, n (%)
Total	193	258,794	83 (43)	149,294 (58)
Number of enrollments				
100–499	102	27,182	37 (37)	9,987 (37)
500–999	35	22,636	18 (51)	11,942 (52)
>1000	56	208,976	28 (50)	127,365 (61)
Participant settings				
Outpatient	38	53,341	17 (45)	27,866 (52)
Inpatient	112	94,589	46 (41)	36,650 (38)
Health care workers	26	104,516	14 (54)	82,640 (79)
Not specified	17	6,348	6 (35)	2,138 (35)
Sites				
Single center	95	77,120	37 (39)	28,903 (37)
Multicenter	77	167,067	38 (49)	114,688 (69)
Not specified	21	14,607	8 (38)	5,703 (39)
Location				
North America	58	63,273	27 (47)	41,331 (65)
South America	11	9,193	2 (18)	1,750 (19)
Africa	19	6,858	9 (47)	3,368 (51)
Asia/Australia	14	25,050	4 (29)	2,402 (10)
Europe	77	64,436	32 (42)	28,159 (44)
Multiple locations	14	89,984	9 (64)	72,284 (80)
Funding sources				
Academic grant/government	139	161,174	59 (43)	76,358 (48)
Industry	45	89,339	19 (42)	70,096 (78)
Not specified	9	8,281	5 (56)	2,840 (34)
Type of interventions				
Humanized monoclonal antibody vs placebo/standard of care	14	4,230	2 (14)	410 (10)
Hydroxychloroquine/chloroquine vs placebo/standard of care	33	53,085	20 (61)	41,229 (78)
Vaccine vs. placebo	9	21,078	2 (22)	1,380 (7)
Convalescent plasma/ immunoglobulin vs placebo/standard of care	12	4,387	1 (8)	138 (3)
Hyperbaric oxygen/ozone therapy vs standard of care	3	508	0 (0)	0 (0)
Favipiravir vs placebo/standard of care	2	200	1 (50)	100 (50)
Lopinavir/ritonavir vs. placebo/standard of care	1	1,220	0 (0)	0 (0)
Remdesivir vs placebo/standard of care	3	8,400	3 (100)	8,400 (100)
Supplements/Herbs vs. placebo/standard of care	13	8,306	4 (31)	1,910 (23)
Multiple medication comparisons	57	126,517	32 (56)	83,865 (66)
Other medications[a] vs. placebo/standard of care	46	30,863	18 (39)	11,862 (37)

[a]Other medications include azoximer bromide, amiodarone, almitrine, ABX464, aviptadil, anakinra, azithromycin, budesonide, bactek-R, ciclesonide, colchicine, doxycycline, dalargin, DAS181, dornase alfa inhalation solution, dociparstat, dapagliflozin, escin, IMU-838, IFX-1, imatinib, ifenprodil, lenzilumab, nitazoxanide, nafamostat mesylate, naproxen, pacritinib, ruxolitinib, remestemcel-L, symbicort rapihaler, steroid, and VPM1002.

This leads to loss of potential patients who might benefit from these interventions. The exclusion of patients with kidney disease, as highlighted in this report, will limit the generalizability of results of these trials to the kidney disease population. Patients with severe kidney disease, including those requiring renal replacement therapy, are the most vulnerable patient groups to COVID-19 that nephrology practitioners encounter. The exclusion of these patients means that clinical decisions regarding their care will be less likely to be evidence-driven, exposing patients in some cases to excess risks and in some cases, depriving them of an effective intervention. Scientific rationale (lack of efficacy, safety concern, or other) should be provided for future trials that exclude patients with kidney disease.

Several studies exclude patients on the basis of weak measures of renal function. Some used serum creatinine rather than eGFR as the cutoff criteria, which might not be an accurate representation of underlying kidney disease. Moreover, 18 trials (9%) excluded patients on the basis of renal impairment not further specified, which might lead to the exclusion of patients with mild kidney disease. We believe that eGFR should be used to be consistent with other trials, to more accurately reflect kidney function. and to renally adjust medication doses. Furthermore, future studies should record and clarify whether abnormal renal function is secondary to AKI, CKD, or AKI superimposed on CKD.

In conclusion, more than 40% of COVID-19 trials excluded patients with kidney disease. Because

Table 2. Number of trials (number of enrollments) with each exclusion criterion regarding kidney disease for each intervention

Intervention	No exclusion for kidney disease	Threshold GFR <15	Threshold GFR 15–30	Threshold GFR 30–60	Renal impairment, not further specified	Other criteria[a]
Humanized monoclonal antibody vs. placebo/standard of care	12 (3,820)	0	2 (410)	0	0	0
Hydroxychloroquine/chloroquine vs. placebo/standard of care	13 (11,856)	3 (5,260)	12 (15,220)	0	2 (16,739)	3 (4,010)
Vaccine vs. placebo	7 (19,698)	0	0	0	2 (1,380)	0
Convalescent plasma/ immunoglobulin vs. placebo/standard of care	11 (4,249)	0	0	0	0	1 (138)
Hyperbaric oxygen/ozone therapy vs. standard of care	3 (508)	0	0	0	0	0
Favipiravir vs. placebo/standard of care	1 (100)	0	1 (100)	0	0	0
Lopinavir/ritonavir vs. placebo/standard of care	1 (1,220)	0	0	0	0	0
Remdesivir vs. placebo/standard of care	0	0	1 (800)	2 (7,600)	0	0
Supplements/Herbs vs. placebo/standard of care	9 (6,396)	0	0	1 (450)	2 (760)	1 (800)
Multiple medication comparisons	25 (42,652)	3 (2,550)	18 (16,015)	4 (1,910)	6 (62,490)	1 (900)
Other medications[b] vs. placebo/standard of care	28 (19,001)	1 (500)	8 (8,454)	1 (120)	6 (1,832)	2 (956)

[a]Other criteria include history of nephrotic syndrome (0.2%), history of kidney stone (0.3%) and various serum creatinine cutoffs (2.1%).
[b]Other medications include azoximer bromide, amiodarone, almitrine, ABX464, aviptadil, anakinra, azithromycin, budesonide, bactek-R, ciclesonide, colchicine, doxycycline, dalargin, DAS181, dornase alfa inhalation solution, dociparstat, dapagliflozin, escin, IMU-838, IFX-1, imatinib, ifenprodil, lenzilumab, nitazoxanide, nafamostat mesylate, naproxen, pacritinib, ruxolitinib, remestemcel-L, symbicort rapihaler, steroid, and VPM1002.

patients with kidney disease are at high risk of COVID-19 exposure, infection, and severe disease, and because COVID-19 itself leads to AKI, future trials should include patients with kidney disease (AKI, CKD, or end-stage renal disease), as suggested by the Kidney Health Initiative and the US Food and Drug Administration.[8,9] eGFR rather than serum creatinine should be used to assess kidney function and to adjust doses of renally cleared interventions. Focusing on the efficacy and safety of various potential interventions for COVID-19 among the kidney disease population is of critical importance.

DISCLOSURE

MES has participated in scientific advisory boards for Gilead in the area of Viral Hepatitis. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

SUN is supported by the American Heart Association (15FTF25980003) and by the National Institute of Diabetes and Digestive and Kidney Diseases (1U01DK123818). The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association or the National Institutes of Health.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Recommendations for dosing in adults with renal impairment.

Table S2. Number of trials with each exclusion criterion regarding kidney disease.

Table S3. Predictors for exclusion criteria regarding kidney disease.

REFERENCES

1. Harapan H, Itoh N, Yufika A, et al. Coronavirus disease 2019 (COVID-19): A literature review. *J Infect Public Health*. 2020;13:667–673.
2. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98:209–218.
3. Batlle D, Soler MJ, Sparks MA, et al. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. *J Am Soc Nephrol*. 2020;31:1380–1383.
4. Coresh J. Update on the burden of CKD. *J Am Soc Nephrol*. 2017;28:1020.
5. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Int Urol Nephrol*. 2020;52:1193–1194.
6. Ikizler TA. COVID-19 and dialysis units: what do we know now and what should we do? *Am J Kidney Dis*. 2020;76:1–3.
7. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol*. 2020;31:1384–1386.
8. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry*. Published May 2020. Rockville, MD: Food and Drug Administration.
9. Kidney Health Initiative. *Making the Case for Change: Including People with Kidney Diseases in COVID-19 Trials*. Washington, DC: American Society of Nephrology; 2020.