The Exclusion of Patients with CKD in Prospectively Registered Interventional Trials for COVID-19—a Rapid Review of International Registry Data

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The exclusion of patients with CKD from clinical trials has been a barrier to therapeutic advancement in CKD for the last two decades.[1] These inequities were highlighted by the Kidney Disease Improving Global Outcomes Controversies Conference, with the ambition of ensuring that individuals with CKD are included in relevant clinical trials.[2] The coronavirus disease 2019 (COVID-19) pandemic's global effect has led to rapid clinical trial registration and commencement in search of effective treatments. Individuals with CKD are at higher risk of COVID-19–related mortality.[3] It is unclear, however, if these individuals have equitable access to clinical trial recruitment. Therefore, we aimed to assess the CKD-related inclusion and exclusion criteria for COVID-19 trials.

METHODS

We assessed inclusion and exclusion criteria of all registered interventional clinical trials for COVID-19 from data available on the World Health Organization International Clinical Trials Registry Platform[4] (WHO-ICTRP; data extracted April 22nd, 2020). Clinical trials were divided into "pharmaceutical" and "nonpharmaceutical" trials. The former was defined as any medication that would be regulated by the Food and Drug Administration or a similar regulatory body. All other trials were classified as nonpharmacologic, including "traditional Chinese medicine" clinical trials. Interventions and exclusion criteria for each trial were independently reviewed and extracted by two assessors blinded to other trial details. Pharmaceutical intervention suitability for patients with CKD was independently assessed by two blinded specialist renal pharmacists using summary of product characteristics (equivalent of United States prescribing information), British National Formulary[5] and the Renal Drug Database.[6] The study's primary analysis considered trial exclusions for any type of nonend stage and end stage CKD. AKI was assessed for this analysis.

RESULTS AND DISCUSSION

In total, 484 trials were identified from WHO-ICTRP and included in the analysis as shown in Figure 1; 364 pharmaceutical trials testing 120 different medications were identified (Supplemental Material). The trials' core characteristics are shown in Table 1. Forty (33.3%) medications either were contraindicated or had insufficient data available to assess their suitability in CKD. Twenty-five medications (20.8%) were categorized as appropriate for use in CKD with caution. In total, 218 (45.0%) trials had exclusion criteria on the basis of CKD. Sixty-three (13.0%) trials excluded CKD but gave an unclear or vague description of CKD, such as "kidney dysfunction." Additionally, 189 (51.9%) of the clinical trials were classified by the investigators as "late-phase" (2b, 3, or 4) clinical trials. The most common intervention that excluded individuals with CKD was chloroquine/hydroxychloroquine in 59 pharmaceutical trials (52.7%).

Factors associated with exclusion of individuals with CKD were assessed using binary logistic regression and are presented in Supplemental Table 1. Pharmaceutical trials involving participants from China, particularly those testing chloroquine/hydroxychloroquine, antivirals, and antibacterials, were more likely to exclude individuals with CKD, whereas those from Europe were less likely.

These data suggest that patients with CKD are being excluded from almost half of all registered clinical trials for COVID-19. For the pharmaceutical compounds being tested, there were few pharmacologic reasons why patients with CKD should have been excluded from the studies reviewed. These findings raise concerns

Published online ahead of print. Publication date available at www.jasn.org.

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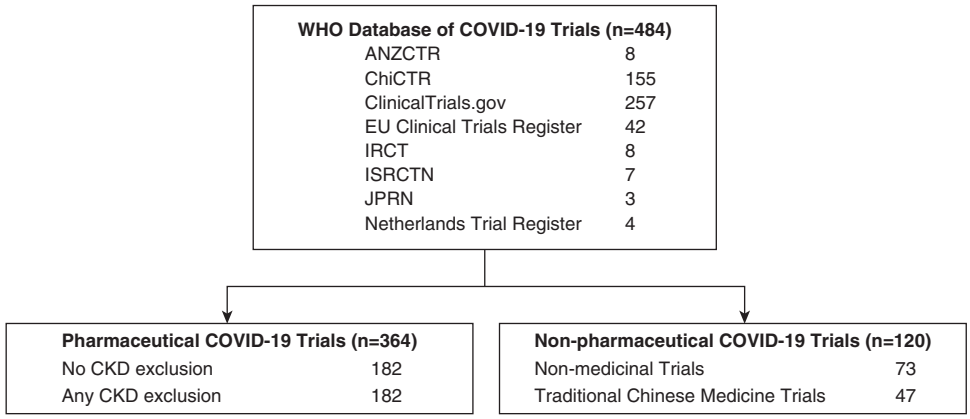

Figure 1. Registry sources of the COVID-19 trials identified and their classification by interventional category flowchart. ANZCTR, Australian New Zealand Clinical Trials Registry; ChiCTR, Chinese Clinical Trial Registry; IRCT, Iranian Registry of Clinical Trials; ISRCTN, International Standard Randomised Controlled Trial Number; JPRN, Japan Primary Registries Network; WHO, World Health Organization.

that patients with CKD and the clinicians looking after them may be left without an adequate evidence base from which to offer tested treatments to a group of patients known to be at risk of the worst outcomes from COVID-19. The majority of the trial pharmaceutical compounds have well-understood pharmacokinetic and pharmacodynamics properties and are used in CKD. For instance, hydroxychloroquine is a mainstay of treatment for patients with lupus who have CKD.[7] Inconsistencies were also noted in the definition of CKD used in trials; 13% of trials' exclusion criteria had no specific CKD definition, with terms such as "kidney disease" or "kidney dysfunction" used. Potential participants with more advanced CKD stages were more likely to be excluded, with approximately a third of trials excluding those on dialysis and a similar number of transplant recipients. This suggests that inclusivity of future COVID-19 trials in relation to CKD

Table 1. Trial descriptors

Trial Descriptor	All Trials, % (IQR)	Pharmaceutical, % (IQR)	Nonpharmaceutical, % (IQR)
N	484	364	120
Interventions per trial, median	1 (1–2)	1 (1–2)	1 (1–1)
Phase			
Early, 1–2a	—	112 (30.8)	—
Late, 2b–4	—	189 (51.9)	—
Not specified	—	63 (17.3)	—
Country of participants, *n*			
China	224 (46.3)	150 (41.2)	74 (61.7)
Europe	143 (29.6)	116 (31.9)	27 (22.5)
North America	82 (16.9)	69 (19.0)	13 (10.8)
Other	57 (11.8)	50 (13.7)	7 (5.8)
Intervention, *n*			
Chloroquine/hydroxychloroquine	—	112 (30.8)	—
Corticosteroids	—	16 (4.4)	—
Antibacterials	—	20 (5.5)	—
Antivirals	—	71 (19.5)	—
None of the above	—	195 (53.6)	—
Exclusions, *n*			
Any CKD-related exclusion	218 (45.0)	182 (50.0)	36 (30.0)
Hemodialysis/peritoneal dialysis	167 (34.5)	137 (37.6)	30 (25.0)
Renal transplantation	147 (30.4)	122 (33.5)	25 (20.8)
Nonend stage CKD	161 (33.3)	130 (35.7)	31 (25.8)
3A	26 (5.4)	23 (6.3)	3 (2.5)
3B	27 (5.6)	24 (6.6)	3 (2.5)
4	87 (18.0)	80 (22.0)	7 (5.8)
5	97 (20.0)	89 (24.5)	8 (6.7)
CKD exclusion but unclear criteria	63 (13.0)	41 (11.3)	22 (18.3)

Total for country of participants is >484 as some studies included participants from more than one category. IQR, interquartile range; —, non-applicable.

could be improved through more precise CKD definitions and consideration of medication appropriateness, perhaps with dose adjustments where applicable.

The reasons for the international differences in exclusion of patients with CKD from trials are not clear but may related to the pandemic's global evolution or differing understandings of CKD's classification and implications. Because of the time-sensitive nature of this analysis, we did not prospectively register this study, and this may be regarded as a limitation.[8] However, this potential bias was minimized by blinding and duplicating all assessments to the trials' characteristics. A further weakness was that a trial's exclusion criteria were directly on the basis of those reported to WHO-ICTRP, and we did not perform analysis from a trial's published protocol.

The scientific community has a responsibility to build an evidence base for the treatment of all patients with COVID-19, including those with CKD who may be the most clinically vulnerable. This highly time-sensitive matter must be addressed by investigators, regulators, and the nephrology community to improve clinical trial design and enhance equitable access to new treatments and trial inclusion for patients with CKD.

DISCLOSURES

All authors have nothing to disclose.

FUNDING

M. Graham-Brown is funded by a National Institute for Health Research Academic Clinical Lectureship award. K. Hull is funded by a National Institute for Health Research Academic Clinical Fellow award. H. Sekvaskandan is funded by Kidney Research UK grant TF_009_20181123.

ACKNOWLEDGMENTS

The authors acknowledge the full contribution of the following individuals in relation to this project—blinded assessment of trial data: Dr. Terrina Abd Rahim, Dr. Abubaker Obeidalla, Dr. Ismet Boral, Mr. Robert Grant, Dr. Susil Pallikadavath, and Dr. Jorge Jesus-Silva; blinded assessment of medication data: Mr. Dipesh Patel and Ms. Amy Page; and development of research idea and redrafting of manuscript: Prof. Nigel Brunskill.

The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, the Department of Health and Social Care, or Kidney Research UK.

Matthew Graham-Brown, Rupert Major, Yahya Mostafa Makkeyah, and Haresh Sekvaskandan developed the research idea; Yahya Mostafa Makkeyah performed data extraction; Rupert Major performed data processing; Matthew Graham-Brown, Katherine Hull, Apexa Kuverji, and Haresh Sekvaskandan performed blinded assessment of data; Rupert Major performed statistical analysis; Rupert Major wrote the initial draft of the manuscript; Matthew Graham-Brown and Rupert Major redrafted the manuscript; and all authors approved the final manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020060877/-/DCSupplemental.

Supplemental Material. Supplemental data.

Supplemental Table 1. Risk factors for CKD exclusion from pharmaceutical clinical trials for patients with COVID-19. Intervention comparator is nonpharmaceutical trials.

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