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A Systematic Review of COVID-19 and Kidney Transplantation

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Introduction: Kidney transplant recipients are at increased susceptibility to many viral infections leading to justifiable anxiety about the effects of coronavirus disease 2019 (COVID-19).

Methods: We performed literature searches from multiple resources in April and August 2020 for relevant English and Chinese literature. Abstracts were screened, followed by full-text review with data extraction of reports that included at least 20 kidney transplant recipients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and completed outcomes.

Results: Twenty studies had sufficient data, which we have summarized. Studies were predominantly descriptive and came from France, Italy, Spain, Turkey, United Kingdom, and United States. Quality assessment demonstrated limitations in selection of comparison groups and controlling for additional factors. Mortality rates from published studies were variable. Based on early data early from Spain, 46% of patients who developed COVID-19 within 60 days of transplantation died. Acute kidney injury was common, and mycophenolate was discontinued in most patients.

Conclusion: Given the rapid global spread of COVID-19, reliable evidence is needed to inform public health policies. Hospitalized kidney transplant recipients with COVID-19 are at a high risk of death in early reports but interpretation of these data requires caution, as studies were susceptible to period effects. Reassuringly, the quality of observational data is improving. Detailed and comprehensive data collection through linked registries will be necessary to conduct accurate analyses of risk factors for adverse outcomes, not least given the risks of stopping imunosuppression. This report highlights the early mortality excess in transplant recipients but medium- and longer-term outcomes remain uncertain and merit careful investigation.

Kidney Int Rep (2021) **6,** 24–45; https://doi.org/10.1016/j.ekir.2020.10.023
KEYWORDS: COVID-19; kidney transplantation; systematic review

On December 31, 2019, the Wuhan Health Commission in China reported an outbreak of atypical pneumonia to the World Health Organization. The causative pathogen was found to be the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) capable of human-to-human transmission through respiratory droplets.[1] The associated disease was named COVID-19, and its spectrum of severity ranges from no symptoms to life-threatening organ dysfunction, the scale of which can place extreme burden on health care resources without control of transmission.[2] After spread across several continents, COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020.

Severe lung injury and other organ-threatening complications in COVID-19 are understood to be the result of a dysregulated systemic inflammatory response in the days after infection, leading to some immunosuppressive therapies being repurposed both inside and out of clinical trial settings in conventional management.[3–5] Only low-dose dexamethasone has so far demonstrated mortality benefit compared with usual practice.[6]

Immunosuppressant drugs used to prevent allograft rejection render kidney transplant recipients at increased susceptibility to many viral infections, and such

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Received 3 July 2020; revised 25 September 2020; accepted 21 October 2020; published online 3 November 2020

infections are an important cause of morbidity and mortality in this population.[7] The immune response to SARS-CoV-2 infection in immunosuppressed kidney transplant recipients, many with other comorbidities, may result in differences in presentation, outcomes, and therapeutic responses compared with the general population.

Given the rapid and global spread of COVID-19, there is a need to gather evidence and disseminate as quickly as possible. Our aim was to conduct a complete systematic review of the early literature to synthesize, analyze, and appraise what has been learned so far to help clinicians and policy makers better understand the risks to kidney transplant recipients, as well as identify gaps for future collaborative research for this global health challenge.

METHODS

Search Strategy

Inclusion and exclusion criteria were formulated to ensure comprehensive searching and screening for articles relevant to COVID-19 in chronic kidney disease, specifically including kidney transplantation. Variables of interest were defined based on the PICOS (patient/population, intervention, comparison, outcomes, study designs) strategy.[8] Our protocol was prospectively published via PROSPERO (CRD42020182134).

Initial searches were conducted on April 28, 2020, including all relevant English- and Chinese-language research up to that date from December 1, 2019; papers not written in these languages were excluded because of a lack of resources to obtain timely translation. Published and nonpublished literature was searched on MEDLINE (Ovid), EMBASE (Ovid), China National Knowledge Infrastructure, the Wanfang database, the Chinese Biomedical Literature Database, clinicaltrials.gov, the Chinese Clinical Trial Register, the World Health Organization database of COVID-19 research, and the Chinese Medical Journal Network. Search terms are listed in Supplementary Material S1. An updated search was deemed necessary due to the rapidly evolving evidence base and was conducted onAugust 4, 2020, via MEDLINE (Ovid), EMBASE (Ovid), World Health Organization COVID19 database, and bioRxiv and medRxiv preprint servers. The strategy for the update searches is attached in Supplementary Material S2.

Screening, Data Extraction, and Quality Assessment

Duplicates were removed from the studies generated by both searches and the remaining studies were imported to the SysRev Platform (https://sysrev.com). Screening was undertaken at abstract level by separate teams of 2 independent authors for both English and Chinese; a senior author adjudicated where there was nonconcordance. Reference lists were hand-searched for any additional studies that may have been missed. Full-text articles were then further assessed for eligibility, including the exclusion of case reports or studies with populations of interest of fewer than 20 confirmed cases. As all studies were observational, further quality assessment was undertaken using the Newcastle-Ottawa Quality Assessment Scale.9 Where articles did not report all outcomes specifically in kidney transplant populations, we contacted authors to request disaggregated data (Supplementary Material S3).

Data were extracted for each included study, including online publication date, study population, timeframe, total number of cases (including how many patients had completed outcomes, that is, death or recovery to discharge), patient characteristics, clinical presentation, outcomes, baseline immunosuppression adjustment, and COVID-19 therapy. Inpatient mortality for each study was calculated as a proportion of patients with completed outcomes.

RESULTS

Study Identification

The PRISMA flow diagram is shown in Figure 1. A total of 1377 studies were identified through database searching, after which 762 remained after deduplication; of these, a further 695 were excluded after abstract screening, leaving 65 that met criteria for full-text assessment for eligibility with no additional articles identified after hand-searching reference lists. A further 47 studies were excluded after detailed assessment. To be more comprehensive, we included 2 additional studies published shortly after our search was completed.[10,11] In total, 20 studies underwent data extraction.

Quality Assessment

There were no randomized controlled trials or case-control studies. Comparative analysis between different exposure groups was limited. Sánchez-Álavarez *et al.*[12] was a report from a national COVID-19 registry across Spain, whereas Pascual *et al.*[13] and Pérez-Sáez *et al.*[14] reported on subgroups from this registry (those within 60 days of transplantation, and those treated with tocilizumab respectively). Bell *et al.*[15] and Ravanan *et al.*[11] reported from national transplant registries in Scotland and England, respectively, whereas Manganaro *et al.*[16] reported on from a regional registry in Italy. Kates *et al.*[10] reported on data entered to a registry by more than 50 transplant centers, almost all from the United States, whereas Cravedi *et al.*[17] was a report of a consortium registry of 12 transplant centers across the United States, Italy, and

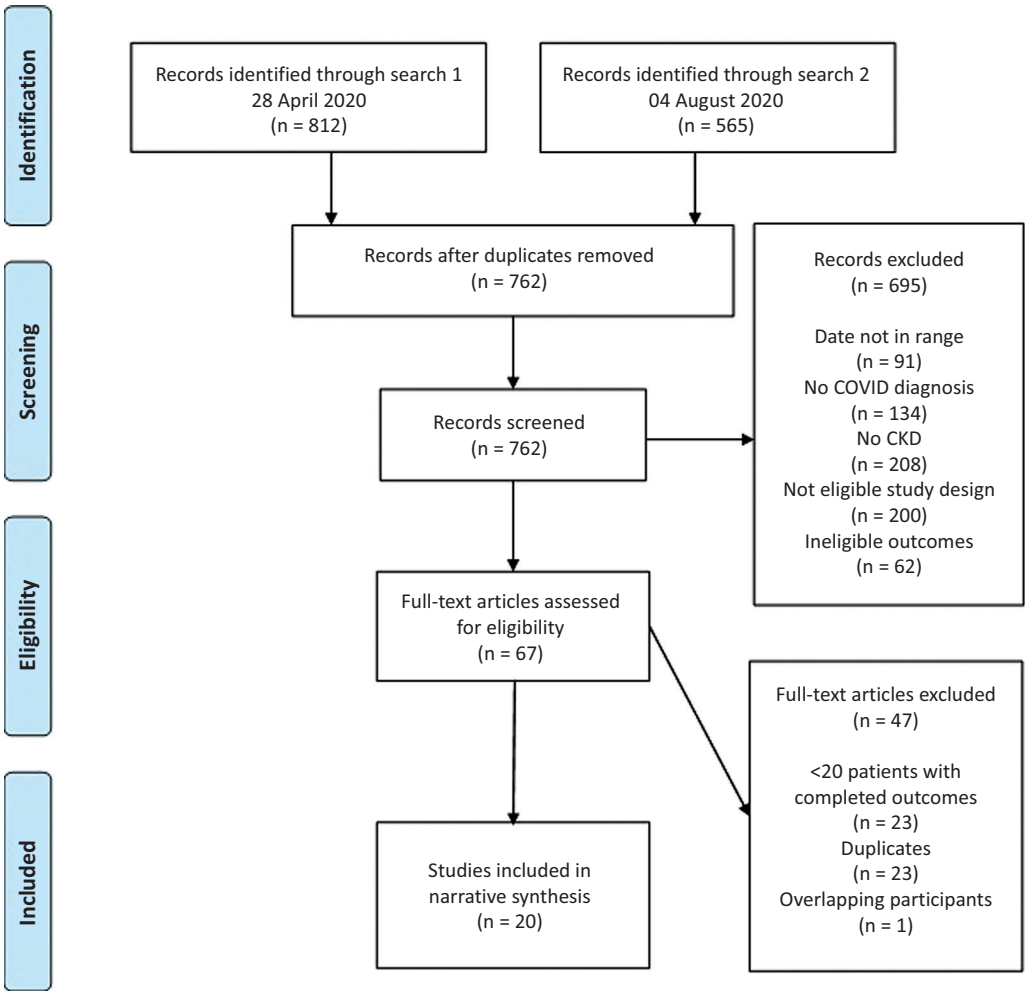

Figure 1. PRISMA flow diagram.

Spain. Boyarsky *et al.*[18] and Vistoli *et al.*[19] were cross-sectional reports of national surveys from the United States and Italy, respectively. The remaining studies were either single-center or small multicenter case series of either inpatients, or both inpatient and outpatient kidney transplant recipients with COVID-19. Using death as the main outcome of interest, formal quality assessment is shown in Table 1 using the Newcastle-Ottawa Quality Assessment Scale.[9]

Quality assessment demonstrated consistent weaknesses in selection of control groups (e.g., home dialysis patients on the transplant waiting list) and inadequate control for additional confounding factors. Case series are descriptive and do not make comparisons with a control group, whereas single-center reports may yield biased results when compared with the source population. Kates *et al.*[10] was susceptible to selection bias, as participating centers may not have systematically submitted all cases. Some studies did not report how many patients had been discharged, meaning mortality estimates may have been inaccurate due to misclassification of patients who died after the end of follow-up, but more recent reports had longer and more complete follow-up. Although Boyarsky *et al.*[18] and Vistoli *et al.*[19] had high response rates to their surveys, they may not be completely reliable, as they were not linked to individual patient records.

Study Populations

All studies identified by our search are listed in Supplementary Table S4, along with other studies reporting on ≥5 kidney transplant recipients. Our searches of studies with ≥20 recipients with confirmed COVID-19 and completed outcomes identified studies from only 6 countries (France, Italy, Spain, Turkey, United Kingdom, and United States); at least 5 of the 7 studies with patients from United States included cases from New York City. There have been smaller published studies not included in our review from Belgium, China, Iran, Netherlands, Portugal, and Switzerland.

We note that some studies had overlapping cohorts: patients from Mohamed *et al.*[20] would be included in Ravanan *et al.*,[11] whereas patients in Pereira *et al.*[21] would have been included in Lubetzky *et al.*[22] Some cases from Rodriguez-Cubillo *et al.*[23] are

Table 1. Description of each study design and quality assessment using the Newcastle-Ottawa Quality Assessment Scale, listed by order of online publication date

Study	Study design	Selection	Comparability	Outcome
Manganaro *et al.*[16]	Single-center case series	☆☆★★	☆☆	☆☆☆
Boyarksy *et al.*[18]	Cross-sectional national survey	☆☆☆★	☆☆	☆☆☆
Pereira *et al.*[21]	Two-center case series	★☆★★	☆☆	★☆☆
Sánchez-Álvarez *et al.*[12]	National registry cohort	★★☆★	★☆	☆★☆
Vistoli *et al.*[19]	Cross-sectional national survey	★☆☆★	☆☆	☆☆☆
Rodriguez-Cubillo *et al.*[23]	Single-center case series	★☆★★	☆☆	★★★
Pascual. *et al.*[13]	National registry case series	★☆★★	☆☆	★☆☆
Chen *et al.*[27]	Single-center case series	★☆★★	☆☆	★★★
Mehta *et al.*[28]	Single-center case series	★☆★★	☆☆	★★★
Bossini *et al.*[25]	Multicenter case series	★☆★★	☆☆	★★★
Cravedi *et al.*[17]	Multicenter case series	★☆★★	☆☆	★★☆
Chaudhry *et al.*[26]	Multicenter case series	★☆★★	☆☆	★☆☆
Pérez-Sáez *et al.*[14]	National registry case series	★☆★★	☆☆	★★★
Demir *et al.*[24]	Multicenter case series	☆☆★★	☆☆	★☆☆
Lubetzky *et al.*[22]	Single-center case series	★☆★★	☆☆	★★★
Bell *et al.* (preprint)[15]	National registry case series	★☆★★	☆☆	★★★
Mohamed *et al.*[20]	Single-center case series	★☆★★	★☆	★★★
Kates *et al.*[10]	Multicenter case series	☆☆★★	☆☆	★★★
Benotmane *et al.*[29]	Single-center case series	★☆★★	☆☆	★★★
Ravanan *et al.*[11]	National registry cohort	★★★★	★☆	★★★

From left to right, quality items were starred black if they fulfilled predefined criteria: selection was starred on representativeness of patients with the exposure of interest (kidney transplant), selection of the nonexposed group, ascertainment of exposure, and demonstration that outcome of interest (death) was not present at start of the study; comparability was starred on the study controlling for the exposure of interest, and any additional factor; outcome was starred on how the outcome was assessed, whether follow-up was long enough for the outcome to occur, and whether loss to follow-up was adequate enough to be unlikely to introduce bias.

likely to have been included in the registry report by Sánchez-Álvarez *et al.*,[12] whereas Pascual *et al.*[13] and Pérez-Sáez *et al.*[14] were reports of subgroup analyses from this registry. Cravedi *et al.*[17] excluded any patients from studies that had already been published, but these were smaller studies not included in our summary. Kates *et al.*[10] did not report which centers submitted data to its registry but there were more than 50, of which >98% were from the United States; our review includes 6 other studies with data from the United States that may have overlapped. Some centers from the United States and Italy reported in our review are likely to have contributed to the surveys published by Boyarsky *et al.*[18] and Vistoli *et al.*[19]

Data Analysis

Data and results from each study are summarized in Table 2. The 20 studies were published online between April 10 and August 11, 2020; one was a preprint with the remainder in journals. The last day of follow-up for each study ranged from March 17 to May 31, 2020. The studies ranged from 24 to 489 kidney transplant recipients in total.

Patient Characteristics

Of the studies with available patient demographic data, average age ranged from 45 years in Demir *et al.*[24] to 66 years in Rodriguez-Cubillo *et al.*[23] The percentage of male patients ranged from 46% in Pascual *et al.*[13] to 79% in Bossini *et al.*[25]

Clinical Presentation

Fever was common in studies, ranging from 52% to 95%; cough ranged from 49% to 78%, and dyspnea from 28% to 70%. Gastrointestinal symptoms were also reported, as high as 53% in Chaudhry *et al.*[26] Four studies reported data on acute kidney injury or graft dysfunction at presentation, ranging from 28% in Mohamed *et al.*[20] to 77% in Chen *et al.*[27] No report described asymptomatic infection.

Baseline Immunosuppression Adjustment

A wide range of approaches was taken to adjust immunosuppression both between and within the studies. The dominant practice across other studies was to favor withholding or reducing antiproliferative drugs or mammalian target of rapapmycin inhibitor over reduction in calcineurin inhibitor dose.

COVID-19 Therapy

Thirteen studies reported the use of COVID-19 therapies. Hydroxychloroquine was used in 11 studies, either alone or in combination with another therapy, with the proportion of patients receiving the drug ranging from 38% to 100%. Ten studies either started corticosteroid therapy or increased dosage. High-dose corticosteroid was reported in 6 studies for between 4% and 62% of patients. Remdesivir use was reported

Table 2. Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
Manganaro *et al.*[16]	10 April	All inpatients and outpatients with COVID-19 confirmed by swab	22 Nephrology and Dialysis Units, Piedmont and Aosta Valley, Italy	Up to 27 March	26	• Age median 61 y (range 26–80)		• ICU admission ~5/26 (21%) (for dialysis patients ~8/102 [8%])		
Boyarsky *et al.*[18]	13 April	Patients with COVID-19	88/111 centers conducting >100 solid organ transplants/year, United States	Up to 24 March to 31 March when survey was conducted	103			• Mild illness (no pneumonia) 58/103 (56%) • Moderate illness (pneumonia) 18/103 (18%) • Critical illness 27/103 (26%)		
Pereira *et al.*[21]	24 April	All inpatients and outpatients with COVID-19 confirmed by RT-PCR	Two multiple solid organ transplant centers, New York City, United States	13 March to 3 April	51 (46 kidney-only, 3 heart-kidney, 1 liver-kidney, 1 pancreas-kidney)			• Death or ICU admission 13/51 (25%)		
Sánchez-Álvarez *et al.*[12]	27 April	Inpatients and outpatients who tested positive for COVID-19 entered to COVID-19 Registry of Spanish Society of Nephrology	Health centers across the Autonomous Communities of Spain	18 March to 11 April	~286 (~269 hospitalized; ~122 recovered or died)[a]	• Age (y) median 60 ± 13 • Sex: males ~190/~286 (66%)[a] • ACEI/ARB ~110/286 (39%)*		• Death ~53/~122 (43%) (for in-center HD ~138/~230 [60%])[a] • ICU admission ~25/~286 (9%)* • Mortality by age OR 1.09 (95% CI 1.06 – 1.13) • Mortality by pneumonia OR 5.83 (95% CI 1.61–21.2)		• LPV/r ~109/~286 (38%)[a] • HCQ ~249/~286 (87%)[a] • Steroids ~110/~286 (39%)[a] • Interferon ~16/~286 (6%)[a] • Tocilizumab ~23/~286 (8%)[a]
Vistoli *et al.*[19]	3 June	Reported COVID-19–positive inpatients and outpatients according to survey of kidney transplant centers	39/41 public kidney transplant centers, Italy	Up to 17 March	60 (57 hospitalized)	• Transplanted between 1 February and 15 March 3/60 (5%)		• Death 11/57 (19%) • ICU 17/57 (30%)		

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
Rodriguez-Cubillo *et al.*[23]	12 June	Confirmed COVID-19 (RT-PCR) referred to a kidney transplant center	Kidney transplant center, Madrid, Spain	15 March to 24 April; follow-up to 19 May	29 (29 recovered to discharge or died)	• Age (y) median 66 (IQR 59–72) • Sex: male 17/29 (59%) • Time since transplant (mo) median 99 (IQR 26–171) • Comorbidities: diabetes 11/29 (38%), obesity 15/29 (52%) • Baseline IS: tacrolimus 19/29 (66%), ciclosporin 6/29 (21%), MPA 22/29 (76%), mTORi 8/29 (28%), azathioprine 1/29 (3%), prednisolone 23/29 (79%)	• Symptomatic 26/29 (90%) • Fever 20/29 (69%) • Cough 17/29 (59%) • Dyspnea 14/29 (48%) • Diarrhea 14/29 (48%) • AKI 14/29 (48%) • Oxygen requirement 7/29 (24%) • CXR no changes 11/29 (38%) • D-dimer (ng/ml) median 1429 (IQR 754–2358) • Ferritin (ng/ml) median 647 (IQR 348–1682) • LDH (iu/l) median 488 (IQR 360–712)	• Death 6/29 (21%); with AKI 4/14 (29%); patients treated with cyclosporin strategy 3/32 (13%), people treated with IS minimization 3/6 (50%) • Recovery from AKI to baseline renal function 10/10 (100%) • RRT 3/29 (10%) • Suspected acute rejection 0/29 (0%) • Mechanical ventilation 5/29 (17%) • Recovery from mechanical ventilation 3/5 (60%)	• Switched to ciclosporin and prednisolone 23/29 (79%) • Cyclosporin level (ng/ml) median 60 (IQR 40–83) • Tacrolimus reduced 3/19 (16%) • Prednisolone only 3/29 (10%) • Antiproliferative stopped 23/23 (100%) • mTORi stopped 8/8 (100%)	• HCQ 27/29 (93%) • Antibiotics 29/29 (100%) • High-dose steroids 18/29 (62%) • Tocilizumab 9/29 (31%) • i.v. Ig 8/29 (28%) • Anticoagulation 24/29 (83%)
Pascual *et al.*[13]	19 June	Inpatients with confirmed COVID-19 (RT-PCR) within 60 d of kidney transplantation, entered to COVID-19 Registry of Spanish Society of Nephrology	12 transplant centers, Spain	17 March to 18 April	24 (of 265 transplants within 60 d) (do not specify how many recovered to discharge)	• Age: ≥65 y 12/24 (50%) • Sex: male 11/24 (46%) • Comorbidities: diabetes 12/24 (50%) • Deceased donor 23/24 (96%) • DGF 12/24 (50%) • Acute rejection 2/24 (8%) • Baseline IS: prednisone 24/24 (100%), tacrolimus 24/24 (100%), MMF 21/24 (88%), mTORi 2/24 (8%)	• Fever 15/24 (63%) • Cough/rhinorrhea 14/24 (58%) • Dyspnea 14/24 (58%) • Pneumonia 22/24 (92%) • Lymphopenia 24/24 (100%)	• Death 11/24 (46%) • Renal failure 13/24 (54%) • Mechanical ventilation 9/24 (38%) • ICU admission 4/24 (17%)		• HCQ 22/24 (92%) • Glucocorticoids 12/24 (50%) • LPV/r 8/24 (33%) • Tocilizumab 8/24 (33%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
Chen *et al.*[27]	23 June	Inpatients with confirmed COVID-19 (RT-PCR) in addition to radiographic evidence	Single center, New York City, United States	18 March to 10 April	30 (29 recovered to discharge or died)	• Age (y) mean 56 ± 12 • Sex: males 16/30 (53%) • Race: African descent 22/30 (73%), Hispanic 5/30 (17%), Caucasian 2/30 (7%), Asian 1/30 (3%) • BMI (kg/m^2) mean 28.7 (SD 6.9) • Time since transplant (y) median 7 (IQR 4–14) • Deceased donor 18/30 (60%) • Cause of ESRD: hypertension 13/30 (43%), diabetes 11/30 (36%), HIV 2/30 (7%), ADPKD 2/30 (7%), SLE 2/30 (7%) • Comorbidities: diabetes 14/30 (47%), vascular diseases 11/30 (37%), obesity 10/30 (33%), asthma/COPD 0/30 (0%) • Baseline creatinine (mg/l) median 1.3 (IQR 1.0–1.8) • CKD stage: 3 14/30 (47%), 4 1/30 (3%), 2/30 (7%) • Baseline IS: tacrolimus 26/30 (87%), ciclosporin 3/30 (10%), MMF 12/30 (40%), prednisone 30/30 (100%) • Baseline tacrolimus level (ng/ml) mean 7.0 (SD 5.6)	• Fever 22/30 (73%) • Cough 20/30 (67%) • GI symptoms 13/30 (43%) • Oxygen requirement 27/30 (90%) • Intubated pre-hospital/in ED 2/30 (7%) • AKI 23/30 (77%) • Creatinine (mg/ml) median 1.8 (IQR 1.4–2.7) • LDH (units/l) median 294 (238–427) • CRP (mg/l) median 76 (IQR 44–147) • ESR (mm/h) median 72 (IQR 58–80) • Ferritin (μg/l) median 979 (IQR 422–1977) • D-dimer (μg/ml) median 2900 (IQR 1053–5142) • WCC (x103/mm^3) median 6.7 (IQR 4.6–9.0)	• Deaths 6/29 (21%) • Mechanical ventilation 7/30 (23%) • RRT 4/30 (13%) • Ischaemic stroke 2/30 (7%)	• CNI withheld 29/29 (100%) • MMF withheld 12/12 (100%) • High-dose MP 18/30 (60%)	• HCQ + AZM 30/30 (100%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
							• Neutrophils (x103/mm^3) median 4.9 (IQR 3.3–6.3) • Lymphocytes (x103/mm^3) median 0.7 (IQR 0.5–1.0) • Procalcitonin (ng/ml) median 0.2 (IQR 0.1–1.3)			
Mehta *et al.*[28]	23 June	Attendees to ED with confirmed COVID-19 (RT-PCR) of 44 who reported symptoms to an outpatient monitoring system	Kidney transplant center, New York City, United States	15 March to 12 April	34 (33 recovered to discharge or died)	• Age (y) median 59 (IQR 53–64) • Sex: male 22/34 (65%) • Race: African American 15/34 (44%), Hispanic 8/34 (24%), Asian 2/34 (7%), white 7/34 (21%), other 2/34 (7%) • BMI (kg/m^2) median 27.4 (IQR 24.0–31.5) • Time since transplant (mo) median 37 (IQR 19–54); within 12 mo 14/30 (41%) • Deceased donor: 27/34 (79%) • Baseline IS: tacrolimus 29/34 (85%), cyclosporin 1/34 (3%), MMF 33/34 (97%), belatacept 6/34 (18%), everolimus 1/34 (3%), prednisone 34/34 (100%)	• Time from symptoms to presentation (d) median 8 (IQR 5–10) • Fever or cough 19/34 (56%) • Diarrhea 5/34 (15%) • Hypoxia 18/34 (3%) • CXR: bilateral airspace opacification 32/34 (94%) • Lymphopenia 32/34 (94%) • CRP (mg/l) median 101 (range 2–389)	• Deaths 6/33 (18%) • Discharged from ED 9/34 • Readmitted with progressive illness 7/9 • LOS (d) median 10 (IQR 5–16) • AKI during admission 18/34 (53%) • RRT 0/34 (0%)	• MMF withheld 26/33 (79%) • MMF reduced 6/33 (18%) • Belatacept held/delayed 6/6 (100%) • CNI held 0/30 (0%)	• HCQ 33/34 (97%) • AZM 27/34 (79%) • Tocilizumab or recruited to RCT clazakizumab vs placebo 9/34 (27%)
Bossini *et al.*[25]	6 July	Symptomatic inpatients and outpatients assessed either in ED or clinic with confirmed COVID-19 (RT-PCR)	Kidney transplant outpatient center and 3 admitting hospitals, Brescia, Italy	1 March to 16 April	53 (45 hospitalized; 42 recovered to discharge or died)	• Age (y) median 60 (IQR 50–67) • Sex: males 42/53 (79%) • Cause of ESRD: PKD 12/53 (23%), IgA 8/53 (15%), other GN 6/53 (11%), CAKUT 5/53	• Temperature >37.5°C 51/53 (96%) • Cough 26/53 (49%) • Dyspnea 15/53 (28%)	Inpatients only: • Death 15/42 (36%); due to ARDS 14/15 (93%), due to likely bacterial sepsis 1/15 (7%)	Inpatients: • Withdrawal of usual IS 42/45 (93%) • MMF withdrawn & CNI halved 3/45 (7%) • Started or increased	• HCQ + AZM 39/53 (79%) (including all outpatients) Inpatients only: • LPV/r 18/45 (40%) • DRV/r 14/45 (31%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
						(9%), other 5/53 (9%), not determined 17/53 (32%) • Comorbidities: diabetes 11/53 (21%), cardiac diseases 10/53 (19%), previous DVT 4/53 (8%), other 4/53 (8%) • Time since transplant (y) median 9 (IQR 4–16) • Deceased donor 48/53 (91%) • Induction IS: ATG 17/38 (45%), basiliximab 14/38 (37%), alemtuzumab 6/38 (38%), other 1/38 (3%) • Baseline IS: tacrolimus 31/53 (58%), cyclosporin 17/53 (32%), MMF 32/53 (60%), mTORi 6/53 (11%), glucocorticoid 30/53 (57%) • Baseline creatinine (mg/dl) median 1.8 (IQR 1.5–2.4)	• GI symptoms 9/53 (17%) • CXR: no infiltrates 1/39 (3%), bilateral infiltrates 27/39 (69%) Inpatients only: • Time from symptoms to presentation (d) median 7 (IQR 4–10) • WCC (10^9/l) median 5.6 (IQR 4.1–7.4) • Neutrophils (10^9/l) median 4.1 (IQR 2.9–6.8) • Lymphocytes (10^9/l) median 0.6 (IQR 0.4–1.1) • LDH (units/l) median 263 (IQR 213–323) • CRP (mg/l) median 39 (IQR 16–103) • Creatinine increase compared to baseline (%) median 21 (IQR 7–30) • Ferritin (μg/l) median 433 (IQR 284–872) • Fibrinogen (mg/dl) median 540 (IQR 380–625)	• ARDS 27/45 (60%) • ICU 10/45 (22%) • Mechanical ventilation 9/45; 8/9 (89%) died • Creatinine increase compared with baseline (%) −8 (IQR −20 to 7) (from 1 center = 28 patients) • LOS (d) median 11 (IQR 7–16)	to MP 16 mg or equivalent 34/45 (76%) • Glucocorticoid dose unchanged 11/45 (24%) Outpatients: • MMF withdrawn & CNI halved 4/8 (50%) • MMF withdrawn only 1/8 (13%) • Low-dose MMF maintained 1/8 (13%) • mTORi withdrawn & CNI halved 1/8 (13%) • CNI halved 1/8 (13%) • Started or increased to MP or equivalent 16mg 3/8 (38%) • Glucocorticoid dose unchanged 5/8 (62%)	• Dexamethasone 18/45 (40%) • Tocilizumab in addition to dexamethasone 8/18 (44%) • Prophylactic heparin 23/45 (51%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
							• D-dimer (ng/ml) median 414 (IQR 101–677)			
Cravedi *et al.*[17]	10 July	Inpatients with confirmed COVID-19 (RT-PCR) participating in the TANGO consortium (www.tangoxstudy.com) (excluded patients included in prior publications)	12 transplant centers across the United States (5), Italy (4), and Spain (2)	2 March to 15 May	144 (do not specify how many recovered to discharge)	• Ages (y) median 62 (IQR 52 – 69) • Sex: male 94/144 (65%) • Race: Hispanic 56/144 (40%), White 43/144 (31%), African American 35/144 (25%) • Comorbidities: diabetes 75/144 (52%), obesity 71/144 (49%), heart disease 41/144 (28%), lung disease 27/144 (19%), cancer 22/144 (15%), smoking history 39/144 (27%), HIV 3/144 (2%), ACEI 20/144 (14%), ARB 24/144 (17%) • Cause of ESRD: diabetes 43/144 (30%), glomerular disease 25/144 (16%), hypertension 20/144 (14%), PKD 13/144 (9%) • Time since transplant (y) median 5 (IQR 2–9), <1 y 23/144 (16%) • Deceased donor 112/144 (78%) • Baseline IS: tacrolimus 131/144 (91%), MMF 111/144 (77%), everolimus 11/144 (8%), prednisolone 125/144 (89%)	• Fever 96/144 (67%) • Dyspnea 97/144 (68%) • Diarrhea 55/144 (38%) • Myalgia 76/144 (53%) • Symptoms onset to admission (d) median 6 (IQR 3–8) • WCC (10^9/L) median 6.4 (IQR 4.6–8.3) • Lymphocytes (x10^9/l) median 0.9 (IQR 0.5–3.1) • Creatinine (mg/dl) median 1.5 (IQR 1.1–1.9) • CRP (mg/l) median 41 (IQR 12–125) • Ferritin (µg/l) median 1260 (IQR 523 - 2620) • D-dimer (µg/ml) median 1.12 (0.62–2.00) • IL-6 (ng/ml) 37 (8–95) • Procalcitonin (ng/ml) median 0.3 (IQR 0.1–1.0)	• Death 46/144 (32%); by age (y) >60 vs ≤60 OR 1.07 (95% CI 1.02–1.14) • ICU admission 43/144 (30%); died 22/43 (51%) • Mechanical ventilation 42/144 (29%) • ECMO 3/144 (2%) • AKI 74/144 (51%) • Symptom onset to death (d) median 15 (IQR 8–22) • Symptom onset to discharge (d) median 22 (IQR 15–35) • Follow-up (d) median 52 (IQR 16–66)	• Tacrolimus withheld 32/131 (25%) • Steroid increased 95/125 (76%)	• HCQ 101/144 (70%) • Antibiotics 106/144 (74%) • Tocilizumab 19/144 (13%) • Remdesivir 9/144 (6%) • LPV/r 7/144 (5%) • DRV/r 3/144 (2%) • Darunavir-cobisistat 1/144 (1%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
Chaudhry *et al.*[26]	12 July	All inpatient and outpatient SOT recipients with confirmed COVID-19 (RT-PCR)	5 hospitals within a quaternary care academic institution, Michigan, United States	20 March to 18 April	38 (26 hospitalized)[b]	• Age (y): median 61.5 (IQR 52–70) • Sex: males 26/38 (68%) • Race: Black 31/38 (82%) • Comorbidities: COPD 5/38 (13%), CKD 35/38 (92%), heart failure 8/38 (21%), coronary artery disease 3/38 (8%), diabetes 27/38 (71%), hypertension 37/38 (97%), malignancy 3/38 (8%), smoking history 7/38 (18%) • BMI (kg/m^2) median 28 (IQR 26–33)	• Cough 23/38 (61%) • Fever 22/38 (58%) • Dyspnea 21/38 (55%) • Altered mentation 7/38 (18%) • Diarrhea 20/38 (53%) • Myalgia 15/38 (40%) • Fatigue 15/38 (40%) • Symptom duration (d) median 7 (IQR 2–10) • WCC (10^9/l) median 5.8 (IQR 4.7–8.8) • Lymphocytes (10^9/l) median 0.5 (IQR 0.4–0.8) • CRP (mg/dl) median 7.5 (IQR 2.4–13.5) • Abnormal CXR/CT chest 24/38 (64%)	• Death 7/38 (18%) • ICU admission 12/38 (32%) • Mechanical ventilation 11/38 (29%) • ARDS: mild 0/11 (0%), moderate 4/11 (36%), severe 7/36 (64%) • AKI requiring RRT 5/38 (13%) • Secondary bacterial infection 7/38 (18%) • Hospital LOS (d) median 4 (IQR 2–20)		
Pérez-Sáez *et al.*[14]	12 July	Inpatients identified through national COVID-19 registry with confirmed COVID-19 (RT-PCR) who received tocilizumab based on individual hospital protocols for increased disease severity. All patients had at least one of the following: increased IL-6; increase in other inflammatory markers; rapidly progressive ARDS.	29 hospitals, Spain (27 completed request for additional data)	Up to 9 May (follow-up to 15 May)	80 (of 468 included in the registry) (80 recovered to discharge or died)	• Age (y): mean 59 (SD 12) • Sex: Males 54/80 (68%) • Race: Caucasian 71/80 (89%) • Comorbidities: diabetes 23/80 (29%), lung disease 7/80 (9%), IHD 13/80 (16%), cancer history 17/80 (22%), BMI >30 kg/m^2 14/80 (18%),	• Fever 65/80 (81%) • Dyspnea 46/80 (58%) • Respiratory symptoms 62/80 (78%)	• Death 26/80 (33%) • ICU admission 24/80 (30%) • NIV 33/80 (44%) • Mechanical ventilation 19/80 (24%)	• CNI withheld 4/66 (6%) • MMF/mTORi withheld 26/78 (33%) • Both CNI & MMF/mTORi withheld 43/80 54%)	• Tocilizumab 80/80 (100%) • Tocilizumab > 1dose 16/80 (20%) • HCQ 79/80 (99%) • AZM 59/80 (74%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
		Additional patients were identified after contacting centers				ACEI/ARB 26/80 (33%), smoking history 17/80 (21%) • Cause of ESRD: diabetes 15/80 (19%), vascular 7/80 (9%), glomerular 17/80 (21%), PKD 14/80 (18%) • Time since transplant (mo) median 72 (IQR 17 – 165) • Re-transplantation 21/80 (26%) • Induction: ATG 33/80 (41%) • Baseline IS: CNI 66/80 (83%), prednisolone 73/80 (91%), MMF 64/80 (80%), mTORi 14/80 (18%)	• GI symptoms 38/80 (48%) • CXR changes 78/80 (98%) • Symptom onset to admission (d) median 4 (IQR 3–8) • Moderate/severe ARDS 6/80 (8%) • Oxygen saturation (%) median 95 (IQR 91 – 97) (n = 40) • WCC (10^9/l) mean 6.8 (SD 3.1) • Lymphocytes (10^9/l) mean 0.8 (SD 0.6) • CRP (mg/l) median 49 (IQR 10–49) • Procalcitonin (ng/ml) median 0.24 (IQR 0.1–1.1) • IL-6 (pg/ml) median 52 (IQR 33–110) • LDH (units/l) median 335 (IQR 257–485) • Ferritin (ng/ml) median 698 (IQR 393–1677) • D-dimer (mcg/l)	• AKI 36/80 (45%) • AKI requiring dialysis 15/80 (19%) • Acute rejection 1/80 (1%) • Time admission to ICU (d) median 7 (IQR 4–12) • Follow-up time (d) median 25 d (IQR 17–35)		• Other antibiotic 61/80 (76%) • Steroids 64/80 (80%) • i.v. Ig 12/80 (15%) • Interferon 5/80 (6%) • LPV/r or remdesevir 39/80 (49%) • Anakinra 6/80 (8%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
							median 900 (IQR 475–1730) • Pneumonia on CXR 78/80 (98%)			
Demir *et al.*[24]	13 July	Inpatients and outpatients with confirmed COVID-19 (RT-PCR)	5 transplant centers, Istanbul, Turkey	1 February to 4 May (followed-up for at least 15 d)	44 (1 excluded as "without typical findings", 3 lost to follow-up) (39 hospitalized - do not specify how many recovered to discharge)	• Age (y): mean 45 (SD 15) • Sex: male 20/40 (50%) • Cause of ESRD: hypertension 4/40 (10%), diabetes 2/40 (5%), chronic GN 13/40 (33%) • Comorbidities: lung disease 3/40 (8%), ACEI/ARB 18/40 (45%), hypertension 26/40 (65%) • Time since transplant (mo) median 75 (IQR 32–128) • Deceased donor 5/40 (13%) • Induction IS: ATLG 22/40 (55%), basiliximab 3/40 (8%) • Baseline IS: tacrolimus 31/40 (78%), cyclosporine 5/40 (13%), mTORi 4/40 (10%), mycophenolate 36/40 (90%), steroids 40/40 (100%)	• Fever 25/40 (63%) • Cough 30/40 (75%) • Dyspnea 21/40 (53%) • Diarrhea 10/40 (25%) • Oxygen saturation (%) median 96 (IQR 93 – 98) • Creatinine (mg/dL) median 1.6 (IQR 1.2–2.2) • WCC (10^9/l) median 5.2 (IQR 4.0–7.0) • Lymphocytes (10^9/l) median 0.7 (IQR 0.5–1.0) • CRP (mg/l) median 45 (IQR 24–88) • LDH (units/l) median 257 (IQR 198–370) • D-dimer (ng/ml) median720 (IQR 510–1734) • Ferritin (ng/ml) median 358 (IQR 173–992)	• Death 5/40 (13%) • NIV 4/40 (10%) • Mechanical ventilation 6/40 (15%) • Follow-up time (d) 32 (IQR 23–44) • LOS (d) median 9 (IQR 5 – 12)	• CNI withheld 11/36 (30.6%) • Antimetabolite withheld 40/40 (100%)[c] mTORi 4/4 (100%)	• Favipiravir 18/40 (45%) • Tocilizumab 5/40 (13%) • Anakinra 3/40 (8%) • Antibiotics 24/40 (60%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
							• Graft dysfunction 14/40 (35%)			
Lubetzky *et al.*[22]	17 July	Consecutive inpatients and outpatients with confirmed COVID-19 (RT-PCR)	Transplant center, New York, United States	13 March to 20 April	54 (39 hospitalized; 37 recovered to discharge or died)	• Age (y): median 57 (range 29 – 83) • Sex: male 38/54 (70%) • Race: white 17/54 (31%), Hispanic 17/54 (31%), black 13/54 (24%), Asian 6/54 (11%), Middle Eastern 1/54 (2%) • BMI (kg/m^2): (median) 28 (IQR 18–43) • Comorbidities: diabetes 16/54 (30%), cardiovascular disease 19/54 (35%), stroke 4/54 (7%), lung disease 8/54 (15%), antihypertensives 50/54 (93%), ACEI/ARB 19/54 (37%), smoking 12/54 (22%) • Baseline creatinine (mg/dl) mean 1.5 (SD 0.7) • Cause of ESRD: hypertension 11/54 (20%), diabetes 14/54 (26%), GN 13/54 (24%), lupus 2/54 (4%), PKD 3/54 (6%) • Time since transplant (y): median 4.7 (range 0.3 -35) • Deceased donor 17/54 (31%) • IS induction: T-cell depleting agent 39/54 (72%) • Baseline IS: steroids 22/54 (41%), CNI 52/54 (96%), belatacept 1/54 (2%), MMF 52/54 (96%), mTORi 2/54 (4%)	All patients: • Fever 40/54 (74%) • Cough/upper respiratory tract symptoms 32/54 (59%) • Dyspnea 28/54 (52%) • Fatigue/myalgia 23/54 (43%) • Diarrhea 21/54 (39%) • Confusion 6/54 (11%) • Time symptoms to diagnosis (d): mean 8 (SD 6) Inpatients: • Oxygen saturation (%) median 93 (89 – 96) • Creatinine (mg/dl) mean 2.6 (SD 2.3) • WCC (10^9/l) median 5.7 (IQR 3.6–8.0) • Lymphocytes (10^9/l) median 0.6 (IQR 0.3–1.0) • D-dimer (ng/ml) median 394 (IQR 278–589)	Inpatients: • Death 7/39 (18%) • Mechanical ventilation 11/39 (28%) • AKI 20/39 (51%) • RRT 4/39 (10%) • AKI: resolved 9/20 (45%), partially resolved 5/20 (25%), not resolved 6/20 (30%), dialysis dependent at follow-up 3/20 (15%) • Follow-up (d) median 29 (range 5–53) Outpatient: • Complete symptom resolution 14/15 (93%) • Follow-up (d) median 37 (range 21–40)	• Tacrolimus reduced 17/52 (33%) • Tacrolimus withheld 0/52 (0%) • MMF halved 15/52 (29%) • MMF withheld 24/52 (46%) • Additional steroid 5/54 (9%) • Remained steroid free 29/32 (91%)	Inpatient: • HCQ 31/39 (79%) • Remdesivir 2/39 (5%) • IL-6 receptor inhibitor 2/39 (5%) • Convalescent plasma 1/39 (3%) • AZM 7/39 (18%) • Doxycycline 8/39 (21%) Outpatient: • HCQ 1/15 (7%) • AZM 5/15 (33%) • Doxycycline 1/15 (7%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
							• Ferritin (ng/ml) median 1498 (IQR 383–2646) • IL-6 (pg/ml) median 8 (IQR 4.5–92) • Procalcitonin (ng/ml) median 0.3 (IQR 0.1–0.6) • AKI 20/39 (51%)			
Bell *et al.*[15]	21 July (posted)	Notified confirmed COVID-19 as identified through the Scottish Renal Registry through linkage to Health Protection Scotland	Scotland, UK (100% patient- and unit-level coverage)	Up to 31 May	24 (of 3286 functioning kidney transplants)	• Age (y): 20–44 4/24 (17%), 45–64 12/24 (50%), 65–74 5/24 (21%), ≥75 3/24 (13%) • Sex: male 13/24 (54%) • Cause of ESRD: GN 3/24 (13%), interstitial 12/24 (50%), Multisystem 3/24 (13%), diabetes 3/24 (13%) • Time since transplant (y): <1 0/24 (0%), >10 14/24 (58%) • Scottish Index of Multiple Deprivation: 1 (most deprived) 7/24 (29%), 5/24 (21%), 4/24 (17%), 5/24 (21%), 3/24 (13%)		• Death 7/24 (29%)		
Mohamed *et al.*[20]	31 July	Consecutive inpatients and outpatients with confirmed COVID-19 (RT-PCR)	Kidney transplant center, London, UK	Up to end of April	28 (of 1434 functioning transplants) (25 hospitalized – 25 recovered to discharge or died); comparison with 32 patients active on transplant waiting list (of 321) (14 hospitalized)	• Age (y) median 57 (range 25–72) • Sex: male 16/28 (57%) • Time since transplant (mo) median 39 (range 1–227 mo); within 1 y 7/28 (25%); within 3 mo 1/28 (4%) • Donor: deceased 22/28 (79%) • BMI (kg/m^2) median 28 (range 19–38) • Comorbidities: diabetes 10/28	• Healthcare-associated infection 2/28 (7%) • Fever 13/25 (52%) • Dyspnea 10/25 (40%) • Cough 13/24 (54%) • GI symptoms 7/25 (28%)	• Death 9/25 (36%); (vs 5/14 (36%) on waiting list) • ICU 5/25 (20%); died 4/5 (80%) • RRT 2/25 (8%)	• MMF withdrawal 19/21 (90%) • MMF halved 1/21 (5%) • Azathioprine withdrawal 3/3 (100%) • Prednisolone increased from 5 to 10 mg 12/27[d]	• RECOVERY trial (dexamethasone arm) 1/25 (4%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
						(37%), IHD 5/28 (18%), chronic lung disease 4/28 (14%), chronic liver disease 0/28 (0%), PVD 1/28 (4%) • Induction IS: IL2RA 21/27 (78%), ATG 6/27 (22%)[d] • Baseline IS: tacrolimus + MMF + prednisolone 16/27 (59%), ciclosporin + MMF + prednisolone 5/27 (19%), tacrolimus + azathioprine + prednisolone 3/27 (11%), cyclosporin + prednisolone 2/27 (7%), tacrolimus + prednisolone 1/27 (4%)[d] • Baseline creatinine (μmol/l) median 155 (range 68–356)	• AKI 7/25 (28%) • Creatinine (μmol/l) 255 (range 58–566) • Hb (g/l) median 108 (range 81–157) • WCC (10^9/l) median 6.8 (range 3.0–18.0) • Neutrophils (10^9/l) median 5.5 (range 1.0–17.0) • Lymphocytes (10^9/l) median 0.6 (range 0.2–1.7) • CRP (mg/l) median 85 (range 7–367) • CXR ground-glass shadowing or consolidation 19/25 (76%)			
Kates *et al.*[10]	7 August	Any inpatient or outpatient SOT recipient with confirmed COVID-19 (RT-PCR) reported through an electronic case report form	>50 transplant centers, >98% United States	7 March to 15 April; all cases followed-up for 28 d	318 kidney-only or kidney-pancreas recipients	• Age (y) 56 (IQR 46–66) • Sex: male 186/318 (59%) • Race: Asian/Pacific Islander 18/318 (6%), black 150/318 (47%), white 130/318 (41%), other/unknown 20/318 (6%); Hispanic ethnicity 59/318 (19%) • Geographic location: United States – Northeast 151/318 (48%), Midwest 72/318 (23%), South 46/318 (15%), West 44/318 (14%); international 5/318 (2%)	• Healthcare-associated infection 39/318 (12%) • Fever 186/318 (59%) • Cough 235/318 (74%) • Dyspnea 187/318 (59%) • GI symptoms 156/318 (49%) • WCC (x 10^9/l) median 5.8 (IQR 4.3–8.4) (not reported in 34/318 [11%])	• Deaths within 28 d 57/318 (18%) • Hospitalization 254/318 (80%) • ICU 107/254 (42%) • Mechanical ventilation 87/254 (34%) • Vasopressors 74/254 (29%) • AKI 130/318 (41%)	• IS modified 241/318 (76%)	• CQ/HCQ 197/318 (62%) • AZM 110/318 (35%) • Anti-IL6 39/318 (12%) • High-dose steroids 35/318 (11%) • Convalescent plasma 10/318 (3%) • Protease inhibitor 9/318 (3%) • Remdesivir 9/318 (3%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
						• Time since kidney transplant (y) median 5 (IQR 2–10) • Transplanted in 2020 9/318 (3%) • Comorbidities: coronary artery disease 68/318 (21%), heart failure 30/318 (9%), diabetes 170/318 (54%), CKD 134/318 (42%), haemodialysis 25/318 (8%), chronic lung disease 29/318 (9%), malignancy 8/318 (3%), HIV 5/318 (2%), BMI >30 kg/m^2 116/318 (37%) • ≥2 of age >65 y, heart failure, chronic lung disease and obesity 53/318 (17%) • Baseline IS: CNI + antiproliferative + steroid 176/318 (55%), CNI + steroid 49/318 (15%), CNI + antiproliferative 39/318 (12%), mTORi regimen 16/318 (5%), other 64/318 (20%) • Recently augmented IS 26/318 (8%) • Blood type: A 95/318 (34%), B 49/318 (18%), AB 14/318 (5%), O 118/318 (43%)	• Neutrophils (x 10^9/l) 4.3 (3.1–6.3) (not reported in 34/318 [11%]) • Lymphocytes (x10^9/l) 0.7 (0.4–1.0) (not reported in 34/318 [11%]) • CXR: abnormal 207/271 (76%); not performed 47/318 (15%) • CT chest: abnormal 59/60 (98%); not performed 258/318 (81%)	• New RRT 42/318 (13%) • Acute rise in LFT >3x ULN 21/318 (7%) • Acute MI 7/318 (2%) • VTE 8/318 (3%) • Bacterial pneumonia 23/318 (7%) • Bloodstream infection 17/318 (5%) • Acute TCMR or AMR 1/318 (0%)		• i.v. Ig 3/318 (1%) • Other experimental treatments 18/318 (4%) • Clinical trial 23/318 (5%)
Benotmane *et al.*[29]	10 August	Consecutive inpatients with COVID-19 diagnosed by RT-PCR or typical CT chest lesions	Kidney transplant center, Strasbourg, France	4 March to 7 April; followed-up to 13 May	40	• Age (y) median 64 (IQR 55–68) • Sex: male 31/40 (78%) • BMI (kg/m^2) median 30 (IQR 24–33)	• Fever 38/40 (95%) • Cough 31/40 (78%) • Dyspnea 28/40 (70%)	• Deaths 9/40 (23%) • Severe disease (oxygen requirement >6 l/min or ICU admission or	• MMF/MPA withdrawal 34/34 (100%) • CNI withdrawal 15/35 (43%)	• AZM 26/40 (65%) • Other antibiotics 40/40 (100%) • LPV/r 1/40 (3%) • HCQ 15/40 (38%)

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Table 2. (Continued) Summary of clinical data and outcomes from all included studies listed by order of online publication date

Study	Online publication date in 2020	Study population	Setting	Timeframe in 2020	Total number of cases	Patient characteristics	Clinical presentation	Outcomes	Baseline IS adjustment	COVID-19 therapy
						• Comorbidities: cardiovascular disease 16/40 (40%), respiratory disease 9/40 (23%), diabetes 19/40 (48%); ACEI/ARB 15/40 (38%) • Time since kidney transplant (y) median 7 (IQR 3–15) • Induction IS: ATG 18/40 (44%), anti-CD25 19/40 (46%), none 3/40 (7%) • Baseline IS: tacrolimus 21/40 (53%), ciclosporin 14/40 (35%), MMF/MPA 34/40 (85%), mTORi 6/40 (15%), azathioprine 1/40 (3%), corticosteroids 23/40 (58%), belatacept 2/40 (5%), eculizumab 1/40 (3%)	• Diarrhea 12/40 (30%) • Neurological symptoms 15/40 (38%) • RT-PCR negative 2/40 (5%); subsequent serology positive 2/2 (100%) • Viral load (log copies/reaction) 5.2 (3.8–6.7)	death) 18/40 (45%) • RNAaemia 8/31 (26%) • Seropositivity 31/31 (100%) (survivors only >14 d)	• mTORi withdrawal 6/6 (100%) • Belatacept delayed 1/2 (50%)	• Tocilizumab 4/40 (10%) • High-dose corticosteroids 14/40 (35%) • Antifungal 1/40 (3%)
Ravanan *et al.*[11]	11 August	SOT recipients with functioning graft as of 1 February with notified COVID-19 (RT-PCR) as identified through the NHS Blood and Transplant registry with linkage to Public Health England and the NHS Digital Tracing Service	England, UK	1 February to 20 May	489 (of 33,972 kidney-only or kidney-pancreas recipients); compared with 188/4241 patients active on the waiting list			• Deaths 128/489 (26%) (vs 18/188 [10%] in waitlisted patients)		

ACEI/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II-receptor blocker; AKI, acute kidney injury; AMR, antibody-mediated rejection; ARDS, adult respiratory distress syndrome; ATG, anti-thymocyte globulin; AZM, azithromycin; CAKUT, congenital abnormality of the kidneys and urinary tract; CI, confidence interval; CKD, chronic kidney disease; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus Disease 2019; CQ, chloroquine; CRP, C-reactive protein; CT, computed tomography; CXR, chest x-ray; DGF, delayed graft function; DRV/r, darunavir/ritonavir; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ED, emergency department; ESRD, end-stage renal disease; GI, gastrointestinal; GN, glomerulonephritis; HCQ, hydroxychloroquine; HIV, human immunodeficiency virus; ICU, intensive care unit; IHD, ischaemic heart disease; IL-6, interleukin-6; IQR, interquartile range; IS, immunosuppression; LDH, lactate dehydrogenase; LOS, hospital length of stay; LPV/r, lopinavir/ritonavir; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; NHS, National Health Service; NIV, non-invasive ventilation; OR, odds ratio; PKD, polycystic kidney disease; RCT, randomized controlled trial; RRT, renal replacement therapy; RT-PCR, reverse transcriptase polymerase chain reaction; SD, standard deviation; SOT, solid organ transplant; TCMR, T-cell mediated rejection; ULN, upper limit of normal; WCC, white cell count.

[a]Data reported as percentages of a total 868 patients receiving RRT.

[b]Unclear how many patients were discharged, as authors reported 26 discharged but also reported 7 died and 6 remained ventilated.

[c]Antimetabolite reported withheld in 40 of 40, but only 36 of 40 were on MMF at baseline.

[d]Data available for 27 of 28 patients (missing for 1 patient).

Note: Mohamed *et al.*[20] overlaps with Ravanan *et al.*[11]; Pereira *et al.*[21] overlaps with Lubetzky *et al.*[22]; Pascual *et al.*[13], Pérez-Sáez *et al.*[14], ± Rodriguez-Cubillo *et al.*[23] overlap with Sánchez-Álvarez *et al.*[12] Studies may overlap with Kates *et al.*[10]

in only a few studies, in a small number of patients. Eleven studies reported the use of an anti–interleukin-6 therapy. Pérez-Sáez *et al.*[14] described the experience of tocilizumab use based on inpatient cases entered to the Spanish Society of Nephrology registry.

Outcomes

Inpatient mortality was calculated where possible as a proportion from patients with completed outcomes (i.e., death or recovery to discharge), with the intention of reducing bias by misclassification of patients who remain hospitalized but may die later. In the largest national registry reports, mortality was 43% among mostly inpatients with completed outcomes in Sánchez-Álvarez *et al.*[12] from Spain up until April 11, and 26% in mostly inpatients reported by Ravanan *et al.*[11] from England up until May 20, although the number of patients who may subsequently recover from both studies was not known. In the largest multicenter series, Cravedi *et al.*[17] reported 32% mortality in 144 inpatients, although it did not specify how many recovered to discharge, whereas Kates *et al.*[10] reported 28-day mortality as 18% from its dataset in which 254 of 318 patients were hospitalized. Of other studies from which inpatient mortality could be calculated, mortality was 7 of 39 patients (18%) in Lubetzky *et al.*[22] across New York, 6 of 29 patients (21%) in both Rodriguez-Cubillo *et al.*[23] in Madrid and Chen *et al.*[27] in New York City, 15 of 42 patients (36%) in Bossini *et al.*[25] in Brescia, and 9 of 25 patients (36%) Mohamed *et al.*[20] in London.

Cravedi *et al.*[17] found 7% increased mortality in people aged >60 years compared with those aged ≤60 years. In subgroup reports from the national registry in Spain, Pascual *et al.*[13] reported 46% mortality among patients within 60 days of transplantation, whereas Pérez-Sáez *et al.*[14] reported 33% mortality among patients with severe COVID-19 treated with tocilizumab.

The proportion of patients requiring intensive care was variable, from 9% of inpatients across Spain according to early registry data,[12] to 42% of inpatients in the large multicenter series report by Kates *et al.*[10] including 34% requiring mechanical ventilation.[10] Acute kidney injury was common, ranging from 41% in Kates *et al.*[10] with 13% requiring extracorporeal renal replacement therapy, to 53% in Mehta *et al.*,[28] although none required renal replacement therapy. There were very few reports of acute rejection, with only 1 case of 318 in Kates *et al.*[10] Benotmane *et al.*[29] reported RNAemia in 26% and seropositivity in 100% of survivors.

DISCUSSION

Our systematic review of the early literature up to August 11, 2020, suggests that kidney transplant recipients hospitalized with COVID-19 experience poor outcomes, especially in the early post-transplant period.

The limitations of the literature so far require appreciation. Over time, published studies evolved from reports from a small number of centers, to larger multicenter studies and national registries. To reduce bias by smaller studies, we reported only those studies with completed outcomes for at least 20 kidney transplant recipients with confirmed COVID-19. Small studies may be more likely to be published by centers who accumulate more complex or unwell patients or by centers who are affected particularly unfavorably, both of which may introduce important bias; they may also exert a period effect, reflecting more overwhelming circumstances in the earlier stages of the pandemic.

Variation in reported mortality also could be due to strong period effects, with differences in thresholds for hospitalization, availability of resources, and management practices. Data from Sánchez-Álvarez *et al.*[12] found mortality of 43% from the Spanish Society of Nephrology COVID-19 registry in which 94% were inpatients. However, this is likely to be exaggerated as this was an early report based on data reported up to April 11, and approximately 147 patients remained alive but not yet recovered so were not included in our mortality calculation; fewer patients were admitted to intensive care unit compared with other reports which also may be an important period effect related to stretched resources.

The other large national registry report was Ravanan *et al.*,[11] who identified all solid organ transplant recipients from the National Health Service Blood and Transplant and linked this to confirmed COVID-19 cases through Public Health England and the National Health Service Digital Tracing Service. Of more than 30,000 prevalent kidney or kidney-pancreas recipients in England, there were 489 cases of COVID-19 of whom 128 died (26%) up to May 20.[11] This was compared with deaths in 18 of 188 (10%) patients waitlisted for transplantation but this comparison should be treated with caution, as many of these will have been in-center hemodialysis patients with more access to testing for milder or asymptomatic disease than transplant recipients in the community during the period of study. It was not possible to distinguish inpatients and outpatients from the available data sources, but as data were collected up to May 20, most cases were likely to be inpatients.

Large multicenter series were published by Cravedi *et al.*[17] and Kates *et al.*[10] Cravedi *et al.*[17] reported data for inpatients with COVID-19 from centers in Italy, Spain, and the United States already participating in the TANGO consortium, an

international network formed initially to investigate the recurrence of glomerular disease after transplantation. Kates *et al.*[10] reported outcomes from a registry hosted by the University of Washington to which cases were submitted from >50 centers, >98% of which were from United States after invitations through the American Society of Transplantation and American Society of Transplant Surgeons.[10] Entered data were not independently verified and its representativeness is uncertain as the extent to which cases from participating centers were systematically submitted is not known, with the authors acknowledging susceptibility to bias.

Studies from the United States reported high proportions of black patients, although no study investigated for associations between ethnicity or other socioeconomic factors with outcomes. From all solid organ transplant recipients in England, 38 of 129 Asian recipients (30%) and 27 of 95 (28%) black recipients died, compared with 79 of 334 white recipients (24%). In total, 2.4% of Asian recipients and 3.6% of black recipients have been diagnosed with COVID-19, compared with 1.0% of white recipients.[11]

The withdrawal of antiproliferative drugs such as mycophenolate, an inhibitor of T- and B-cell proliferation, was practiced almost universally, in keeping with expert consensus for even mild disease.[30,31] Our review highlighted the myriad of different management strategies used in different centers, including antivirals, hydroxychloroquine, corticosteroids, and tocilizumab. Establishing the effectiveness of therapies requires well-designed clinical trials; as high-risk patients, kidney transplant recipients may benefit from both prophylactic and therapeutic trials. The RECOVERY trial demonstrated mortality benefit in treatment with dexamethasone 6 mg daily for patients with COVID-19 requiring oxygen in June 2020, with the World Health Organization consequently recommending the use of systemic corticosteroids in severe and critical cases.[6,32] The RECOVERY trial has stopped recruiting patients to its lopinavir/ritonavir arm because of lack of benefit.[33] Few patients in studies were reported to have been treated with remdesivir.

Acute kidney injury was seen in several studies, although not all studies reported their definition and alternative terminology such as "renal failure" was also mentioned. Acute kidney injury is not uncommon in COVID-19, and its pathophysiology remains uncertain, but direct parenchymal infection and microangiopathy mediated by complex inflammatory processes have been suggested.[34] In transplant kidneys, there may be additional mechanisms, such as acute rejection from underimmunosuppression, or calcineurin inhibitor toxicity through drug-drug interactions (e.g., lopinavir/ritonavir); however, there were few reports of acute rejection in our review, but there may have been less investigation for this because of unwillingness to augment immunosuppression if it were diagnosed; we did not identify any histopathological series; and case reports of biopsies are prone to bias so systematic cross-sectional or longitudinal study designs would need to be considered. Studies in the coming months and years will need to address the longer-term impact of COVID-19 on graft function and permanent graft loss.

Pascual *et al.*[13] reported deaths in almost half the patients in Spain who acquired COVID-19 within 60 days of transplantation (11 of 24 [of 265 transplants in total]) up to April 18. Nearly all were recipients of deceased donor transplants with delayed graft function reported in half, but the authors did not report whether SARS-CoV-2 infection was acquired in health care settings or in the community. Although these findings are alarming, it will also have been affected by period effects from the start of the pandemic and there may now be opportunities to better minimize transmission in acute transplantation through planning and infrastructure. Several deceased- and live-donor programs were suspended with the aim of preventing high-risk patients acquiring SARS-CoV-2 infection perioperatively, limiting the use of lymphocyte-depleting antibodies as induction agents or in treatment of severe rejection, and avoiding use of limited inpatient resources. As services are restored, outcomes should be audited closely, and the risks and benefits should be nevertheless considered on an individualized basis given the apparent increased risk with heightened immunosuppression.

As the pandemic continues, we will need to use more systematic national and international registries with appropriate control groups and linkage to other sources, such as community test results and hospital records, to allow timely, large-scale analyses that can better inform policies and practices. Serological surveys of transplant recipients using validated antibody assays could be valuable in capturing the prevalence of asymptomatic and mild infection that did not result in inpatient admission or community viral RNA testing; such surveys will be important to obtain more accurate mortality and hospitalization estimates, follow-up potential longer-term complications, and identify the factors that are associated with more favorable outcomes.

Limitations

In the absence of available data, we were unable to undertake time-to-event analysis, therefore we report mortality as a proportion of patients with completed outcomes to avoid misclassification of patients who remain hospitalized but may die after surviving the

study period. However, this might be biased in the opposite direction if most of those who remained hospitalized were patients who were slowly recovering and more likely to survive.

Our searches included studies in English or Chinese only, with studies meeting inclusion criteria from France, Italy, Spain, Turkey, the United Kingdom, and the United States only. Searches in more languages may have resulted in a broader perspective, including more experiences in middle-income economies. As well as studies from Europe and North America, there were studies published from China and Iran from early in the pandemic that did not fulfill our criteria for inclusion because of smaller numbers of confirmed cases. It would be beneficial to obtain updated reports from centers such as these, as well as others in Africa, Asia, and Latin America.

The Newcastle-Ottawa Quality Assessment Scale was of limited value in objective quality assessment. It is designed to be semi-quantitative, but the crude equivalence of all the constituent assessment items may be misleading.

CONCLUSION

Our review of the literature in the early phase of the COVID-19 epidemic suggests that hospitalized kidney transplant recipients with COVID-19 are at a high risk of death. The quality of observational data is improving. Detailed and comprehensive data collection through registries and linkage with health records will be necessary to conduct analyses of risk factors for adverse outcomes, not least given the risks of stopping immunosuppression. Indeed, to optimize clinical care, we should ensure that nonhospitalized patients are included and existing registries are supported and commissioned to answer important questions that affect screening and management.

We are reassured that we have developed a reproducible search strategy that can be effectively redeployed at appropriate intervals during the pandemic and beyond to be able to conduct meta-analyses of accumulating data in the future.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We are grateful to the authors of Manganaro *et al.*,[16] Kates *et al.*,[10] and Mohamed *et al.*[20] for providing additional data and clarifications as requested.

Insilica, LLC, owners of Sysrev, gifted the review team a grant worth $2000 total to support screening and data extraction. This research did not receive any other specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Material S1. Initial search. Tables S1 and S1.1–S1.4 and Appendices S1.5–S1.8.

Supplementary Material S2. Updated searches. Tables S1 and S2.1, Appendices S2.2 and S2.3, and Table S2.4.

Supplementary Material S3. Example data request.

Table S4. List of reports of ≥5 kidney transplant recipients by country and center.

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