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Predictors of disease severity and outcome of hospitalized renal transplant recipients with COVID-19 infection: a systematic review of a globally representative sample

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Introduction. COVID-19 presents a special challenge to the kidney transplant population.

Methods. A systematic review of articles that examined COVID-19 in kidney transplant recipients was performed. Patients' demographics, clinical, laboratory and radiological presentations, immunosuppression modification, and COVID-19 specific management were abstracted and analyzed. COVID-19 severity was classified into mild, moderate, and severe. Disease outcome was classified by whether the patient was discharged, still hospitalized, or died.

Results. 44 articles reporting individual data and 13 articles reporting aggregated data on 149 and 561 kidney transplant recipients respectively with COVID-19 from Asia, Europe and America fulfilled all inclusion and exclusion criteria. Among studies reporting case specific data, 76% of cases had severe disease. Compared to patients with mild/moderate disease, patients with severe disease had higher CRP, LDH, Ferritin, D-dimer and were more likely to have bilateral lung involvement at presentation and longer time since transplantation ($P < 0.05$ for all). Recipients' age, gender and comorbidities did not impact disease severity. Patients with severe disease had a more aggressive CNI reduction and more antiviral medications utilization. Outcome was reported on 145 cases, of those 34 (23%) died all with severe disease. Longer duration from transplant to disease diagnosis, hypoxia and higher LDH were associated with mortality ($P < 0.05$). Different immunosuppression reduction strategies, high dose parenteral corticosteroids use and various antiviral combinations did not demonstrate survival advantage. Similar finding was observed for studies reporting aggregated data.

Conclusion. COVID-19 in kidney transplant patients is associated with high rate of disease severity and fatality. Higher LDH and longer time since transplantation predicted both disease severity and mortality. None of the COVID-19 specific treatment correlated with, or improved disease outcome in kidney transplant recipients.

Key words: coronavirus disease 2019, COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2, novel coronavirus; coronavirus pandemic, renal transplant, transplant recipient, immunosuppression.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel, highly contagious, and pathogenic disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and responsible for the current global pandemic outbreak which took the health care community by surprise [1]. Although COVID-19 was introduced to the human population from the animal kingdom, the spread in the human population has been entirely driven by human to human transmission [2, 3]. Transmission is primarily through droplets or direct contact but indirect contact through contaminated surfaces has also been documented [4]. In host cells, the SARS-CoV-2 virus binds to host cell angiotensin converting enzyme 2 (ACE2) receptors which are highly expressed in the lung epithelium, heart, ileum, kidney, and bladder [5]. The interaction of virus affected cells with host immune systems namely innate and adaptive immune cells results in a constellation of symptoms [4]. In the general population, there are 3 major patterns of clinical illness with mild flu-like symptoms, non-life-threatening pneumonia, or severe pneumonia progressing to adult respiratory distress syndrome (ARDS) requiring advanced life support [3, 6]. Other systems involvement like cardiovascular, neurological, renal, and gastrointestinal, have also been commonly

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reported [7]. Cytokine storm syndrome, secondary hemophagocytic lymphohistiocytosis, and coagulation disorders have also been reported and are some of the determinants of disease severity [3]. Recently, the World Health Organization (WHO) classified COVID-19 severity into mild, moderate and severe according to symptomatology and clinical presentations [8, 9].

Kidney transplant recipients are prone to be infected by opportunistic pathogens and hence can be assumed to be one of the most vulnerable groups in the COVID-19 pandemic. Although the true impact of COVID-19 on transplant recipients is mostly unknown, it is imperative to anticipate the potential consequences of COVID-19 in this at-risk population. Kidney transplant recipients with COVID-19 pose unique challenges, including the potential for rapid clinical progression, risk of increased mortality, and need to manage immunosuppressive medications with limited data, possibility of drug-drug interaction, and short and long term risk of allograft rejection or loss. With the start of the COVID-19 pandemic, multiple case reports and case series emerged from around the globe describing: the clinical presentation; anecdotal immunosuppression management; course of kidney transplant and other solid organ transplant recipients. These reports showed wide variation in the reported disease severity, immunosuppression modification and changes, antiviral treatment and outcome which left the transplant community without reasonable direction on how best to manage kidney transplant patients with COVID-19. With the current expectation that the pandemic might be more prolonged than initially anticipated, we need guidance, extensive research, and critical evaluation of available evidence and risk-benefit calculations on how to treat COVID-19 in kidney transplant recipients. In this article, we sought to review the available evidence using a systematic approach that included all reported COVID-19 cases in kidney transplant recipients that required hospitalization. We aimed to do a systematic review of COVID-19 in renal transplant recipients to identify factors associated with disease severity and mortality with special emphasizes on immunosuppression and virus-specific management plans.

MATERIAL AND METHODS

We performed a systematic review to assess the evidence regarding predictors of COVID-19 severity and outcome in kidney transplant recipients. Studies that (i) examined COVID-19 in kidney transplant recipients, (ii) provided case-specific or aggregate information for renal transplant recipients, (iii) were published in the English language, and (iv) in the adult population with (v) available full texts were included in the review. Studies were excluded if they (i) were not related to COVID-19; (ii) looked at any coronavirus other than novel coronavirus sars 2; (iii) were laboratory, genetic or bench studies; (iv) were not original studies; (v) looked at transplant patients other than kidney transplant recipients; (vi) did not include management strategies for COVID-19 in kidney transplant recipients or (vii) looked at infection control strategies and (viii) did not include individual or aggregate data for renal transplant recipients alone or did not include outcome for hospitalized patients. We systematically searched for articles indexed in PubMed (NLM) and Medline (Ovid) using keywords and mesh terms with the last date of search being July 16, 2020. Concepts used in the search included SARS-COV-2, COVID-19 and renal transplant. Search strategy for PubMed database is provided in supplementary Table 1. Bibliographies of selected articles were searched for additional studies not identified through our initial database search. All abstracts and full texts were independently reviewed by two authors and any discrepancies resolved by consensus. RefWorks [ProQuest, Ann Arbor, MI] was used as a citation manager for the removal of internal and external duplicates among the databases. Two authors independently reviewed and abstracted information and findings tabulated into descriptive evidence tables. Separate evidence tables were created for studies providing individual data as well as for those providing aggregate data for capturing maximum information. Data collected included country of origin, time of publication, patient demographics and comorbidities, transplant information, baseline renal function, clinical symptoms, diagnosis of COVID-19, significant laboratory values, imaging studies, baseline and change in immunosuppression, COVID-19 specific treatment, ICU admission and intubation and clinical outcome. The risk of bias and clinical heterogeneity for included observational studies were appraised in two ways – firstly, setting strict inclusion and exclusion criteria for selection of articles and secondly, through quality assessment tool published by the National Institute of Health (NIH). Risk of bias was independently assessed by the two authors and any disagreement resolved by a third author. As COVID-19 is a new venture with daily upcoming new information, maximum attempt was made to collect and include majority of data for a full-fledged review. Quality control was assured and

accomplished by (i) independent search of database by two authors; (ii) independent search of all titles and abstracts by two authors; (iii) screeners blinded to journal name and authors and (iv) independent review of all selected full-text articles by two authors. An MS Excel workbook (Microsoft Corp, Redmond, WA) was used to enter the data from different selected articles. Tests were done to compare the abstracted information from the articles by disease severity and outcome. COVID-19 severity was classified as per the World Health Organization (WHO) classification into mild (symptoms of upper respiratory tract infection, fever, fatigue, myalgia, GI symptoms, dyspnea), moderate (pneumonia with no need for supplemental oxygen) and severe/ critical disease (pneumonia with either respiratory rate > 30 breaths/min or severe respiratory distress or hypoxemia with oxygen saturation ≤ 93%; the presence of ARDS, acute kidney injury (AKI), or coagulation disorder) [8, 9]. AKI was determined as reported by the author of original publication. Disease outcome was classified by whether the patient was discharged, still hospitalized or died at the time of case publication. Continuous variables were compared with the Wilcoxon rank-sum test or Kruskal-Wallis test and categorical variables using the chi-squared test or Fisher's exact test as applicable. We considered any missing variables as missing at random and analyzed only available data. All analyses were done using STATA (Version 14, StataCorp, College Station, Texas). The significance value was set at $P \leq 0.05$.

RESULTS

Five hundred and sixty citations were identified through the database search and additional sources. Following the removal of duplicates, 288 unique citations were identified, and these were reviewed. Of the 288 citations, 69 full-text articles were assessed for eligibility. 57 articles fulfilled all the inclusion and exclusion criteria and were included in the review. Among these, 44 articles that included 149 COVID-19 cases in renal transplant recipients reported individual data and were selected for further univariate analysis by disease outcome and severity. 13 articles reported aggregate data on 561 renal transplant patients alone excluding other solid organ transplants and were tabulated in separate evidence table. The article selection process is outlined through PRISMA diagram [10] (Figure 1). Appraisal of study quality as well as assessment of risk of bias was conducted based on the NIH quality assessment tool. The studies were assessed for different criteria including study objective clearly stated, case definition, study population, subjects comparable, intervention clearly described, outcome measures clearly and consistently defined, length of follow up, result well-described or not etc. Majority of the studies included in this review were graded between good to fair with little or least risk of bias.

OVERALL PATIENT CHARACTERISTICS

44 articles reporting individual case data and 13 articles reporting aggregate data on renal transplant recipients were included in the review. There were articles with missing data for some of the variables. The missing data was considered to be missing at random and only the available data was analyzed and no imputation or statistical modeling was applied to account for missing data [11]. All the 44 articles included in the review except one were either case reports or case series reporting on 149 cases of COVID-19 in renal transplant recipients. The remaining non-case report article was a review article but was included due to the inclusion of a unique case report in the review. Baseline demographics, patient's presentation, results of radiological and immunological markers and COVID-19 severity of these 149 cases are summarized in Table 1. As demonstrated in Table 1, articles were globally representative with 16 articles originating from Asia [(China 12), Thailand (1), Iran (2), Korea (1)], 20 from Europe [Italy (8), Spain (2), France (2), Turkey (3), UK (2), Portugal (1), Poland (1), and Netherlands (1)], and 8 from America [North America (7), and South America (1)]. The average (range) age of patients included was 53 years (21–80 years) with the majority of the cases (79%) being younger than 65 years of age. The majority of patients were men (75%), with 81% of cases having at least one comorbidity with hypertension (HTN) (71%), diabetes mellitus (30%), and heart disease (21%) being the most commonly reported comorbidities. The recipients were between 0 to 31 years post-renal transplant with the majority being hospitalized within 7 days of symptom onset predominantly with fever (87%), cough (58%), shortness of breath (SOB) (50%), gastrointestinal (GI) symptoms (22%), and myalgia (17%). Among those reported, the majority had typical radiological picture of COVID-19 with bilateral lung involvement, and 94% had increased inflammatory markers including

C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and d-dimer. Acute kidney allograft injury (AKI) developed in 71 (49%) of the cases, 30 (20%) developed adult respiratory distress syndrome (ARDS) while 69% required supplemental oxygen therapy. When classified according to the WHO classification, 113 (76%) cases had severe disease mainly due to development of hypoxia, AKI and/or ARDS. Main causes of disease severity are included in Table 1.

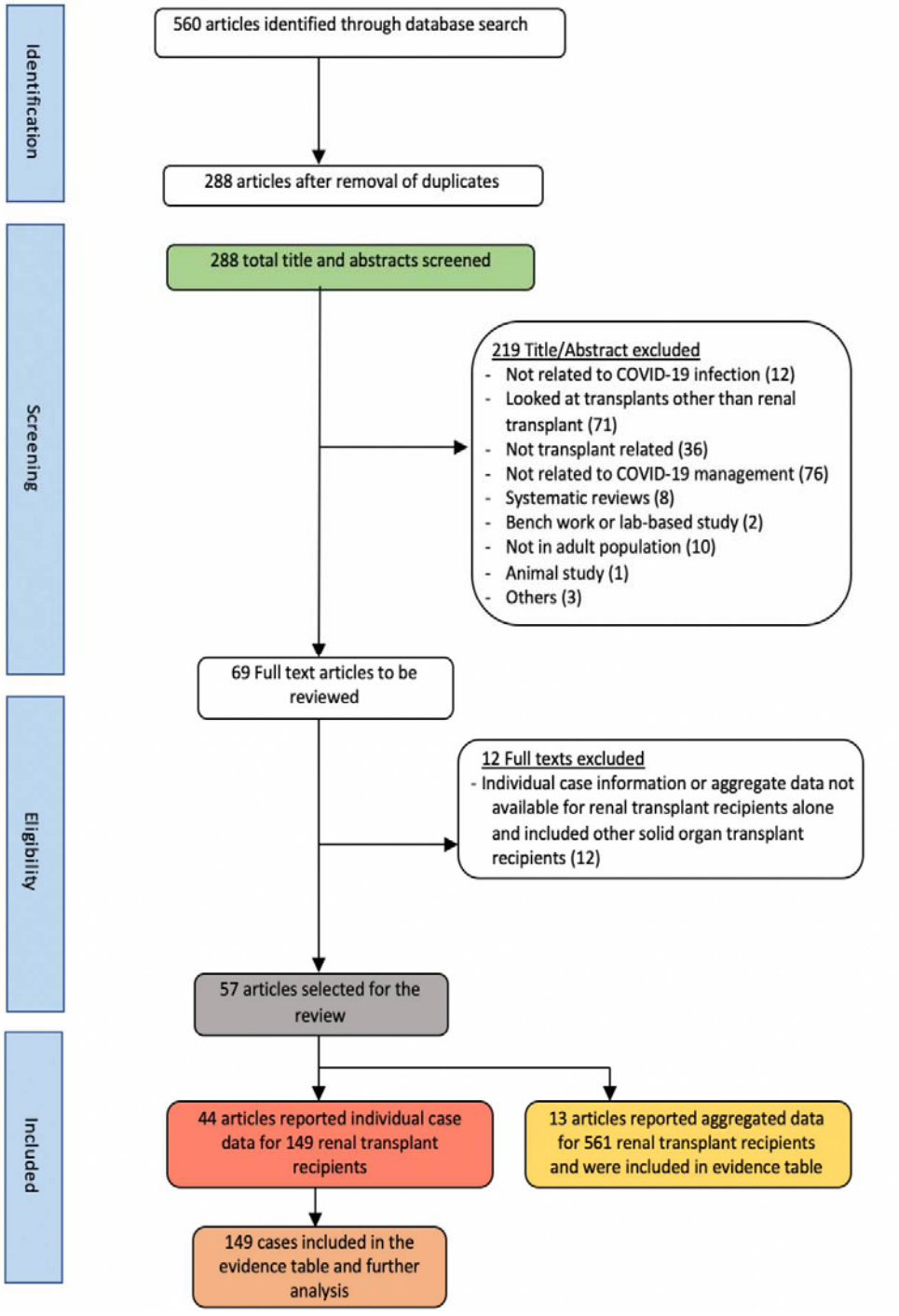

Figure 1. PRISMA flowchart summarizing the article selection process.

Table 2 summarizes the management and the clinical outcomes of the 144 patients. A combination of corticosteroids, calcineurin inhibitor (CNI) (especially tacrolimus) and antimetabolite (namely mycophenolate mofetil (MMF) and mycophenolic acid (MPA)) was the predominant maintenance immunosuppression. Of the 149 cases, 137 cases had reduction in their baseline immunosuppression. Only

12 cases were managed without making changes to their baseline immunosuppressants with or without an increase in the dose of steroid therapy and none of these cases progressed to mechanical ventilation, and all fully recovered. COVID-19 specific treatment was provided in 128 of the 144 cases with mono or combination therapy including lopinavir/ritonavir (Lop/r), hydroxychloroquine (HCQ), oseltamivir, mizoribine (Miz), umifenovir, and darunavir/cobicistat (Dar/c). Of those articles who reported, 19 cases received monoclonal antibody tocilizumab and only 3 cases received remdesivir. Concomitant antibiotics was administered in 93 (80%) of cases and 28 (34%) received azithromycin. Among the 144 cases with reported outcome, death occurred in 34 (23.6%) cases while 36 (25%) patients remained hospitalized and 74 (51%) patients were discharged from the hospital. Although mortality rate varied by month of publication but when time period stratified by early period (March to May) and late period (June–July) the mortality rate was found to be similar between the two time periods and similar to overall mortality rate. The average duration from onset of symptom to outcome was 23.6 days. There were two cases of non-biopsy proven graft rejection and 1 case of hemophagocytic disease and thromboembolic disease each [12, 13].

Table 3 summarizes the findings from studies reporting aggregate data for management of COVID-19 in 561 renal transplant recipients. Among the 13 articles, 2 originated from Asia [Iran (2)], 6 from Europe [Spain (4), Italy (1) and Turkey (1)] and 5 from USA [North America (4) and South America (1)]. As demonstrated in the table, the average age ranged between 45 to 75 years with majority of patients being male. Hypertension was the commonly reported comorbidity followed by diabetes and heart disease. The median time since transplant ranged between 0.09 years to 10.7 years. Predominant symptoms included fever, shortness of breath and diarrhea. When reported AKI was present in 23% to 74% of the patients. For majority of the patients' immune markers including CRP, LDH and d-Dimer was elevated. CNI, MMF and steroid was the most common baseline immunosuppressants used which in most of the cases were either reduced or withdrawn followed by maintenance therapy with steroid. Covid-19 specific treatment was used in majority of cases with mostly HCQ being used followed by Lop/r and antibiotics. Tocilizumab was reported in 7% to 74% of patients. The mortality rate ranged between 6% to 50%. All the studies were published between May and July. The average mortality rate was found to be 26% which was similar to the mortality rate of 23.6% reported by studies with individual case data.

CHARACTERISTICS AND FACTORS AFFECTING DISEASE SEVERITY

Demographics, clinical, laboratory, and immunological factors

Table 4 summarizes factors associated with disease severity. As demonstrated in Table 4, the majority of patients were hospitalized within 7 days from symptom onset with no significant difference between disease severity groups. There was no significant difference between patients with mild/moderate disease and those with severe disease in terms of age ($P = 0.15$), gender ($P = 0.66$), comorbidities ($P > 0.05$) and baseline immunosuppression with the exception of corticosteroid which was utilized more in patients with severe disease. When reported, ACEi/ARB was more commonly used in patients with severe disease (34% vs 6%, $P = 0.03$). More cases with severe disease had radiological evidence of bilateral lung involvement (84% vs 36%) with only 8% of severe disease cases compared to 46% of mild/moderate disease had no lung involvement ($P = 0.00$). Although the proportion of patients with lymphopenia was comparable between the groups, patients with severe disease had higher CRP ($P = 0.005$), higher LDH ($P = 0.0004$), higher Ferritin ($P = 0.05$), higher d-Dimer (0.008) and higher serum creatinine at presentation ($P < 0.001$). Overall, 34% of cases required ICU support. Patients with severe disease were more likely to require ICU care (Table 4).

Reduction or withdrawal of baseline immunosuppressant was more commonly undertaken in patients with severe disease as compared to mild/moderate disease (96% vs 78%, $P = 0.001$) mainly by CNI reduction or elimination (73% vs 44%, $P = 0.002$) and an increase in corticosteroid use (69% vs 31%, $P = 0.00$). There was no significant difference between groups in the antimetabolite dose reduction. Significant differences were also observed among the groups in terms of antiviral treatment. Among the severe versus mild/moderate disease cases, 47% vs. 14%, 6% vs 20% and 76% vs. 43% received Lop/r ($p = 0.001$), oseltamivir ($p = 0.02$) and HCQ ($p = 0.00$) respectively. The immunomodulatory agent tocilizumab was used in 19 cases all of which were with severe disease. Of those who received tocilizumab, 10 required intubation and 6 required ICU management and 7 died. Anti-bacterial therapy was used in 87% of severe cases as compared to 60% of mild/moderate disease ($p = 0.001$) with no significant difference in azithromycin use between the groups ($P = 0.78$).

Table 1

Currently available evidence on demographics and initial disease presentation of 149 hospitalized renal transplant recipients with COVID 19 infection

Author (Country)	Age	Gender	Time since TX (yrs.) Type of TX	Comorbidities	Use of ACEi/ ARB	COVID severity	Cause of severity	AKI	CT scan/ CXR; lung involvement	Immunological marker	Time from sx to COVID +ve (days)	SO_2 (%)	Site for COVID detection (RT-PCR)	Symptoms
Abrishami *et al.* [25] (Iran)	29	F	8	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	88	NP swab	Fever, cough
	32	M	12	HTN	NS	Severe	↓SO_2	No	NS	↑CRP,↑LDH	NS	85	NP swab	Fever, cough, SOB, myalgia, GI s/s
	58	M	14	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	88	NP swab	Fever, ARDS
	38	M	15	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP	NS	84	NP swab	Cough, myalgia, SOB, ARDS
	54	M	18	Asthma, IHD	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	90	NP swab	Fever, cough, ARDS
	46	M	3	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP	NS	85	NP swab	Fever, cough, SOB
	66	M	4	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	85	NP swab	Fever, ARDS
	32	M	17	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	84	NP swab	Fever, cough, SOB, GI s/s, ARDS
	64	M	6	None	NS	Severe	↓SO_2	No	NS	↑LDH	NS	90	NP swab	Fever, cough, SOB, GI s/s, ARDS
	64	M	3	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	84	NP swab	Fever, cough, ARDS
	49	F	17	HTN	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	90	NP swab	Cough, headache
	40	F	16	None	NS	Severe	↓SO_2, AKI	Yes	NS	↑CRP,↑LDH	NS	88	NP swab	Fever, ARDS
Ahmad *et al.* [26] (UK)	53	M	8	Obesity	NS	Severe	↓SO_2, AKI, supp. O_2	Yes	Bilateral	↑CRP, ↑D-dimer, ↑Ferritin, ↑Procalcitonin,	25	84	NP swab	Cough, SOB
Alberici *et al.* [27] (Italy)	70	F	17	HTN	Yes	Severe	Supp. O_2	No	NS	NS	NS	NS	NS	Fever
	47	F	9	NS	Yes	Severe	Supp. O_2, AKI	Yes	NS	NS	NS	NS	NS	Fever, ARDS
	71	M	13	IHD	Yes	Severe	Supp. O_2, ARDS	No	NS	NS	NS	NS	NS	Fever, ARDS
	57	M	1.4	HCV	No	Severe	Supp. O_2, ARDS	No	NS	NS	NS	NS	NS	Fever, ARDS
	51	M	13	HTN, HCV	No	Severe	Supp. O_2	No	NS	NS	NS	NS	NS	Fever
	46	M	2.5	HTN	No	Severe	Supp. O_2	No	NS	NS	NS	NS	NS	Fever

	59	M	5	HTN	Yes	Severe	Supp. O_2, ARDS	No	NS	NS	NS	NS	NS	Fever, ARDS
	70	F	15	HTN	Yes	Severe	Supp. O_2, ARDS, AKI	Yes	NS	NS	NS	NS	NS	Fever, ARDS
	60	M	8	HTN	Yes	Mild/Mod		No	NS	NS	NS	NS	NS	Fever
	73	M	6	HTN, DM	Yes	Severe	Supp. O_2, ARDS	No	NS	NS	NS	NS	NS	Fever, ARDS
	59	M	10	HTN, DM, IHD	Yes	Severe	Supp. O_2, ARDS, AKI	Yes	NS	NS	NS	NS	NS	Fever, ARDS
	63	M	15	HTN	No	Severe	Supp. O_2, ARDS	No	NS	NS	NS	NS	NS	Fever, ARDS
	49	M	1.75	HTN	No	Severe	Supp. O_2, ARDS, AKI	Yes	NS	NS	NS	NS	NS	Fever, ARDS
	60	F	1.75	HTN	No	Severe	Supp. O_2, ARDS	No	NS	NS	NS	NS	NS	Fever, ARDS
	57	M	10	HTN	No	Mild/Mod		No	NS	NS	NS	NS	NS	Fever
	54	M	17	HTN	Yes	Severe	Supp. O_2, ARDS	Yes	NS	NS	NS	NS	NS	Fever, ARDS
	60	M	13	HTN, IHD	No	Mild/Mod		No	NS	NS	NS	NS	NS	Fever
	50	M	9	HTN	No	Mild/Mod		No	NS	NS	NS	NS	NS	Fever
	69	M	21	HTN, DM	No	Severe	AKI	Yes	NS	NS	NS	NS	NS	Fever
	44	M	13	HTN	No	Mild/Mod		No	NS	NS	NS	NS	NS	Fever
Arpali *et al.* [28] (Turkey)	28	F	0.5, LDKT	Lupus like syndrome	No	Mild/Mod		No	No finding	↑CRP, Lymphopenia	6	98	NP swab	Fever, sore throat, rhinorrhea
Banerjee *et al.* [29] (UK)	48	M	31, DDKT	HTN	No	Mild/Mod		No	NS	NS	NS	NS	Nose and throat swab	Fever, cough
	67	F	1, DDKT	HTN, DM	Yes	Severe	↓SO_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP,↑LDH	NS	80	Nose and throat swab	Fever, cough, SOB, ARDS
	54	F	0.25, DDKT	HTN, DM	No	Severe	↓SO_2, AKI	Yes	Bilateral	↑CRP	NS	60	Nose and throat swab	SOB, ARDS
	65	M	2, DDKT	HTN	No	Severe	Supp. O_2	No	NS	NS	NS	NS	Nose and throat swab	SOB
	69	F	0.08, DDKT	DM, HTN, Hypothyroidism	No	Severe	↓SO_2, AKI	Yes	Unilateral	Lymphopenia	1	82	Nose and throat swab	Fever, SOB, GI s/s
	54	M	7	HTN, HUS	Yes	Severe	AKI	Yes	NS	NS	3	NS	Nose and throat swab	Fever, cough
	45	M	2.5	HTN	No	Severe	↓SO_2, AKI	Yes	Bilateral	↑CRP,↑ferritin, ↑LDH, ↑D-dimer	NS	90	Nose and throat swab	Fever, cough, SOB
Billah *et al.* [30] (USA)	44	M	7, DDKT	NS	No	Severe	↓SO_2, AKI	Yes	Bilateral	↑LDH, ↑Ferritin, ↑D-dimer	NS	91	NP swab	SOB, resp. failure, catabolic state

Bussalino *et al.* [31] (Italy)	32	M	3, DDKT	HTN, Pericarditis	No	Severe	AKI	Yes	Bilateral	↑LDH, ↑Ferritin, ↑CRP, ↑IL6, ↑Procalcitonin,	1	95	NP swab	Fever, non-productive cough
Chen *et al.* [32] (China)	49	M	6, DDKT	HTN	Yes	Severe	↓SO_2	No	Bilateral	Lymphopenia, ↑CRP	18	90	Oropharyngeal swab	Fever, SOB, cough, GI s/s
Chen *et al.* [33] (China)	29	M	10, LDKT	NS	NS	Severe	↓SO_2, AKI, supp. O_2	Yes	Bilateral	Lymphopenia, ↑CRP	6	80	NP swab	Fever, cough
Cheng *et al.* [34] (China)	48	M	11	None	No	Severe	↓SO_2	No	Bilateral	↑CRP, ↑Procalcitonin	10	92	NP swab	Fever, SOB, chest tightness
	65	F	12	None	No	Severe	↓SO_2	No	NS	↑CRP, Lymphopenia	4	83	NS	Fever, cough, SOB, myalgia
Dirim *et al.* [35] (Turkey)	55	F	5, DDKT	HTN	Yes	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP,↑LDH, ↑Ferritin	NS	NS	NP swab	Fever, cough, SOB
Faguer *et al.* [36] (France)	51	M	NS	NS	NS	Severe	Supp. O_2, AKI	Yes	NS	↑CRP,↑Ferritin, ↑IL6, ↑AST, ↑ALT	NS	NS	Bronchoalveolar lavage	Fever, cough, SOB
Fontana *et al.* [37] (Italy)	61	M	15, DDKT	CKD, Parkinsonism	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP, ↑LDH	11	95	Oropharyngeal and nasal swab	Fever
Fung *et al.* [38] (USA)	47	M	7.4, LDKT	HTN, DM, CVD	No	Severe	Supp. O_2, AKI, ARDS	Yes	Bilateral	Lymphopenia, ↑CRP, ↑LDH	14	NS	NP swab	Fever, SOB, cough, myalgia, ARDS
	73	M	4.8, LDKT	HTN, DM, CAD, HLD	No	Mild/Mod		No	No finding	Lymphopenia, ↑CRP	21	NS	NP swab	Fever, SOB, cough, chest pain, myalgia, diarrhea
	77	M	10.8, DDKT	CAD, Sarcoid	No	Severe	AKI	Yes	No finding	Lymphopenia, ↑CRP, ↑LDH	2	NS	NP swab	Fever, fatigue
	61	F	0.33, DDKT	DM, HLD	No	Mild/Mod		No	No finding	Lymphopenia	3	NS	NP swab	Fever, cough
	71	F	0.42, DDKT	DM, CAD, CVD	No	Severe	Supp. O_2	No	Bilateral	Lymphopenia, ↑CRP, ↑D-dimer	14	NS	NP swab	Fever, cough, fatigue, anosmia
	52	M	1.1, LDKT	HTN, DM, HLD, Hypothyroidism	No	Mild/Mod		No	No finding	Lymphopenia	3	NS	NP swab	Fever, cough, myalgia, fatigue
	44	M	9.3, DDKT	HTN, CKD	No	Severe	Supp. O_2, AKI, ARDS	Yes	Unilateral	Lymphopenia, ↑CRP, ↑D-dimer	6	NS	NP swab	Fever, SOB, cough, diarrhea, ARDS

Gandolfini *et al.* [39] (Italy)	75	M		HTN, COPD, IHD Obesity,	NS	Severe	Supp. O_2	No	Bilateral	↑CRP, ↑Procalcitonin, ↑LDH	3	NS	NP swab	Fever, SOB, cough, myalgia
	52	F		HTN	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP, ↑Procalcitonin, ↑LDH	2	NS	NP swab	Fever, SOB, cough, myalgia
Guillen *et al.* [40] (Spain)	50	M	4, DDKT	HTN	Yes	Severe	AKI	Yes	Bilateral	↑D-dimer, Lymphopenia, ↑Procalcitonin	7	98	NP & Oropharyngeal swab	Fever, GI s/s, cough
Hsu *et al.* [13] (USA)	39	M	3	HTN, DM, Obesity, Heart TX	Yes	Severe	↓SO_2	No	Bilateral	Lymphopenia, ↑CRP,↑LDH, ↑D-dimer, ↑Troponin, Hemophagocytic blood picture	3	90	NP swab	Fever, cough, SOB, sore throat, fatigue, myalgia
Huang *et al.* [41] (China)	58	M	12	NS	NS	Severe	Supp. O_2	No	Bilateral	NS	7	NS	NP swab	Fever, SOB, cough
Jiang *et al.* [42] (China)	70	F	10, DDKT	HTN, Bronchitis, HLD	NS	Severe	↓SO_2, supp. O_2, AKI	Yes	Bilateral	↑CRP	NS	90	Oropharyngeal swab	Fever, SOB, cough, fatigue
Johnson *et al.* [43] (USA)	57	M	0.7, DDKT	DM	NS	Severe	↓SO_2, AKI	Yes	Bilateral	Lymphopenia	10	93	NS	Fever, SOB, fatigue, myalgia
Kates *et al.* [44] (USA)	54	M	20, DDKT	HTN, DM	Yes	Severe	↓SO_2, AKI	Yes	Bilateral	NS	4	88	NP swab	Fever, SOB, cough, GI s/s
Kim *et al.* [45] (Korea)	36	M	4, LDKT	NS	NS	Severe	AKI	Yes	Bilateral	Lymphopenia, ↑CRP	5	95	NP swab	Fever, cough, GI s/s
	56	M	9, LDKT	DM	NS	Severe	AKI	Yes	Bilateral	↑CRP	NS	95	NP swab	Cough
Kocak *et al.* [46] (Turkey)	28	F	0.5, LDKT	Lupus like syndrome	No	Mild/Mod		No	None	↑CRP, Lymphopenia	NS	94	NP swab	Fever, sore throat, rhinorrhea, malaise
	56	F	0.25, LDKT	HTN	No	Severe	AKI	Yes	Bilateral	↑CRP	8	96	NP swab	Fever, diarrhea
Kolonko *et al.* [47] (Poland)	61	M	0.2, LDKT	HTN, DM	NS	Severe	AKI	Yes	Bilateral	↑CRP	NS	NS	NP swab	Fever, ileus
	24	M	0.3, LDKT	HTN	NS	Mild		No	No finding	↑CRP	NS	NS	NP swab	Non-specific
	42	M	0.2, LDKT	HTN	NS	Mild		No	Not done	Lymphopenia, ↑IL6	NS	NS	NP swab	Non-specific
Machado *et al.* [12] (Brazil)	69	M	6, DDKT	HTN, DM, HBV, Liver TX	Yes	Severe	AKI	Yes	Bilateral	Lymphopenia, ↑CRP, ↑LDH, ↑D-dimer, ↑AST, ↑ALT	4	96	NP swab	Fever, SOB, GI s/s, fatigue, confusion

Maritati *et al.* [48] (Italy)	51	M	1, LDKT	HTN	No	Severe	Supp. O_2, ARDS	No	Bilateral	Lymphopenia, ↑CRP, ↑LDH, ↑IL6,↑Ferritin, ↑D-dimer	NS	98	NP swab	Fever, cough, SOB
	63	F	4, DDKT	HTN, Obesity	No	Severe	Supp. O_2, ARDS	No	Bilateral	Lymphopenia, ↑CRP, ↑LDH, ↑D-dimer	8	NS	NP swab	Fever, cough
	73	M	0.2, DDKT	HTN, DM, Obesity	No	Severe	Supp. O_2	No	Bilateral	Lymphopenia, ↑CRP, ↑LDH, ↑D-dimer,	NS	94	NP swab	SOB
	72	M	8, DDKT	HTN, Obesity	No	Severe	Supp. O_2, ARDS, AKI	Yes	Bilateral	Lymphopenia, ↑CRP, ↑LDH, ↑IL6, ↑D-dimer, ↑Ferritin	NS	NS	NP swab	Fever, SOB, cough
	71	F	7, DDKT	HTN, CAD	No	Severe	Supp. O_2, ARDS	No	Bilateral	Lymphopenia, ↑CRP, ↑LDH, ↑D-dimer,	NS	98	NP swab	Fever, SOB, cough
Marx D *et al.* [49] (France)	58	M	2	CAD, CA, Renal vein thrombosis	No	Mild/Mod		No	Bilateral	↑CRP, ↑D-dimer,↑IL6	6	96	NP swab	Fever, cough
Mella *et al.* [50] (Italy)	41	M	14.6	HTN	NS	Severe	Supp. O_2, ↓SO_2, AKI	Yes	NS	↑CRP, ↑D-dimer, ↑Procalcitonin, ↑LDH,↑Ferritin	NS	<93%	NP swab	Fever, cough
	65	M	0.02	HTN, DM, CVD	NS	Severe	Supp. O_2, ↓SO_2, AKI	Yes	NS	↑CRP, ↑D-dimer, ↑LDH, ↑Ferritin	NS	<93%	NP swab	Fever, cough
	54	M	5.6	CVD	No	Severe	Supp. O_2, ↓SO_2,	NS	NS	↑CRP, ↑IL6, ↑LDH	NS	<93%	NP swab	Fever, diarrhea
	62	M	12.8	HTN, CVD, HCV	NS	Severe	Supp. O_2, ↓SO_2,	NS	NS	↑CRP, ↑D-dimer, ↑IL6,↑ LDH,↑Ferritin	NS	<93%	NP swab	Fever, SOB, diarrhea
	49	M	17.6	CVD, HCV	No	Severe	Supp. O_2, ↓SO_2,	NS	NS	↑CRP, ↑D-dimer, ↑LDH,↑Ferritin	NS	<93%	NP swab	Fever, cough
	62	M	8.6	HTN, CVD	No	Severe	Supp. O_2, ↓SO_2,	NS	NS	↑CRP, ↑D-dimer,↑IL6, ↑LDH,↑Ferritin	NS	<93%	NP swab	Fever, SOB
Meziyerh *et al.* [51] (Netherlands)	35	M	4	NS	No	Severe	AKI	Yes	Bilateral	↑IL6, ↑ALT, Lymphopenia	NS	99	NP swab	Fever, SOB, cough, GI s/s, myalgia

Mohan *et al.* [52] (USA)	70	M	5	NS	NS	Severe	AKI	Yes	No finding	↑CRP, Lymphopenia, ↑LDH, ↑IL6	NS	NS	NS	Fever, cough, fatigue
	64	M	19.3	NS	NS	Mild/Mod		No	Bilateral	NS	NS	NS	NS	Fever, cough, fatigue
	28	M	3.5	NS	NS	Severe	AKI	Yes	Bilateral	↑CRP, Lymphopenia, Procalcitonin	NS	NS	NS	Fever, cough, myalgia
	51	M	9.8	NS	NS	Severe	AKI	Yes	Bilateral	↑CRP, ↑Procalcitonin, ↑IL6	NS	NS	NS	Fever, cough
	32	F	1.2	NS	NS	Mild/Mod		No	Unilateral	↑CRP,↑LDH	NS	NS	NS	Fever, SOB, GI s/s
	21	M	3.8	NS	NS	Mild/Mod		No	NS	NS	NS	NS	NS	Fever, fatigue, GI s/s
	36	M	3.2	NS	NS	Mild/Mod		No	Unilateral	↑CRP, ↑Ferritin	NS	NS	NS	Fever, myalgia
	72	F	4.1	NS	NS	Mild/Mod		No	No finding	NS	NS	NS	NS	Fever, cough, SOB
	51	F	0.75	NS	NS	Severe	Supp. O_2	No	Bilateral	↑CRP,↑Procalcitonin,↑IL6, ↑LDH,↑Ferritin	NS	NS	NS	Fever, cough, SOB
	76	M	11.3	NS	NS	Mild/Mod		No	No finding	↑CRP, Lymphopenia, ↑IL6	NS	NS	NS	Fever, GI s/s
	61	M	0	NS	NS	Severe	Supp. O_2, AKI	Yes	No finding	↑CRP, Lymphopenia, ↑Procalcitonin, ↑IL6,↑LDH, ↑ferritin	NS	NS	NS	Fever, SOB, cough
	22	M	2.8	NS	NS	Severe	Supp. O_2, AKI	Yes	No finding	↑CRP, Lymphopenia, ↑Procalcitonin, ↑ferritin	NS	NS	NS	Fever, SOB
	78	M	9.75	NS	NS	Severe	Supp. O_2	No	Bilateral	↑CRP,↑ferritin, ↑LDH, Lymphopenia	NS	NS	NS	SOB, malaise
	72	F	10	NS	NS	Mild/Mod		No	Bilateral	↑CRP,↑ferritin, ↑LDH, ↑IL6	NS	NS	NS	Fever, cough, hemoptysis
	25	F	6.7	NS	NS	Severe	AKI	Yes	Bilateral	↑CRP, Lymphopenia, ↑Procalcitonin, ↑ferritin	NS	NS	NS	Cough, GI s/s

Nair *et al.* [53] (USA)	51	M	0.33, DDKT	HTN, DM, CAD	NS	Mild/Mod		No	No finding	None	NS	NS	NP swab	Fever, cough
	37	M	7, LDKT	HTN, DM	NS	Mild/Mod		No	No finding	Lymphopenia, ↑CRP,↑Ferritin	NS	NS	NP swab	Cough, myalgia
	63	F	9, LDKT	HTN	NS	Mild/Mod		No	Unilateral	↑CRP	NS	NS	NP swab	Fever, cough, myalgia, headache
	31	F	4, LDKT	HTN, DM	NS	Mild/Mod		No	Unilateral	None	NS	NS	NP swab	Fever, myalgia, headache, GI s/s
	56	M	20, DDKT	HTN, DM	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP,↑Ferritin	NS	NS	NP swab	Fever, cough, fatigue
	80	M	14, LDKT	HTN, DM, CAD	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP,↑Ferritin	NS	NS	NP swab	Fever, myalgia, fatigue, GI s/s
	45	M	3, DDKT	HTN, DM	NS	Severe	Supp. O_2, AKI	Yes	Unilateral	↑CRP,↑Ferritin	NS	NS	NP swab	Fever, cough, myalgia, GI s/s
	68	M	17	HTN, DM	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP,↑Ferritin	NS	NS	NP swab	Fever, SOB, cough
	75	F	9, LDKT	HTN, CA	NS	Severe	Supp. O_2	No	Bilateral	Lymphopenia, ↑CRP,↑Ferritin	NS	NS	NP swab	Fever, SOB, cough, fatigue
	57	F	3, DDKT	HTN, DM	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP,↑Ferritin	NS	NS	NP swab	Cough, Fatigue, SOB
Namazee *et al.* [54] (Iran)	63	F	20, DDKT	HTN	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP	7	78	Oropharyngeal swab	Cough, SOB
Ning *et al.* [55] (China)	29	M	1.25, LDKT	HTN	Yes	Severe	AKI	Yes	Bilateral	NS	2	NS	Oropharyngeal swab, sputum	Fever, cough, GI s/s, hematuria, fatigue
Ruiz *et al.* [56] (Spain)	78		8.3	HTN, CA	No	Severe	↓SO_2	No	Unilateral	NS	NS	89	NP swab	Fever, SOB
	73	M	1.8	HTN, DM	Yes	Severe	Supp. O_2	No	Unilateral	↑IL6	NS	94	NP swab	Fever, SOB, cough
	80	M	3.8	HTN, DM, PAD	No	Severe	↓SO_2	No	No finding	NS	NS	90	NP swab	SOB, cough, myalgia
	71	F	6	HTN	No	Severe	Supp. O_2	No	Bilateral	↑IL6	NS	97	NP swab	Fever, SOB, cough, sore throat
	71	M	30.1	HTN, DM, CAD	No	Severe	Supp. O_2	No	Bilateral	NS	NS	100	NP swab	Fever, GI s/s
	76	M	14.8	HTN, Obesity	Yes	Severe	Supp. O_2	No	Bilateral	NS	NS	96	NP swab	Fever rhinorrhea
	39	M	16.8	HTN	Yes	Severe	Supp. O_2, ARDS	No	No finding	NS	NS	100	NP swab	Fever, myalgia, ARDS
	65	M	6.5	HTN, DM, OSA	No	Severe	Supp. O_2, ARDS	Yes	Unilateral	NS	NS	93	NP swab	Fever, SOB, cough, ARDS

Seminari *et al.* [57] (Italy)	50	M	4	HTN, DM	No	Mild/Mod		No	Unilateral		9	NS	NP swab	Fever, cough
Shingare *et al.* [58] (Italy)	35	M	0.05, LDKT	HTN	NS	Mild/Mod		No	No finding	Lymphopenia, ↑CRP	NS	99	NP swab	Cough
	45	M	0.02, LDKT	CKD	No	Mild/Mod		No	No finding	Lymphopenia	NS	98	NP swab	Throat irritation
Silva *et al.* [59] (Portugal)	35	F	3, LDKT	HTN, DM, Pancreas TX	No	Mild/Mod		No	No finding	↑CRP, ↑LDH	12		NP swab	Fever, myalgia
	37	M	6, LDKT	HTN, Obesity, Gout	No	Severe	↓SO_2, AKI	Yes	Bilateral	↑CRP, ↑LDH	14	<93%	NP swab	Fever, myalgia, diarrhea
	56	M	1, DDKT	HTN, DM	No	Mild/Mod		No	Bilateral	↑CRP, ↑LDH	7		NP swab	Fever, cough
	63	M	1, DDKT	HTN, Obesity, OSA	No	Severe	↓SO_2, AKI	Yes	Bilateral	↑CRP, ↑LDH	8	<93%	NP swab	Fever, cough, diarrhea, anosmia
	63	F	25, DDKT	HTN, CAD, CVD, Obesity	No	Severe	↓SO_2, AKI, ARDS	Yes	Bilateral	↑CRP,↑LDH	0	<93%	NP swab	Fever, SOB, abdominal pain, nausea
Thammathiwat *et al.* [60] (Thailand)	58	M	2, LDKT	HTN, DM	Yes	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑IL6	19	94	Nasal swab	Fever, SOB, diarrhea, cough, myalgia, nausea
Wang *et al.* [61] (China)	49	M	2	HTN, DM	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	Lymphopenia, ↑CRP	7	NS	NP swab	Fever, SOB
Zhang H *et al.* [62] (China) (China)	38	M	0.42, DDKT	NS	NS	Mild/Mod		No	Bilateral	Lymphopenia, ↑CRP	NS	99	Lower respiratory tract	Fever, cough
	64	M	4.2, DDKT	CA	NS	Severe	AKI	Yes	Bilateral	Lymphopenia, ↑CRP	NS	96	Lower respiratory tract	Fever, cough, SOB, myalgia
	37	F	0.58, DDKT	HTN	NS	Mild/Mod		No	Bilateral	Lymphopenia, ↑CRP	NS	99	Lower respiratory tract	Fever, cough
	47	M	1.1, DDKT	NS	NS	Mild/Mod		No	Bilateral	Lymphopenia, ↑CRP	NS	98	Lower respiratory tract	Fever, cough, myalgia
	38	M	2.7, DDKT	HTN, DM	NS	Mild/Mod		No	Bilateral	Lymphopenia, ↑CRP	NS	97	Lower respiratory tract	Fever, cough, myalgia
Zhang M *et al.* [63] (China)	49	M	NS	NS	NS	Mild/Mod		No	Bilateral	Lymphopenia	10	NS	NP swab	Fever, fatigue

Zhong *et al.* [64] (China)	48	M	17, LDKT	NS	No	Mild/Mod		No	Bilateral	↑CRP	8	NS	NP aspirate	Fever, cough, myalgia, fatigue
Zhu *et al.* [65] (China)	24	M	NS	None	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP	26	95	Throat swab	Fever
	55	M	NS	CHD, AF	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP, Lymphopenia	2	95	Throat swab	Fever, SOB, fatigue
	29	M	NS	None	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP, Lymphopenia	7	95	Throat swab	Fever, SOB, cough, GI s/s, fatigue
	30	M	NS	HTN	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP, Lymphopenia	12	95	Throat swab	Fever, SOB, cough, fatigue
	50	M	NS	HTN	NS	Severe	Supp. O_2	No	Bilateral	↑CRP, Lymphopenia, ↑ALT	11	95	Throat swab	Fever, SOB, cough, fatigue
	65	F	NS	None	NS	Severe	Supp. O_2	No	Bilateral	↑CRP, Lymphopenia	4	95	Throat swab	Fever, SOB, cough, GI s/s, fatigue
	52	M	NS	HTN, CHD	NS	Severe	Supp. O_2	No	Bilateral	↑CRP, Lymphopenia, ↑ALT	5	95	Throat swab	Fever, SOB, cough, fatigue
	49	M	NS	None	NS	Severe	Supp. O_2	No	Bilateral	↑CRP,↑ALT	9	95	Throat swab	Fever, SOB, cough, GI s/s, fatigue
	59	M	NS	HTN, COPD, HHD	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP, Lymphopenia, ↑ALT	4	95	Throat swab	Fever, SOB, cough, fatigue
	37	F	NS	HTN	NS	Severe	Supp. O_2, AKI	Yes	Bilateral	↑CRP, Lymphopenia, ↑ALT	2	95	Throat swab	Fever, SOB, cough, fatigue
Zhu *et al.* [66] (China)	52	M	12, LDKT	NS	NS	Severe	Supp. O_2	No	Bilateral	Lymphopenia, ↑CRP, ↑IL6, ↑TNFα	8	96	Throat swab	Fever, SOB, GI s/s, fatigue

NS – Not Specified; Supp. – Supplementary; TX – Transplant; AKI – Acute Kidney Injury; Sx. – symptom; SO_2 – Oxygen saturation; SOB – Shortness of breath; OSA – Obstructive sleep apnea; CAD – Coronary Artery Disease; CVD – Cerebrovascular disease; PAD – Peripheral Artery Disease; HLD – Hyperlipidemia; GI s/s – Gastrointestinal sign symptom; DDKT – Deceased donor kidney transplant; LDKT – Living donor kidney transplant; HTN – Hypertension; CHD – Congestive heart disease, AF – Atrial fibrillation; HHD – Hypertensive heart disease; IHD – Ischemic Heart disease; CA – Cancer; HCV – Hepatitis C virus infection; NP swab – Nasopharyngeal swab

Supplementary Table 1

PubMed search strategy

Provider/Interface National Library of Medicine
Database PubMed
Date searched 7/16/2020
Database update 7/16/2020
Search developer(s) Irtiza Hasan; Tasnuva Rashid
English only? Yes

1	coronavirus [mesh]
2	corona virus [mesh]
3	(coronavirus [tiab] OR coronavirus [tiab] OR coronavirus* [tiab] OR covid19 [tiab] OR covid-19 [tiab] OR SARS-CoV-2 [tiab])
4	#1 OR #2 OR #3
5	transplantation [mesh]
6	transplant [mesh]
7	renal transplant [mesh] OR renal transplantation [mesh] OR kidney transplant [mesh] OR kidney transplantation [mesh]
8	renal transplant [tiab] OR renal transplantation [tiab] OR kidney transplantation [tiab] OR kidney transplant [tiab]
9	#5 OR #6 OR #7 OR #8
10	#4 AND #9
11	#10 AND english [la]

Table 2

Currently available evidence on management and outcome of COVID19 infection in renal transplant recipients

Author	Age	COVID severity	Baseline Immunosuppressant	Change in Immunosuppressant	COVID specific treatment	Antibacterial/ other medication	Time from s/s to hospitalization	Time for s/s to outcome (day)	Need for ICU	Type of O_2 therapy	Clinical outcome
Abrishami *et al.* [25] (Iran)	29	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	NS	None	Discharged
	32	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Discharged
	58	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	38	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	54	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	46	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	None	Discharged
	66	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	32	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	64	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	64	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	49	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	NS	None	Discharged
	40	Severe	Pred., Tac., MMF	↓dose of all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
Ahmad *et al.* [26] (UK)	53	Severe	Pred., Bel., MMF	Withhold MMF & Bel.; ↑Pred.	None	NS	25	42	Yes	MV	Discharged
Alberici *et al.* [27] (Italy)	70	Severe	CNI, mTOR inhibitor	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	NIV	Discharged
	47	Severe	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ, Toci	NS	NS	NS	Yes	MV	Hospitalized
	71	Severe	CNI, MMF, Pred.	Withhold all; MP	None	NS	NS	NS	No	NIV	Death
	57	Severe	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ, Toci	NS	NS	NS	Yes	MV	Death
	51	Severe	MMF, CNI	Withhold all; MP	Lop/r, HCQ, Toci	NS	NS	NS	No	NIV	Discharged
	46	Severe	MMF, CNI	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	NIV	Discharged
	59	Severe	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	70	Severe	CNI, Pred.	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	Yes	MV	Death
	60	Mild/Mod	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	None	Hospitalized
	73	Severe	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	NIV	Hospitalized
	59	Severe	MMF, Pred.	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	NIV	Hospitalized
	63	Severe	CNI, MMF	Withhold all; MP	Lop/r, HCQ, Toci	NS	NS	NS	No	NIV	Death
	49	Severe	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ, Toci	NS	NS	NS	No	NIV	Hospitalized
	60	Severe	CNI, MMF, Pred.	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	NIV	Hospitalized
	57	Mild/Mod	CNI, MMF	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	None	Hospitalized
	54	Severe	CNI, Pred.	Withhold all; MP	Dar/r, HCQ	NS	NS	NS	No	NIV	Hospitalized
	60	Mild/Mod	CNI	Withhold all; MP	Lop/r, HCQ	NS	NS	NS	No	None	Hospitalized
	50	Mild/Mod	CNI, MMF, Pred.	Withhold all; MP	Dar/r, HCQ	NS	NS	NS	No	None	Hospitalized
	69	Severe	CNI, Pred.	Withhold all; MP	Dar/r, HCQ	NS	NS	NS	No	None	Hospitalized
	44	Mild/Mod	CNI, mTOR inhibitor	Withhold all; MP	Dar/r, HCQ	NS	NS	NS	No	None	Hospitalized
Arpali *et al.* [28] (Turkey)	28	Mild/Mod	Pred., Tac.	No change	Oseltamivir	NS	2	1	No	None	Discharged

Banerjee *et al.* [29] (UK)	48	Mild/Mod	Pred., Aza.	No change	None	NS	NA	NS	NS	None	NA
	67	Severe	Pred., Tac., MMF	Withhold Tac. & MMF	None	NS	NS	12	Yes	MV	Death
	54	Severe	Pred., Tac., MMF	Withhold Tac. & MMF	Oseltamivir	NS	NS	NS	Yes	MV	Hospitalized
	65	Severe	Pred., Tac., MMF	Withhold MMF	NS	NS	NS	NS	No	NC	Hospitalized
	69	Severe	Pred., Tac., MMF	↓Tac.; withhold MMF	None	Doxycycline	NS	NS	No	NC	Hospitalized
	54	Severe	Tac., MMF	Withhold MMF	None	No	NA	11	No	None	NA
	45	Severe	Pred., Tac., Aza.	↓Tac.; Aza.; Pred. (increased dose)	NS	NS	NS	4	No	NC	Hospitalized
Billah *et al.* [30] (USA)	44	Severe	Pred., Tac., MMF	↓Tac.; no change to MMF; MP.	NS	NS	NS	31	Yes	MV	Hospitalized
Bussalino *et al.* [31] (Italy)	32	Severe	Pred., Tac., MMF	No change; Pred. (increased dose)	Oseltamivir, HCQ	Ceftaroline	3	12	No	None	Discharged
Chen *et al.* [32] (China)	49	Severe	Pred., Tac., MMF	Withhold all; MP.	Umifenovir Ribavirin	Moxifloxacin	15	22	Yes	NC	Discharged
Chen *et al.* [33] (China)	29	Severe	MP, Tac., MMF	↓MMF	Oseltamivir, INFα-2b	Ceftazidime, Moxifloxacin	6	28	No	NC	Discharged
Cheng *et al.* [34] (China)	48	Severe	Pred., Tac., MMF	Withhold all; MP	None	NS	13	35	No	None	Discharged
	65	Severe	Pred., Tac., MMF	Withhold all; MP	Umifenovir, IVIG	Moxifloxacin	9	50	No	NIV	Discharged
Dirim *et al.* [35] (Turkey)	55	Severe	Pred., Tac., MMF	↓Tac.; withhold MMF	HCQ	NS	7	10	Yes	MV	Death
Faguer *et al.* [36] (France)	51	Severe	Pred., Tac., MMF	Withhold Tac., MMF; Dexamethasone	Toci	NS	NS	NS	Yes	MV	Hospitalized
Fontana *et al.* [37] (Italy)	61	Severe	Pred., CNI	↓dose of CNI; MP	HCQ, Toci., IVIG	Meropenem	2	24	No	NC	Discharged
Fung *et al.* [38] (USA)	47	Severe	Pred., Tac., MMF	Withhold Tac., MMF	Remdesivir	Cefepime, Meropenem	NS	29	Yes	MV	Discharged
	73	Mild	Tac., MMF	↓Tac.; withhold MMF	None	Vancomycin, Azithromycin	NS	7	No	None	Discharged
	77	Severe	Pred., Tac., MMF	Withhold MMF	None	Ceftriaxone, Doxycycline	NS	11	No	None	Discharged
	61	Mild	Pred., Tac., MMF	↓Tac.	None	NS	NS	NS	No	None	NA
	71	Severe	Pred., Tac., MMF	↓MMF	None	NS	NS	10	No	NC	Discharged
	52	Mild	Pred., Tac., MMF	No change	None	NS	NS	NS	No	None	NA
	44	Severe	Pred., Tac., MMF	Withhold Tac., MMF; MP	Withhold Tac., MMF	Ceftriaxone, Azithromycin			Yes	MV	Hospitalized

Gandolfini *et al.* [39] (Italy)	75	Severe	Pred., Tac., MMF	Withhold Tac. & MMF	HCQ	NS	3	5	NS	NIV	Death
	52	Severe	Pred., Tac., MMF	Withhold Tac. & MMF	HCQ, Dar/c	NS	1	14	NS	NIV	Hospitalized
Guillen *et al.* [40] (Spain)	50	Severe	Pred., Tac., Ever.	Withhold Tac. & Ever.; INFβ	Lop/r, HCQ	Azithromycin, Ceftaroline, Meropenem	7	19	Yes	NC	Hospitalized
Hsu *et al.* [13] (USA)	39	Severe	Pred., Tac., MMF	Withhold MMF	HCQ, Remdesivir	None	4	15	Yes	NC	Discharged
Huang *et al.* [41] (China)	58	Severe	Pred., MMF	Withhold MMF; MP	Oseltamivir, Lop/r	Moxifloxacin	4	40	Yes	MV	Death
Jiang *et al.* [42] (China)	70	Severe	Pred., CNI, MMF	↓MMF; Withhold CNI; MP	Convalescent plasma	Moxifloxacin, Piperacillin/ Tazobactam	NS	52	No	CPAP	Discharged
Johnson *et al.* [43] (USA)	57	Severe	Tac., MPA	↓Tac. & MPA	HCQ	Cefepime, Azithromycin	8	23	NS	NC	Discharged
Kates *et al.* [44] (USA)	54	Severe	Tac., MMF	↓Tac.; Withhold MMF; Pred.	HCQ	Ceftriaxone Azithromycin	3	13	No	NC	Discharged
Kim *et al.* [45] (Korea)	36	Severe	Pred., Tac., MMF	Withhold all; MP	Lop/r, HCQ	None	5	23	No	None	Discharged
	56	Severe	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin	NS	NS	No	None	Discharged
Kocak *et al.* [46] (Turkey)	28	Mild/Mod	Pred., Tac.	No change	Oseltamivir	None	NS	NS	No	None	Discharged
	56	Severe	Pred., Tac., MMF	Withhold Tac. & MMF	HCQ	Ceftriaxone	7	10	No	None	Discharged
Kolonko *et al.* [47] (Poland)	61	Severe	Pred., Tac., MMF	Withhold MMF	None	Meropenem, Levofloxacin	NS	NS	No	None	Death
	24	Mild/Mod	Pred., Tac., MMF	↓MMF & Pred.	None	NS	NS	NS	No	None	Discharged
	42	Mild/Mod	Pred., Tac., MMF	↓Dose of all	None	NS	NS	23	No	None	Discharged
Machado *et al.* [12] (Brazil)	69	Severe	Pred., Tac., MMF	↓Tac.; withhold MMF, Pred. (increased dose)	HCQ	Ceftriaxone, Azithromycin	1	13	No	None	Discharged
Maritati *et al.* [48] (Italy)	51	Severe	Pred., Tac., MPA	Withhold Tac. & MPA; MP	Lop/r, HCQ, Toci., IVIG	NS	8	49	Yes	MV	Hospitalized
	63	Severe	Pred., Tac., MPA	Withhold Tac. & MPA; MP	HCQ, Toci.	NS	4	15	Yes	MV	Death
	73	Severe	Pred., Tac., MPA	Withhold Tac. & MPA; MP	Toci.	NS	3	37	No	NC	Discharged
	72	Severe	Pred., Tac., mTORi	Withhold Tac. & mTORi; MP	Lop/r, HCQ, Toci.	NS	NS	53	NS	MV	Death
	71	Severe	Pred., Tac., MPA	Withhold Tac. & MPA; MP	HCQ, Toci., IVIG	NS	NS	37	NS	CPAP	Discharged

Marx D *et al.* [49] (France)	58	Mild/Mod	Pred., MMF, Bel.	Withhold MMF & Bel.	None	NS	6	24	NS	None	Discharged
Mella *et al.* [50] (Italy)	41	Severe	Pred., Tac.	Withhold Tac.; MP	Dar/r, HCQ, Toci.	Cefepime, Azithromycin	NS	17	NS	MV	Death
	65	Severe	Pred., Tac., MMF	Withhold Tac. & MMF; MP	Dar/r, HCQ, Toci.	Cefepime	NS	17	NS	MV	Death
	54	Severe	Pred., Tac.	Withhold Tac.; MP	HCQ, Toci.	NS	NS	20	NS	NIV	Discharged
	62	Severe	Pred., Tac., MMF	Withhold Tac. & MMF; MP	HCQ, Toci.	Piperacillin/Tazobactam	NS	26	NS	MV	Death
	49	Severe	Pred., Tac., MMF	Withhold Tac. & MMF; MP	HCQ, Toci., IVIG	Ceftaroline	NS	21	NS	NIV	Discharged
	62	Severe	Pred., Tac.	Withhold Tac.; MP	HCQ, Toci.	Amoxiclav	NS	8	NS	MV	Death
Meziyerh *et al.* [51] (Netherlands)	35	Severe	Pred., Ever.	Withhold Ever.	Chloroquine, Lop/r	Cefuroxime Ceftriaxone	10	15	Yes	NC	Discharged
Mohan *et al.* [52] (USA)	70	Severe	Bel., MMF, Pred.	Withhold MMF & Bel.	HCQ	Azithromycin	21	NS	NS	None	Death
	64	Mild/Mod	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin	4	NS	NS	NS	Discharged
	28	Severe	Pred., Tac., Aza., Ada.	Withhold Aza.	HCQ	Azithromycin	1	NS	NS	NS	Discharged
	51	Severe	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin	9	NS	NS	NS	Discharged
	32	Mild/Mod	Pred., Tac., MMF	Withhold MMF	HCQ	NS	0	NS	NS	NS	Discharged
	21	Mild/Mod	Tac., MMF	None	NS	NS	4	NS	NS	NS	Discharged
	36	Mild/Mod	Bel., Tac., MMF, Pred.	Withhold MMF.	HCQ	NS	2	NS	NS	NS	Discharged
	72	Mild/Mod	Tac., MMF	Withhold MMF & Tac.	HCQ	Azithromycin	3	NS	NS	NS	Discharged
	51	Severe	Pred., Tac., MMF	Withhold MMF	HCQ	NS	1	NS	NS	MV	Hospitalized
	76	Mild/Mod	Tac., Leflu.	Withhold Leflu.	HCQ	NS	1	NS	NS	NS	Discharged
	61	Severe	Tac., MMF	Withhold MMF & Tac; MP	NS	NS	1	NS	NS	MV	Hospitalized
	22	Severe	Tac., Pred.	↓Tac. & Pred.	HCQ, Toci.	Azithromycin	2	NS	NS	MV	Hospitalized
	78	Severe	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin	7	NS	NS	MV	Death
	72	Mild/Mod	Tac., MMF	Withhold MMF	HCQ	Azithromycin	4	NS	NS	NS	Hospitalized
	25	Severe	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin	7	NS	NS	NS	Hospitalized
Nair *et al.* [53] (USA)	51	Mild/Mod	Pred., Tac., MMF, mTOR	No change	None	None	NS	NS	No	None	Discharged
	37	Mild/Mod	Pred., Tac., MPA,	Withhold MPA	HCQ	Azithromycin	NS	NS	No	None	Discharged
	63	Mild/Mod	Tac., MPA,	Withhold MPA	HCQ	Azithromycin, Ceftriaxone	NS	NS	No	None	Discharged
	31	Mild/Mod	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin Ceftriaxone,	NS	NS	No	None	Discharged
	56	Severe	Pred., Tac., MMF	Withhold MMF, Tac.	HCQ	Azithromycin, Ceftriaxone	NS	NS	Yes	MV	Death
	80	Severe	Tac., MMF	Withhold MMF, Tac.; MP	HCQ	Azithromycin, Vancomycin	NS	NS	Yes	MV	Discharged

	45	Severe	Pred., Tac., MMF	Withhold MMF; MP	HCQ	Azithromycin, Ceftriaxone, Vancomycin Piperacillin/ Tazobactam	NS	NS	No	NC	Discharged
	68	Severe	Pred., Tac., MMF	Withhold MMF	HCQ	Azithromycin, Vancomycin, Piperacillin/ Tazobactam	NS	NS	Yes	HFOT	Discharged
	75	Severe	Pred., mTOR	Withhold mTOR	HCQ	Azithromycin	NS	NS	Yes	MV	Death
	57	Severe	Tac., MMF	Withhold MMF; High dose Pred.	HCQ	Azithromycin, Ceftriaxone, Levofloxacin	NS	NS	Yes	MV	Death
Namazee *et al.* [54] (Iran)	63	Severe	CNI, MMF	Withhold all; Hydrocortisone	Lop/r, HCQ, Oseltamivir	Cefepime, Vancomycin	7	12	Yes	MV	Death
Ning *et al.* [55] (China)	29	Severe	MMF, CNI, MP.	No change	Lop/r, IVIG	Moxifloxacin	2	15	No	None	Discharged
Ruiz *et al.* [56] (Spain)	78	Severe	Pred., Tac.	↓Tac.	Lop/r	NS	NS	5	No	HFOT	Death
	73	Severe	Pred., Tac., MMF	↓Tac.; withhold MMF & Pred.	Lop/r, HCQ, IVIG	NS	NS	23	No	NC	Hospitalized
	80	Severe	Pred., Tac., MMF	↓Tac.; withhold MMF	Lop/r, HCQ	NS	NS	28	No	NC	Hospitalized
	71	Severe	Pred., Tac., MMF	↓Tac., withhold MMF & Pred.; MP.	Lop/r, HCQ, IVIG,	NS	NS	16	No	CPAP	Death
	71	Severe	Tac.	↓Tac.	HCQ, IVIG	NS	NS	9	No	NC	Discharged
	76	Severe	Pred., Rap., MMF	Withhold MMF; MP	HCQ	NS	NS	13	No	CPAP	Discharged
	39	Severe	Pred., Tac., Ever.	Withhold Tac. & Ever.; MP	HCQ	NS	NS	16	No	HFOT	Hospitalized
	65	Severe	Pred., Tac., MMF	↓Tac. & MMF	Lop/r, HCQ	NS	NS	17	No	HFOT	Hospitalized
Seminari *et al.* [57] (Italy)	50	Mild/Mod	Tac., MMF	No change	None	Ceftriaxone	9	13	No	None	Discharged
Shingare *et al.* [58] (Italy)	35	Mild/Mod	Pred., Tac., MMF	↓Tac. & Pred.; Withhold MMF	HCQ	Cotrimoxazole, Azithromycin	NS	28	No	None	Discharged
	45	Mild/Mod	Pred., Tac., MMF	↓dose of all	NS	NS	NS	52	No	None	Discharged
Silva *et al.* [59] (Portugal)	35	Mild/Mod	Pred., Tac., Aza.	Withhold Aza.; ↑Pred.	None	None	NS	30	No	NS	NA
	37	Severe	Pred., Tac., MMF	↓Tac.; Withhold MMF; ↑Pred.	HCQ	None	NS	30	No	NS	Discharged
	56	Mild/Mod	Pred., Tac., MMF	↓Tac.; Withhold MMF; ↑Pred.	None	None	NS	37	No	NS	Discharged
	63	Severe	Pred., Tac., MMF	↓Tac.; Withhold MMF; ↑Pred.	HCQ	None	NS	27	No	NS	Discharged
	63	Severe	Pred., CNI, Aza.	Withhold CNI & Aza.; ↑Pred.	HCQ,	NS	NS	10	Yes	NS	Death

Thammathiwat *et al.* [60] (Thailand)	58	Severe	Pred., Tac., MMF	Withhold Tac. & MMF; ↑Pred.	Dar/r, HCQ, Favipiravir, Toci.	Ceftriaxone, Azithromycin	18	NS	No	NC	Discharged
Wang *et al.* [61] (China)	49	Severe	Pred., CNI, MMF	No change; MP	Lop/r, Ribavirin, INF-α	None	7	14	No	NC	Discharged
Zhang H *et al.* [62] (China)	38	Mild/Mod	Pred., Tac., MMF	↓Tac.; withhold MMF	Oseltamivir, Umifenovir	No	15	17	No	None	Discharged
	64	Severe	Pred., Rap., MMF	Withhold Pred. & MMF; MP	Oseltamivir, Umifenovir, IVIG	Cefixime	4	32	No	None	Hospitalized
	37	Mild/Mod	Pred., Tac., MMF	Withhold Tac. & MMF	Oseltamivir, Umifenovir, IVIG	Cefixime	1	12	No	None	Hospitalized
	47	Mild/Mod	Pred., Tac., MMF	Withhold Tac. & MMF	Oseltamivir, Arbidol	No	4	19	No	None	Hospitalized
	38	Mild/Mod	Pred., Tac., MMF	No change	Oseltamivir, Arbidol	No	8	8	No	None	Discharged
Zhang M *et al.* [63] (China)	49	Mild/Mod	Pred., Tac., MMF	Withhold all; MP	Umifenovir	None	9	35	No	None	Discharged
Zhong *et al.* [64] (China)	48	Mild/Mod	Tac. & MMF	Continue Tac.; withhold MMF; MP	Umifenovir, Oseltamivir, INFα, IVIG,	Moxifloxacin	10	61	NS	None	Discharged
Zhu *et al.* [65] (China)	24	Severe	Pred., Tac., MMF	No change	NS	NS	27	43	NS	NC	Discharged
	55	Severe	Pred., Tac., MMF	↓Tac.; withhold MMF;	IVIG	NS	5	48	NS	NIV	Discharged
	29	Severe	Pred., Tac., MMF	Withhold MMF; MP.	NS	NS	7	37	NS	NC	Discharged
	30	Severe	Pred., Tac., MMF	Withhold MMF & Tac.; MP.	IVIG	NS	21	37	NS	NC	Discharged
	50	Severe	Pred., Tac., MMF	Withhold MMF & Tac.; MP.	IVIG	NS	8	34	NS	NC	Discharged
	65	Severe	Tac., MMF	Withhold MMF & Tac.; MP.	IVIG	NS	4	49	NS	NIV	Hospitalized
	52	Severe	Pred., Tac., MMF	Withhold MMF & Tac.; MP.	IVIG	NS	7	20	NS	NC	Discharged
	49	Severe	Tac., MMF	Withhold MMF & Tac.; MP.	NS	NS	9	34	NS	NC	Discharged
	59	Severe	Miz., CNI	Withhold all; MP.	IVIG	NS	8	6	NS	NIV	Death
	37	Severe	Pred., Tac., MMF	Withhold MMF & Tac.; MP.	IVIG	NS	10	31	NS	NC	Discharged
Zhu *et al.* [66] (China)	52	Severe	Pred., Tac., MMF	Withhold all; MP.	Umifenovir, INFα, IVIG	Moxifloxacin, Biapenem	8	21	NS	NC	Discharged

NS – Not specified; NA – Not Applicable; Mod – Moderate; Pred. – Prednisone; Tac. – Tacrolimus; MMF – Mycophenolate mofetil; MPA – Mycophenolic Acid; Miz. – Mizoribine; Bel. – Belatacept; Aza. – Azathioprine; Ada. – Adalimumab; Leflu. – Leflunomide; Toci. – Tocilizumab; Lop/r – Lopinavir/ritonavir; Dar/c – Darunavir/cobicistat; NC – Nasal canula; Rap. – Rapamycin; Ever. – Everolimus; MP. – Methylprednisolone; INF α – Interferon α; CNI – Calcineurin Inhibitor

Table 3

Diagnostic and therapeutic evidences regarding management of COVID-19 in Renal transplant recipients from aggregated data

Author **No. of K TX** **Median time since TX (yrs.)** **DDKT (%)**	Median age (yrs.) Gender (%)	Comorbidity (%)	ACEI (%)	AKI (%)	Symptom (%)	Baseline Immuno suppressant (%)	Change in Immuno suppressant (%)	Antiviral (%)	Laboratory data (%)	Median time to outcome (days)	Hospitalized (%) Mortality rate (%) ICU (%) MV (%) RRT (%)
Akalin *et al.* [67] (USA) **36 K TX–** **DDKT (75%)**	60 yrs. Male (72%)	HTN (94%) DM (69%) HD (17%)	–	–	Fever (58%) Diarrhea (22%) SOB (44%)	CNI (97%) MMF (94%) Pred. (86%)	Withdrew- CNI (21%) MMF (86%)	HCQ – (86%) Azith. – (46%) Toci. – (7%) High dose steroid – (7%)	Viral pneumonia on x-ray (96%) ↑CRP, d-Dimer, ferritin	21	78% 28% – 39% 21%
Montagud-Marrahi *et al.* [68] (Spain) **33 K TX** **10.7 yrs.** **–**	57.3 yrs. Male (57.6%)	–	–	–	–	CNI (58%) MMF (63%) mTOR (42%) Pred. (79%)	Withdrew CNI and MMF/mTOR Maintain steroid (15–20 mg/dl) – (100%)	(Lop/r + Azith. + HCQ) – (81%) (Azith. + HCQ) – (4%) HCQ – (8%) Azith. – (4%) Toci. – (50%)	Viral pneumonia on x-ray (73%)	12	79% 6% 52% 6% –
Machado *et al.* [12] (Brazil) **40 K TX** **10.3 yrs.** **–**	58.6 yrs. Male (83%)	HTN (80%) DM (20%) HD (15%)	–	23%	Fever (98%) Diarrhea (23%) SOB (28%)	CNI (90%) MMF (75%) Pred. (80%) mTOR – (15%) Belatacept – (3%)	Withdrew- CNI – (72%) MMF – (90%) Maintain steroid (81%) Reduce-CNI – (22%) MMF – (3%)	HCQ – (80%) Toci. – (15%) Oseltamivir – (10%) Antibiotic– (53%)	Viral pneumonia on x-ray (85%) ↑CRP, LDH, d-Dimer	–	58% 20% 13% – –
Husain *et al.* [69] (USA) **41 K TX** **3.5 yrs.** **DDKT (56%)**	49 yrs. Male (73%)	HTN (90%) DM (27%)	22%	–	Fever (80%) Diarrhea (27%) SOB (39%)	CNI (76%) MMF (76%) Pred. (39%)	Reduction in Immunosuppressants (63%)	–	Viral pneumonia on x-ray – (NS)	12	32% – – – –
Crespo *et al.* [70] (Spain) **16 K TX** **4 yrs.** **DDKT (94%)**	73.6 yrs. Male (75%)	HTN (88%) DM (80%) HD (50%)	13%	33%	Fever (100%) Diarrhea (25%) SOB (75%)	CNI (88%) MMF (50%) Pred. (81%) mTOR (31%)	Withdrew- CNI – (71%) MMF – (100%) mTOR – (80%) Maintain steroid (38%)	HCQ – (81%) Toci. – (25%) Lop/r – (31%) Antibiotic – (88%)	Viral pneumonia on x-ray – (93.3%) ↑LDH, CRP, d-Dimer, IL6	21	56% 50% 13% 13% 19%
Pascual *et al.* [71] (Spain) **24 K TX** **0.09 yrs. –**	66.5 yrs. Male (46%)	HTN (92%) DM (50%)	–	54%	Fever (63%) Diarrhea (13%) SOB (58%)	CNI (100%) MMF (100%) mTOR (18%) Pred. (100%)	Withdrew- CNI – (64%) MMF – (96%)	HCQ – (92%) Toci. – (33%) Lop/r – (33%) Antibiotic– (88%)	Viral pneumonia on x-ray – (NS)		100% 46% 17% 38% –

Bossini *et al.* [72] (Italy) 53 K TX 9.2 yrs. DDKT (85%)	60 yrs. Male (79%)	HTN (79%) DM (21%) HD (19%)	38%	33%	Fever (96%) Diarrhea (28%) SOB (17%)	CNI (91%) MMF (60%) Pred. (57%) mTOR (11%)	Withdrew All Immunosuppressants Maintain Methylprednisolone 16 mg/day	HCQ – (34%) Toci. – (74%)	Viral pneumonia – (69%), ↑LDH, CRP, ferritin, d-Dimer		85% 33% 22% 19% –
Cravedi *et al.* [73] (USA) 144 K TX 5 yrs. DDKT (78%)	60 yrs. Male (65%)	HTN (95%) DM (52%) HD (28%)	31%	52%	Fever (67%) Diarrhea (38%) SOB (67%)	CNI (91%) MMF (77%) Pred. (86%) mTOR (8%)	Withdrew- CNI – (23%) MMF – (68%)	HCQ – (71%) Toci. – (13%) Antibiotic – (74%)	Viral pneumonia on x-ray – (NS) ↑LDH, IL6	52	100% 32% – 29% –
Ghaffari Rahbar *et al.* [74] (Iran) 19 K TX 9.6 yrs. DDKT (42%)	47.6 yrs. Male (68%)	HTN (32%) DM (21%)	58%	74%	Fever (74%) SOB (68%)	CNI (100%) MMF (95%) Steroid (NS)	Withdrew- CNI – (68%) MMF – (100%) CNI reduction – 58%	HCQ – (95%) Lop/r – (79%) Oseltamivir – (68%)	Viral pneumonia on x-ray – (53%), ↑CRP, IL6, LDH, ferritin, d-Dimer	13	100% 48% 53% 30% 16%
Perez-Saez *et al.* [75] (Spain) 80 K TX 6 yrs.	59.3 yrs. Male (68%)	HTN (89%) DM (29%) HD (16%)	33%	45%	Fever (81%) SOB (58%) Diarrhea (48%)	CNI (83%) MMF (80%) Steroid (91%) mTOR (18%)	Withdrew- CNI – (5%) MMF – (34%) CNI + MMF/mTOR – (56%) Steroid maintenance – (80%)	HCQ – (99%) Lop/r – (49%) Toci. – (20%) Azith. – (74%)	Viral pneumonia on x-ray – (98%),↑CRP, IL6, LDH, ferritin, d-Dimer		100% 33% 30% 44% –
Demir *et al.* [76] (Turkey) 40 K TX 6.2 yrs. DDKT (13%)	45 yrs. Male (50%)	HTN (65%) HD (8%)	45%		Fever (63%) SOB (53%) Diarrhea (25%)	CNI (90%) MMF (90%) Steroid (100%) mTOR (10%)	Withdrew- CNI – (28%) MMF – (100%) Steroid maintenance – (80%)	Toci. – (13%) Antibiotic – (60%)	Viral pneumonia on x-ray – (NS) ↑CRP, IL6, LDH, ferritin, d-Dimer	32	100% 13% 18% 15% –
Lubetzky *et al.* [77] (USA) 54 K TX 4.7 yrs. DDKT (31%)	57 yrs. Male (70%)	HTN (93%) DM (30%) HD (35%)	37%	39%	Fever (74%) SOB (52%) Diarrhea (39%)	CNI (100%) MMF (100%) Steroid (37%)	Withdrew- MMF – (61%) Decrease CNI – (46%)	HCQ – (79% of hospitalized pts) Azith. – (38%)	Viral pneumonia on x-ray – (86%) ↑CRP, IL6, d-Dimer		72% 13% – 20% 8%
Monfared *et al.* [78] (Iran) 22 K TX 8.5 yrs. DDKT (100%)	52 yrs. Male (68%)	HTN (73%) DM (36%) HD (5%)	54%	55%	Fever (68%) SOB (64%) Diarrhea (18%)	CNI (95%) MMF (100%) Steroid (100%)	Withdrew-MMF – (95%) CNI – (12%) Decrease CNI – (88%) Maintenance steroid Hydrocortisone (100%)	HCQ – (100%) Oseltamivir – (86%) Lop/r – (77%)	Viral pneumonia on x-ray – (91%)	12	100% 27% – 23% –

DDKT – Deceased donor Kidney Transplantation; K TX – Kidney transplant; AKI – Acute kidney Injury; HTN – Hypertension; DM – Diabetes Mellites; HD – Heart Disease; SOB – Shortness of breath; Toci. Tocilizumab; CNI – Calcineurin inhibitor; MMF – Mycophenolate Mofetil; Azith. – Azithromycin; HCQ – Hydroxychloroquine.

Table 4

Demographics and clinical data for COVID19 infection in renal transplant recipients in relation to disease severity

		All	COVID severity (149)		P-value
			Mild/Moderate (36)	Severe (113)	
Age n (%) *	≤ 65 yrs.	118 (79)	32 (89)	86 (76)	0.15
	>65 yrs.	31 (21)	4 (11)	27 (24)	
Gender n (%) *	Male	112 (75)	26 (72)	86 (76)	0.66
	Female	37 (25)	10 (28)	27 (24)	
Comorbidities n (%) *	HTN	89 (71)	20 (74)	69 (70)	0.65
	DM	37 (30)	10 (38)	27 (27)	0.27
	Heart disease	26 (21)	4 (15)	22 (22)	0.59
	Others	36 (29)	8 (30)	28 (28)	0.89
Time since Transplantation in years mean (range) (NS-12)		7.49 (0–31)	5.6 (0.02–31)	8.1 (0–30.1)	**0.01**
Multiorgan transplant n (%) *		3 (2)	1 (3)	2 (2)	0.57
Time from symptom onset to hospitalization n (%) * **(NS-87)**	≤ 7 days	40 (65)	11 (69)	29 (63)	0.68
	> 7 days	22 (35)	5 (31)	17 (37)	
Time from symptom to recovery n (%) * **(NS-70)**	≤ 3 wks.	41 (52)	7 (47)	34 (53)	0.65
	> 3 wks.	38 (48)	8 (53)	30 (47)	
Symptom n (%) *	Fever	130 (87)	31 (86)	99 (88)	0.81
	Cough	87 (58)	19 (53)	68 (60)	0.43
	Myalgia	26 (17)	10 (28)	16 (14)	0.06
	Dyspnea/SOB	65 (50)	3 (10)	62 (63)	**0.00**
	Gastrointestinal S/S	33 (22)	5 (14)	28 (25)	0.17
Oxygen Saturation n (%) * **(NS-74)**	> 93%	39 (52)	8 (100)	31 (46)	**0.005**
	≤ 93%	36 (48)	0 (0)	36 (54)	
X-ray/CT Scan n (%) * **(NS-45)**	No change	19 (18)	13 (46)	6 (8)	**0.000**
	Unilateral change	11 (11)	5 (18)	6 (8)	
	Bilateral change	74 (71)	10 (36)	64 (84)	
Blood test range median (range)	Lymphopenia (NS-47)	61 (60)	15 (56)	46 (61)	0.60
	CRP (NS-47)	68.5 (1.9–337)	33 (1.9–134)	78 (2.7–337)	**0.005**
	LDH (NS-89)	462.7 (80–1855)	239.3 (113–383)	518.60 (80–1855)	**0.0004**
	Ferritin (NS-113)	2599.36 (93–52005)	562.8 (93–1664)	3006.67 (155–52005)	0.05
	IL6 (NS-121)	660.13 (2.7–11854)	38 (8–120)	829.79 (2.7–11854)	0.48
	d-Dimer (NS-122)	1107.02 (0.37–12552)	1 (0.39–2.03)	1358.38 (0.37–12552)	**0.008**
	Creatinine (NS-40)	2.5 (0.6–11)	1.4 (0.75–3.9)	2.7 (0.6–11)	**0.0001**
Baseline Immunosuppressant n (%) *	CNI	134 (90)	34 (94)	100 (89)	0.31
	MMF/MPA	122 (82)	29 (81)	93 (82)	0.80
	Azathioprine	5 (3)	2 (6)	3 (3)	0.59
	Steroid	123 (83)	25 (69)	98 (87)	**0.02**
	Belatacept	4 (3)	2 (6)	2 (2)	0.24
	mTOR	9 (6)	2 (6)	7 (6)	1.0
Use of ACEi/ARB (NS-71)		22 (28)	1(6)	21 (34)	**0.03**
ICU admission n (%) * **(NS- 31)**		40 (34)	0 (0)	40 (45)	**0.00**
Change in immunosuppressant n (%) *		137 (92)	28(78)	109 (96)	**0.001**
Reduction in Calcineurin Inhibitor (CNI) n (%) *		99 (66)	16 (44)	83 (73)	**0.002**
Reduction in antimetabolite (MMF/MPA) n (%) *		112 (78)	23 (66)	89 (82)	0.06
Change in steroid treatment n (%) *	Increased	85 (61)	9 (31)	76 (69)	**0.000**
	Decreased/Discontinued	6 (4)	4 (14)	2 (2)	
	No change	48 (35)	16 (55)	32 (29)	
Lop/r or Dar/c n (%) * **(NS-15)**		52 (39)	5 (14)	47 (47)	**0.001**
Oseltamivir n (%) * **(NS-15)**		13 (10)	7 (20)	6 (6)	**0.02**
HCQ n (%) * **(NS-15)**		90 (67)	15 (43)	75 (76)	**0.000**
Tocilizumab n (%) *		19 (13)	0 (0)	19 (17)	**0.007**
IVIG n (%) * **(NS-15)**		10 (7)	1 (3)	9 (9)	0.45
Azithromycin n (%) * **(NS-67)**		28 (34)	8 (32)	20 (35)	0.78
Antibacterial n (%) * **(NS-33)**		93 (80)	18 (60)	75 (87)	**0.001**
Clinical outcome n (%) *	Death	34 (23)	0 (0)	34 (30)	**0.000**
	Hosp/Discharge	112 (77)	33 (100)	79 (70)	

* All % expressed as column percentage

NS – Not specified; HTN – Hypertension; DM – Diabetes mellitus; SOB: Shortness of breath; CRP – C reactive protein; LDH – Lactate dehydrogenase; IL 6 – Interleukin 6; MMF – Mycophenolate Mofetil; MPA – Mycophenolic Acid; Lop/r – Lopinavir/ritonavir; Dar/c – Darunavir/cobicistat; HCQ – Hydroxychloroquine; IVIG – Intravenous Immunoglobulin; CNI – Calcineurin inhibitor (Tacrolimus and Cyclosporine).

Immunosuppressant and antiviral management

CHARACTERISTICS AND FACTORS AFFECTING COVID-19 OUTCOME (Table 5)

Outcome was reported on 144 cases of whom 74 (51%) were discharged, 36 (25%) remained hospitalized with improved condition and 34 (23%) patients did not survive the disease. All fatalities occurred in those who had severe disease. When stratified by continent, the fatality rate was numerically highest in Europe (27%) compared to Asia (26%) and America (14%). Table 5 summarizes patients' demographics, clinical presentation and management received by disease outcome.

Demographic and clinical factors

Compared to patients who were either discharged or remained hospitalized, patients who died had longer duration from transplant to disease diagnosis (P = 0.03) and all had severe disease (P = 0.001). Oxygen saturation ≤93% was more common in those who died than those who remained hospitalized (P = 0.00) while gastrointestinal symptoms were more common in those who recovered (P = 0.05). Interestingly, presence of other comorbidities, AKI development and ACEi/ARB use did not impact overall disease outcome.

Laboratory and immunological factors

Among various immunological biomarkers reported, only LDH level correlated with outcome. LDH was elevated in 68% of those who died as compared to 29% in those who were either hospitalized or discharged (p = 0.001). The significance was still maintained when LDH level was classified as ≤300 U/L and > 300 U/L with majority deaths (95%) occurring in patients with LDH level >300 mg/dl (p = 0.001). A box plot for different immunological markers and serum creatinine stratified by disease severity and disease outcome is outlined in Figure 3.

Post-hospitalization management

Overall change in immunosuppression was more aggressive in those who died or remained hospitalized (P = 0.002). Immunosuppression change was mainly driven by reducing or eliminating CNI in 79% and 86% in deceased and hospitalized patients, respectively, compared to only 54% in patients who were discharged (P = 0.001). Steroid monotherapy was also more common in those who died (56%) or remained hospitalized (69%) compared to only 38% in those who were discharged (P = 0.01). The antiviral agents Lop/r or Dar/c, HCQ and antibacterial agents were more commonly used in those who did not survive the disease or required prolong hospitalization. (P < 0.05 for both). There was no difference in oseltamivir, azithromycin, tocilizumab or IVIG utilization among the 3 outcome groups. The majority of the patients who died required ICU support (78%) and non-invasive ventilation or mechanical ventilation (P < 0.001).

THERAPEUTIC MANAGEMENT AND DISEASE SURVIVAL

We then divided the 144 cases with reported outcome into survivors and non-survivors to determine if there was any difference in survival according to the different strategies of immunosuppression modification or antiviral combinations. As demonstrated in Table 6, more aggressive reduction in immunosuppression was undertaken in non-survivors (26% vs 12%; p = 0.03). Corticosteroid dose increase or IV methylprednisolone use were not associated with survival. There was no significant difference in survival between different antiviral combinations with the exception of higher mortality in those who received Lop/r and HCQ combination (55% vs 30%%, P = 0.02) and HCQ at a dosage of 400 mg once daily (44% vs 19%, P = 0.04).

Effect of time of publication on disease survival

To explore if disease survival has changed overtime, we analyzed the mortality rate according to the time of publication of each report. We compared survival between early reports (published on or before May 31st, 2020, n = 29 studies) and late reports (published from June 1st to July 16th 2020, n = 15 studies). Overall mortality rate was comparable between the early (23.6%) and late (23.6%) reports, Figure 2.

DISCUSSION

In the current study, we identified demographic, clinical, laboratory, radiological, and treatment specific factors associated with disease severity and mortality in 149 globally representative cases of kidney transplant recipients with COVID-19. Our case series limited to aggregated data on 561 renal transplant recipients

also reported similar findings. Results indicate that severe disease (76%) and mortality (23%) were much higher in kidney transplant recipients compared to the general population. According to a review by Patel *et al.* the mortality rate for hospitalized patients in the general population was found to be around 13% [14]. We also demonstrated that dyspnea, radiological evidence of bilateral lung involvement, ACEi/ARB use, higher LDH, CRP, ferritin and d-Dimer levels were all factors that correlated with disease severity while older recipient age and presence of comorbidities did not. Mortality occurred only in patients with severe disease and was higher in patients older than 65 years, those with longer duration from transplant to disease diagnosis and in those with hypoxia and higher LDH at presentation. Despite the higher rate of AKI, mortality did not relate to AKI development which is in contrast to studies in the general population. Despite aggressive CNI dose reduction and higher utilization of intravenous corticosteroid, antiviral and antibacterial agents in those with severe disease, none of the treatment combinations demonstrated a clear survival advantage. Interestingly, HCQ and Lop/r combination and high once daily dose of HCQ were more commonly utilized in those who did not survive.

In the current study, we used a standardized classification for COVID-19 severity developed by the WHO. We demonstrated that the majority (76%) of the hospitalized kidney transplant recipients reported, had severe COVID-19 which is in striking contrast to the reported disease severity of 5% in hospitalized patient in the general population [15]. While under-reporting of mild cases and excluding patients managed in the outpatient setting could have modified the true incidence of COVID-19 severity in the kidney transplant population, this alarming rate of disease severity suggests that close monitoring of kidney transplant recipients who develop COVID-19 should be undertaken especially since all reported disease fatalities were in patients who had severe disease. In spite of differences in severity, the overall presentation of COVID-19 in renal transplant recipients was similar to the pattern observed in the general population.

We identified a slightly different risk factor profile for COVID-19 severity in kidney transplant recipients compared to the general population. While studies in the general population indicated that age, gender, and comorbidities are prognostic factors for disease severity, the current study demonstrated that none of these factors correlated with disease severity in the kidney transplant recipients [16, 17]. However, symptomatology especially dyspnea, and radiological evidence of bilateral lung involvement at presentation were factors associated with disease severity in this group of patients. Similar to studies of COVID-19 in the general population, we found increased inflammatory markers especially elevated CRP, LDH, Ferritin and d-Dimer levels to be associated with disease severity in the hospitalized kidney transplant recipients and therefore these markers should be monitored at presentation of any COVID-19 patients to identify those patients at risk of developing severe COVID-19 [6] [18]. Although serum creatinine was higher in those with severe disease, this was probably related to including AKI as defining criteria of disease severity. One important observation is the high rate of AKI in kidney transplant recipients. In contrast to reports from hospitalized COVID-19 cases in the general population where the incidence of AKI was found to be between 4 and 10%, the incidence of AKI in hospitalized kidney transplant recipients was much higher at 49% [19]. Interestingly, ACEi/ARB were more commonly in use in cases who developed severe disease. The reason for the association between ACEi/ARB uses and disease severity is unclear but could be related to higher rates of AKI and hence severe disease with ACEi/ARB use. Since we could not perform a multivariate analysis due to the small number of cases, the association between ACEi/ARB and disease severity in kidney transplant recipients should be further explored in future studies.

Reported COVID-19 fatality rate in the general population ranged between 2% and 15% and varied according to geographical location. In the US, the case fatality rate was found to be 1.7% with variation by county [20, 21]. A study by Buckner *et al.* reporting the clinical feature and outcome of COVID-19 in hospitalized general population in Seattle region identified a high case fatality rate of 33% in non-kidney transplant recipients but the older age and the multiple comorbidies of the study participants explain these results [22]. In contrast, the current study demonstrated that the fatality rate in the hospitalized kidney transplant recipients was much higher at 23% and remained relatively stable overtime (Figure 2) which is not surprising giving the higher observed rate of severe disease in this group of patients. Factors associated with disease fatality in kidney transplant recipients were also slightly different from the general population. While AKI was associated with high mortality in the general population, AKI was not found to correlate with fatality in kidney transplant patients

[19, 23]. Reason for the difference of the impact of AKI on outcome between the general and the kidney transplant populations is unclear and needs further investigation. Longer duration from transplant to disease diagnosis was associated with worse survival. Although this could be related to other confounders such as older patients' age, this finding still implies that kidney transplant patients are at risk of dying after acquiring COVID-19 even if they were transplanted many years prior to disease diagnosis. Compared to studies in the general population that showed that CRP, IL-6, and ferritin to be predictors of mortality, elevated LDH was the only immunological predictor of both severity and worse outcome in kidney transplant patients. The higher observed mortality developed despite aggressive reduction in immunosuppression medication (especially CNI), and higher utilization of antiviral agents. It is important to mention that increasing corticosteroid dose or escalation to parenteral methylprednisolone were not associated with survival advantage. While none of the different antiviral combinations were associated with survival advantage, HCQ and Lop/r combination and higher daily HCQ dosage were more commonly utilized in non-survivors. Reason for the higher mortality of these medication combinations is unclear but could be related to higher disease severity which led to the desperate use of these experimental regimens. Irrespective of the cause, the lack of survival advantage of any specific antiviral or antiviral combination along with the stable fatality rate over the last 5 months suggests that the increased fatality rate of COVID-19 in hospitalized kidney transplant patient is probably related to a host of other factors including lack of in vivo efficacy of the available anti-viral agents, lack of drugs targeting COVID-19 virus, virulence of the virus, and disease associated complications including AKI, ARDS and multiorgan failure [24]. One important take home message however was the relative safety of short-term reduction or withdrawal of immunosuppression medications as only 2 patients experienced non-biopsy proven acute rejection.

Although the current study has various strengths, there are some limitations. This study relied on previously published reports to extract the demographic, clinical, laboratory and management related information which was utilized to perform data analysis. In some cases, some of the necessary information was missing which could have affected our results. For a better understanding of COVID-19 there is a need for access to data even if provided in supplementary section or as appendix. Secondly, there is a need for using standard case definition as well as definition of study parameters for generalizability as well as comparability with other studies. A relatively small sample size could have reduced the statistical power to observe different association. Relying on previously published reports has also limited our ability to perform a multivariate analysis to identify independent predictors of disease severity or mortality in COVID-19 infected kidney transplant recipients. We also cannot exclude the possibility of publication bias where milder cases are less likely to be reported. Although we tried to reduce the risk of bias in the study but there is a possibility of presence of inherent clinical heterogeneity which might limit our generalizability. We limited our literature search to July 16th, 2020 and did not include any published records after this date. Also, literature focusing on COVID-19 is growing rapidly and hence the rates from this study might change when newer studies are added to the database. Due to these limitations, the results of this study should be viewed as preliminary information. As the disease continues to spread around the globe, large scale multicenter studies are needed to clarify appropriate management strategies of COVID-19 in kidney transplant recipients.

CONCLUSION

Using a globally representative sample of COVID-19 in 149 hospitalized kidney transplant recipients we conclude that severe COVID-19 is more common in this population affecting 76% of cases. Although mortality rate was only 23%, mortality in hospitalized kidney transplant recipients was much higher than the reported COVID-19 global mortality rate in the general population. AKI was highly prevalent in kidney transplant patients but it did not correlate with death. Elevated LDH at presentation and longer time since transplantation were associated with both disease severity and mortality. Immunosuppression management and antiviral utilization varied widely among different reports reflecting the lack of consensus on how best to manage these patients. Despite aggressive CNI dose reduction and higher utilization of antiviral and antibacterial agents in those with severe disease, none of the treatment combinations demonstrated a survival advantage including increasing corticosteroid dose or escalation to parenteral methylprednisolone. Lop/r and HCQ combination and high once daily dose of HCQ were more commonly utilized in non-survivors, an association that needs to be further confirmed in future studies.

Table 5

Factors affecting the outcome of COVID19 infection in hospitalized renal transplant recipients

			Outcome (144)			P-value
			Death (34)	Continued Hospitalization (36)	Discharged (74)	
Age n (%)*	≤ 65 yrs.		23 (68)	30 (83)	60 (81)	0.21
	> 65 yrs.		11 (32)	6 (17)	14 (19)	
Gender n (%)*	Male		24 (71)	26 (72)	59 (80)	0.50
	Female		10 (29)	10 (28)	15 (20)	
Comorbidities n (%)* (NS-28)	HTN		21 (68)	25 (86)	39 (64)	0.08
	DM		5 (16)	9 (31)	20 (33)	0.20
	Heart disease		9 (29)	3 (10)	14 (23)	0.20
Time of publication n (%)	Early period (March-May)		21 (62)	44 (59)	24 (67)	0.77
	Late period (June-July)		13 (38)	30 (41)	12 (33)	
Time since Transplantation in years mean (range)			9.8 (0.02–25)	5.9 (0–21)	7.0 (0.02–30.1)	**0.03**
COVID infection severity n (%)*	Mild/Moderate		0 (0)	8 (22)	24 (32)	**0.001**
	Severe		34 (100)	28 (78)	50 (68)	
Symptoms n (%)*	Fever		30 (88)	31 (86)	64 (86)	0.96
	Cough		21 (62)	18 (50)	44 (59)	0.55
	Myalgia		2 (6)	5 (14)	17 (23)	0.06
	Gastrointestinal S/S		4 (12)	6 (17)	23 (31)	0.05
	Dyspnea/SOB		18 (62)	19 (79)	28 (39)	**0.002**
	AKI		20 (63)	19 (53)	31 (43)	0.17
X-ray/CT Scan n (%)* (NS-43)	No change		1 (6)	4 (18)	11 (18)	0.51
	Unilateral changes		1 (6)	4 (18)	6 (10)	
	Bilateral changes		15 (88)	14 (64)	45 (73)	
Oxygen Saturation n (%)* (NS-69)	> 93%		2 (11)	10 (67)	27 (64)	**0.00**
	≤ 93%		16 (89)	5 (33)	15 (36)	
Blood test range, median (range)	Lymphopenia (NS-45)		10 (50)	13 (68)	36 (60)	0.51
	CRP (NS-44)	≤ 10 mg/L	4 (15)	1 (6)	15 (26)	0.17
		>10 mg/L	22 (85)	15 (94)	43 (74)	
	Ferritin (NS-108)	≤ 1000μg/L	7 (64)	5 (56)	12 (75)	0.66
		>1000μg/L	4 (36)	4 (44)	4 (25)	
	LDH (NS-86)	≤ 300 U/L	1 (5)	5 (42)	12 (48)	**0.003**
		>300 U/L	20 (95)	7 (58)	13 (52)	
	Creatinine level		2.82 (1.2–6.1)	2.9 (1.15–11)	2.1 (0.6–8)	0.04
Use of ACEi/ARB (NS-71)			5 (36)	9 (35)	7 (21)	0.44
Change in immunosuppressant n (%)*			34 (100)	36 (100)	64 (86)	**0.005**
Reduction of CNI n (%) *			27 (79)	31 (86)	40 (54)	**0.001**
Reduction of Antimetabolite (MMF/MPA) n (%)*			27 (90)	27 (75)	57 (78)	0.29
Steroid monotherapy, n (%)*			19 (56)	24 (69)	25 (38)	**0.01**
Increase in steroid treatment n (%)*			25 (74)	22 (63)	37 (56)	0.24
Increased to IV MP			22 (65)	18 (51)	30 (45)	0.19
Increased dose of oral steroid			2 (6)	3 (9)	7 (11)	0.92
Increased to IV steroid other than MP			1 (3)	1 (3)	0 (0)	0.26
Lop/r or Dar/c n (%)* (NS-15)			20 (61)	21 (68)	11 (17)	**0.00**
Oseltamivir n (%)* (NS-15)			1 (3)	4 (13)	8 (12)	0.32
HCQ (NS-15)			28 (85)	25 (81)	37 (57)	0.006
Tocilizumab			7 (21)	6 (17)	6 (8)	0.15
IVIG (NS-15)			1 (3)	3 (10)	6 (9)	0.57
Azithromycin (NS-66)			6 (38)	6 (55)	16 (31)	0.32
Antibacterial (NS-32)			28 (93)	23 (96)	42 (72)	**0.009**
ICU admission (NS-31)	Yes (40)		21 (78)	10 (30)	9 (17)	**0.00**
	No (73)		6 (22)	23 (70)	44 (83)	
O_2 therapy (NS-15)	CPAP		1 (3)	0 (0)	3 (5)	**0.00**
	HFOT		1 (3)	3 (9)	1 (2)	
	Mechanical ventilation		25 (78)	9 (26)	4 (6)	
	Nasal cannula		0 (0)	6 (18)	20 (32)	
	NIV		4 (13)	7 (21)	7 (11)	
	None		1 (3)	9 (26)	28 (44)	

* All % expressed as column percentage

NS – Not specified; HTN – Hypertension; DM – Diabetes mellitus; SOB: Shortness of breath; CRP – C reactive protein; LDH – Lactate dehydrogenase; IL 6 – Interleukin 6; CPAP: Continuous positive airway pressure; HFOT – High flow oxygen therapy; NIV – Noninvasive ventilation; CNI: Calcineurin inhibitor; MMF – Mycophenolate Mofetil; MPA – Mycophenolic Acid; MP: Methyl prednisone; Lop/r – Lopinavir/ritonavir; Dar/c – Darunavir/cobicistat; HCQ – Hydroxychloroquine; IVIG – Intravenous Immunoglobulin

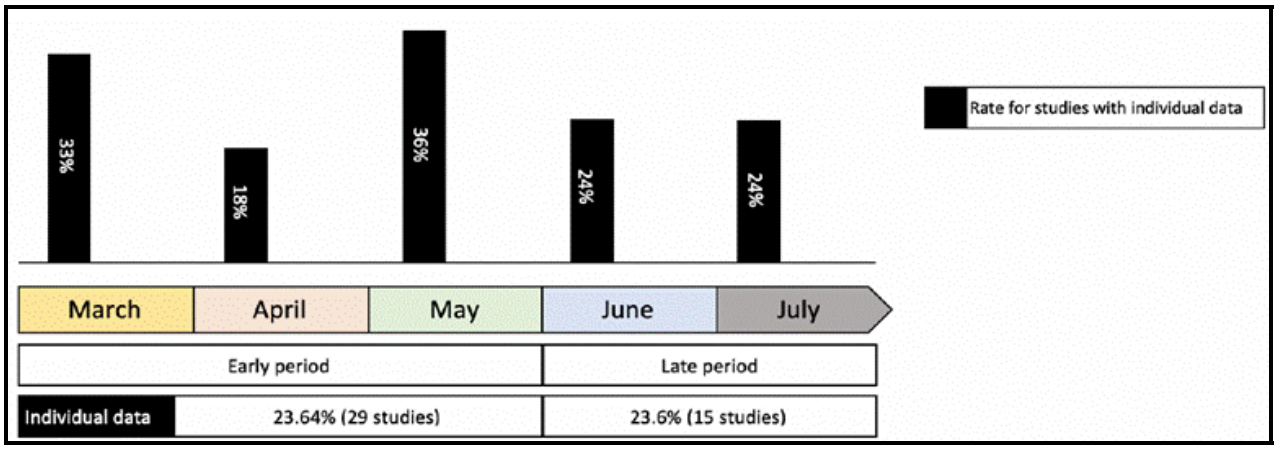

Figure 2. Mortality rate based on snapshot of time period captured by the studies

Table 6

Difference in survival based on therapeutic factors

		Survival (144)		P-value by strata	Overall P-value
		No (34)	Yes (110)		
Change in Immunosuppression					
Change in Immunosuppressant dose, n (%) *	No change 10(7)	0 (0)	10 (9)	0.12	**0.04**
	↓dose of all 22 (15)	9 (26)	13 (12)	**0.03**	
	Discontinue 1 or more immunosuppressant(s) 112 (78)	25 (74)	87 (79)	0.49	
Steroid monotherapy, n (%) *		19 (56)	49 (49)	NA	0.55
Steroid dose change, n (%) *	Increased 84 (62)	25 (74)	59 (58)	0.15	0.19
	Decreased/ Discontinued 6 (4)	0 (0)	6 (6)	0.34	
	No change 45 (33)	9 (26)	36 (36)	0.40	
Type of Steroid dose increase, n (%) *	Oral steroid changed to IV Methyl prednisolone 70 (52)	22 (65)	48 (48)	0.08	0.15
	Oral steroid changed to other IV steroids (Hydrocortisone or Dexamethasone) 2 (1)	1 (3)	1 (1)	0.44	
	Oral steroid dose increased 12 (9)	2 (6)	10 (10)	0.73	
Antiviral combination					
HCQ ±Azithromycin, n (%) * (NS-66)	Both 26 (33)	6 (38)	20 (32)	0.76	0.35
	Either one 16 (21)	5 (31)	11 (18)	0.30	
	None 36 (46)	5 (31)	31 (50)	0.26	
Lop/r± HCQ, n (%) * (NS-15)	Both 47 (37)	18 (55)	29 (30)	**0.02**	**0.009**
	Either one 48 (37)	12 (36)	36 (38)	0.91	
	None 34 (26)	3 (9)	31 (32)	0.01	
Dose of Anti-viral					
HCQ n (%) *, (NS-102)	400 mg BID 2 (5)	0 (0)	2 (8)	0.49	0.12
	400 mg QD 12 (29)	8 (44)	4 (19)	**0.04**	
	200 mg BID 13 (31)	6 (33)	7 (31)	0.77	
	400 mg BID stat followed by 200 mg QD from day 2. 15 (35)	4 (23)	11 (44)	0.20	
Lop/r n (%) *, (NS-115)	400/100 BID 18 (62)	9 (70)	9 (56)	0.70	0.46
	200/100 BID 8 (28)	2 (15)	6 (38)	0.24	
	Other 3 (10)	2 (15)	1 (6)	0.57	
Oseltamivir n (%) *, (NS-123)	30 mg QD 1 (5)	0 (0)	1 (5)	NA	0.37
	75 mg QD 1 (5)	1 (33)	0 (0)		
	75 mg BID 1 (5)	0 (0)	1 (5)		
	Not specified 19 (85)	2 (67)	17 (90)		
Umifenovir n (%) *, (NS-94)	200 mg TDS 8 (40)	0 (0)	8 (42)	NA	1.0
	Not specified 12 (60)	1 (100)	11 (58)		
Tocilizumab, n (%) *		7 (21)	12 (11)	NA	0.15

*All % expressed as column percentage

NS – Not specified; NA – Not applicable; Lop/r – Lopinavir/ritonavir; HCQ – Hydroxychloroquine.

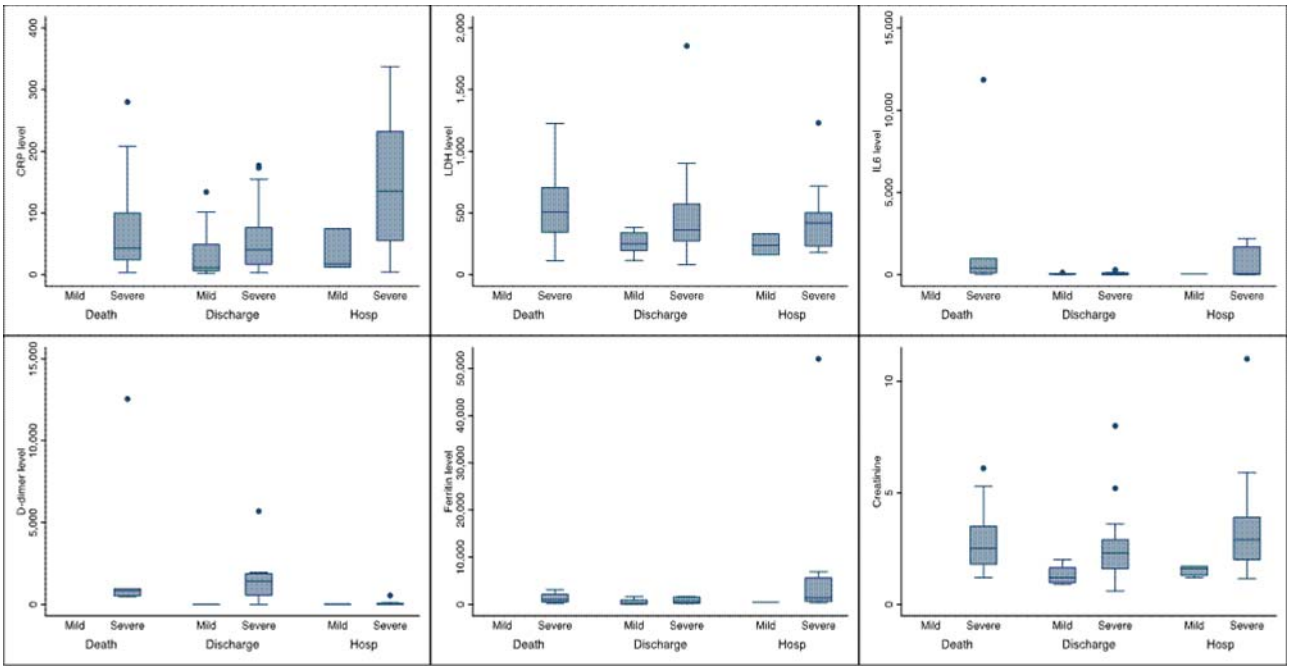

Figure 3. Box plot for immunological markers and serum creatinine stratified by disease severity and outcome for COVID-19 in renal transplant recipients. Boxes and whiskers represent the distribution of immunological markers and serum creatinine and the dots are the values greater than the third quartile and are considered outliers.

Introducere. *COVID-19 reprezintă o provocare pentru pacienții candidați pentru transplant renal.*

Metode. *A fost realizată o sinteză sistematică ce a evaluat infecția COVID-19 la pacienții transplantați renal. Caracteristicile clinice, de laborator, radiologice, modificările terapiei imunosupresoare au fost analizate. Severitatea COVID-19 a fost clasificată în ușoară, moderată și severă. Efectul urmărit a fost evoluția pacientului – externare, spitalizare sau deces.*

Rezultate. *44 de articole cu date individuale și 13 articole cu date multiple de la 149, respectiv 561 de pacienți cu transplant renal și infecție COVID-19 din Asia, Europa și America au întrunit criteriile de includere. 76% dintre pacienți au avut boală severă. Pacienții cu boală severă au avut niveluri mai mari ale CRP, LDH, feritinei și D-Dimeri, precum și afectare pulmonară bilaterală la momentul internării. Genul, vârsta și comorbiditățile nu au influențat severitatea bolii. Pacienții cu boală severă au avut o reducere progresivă a CNI și au necesitat mai multe tratamente antivirale. Efectul a fost raportat la 145 de cazuri dintre care 34 (23%) au decedat. Durata mai mare de la transplant, hipoxia și niveluri mai mari ale LDH s-au asociat cu mortalitatea. Strategiile de reducere ale imunosupresiei, nivelurile mari ale cortcoizilor administrați parenteral și combinațiile de antivirale nu au fost un avantaj. Observații similare au fost făcute în studiile altor cazuri.*

Concluzii. *Infecția COVID-19 este asociată cu o rată mare a severității bolii și a mortalității. Nivelurile ridicate ale LDH și durata mai mare de la transplant au prezis severitatea și mortalitatea bolii. Niciun tratament împotriva COVID-19 nu s-a asociat cu o îmbunătățire a prognosticului bolii la pacienții transplantați renal.*

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