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CYCLOSPORINE A IMPROVES OUTCOME OF KIDNEY TRANSPLANT RECIPIENTS WITH CORONAVIRUS DISEASE 2019: A META-ANALYSIS

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Abstract

Kidney transplant recipients are at an elevated risk of COVID-19 mortality. Cyclosporine A with COVID-19 could enhance kidney transplant recipients results since cyclosporine A has both antiviral and immunomodulatory properties. Therefore, we aimed to explore the link between the use of cyclosporine A with COVID-19 in kidney transplant recipients as maintenance immunosuppression and mortality, severity, acute kidney injury, and the need for intensive care unit care.

We searched comprehensive literature from various databases. Cyclosporine A was continued at low dose to maintain certain target concentrations and only discontinued in case of life-threatening situation. The major outcome was death, and the secondary outcomes were extreme COVID-19, acute kidney injury, and the need for intensive care unit treatment.

A total of 146 patients from 5 studies were analyzed. The use of cyclosporine A as maintenance immunosuppressive therapy in kidney transplant recipients was associated significantly with lower mortality from COVID-19 (RR 0.36 [0.16, 0.85], p=0.02; I^2: 0%, p=0.44). The use of cyclosporine A in kidney transplant recipients with COVID-19 was not significant for lower risk of severe COVID-19 (RR 0.81 [0.55, 1.18], p=0.27; I^2: 0%, p=0.60). The use of cyclosporine A was not associated with the risk of acute kidney injury (RR 1.03 [0.07, 15.41], p=0.98; I^2: 64%, p=0.10) or intensive care unit admission (RR 0.96 [0.18, 5.09], p=0.96; I^2: 0%, p=0.87).

The use of cyclosporine A for the maintenance of kidney graft during COVID-19 is associated with lower mortality than other immunosuppressive therapy regimens.

Keywords: *. Kidney transplant, mortality, COVID-19, cyclosporine A, acute kidney injury.*

Introduction

In the city of Wuhan, central China's Hubei province, unusual pneumonia cases were recorded in December 2019. As of January 12th, 2020, the World Health Organization (WHO) announced that the disease was caused by a new coronavirus, known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Since WHO announced COVID-19 to be a pandemic on 11 March 2020, over 21.2 million people had already been affected worldwide with deaths of over 760,000 people [*WHO, 2020; Zhu N et al., 2020*]. The SARS-CoV-2 belongs to the β-coronavirus cluster with clinical spectrum, ranging from mild diseases to severe pneumonia and critically ill cases [*Sun P et al., 2020*].

The current condition of COVID-19 introduces significant challenges to the treatment of patients with kidney disease, in particular kidney transplant recipients (KTR). Immunosuppression in maintenance is historically a medication regimen composed of small molecules administered in a stable KTR [*Bodell M et al., 2015*]. The course and outcome of COVID-19 depend on the cellular immunity but is weakened in KTR due to the chronic condition of immunosuppression. As a result, KTR may have increased risk of COVID-19 infection and severity [*Kronbichler A et al., 2020*]. Present guide-

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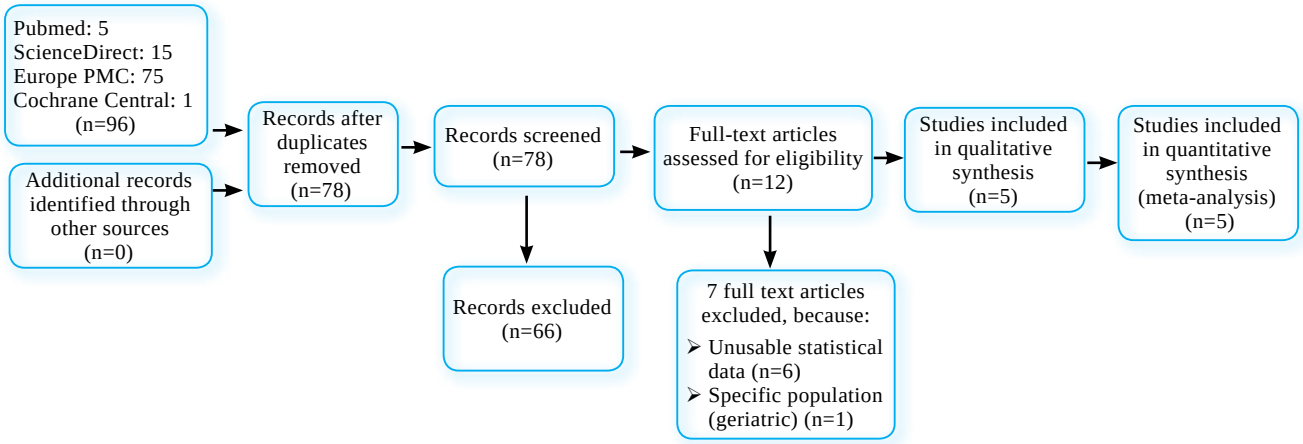


Figure 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.*

lines on KTR treatment with COVID-19 include the use of antivirals and immunosuppression reduction [*Bossini N et al., 2020; López V et al., 2020*].

Cyclosporine A (CsA) is a calcineurin inhibitor (CNI) that operates exclusively with T cells and is commonly used as an immunosuppressant medication to prevent graft rejection after a solid organ transplant [*Glowacka P et al., 2020*]. Non-immunosuppressive CsA derivatives decreased the human coronavirus 229E N protein expression needed for viral reproduction. Based on in vitro results, conversion to CsA could potentially improve outcomes in KTR with COVID-19 because CsA has both antiviral and immunomodulatory properties [*Kronbichler A et al., 2020*]. However, data on the outcomes of KTR with COVID-p19 treated with CsA are limited. Therefore, we aimed to explore the association between the use of CsA as maintenance immunosuppression and mortality, severity, AKI, and the need of ICU care in KTR with COVID□19 from the current available studies.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Material and methods

This meta-analysis was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility criteria

All articles in adult KTR patients diagnosed with COVID-19 with information regarding immunosuppressive therapy (IST) regimens, and outcome especially mortality, clinical grouping with validated definition, AKI, and the need of ICU care were included in this meta-analysis. Articles other than original research such as case report or case series with small number of subjects involved, review articles, letters to editor, editorial or commentaries, and non-English articles were excluded.

Search strategy and study selection

We searched the PubMed, EuropePMC, ScienceDirect, and Cochrane Central databases up till September 2020 using search terms: “Cyclosporine” or “Ciclosporin” and “Kidney transplant” or “Kidney allograft” and “COVID-19” or “SARS-CoV-2” and “Mortality” or “Clinical severity”; search results were limited to the year 2020. Full text of all articles including the cross references related to our topics were retrieved. Duplicates were then removed. Authors then screened the articles independently by its abstracts for relevance. The articles were thoroughly reviewed and only those which met the eligibility criteria were analyzed. Dispute among investigators was resolved through discussion and consultation with the senior investigator (W.B).

Data extraction

Data from included studies were extracted independently using a piloted data extraction form by two authors (D.P, R.D.A). The data extraction form included authors, year of the study, study design, age, IST regimen, history of significant comorbidities: diabetes mellitus (DM), hypertension, mortality, severity, AKI, and the need of ICU care. The major outcome was death, and the secondary out-

comes were severe COVID-19, AKI, and the need for ICU treatment.

The diagnosis of COVID-19 was based on the positive reverse transcription-polymerase chain reaction test (RT-PCR). Hydroxychloroquine (HCQ) was given to all patients 400 mg twice daily for the first 24 hours, followed by 200 mg twice daily for at least 5 days (unless contraindicated). Antiviral, antibiotic, cytokine-targeted therapy, intravenous immunoglobulin (IVIG), high-dose corticosteroids, and convalescent plasma were administered on a case-by-case basis. Immunosuppressive therapy regimens were adjusted, either discontinued or maintained at lower dose.

Statistical analysis

Using Review Manager 5.4 (The Cochrane Partnership, 2020) and Systematic Meta-Analysis, Version 3, the meta-analysis was carried out. For the measurement of dichotomous variables, Mantel-Haenszel formula was used. Given the variability, random effect models were used. The Q-statistic test and I^2 test estimated heterogeneity. I^2 test > 50% indicated substantial heterogeneity across the studies. Leave-one-out analysis was also performed to assess how each individual study affected the overall estimate of the rest of the studies should significant heterogeneity present. Risk ratios (RRs) with 95 percent confidence intervals (CIs) have been published. The P-value was set to ≤0.05 for two tailed and statistical significances. A qualitative publication bias evaluation with a funnel plot was carried out; an asymmetric shape suggests bias of publication. The regression-based Egger test was conducted to determine the impact of a small sample.

Results

Baseline characteristics and study selection

A total of 96 records were identified, and 78 remained after duplicates removed. Sixty-six records were excluded after reviewed by abstracts. Twelve full-text articles carefully examined for eligibility and 7 articles were excluded because: 1) the data presented were unusable for dichotomous variables of interest (n=6) and 2) specific population (geriatric population) (n=1). Finally, 5 studies were included in qualitative and quantitative synthesis. The PRISMA flow diagram is presented in figure 1. There was a total of 146 subjects from 5 included studies. All studies were observational

Table 1

Characteristics of the included studies

Authors & year	Country	Design	Samples	COVID-19 treatment	IST adjustment	Age	DM (%)	hypertension (%)	Outcome
Demir E et al., 2020	Turkey	Observational retrospective	40	◦ HCQ ◦ Azithromycin ◦ Tocilizumab, anakinra ◦ Favipiravir (resistant cases)	◦ Antimetabolites stopped ◦ CNI dose reduced ◦ CNI stopped (if hypoxemic)	44.9±14.8	5	65	Severe COVID-19
Rodriguez-Cubillo B et al., 2020	Spain	Observational retrospective	29	◦ HCQ ◦ Tocilizumab ◦ High-dose corticosteroid ◦ IVIG	◦ Antimetabolites stopped & CNI dose reduced (group I) ◦ Switched to CsA or usual CsA dose continued at low dose (group II)	63.3±12.9	37.9	96.5	Mortality, severe COVID-19, AKI, ICU admission
Ghaffari Rahbar M et al., 2020	Iran	Observational retrospective	19	◦ HCQ ◦ Oseltamivir, lopinavir/ritonavir, ribavirin, favipiravir ◦ IVIG ◦ Convalescent plasma	◦ Antimetabolites stopped ◦ mTOR inhibitors stopped ◦ CNI dose reduced ◦ CNI stopped (if hypoxemic)	47.6±12.4	21.1	31.6	Mortality
Devresse A et al., 2020	Belgium	Observational retrospective	18	HCQ	◦ Antimetabolites stopped ◦ mTOR inhibitors dose reduced - stopped ◦ CNI dose reduced	57 (41-73)	22	78	Mortality, severe COVID-19, AKI, ICU admission
Benotmane I et al., 2020	France	Observational retrospective	40	◦ HCQ ◦ Azithromycin ◦ Lopinavir/ritonavir ◦ Tocilizumab ◦ High-dose corticosteroid	◦ Antimetabolites stopped ◦ mTOR inhibitors stopped ◦ CNI stopped (42.6%)	63.8 (54.6-68.2)	47.5	82.5	Severe COVID-19

retrospective in design [*Benotmane I et al., 2020; Demir E et al., 2020; Devresse A et al., 2020; Ghaffari Rahbar M et al., 2020; Rodriguez-Cubillo B et al., 2020*]. Characteristics of the included studies are demonstrated in table 1.

Cyclosporine use and mortality In this meta-analysis in table 2, the use of CsA as maintenance IST in KTR was associated significantly with lower mortality from COVID-19 (RR 0.36 [0.16, 0.85], p=0.02; I^2: 0%, p=0.44). No significant heterogene-

TABLE 2

Cyclosporine A use and mortality. Cyclosporine A use was associated with lower mortality. IST: immunosuppressive therapy.

Study or Subgroup	Cyclosporine A		Other IST		Weight	Risk Ratio 95%CI			
	Events	Total	Events	Total		M-H	Random	M-H	Random
Devresse A et al., 2020	1	5	2	13	15.4%	1.30	[0.15, 11.36]		
Ghaffari Rahbar M et al., 2020	2	9	7	10	43.5%	0.32	[0.09, 1.15]		
Rodriguea-Cubillo B 2020	3	23	3	6	43.5%	0.26	[0.07, 0.98]		
Total (95%CI)	-	37	-	29	100.0%	0.36	[0.16, 0.85]		
Total events	6		12						
Heterogeneity	Tau^2=60.00; Chi^2=1.63; df=2(P=0.44; I^2=0%								
Test for ovral effect	Z=2.33 (p=0.02)								

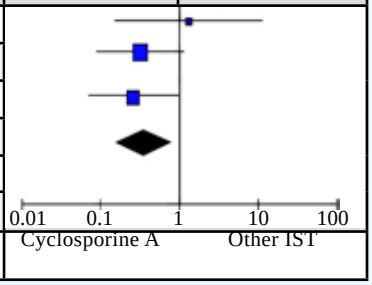
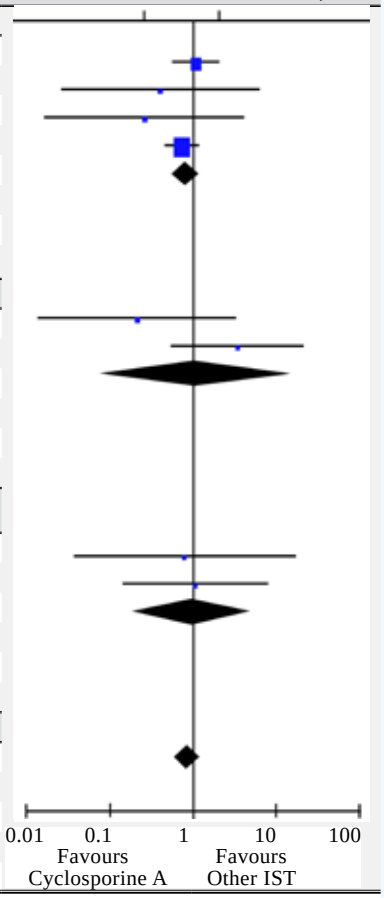


TABLE 3

Cyclosporine A use and secondary outcome. Cyclosporine A use was not associated with severe COVID-19, AKI, and need of ICU care.

Study or Subgroup	Cyclosporine A		Other IST		Weight	Risk Ratio 95%CI			
	Events	Total	Events	Total		M-H	Random,	M-H	Random,
3.3.1. Severe Covid-19									
Benotmane I et al., 2020	7	14	12	26	29.7%	1.08	[0.56, 2.11]		
Demir E et al., 2020	0	5	7	35	1.8%	0.40	[0.03, 6.13]		
Devresse A et al., 2020	0	5	4	13	1.7%	0.26	[0.02, 4.10]		
Rodriguez-Cubillo B et al., 2020	14	23	5	6	56.3%	0.72	[0.45, 1.19]		
Subtotal (95%CI)		47		80	89.5%	0.81	[0.55, 1.18]		
Total events	21		28						
Heterogeneity	Tau^2=0.00; Chi^2=1.85; df=3 (P=0.60); I^2=0%								
Test for ovral effect	Z=1.10 (p=0.27)								
3.3.2. Deresse AKI									
Devresse A et al., 2020	0	5	5	13	1.8%	0.21	[0.01, 3.26]		
Rodriguez-Cubillo B et al., 2020	13	23	1	6	4.0%	3.39	[0.55, 21.03]		
Subtotal (95%CI)		28		19	5.8%	1.03	[0.07, 15.41]		
Total events	13		6						
Heterogeneity	Tau^2=2.49; Chi^2=2.77; df=1 (p=0.10); I^2=64%								
Test for ovral effect	Z=0.02 (p=0.98)								
3.3.3. Need of ICU care									
Devresse A et al., 2020	0	5	1	13	1.4%	0.78	[0.04, 16.50]		
Rodriguez-Cubillo B et al., 2020	4	23	1	6	%	1.04	[0.14, 7.70]		
Subtotal (95%CI)		28		19	4.7%	0.96	[0.18, 5.09]		
Total events	4		2				[]		
Heterogeneity	Tau^2=00.00; Chi^2=0.03; df=1 (p=0.87); I^2=0%								
Test for ovral effect	Z=0.05 (p=0.35)								
Total (95%CI)		103		118	100%	0.84	[0.58, 1.21]		
Total events	38		36						
Heterogeneity	Tau^2=00.00; Chi^2=5.16; df=7 (p=0.64); I^2=0%								
Test for ovral effect	Z = 0.94 (P=0.35)								
Test for subgroup differences	Chi^2=0.07; df=2 (p=0.97); I^2=0%								



Notes: *IST: immunosuppressive therapy, AKI: acute kidney injury, ICU: Intensive Care Unit.*

ity was observed among studies for mortality.

Cyclosporine use and secondary outcome

The use of CsA in KTR with COVID-19 was not significant for lower risk of severe COVID-19 in table 3 (RR 0.81 [0.55, 1.18], p=0.27; I^2: 0%, p=0.60). The use of CsA was not associated with the risk of AKI (RR 1.03 [0.07, 15.41], p=0.98; I^2: 64%, p=0.10) or ICU admission (RR 0.96 [0.18, 5.09], p=0.96; I^2: 0%, p=0.87).

Publication bias

Despite the paucity of the number of the studies, the funnel plot analysis showed an asymmetrical distribution for mortality and severe COVID-19 (Fig. 2a, b) indicating possible publication bias. Egger's test revealed an indication of small-study effect regarding severe COVID-19 (p=0.044) but not for mortality (p=0.139).

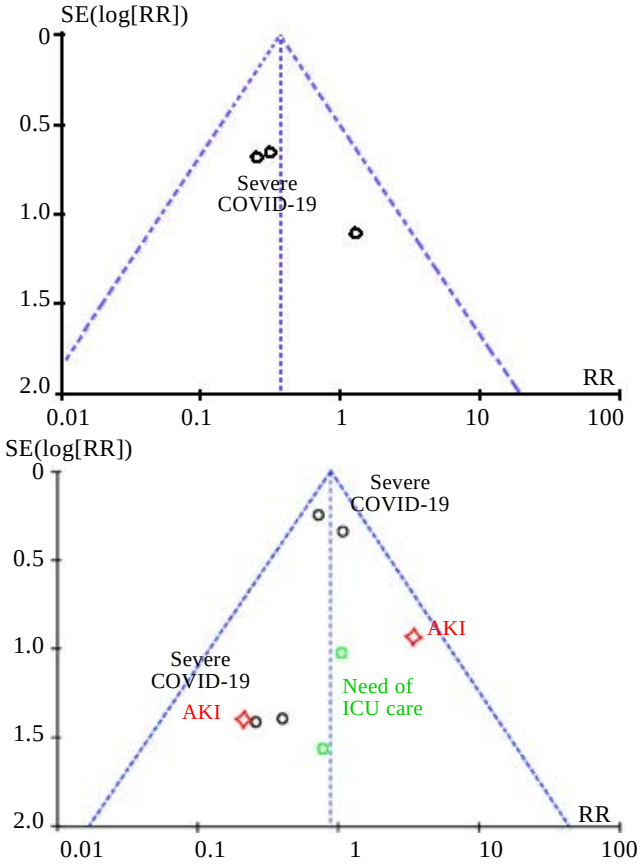


Figure 2. *Funnel plot analysis. Funnel plot analysis showed an asymmetrical distribution for mortality and severe COVID-19*

Discussion

The primary outcome of this meta-analysis indicated that the use of CsA in maintenance immunosuppression of KTR with COVID-19 was associated with lower mortality. Although it was not associated with any of the secondary outcome (severe COVID-19, AKI, ICU admission), it still has clinical importance. These findings might aid the decision regarding IST management in KTR with COVID-19 during global pandemic. The mortality of patients with severe COVID-19 pneumonia is high especially in patients with comorbidities [*Yang X et al., 2020*]. Cardiometabolic comorbidities (DM, hypertension, coronary artery disease) are commonly found in KTR. Moreover, the additional risk due to immunosuppression might increase mortality in this population. Meanwhile, balance between infection and rejection should be maintained, hence management of KTR with COVID-19 poses greater complexity.

Earlier, a letter to the editor reporting a KTR patient with COVID-19 pneumonia showed that withdrawal of antimetabolite and conversion to low dose CsA resulted in good outcome and stable allograft function as well [*Kemmner S et al., 2020*]. However, studies about the outcome of CsA in KTR with COVID-19 are scarce and mainly observational in design. This is the first meta-analysis, to our knowledge, to examine the relationship between CsA usage and KTR mortality with COVID-19. The present study showed that the use of CsA as immunosuppressive regimen reduced mortality (risk ratio) to 0.36 in KTR with COVID-19.

The decision to switch into low-dose CsA was based on in vitro data that reported suppression of viral replication for various coronaviruses at non-cytotoxic concentrations [*de Wilde A et al., 2011*]. During their life cycle many viruses use active immunophilin pathways [*Willicombe M et al., 2020*]. Cyclophilin A is a member of immunophilin family, which plays pivotal role in numerous inflammatory diseases and facilitates virus replication. Cyclosporine A works by connecting it with cyclophilin A [*Glowacka P et al., 2020*]. The CsA concentration needed to inhibit viral replication, however, far exceeds serum levels that are usually below 200 *ng/mL* [*Poulsen N et al., 2020*]. Previous study about the relationship between nasopharyngeal viral loads and severity of COVID-19 reported that there was no association between the use of CsA and nasopharyngeal viral loads [*Benotmane I et al., 2020*]. Consequently, no association was demonstrated between the use of CsA and severe COVID-19 in the present study.

The clinical course of COVID-19 is categorized in four stages: 1) asymptomatic 2) early infection 3) pulmonary involvement and 4) systemic hyperinflammation. The last stage has the highest mortality and associated with cytokine-storm syndrome [*Huang C et al., 2020; Willicombe M et al., 2020; Zhou F et al., 2020*]. Prior studies have shown that cyclosporine can be used safely in critically ill patients with serious infections, inflammatory disorders, and even circulatory vulnerable. The use of CsA has also been useful in mortality of Stevens Johnson syndrome and toxic epidermal necrolysis [*Cung T et al., 2015; Zimmermann S et al., 2017; Poulsen N et al., 2020*]. The rationale for using CsA in severe COVID-19 is currently being investigated in a randomized clinical trial. Though the effect of T-cell depletion by CsA on cytokine storm state of COVID-19 still unclear, the immunomodulatory effect in KTR with COVID-19 improved mortality in the present study [*Bhaskar S et al., 2020*].

The result of present meta-analysis justifies the continued usage of CsA in KTR with COVID-19 unless in the event of severe hypoxemia, leucopenia, or AKI. Nonetheless, switching other IST regimen (antimetabolites, mTOR inhibitors, tacrolimus) to CsA during COVID-19 still requires additional clinical trials with clinically relevant outcome. Also, the possibility of rejection and graft failure with the use of CsA should always be anticipated.

The limitation of our current study was largely due to the shortage of studies related to the topic which contributed to the presence of publication bias. All the study included also observational by nature and the protocols for COVID-19 management varies (e.g., use of antivirals, anticoagulants, and antibiotics). Finally, the incidence of acute rejection or graft loss only reported in one study [*Ghaffari Rahbar M et al., 2020*].

CONCLUSION

The use of CsA for maintenance of kidney graft during COVID-19 is associated with lower mortality than other IST with comparable risk of developing AKI. Kidney transplant recipients with CsA in the IST regimen might be benefited from its immunomodulatory effect during COVID-19 systemic hyperinflammation state.

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