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# Immune Suppressive Medications Role in the Prognosis of COVID-19 Among Kidney Transplant Recipients

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**Keywords.** kidney transplantation, COVID-19, prognosis, immune suppression

**Introduction.** Kidney transplant recipients are among the most critical individuals when facing COVID-19 pneumonia with increased risk of morbidities and mortalities. Immune suppressive medications are essential to prevent from rejection, while due to their immune-associated properties, these drugs are one of the major culprits for severe pneumonia. The current study aims to investigate the role of these agents in prognosis of COVID-19 pneumonia.

**Methods.** The current cross-sectional study was conducted on 139 kidney transplanted recipients hospitalized due to COVID-19 pneumonia. The transplant-related medications including angiotensin convertase enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), corticosteroids, calcineurin inhibitors, mycophenolate mofetil, and mammalian targets of rapamycin inhibitors were recorded and their prognosticating role in the mortality and survival of the patients was evaluated through logistic and cox regression in crude and adjusted models: 1) age and gender, and 2) age, gender, medical diseases and COVID-19 severity.

**Results.** Based on logistic regression assessment, none of the consumed drugs by kidney transplant recipients had a preventive role in the mortality of the patients in either crude or adjusted models ($P > .05$). However, cox regression measures revealed that treatment with ACEI/ARB was accompanied by longer survival in the crude (HR = 0.532, 95% CI: 0.333 to 0.851, $P = .008$) and adjusted models 1 (HR = 0.515, 95% CI: 0.318 to 0.833, $P = .007$) and 2 (HR = 0.583, 95% CI: 0.349 to 0.975, $P = .040$), respectively.

**Conclusions.** Based on the findings of the current study, ACEI/ARB use was accompanied with decreased length of ICU stay among the kidney transplant patients with COVID-19 infection, while the other medications did not have any effect.

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## INTRODUCTION

By the late days of 2019, the novel coronavirus 2019 disease (COVID-19) emerged in Wuhan, China and rapidly spread over the world.[1] Most of the infected individuals were asymptomatic or represented mild flu-like symptoms; however, approximately 20% of the patients presented moderate to severe course of the disease and less than 5% progressed to critically-ill patients.[2] Risk factors for progression to the severe form of

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COVID-19 include old age, male gender, medical disease such as hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, respiratory disease and obesity. Nevertheless, the rate of mortality variably differs from 1 to 7.2% in different communities and even reaches 49% among critical populations.[3]

Kidney transplantation requires lifelong immunosuppressive medications, drastically limiting the risk of organ rejection. Accordingly, due to immune suppression and comorbidities associated with chronic kidney disease, the kidney transplant individuals are at increased risk for severe COVID-19 infection, related adverse events and mortality compared with the general population.[4]

Severe course of COVID-19 infection might lead to requirement for ICU admission which is one of the alarm signs of probable devastating outcomes. It is yet unclear whether the presence of immunosuppression increases the complications of COVID-19 in kidney transplant individuals.[5] Some experts highlight the incompetent immune of the patients representing increased risk of adverse events, while the others suggest that immunosuppression may reduce the frequency of cytokine storms, a significant cause of elongated hospitalization, ICU stay and mortality.[2,4] Accordingly, the current study aims to dedicatedly investigate the effect of immunosuppressive agents applied in kidney transplantation on the length of ICU stay due to COVID-19 infection.

## MATERIALS AND METHODS

### Study Population

The current cross-sectional study was conducted on 139 kidney transplanted recipients coming down with COVID-19 admitted at Khorshid or Alzahra Hospitals affiliated with Isfahan University of Medical Sciences from April 2020 to December 2021.

The study protocol was primarily proposed to the Ethics Committee of Isfahan University of Medical Sciences and approved via code number "IR.MUI.MED.REC.1400.220". Then, the patients; their legal guardians got informed about the potential use of the medical data for scientific research, they were reassured regarding the confidentiality of their personal information and signed written consent for participation in the study.

Over 18-year-old individuals with active medical records of kidney transplantation who had a positive real-time polymerase chain reaction (RT-PCR) test or clinical symptoms of COVID-19 infection along with CT scan compatible with COVID-19 infection[6] were included in the study. Incomplete medical data, unavailability of high resolution chest CT scan and reluctance for participation in the study were considered as the exclusion criteria.

The patients entered into the study through convenience sampling until achieving the desired number of patients based on the biostatistician calculation.

### Data Collection

The main scope of this study was to evaluate the influence of medications applied by the kidney transplanted recipients on the mortality of those who were infected with COVID-19.

Given that, the patients' medical records were retrieved form the archives of the index hospitals.

The demographic characteristics (age and gender) and medical data including hypertension, diabetes mellitus, and cardiovascular disease were recruited from the medical records.

Moreover, the medications including angiotensin convertase enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), corticosteroids, calcineurin inhibitors (cyclosporine and tacrolimus), mycophenolate mofetil, mammalian targets of rapamycin inhibitors (mTORI) (sirolimus and everolimus), statins and insulin that the patients were currently applied, were recorded in the study checklist.

The glomerular filtration rate (GFR) of the patients was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The measurement was done before discharge/ death.

### COVID-19 Manifestations

Moreover, the severity of lung involvement due to COVID-19 infection was determined using a 4-score scale using the manifestations in lung HRCT: 1) normal stage: normal chest with score of zero, 2) mild stage: subpleural ground glass opacity and consolidation, nodular ground glass opacification mostly involving the lower or

middle lobes of the lungs bilaterally (score 1), 3) progressive stage: large and multiple involvements of the lungs with consolidation and increased interlobular presentation. Pleural effusion and lymphadenopathy are rare in this stage (score 2), and 4) severe stage: massive involvement in both lungs occupying more than 50% of the lungs with a white lung view (score 3).[7]

The next assessment of the study was the COVID-19 infection severity categorized as the following:

- Mild: fever with body temperature < 38 °C and no chest involvement in HRCT
- Moderate: evidence of chest involvement in HRCT (< 50%) but no fall in oxygen saturation (≥ 94%)
- Severe: remarkable chest involvement in HRCT (≥ 50%), oxygen saturation of less than 94% and respiratory rate > 30/min.[8]

### Statistical Analysis

The obtained data were entered into the STATA version 14. Descriptive data were presented in mean, standard deviation, percentages, and absolute numbers. The categorical data were compared using Chi-Square test or Fisher's exact test. Independent t-test or ANOVA were applied to compare the continuous variables. Univariate and multivariate logistic regression test was used to find the association between the length of ICU admission and type of medications in both crude and adjusted models. Given that, the adjusted models were primarily adjusted for age and gender. In the next step, they were adjusted for the previous variables as well as the medical diseases and COVID-19 infection severity. *P* value of less than .05 was considered as a significant level.

## RESULTS

In the current study, data of 139 kidney transplanted patients admitted due to COVID-19 pneumonia were recruited. The study population predominantly consisted on males (54%) and had the mean age of 53.03 ± 14.06 years old. According to the hospitalization outcome, the patients were divided into two groups of deceased (n = 18) and

**Table 1.** Baseline Information

| Variables | Vitality status | | Total | *P* |
|---|---|---|---|---|
| | Deceased (n = 18) | Discharged (n = 121) | | |
| Demographic characteristics | | | | |
| Age, y (mean ± SD) | 52.4 ± 13.93 | 57.67 ± 14.46 | 53.03 ± 14.06 | .134€ |
| Gender (male), n (%) | 11 (61.1) | 53 (43.8) | 75 (54.0) | .169* |
| Medical history, n (%) | | | | |
| Diabetes mellitus | 11 (61.1) | 48 (39.7) | 59 (42.4) | .086* |
| Hypertension | 13 (72.2) | 63 (52.1) | 76 (54.7) | .109* |
| Cardiovascular disease | 2 (11.1) | 7 (5.8) | 6 (6.5) | .329** |
| Current chronic medications, n (%) | | | | |
| Statins | 8 (44.4) | 35 (28.9) | 43 (30.9) | .182* |
| Insulin | 9 (50) | 25 (20.7) | 34 (24.5) | .015** |
| ACEI/ARB | 6 (33.3) | 26 (21.5) | 32 (23.0) | .366** |
| Corticosteroids | 15 (83.3) | 106 (87.6) | 121 (87.1) | .705** |
| Calcineurin inhibitor | 13 (72.2) | 92 (76.0) | 105 (75.5) | .771** |
| Mycophenolate | 16 (88.9) | 92 (76.0) | 108 (77.7) | .362** |
| MTORI | 4 (22.2) | 21 (17.4) | 25 (18.0) | .742** |
| CKD stage, n (%) | | | | |
| 1 | 0 (0.0) | 2 (1.7) | 2 (1.4) | .134** |
| 2 | 1 (5.6) | 26 (21.5) | 27 (19.4) | |
| 3 | 8 (44.4) | 62 (51.2) | 70 (50.4) | |
| 4 | 6 (33.3) | 15 (12.4) | 21 (15.1) | |
| 5 | 3 (16.7) | 16 (13.2) | 19 (13.7) | |

*Chi Square **Fisher's Exact test €t-test
Abbreviations: ACEI, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; mTORI, mammalian targets of rapamycin inhibitors.

discharged (n = 121).

The studied groups were similar considering their demographic, medical history, current chronic medications (except for insulin ($P$ = .015)) and stage of CKD ($P$ > .05). Detailed information is demonstrated in Table 1.

Table 2 shows COVID-19 infection related clinical data in the studied patients. Accordingly, the medications applied to manage COVID-19 including remdesivir ($P$ = .561) and corticosteroid use ($P$ = .999) and requirement for hemodialysis ($P$ = .969) during the hospitalization were similar between the groups, while the parameters including lung involvement in HRCT ($P$ < .001), disease severity ($P$ < .001) and intubation requirement ($P$ < .001) were remarkably different between deceased individuals and the survivors.

On-admission vital signs assessments revealed remarkable higher respiratory rate ($P$ = .018) and lower oxygen saturation ($P$ = .022) among those who did not survive. Except for CRP ($P$ = .005), other laboratory measures were similar between the groups ($P$ > .05) (Table 3).

Table 4 shows logistic regression models for the prognostic role of renal transplant medications to prevent from death due to COVID-19 pneumonia. Based on this table, none of the drugs had a preventive role in either crude or adjusted models ($P$ > .05).

The mean duration of survival in the included patients was 9.85 ± 6.75 days (range: 2 to 33 days). Table 5 shows the survival duration of the

**Table 2.** COVID-19 Infection Related Clinical Information

| Variables | Vitality status | | Total | *P* |
|---|---|---|---|---|
| | Deceased (n = 18) | Discharged (n = 121) | | |
| COVID-19 treatment, n (%) | | | | |
| Remdesivir | 3 (16.7) | 31 (25.6) | 34 (24.5) | .561** |
| Corticosteroids | 17 (94.4) | 112 (92.6) | 129 (92.8) | .999** |
| Lung involvement in HRCT, n (%) | | | | |
| Mild stage | 0 (0) | 69 (57.0) | 69 (49.6) | < .001* |
| Moderate stage | 13 (72.2) | 46 (38.0) | 59 (42.4) | |
| Severe stage | 5 (27.8) | 6 (5.0) | 11 (7.9) | |
| Disease severity, n (%) | | | | |
| Mild | 0 (0.0) | 31 (25.6) | 31 (22.3) | < .001** |
| Moderate | 4 (22.2) | 83 (68.6) | 87 (62.6) | |
| Severe | 14 (77.8) | 7 (5.8) | 21 (15.1) | |
| In-hospital hemodialysis requirement | 1 (5.6) | 7 (5.8) | 8 (5.8) | .969* |
| Mechanical ventilation requirement | 7 (38.9) | 2 (1.7) | 9 (6.5) | < .001** |

*Chi Square **Fisher's Exact test €t-test
Abbreviations: HRCT, high-resolution computed tomography.

**Table 3.** On-admission Vital Sign and Laboratory Measures

| Variables | Vitality status | | Total | *P* (independent t-test) |
|---|---|---|---|---|
| | Deceased (n = 18) | Discharged (n = 121) | | |
| Respiratory rate, /min | 25.72 ± 6.34 | 21.69 ± 6.70 | 22.21 ± 6.77 | .018 |
| Oxygen saturation (%) | 82.72 ± 13.13 | 90.62 ± 6.30 | 89.60 ± 7.93 | .022 |
| Hemoglobin, g/dL | 11.00 ± 2.98 | 11.87 ± 2.30 | 11.76 ± 2.40 | .150 |
| WBC, * $\times 10^3$, µL | 8.88 ± .51 | 8.71 ± .51 | 8.73 ± .51 | .240 |
| Lymphocyte, $\times 10^3$, µL | 6.25 ± .61 | 6.53 ± .65 | 6.49 ± .65 | .089 |
| Platelet*, $\times 10^6$, µL | 12.00 ± .44 | 12.06 ± .39 | 12.01 ± .43 | .580 |
| Sodium, meq | 136.28 ± 5.69 | 136.87 ± 4.62 | 136.79 ± 4.75 | .625 |
| Potassium, meq | 4.85 ± .71 | 4.61 ± .81 | 4.64 ± .80 | .232 |
| CRP, mg/dL | 83.38 ± 37.10 | 53.26 ± 41.95 | 57.16 ± 42.46 | .005 |
| Creatinine, mg/dL | 2.71 ± 1.72 | 2.20 ± 1.76 | 2.27 ± 1.76 | .258 |

*calculated using Ln
Abbreviations: CRP, C-reactive protein; WBC, white blood cells.

**Table 4.** Logistic Regression Models to Prognosticate Kidney Transplantation Medications Role in the Prevention of COVID-19 Related Pneumonia

| Variable | Crude model | | | Model 1* | | | Model 2** | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | *P* | 95% CI | OR | *P* | 95% CI | OR | *P* | 95% CI |
| ACEI/ ARB | 0.621 | .400 | 0.205 to 1.885 | 0.680 | .503 | 0.220 to 2.100 | 0.957 | .960 | 0.166 to 5.507 |
| Corticosteroids | 2.070 | .345 | 0.458 to 9.362 | 1.944 | .400 | 0.414 to 9.137 | 1.127 | .920 | 0.109 to 11.644 |
| Calcineurin inhibitors | 1.306 | .810 | 0.147 to 11.593 | 1.062 | .957 | 0.120 to 9.429 | 2.264 | .538 | 0.168 to 30.555 |
| Mycophenolate mofetil | 0.324 | .200 | 0.058 to 1.816 | 0.337 | .210 | 0.061 to 1.846 | 0.139 | .156 | 0.009 to 2.115 |
| mTORI | 0.870 | .906 | 0.086 to 8.830 | 0.605 | .676 | 0.057 to 6.392 | 1.980 | .648 | 0.106 to 37.147 |
| Statins | 0.524 | .223 | 0.185 to 1.483 | 0.551 | .276 | 0.188 to 1.612 | 0.448 | .349 | 0.083 to 2.404 |

Abbreviations: ACEI, angiotensin convertase inhibitor; ARB, angiotensin receptor inhibitor.
*Model 1: Adjusted for age and gender
**Model 2: adjusted for age, gender, medical diseases and COVID-19 severity

**Table 5.** The Factors Associated With Survival Period of the Studied Population

| Variable | Survival period (mean ± SD) | *P* |
|---|---|---|
| Gender | | |
| Male | 9.69 ± 6.70 | .764* |
| Female | 10.03 ± 6.49 | |
| Diabetes mellitus | | |
| Yes | 10.80 ± 6.40 | .145* |
| No | 9.15 ± 6.64 | |
| Hypertension | | |
| Yes | 11.28 ± 7.01 | .005* |
| No | 8.13 ± 5.56 | |
| Cardiovascular disease | | |
| Yes | 10.78 ± 7.36 | .663* |
| No | 9.78 ± 6.53 | |
| Statins | | |
| Yes | 10.95 ± 5.70 | .186* |
| No | 9.35 ± 6.89 | |
| Insulin | | |
| Yes | 10.24 ± 4.78 | .695* |
| No | 9.72 ± 7.06 | |
| ACE/ARB | | |
| Yes | 12.78 ± 7.95 | .016* |
| No | 8.97 ± 5.85 | |
| Corticosteroids | | |
| Yes | 10.07 ± 6.60 | .314* |
| No | 8.39 ± 6.27 | |
| Calcineurin inhibitor | | |
| Yes | 9.73 ± 6.50 | .717* |
| No | 10.21 ± 6.85 | |
| Mycophenolate mofetil | | |
| Yes | 9.99 ± 6.69 | .637* |
| No | 9.35 ± 6.21 | |
| mTORI | | |
| Yes | 11.36 ± 5.21 | .205* |
| No | 9.52 ± 6.80 | |
| Remdesivir | | |
| Yes | 9.15 ± 6.39 | .476* |
| No | 10.08 ± 6.64 | |
| Corticosteroids | | |
| Yes | 9.88 ± 6.56 | .862* |
| No | 9.50 ± 6.94 | |
| In-hospital hemodialysis requirement | | |
| Yes | 10.75 ± 8.10 | .691* |
| No | 9.79 ± 6.50 | |
| Mechanical ventilation | | |
| Yes | 11.00 ± 7.12 | .589* |
| No | 9.77 ± 6.55 | |
| CKD stage | | |
| 1 | 3.50 ± 2.12 | .342** |
| 2 | 8.85 ± 6.46 | |
| 3 | 9.60 ± 6.59 | |
| 4 | 11.05 ± 6.89 | |
| 5 | 11.53 ± 6.31 | |
| Lung involvement in HRCT | | |
| Mild stage | 9.70 ± 693 | .675** |
| Moderate stage | 9.71 ± 6.18 | |
| Severe stage | 11.55 ± 6.57 | |
| Disease severity | | |
| Mild | 8.84 ± 5.80 | .463** |
| Moderate | 9.90 ± 6.76 | |
| Severe | 11.14 ± 6.88 | |

*Independent t-test
**ANOVA

evaluated patients considering different variables illustrating that among the medications, treatment with ACEI/ARB ($P$ = .016) was the only parameter that remarkably led to elongated survival time in the patients.

Cox regression showing the prognostic role of renal transplantation medications in survival of patients with COVID-19 pneumonia in Table 6 revealed that ACEI/ ARB were the only medications leading to increased survival of the patients in all

**Table 6.** Cox Regression

| Variable | Crude model | | | Model 1* | | | Model 2** | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | *P* | 95% CI | HR | *P* | 95% CI | HR | *P* | 95% CI |
| ACEI/ ARB | 0.532 | .008 | 0.333 to 0.851 | 0.515 | .007 | 0.318 to 0.833 | 0.583 | .040 | 0.349 to 0.975 |
| Corticosteroids | 0.869 | .646 | 0.477 to 1.583 | 0.790 | .447 | 0.430 to 1.450 | 0.753 | .382 | 0.399 to 1.421 |
| Calcineurin inhibitors | 0.949 | .876 | 0.493 to 1.829 | 0.855 | .641 | 0.444 to 1.647 | 0.728 | .362 | 0.368 to 1.440 |
| Mycophenolate mofetil | 0.922 | .723 | 0.588 to 1.446 | 1.006 | .980 | 0.638 to 1.585 | 1.008 | .973 | 0.622 to 1.634 |
| mTORI | 0.770 | .469 | 0.379 to 1.565 | 0.635 | .202 | 0.316 to 1.276 | 0.568 | .127 | 0.275 to 1.174 |
| Statins | 0.756 | .178 | 0.503 to 1.136 | 0.811 | .326 | 0.535 to 1.232 | 0.918 | .696 | 0.599 to 1.407 |

*Model 1: Adjusted for age and gender
**Model 2: adjusted for age, gender, medical diseases and COVID-19 severity
Abbreviations: ACEI, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; mTORI, mammalian targets of rapamycin inhibitors; HR, hazard ration.

crude and adjusted models. Accordingly, treatment with ACEI/ ARB caused decreased mortality for 47, 49, and 42% in the crude ($P$ = .008), adjusted for age and gender ($P$ = .007) and adjusted for age, gender, medical diseases and COVID-19 severity models ($P$ = .040), respectively (Figure 1).

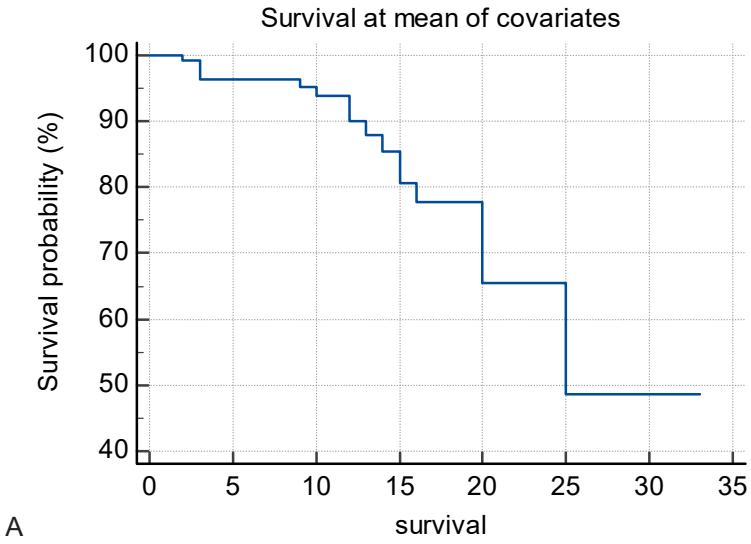
## DISCUSSION

In the current study, we aimed to evaluate the contributing role of medications applied by the kidney transplanted patients in the mortality of patients came down with COVID-19 pneumonia. Accordingly, we found that except for ACEI/ ARB that significantly increased the longevity of the patients, none of the other medications including corticosteroids, calcineurin inhibitors, mycophenolate mofetil, mTORI, statins and insulin had affected the survival period in the studied cases. Moreover, none of the medications, even ACEI/ ARB, was a standalone determinant of the patients' prognosis.

Kidney transplanted patients are among the most critical individuals who are prone to remarkable adverse events than the general population following COVID-19 infection. This vulnerability occurs due to both immunocompromised status and impaired kidney function of these individuals. Nevertheless, the issue of continuing immune suppressive agents in this group of patients during COVID-19 infection has not been well-responded. Rarely have studies dedicatedly evaluated the effects of medications applied in kidney transplantation on the mortality and longevity in COVID-19 infection.

Rarity of knowledge is available regarding the effect of ACEI/ARB use in kidney transplanted patients during COVID-19. Moreover, the applicable data are controversial. In agreement with our findings, Soler *et al.* found a direct protective role for these agents to elongate survival of kidney transplanted patients; however, this findings was achieved in crude model of cox regression and the adjustment for COVID-19 severity revealed no association.[9] Similarly, Mancia *et al.*[10] and Soleimani *et al.*[11] found that the discontinuation of ACEI/ARB in individuals with hypertension under medication with these agents increased risk of mortality, invasive ventilation, and acute kidney injury in COVID-19 infected patients. Nevertheless, most of the studies in the literature represented no role for ACEI/ARB in kidney transplanted recipients to have a prognostic role for mortality prediction or a positive role in survival.[2,12-14]

ACEI and ARB are the medications blocking renin-angiotensin system (RAS). Various studies have investigated the effect of RAS blockade on the outcomes of COVID-19 in CKD and kidney transplanted individuals. Although some studies on the general population stated no effect for RAS blockade on the severity and clinical outcomes of COVID-19,[15-17] some presented that long-term use of RAS blocking agents might lead to lung involvement and renal failure.[18] The reason for which the use of ACEI/ ARB in COVID-19 is a question refers to the pathophysiology of lung involvement in COVID-19 infection where the viruses use ACE2 as a receptor to enter type II pneumocytes or alveolar epithelial type II; therefore, the presence of ACE2 protein in lungs is important for virus cell entry.[19] Preliminary studies reported that RAS blockade upregulates ACE2 expression in different organs and tissues; therefore, long-term use of ACEI/ARB might deteriorate SARS-CoV-2 infection severity.

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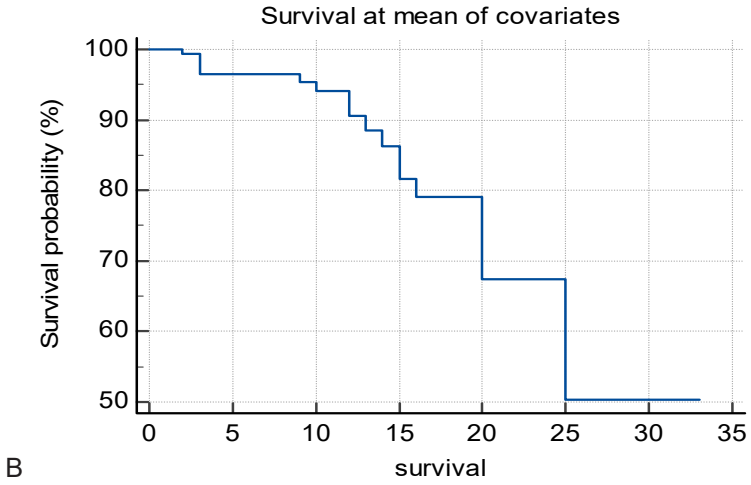


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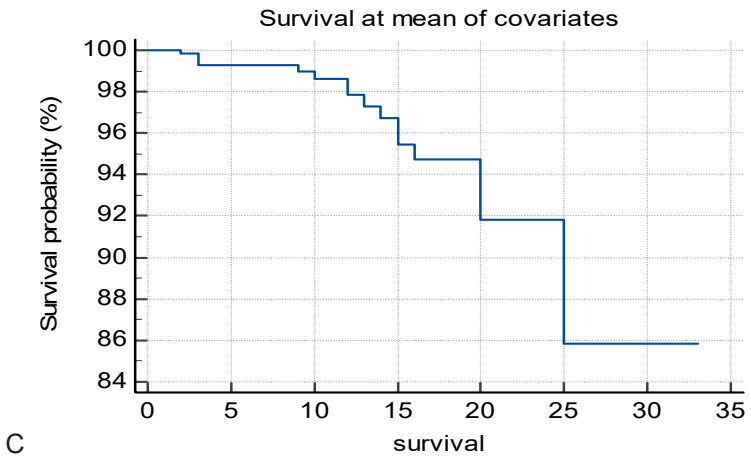


C

Cox regression model in (A) crude, (B) adjusted for age and gender and (C) adjusted for age, gender, medical diseases and COVID-19 severity

Thus, the advantage of RAS blocking agents use should be weighed over its potential effects on COVID-19 infection in kidney transplant cases.[20]

Although our results did not find that treatment

with steroids in kidney transplant recipients as a contributing factor to reduce mortality, the major body of evidence has supported to continue steroids in the individuals with solid organ transplantation who came down with severe COVID-19 requiring hospitalization, ICU admission and mechanical ventilation. These studies emphasized that steroid therapy as a cornerstone approach in solid organ transplantation was accompanied by less mortality among critically-ill patients as well as considerable response to COVID-19 treatment;[21-23] however, a review by Calderón-Parra *et al.* contrarily represented increased risk of adverse events due to COVID-19 infection in cases applying corticosteroids for a long period of time.[24] Given that, further investigations are required fro responding to this question. It should not be forgotten that corticosteroid therapy is a critical treatment in approach to COVID-19.

Calcineurin inhibitors, cyclosporine and tacrolimus, are the basis of immune suppression in solid organ transplantation. It has been proposed that these agents can limit viral replication through binding to intracellular cyclophilins, inactivating peptidyl-prolyl cis/trans isomerase function.[25] Despite the study conducted by Cavagna and colleagues presenting promising data in terms of chronic calcineurin inhibitor use to reduce the severity of COVID-19 infection and lowering the probability of superinfection,[26] surfing the literature revealed consistent outcomes with our findings in terms of no significant role for this group of drugs in the severity of COVID-19 infection and its negative consequences such as ICU admission, duration of hospitalization and mortality rate.[24,27]

Mycophenolate mofetil is one of the mainstays in the management of kidney transplantation; however, it seems that potent cytostatic effects of this agent on T and B lymphocytes, contributes to lymphopenia and compromising the humoral immune response to the virus.[28] Given that, Requião-Moura *et al.* represented higher rate of adverse events and mortality due to COVID-19 infection among the individuals under mycophenolate mofetil therapy.[29] Similarly, Kolla *et al.* in a large cohort study on more than 60400 patients represented increased risk of hospitalization and mortality among the kidney transplant patients using mycophenolate mofetil.[4] Although our results showed no effect for this agent to increase mortality rate, some experts proposed to cease or decrease the dose of mycophenolate mofetil considering the synergistic properties of the drug with the mechanism by which SARS CoV-2 induces impaired immune response.[4,30] Further investigations might open better vision in this issue.

Regardless of our results detecting no role for mTORI to decrease the length of ICU stay, this group of drugs can potentially mitigate COVID-19 infection severity from two aspects. Primarily, mTORI agents inhibit the PI3K-AKT-mTOR pathway, required for intracellular virus replication, and increases the quality and functionality of memory T cells, ultimately modulating human innate response and mitigating immunosenescence. Secondarily, these drugs can attenuate cytokine storm and reduce the severity and progression of the viral infection. Given that, Requião-Moura *et al*.[29] and de Andrade *et al*.[31] favored to continue mTORI for kidney transplant recipients. However, other studies were in agreement with us representing neither protective nor deteriorative role for mTORIs in severe COVID-19 infection.[2,12]

Regardless of subpopulation, statin use have been accompanied by reduced risk of ICU admission, ICU death and all-cause mortality among the patients with severe COVID-19. Various pathophysiological reasons have been proposed for statins to reduced adverse events following COVID-19 including cardioprotective, anti-inflammatory, immunomodulating and vasoprotective properties of these agents. In addition, statins can modulate SARSCoV-2 virus entry by acting on the ACE2 and CD147 receptors and lipid raft engagements.[32-34]

In summary, paucity of knowledge is available in terms of the influence of immune suppressive agents applied in kidney transplantation on the mortality in COVID-19 infection. Accordingly, this dedicated title in this study is a significant strength of the current investigation. However, small sample population is one of the limitations of our assessment. Furthermore, despite all the efforts made to control the potential confounding variables in logistic and cox regression analysis, there might be some neglected variables that could

have affected the outcomes such as the duration of each agent use, the interval between transplantation and COVID-19 infection and the anti-COVID-19 vaccination state.

## CONCLUSIONS

Based on the findings of the current study, ACEI/ ARB use was accompanied with decreased length of ICU stay among the kidney transplant patients with COVID-19 infection, while the other medications did not have any effect.

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## AUTHORS' STATEMENT

The manuscript has been read and approved by all the authors, and all agreed to submit the current manuscript in Current Transplantation Reports.

### Ethics Approval

The study was proposed for the Ethics Committee of Isfahan University of Medical Sciences and approved via code number "IR.MUI.MED.REC.1400.220". Besides, its protocol was registered in Iranian Registry for Clinical Trials and accepted via code number 240051.The patients/ their legal guardians got informed about the potential use of the medical data for scientific research, they were reassured regarding the confidentiality of their personal information and signed written consent for participation in the study.

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Isfahan University of Medical Sciences sponsored the study with the grant number 240051.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

### Authors' Contribution

F. M. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

M. M. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

Sh. Sh. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

M. M. was contributed in literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review

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