Risk Factors of Moderate or Severe COVID-19 in Kidney Transplant Recipients

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Abstract

Background: COVID-19, identified in 2019, has significantly impacted healthcare, especially transplant medicine. This study examines COVID-19 in kidney transplant patients, focusing on risk factors of moderate or severe outcomes.

Methods: A retrospective analysis was conducted on 43 kidney transplant recipients who contracted COVID-19 between April 2020 and October 2023. Patients were classified into mild (N=29), moderate (N=6), and severe (N=8) groups based on the COVID-19 treatment guidelines. Clinical characteristics, immunosuppressive regimens, metabolic factors, vaccination status, and disease outcomes were analyzed. Univariate and multivariate logistic regression were performed to identify risk factors of moderate or severe COVID-19.

Results: The overall mortality rate was 4%, with a 25% mortality rate in severe cases. In univariate analysis, obesity (OR: 4.69, p=0.04) and diabetes mellitus (OR: 6.25, p=0.01) were significantly associated with an increased risk of moderate or severe COVID-19. In multivariate analysis, while statistical significance was not reached, obesity (OR: 8.50, p=0.08), diabetes mellitus (OR: 5.35, p=0.07), and mTOR inhibitor use (OR: 8.60, p=0.06) showed trends toward an increased risk. Age ≥65 years was not significantly associated with severe COVID-19 (OR: 8.42, p=0.18). Conversely, receiving ≥3 doses of COVID-19 vaccination was significantly associated with a reduced risk of moderate or severe disease (OR: 0.07, p=0.03), highlighting the protective effect of booster vaccinations.

Conclusion: Diabetes mellitus, obesity, and mTOR inhibitor use may contribute to severe COVID-19 in kidney transplant recipients, necessitating proactive monitoring and immunosuppressive management. Booster vaccinations play a crucial role in reducing disease severity in this high-risk population. Early intervention strategies, including optimizing metabolic control and immunosuppressive therapy, should be prioritized to improve patient outcomes. Further large-scale studies are warranted to confirm these findings.

Key words: COVID-19, kidney transplantation, vaccine, virus, infection

Background

COVID-19 was first reported as a cluster of pneumonia cases in Wuhan, Hubei Province, China, in 2019, and subsequently spread worldwide. In Japan, the first domestic case was confirmed in January 2020, followed by repeated waves of explosive outbreaks. As of May 2023, COVID-19 has been reclassified as a Class V infectious disease. The strain on healthcare systems caused by the COVID-19 pandemic has significantly impacted transplant medicine, leading many facilities to restrict or even suspend transplant surgeries. Despite the imminent risk of healthcare system collapse, we have continued transplant

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medicine based on the fundamental guidelines established by the COVID-19 Response Committee organized by the Japan Society for Transplantation.

In the early stages of the COVID-19 pandemic, there were no established infection control measures, preventive strategies, or treatments. However, with the accumulation of knowledge and insights gained over time, treatment protocols have now been established. Nevertheless, COVID-19 remains highly infectious and can cause fatal pneumonia, particularly in dialysis patients and organ transplant recipients on immunosuppressive therapy, who are at high risk of severe disease. In this report, we examine and discuss the risk factors of severe COVID-19 infection in post-kidney transplant patients at our institution.

Patients and Methods

We conducted a retrospective analysis of kidney transplant recipients who were followed at our institution and affiliated outpatient clinics and contracted COVID-19 between April 2000 and October 2023. The cases were classified according to the most severe clinical presentation observed during the treatment period. We compared and analyzed patient demographics, initial symptoms, treatment methods, outcomes, the presence of acute kidney injury (AKI), the presence of sequelae, and the number of vaccine doses received.

The severity of COVID-19 was classified according to the "Guidelines for the Treatment of COVID-19."[1] Mild cases were defined as those with respiratory symptoms but without findings of pneumonia and with an oxygen saturation (SpO2) of 96% or higher. Moderate I cases were defined as those with dyspnea and pneumonia findings, with SpO2 between 93% and 96%. Moderate II cases were defined as those requiring oxygen therapy with SpO2 below 93%. Severe cases were defined as those requiring ICU admission or mechanical ventilation. In this study, we combined cases classified as Moderate I and Moderate II into a single category of Moderate.

Body mass index was classified according to the criteria of the Japan Society for the Study of Obesity, with obesity defined as ≥25 kg/m² and underweight defined as <18.5 kg/m².

Acute kidney injury (AKI) was defined according to the KDIGO criteria, which include: (1) an increase in serum creatinine by ≥0.3 mg/dl within 48 hours, (2) an increase in serum creatinine to ≥1.5 times the baseline within 7 days, or (3) a urine output of ≤0.5 ml/kg/h for more than 6 hours.[2] Sequelae were defined according to the World Health Organization's criteria as symptoms persisting for more than two months that could not be explained by other diagnoses.

Statistical analysis

All statistical analyses were performed using EZR version 4.4.1 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[3] The distribution of variables was compared between groups using the chi-square test or Fisher's exact test for categorical data, and Student's t-test for continuous data. Continuous data were presented as median (IQR). Risk factors of moderate or severe COVID-19 infection were examined using univariable and multivariable logistic regression models, with results expressed as odds ratios and 95% CI.

Results

A total of 43 kidney transplant recipients with COVID-19 were included and categorized into three severity groups: mild (N=29), moderate (N=6), and severe (N=8). The baseline characteristics of the patients are summarized in Table 1. The median age was 52 years (IQR: 20–75), with no significant differences among severity groups. Obesity was more prevalent in the moderate group (50%) but did not reach statistical significance (p=0.25). Diabetes mellitus was significantly associated with moderate-to-severe disease (p=0.03), with a prevalence of 50% in both the moderate and severe groups, compared to 13% in the mild group. No significant differences were observed in sex, smoking history, HLA A24 typing, duration from transplantation, primary disease, serum creatinine level, donor type, or immunosuppressive agents used. The majority of patients were on a regimen of calcineurin inhibitors, antimetabolites, and steroids. Most patients presented with symptoms at diagnosis, with fever being the most common (60%). When comparing the moderate and severe groups, although no significant differences were observed, the severe group tended to have a higher median age and a higher proportion of male patients.

Table1. Patient Characteristics

		Total (N=43)	Mild (N=29)	Moderate (N=6)	Severe (N=8)	P value
		n(%)	n(%)	n(%)	n(%)	
Age (y)	Median (IQR)	52 (20-75)	52 (20-75)	52 (39-57)	52 (51-73)	0.06
Sex	Male	22 (51)	14 (48)	2 (33)	6 (75)	0.26
Body mass index	Underweight	7 (16)	6 (21)	0	1 (13)	0.51
	Normal	26 (60)	19 (66)	3 (50)	4 (50)	0.88
	Obesity	10 (23)	4 (14)	3 (50)	3 (18)	0.25
Duration from transplantation (mo)	Median (IQR)	60 (3-324)	36 (3-324)	60 (6-144)	66 (6-282)	0.51
Smoking	Never	21 (48)	13 (44)	4 (66)	4 (50)	0.20
	Current/Former	20 (46)	16 (55)	1 (16)	3 (37)	
	Unknown	2 (4)	0	1 (16)	1 (12)	
Diabetes mellitus	Yes	11 (25)	4 (13)	3 (50)	4 (50)	0.03*
Primary disease	CGN	7 (16)	5 (17)	1 (16)	1 (12)	0.95
	DMN	6 (13)	2 (6)	2 (33)	2 (25)	0.18
	ADPKD	6 (13)	3 (10)	0	3 (37)	0.11
	IgAN	6 (13)	5 (17)	1 (16)	0	0.50
	Nephrosclerosis	5 (11)	3 (10)	1 (16)	1 (12)	0.91
	SLE	2 (4)	2 (6)	0	0	0.61
	NPHP	2 (4)	2 (6)	0	0	0.61
	RN	2 (4)	2 (6)	0	0	0.61
	Other	7 (16)	4 (13)	1 (16)	2 (25)	0.78
Serum creatinine level at the time of diagnosis (mg/dL)	Median (IQR)	1.35 (0.66-5.43)	1.31 (0.66-5.42)	1.52 (0.9-2.99)	1.63 (0.99-3.0)	0.62
HLA A24 typing	Yes	17 (39)	10 (34)	3 (50)	4 (50)	0.62
Donor type	Deceased	7 (16)	5 (17)	0	2 (25)	0.44
Calcineurin inhibitors	No	2 (4)	2 (6)	0	0	0.60
	Tacer	30 (69)	20 (68)	5 (83)	5 (62)	
	CsA	11 (25)	7 (24)	1 (16)	3 (37)	
Antimetabolites	No	2 (4)	1 (3)	0	1 (12)	0.47
	MMF	29 (67)	23 (79)	2 (33)	4 (50)	
	AZ	1 (2)	1 (3)	0	0	
	MZ	11 (25)	4 (13)	4 (66)	3 (37)	
Steroids	No	3 (6)	3 (10)	0	0	0.46
	PSL	37 (86)	23 (79)	6 (100)	8 (100)	
	mPSL	3 (6)	3 (10)	0	0	
mTOR inhibitors	No	30 (69)	22 (75)	3 (50)	5 (62)	0.39
	Yes	13 (30)	7 (24)	3 (50)	3 (37)	
Numbers of vaccinations	0	6 (13)	3 (10)	2 (33)	1 (12)	0.38
	1	1 (2)	1 (3)	0	0	
	2	13 (30)	7 (24)	3 (50)	3 (37)	
	3	13 (30)	10 (34)	1 (16)	2 (25)	
	4	4 (9)	4 (100)	0	0	
Symptoms at diagnosis	Yes	39 (90)	26 (89)	6 (100)	7 (87)	0.68

*p < 0.05, **p < 0.01

ADPKD, Autosomal Dominant Polycystic Kidney Disease; AZ, azathioprine; CGN, chronic glomerulonephritis; CsA, cyclosporine; DMN, Diabetic Nephropathy; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; mPSL, methylprednisolone; MZ, mizoribine; NPHP, nephronophthisis; PSL, prednisolone; RN, reflux nephropathy; SLE, systemic lupus erythematosus; TacER, tacrolimus extended-release.

The major outcomes of the study, including disease severity, mortality, and other relevant metrics, are summarized in Table 2. A total of 48% of the patients required hospitalization, with all cases in the moderate and severe groups requiring admission. The median length of hospital stay was 10 days (IQR: 3-55 days). Regarding treatment, 48% of the patients in the mild group were managed with observation alone. However, the moderate and severe groups required treatment primarily with antiviral drugs and immunosuppressive/immunomodulatory drugs, with 50% of the severe group requiring mechanical ventilation. Additionally, in the moderate and severe groups, many patients required dose reduction or discontinuation of calcineurin inhibitors and antimetabolites. Acute Kidney Injury (AKI) occurred in 16% of the total cohort. The incidence of AKI was significantly higher in the moderate and severe groups compared to the mild group ($p = 0.009$). Prognosis included 2 deaths (4%), with a mortality rate of 25% in the severe group. Sequelae were observed in 9 cases (20%), with respiratory symptoms, including cough, being the most common.

The results of the univariate analysis regarding the risk of moderate or severe COVID-19 are presented in Table 3. In the univariate analysis, obesity and diabetes mellitus were significantly associated with moderate-to-severe COVID-19 in kidney transplant recipients. Obesity (BMI $\geq$25 kg/m^2) was present in 14% of patients in the mild group and 43% in the moderate-to-severe group, with an odds ratio (OR) of 4.69 (95% CI: 1.05–20.9, p=0.04). Similarly, diabetes mellitus was observed in 13% of patients with mild disease and 50% of those with moderate-to-severe disease, with an OR of 6.25 (95% CI: 1.40–27.7, p=0.01). On the other hand, receiving more than 3 vaccinations appeared to be protective against moderate or severe COVID-19, with an OR of 0.26 (95% CI: 0.05–1.21). Although this suggests a trend towards reduced risk, the P-value was 0.08, which did not reach statistical significance.

Table2. Major outcomes

		Total (N=43)	Mild (N=29)	Moderate (N=6)	Severe (N=8)	P value
		n(%)	n(%)	n(%)	n(%)	
Hospital admission		21 (48)	7 (24)	6 (100)	8 (100)	<0.001***
Length of hospital stay	Median (IQR)	10 (3-55)	6 (3-9)	13 (7-38)	20 (8-55)	0.03*
Pneumoniae		13 (30)	0	6 (100)	8 (100)	<0.001***
Treatments	Observation	14 (32)	14 (48)	0	0	0.006**
	Antiviral drugs	21 (48)	11 (37)	2 (33)	8 (100)	0.005**
	immunosuppressive/ immunomodulatory drugs	6 (13)	0	2 (33)	4 (50)	0.001**
	Anticoagulant	2 (4)	0	1 (16)	1 (12)	0.11
	neutralizing antibody drugs	10 (23)	6 (20)	2 (33)	2 (25)	0.83
	Mechanical ventilation	0	0	0	4 (50)	<0.001***
Adjustment of immuno-suppressant	None	27 (62)	22 (75)	3 (50)	2 (25)	0.23
	Reduction of Calcineurin inhibitors	6 (13)	2 (6)	0	4 (50)	0.009**
	Reduction of Antimetabolites	16 (37)	7 (24)	3 (50)	6 (75)	0.09
AKI		7 (16)	1 (3)	3 (50)	3 (37)	0.009**
Hemodialysis		1 (2)	0	0	1 (12)	0.10
Prognosis	Death	2 (4)	0	0	2 (25)	0.01*
Sequelae		9 (20)	7 (24)	0	2 (25)	0.48

*p < 0.05, **p < 0.01

AKI, acute kidney injury

Table3. Univariate Analysis of Risk Factors for Moderate or Severe COVID-19.

		Mild (N=29)	Moderate or Sever (N=14)	Univariate Model	
		n (%)	n (%)	OR (95% CI)	P value
Age	≧65	5 (17)	4 (28)	1.92 (0.42-8.67)	0.94
	＜65	24 (83)	10 (71)	0.52 (0.11-2.35)	
Sex	Male	14 (48)	8 (57)	1.43 (0.39-5.16)	0.58
	Female	15 (52)	6 (43)	0.70 (0.19-2.53)	
Obesity	Yes	4 (14)	6 (43)	4.69 (1.05-20.9)	0.04*
	No	25 (86)	8 (57)	0.21 (0.04-0.95)	
Smoking	Yes	16 (55)	4 (28)	0.40 (0.09-1.66)	0.20
	No	13 (44)	7 (50)	2.46 (0.60-10.0)	
Diabetes mellitus	Yes	4 (13)	7 (50)	6.25 (1.40-27.7)	0.01*
	No	25 (86)	7 (50)	0.16 (0.03-0.70)	
mTOR inhibitors	Yes	7 (24)	6 (42)	2.36 (0.60-9.16)	0.21
	No	21 (72)	8 (57)	0.42 (0.10-1.65)	
Serum creatinine level (mg/dL)	＞2.0	3 (10)	4 (28)	3.85 (0.71-20.6)	0.11
	≦2.0	26 (89)	9 (64)	0.26 (0.04-1.39)	
Numbers of Vcaccinations	0	3 (10)	3 (21)	2.44 (0.41-14.5)	0.32
	2	7 (24)	6 (42)	2.33 (0.57-9.37)	0.23
	≧3	14 (48)	3 (21)	0.26 (0.05-1.21)	0.08

Univariate logistic regression analysis was performed to assess the association between each variable and the outcome.
*p < 0.05, **p < 0.01

CI, confidence interval; OR, odds ration; mTOR, mammalian target of rapamycin

The results of the multivariate analysis are shown in Figure 1. A logistic regression model was used for the multivariate analysis, adjusting for confounding factors. Age, obesity, diabetes mellitus, mTOR inhibitor, and numbers of vaccinations were included as independent variables in the logistic regression model.

Among the evaluated variables, obesity (OR: 8.50, 95% CI: 0.87–82.89, p=0.08), diabetes mellitus (OR: 5.35, 95% CI: 0.46–62.99, p=0.07), and mTOR inhibitor use (OR: 8.60, 95% CI: 0.95–77.42, p=0.06) showed a trend toward an increased risk of severe disease, although these associations did not reach statistical significance. Age ≥65 years (OR: 8.42, 95% CI: 0.74–96.28, p=0.18) was also not significantly associated with severe COVID-19 in this cohort.

However, a higher number of vaccinations (≥3 doses) was significantly associated with a reduced risk of moderate or severe COVID-19 (OR: 0.07, 95% CI: 0.01–0.80, p=0.03), highlighting the protective effect of booster vaccinations in kidney transplant recipients.

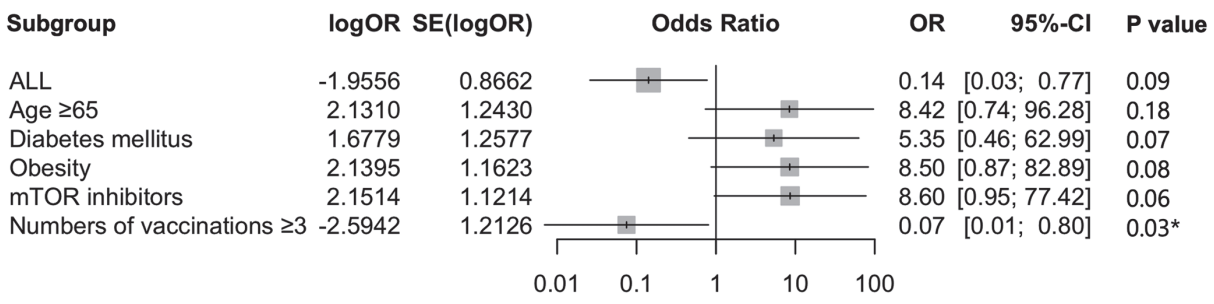

Figure 1. Forest plot of multivariate analysis of risk factors of moderate or severe COVID-19 in kidney transplant patients.
Logistic regression model was used for the multivariate analysis, adjusting for confounding factors. Age, diabetes mellitus, obesity, mTOR inhibitors, and numbers of vaccinations were included as independent variables in the logistic regression model.

Discussion

In this study, the overall mortality rate was 4%, but it rose to 25% among patients with severe COVID-19. Previous studies have shown that mortality rates vary based on disease severity and comorbidities, with solid organ transplant recipients experiencing mortality rates of around 20% and critically ill patients exceeding 30%.[4, 5] Identifying risk factors for severe COVID-19 in kidney transplant recipients is crucial for implementing preventive strategies. This study focused on metabolic factors, immunosuppressive therapy, age, and vaccination status as potential risk factors of moderate or severe COVID-19.

Metabolic Factors: Obesity and Diabetes Mellitus

In this study, obesity and diabetes mellitus were identified as potential risk factors of severe COVID-19 in kidney transplant recipients. While both conditions were significantly associated with disease severity in univariate analysis, multivariate analysis suggested a trend toward an increased risk, highlighting their potential clinical relevance. These findings are consistent with studies on COVID-19 in immunosuppressed populations, particularly kidney transplant recipients, where diabetes mellitus has been consistently identified as a risk factor of poor outcomes.[6, 7] There are also reports indicating that the risk of severe COVID-19 and mortality in obese patients increases by approximately 20–50%.[8-10]

Metabolic factors, including obesity and diabetes mellitus, contribute to severe COVID-19 through chronic inflammation, immune dysregulation, endothelial dysfunction, and coagulation abnormalities. Obesity is associated with persistent low-grade inflammation, increased pro-inflammatory cytokines (IL-6, TNF-α, CRP), and impaired immune responses, leading to delayed viral clearance and heightened risk of cytokine storm and ARDS. Similarly, diabetes mellitus disrupts immune function, reducing T-cell activity and neutrophil chemotaxis while promoting systemic inflammation and endothelial dysfunction, increasing susceptibility to severe COVID-19. Additionally, obesity-related pulmonary dysfunction, such as reduced lung compliance and alveolar hypoventilation, exacerbates respiratory failure. Given these mechanisms, early identification and management of metabolic risk factors in kidney transplant recipients with COVID-19 are essential to improving outcomes.

Immunosuppressive Therapy

The use of mTOR inhibitors was associated with an increased risk of severe disease. While mTOR inhibitors are essential for preventing graft rejection, their immunosuppressive effects may impair viral clearance and modulate inflammatory responses, potentially leading to more severe COVID-19 outcomes. However, some studies suggest that mTOR inhibitors might have therapeutic potential in COVID-19 by modulating immune responses, though more data are needed to establish clear guidelines.[11]

In patients with moderate to severe COVID-19, dose reduction of various immunosuppressive agents, including calcineurin inhibitors and antimetabolites, is recommended according to guidelines to reduce the risk of mortality. However, it is also essential to maintain adequate immunosuppression to prevent graft rejection.[12-14]

Age

Interestingly, in this cohort, age ≥65 years was not identified as a significant risk factor for severe COVID-19. This finding contrasts with extensive studies that have established advanced age as a major determinant of COVID-19 severity. Older individuals generally exhibit a decline in immune response, and when combined with immunosuppressive therapy, their susceptibility to severe infections is further heightened.[15, 16] This discrepancy suggests that metabolic factors and the effects of immunosuppressive therapy may have a greater impact on disease severity in kidney transplant recipients.

Vaccination Status

Receiving ≥3 doses of COVID-19 vaccine was significantly associated with a reduced risk of moderate-to-severe disease. Organ transplant recipients are known to have a diminished immune response to the initial doses of the COVID-19 vaccine. Multiple studies have demonstrated that a third dose of an mRNA vaccine significantly enhances serological response in kidney transplant recipients and strengthens clinical protection against severe COVID-19.[17] The findings of this study underscore the importance of booster vaccination in immunosuppressed patients.

Limitations

This study has several limitations that should be considered when interpreting the findings.

1. Influence of Immunosuppressive Therapy

Lifelong immunosuppressive therapy in kidney transplant recipients may have masked the impact of

smoking on COVID-19 severity. Calcineurin inhibitors (e.g., tacrolimus) have been suggested to possess antiviral properties,[18] while mycophenolate mofetil (MMF) has been associated with worse COVID-19 outcomes.[19] These immunosuppressants may have altered the immune response, influencing disease severity in smokers.

2. Impact of Underlying Comorbidities

Smoking is a known risk factor for COPD and cardiovascular disease, both linked to severe COVID-19.[20] However, this study did not assess COPD presence, which may have influenced the lack of a significant association. Previous studies reported an OR of 4.38 for severe COVID-19 in COPD patients and 1.98 in current smokers, suggesting COPD as a stronger determinant of severity. Future studies incorporating spirometry may provide better risk assessment.

3. Smoking and COVID-19 Pathophysiology

Smoking increases ACE2 expression, potentially enhancing viral entry.[21] However, some studies suggest complex immunomodulatory effects of smoking, with paradoxical findings on disease severity.[22] In kidney transplant recipients, interactions between smoking, immunosuppression, and metabolic comorbidities may have attenuated its independent effect on severity.

4. Sample Size and Data Collection

The small sample size (N=43) may have limited statistical power. Additionally, the lack of detailed smoking-related data (e.g., pack-years, duration, cessation timing) may have restricted assessment of smoking's true impact. Future studies with larger cohorts and comprehensive smoking histories are needed.

Conclusion

This study highlights diabetes mellitus, obesity, and mTOR inhibitor use as potential risk factors of severe COVID-19 in kidney transplant recipients, while booster vaccinations (≥3 doses) significantly reduced disease severity. Interestingly, age ≥65 years was not a significant risk factor, suggesting that metabolic and immunosuppressive factors may have a stronger impact in this population. To improve outcomes, early identification of high-risk patients, careful immunosuppressive management, and prioritization of booster vaccinations are essential. Further large-scale studies are needed to confirm these findings and optimize treatment strategies for kidney transplant recipients with COVID-19.

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Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose.

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