Survival of transplanted patients infected with moderate and severe COVID-19 in Mexico

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Abstract

Introduction: The infection with SARS-CoV-2 that affects the entire world has been shown to be more severe in patients with comorbidities. The object of this study was to know the survival of renal transplant patients infected with this coronavirus.

Material and methods: Eligible were renal transplant patients with SARS-CoV-2 infection requiring hospitalization (moderate and severe degree) from the start of the pandemic to September 28, 2020. Survival analysis was performed with Kaplan-Meier tables in days, using statistical package SPSSw v25.

Results: Data was collected for 66 patients from 4 renal transplant facilities; the mean age was 39.5 years (IQR 30.0-49.5); global survival was 59.10%. Difference of 67.50% vs 46.15% was observed between receivers from living and dead donors respectively (without Log Rank significance of 0.068); 70.25% survival in patients with low immunological risk and 44.82% for high risk (Log Rank 0.034).

Conclusions: Comorbidities and immunosuppression greatly influence mortality in renal transplant patients immunological risk presents an important determinant of patient survival.

Background

Disease by coronavirus (COVID-19) is a disease with high transmission, and has represented a general problem in the world, with significant morbidity and mortality [1]. People with renal transplant, through their condition of immunosuppression, are more susceptible, show more progression to pneumonia, acute graft dysfunction, and a higher possibility of over infection and of presenting a higher number of comorbidities [2]. Pneumonia in transplanted patients is more severe, with worse results; clinical symptoms have been described with dyspnea in 70.8%, fever (62.5%), followed by cough in 45.8% and with findings in ground glass tomography in 95.8% of cases [3-5]. Even so, there are many questions concerning the behavior of transplanted patients that suffer with COVID-19 [6].

It is recommended that transplanted patients with mild cases be handled as outpatients, with the recommendation of quarantine and alarm systems to recognize a moderate or severe case [7]. In some studies reported cases, in these patients with immunosuppression, infection with coronavirus may be grave and require hospital admission, [8-9] and the majority of these patients reduced their immunosuppression and were treated with support therapy; which included the suspension of inhibitors of calcineurin or rapamycin in mammalian cells, or mTOR (*mammalian Target of Rapamycin*), in addition of anti-proliferative drugs, in this case azatioprin or mycophenolate mofetil [10-12].

The handling of immunosuppression in the transplanted patient infected with SARS-CoV-2 is varied in regards to symptomology, age, comorbidities and the severity of COVID-19, which determines the best strategy; mild cases without comorbidities, and youths should continue immunosuppression in the same way, and those with comorbidities should consider reducing azatioprin, mycophenolate or mTOR [13-14]. Moderate and severe cases should consider the suspension of

immunosuppression, maintaining only endovenous steroids, mainly methylprednisolone, in addition to considering restarting previous immunosuppression, first calcineurin inhibitor, from 5 to 15 days after symptoms have disappeared [13].

Material and Methods

Design

A prospective cohort of renal transplant patients from the Instituto Mexicano del Seguro Social (IMSS) belonging to 4 renal transplant units in Mexico were studied.

Patients

Eligible were patients insured by IMSS with kidney transplant infected with SARS-CoV-2 from the beginning of the pandemic to September 28, 2020, who required hospitalization for moderate or severe infection.

Obtaining data

The data of interest were: age, weight, gender, biochemical parameters, type of renal donor, comorbidities, induction used, immunological risk, days of hospitalization, days of medical care, onset of symptoms, acute graft dysfunction, need for renal replacement therapy (RRT), need for mechanical ventilator, and clinical outcome.

Statistics

Data are presented as mean and standard deviation for continuous variables, or as frequency or means and interquartile range for nominal variables or those with skewed distribution. The difference of means was established with chi squares or Student t. Analysis of survival was performed with Kaplan-Meier tables in days. Statistical significance was established with $p < 0.05$. Analysis was performed with the statistical package SPSSw v25.

Results

Data was collected from 66 patients with renal transplant that suffered infection with moderate or severe SARS-CoV-2 who required medical hospitalization. A general analysis was made of the general characteristics of the patients and biochemical parameters, as well as the difference between patients returned home due to improvement and those who died. 39 patients returned home due to improvement (59.10%), 27 patients died (40.90%). The mean age was 39.5 years, with interquartile range (IQR) of 30.0 to 49.5 years. Baseline creatinine previous to infection with coronavirus was 1.30 mg/dl as mean, with IQR of 1.10 to 1.70 mg/dl, which was also elevated upon entry of patients, with a mean of 1.67 mg/dl (IQR of 1.11-3.57 mg/dl), due to multiple factors that caused acute dysfunction in many of the patients from entry. See the biochemical parameters on Table 1.

Statistically significant differences were found between the two groups, returned home compared with died, in glucose levels, urea and creatinine (Table 1).

Of the total, 41 were male (62.10%), the most frequent comorbidity was hypertension (HT) in 51 patients (77.30%), diabetes was second in 18 renal receivers (27.30%), followed by obesity with 16 persons (24.20%). By type of donor, the majority were from living donors, 40 cases (60.60%), 26 from deceased donors (39.40%). Current induction and immunosuppression is observed in Table 2.

The differences between groups were observed in the presence of hypertension only among the comorbidities; in the case of outcomes this difference was observed in acute graft dysfunction, the need for renal substitution therapy, mechanical ventilation and those who returned home due to improvement (Table 2).

The main complications, in addition to the respiratory ones expected due to the severity of the infectious disease, were acute graft dysfunction, which was presented in 39 transplants (59.10%), and the need for renal replacement therapy in 10 cases (15.20% of the total of

Table 1. Baseline characteristics. Transplant patients with moderate or severe COVID-19

Variable	Total (66 px)		Returned home (39 px)		Died (27 px)		
	Mean	IQR	Mean	IQR	Mean	IQR	p (*)
Age (years)	39.5	30-49.5	36	28-48	40	33-54	0.471
Weight (kilograms)	65	55.75-74.00	64	55-71	65	59-78	0.208
Height (meters)	1.6	1.55-1.67	1.6	1.54-1.67	1.58	1.55-1.68	0.739
Days transplanted (days)	1941	583-3785	2554	1294-4239	1125	340-3358	0.119
Baseline creatinine	1.3	1.1-1.7	1.3	1.2-1.5	1.3	1.1-1.8	0.739
Days of hospitalization	8	5-14.25	8	5.0-17.0	8	3.0-12.0	0.240
Days between symptoms and medical care	5	2-7	4	1.0-10.0	7	4.0-10.0	0.296
Glucose (mg/dL)	112	89-168	104.5	75-140	111.75	92-365	0.013
Urea (mg/dL)	50	26.5-122	20.25	13.5-39	150.5	51-215	0.008
Creatinine (mg/dL)	1.67	1.11-3.57	1.37	1.04-1.56	4.46	1.27-10.39	0.008
Sodium (mEq/L)	135	130-139	137	135-139	129.5	126-131	0.235
Potassium (mEq/L)	4.5	3.85-5.4	4.15	4.10-4.32	5.5	3.37-7.47	0.139
Albumin (g/dL)	3.6	3.2-3.8	3.45	2.6-3.9	3.2	2.87-3.82	0.158
Uric acid (mg/dL)	5.2	5.1-6.7	5.2	5.1-5.3	7.75	5.2-11.27	0.100
Leukocytes (10^3/uL)	7500	5100-12300	7800	5350-11900	6915	4500-13840	0.678
Hemoglobin (g/dL)	12.5	11.0-14.6	13.3	11.6-14.65	11.75	10.2-14.52	0.249
Neutrophils (10^3/uL)	6350	3770-10000	6760	3747-9565	5645	3582-11602	0.922
Fibrinogen (g/L)	692	589.5-920	790	530-985	682	618-858	0.918
D dimer (ng/mL)	182	3.08-615.5	231	3.48-596	182	2.4-696	0.495
C reactive protein (mg/L)	151	21-253	29.4	11.1-44	191	66.45-313.35	0.244
Ferritin (ng/mL)	741.7	316.9-1512.7	869	337-1073	614	250-2317	0.678
(*) expressed in Student t							
COVID-19: coronavirus disease; px: patients; IQR: interquartile range							

all cases, while among those with acute dysfunction corresponded to 25.64%). Mechanical ventilation was needed in 27 patients (40.90%), of whom 4 managed to survive (6.06% of the total and 22.22% of those that required ventilation).

The symptoms most associated were: fever in 50 patients (75.80%), dyspnea in 47 (71.20%), cough in 44 (66.70%), the rest of the associated signs and symptoms in the transplants are seen in Table 3.

Survival analysis by Kaplan-Meier was 59.10% that were observed for up to 52 days, longer stay in one of the patients; of the deaths presented from the day of entry, the first of them was 3 hours after entry, and from there until day 22 of the hospital stay as the patient with the most time with hospital stay before dying (Figure 1).

In the difference in survival by type of donor, a difference was found, with 67.50% for patients that received renal graft from a living

Table 2. Comorbidities, peri-transplant characteristics, outcomes

| Variable		Total (66 px)		Returned home	Died (27 px)	
		Frequency	%	Frequency	Frequency	p (*)
Sex						0.690
	Male	41	62.1	25	16	
	Female	25	37.9	14	11	
Hypertension		51	77.3	26	25	0.013
Diabetes mellitus		18	27.3	9	9	0.358
Obesity		16	24.2	7	9	0.152
Pulmonary disease		2	3.0	0	0	0.084
Type of donor						0.085
	Living	40	60.6	27	13	
	Deceased	26	39.4	12	14	
Induction						0.127
	Basiliximab	31	47.0	22	9	
	Thymoglobulin	29	43.9	16	13	
	Without induction	6	9.1	4	2	
Immunosuppression						0.569
	Tacrolimus-MMF-PDN	36	54.6	21	15	
	Tacrolimus-AZA-PDN	7	10.6	5	2	
	Sirolimus-MMF-PDN	13	19.7	10	3	
	Sirolimus-AZA-PDN	1	1.5	1	0	
	Cyclosporin-MMF-PDN	9	13.6	3	6	
Acute graft dysfunction		39	59.1	19	20	0.039
Need for RRT		10	15.2	2	8	0.005
Mechanical ventilation		27	40.9	4	23	0.001
Returned home due to improvement		39	59.1	39	0	0.001
(*): expressed in chi squared						
px: patients; MMF: mycophenolate mofetil; PDN: prednisone; RRT: renal replacement therapy						
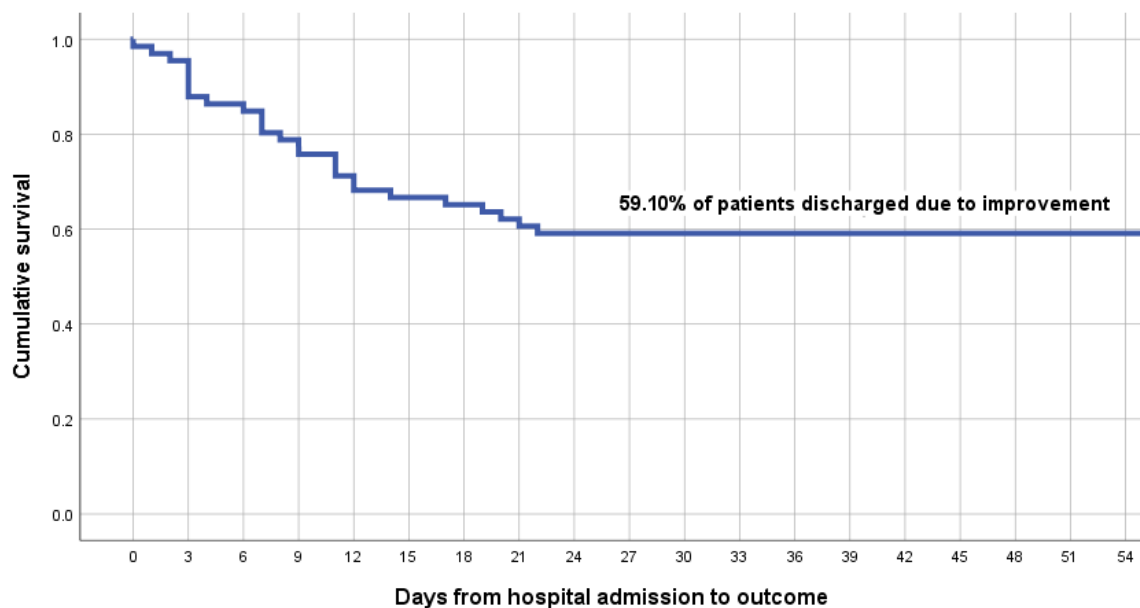
Figure 1. Survival of kidney transplant patients with moderate and severe COVID-19

Table 3. Signs and symptoms associated to infection by COVID-19 in transplant patients

	Total (66 px)		Returned home (39 px)	Died (27 px)	
Variable	**Frequency**	**%**	**Frequency**	**Frequency**	**_p (*)_**
Fever	50	75.8	28	22	0.367
Dyspnea	47	71.2	23	24	0.008
Cough	44	66.7	25	19	0.595
Arthralgias	28	42.4	16	12	0.782
Myalgias	27	40.9	16	11	0.982
Headache	23	34.8	10	13	0.059
Diarrhea	15	22.7	8	7	0.266
Odynophagia	13	19.7	5	8	0.091
Thorax pain	9	13.6	4	5	0.336
Conjuntivitis	4	6.1	2	2	0.703
Dysuria	4	6.1	2	2	0.703
Nausea	4	6.1	1	3	0.152
Vomit	4	6.1	1	3	0.152
Abdominal pain	3	4.3	2	1	0.702
Rhinorrhea	2	3.0	0	2	0.084

(*): expressed in chi squared; COVID-19: coronavirus disease; px: patients
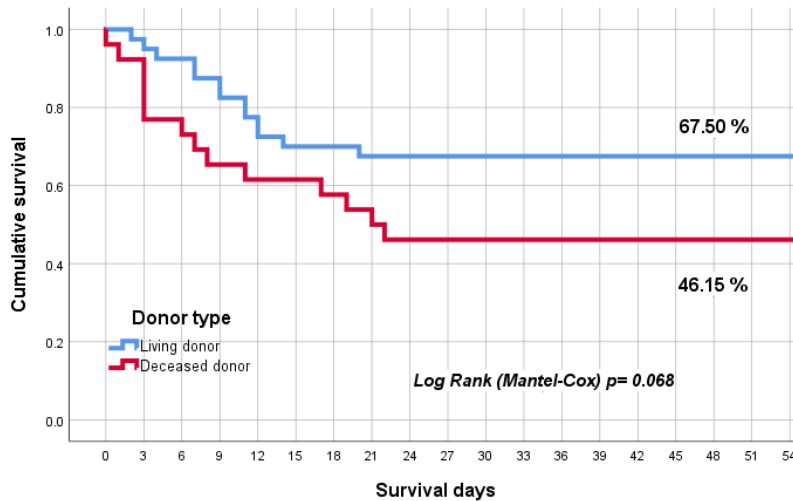
Figure 2. Survival of the kidney transplant patient with COVID-19, in relation to the type of donor
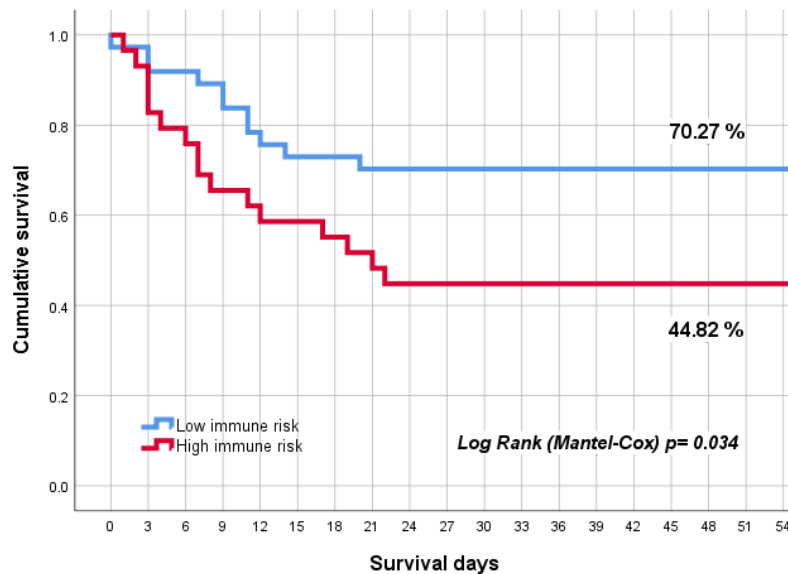
Figure 3. Survival of the kidney transplant patients with COVID-19, in relation to immunological risk

donor against 46.16% of those from a deceased donor, although without statistically significant evidence, with a Log Rank (Mantel-Cox) of 0.068 (Figure 2).

There was also a difference regarding immunological classification as low or high risk, where the difference in survival was observed with 70.27% for those classified as low immunological risk against 44.82% of those with high risk, with a statistically significant difference in a Log Rank (Mantel-Cox) of 0.034 (Figure 3).

Discussion

Data was collected for 66 renal transplant patients in Mexico infected with SARS-CoV-2 diagnosed as moderate or severe from the start of the pandemic to September 28, 2020, one of the largest studies reported in this group of patients in the world (66 patients).

In Mexico, a register was begun through the Centro Nacional de Transplants (CENATRA, National Transplant Center) of all transplant patients infected with coronavirus, so that by September 28, 170 persons were confirmed, of whom 46 had died (27.05%), [15-16] the difference with our cohort being that we only included moderate and severe cases, excluding asymptomatic and mild cases managed as outpatients; making only 4 units of renal transplant, where we could observe a mortality of 40.9%; representing a difference of 13.85% among the moderate and severe cases in out series. Of all the patients in Mexico by CENATRA, [15-16] 29 patients were handled as outpatients (17.05%).

There are few studies that speak of the lethalness of infection with SARS-CoV-2 in the transplanted patient. Demir, *et al.* [17] studied 40 receptors of renal transplant with moderate (33 cases) and severe (7 cases) pneumonia, study highly comparative to ours, with a mean age of 44.9 years (our mean was 5.4 years younger); they had a distribution by gender of 50% each, while our study included more males with 62.1% of cases (41/66). Hypertension was the most common comorbidity in both (65% for the study by Demir and 77.3% in ours), followed for them by cardiac and pulmonary disease, where there was a difference in our Mexican population, where it was diabetes and obesity, with 27.3 and 24.2, respectively, diseases that greatly contribute to mortality in our patients, even though the difference between patients that survived against those that died was significant for hypertension, with a tendency towards significance in the variable of obesity, since the mortality in the Demir study was 12.5% vs 40.9% in our population. It is important to mention that Mexico is among the first places in incidence and prevalence of these three comorbidities, which outside the context of immunosuppression (in this case, renal transplant), are the 3 comorbidities related with death in patients with COVID-19 in the world, so they are independent factors that increase the risk of death, as also observed in our study.

There was an important relation between patients with severe pneumonia and the use of polyclonal drugs [17] used in patients with habitual high immunological risk, although the outcome was different as in our case we could observe a condition similar to the relation with the type of induction (for low and high immunological risk), which in the case of the present study was related with survival, finding in the Kaplan-Meier curves of mortality only 29.73% for those receptors categorized as low immunological risk against 55.18% for those categorized as high immunological risk.

Symptoms also had peculiarities and differences, where in some studies [17] cough was the main symptom (75%), followed by fever (62.5%), dyspnea (52.5%), and diarrhea (25%), unlike the present where the four main ones were fever (75.8%), dyspnea in 71.2% of the cases, cough in 66.7% and arthralgias as the fourth symptom in 42.4%, while diarrhea was located as the seventh symptom in decreasing order, with 22.7%.

Demir also evaluated creatinine upon entry, with very similar measurements; in the case of theirs it was 1.6 (IQR 1.2-2.2), and ours showed a mean of 1.67, with the difference lying in the broader interquartile range of 1.11 to 3.57, possibly reflecting the difference in graft dysfunction, where there was a difference of 24.1%, due to the fact that their study showed an alteration in renal graft functionality of 35% contra 59.1% in the present study. Finally, there were also differences observed between patients that requires ventilation, with 25% in the case of Demir [17] compared with the present study with 40.9% requiring mechanical ventilation, condition of severity in which only 4 of 27 patients survived.

Early mortality in receptors of renal transplant is very variable, with ranges from 6% up to 25% [17-21] in various studies, unnerving against the fact that in our patients it was 40.9%, stressing that in the present study this mortality was only in moderate and severe patients; however, the national statistics in Mexico [15-16] show the data of death associated with infection by SARS-CoV-2 in 27.05%, similar to the figures in these references, possibly explained by the comorbidities peculiar to Mexico, with greater incidence and prevalence of diabetes, obesity and hypertension.

Conclusions

Global survival was 59.10%, with comorbidities such as hypertension, diabetes mellitus and obesity; association with immunosuppression influenced mortality in transplanted renal patients; immunological risk presented an important factor in patient survival with 70.25% survival in those with low immunological risk and 44.82% for those with high risk. The type of donor had a difference of proportions, considering 67.50% vs 46.15% between living and deceased donors, respectively, although that may be due to the small sample size.

Acknowledgements

Conflict of interest

The authors state no conflicts of interest.

Study limitations

By being an observational study, there is no mention of the impact of treatment offered the patients.

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