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Risk of Severe Coronavirus Disease 2019 Infection in Kidney Transplant Recipients

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ABSTRACT

Background. Despite all efforts, the incidence of severe coronavirus disease 2019 (COVID-19) infection has been high in renal transplant recipients, as in other groups (eg, older adults, patients with comorbidities or immunosuppression). The detection of any possible predictor of gravity could improve the early approach in these patients.

Patients and methods. We registered data from renal transplant recipients with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection in our area for a year (March 2020 to March 2021). We collected demographics, comorbidity, body mass index, lymphocyte count, and vitamin D levels before the diagnosis. We performed statistical analysis using SPSS Statistics version 20 (IBM Corp, Armonk, NY, United States).

Results. Of 63 patients, 57.1% required hospital admission and 14.3% required intensive care. The incidence of acute renal failure was 28.6%; 34.9% developed hyperinflammatory syndrome; 67% had lymphopenia, which was severe in 13.1%; and 11 patients died. There was significant correlation between lymphocyte count before and during the infection. For hospitalization, we found differences in age, pulmonary disease, and renal function. Related factors for admission to an intensive care unit were obesity, severe lymphopenia, altered renal function, and low level of vitamin D. Predictors for mortality were age, renal function, and minimum lymphocyte count.

Conclusion. In kidney transplant recipients with COVID-19 infection, renal function determines hospitalization, and body mass index determines admission to an intensive care unit. Previous vitamin D levels are also significantly lower in patients requiring intensive care. The analysis of lymphocyte count previous to infection is correlated with the minimum level during the disease, which is a predictor of mortality, and could be a prognosis factor.

FOR over a year, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) has afflicted millions of people all over the world. Despite the combined effort to prevent its spread in our community, many patients with kidney chronic disease have experienced coronavirus disease 2019 (COVID-19) infection. Thanks to the early intervention of medical societies in recording cases, we have been able to obtain precise and useful epidemiologic data [1]. As expected, hospitalization and mortality rates have been higher among transplant recipients [2,3]. However, the evolution of disease has been variable and, in some cases, similar to the general population [4].

Research groups have worked to identify potential predictors of severity, to improve early management, and to reduce

complications as much as possible [5,6]. In our population, kidney disease and other comorbidities are common. All of them are associated with an increased risk of severe infection; they imply biological aging, and the majority are not modifiable [7]. Adjustments to the immunosuppressive regimen is often used in many infections of different etiologies, and we have also applied it to COVID-19 [8], although the optimal approach is not defined.

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Table 1. Baseline Characteristics and Variables During Infection

| Variables Before Infection | Average ± SD (Interval)Percentage/n | Variables During Infection | Percentage/n |
|------------------------------|-------------------------------------|-----------------------------|---------------------|
| Age (y) | 54.5 ± 12.9 (20-87) | Nosocomial contact | 28.6%/18 |
| Months with RRT | 158 ± 125 (13-516) | Hospitalization | 57.1%/36 |
| Months until transplant | 112 ± 107 (1-369) | Days of hospital stay | 18.8 ± 15 |
| BMI (kg/m ²) | 27.7 ± 4.7 (18-40) | Intensive care | 14.3%/9 |
| Creatinine (mg/dL) | 1.51 ± 0.6 (0.6-3.6) | Orotracheal intubation | 9.5%/6 |
| Glomerular filtrate (cc/min) | 53 ± 20 (17-100) | Hyperinflammatory syndrome | 34.9% (n = 21/61) |
| Lymphocytes (U/ μ L) | 1857 ± 970 (336-5190) | Lymphopenia | 67.2% (n = 41/61) |
| Vitamin D (ng/mL) | 20.43 ± 8.1 (3.7-40) | Severe lymphopenia | 13.1%/8 |
| Gender | Male 57.1%/36 | Minimum lymphocyte count | 874 ± 912 (40-4890) |
| Diabetes | 20.6%/13 | AKI | 28.6%/18 |
| Pulmonary disease | 28.6%/18 | Increased proteinuria | 13.1%/8 |
| Cardiac pathology | 28.6%/18 | Corticoids | 53.9%/34 |
| Hypertension | 82.5%/52 | Immunosuppression reduction | 46%/29 |
| Blood type A-0-B | 50.8%/32–41.2%/26–7.9%/5 | Death | 17.5%/11 |

AKI, acute renal injury; BMI, body mass index; RRT, renal replacement therapy; SD, standard deviation

Several clinical and analytical risk parameters that involve worse prognoses (eg, hypoxemia, inflammatory syndrome, lymphopenia) had been identified before and throughout the evolution of the disease [9,10].

We carried out an observational study with kidney transplant recipients diagnosed with SARS-COV-2 to identify its course and complications and to find predictor factors previous to and during the disease.

PATIENTS AND METHODS

We created a register (from March 2020 to March 2021) of COVID cases among our renal transplant recipients. We collected data such as demographics, diabetes, cardiac or pulmonary disease, and body mass index (BMI). We also considered if there was nosocomial or community contact, the initial and late symptoms, the need of hospitalization, admission in an intensive care unit (ICU), and oro-tracheal intubation.

Regarding the analytical parameters, we registered data about hyperinflammatory syndrome, renal function (creatinine and estimated glomerular filtrate by Modification of Diet in Renal Disease), total lymphocytes (average of the last 3 analyses previous to the infection), proteinuria and vitamin D, all of them before and during COVID-19 disease (Table 1). We also registered the different treatments and changes of immunosuppressive therapy. We defined hyperinflammatory syndrome when patients met any 2 or more of the following criteria: ferritin >500 ng/mL, C-reactive protein >100 mg/dL, lactate dehydrogenase >300 U/L, D-dimer >1000 ng/mL, or interleukin-6 >40 pg/mL. For severe lymphopenia, we established a value of < 300 cells/ μ L based on the definition of severe immunodeficiency with CD4 <200 cells/ μ L (CD4: 65% of total lymphocytes).

The statistical analysis was performed using SPSS Statistics version 20 (IBM Corp, Armonk, NY, United States). For qualitative variables we used the χ^2 test and the Student *t* test for the quantitative ones. We analyzed correlations and applied the binary logistic regression for severe lymphopenia, ICU admission, and the primary outcomes of death and hospitalization.

RESULTS

A total of 63 cases were detected (36 males; 57.1%) with a median age of 54.5 ± 12.9 years. 57.1% needed hospitalization,

Table 2. Correlations

| Correlations | P | R of Pearson |
|---|------|--------------|
| Previous lymphocytes and GFR | .07 | 0.337 |
| Previous lymphocytes and minimum lymphocyte count | .000 | 0.568 |
| GFR and days of hospitalization | .016 | -0.405 |
| Vitamin D and days of hospitalization | .013 | -0.429 |
| BMI and minimum lymphocyte count | .016 | -0.307 |

BMI, body mass index; GFR, glomerular filtration rate

and 14.3% needed ICU admission; 20.6% and 28.6% of the patients had diabetes and pulmonary disease preceding the COVID-19 infection. More than a half (50.8%) had blood type A, and 41.2% had blood type B. The immunosuppressive therapy included tacrolimus in 82.5% of the patients. The infection was nosocomial in 28.6% of the cases. Mortality rate was 17.5% (11 patients) (Table 1).

In 2 outpatients with mild symptoms, no laboratory follow-up information was available. Of the remaining patients, 67% had mild lymphopenia, which was severe in 13.1% of patients, and 34.4% of the patients met the criteria for hyperinflammatory syndrome. The rate of acute renal failure was 28.6%, with worsening of proteinuria in 13.1%.

All patients were under low-dose corticoid therapy, and 53.9% received a higher dose during COVID-19 occurrence (oral or intravenous). Mycophenolate was reduced or suspended in 46% of the cases.

We found significant correlation between previous lymphocytes and minimum lymphocyte count during the infection (*r* = 0.568; *P* = .000). It was also inversely correlated with BMI (*r* = -0.307; *P* = .016) (Table 2).

In the univariate analysis for hospital admission (Table 3), we found significant differences regarding pulmonary disease, age, and renal function. Those who were older, had previous pulmonary pathology or had worse renal function, required hospital admission more frequently.

Concerning ICU admission, BMI was higher, renal function was worse, vitamin D level and minimum lymphocyte count

Table 3. Univariate Analysis

| | | | | | |
|--------------------|---|---|--|--|--|
| Hospital Admission | Pulmonary disease 77.8% vs 48.9% (<i>P</i> = .033) | Age 57.7 ± 14 vs 50.3 ± 8.9 (<i>P</i> = .023) | Creatinine 1.64 ± 0.6 vs 1.33 ± 0.5 (<i>P</i> = .041) | GFR 46.4 ± 17 vs 61.8 ± 22 (<i>P</i> = .003) | |
| ICU Admission | BMI 31.3 ± 3.3 vs 27.1 ± 4.6 (<i>P</i> = .011) | Creatinine: 2 ± 0.4 vs 1.4 ± 0.5 (<i>P</i> = .003) | GFR 34.7 ± 12 vs 56 ± 20 (<i>P</i> = .004) | Vitamin D 14,5 ± 8.1 vs 21,3 ± 7.8 (<i>P</i> = .027) | Severe lymphopenia: 19.5% vs 0% (<i>P</i> = .032) |
| Mortality | Age: 66 ± 11 vs 52.1 ± 11,9 (<i>P</i> = .001) | Creatinine: 2 ± 0.58 vs 1.41 ± 0.56 (<i>P</i> = .003) | GFR: 36.2 ± 15 vs 56.5 ± 20 (<i>P</i> = .003) | Nosocomial contact 38.9% vs 8.9% (<i>P</i> = .009) | Minimum lymphocyte count 290 ± 237 vs 1002 ± 955 (<i>P</i> = .018) |

BMI, body mass index; GFR, glomerular filtration rate; ICU, intensive care unit.

Table 4. Multivariate Analysis

| | Variables | <i>P</i> | Exp(B) |
|--------------------|---------------------------|----------|--------|
| Hospitalization | Glomerular filtrate | .029 | 0.886 |
| ICU Admission | Body mass index | .04 | 1.593 |
| Severe Lymphopenia | Previous lymphocyte count | .045 | 0.998 |
| Death | Minimum lymphocyte count | .026 | 1.149 |
| | Age | .008 | 0.991 |

ICU, intensive care unit

were lower in patients admitted to the ICU than non-ICU hospitalized patients.

Results for mortality showed significant differences in the following variables: age, renal function, minimum lymphocyte count, and nosocomial contact. For the regression analysis (Table 4), glomerular filtration rate was a predictor of hospitalization (*P* = .029, Exp[B] 0.886) and BMI of ICU admission (*P* = 0.04, Exp[B] 1.593). Previous lymphocytes were predictors of severe lymphopenia (*P* = .045, Exp[B] 0.998). Only the age (*P* = .026, Exp[B] 1.149) and the minimum lymphocyte count turned out to be predictors of mortality.

DISCUSSION

Previous factors to diagnosis

Several studies of potential predictors of gravity in COVID-19 infection showed consistent results for older adults and comorbidity [5] (especially pulmonary disease, obesity, and immunosuppression). Among our patients, 28.6% had some type of pulmonary disease, the majority of which were obstructive (COPD and OSAS). These groups have significantly higher rates of hospitalization and mortality because of acute pulmonary injury. Obesity has been associated with a chronic inflammatory condition and altered immune regulation [11], which favors infections. Kidney transplant recipients have a higher prevalence of being overweight; the median BMI in our study was higher in those with severe hyperinflammatory syndrome and in those requiring intensive care.

The presence of decreased renal function is also common among transplant recipients. Uremia causes lower immunologic response as it has been proved after vaccination, so the infection and tumor rates are higher [12]. Renal function is also expected

to be a risk factor in COVID-19 infection [5]. We found GFR as a predictor of hospitalization in our population.

Moreover, vitamin D levels before the infection were significantly lower in patients requiring ICU admission and is associated with worse prognoses.

Lymphocyte count is usually related with infection and death from many causes [6]. Lymphopenia is considered an immunohematologic biomarker [13] that reflects a premature aging with less production of “naive” lymphocytes in the thymus and increased number of memory cells. This occurs frequently in uremic syndrome and is also present before transplantation, increasing the risk of infections predominantly produced by viruses. Furthermore, it does not seem that transplantation can revert this situation [13–15]. In COVID infection, lymphopenia has showed a prognostic value before [16] and during the disease [8–10]. The average previous lymphocyte count in our study was related to the minimum level during the infection and was a predictor of severe lymphopenia.

Factors during COVID-19 disease

At the time of diagnosis, symptoms are different from one patient to another. Dyspnea and fever were found to be the main manifestations in hospitalized patients. Although we did not collect data from imaging tests, both symptoms are related to established pneumonia. Among the analytical parameters, hyperinflammatory syndrome was more frequent in patients with obesity, lower GFR, and lower vitamin D levels. These results were associated with severe lymphopenia.

Renal injury (either acute kidney injury or superimposed acute renal injury or chronic kidney disease) and increased proteinuria appeared in 28.6% and 13.1% of patients, respectively, and occurred more frequently in patients with low vitamin D levels. Several pathologic mechanisms have been proposed (eg, direct cell injury or cytokine storm with consequent podocyte and tubular damage). Some cases of collapsing nephropathy have also been described [17].

Lymphopenia clearly seems a marker for poor prognosis, as was shown in several studies, and has become a predictor of mortality. We also found minimum lymphocyte count to be a useful factor.

All patients were receiving low-dose steroids, and more than half increased it. This change in treatment took place in different stages in each patient, some of them promptly and possibly coinciding with the viremic phase (which would have stimulated viral replication and lymphopenia). Nevertheless, in the majority of cases, high-dose steroids were used in the inflammatory phase of the disease. Some protocols included other drugs such as ritonavir, hydroxychloroquine, and remdesivir. Analyses of these drugs were not part of the aim of this study. Since the pandemic started, there was a general consensus in decreasing or avoiding antimetabolite treatment, as is done for the management of other opportunistic infections (eg, poliovirus, cytomegalovirus). In our series, mycophenolate was modified in 46% of patients. However, 1 study [4] did not find differences between the intensity of immunosuppression and mortality. This possibly reflects the higher influence of immunologic baseline conditions related to age, uremia, and possible previous use of antithymocyte globulin, which produces a premature immunosenescence [18]. This could be the reason why previous lymphocyte count determines the evolution of COVID-19 disease. In any case, it is evident that mycophenolate, which promotes lymphopenia (overall in association with tacrolimus [19] more than cyclosporine), should be stopped or at least reduced.

In conclusion, previous markers of bad prognoses, as appears to be the case with obesity, hypovitaminosis D, and lymphopenia, could help to identify those patients who need additional medical care. Thus, the accuracy with which hospitalization and treatment are considered could be improved. We could regulate immunosuppression in a more individualized way, including immunomodulatory drugs [20,21] like lymphocyte-stimulating agents, as long as we do not find effective antivirals.

CONCLUSIONS

In kidney transplant recipients with COVID-19 infection, renal function seems to determine hospital admission, and BMI determines the admission in an ICU. Previous vitamin D levels are also significantly lower in patients who required intensive care.

The analysis of lymphocyte count previous to infection is correlated with the minimum level during the disease, which is a predictor of mortality, and that could be a prognostic factor.

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