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RESEARCH ARTICLE

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COVID-19 pneumonia in kidney transplant recipients: A promising treatment algorithm in the absence of a disease-specific drug

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Abstract

There is no consensus on the management of coronavirus disease 2019 (COVID-19) and modification of immunosuppressive therapy in kidney transplant recipients (KTRs). In this study, we examined the clinical outcome of our KTRs with COVID-19 disease, who were treated with a broad-spectrum anti-inflammatory protocol. This protocol is essentially composed of intravenous immunoglobulin +/- tocilizumab in KTRs with severe COVID-19 pneumonia. Among 809 KTRs, 64 patients diagnosed with COVID-19 disease between April 2020 and February 2021, were evaluated. Twenty-nine patients with pneumonia confirmed by chest computed tomography (CCT) were hospitalized. The treatment protocol included high-dose intravenous methylprednisolone, favipiravir, enoxaparin, and empirical antibiotics. Patients with pneumonic involvement of more than 25% on CCT with or without respiratory failure were given a total of 2 g/kg intravenous immunoglobulin (IVIg) therapy. Nonresponders received tocilizumab, an interleukin-6 receptor antibody. Of the 29 patients with pneumonia, 6 were treated in other hospitals. These six patients did not receive IVIg and 5 of them deceased. In our center, IVIg treatment was applied to 15 of 23 patients. Seven of them required tocilizumab. Respiratory parameters improved significantly in all but one patient after IVIg ± tocilizumab treatment. The mortality rate was 6.6% in patients who received IVIg therapy and 35.7% in those who did not ($p = 0.08$). The mortality rate was higher in patients who received treatment in external centers (2.2% vs. 26.3%; $p = 0.0073$). The treatment of KTRs with severe COVID-19 pneumonia in organ transplant centers with significant experience yields better results. The administration of broad-spectrum anti-inflammatory treatment in this patient group was safe and provided excellent outcomes.

KEYWORDS
COVID-19, IVIg, kidney transplantation, pneumonia

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was initially seen in China and then spread worldwide. By February 2021, the number of confirmed cases of infection was over 111 million; there have been almost 2.5 million deaths reported globally since the start of the pandemic.[1] The severe form of COVID-19 has been associated with older age and comorbidities, such as diabetes, hypertension, morbid obesity, coronary heart disease, and chronic obstructive pulmonary disease.[2] Patients with solid organ transplantation are prone to increased risk of infection and poor outcomes due to their long-term immunocompromised status and existing comorbidities. Compared with the general population, kidney transplant recipients (KTRs) infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have higher rates of severe disease (44% vs. 6.1%) and mortality (24%–28% vs. 1.4%–4.3%).[3,4]

To date, there is no clear consensus on the management of COVID-19 and modification of immunosuppressive therapy in KTRs. Also, there is no drug with proven efficacy against COVID-19. Intravenous immunoglobulin therapy (IVIg) has been tried in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which are members of the coronavirus family, and some beneficial effects have been reported.[5–7]

IVIg is a blood product containing polyclonal immunoglobulin G obtained from pooled healthy donors.[8] IVIg may regulate the immune response by blocking proinflammatory cytokines, neutralizing activated complement components, and modulating B-cell functions.[9]

In this study, we examined the clinical outcome of our KTRs with COVID-19 disease, who were treated in our center or in different hospitals that do not have organ transplant units. Thus, we aimed to determine the effect of differences in decision-making on the course of COVID-19 that may occur between centers. Also, we examined the demographics and clinical and laboratory parameters associated with COVID-19 infection in KTRs and investigated the efficacy of IVIg in the management of COVID-19 pneumonia.

2 | METHODS

Currently, 809 KTRs are being followed at Health Sciences University Bozyaka Organ Transplantation and Research Center. Among these, patients diagnosed as having COVID-19 between April 2020 and February 2021 were evaluated. Chest CT (CCT) images were obtained from all patients who were admitted with respiratory failure, a high respiratory rate (≥24/min.), or low oxygen saturation (SpO_2 < 93%). Respiratory failure (Rf) is defined by an arterial oxygen tension (P_{aO2}) of <60 mmHg or an arterial carbon dioxide tension (P_{aCO2}) of >45 mmHg or both.[10] COVID-19 disease was classified as mild, moderate, and severe according to the severity of pneumonic infiltration in CCT. The KTRs with pneumonia with or without Rf were hospitalized in COVID-19 units, and patients with the mild clinical presentation were managed as outpatients. The treatment of all patients followed in our center was administered on a consensus basis by the surgeon, nephrologist, and infectious diseases specialist in the organ transplant unit.

The patients were divided into two groups as those receiving treatment in our center or in a different center.

SARS-CoV-2 infection was detected in nasopharyngeal swabs using real-time reverse-transcription polymerase chain reaction (RT-PCR). In the event of a negative quantitative RT-PCR test result, if the patient had a clinical presentation compatible with COVID-19 infection and supported by CT images, a second nasopharyngeal swab was performed.

Routine blood tests included complete blood count, coagulation profile, kidney and liver function tests, lactate dehydrogenase, electrolytes, myocardial enzymes, serum ferritin level, C-reactive protein (CRP), D-dimer, and procalcitonin. Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes clinical practice guidelines.[11]

In this study, our policy in the management of immunosuppression was compatible with ERA-EDTA DESCARTES expert opinion.[12] The immunosuppressive drug regimen was modified in all patients. In patients without pneumonia, MPA, AZA, or mTORi was discontinued and the immunosuppression protocol was arranged as steroid (3 mg/kg/day) and CNI. Also, considering the immunological risk of each patient, a reduction of 30% to 50% was made in CNI drug dosages for the first 5 days of COVID-19 treatment. Patients with improvement in clinical course and laboratory findings after favipiravir treatment were switched to maintenance CNI dose.

Antimetabolites (mycophenolate mofetil, mycophenolic acid, or azathioprine) were stopped and calcineurin inhibitors (tacrolimus or cyclosporine) were interrupted in all individuals with COVID-19 pneumonia. High-dose intravenous methylprednisolone (40–80 mg/day, with or without initial pulse treatment 250 mg/d for three consecutive days) was administered according to the severity of the disease. Starting from the day of hospitalization, all patients received both favipiravir (Avigan Tablet, 200 mg; FUJIFILM Toyama Chemical Co., Ltd.) with a loading dose of 2 × 1600 mg and a maintenance dose of 2 × 60 mg for 5 to 7 days and a subcutaneous injection of enoxaparin (4000 Anti-XA IU/0.4 mL, SANOFI health products Co., Ltd.) at a dose of 40 mg twice daily. In addition, the patients were administered an empirical antibiotic therapy, including beta-lactam antibiotic plus macrolide or respiratory quinolone.

Patients with bilateral pneumonic involvement of more than 25% of the parenchyma on lung imaging (CCT) and/or respiratory failure were given a total of 2 g/kg IVIg treatment in divided doses within 5 days (Intratect 5 g/100 ml; Biotest AG). To administer IVIg treatment, following the regulation published in the Official Gazette (Dated July 15, 2018; No.: 30479), an off-label use certificate was prepared for each patient, and approval was

obtained from the Ministry of Health. In all patients, IVIg treatment was started within the first 24-48 h after hospitalization. Following this treatment, patients who did not achieve an arterial oxygen tension (P_{aO2}) of ≥60 mmHg and/or carbon dioxide tension (P_{aCO2}) of less than 45 mmHg were accepted as non-responders. These patients received tocilizumab (Actemra/RoActemra; 400 mg/20 ml; F. Hoffmann-La Roche Ltd.), an interleukin (IL)−6 receptor antibody, with a total dose of 800 mg. The treatment flowchart of patients with COVID-19 pneumonia is depicted in Figure 1. Our treatment flowchart was sent to all external centers where our patients were treated, and the same treatment practices were recommended as much as possible.

This study was approved by the hospital's ethics committee for clinical trials (Decision no.: 2021/15). All patients signed written informed consent before the administration of the treatment.

3 | STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 16.0. *p* values of less than 0.05 were considered to be statistically significant. For normally distributed data, we compared means using Student's *t* test, and when data were not normally distributed, we used the Mann–Whitney *U* test. Fisher's exact test was used for the comparison of proportions.

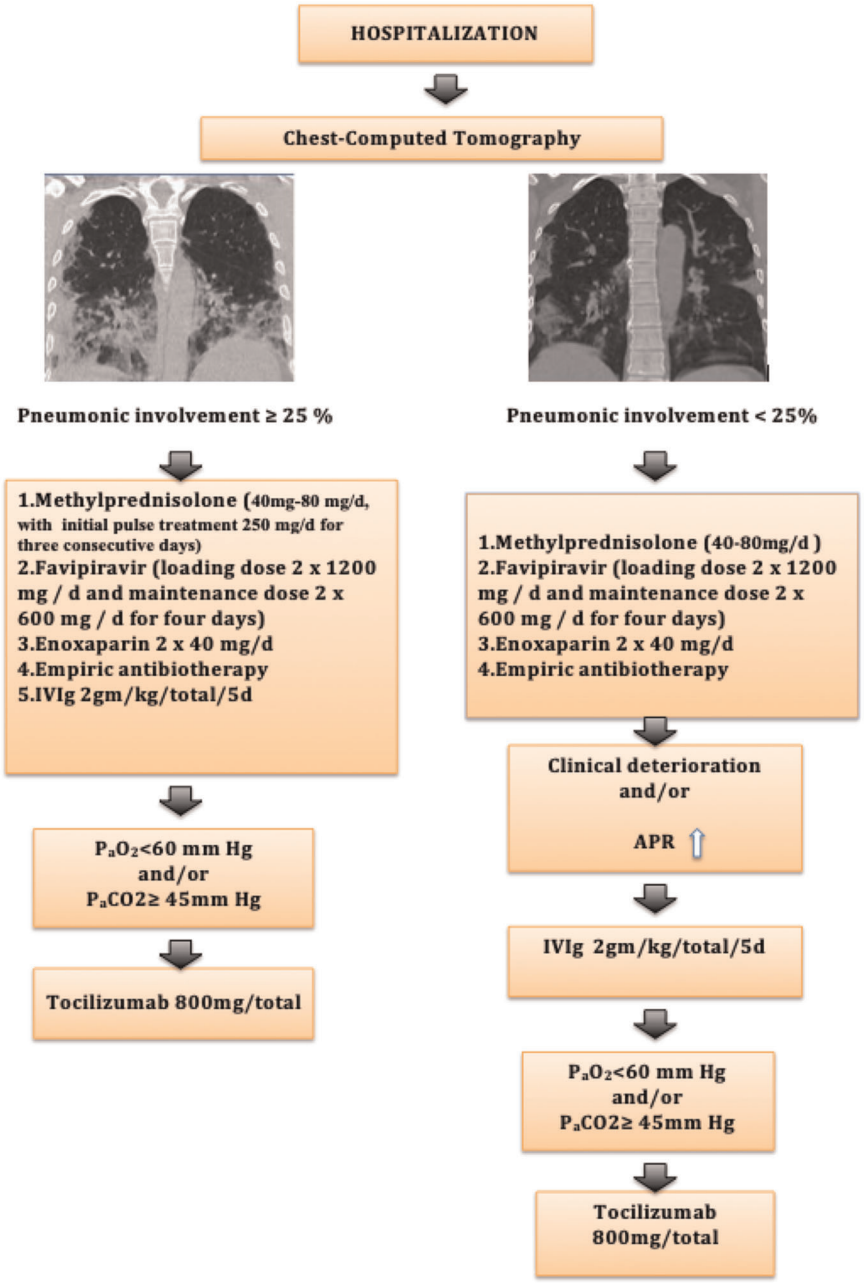

FIGURE 1 The treatment flowchart of patients with COVID-19 pneumonia. COVID-19, coronavirus diease 2019

4 | RESULTS

Among the 809 followed-up patients, 64 (7.9%) were diagnosed as having COVID-19. The mean age of the patients was 51 ± 11 (range, 27–74) years and 52.3% of them were male. Thirty-three patients received a kidney from a living donor and 31 from a deceased donor. Eight patients had a second transplant. As comorbidities, 83.8% of the recipients had hypertension, 22.5% had diabetes, 23.2% had obesity, and 4.8% had chronic obstructive pulmonary disease.

Rabbit antithymocyte globulin (ATG-Grafalon; Fresenius Biotech GmbH) was used in the induction treatment of all KTRs. Fifty-one (79.6%) patients were using calcineurin inhibitor-based triple immunosuppression and 13 were using double immunosuppression. Almost one-third (31.2%) of the patients had a history of delayed graft function (DGF) in the perioperative phase and 22.2% had experienced a rejection episode during the follow-up.

Of the 64 patients with COVID-19, 45 received treatment in our center and 19 in four other hospitals. Twenty-nine (45.3%) patients with pneumonia were hospitalized. Twenty-three of them were treated in our center and the remaining six in other hospitals. The rate of COVID-19 pneumonia in the KTRs who were admitted to our center or other hospitals was 51% and 31.6%, respectively ($p = 0.2$). The average hospital stay was 12 ± 5 (range, 7–28) days. The clinical findings detected in the patients at the time of admission were cough (77%), high fever (50.4%), shortness of breath (30%), loss of taste and smell (26.4%), and diarrhea (19.2%). Thirty-five patients without pneumonia (Group A) were compared with 29 patients with pneumonia (Group B). (Table 1) The demographic data of both groups were similar, and no difference was observed between comorbid diseases and the applied immunosuppressive treatment regimens. There was also no difference between Groups A and B in terms of time after transplantation (92.9 ± 77.6 vs. 88.5 ± 67.4 months respectively, $p = 0.82$). However, compared to patients with mild to moderate and severe pneumonia, patients without pneumonia had statistically significantly lower posttransplant DGF rate (14% vs. 47% and 75%, $p = 0.001$), and higher basal glomerular filtration rate (GFR) value (62 ± 18 vs. 48 ± 21 and 42 ± 24 ml/min/1.72 m^2, $p = 0.008$). As a result, it was determined that the better the allograft function, the lower the risk of pneumonia.

Favipiravir was administered in all patients and enoxaparin was administered in 54 patients as per the protocol. In empirical antibiotherapy, moxifloxacin was used in 34 patients, moxifloxacin, and piperacillin-tazobactam in 15 patients, moxifloxacin and meropenem in 4 patients, and moxifloxacin, meropenem, and linezolid in 3

TABLE 1 Demographics and outcome according to the severity of COVID-19 pneumonia

	Severe pneumonia ($n = 8$), mean ± *SD*	Mild-moderate pneumonia ($n = 21$), mean ± *SD*	Without pneumonia ($n = 35$), mean ± *SD*	*p*
Age (years)	49 ± 7.6	55 ± 11	49 ± 7.6	0.1
Sex (M/F)	3/5	13/4	16/20	0.09
Type of donor (C/L)	5/3	5/12	20/16	0.07
Diabetes mellitus (%)	25	35.3	14	0.1
Hypertension (%)	88	94	78	0.3
Obesity (%)	25	25	22	0.9
History of rejection (%)	12.5	17.6	22	0.7
DGF (%)	75	47	14	**0.001**
Triple IS (%)	88	74	83	0.6
Respiratory failure (%)	100	41	0	**<0.001**
Need for intensive care unit (%)	75	17	0	**<0.01**
Acute kidney injury (%)	88	19	0	**<0.001**
Death (%)	63	6	0	**<0.001**
Baseline GFR (ml/min/1.72 m^2)	42 ± 24	48 ± 21	62 ± 18	**0.008**
Baseline GFR < 60 ml/min/1.72 m^2(%)	88	68	39	**0.01**

Note: Bold *p* value <0.05 is considered significant.

Abbreviations: C/L, cadaveric/living; COVID-19, coronavirus disease 2019; DGF, delayed graft function; GFR, glomerular filtration rate; M/F, male/female; IS, immunsupression.

TABLE 2 Demographic and laboratory characteristics of patients with pneumonia who did and did not receive IVIg therapy

	Patients with pneumonia ($n = 29$), mean ± *SD*	Pneumonia and IVIg treatment ($n = 15$), mean ± *SD*	Pneumonia without IVIg treatment ($n = 14$), mean ± *SD*	*p*
Age (years)	52.6 ± 10.3	53.8 ± 11.9	51.1 ± 8.5	0.5
Sex (M/F)	20/9	9/6	8/6	0.7
Donor type (C/L)	17/12	8/7	9/5	0.2
Diabetes mellitus (%)	33.3	35	30.7	0.8
Hypertension (%)	92.5	100	84.6	0.3
BMI (kg/m^2)	27.9 ± 7.9	26.9 ± 3.4	29.1 ± 11	0.3
Triple IS (%)	78.5	80	76.9	0.7
Respiratory failure (%)	57.6	64.2	50	0.3
Acute kidney injury (%)	44.4	40	50	0.7
Severe pneumonia (%)	28.5	26.6	30.7	0.4
Laboratory results				
Glucose (mg/dl)	174.4 ± 91.2 (96–400)	173.3 ± 101 (98–400)	175.9 ± 80.1 (96–379)	0.9
GFR (ml/min/1.73 m^2)	39.1 ± 23.3 (7–94)	46.3 ± 20 (12–83)	30 ± 24.5 (7–94)	**0.2**
CRP (mg/L)	120 ± 99 (8.1–350)	123 ± 81 (38–350)	117 ± 124 (8.1–321)	0.7
Hemoglobin (g/dl)	11.3 ± 2.0 (6.2–14.9)	12 ± 1.5 (8.9–13.8)	10.6 ± 2.4 (6.2–14.9)	0.3
Leukocyte count (mm^3)	8.5 ± 5.7 (2020–24710)	6.8 ± 3.5 (2020–15850)	10.7 ± 7.2 (3510–15850)	0.07
D-Dimer	2194 ± 6413 (104–32678)	795 ± 1417 (138–5801)	4103 ± 9646 (104–32678)	0.2
Serum albumin	3.3 ± 0.4 (2.4–4.1)	3.2 ± 0.3 (2.4–3.8)	3.6 ± 0.2 (3.1–3.8)	**0.06**
Serum lactate	2.80 ± 2.8 (0.1–12.5)	1.98 ± 1.2 (0.1–5.1)	4.45 ± 4.2 (0.8–12.5)	**0.1**
Need for intensive care (%)		26.6	42.9	**0.45**
Need for mechanical ventilation (%)		13.3	35.7	**0.21**
Death rate (%)		6.6	35.7	**0.08**

Note: Bold *p* value <0.05 is considered significant.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; C/L, cadaveric/living; DGF, delayed graft function; GFR, glomerular filtration rate; IS, immunosuppression; IVIg, intravenous immunoglobulin; /F, male/female.

patients. IVIg treatment was administered only in our center and could be given to 15 of the 23 patients with COVID-19 pneumonia. Additionally, seven patients received tocilizumab treatment. IVIg therapy could not be given to any patients treated in any external centers because they did not apply for off-label use consent to the Ministry of Health Drug and Medical Device Agency.

Pneumonic involvement on CCT of less than 5% was seen in four patients, between 5% and 25% in eight, 26%–50% in nine, 51%–75% in seven, and greater than 75% in one patient. Fifteen (51.7%) of the 29 hospitalized patients had an acute respiratory failure in blood gas analysis. Nine (31%) patients were treated in the intensive care unit and hospitalized for an average of 9.8 ± 5.4 days, six (20.7%) of whom required intubation and mechanical ventilation support. Respiratory support in the remaining nine patients with respiratory failure was provided using noninvasive positive pressure ventilation. According to the severity of the pneumonic infiltration, the patients were studied in three groups: without pneumonia, mild-moderate pneumonia (< 50% involvement), and severe pneumonia (>50% involvement). Those with severe pneumonia had lower basal GFR, high rates of DGF, more frequently experienced Rf, and had high AKI and mortality rates (Table 1).

Six of 19 patients who were treated in different external centers were hospitalized for pneumonia. Four of these patients had severe pneumonia and two had mild-moderate pneumonia. None received IVIg therapy. However, tocilizumab (800 mg total dose) was administered in two patients with severe pneumonia. Five of these six patients died after treatment.

The mean GFR of the patients before COVID-19 was 54.6 ± 21.3 (range, 13–105) ml/min/1.72 m^2. According to the GFR rates at admission, patients were examined in two groups: Group 1 (n = 34) included those with a GFR value less than 60 ml/min/1.72 m^2 and Group 2 (n = 30) consisted of patients with a GFR value ≥60 ml/min/1.72 m^2. In Group 1, GFR was less than 20 ml/min/1.72 m^2 in five patients and less than 10 ml/min/1.72 m^2 in two patients at admission. The kidney functions of these five patients gradually improved during medical treatment. The other two cases were taken into the regular hemodialysis program (three sessions in a week for 4 h each) at the beginning of COVID-19 treatment.

Both groups were compared concerning respiratory functions and clinical outcomes. The frequency of respiratory failure (39% vs. 8%, p = 0.006), the need for intensive care (42% vs. 10%, p = 0.04), the incidence of AKI (31% vs. 0%, p = 0.001), and pneumonia (59% vs. 27%, p = 0.005) was significantly higher in Group 1 compared with Group 2. However, mortality rates were not statistically different between the two groups (15% vs. 3% in Groups 1 and 2, respectively, p = 0.1).

All patients received corticosteroid therapy for 7 days after hospitalization. Patients with pneumonic infiltration less than 25% received methylprednisolone (40 mg/day) and those with ≥25% received methylprednisolone pulse therapy (250 mg/d) in the first three days and then (40 mg/day) for four days. IVIg treatment was given to 15 of 23 (65.2%) patients who received treatment in our center. Among these, the percentage of pneumonic infiltration in CCT was 5%–25% in two, 26%–50% in five, 51%–75% in seven, and greater than 75% in one patient. After IVIg treatment, tocilizumab was added to the treatment in seven patients due to the lack of the expected improvement in acute respiratory failure. In these seven patients, there was a decrease in mean CRP (176.5 ± 127.8 vs. 90.0 ± 68.2 mg/L, p = 0.12) and procalcitonin values (20.1 ± 1.9 vs. 16.5 ± 1.0, p = 0.9) after IVIg therapy. However, an arterial oxygen tension of 60 mmHg and above could not be achieved in any patient. However, following tocilizumab treatment, respiratory parameters (SpO_2, PaO_2) improved significantly in all but one patient. Twenty-nine patients with pneumonia were examined in two groups as those who received IVIg treatment and those who did not. Among the groups, there was no significant difference in the demographic characteristics, renal function parameters, and acute-phase reactants at the time of admission (Table 2). However, an improvement in clinical findings was observed in all 15 patients after the completion of IVIg treatment. Indeed, the need for intensive care (26.6% vs. 42.9%, p = .45) and mechanical ventilation (13.3% vs. 35.7%, p = 0.21) were relatively low in patients who received IVIg treatment compared with those who did not. At the end of the treatment, only one of the 15 patients (6.6%) who received IVIg and five of the 14 patients (35.7%) who did not, died (p = 0.08). In the posttreatment radiodiagnostic evaluation (CCT) of the 15 patients who received IVIg treatment, pneumonic infiltration was completely resolved in 10 of them. Also, pneumonic involvement regressed to the level of 5%–25% in two and less than 5% in two patients. The patient, who had greater than 75% involvement of the lung parenchyma at the time of admission, deceased during the treatment process.

We observed no thromboembolic complications in any patient during and after treatment.

Although not statistically significant, the mortality rate was lower in patients who received IVIg. When the relationship between survival and comorbidity was examined, the mortality rate in diabetic, hypertensive, and obese patients compared to transplant recipients without any additional disease was (7% vs. 10%, p = 0.75), (9.3% vs. 10.0%, p = 0.94) and (13% vs. 8.2%, p = 0.92), respectively.

AKI was detected in 12 of 64 patients (18.8%) at the time of admission or during the treatment process. One patient (1.5%) had graft loss. Six (9.2%) patients died. There were no deaths among 35 KTRs with COVID-19 who were followed up as an outpatient. The mortality rate was higher in patients who received treatment in external centers (2.2% vs. 26.3%, p < 0.001). Compared with those who survived, the deceased patients had higher DGF (83% vs. 27%, p = 0.01) and cadaveric donor rates (83% vs. 44%, p = 0.04), increased AKI risk (83% vs. 13%, p < 0.001), and lower basal GFR values (38 ± 18 vs. 57 ± 21 ml/min/1.72 m^2, p = 0.03).

5 | DISCUSSION

In this study, which was conducted on COVID-19 pneumonia and its treatment in KTRs, we focused on two main points. One was on the assumption that the treatment and care given in this patient group

by experienced organ transplant centers would yield much better results. Indeed, supporting our hypothesis, among the 29 KTRs with pneumonia, only one of the 23 patients treated at our center and five of the six patients managed in external centers died (4.3% vs. 83.3%, $p < 0.001$). This result emphasizes the importance of clinical experience and adherence to the treatment protocol in the management of severe infections in KTRs.

The second point we investigated was whether IVIg treatment would provide an additional benefit and improve survival parameters in this patient group. In our previous case report, we suggested that IVIg could be an important treatment option in a kidney transplant patient who presented with severe COVID-19 pneumonia.[13]

In KTRs, IVIg has been used for the prevention and treatment of antibody-mediated rejection, as an adjunct therapy for the human BK polyomavirus-associated nephropathy, and posttransplant infectious complications, including cytomegalovirus and parvovirus B19.[14–16] Although the clinical results are inconclusive, IVIg has been used in the management of more lethal varieties of coronaviruses as SARS and MERS in the general population.[14] IVIg exerts an anti-inflammatory effect by binding to proinflammatory cytokines or variable anti-idiotypic antibodies. These effects may account for its clinical benefit.[17]

We were only able to administer IVIg treatment to 15 of our 23 patients in this study because the off-label use consent from the Ministry of Health was not received at the optimal time (within 48 h after admission) for every patient. Among a total of 29 patients with COVID-19 pneumonia, the need for intensive care and mechanical ventilation was relatively reduced in patients treated with IVIg. Although it did not reach a statistically significant level, the mortality rate was 6.6% in patients who received IVIg therapy and 35.7% in those who did not ($p = 0.08$). At the end of the study, we performed a post hoc analysis. Under the continuity of current mortality rates in both groups (7% in the IVIg arm and >30% in external centers), we investigated the number of patients required for both groups to make this difference in mortality statistically significant. Thus, we calculated that the p value would be less than 0.001 when 50 patients were reached in both groups.

When we wrote our treatment algorithm, many studies were still ongoing investigating the effectiveness of IVIg in patients with severe COVID-19 pneumonia in the general population (NCT04350580, NCT04381858, NCT04261426).[8] As demonstrated in many studies of KTRs, the course of the COVID-19 in these patients was generally severe and often required intensive care and posttreatment mortality rates were high.[3,4,18,18,19] For this reason, we thought that the use of IVIg in transplant patients who are riskier than the general population in terms of COVID-19 disease had a valid basis.

In a recent systemic review of 20 studies with completed outcomes for KTRs with confirmed SARS-CoV-2 infection, the main approach to maintenance immunosuppression was the withdrawal of antiproliferative drugs with or without a reduction in the calcineurin inhibitor dose. Among these, ten studies started corticosteroid therapy or administered high-dose corticosteroid in between 4% and 62% of patients.[20] In our protocol, we stopped antiproliferative drugs and suspended calcineurin inhibitors for 2 to 5 days in patients with pneumonia. In this group, in addition to high doses of corticosteroids, we used 2 g/kg body weight IVIg in 65% of the patients. With this method, we experienced graft loss in only one patient. The dosage and timing of IVIg therapy are controversial. In a multicenter retrospective study, IVIg decreased the inflammatory response parameters, improved some organ functions, reduced 28-day mortality, and prolonged survival. Moreover, early and high-dose (>15 g/day) administration of IVIg was particularly effective in critically ill patients.[21] In another retrospective study, Xie et al.[22] reported significantly lower 28-day mortality and shorter hospital stay due to COVID-19 pneumonia in patients who received IVIg treatment within 48 h of admission. Also, the rate of patients requiring mechanical ventilation was lower in this group. In line with the literature, we started IVIg treatment within the first 48 h, and we achieved a reduction in the need for intensive care and mechanical ventilation with this treatment.

Patients with COVID-19 have demonstrated high levels of inflammatory cytokines including IL-6. Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody and has been used in the treatment of patients with severe COVID-19. In a prospective randomized study, it was reported that Tocilizumab treatment was not effective in preventing intubation or death in patients hospitalized with moderate COVID-19.[23] This study was conducted on patients with SARS-CoV-2 infection in the general population, and Tocilizumab was the main treatment for the hyperinflammatory state in these cases. Indeed, only 11% of patients were given corticosteroids as concomitant therapy. On the other hand, interim results from CORIMUNO-TOCI (NCT04331808), a phase II, randomized clinical trial, showed that a significantly lower number of the patients needed noninvasive ventilation or mechanical ventilation or died in the tocilizumab group than in the usual care group (24% vs 36%; hazards ratio, 0.58).[24]

In our treatment protocol, RTRs with SARS-CoV-2 infection initially received high-dose IVIg and corticosteroid treatments, which have the potential for cytokine inhibition.[8] Those who did not achieve $PaO_2 \geq 60$ mmHg after this treatment received tocilizumab. These nonspecific immune modulators applied before may have improved the therapeutic results expected from tocilizumab.

In a recent report, including 80 KTRs, tocilizumab efficiently reduced CRP levels and this decrease positively correlated with survival.[25] In another small-scale, single-center study, including 10 KT patients with severe COVID-19, a single dose of tocilizumab (400–600 mg) decreased CRP levels, improved the clinical course, reduced oxygen requirement, and provided hospital discharge in seven patients.[26] In our study, we used tocilizumab in seven patients whose PaO_2 levels were between 50 and 54 mmHg after IVIg treatment. Following tocilizumab, PaO_2 increased above 60 mmHg in all cases. The respiratory parameters improved and all but one patient were discharged with recovery.

All patients with pneumonia received corticosteroid treatment with varying doses (280–910 mg/total dose). In these patients, the

discontinuation of antiproliferative agents and calcineurin inhibitors mandated us to administer high-dose corticosteroids, which was the only option for maintenance immunosuppression. However, we do not consider this as a confounding factor on the efficacy of IVIg and tocilizumab treatments. Our study had several limitations. First of all, it was a single-center, retrospective cohort study, and had no comparative group. Also, the sample size was small, restricting the power of the study. However, it is interesting because it is the first study in which a broad-spectrum anti-inflammatory protocol was used for COVID-19 pneumonia in KTRs.

6 | CONCLUSION

As observed in this study, the treatment of KTRs with severe COVID-19 pneumonia in organ transplant centers with significant experience in issues, such as infection treatment, immunosuppression modification, and treatment complications, yields better results. The administration of broad-spectrum anti-inflammatory treatment in this patient group was safe and provided excellent outcomes.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest with respect to the research, authorship, and/or publication of this article.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

Karatas M, and Tatar E equally contributed to the conception and design of the study. Karatas M, Yıldırım AM, and Uslu A contributed to the assembly, analysis, and interpretation of data. Tatar E, Zengel B, Ari A performed the statistical analysis. Simsek C, Karatas M, and Ari A participated in the drafting of the article. Tatar E, and Uslu A revised the article.

DATA AVAILABILITY STATEMENT

The authors declare that their data are available. If the article is accepted, *The Journal of Medical Virology* can use data related to this article.

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