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COVID-19 in kidney transplant recipients; a DALMATIAN single-center experience

Tina Dogas[1] | **Tonci Brkovic**[1,2] | **Ivana Novak**[1] | **Josipa Radic**[1,2]

[1]Division of Nephrology and Dialysis, University Hospital Centre Split, University of Split, School of Medicine, Split, Croatia

[2]Department of Internal medicine, University of Split, Split, Croatia

Correspondence
Josipa Radic, Division of Nephrology and Dialysis, University Hospital Centre Split, University of Split, School of Medicine, Soltanska 1, 21000 Split, Croatia.
Email: josiparadic1973@gmail.com

Abstract

Introduction: We aimed to explore COVID-19 severity, complications, and outcome predictors in the Dalmatian population of kidney transplant recipients (KTRs).

Methods: KTRs confirmed with acute COVID-19 infection until May 2021 were included and followed up for 6 months.

Results: Out of 50 KTRs average aged 63 years, 36 (72%) were men. Nine (18%) KTRs had no pulmonary infiltration, and twenty-nine (58%) did not require oxygen supplementation. Bilateral pulmonary infiltrates had 29 (58%) while high-flow nasal cannula or mechanical ventilation required 8 (16%) KTRs. The mortality rate was 16%. Acute kidney injury developed in 18 (36%), and acute renal replacement therapy required 2 (4%) KTRs. Nine (18%) KTRs were subsequently rehospitalized. Chronic COVID-19 syndrome reported 23 (58%) KTRs.

Conclusions: D-dimers were found to be the key prognostic factor of clinical complications, emphasizing the importance of underlying thrombotic microangiopathy. Optimal immunosuppressant adjusting in KTRs with acute COVID-19 infection remains to be clarified.

KEYWORDS

COVID-19 infection, kidney transplantation, long-COVID-19, rehospitalization

1 | INTRODUCTION

Since the outbreak in Wuhan, Hubei Province, China, in December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has spread throughout the world at lightning speed and was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. The severity of coronavirus disease 2019 (COVID-19) ranges from asymptomatic or mild upper respiratory illness to severe viral pneumonia with bilateral lung involvement. Acute respiratory distress syndrome (ARDS) evolves in 15%–40% of patients with COVID-19-associated pneumonia. [1, 2] The reported case fatality rate of 1%–5% in general population rises to 8%–15% in patients older than 70 years of age [3]. Besides age, the major risk factors influencing disease severity and mortality are male gender and the number of underlying comorbidities including nowadays widespread obesity, hypertension, cardiovascular disease, diabetes mellitus, malignancy, chronic pulmonary and chronic kidney disease (CKD). Solid organ transplant recipients are at a particularly higher risk of critical illness in addition to chronic immunosuppression, with several studies reporting mortality as high as 28% [3, 4]. Furthermore, existing heterogeneous data according to sample size, inclusion criteria, and definitions of acute kidney injury (AKI), reported a wide range of AKI incidence up to 46%

with renal replacement therapy (RRT) requiring up to 23% [5]. The nature of COVID-19 disease consists of the initial stage of virus replication followed by the second stage of immunopathology. Increasing evidence suggests a predominant pattern of lung injury as cytokine storm whose prominent features are hyperinflammatory innate host immune response by the predominant Th1 cell and classic M1 macrophage polarization and pathologic finding of platelet-fibrin microthrombi being identified in nearly all major organs with endothelial ACE2 expression, the principal gate for SARS-CoV-2 cell entry in humans [2]. Yet, the optimal immunosuppression modification in solid organ transplant recipients remains a subject of discussion. Supported by the evidence from randomized, controlled, open-label RECOVERY trial, which demonstrated survival benefit with dexamethasone, escalated doses of corticosteroid equivalents were encouraged, in particular in the second week of the disease [6]. Over and above, therapeutic management included antimetabolite withdrawal, calcineurin inhibitor dose adjustment, and cessation in severe cases requiring ICU admission, antivirals, that is remdesivir, azithromycin and other antibiotics as well as intravenous immunoglobulins (IVIG) [1]. In addition to many uncertainties regarding the key drivers of the pathologic inflammatory response, a phenomenon so-called chronic COVID-19 syndrome, seemingly independent of the initial disease severity, is recognized [7]. The aim of this study was to explore disease severity and complications together with outcome predictors in the Dalmatian population of kidney transplant recipients (KTRs).

2 | MATERIALS AND METHODS

2.1 | Study design

A prospective, single-center, observational cohort study was conducted from August 2020 to May 2021. KTRs confirmed with acute COVID-19 infection by RT-PCR on nasopharyngeal swab were included. The study's primary outcomes were disease severity and clinical complications as allograft dysfunction, thrombotic events, superimposed infections, rehospitalization, and chronic COVID-19 syndrome. A secondary outcome was identifying prognostic factors influencing rehospitalization and chronic COVID-19 syndrome. Allograft dysfunction was defined according to KDIGO guidelines AKI definition as the increase in serum creatinine by ≥26.5 μmol/L or ≥1.5 times baseline. Chronic COVID-19 syndrome was defined as persistence of infection-related symptoms 12 weeks after the disease onset. Infection-related symptoms considered were fatigue, shortness of breath, effort intolerance, cough, palpitations, insomnia, anxiety, depression, cognitive impairment, anosmia, dysgeusia, hair loss, and skin rash. Patient's demographics, clinical features, treatment interventions, and laboratory findings including complete blood count, coagulation profile, and serum biochemical analyses were extracted from electronic medical records by investigators. KTRs were followed in the outpatient transplant clinic and reassessed in two checkpoints, 3 and 6 months after the disease onset. KTRs interview and physical examination were conducted by trained nephrologists. Information of rehospitalization and chronic COVID-19 syndrome were collected along with available laboratory data. All participants provided written consent after being informed of the study's nature and purpose. The study protocol was approved by the Institutional Ethics Committee and was performed following the guidelines of the latest version of the Helsinki Declaration.

2.2 | Statistical analysis

Categorical data were presented by absolute and relative frequencies. The normality of the distribution of continuous variables was tested by the Shapiro–Wilk test. Continuous data was described by the median and the limits of the interquartile range (IQR). The Mann–Whitney *U* test and the Friedman's test (post-hoc Conover) were used to compare the median between two groups, whereas the Fisher's exact test was used to analyze the differences between proportions. Logistic regression analysis (multivariate–stepwise method) was used to analyze independent factors associated with the late clinical complications as rehospitalization and chronic COVID syndrome, adjusting for known confounders. The receiver operating curve (ROC) was used to determine the optimal threshold, the area under the curve (AUC), specificity and sensitivity of the tested parameters. All *p* values were two-sided. The level of significance was set at an α of 0.05. The statistical analysis was performed using MedCalc® Statistical version 19.6 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2020) and IBM SPSS Stat. 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0.).

3 | RESULTS

3.1 | Patients' characteristics

Since the outbreak of COVID-19 pandemic in March 2020, until May 2021, 50 KTRs out of 220 (23%), resulted SARS-CoV-2 positive by RT-PCR on the nasopharyngeal swab. Most of them were hospitalized at some point of the acute illness and have been followed up in the outpatient transplant clinic 6 months thereafter.

Patients' characteristics are presented in Table 1.

Clinical features at COVID-19 presentation in order of occurrence were fever (88%), fatigue (58%), cough (48%), algic syndrome (42%), shortness of breath (30%), diarrhea (24%), anosmia (12%), cognitive impairment (12%), anxiety (8%), depression (6%), and insomnia (4%) a shown in Table 2.

Approach to immunosuppression modification and overall medical treatment is listed in Table 3.

Forty (80%) KTRs recovered, nine (18%) died and three (6%) ended up with deteriorated allograft function. All deceased KTRs but one had acute respiratory failure requiring mechanical ventilation due to COVID-19 pneumonia, one each of whom was additionally treated for central venous catheter infection, acute appendicitis and pseudomembranous

TABLE 1 Patients' characteristics ($N = 50$)

	Number of patients (%)	
Gender [*n* (%)]		
Men	36 (72)	
Women	14 (28)	
Underlying kidney disease		
Unknown	22 (42)	
Glomerulonephritis	6 (12)	
ADPKD	10 (20)	
Nephroangiosclerosis	2 (4)	
Diabetes mellitus	3 (6)	
Other	7 (14)	
Associated diseases		
Hypertension	43 (86)	
Diabetes mellitus	15 (30)	
Diabetes mellitus or dysregulated glycemia in COVID 19	14 (28)	
Atherosclerosis	11 (22)	
Vaccination prior COVID-19 infection		
Not vaccinated	44 (88)	
One dose within 14 days	2 (4)	
One dose longer than 14 days	2 (4)	
Two doses within 14 days	2 (4)	
	Median(IQR)	**Range**
Age [years]	63 (52–70)	36–79
Body height [cm]	178 (170–183)	158–194
Body weight [kg]	83 (74.5–90)	53–135
BMI at initial hospitalization [kg/m^2]	26.47 (24.29–27.59)	20.45–38.20
Time since KX [years]	8 (3.5–11.5)	1–37
Length of dialysis treatment prior TX [years]	2 (1–5)	0–13

Abbreviations: IQR, interquartile range; ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; TX, kidney transplantation.

TABLE 2 Clinical features at COVID-19 presentation among all study subjects

Pneumonia [*n* (%)]	
None	9 (18)
Mild infiltration	9 (18)
Bilateral infiltrates	29 (58)
Severe bilateral pneumonia involving most of the lung parenchyma	3 (6)
Respiratory failure [*n* (%)]	22 (44)
O_2 [*n* (%)]	
None	29 (58)
1–6 L/min	9 (18)
6–10 L/min	1 (2)
10–15 L/min	2 (4)
HFNO	3 (6)
Mechanical ventilation	5 (10)
Acute renal failure [*n* (%)]	18 (36)
CVVHDF or HD [*n* (%)]	2 (4)
BMI at the time of hospitalization (kg/m^2) [Median (IQR)]	26.47 (24.29–27.59)
Nutrition at the time of hospitalization [*n* (%)]	
Normal (18.5–25 kg/m^2)	9 (18)
Overweight (25–30 kg/m^2)	22 (44)
Obesity I (30–35 kg/m^2)	2 (4)
Obesity II (>35 kg/m^2)	3 (6)
Unknown	13 (26)
Change in body weight during hospitalization [*n* (%)]	
Yes	24 (48)
No	12 (24)
Unknown	1β3 (26)
Change in body weight during hospitalization (kg) [Median (IQR)] (max 13 kg)	3.5 (0–6.5)
Day of illness at hospitalization [Median (IQR)] (max 10 days)	2. (1.–3.)
Length of hospitalization (days) [Median (IQR)] (max 60 days)	10 (5–17)

Abbreviations: IQR, interquartile range; O_2, oxygen; HFNC, high-flow nasal cannula; CVVHDF, continuous veno-venous hemodiafiltration; HD, hemodialysis; BMI, body mass index.

TABLE 3 Medications during acute infection

Baseline immunosuppressants [*n* (%)]	
Cyclosporine A	12 (24)
Tacrolimus	32 (64)
mTOR inhibitor	4 (8)
Azathioprine	1 (2)
Adjacent immunosuppressantsMMF or mTOR inhibitor [*n* (%)]	
Unchanged dose	6 (12)
Halved dose	11 (22)
Minimal dose	10 (20)
Omitted	21 (42)
Not prescribed	1 (2)
Corticosteroids [*n* (%)]	49 (98)
Dose of methylprednisolone or equivalent [*n* (%)]	
Up to 32 mg	26 (52)
32 mg to 79 mg	11 (22)
80 mg to 125 mg	8 (16)
Above 125 mg	5 (10)
Intravenous immunoglobulins [*n* (%)]	9 (18)
Remdesivir [*n* (%)]	38 (76)
Azithromycin [*n* (%)]	37 (74)
Antibiotic [*n* (%)]	
None	14 (28)
One	21 (42)
Two	10 (20)
More than two	4 (8)
ACE inhibitor/Angiotensin receptor blocker [*n* (%)]	7 (14)
Diuretic [*n* (%)]	30 (60)
Inotropics [*n* (%)]	4 (8)
Low-molecular-weight heparin [*n* (%)]	
None	11 (22)
Prophylactic dose	28 (56)
Therapeutic dose	9 (18)
Therapeutic dose of other anticoagulant	2 (4)

Abbreviations: MMF, mycophenolate mofetil, ACE, angiotensin-converting enzyme.

Clostridium difficile enterocolitis and two more for urinary infection. One KTR developed pneumomediastium. As for arterial and venous thrombotic complications, one each of KTRs was diagnosed with pulmonary embolism, stroke, and myocardial infarction, respectively.

TABLE 4 Initial laboratory values (first laboratory at hospital admission or at first outpatient visit during active illness)

Initial laboratory	Median (IQR)	Range
Blood pressure		
Systolic (mmHg)	130 (120–150)	100–195
Diastolic (mmHg)	80 (70–85)	50–110
Leucocyte count (10^9/L)	6.6 (4.6–8.18)	2.8–14.1
Mean corpuscular volume (fL)	85.8 (83.2–89.85)	72.6–94.6
Hemoglobin (g/L)	133.5 (120.25–153)	79–169
Neutrophils (%)	78.2 (70.8–85.1)	48.5–95.5
Lymphocytes (%)	15.1 (8.1–18.6)	2.2–40.6
Platelet count (10^9/L)	214.5 (157–256.75)	99–389
Blood glucose (mmol/L)	6.9 (5.5–8.38)	4–29.3
Albumin (g/L)	35 (30.25–38.9)	19.3–46.4
Urea (mmol/L)	8.9 (6.68–11.08)	4.3–38.8
Creatinine (μmol/L)	134.5 (106–195.75)	72–477
D-dimers (mg/L)	0.7 (0.37–1.48)	0–25.49
Aspartate aminotransferase (U/L)	27 (20–40)	11–174
Alanine aminotransaminase (U/L)	21.5 (17–28)	0–230
Lactate dehydrogenase (U/L)	245 (196–345.8)	0–573
C-reactive protein (mg/L)	51.6 (16–90.5)	2.3–257.6
Procalcitonin (ng/mL)	0.2 (0.1–0.5)	0.02–24.88
proBNP (pg/mL)	996 (229–5396)	86–37 652
pH (pH unit)	7.5 (7.4–7.5)	7.304–7.521
pO_2 (kPa)	7.9 (5.8–12.8)	4.28–20.6
pCO_2 (kPa)	4.2 (3.8–5.9)	2.82–11.5
HCO_3 (mmol/L)	21.2 (18.6–28.9)	0–35.3
Baseline proteinuria (g/L)	0.24 (0.02–126)	0–3537
Baseline albuminuria (g/L)	0.04 (0–6.68)	0–3073
Baseline eGFR (ml/min)	44.4 (30.25–60)	0–103

Abbreviations: IQR, interquartile range; pH, the negative logarithm of the hydrogen ion concentration; pO_2, arterial oxygen partial pressure; pCO_2 arterial carbon dioxide partial pressure; HCO_3, bicarbonate; eGFR, estimated glomerular filtration rate.

3.2 | Laboratory findings

KTRs initial laboratory findings at hospital admission or at first outpatient visit in a for KTRs not being hospitalized are summarized in Table 4.

Only 6 (12%) KTRs had non-sterile urine culture, while 10 (20%) KTRs had not been sampled for urine culture, and eventually 13 (26%) had not records of spot urine sample at all.

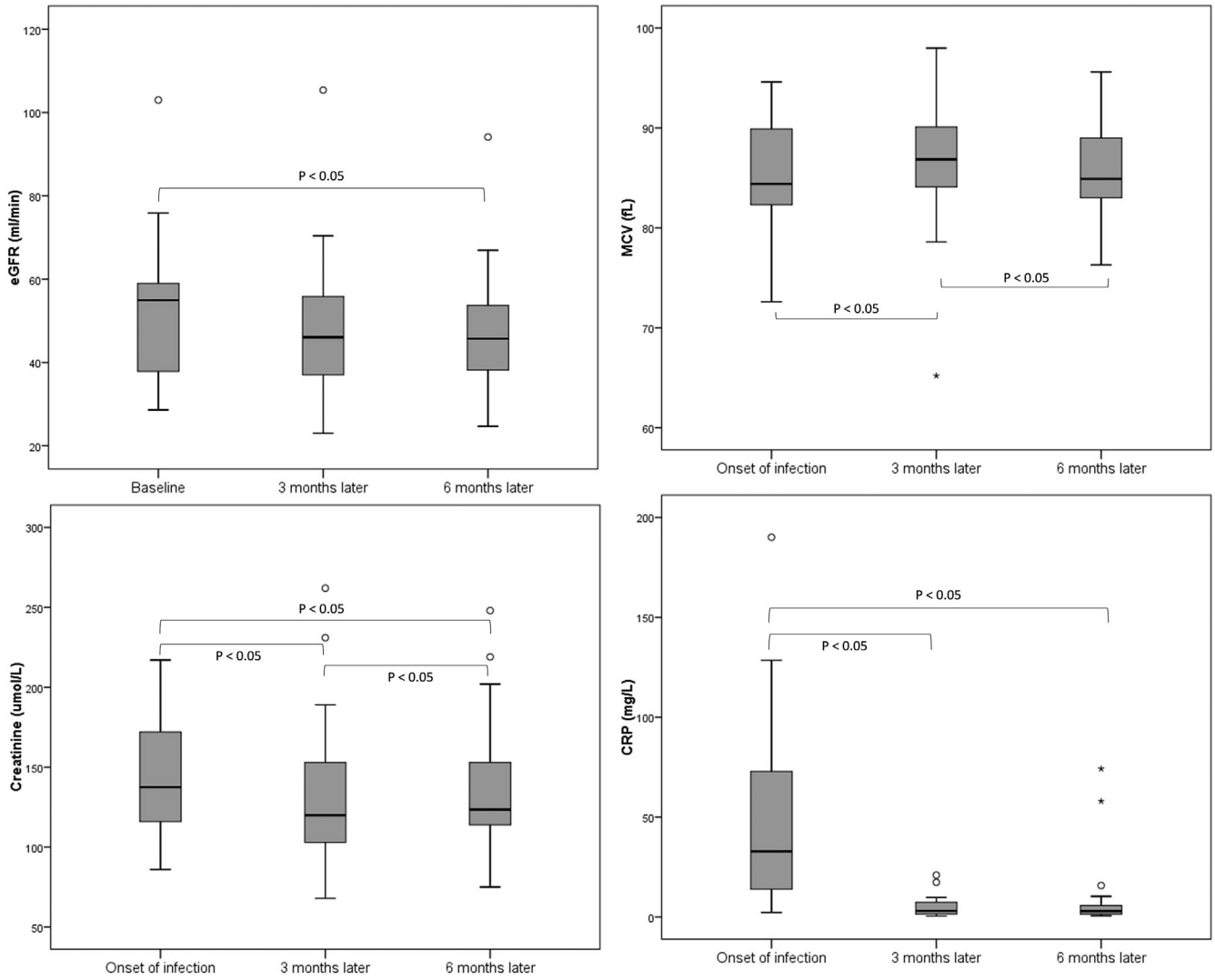

FIGURE 1 Significant differences in laboratory parameters at the onset, 3 and 6 months after COVID-19 infection

3.3 | Rehospitalization

During 6 months follow-up, nine (18%) KTRs were rehospitalized, five (10%) of which due to infections, one due to pulmonary embolism and dysregulated glycemia, one due to myocardial infarction and infection of the cardiac catheterization entrance site in the groin, and two due to worsening of allograft function.

No statistically significant association of rehospitalization with any demographics, underlying and associated kidney diseases, years since transplantation, length of dialysis treatment, or vaccination status was found.

Assessing initial laboratory values at the onset of COVID-19 infection found higher values of leucocyte count, platelet count, D-dimers, and C-reactive protein being likely prognostic for rehospitalization.

When comparing initial and complementary laboratory values 3 and 6 months later, there is a recognizable trend toward improvement of kidney function with acute phase inflammatory parameters returning within the reference range that is shown in Figure 1.

For comparison, none of the acute illness clinical features was as prognostic for rehospitalization. But, no KTRs without pulmonary infiltration was rehospitalized. As many as 45% of rehospitalized patients had mild pulmonary infiltration and 55% bilateral infiltrates.

Independent predictors influencing the likelihood of rehospitalization were identified by logistic regression and shown in Table 5.

Significant bivariate predictors used were platelet count (OR = 1.01) and D-dimers (OR = 4.77).

Multivariate logistic regression (stepwise method) identified D-dimers as a statistically significant contributor to the model (Hosmer–Lemeshow test, $p = 0.31$) that is overall statistically significant ($X^2 = 8.8$, $p = 0.001$) and fully explains between 26% (Cox and Snell) and 37%

TABLE 5 Factors influencing the likelihood of rehospitalization

	ß	Wald	p	OR	95% CI
Bivariate analysis					
Leucocyte count (10^9/L)	0.19	1.65	0.19	1.21	0.90–1.63
Platelet count (10^9/L)	0.01	4.1	**0.04**	1.01	1.01–1.03
D-dimers (mg/L)	1.56	4.47	**0.03**	4.77	1.12–20.3
Pneumonia (none)					
Mild infiltration	22.4	0.001	0.99	–	–
Bilateral infiltrates	19.7	0.0008	0.99	–	–
MCV (fL)	−0.04	0.34	0.56	0.96	0.83–1.11
Creatinine (μmol/L)	−0.01	1.61	020	0.98	0.97–1.01
C-reactive protein (mg/L)	0.08	1.16	0.28	1.01	0.99–1.02
Multivariate analysis					
D-dimers (mg/L)	1.56	4.47	**0.03**	4.77	1.12–20.3
Constant	−2.4	7.9	**0.005**		

Note: Bold values indicate statistically significant $p < 0.05$.
Abbreviations: MCV, mean corpuscular volume; OR, odds ratio; CI, confidence interval.

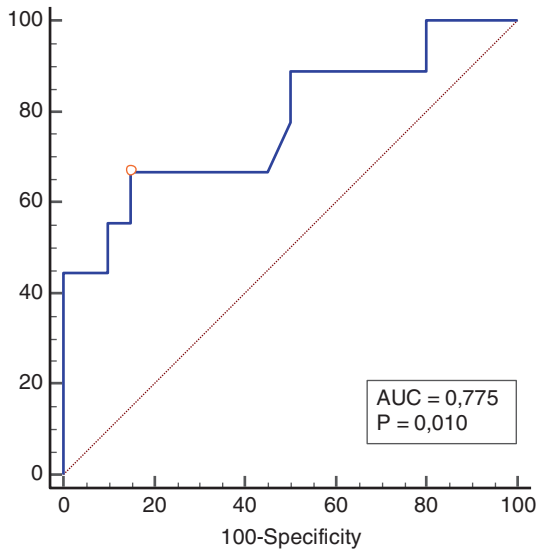

FIGURE 2 Receiver operating curve analysis of sensitivity, specificity, and cutoff values of D-dimers for the likelihood of rehospitalization

(Negelkerke) variance of rehospitalization, accurately classifying 76% of cases.

The ROC was used to determine the optimal threshold (cutoff point) with the AUC defining specificity and sensitivity of the tested parameter as shown in Figure 2.

3.4 | Chronic COVID-19 syndrome

Chronic COVID-19 syndrome developed 23 of 41 KTRs (58%), while 9 died.

Women more often suffered from chronic COVID-19 syndrome. No significant associations with demographics, underlying and associated kidney diseases, years since transplantation, length of dialysis treatment, or vaccination status were found.

Assessing initial laboratory values, at the onset of COVID-19 infection, found higher D-dimers, lower arterial oxygen partial pressure and lower diastolic pressure to be statistically significant predictors of chronic COVID-19 syndrome. A similar but statistically insignificant trend was shown with lower hemoglobin levels, higher platelet count, higher aspartate aminotransferase, and higher arterial carbon dioxide partial pressure.

Clinical features predicting chronic COVID-19 syndrome were algic syndrome, fatigue, and diarrhea.

The severity of clinical features including pulmonary infiltrates, respiratory failure, and allograft function as well as thrombotic complications have not been identified as predictors of chronic COVID-19 syndrome.

As with rehospitalization, the same conclusions could be drawn from comparing initial laboratory values to complementary values 3 and 6 months later.

Logistic regression identified predictors of chronic COVID-19 syndrome as shown in Table 6.

Significant bivariate predictors were female gender (OR = 5.9), D-dimers (OR = 3.82), fever (OR = 3.41), algic syndrome (OR = 6.8) and fatigue (OR = 6.09) while protective predictors were diastolic pressure (OR = 0.91) and acute allograft failure (OR = 0.09).

Multivariate logistic regression (stepwise method) identified fatigue as the sole independent predictor contributing to the statistical significance of the model (Hosmer–Lemeshow test, $p = 0.40$) which is overall

TABLE 6 Factors influencing the likelihood of a long COVID

	ß	Wald	p	OR	95% CI
Bivariate analysis					
Female gender	1.78	5.11	**0.02**	5.92	1.27–27.7
Diastolic blood pressure (mmHg)	−0.09	5.88	**0.02**	0.91	0.84–0.98
D-dimers (mg/L)	1.34	4.002	**0.04**	3.82	1.03–14.2
pO2 (kPa)	−0.42	3.09	0.08	0.66	0.41–1.05
Fever (°C)	1.23	4.32	**0.03**	3.41	1.07–10.9
Algic syndrome	1.91	7.22	**0.007**	6.8	1.7–27.5
Fatigue	1.8	6.3	**0.01**	6.09	1.49–24.9
Acute renal failure	−2.3	4.4	**0.04**	0.09	0.002–0.87
C-reactive protein (mg/L)	−0.01	2.39	0.12	0.98	0.97–1.003
Mean corpuscular volume (fl)	−0.07	1.07	0.30	0.93	0.81–1.07
Multivariate analysis					
Fatigue	3.04	6.87	**0.009**	21.0	2.16–204.6
Constant	−2.64	6.50	**0.01**		

Note: Bold values indicate statistically significant $p < 0.05$.
Abbreviations: OR, odds ratio; CI, confidence interval; pO2, arterial oxygen partial pressure.

statistically significant ($X^2 = 10.7$, $p = 0.001$), fully explaining between 30% (Cox and Snell) and 42% (Negelkerke) variance of chronic COVID-19 syndrome, accurately classifying 77% of cases.

3.5 | Antibody titers

Although antibody titers against SARS-CoV-2 were not collected systematically, that is being sampled at any time within 6 months of follow-up, analysis of available data in electronic medical history suggests lower IgM titers in patients with no requirements for oxygen supplementation and higher IgG titers being inversely correlated to the severity of pulmonary infiltrates.

4 | DISCUSSION

Our Dalmatian single-center study cohort of 50 KTRs confirmed with COVID-19 infection reported a mortality rate of 18% (9 deaths), all but one due to the acute respiratory failure complicated by secondary infections and multiorgan failure requiring inotropic support. AKI was reported in 36% (18) of KTRs, with just 4% (2) requiring acute RRT. Acute tubular injury is the most common etiology of AKI in autopsy and biopsy series, with microangiopathic injury and terminal complement activation (C5b-9) infrequently observed as well, and eventually collapsing glomerulopathy, the pattern of injury already associated with viral infection, in particularly HIV and parvovirus, and at last high risk APOL1 G1 genotype prone to interferon-mediated podocyte injury [7–9]. Proposed mechanisms of AKI are direct cytopathic effect, hemodynamic compromise, the ARDS-AKI axis, glomerular injury, and sporadically rhabdomyolysis [8]. It remains to be clarified if the infection will lead to the increased rates of CKD and end-stage renal disease as well. In our cohort, 6% (3) of KTRs ended up with deteriorated allograft function, two of which had already been diagnosed and treated for chronic antibody-mediated allograft rejection, and one of whom eventually ended up requiring chronic RRT. No acknowledgments of unequivocal allograft rejection neither cytomegalovirus reactivation were found in the follow-up. The rest of the KTRs recovered. A significant proportion of the KTRs had underlying kidney disease of unknown origin (42%), the rest included autosomal dominant polycystic kidney disease (20%), glomerulonephritis (12%), diabetes mellitus (6%), nephroangiosclerosis (4%), and other rare causes (12%). A large proportion of undefined underlying kidney disease was due to previously more restrictive approach to the renal biopsy indications combined with patients frequently being admitted late in the course of the CKD when kidney biopsy is considered to be less informative diagnostic tool. In our cohort of KTRs prevalent comorbidities were hypertension (86%), diabetes mellitus (30%), and clinically relevant atherosclerosis (22%). Clinical features mostly did not differ from the general population, apart from a lower proportion of asymptomatic patients or those experiencing mild symptoms, not requiring hospitalization [10]. Bilateral pulmonary infiltrates were described in 58% (29), severe bilateral pneumonia affecting most of the lung parenchyma in 6% (3), and mild and no infiltration in 18% (9) each. As for oxygen supplementation, 58% (29) of KTR's required none, 18% (9) were administered

low oxygen flow up to 6 liters per minute, 4% (2) up to 15 liters per minute, 6% (3) required high-flow nasal cannula and 10% (5) mechanical ventilation. The majority of KTRs, except for deceased ones, reported weight loss during their hospitalization, with a median of 3.5 kg, up to 13 kg, which is consistent with the literature reports [11–13]. Accordingly, transient increase of erythrocyte mean corpuscular volume at 3 months follow-up checkpoint could be a measure of malnutrition, as an acute illness sequel.

Treatment interventions consisted of immunosuppression adjustment as an escalation of corticosteroid dosages and withdrawal or a dose reduction of an adjacent immunosuppressant, antimetabolite as the most common, while lowering calcineurin trough targets, the backbone of the majority immunosuppression regimes [5]. Because lymphopenia is a prominent feature of viral infections including SARS-CoV-2, discontinuing the antimetabolite may be the foremost reasonable approach with the risk of rejection being outweighed by the potential benefit in countering infection [8, 14]. As regards to calcineurin inhibitors such as cyclosporine and tacrolimus, in-vitro studies have demonstrated activity against SARS-CoV-2 via inhibition of cyclophilin and immunophilin pathways, although clinical data are lacking [8, 14]. In critically ill patients it may be judicious to hold all maintenance immunosuppression [14]. In our cohort, 46% of KTRs were prescribed methylprednisolone of 32 mg and above, with 24% being prescribed 80 mg and above, the so-called mini boluses, up to 250 mg, for a short period of time. Under these circumstances, 28% of the KTRs experienced worsening of glycemic control or diabetes mellitus de novo. According to RECOVERY trial and subsequently meta-analysis of seven RCTs, the patients with severe COVID-19, requiring either mechanical ventilation or high levels of supplemental oxygen, who received steroid therapy, had a lower mortality rate at 28 days compared with the standard care alone [6, 10, 15] despite the potential fear of prolonged viral shedding. In our cohort of KTRs adjacent immunosuppressant was discontinued in 42%, halved in 22%, minimized in 20% and left unchanged in only 12%. Reports regarding mTOR inhibitors are inconclusive. While still advised of being withheld in severe COVID-19, mTOR inhibitors could be exploited for its potentially antiviral, immunomodulatory, and anti-fibrotic properties by reducing proliferation of conventional T-lymphocytes and preserving Treg growth and activity, so mitigating the cytokine storm and progression to severe disease [16, 17]. Further, remdesivir as well as azithromycin were prescribed in a similar proportion of 76% and 74% of our KTRs cohort. Based on in vitro data suggesting activity against coronaviruses and one RCT of 1063 patients, a remdesivir, an adenosine analogue, showed faster recovery time (11 days vs. 15 days, ratio for recovery 1.32, 95% CI: 1.12–1.55) with the most significant improvement seen in non-intubated patients receiving supplemental oxygen. However, despite the improved recovery rate, no mortality benefit was seen, possibly due to the biphasic nature of COVID-19 disease [10]. As regards other immunosuppressants, IVIGs were administered to nine KTRs (18%), due to its anti-inflammatory and immunomodulatory effects with the timing found to be crucial, and the highest impact observed when administered within the first few days of clinical deterioration, and no benefit observed if lung injury and systemic damage has already occurred [18]. Considering aforementioned immunosuppression interventions with at the same time documented no acute allograft rejection in our KTRs cohort, which could be, apart from the bias of small sample size, due to broadly applied multiple higher steroid doses, the mainstay of acute cellular mediated rejection treatment together with IVIGs, the mainstay of acute antibody mediated rejection treatment, that is used in particularly severe COVID-19 cases. Since higher D-dimer levels, of 1 μg/ml and above, in particular sixfold over upper limit, have been associated with poor prognosis and increased mortality in the setting of COVID-19, the anticoagulation prophylaxis, adjusted for disease severity, demonstrated a significant survival benefit [4, 19]. Apart from anti-thrombin activity heparin provokes disruption of tissue factor-heparinase interaction abolishing procoagulant effects of heparinase on the cell surface and blocking viral-cell attachment and cell-to-cell spread [20]. The majority of KTRs in this study were administered low-molecular-weight heparin, 56% in prophylactic and 22% in therapeutic doses. In terms of clinical complications, one each of KTRs was diagnosed with pulmonary embolism, stroke and myocardial infarction, respectively. A relatively small overall number of thromboembolic incidents in our study population is presumably due to in a large degree prescribed anticoagulant prophylaxis. No reports of bleeding complications were found. One KTR underwent surgery for acute appendicitis. Whether appendicitis could be a complication of SARS-CoV-2 is not clear. Pediatric reports suggest an association of appendicitis with multisystem inflammatory syndrome (MIS-c), as has already been known with Kawasaki disease of which MIS-c shares many common features. The proposed mechanism is either inflammation ensuing viral entry through ACE-2 receptors, abundantly present in the terminal ileum, with terminal ileitis, reactive lymphoid hyperplasia and luminal obstruction, or appendicular artery vasculitis [21]. In 6 months follow-up, 9 (18%) KTRs were rehospitalized. For comparison, other reports of rehospitalization rates, mostly referring to the first 30 days from hospital

discharge, ranged between 4.4% and 10% [22, 23]. In our cohort, none of the demographics, comorbidities, or clinical features were found to be prognostic for rehospitalization. But no KTRs without pulmonary infiltration were rehospitalized. Literature reports highlight male gender, multiple comorbidities, unresolved primary illness with lingering symptoms, and shorter initial hospitalization as prognostic for rehospitalization [22]. In our experience, multivariate logistic regression identified D-dimers as the sole independent and statistically significant predictor of rehospitalization accurately classifying 76% of cases. It is consistent with the autopsy findings showing severe endothelial injury and microangiopathy affecting not just lungs, but lower limbs, brain, heart, liver, and kidneys as well. COVID-19-associated molecular patterns and damage-associated molecular proteins seem to result in release of tissue factor and activation of coagulation factors predisposing hypercoagulability [10]. Another report identified an anemia 1 year prior and during acute illness being strongly associated with post-clearance rehospitalization independent of the intensive care unit admission status or other covariates. Similar finding was with AKI as well [24]. Chronic COVID-19 syndrome, also known as post-COVID-19 or long-COVID-19, developed 23 patients (58%) that is consistent with previous reports [25]. In our cohort of KTRs prognostic factors of chronic-COVID-19 syndrome were female gender, fatigue, algic syndrome, fever and D-dimers but only fatigue by multivariate logistic regression was found to be an independent and statistically significant, accurately classifying 77% of cases. According to the literature reports, the most common symptoms of chronic-COVID-19 syndrome were fatigue, muscle weakness, sleep difficulties, anxiety and depression [26]. Although the long-term health consequences of COVID-19 have been reported in KTRs with mild illness not requiring hospitalization, even in absence of pulmonary infiltration, the disease severity, however, appears to correlate with the risk of anxiety and depression as an important psychological complication as well as with impaired pulmonary diffusion capacities [26], supporting the need for post-discharge care in severe cases.

Mainly due to the study timing, the majority of the KTRs in our cohort (88%) had not been vaccinated prior to the COVID-19.

This study has several limitations. It is a single-center study with the small sample size enabling results overestimation. It is important to emphasize the exploratory nature of the study, not being driven by formal hypothesis. Data records have been extrapolated from the patient's electronic medical charts with some lacking. The treatment approach was highly individual and variable across three SARS-CoV-2 infection waves, thus preventing general conclusions.

The strength of our study is a prospective and a comprehensive, although observational, approach to COVID-19 in the Dalmatian population of KTRs through three SARS-CoV-2 infection waves, including rehospitalization rates and chronic-COVID-19 syndrome during 6 months follow-up in the University Hospital Center Split, the largest single-center on the Adriatic coast, from Trieste to Patras.

KTRs with COVID-19 are in a particularly higher risk of adverse outcomes. Many uncertainties regarding immunosuppression adjustment and long-term consequences need to be elucidated with the implementation of the best practice. In our KTRs cohort, D-dimers were found to be the key prognostic factor of clinical complications, emphasizing the importance of underlying thrombotic microangiopathy. A small proportion of thromboembolic incidents could be due to the broadly applied anticoagulant prophylaxis, in dosages adjusted for disease severity. Another specificity of our single-center experience is an unusually liberal approach to steroid dosing with at the same time documented no cases of acute allograft rejection and no significant increase in overall infectious complications including viral reactivations. However, small sample size prevents general conclusions. Furthermore, well structured, multicenter prospective studies are needed.

AUTHOR CONTRIBUTIONS

Conceptualization, validation, and supervision J.R.; methodology, data acquisition and analysis, investigations J.R., T.Đ., T.B., I.N.; original paper draft T.Đ, J.R.; paper review and editing J.R., T.Đ., T.B., I.N; All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILLITY STATEMENT

The data presented in this study are available on request.

INSTITUTIONAL REVIEW BORD STATEMENT

The study protocol was approved by the University Hospital Center Split Ethics Committee, Croatia (Class 500–03/21–01/172) and was performed following the guidelines of the latest version of the Helsinki Declaration.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved, although there were no interventions in this study.

ORCID

Tina Dogas https://orcid.org/0000-0002-8216-1750
Josipa Radic https://orcid.org/0000-0003-2645-7597

REFERENCES

1. Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant. 2020;35:1973-83.
2. Gustine JN, Jones D. Immunopathology of Hyperinflammation in COVID-19. Am J Pathol. 2021;191:4-17.
3. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. N Engl J Med. 2020;382:2475-7.
4. Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. Am J Transplant. 2020;20:3140-8.
5. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. J Nephrol. 2020;33:1213-8.
6. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704.
7. Basic-Jukic N, Juric I, Furic-Cunko V, Katalinic L, Radic J, Bosnjak Z, et al. Follow-up of renal transplant recipients after acute COVID-19—a prospective cohort single-center study. Immun Inflamm Dis. 2021;9:1563-72.
8. Kant S, Menez SP, Hanouneh M, Fine DM, Crews DC, Brennan DC, et al. The COVID-19 nephrology compendium: AKI, CKD, ESKD and transplantation. BMC Nephrol. 2020;21:449.
9. Boudhabhay I, Rabant M, Roumenina LT, Coupry L-M, Poillerat V, Marchal A, et al. Case report: adult post-COVID-19 multisystem inflammatory syndrome and thrombotic Microangiopathy. Front Immunol. 2021;12:680567.
10. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and solid organ transplantation: a review article. Transplantation. 2021;105:37-55.
11. Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, et al. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. Clin Nutr ESPEN. 2020;40:214-9.
12. Anker MS, Landmesser U, Haehling S, Butler J, Coats AJS, Anker SD. Weight loss, malnutrition, and cachexia in COVID-19: facts and numbers. J Cachexia Sarcopenia Muscle. 2021;12:9-13.
13. di Filippo L, de Lorenzo R, D'Amico M, Sofia V, Roveri L, Mele R, et al. COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: a post-hoc analysis of a prospective cohort study. Clin Nutr. 2021;40:2420-6.
14. Abu Jawdeh BG. COVID-19 in kidney transplantation: outcomes, immunosuppression management, and operational challenges. Adv Chronic Kidney Dis. 2020;27:383-9.
15. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. JAMA. 2020;324.
16. Granata S, Carratù P, Stallone G, Zaza G. mTOR-inhibition and COVID-19 in kidney transplant recipients: focus on pulmonary fibrosis. Front Pharmacol. 2021;12:710543.
17. Heron VC, Bach C-AT, Holmes NE, Whitlam JB. Complete recovery from COVID-19 of a kidney-pancreas transplant recipient: potential benefit from everolimus? BMJ Case Rep. 2021;14:e238413.
18. Iannaccone G, Scacciavillani R, Del Buono MG, Camilli M, Ronco C, Lavie CJ, et al. Weathering the cytokine storm in COVID-19: therapeutic implications. Cardiorenal Med. 2020;10:277-87.
19. Billett HH, Reyes-Gil M, Szymanski J, Ikemura K, Stahl LR, Lo Y, et al. Anticoagulation in COVID-19: effect of enoxaparin, heparin, and Apixaban on mortality. Thromb Haemost. 2020;120:1691-9.
20. Kinaneh S, Khamaysi I, Karram T, Hamoud S. Heparanase as a potential player in SARS-CoV-2 infection and induced coagulopathy. Biosci Rep. 2021;41:BSR20210290.
21. Lishman J, Kohler C, de Vos C, van der Zalm MM, Itana J, Redfern A, et al. Acute appendicitis in multisystem inflammatory syndrome in children with COVID-19. Pediatr Infect Dis J. 2020;39:e472-3.
22. Subramaniam A, Lim ZJ, Ponnapa Reddy M, Shekar K. A systematic review and meta-analysis of the characteristics and outcomes of readmitted <scp>COVID</scp> −19 survivors. Intern Med J. 2021;51:1773-80.
23. Bowles KH, McDonald M, Barrón Y, Kennedy E, O'Connor M, Mikkelsen M. Surviving COVID-19 after hospital discharge: symptom, functional, and adverse outcomes of home health recipients. Ann Intern Med. 2021;174:316–25.
24. Lenehan PJ, Ramudu E, Venkatakrishnan AJ, Berner G, McMurry R, O'Horo JC, et al. Anemia during SARS-CoV-2 infection is associated with rehospitalization after viral clearance. iScience. 2021;24:102780.
25. Moreno-Pérez O, Merino E, Leon-Ramirez J-M, Andres M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. J Infect. 2021;82:378-83.
26. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397:220-32.

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