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LETTER TO THE EDITORS

Vulnerabilities in kidney transplant recipients with COVID-19: a single center experience

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Dear Editors,

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has led to a stepwise scale-down of transplant care with an observed increase in waitlist mortality for patients with end-stage-renal-disease (ESRD) [1]. Reports on coronavirus disease-2019 (COVID-19) populations suggest that organ transplant recipients have an age-adjusted hazard of more than four for COVID-19 mortality but specific vulnerabilities and risk factors are missing [2]. Consequently, transplant centers have begun to carefully resume activity at the end of the first wave, but the impact of subsequent waves remains unknown. In a recent simulation study in the United States continuation of kidney transplantation had a survival benefit over delayed transplantation in most scenarios where case fatality rates did not exceed fifty percent [3]. However, specific risk factors for COVID-19 mortality were not taken into account as many are still unknown. It is therefore paramount to learn from the first wave and identify specific vulnerabilities to further guide decision making for the remaining pandemic.

With this letter, we aim to increase awareness on possible factors associated with COVID-19 mortality in kidney transplant recipients (KTRs) by describing differences between survivors and non-survivors.

All known KTRs of our program, who contracted COVID-19, were included from the 1st of March 2020 until the 4th of May 2020 and were followed for 30 days after diagnosis. Diagnosis was established by positive nucleic antigen testing (NAT) for SARS-nCoV-2 from a nasopharyngeal, throat, or combined swabs in patients with clinical suspicion of COVID-19. No pre-emptive or "asymptomatic" swabs were done in our population. Antiviral treatment was initiated, and immunosuppressive drugs adjusted in accordance with opinion-based guidelines [4]. Data on demographics, clinical findings, and treatment were extracted from electronic patient files. Frailty was evaluated by the Rockwood clinical frailty scale based on pre-existent functioning during the prior year [5]. This scale ranges from very fit (1) to terminally ill (9) (Table S1). Comparisons between survivors and non-survivors were investigated by Chi square, Mann–Whitney *U* test in case data had a non-normal distribution and unpaired t test for data with a normal distribution.

A total of 15 KTRs from our transplant program were diagnosed with COVID-19. We identified nine (60%) survivors and six (40%) non-survivors. Findings, with a breakdown per outcome, are shown in Table 1.

There were no differences in symptoms and quick sequential organ failure assessment scores (qSOFA) in surviving patients compared to non-surviving patients.

Median age of the surviving KTRs was 51 years compared to 66 years for the non-surviving patients ($P = 0.095$). Number of years after transplantation tended lower in surviving patients compared to non-surviving patients, 7 vs. 10 years ($P = 0.064$). Percentage of patients, who underwent dialysis prior to transplantation was equal in both groups. However, duration of dialysis prior to transplantation was 2.5 years for surviving patients compared to 3.6 years for non-surviving patients ($P = 0.09$). Surviving patients were a median of 10 years after first dialysis (i.e. renal replacement vintage – RRV) compared to non-surviving patients, who were a median of 16 years ($P = 0.03$). Median number of comorbid conditions was lower in the surviving than in non-surviving patients (1 vs. 3; n.s.). Median Rockwood Clinical Frailty Score was five in non-surviving patients compared to two in the surviving patients ($P = 0.008$).

Acute kidney injury was more often present in non-surviving patients compared to surviving patients (83% vs. 22%; $P = 0.02$). D-dimer levels were not consistently evaluated during the beginning of the pandemic.

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Table 1. Patient characteristics.

	Population (N = 15)	Survivors (N = 9)	Non-survivors (N = 6)	P-value[‡]
Age	56 (49–72)	51 (40–64)	66 (55–74)	0.095
Gender (male)	9 (60%)	6 (67%)	3 (50%)	
Years after transplantation	8 (5–11)	7 (4–9)	10 (6–21)	0.079
Dialysis prior to transplantation	12 (80%)	7 (78%)	5 (83%)	
Years of dialysis pre-transplantation	3.1 (2.1–4.5)	2.5 (0.6–3.5)	3.6 (2.8–6.1)	0.09
Years after first dialysis	11 (7–16)	10 (5–11)	16 (11–25)	0.03
Time from symptom onset to presentation in-hospital (days)	7 (4–10)	7 (6–11)	4 (1–9)	
Co-morbidities				
Hypertension	14 (93%)	8 (89%)	6 (100%)	
Diabetes mellitus	4 (27%)	2 (22%)	2 (33%)	
Obesity	2 (13%)	1 (11%)	1 (17%)	
Cardiovascular disease*	6 (40%)	3 (33%)	3 (50%)	
Chronic lung disease	2 (13%)	1 (11%)	1 (17%)	
Malignancy	3 (20%)	1 (11%)	2 (33%)	
Smoking	1 (7%)	n.a.	1 (17%)	
Use of antihypertensive drugs	8 (53%)	4 (44%)	4 (67%)	
ACE inhibitor	3 (20%)	1 (11%)	2 (33%)	
ARB	6 (40%)	4 (44%)	2 (33%)	
Rockwood frailty scale	4 (2–5)	2 (2–4)	5 (5–6)	0.008
qSOFA score	0 (0–1)	0 (0–1)	1 (0–1)	
Symptoms				
Fever	6 (40%)	4 (44%)	2 (33%)	
Temp. (°C)	37.6 (36.9–38.5)	37.4 (36.5–38.9)	38.0 (36.9–38.4)	
Cough	9 (60%)	6 (67%)	3 (50%)	
Dyspnea	14 (93%)	9 (100%)	5 (83%)	
G-I complaints	5 (33%)	2 (22%)	3 (50%)	
Headache	3 (20%)	3 (33%)	n.a.	
Immunosuppression				
TAC	9 (60%)	7 (78%)	2 (33%)	0.085
CsA	3 (20%)	n.a.	3 (50%)	0.018
EVL	1 (7%)	1 (11%)	n.a.	
MMF	9 (60%)	5 (56%)	4 (67%)	
AZA	1 (7%)	1 (11%)	n.a.	
Pred.	13 (87%)	7 (78%)	6 (100%)	
Duo-therapy	9 (60%)	6 (67%)	3 (50%)	
Triple-therapy	6 (40%)	3 (33%)	3 (50%)	
Blood tests at hospital admission				
Leukocytes ($\times 10^9$/l)	6.90 (4.72–7.79)	5.25 (4.50–7.64)	7.05 (4.61–8.94)	
Leukocytes <4	1 (7%)	1 (11%)	n.a.	
Lymphocytes ($\times 10^9$/l)	0.72 (0.48–0.83)	0.7 (0.21–1.48)	0.78 (0.53–0.83)	

Table 1. Continued.

	Population (N = 15)	Survivors (N = 9)	Non-survivors (N = 6)	P-value‡
Lymphocytes <1	12 (80%)	6 (67%)	6 (100%)	0.186
Thrombocytes ($\times 10^9$/l)	184 (167–247)	183 (168–216)	182 (150–248)	
Thrombocytes <150	2 (13%)	1 (11%)	1 (17%)	
LDH (U/l)	298 (208–363)	235 (185–397)	300 (247–338)	
CRP (mg/l)	65 (40–104)	60.2 (36.3–208.4)	65.0 (43.0–112.5)	
Creatinine (g/dl)	1.43 (1.15–2.23)	1.43 (1.11–2.81)	1.68 (1.04–2.57)	
eGFR (ml/min/1.73 m^2)	42 (21–62)	44 (21–76)	38 (26–62)	
AST (U/l)	28 (20–51)	21 (18–83)	35 (20–47)	
ALT (U/l)	22 (10–48)	18 (9–67)	21 (16–29)	
CK (U/l)	67 (50–182)	97 (52–13 000)	57 (42–513)	
X ray and CT abnormalities	13 (87%)	8 (89%)	5 (83%)	
Other affected organs†				
Kidney	7 (47%)	2 (22%)	5 (83%)	0.02
Heart	2 (13%)	n.a.	2 (33%)	0.063
Liver	4 (27%)	2 (22%)	2 (33%)	
Hospitalization	15 (100%)	9 (100%)	6 (100%)	
Hospitalization (days)	11 (3–14)	5 (2–16)	11 (7–13)	
ICU stay	6 (40%)	3 (33%)	3 (50%)	
Intubation	5 (33%)	2 (22%)	3 (50%)	

ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AZA, azathioprine; CK, creatinine kinase; CRP, C-reactive protein; CsA., cyclosporine A; EVL, everolimus; G-I, gastrointestinal; LDH, lactate dehydrogenase; MMF, mycophenolate-mofetil; n.a., not applicable; qSOFA, quick sequential organ failure assessment; TAC, tacrolimus; Temp., temperature.

Data presented as median (IQR) for continuous variables and number (percentage) for categorized variables.

*Also including peripheral cardiovascular disease.

†Other affected organs than the lungs: Liver (transaminases >2 times the upper limit of normal), Heart (signs of congestive heart failure/new abnormalities on EKG), Kidney (>25% increase in creatinine compared to baseline).

‡Only P values < 0.200 are listed.

Lymphopenia and cardiac involvement tended to be more frequent in non-surviving patients (100% vs. 67%; $P = 0.168$ and 33% vs. 0%; $P = 0.063$). The incidence of other organ involvement was comparable in both groups.

In surviving patients, 33% were on triple and 67% on dual therapy compared to 50% on both triple and dual therapy in non-surviving patients prior to the pandemic (n.s.).

Remarkably, we observed a mortality rate of 40% which is higher than the 20–28% mortality recently reported in KTRs with COVID-19 [6,7]. Furthermore, all patients required hospital admission. The relatively high mortality rate observed is highly suggestive of selection of the most vulnerable patients who sought medical attention for their symptoms. Only patients with a NAT-proven COVID-19 infection upon presentation were included in this study. Patients with milder symptoms, not seeking medical attention, have undoubtedly been missed due to restricted testing policy in the beginning of the pandemic in the Netherlands.

Our cohort is not suited to make inferences on which immunosuppression regiment or adjustment is best for patients with COVID-19, and thus, no conclusions can be drawn on its effect. Baseline differences in immunosuppression in our population likely reflect a transplant era effect in line with the observation that non-survivors tended to be transplanted longer ago.

There is limited evidence favoring any particular antiviral treatment. A statement on the preferred antiviral treatment on our data cannot be made due to a lack of power.

Importantly, frailty before COVID-19 seems a factor associated with mortality [8]. In line with this observation, years after first dialysis and number of years of dialysis pre-transplantation (RRV) were also found to be associated with mortality, possibly acting as a surrogate marker for biological rather than calendar age. The latter was not significantly different between survivors and non-survivors. Our findings are in line with previous reports of the general population and solid organ transplant recipients, in which elderly and patients with comorbid conditions were at increased risk [8–10].

Both frailty scores and RRV, together with recent findings of the U.S simulation study, may support policy to carefully re-initiate transplantation for younger, less frail and pre-emptive patients when incidence rates of infection are below a certain threshold. The role and impact of both frailty and renal replacement vintage should be investigated further in large-scale cohorts and prediction models that include patients with end-stage-renal-disease to help identify individuals that would benefit from direct or delayed transplantation during the pandemic.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Rockwood clinical frailty scale.

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