LETTER TO THE EDITORS

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

Soufian Meziyerh1,2, Danny van der Helm2 & Aiko P. J. de Vries1,2

1 Division of Nephrology, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands
2 LUMC Transplant Center, Leiden University Medical Center, Leiden, The Netherlands
E-mail: s.meziyerh@lumc.nl

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 preemptive 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.

| Outcome | Number of Survivors | Number of Non-Survivors | P-value |
|---------|---------------------|-------------------------|---------|
| Acute kidney injury | 9 (60%) | 7 (40%) | 0.02 |
| Median age | 51 years | 66 years | 0.095 |
| Number of years after transplantation | 7 vs. 10 years | 0.064 |
| Median number of comorbid conditions | 1 vs. 3 | n.s. |
| Median Rockwood Clinical Frailty Score | 2 vs. 5 | 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.
|                  | 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 (x10^9/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 (x10^9/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 (×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 m²)         | 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%)               | 0.02     |
| 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 regimen 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.

Funding

The authors declare no funding was received for this manuscript.

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.

REFERENCES

1. Kumar D, Manuel O, Natori Y, et al. COVID-19: a global transplant perspective on successfully navigating a pandemic. Am J Transplant 2020; 20: 1773.
2. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020; 584: 430.
3. Massie AB, Boyarsky BJ, Werbel WA, et al. Identifying scenarios of benefit or harm from kidney transplantation during the COVID-19 pandemic: a stochastic simulation and machine learning study. Am J Transplant 2020. [Epub ahead of print]. https://doi.org/10.1111/ajt.16117
4. Maggiore U, Abramowicz D, Crespo M, et al. How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion. Nephrol Dial Transplant 2020; 35: 899.
5. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173: 489.
6. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int* 2020; 97: 1083.

7. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med* 2020; 382: 2475.

8. Hoek RAS, Manintveld OC, Betjes MGH, et al. Covid-19 in solid organ transplant recipients: a single center experience. *Transplant Int* 2020. [Epub ahead of print]. https://doi.org/10.1111/tri.13662

9. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054.

10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497.