COVID-19 related mortality in kidney transplant and hemodialysis patients: a comparative, prospective registry based study

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ABSTRACT

Background. COVID-19 has exposed hemodialysis patients and kidney transplant recipients to an unprecedented life-threatening infectious disease raising concerns about kidney replacement therapy (KRT) strategy during the pandemic. The present study investigated the association of type of KRT with COVID-19 severity adjusting for differences in individual characteristics.

Methods. Data on kidney transplant recipients and hemodialysis patients diagnosed with COVID-19 between February 1st and December 1st 2020 were retrieved from ERACODA. Cox regression models adjusted for age, sex, frailty and comorbidities were used to estimate hazard ratios (HR) for 28-day mortality risk in all patients and in the subsets who were tested because of symptoms

Results. In total, 1,670 patients (496 functional kidney transplant and 1,174 hemodialysis) were included. 16.9% of kidney transplant and 23.9% of hemodialysis patients died within 28 days of presentation. The unadjusted 28-day mortality risk was 33% lower in kidney transplant recipients compared with hemodialysis patients (HR: 0.67, 95%CI: 0.52-0.85). In a fully adjusted model, the risk was 78% higher in kidney transplant recipients (HR: 1.78, 95%CI: 1.22-2.61) compared with hemodialysis patients. This association was similar in patients tested because of symptoms (fully adjusted model HR: 2.00, 95%CI: 1.31-3.06). This risk was dramatically increased during the first post-transplant year. Results were similar for other endpoints (e.g. hospitalization, ICU admission, mortality beyond 28 days) and across subgroups.

Conclusions. Kidney transplant recipients had a greater risk of a more severe course of COVID-19 compared with hemodialysis patients; they therefore require specific infection mitigation strategies.

Keywords: COVID-19, dialysis, kidney, mortality, transplantation

KEY LEARNING POINTS

What is already known about this subject?

Kidney failure patients represent a vulnerable population for COVID-19 raising concerns about kidney replacement therapy strategy during the pandemic.

What this study adds?

This study demonstrate that the mortality risk is higher in kidney transplant after adjustment for comorbidities compared with hemodialysis patients. The mortality risk is dramatically increased during the first post-transplant year.

What impact this may have on practice or policy?

Kidney transplant recipients with COVID-19 should be closely monitored; they need intensification of infection mitigation strategies and prioritization in effective and safe COVID-vaccine distribution. Postponing transplantations may be justified in some instances, especially during the highly active phase of the pandemic.

INTRODUCTION

Since the start of the pandemic in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has exposed patients treated with kidney replacement therapy (KRT) to an unprecedented life-threatening infectious disease: COVID-19.[1,2] In-center hemodialysis are at higher risk for COVID-19 related mortality, independent from known risk factors such as obesity, ischemic heart disease and lung disease.[2] Kidney transplant recipients also represent a vulnerable population for viral diseases because of their immunosuppressive agents and are at specifically high risk for COVID-19 related mortality.[3]

COVID-19 reported case fatality rates vary greatly per country owing to differences in public health policy, case ascertainment and testing capacity.[4,5] In the European Renal Association COVID-19 registry, that included 4,298 kidney failure patients, 28-day mortality was 20.0% in 3,285 patients receiving dialysis and 19.9% in 1,013 recipients of a transplant.[6] The ERACODA database (1,073 patients) reported a 28-day case fatality rate of 25.0% in 768 dialysis patients and 21.3% in 305 kidney transplant recipients during the first wave.[7] Other reports based on regional or national registries have also suggested lower mortality in kidney transplant than in hemodialysis patients.[8,9] These data raise the question whether there is an effect of type of KRT in COVID-19 related outcomes. It should be noted that dialysis patients are in general older and have a higher prevalence of comorbid conditions than kidney transplant recipients. When analyzing the association of type of KRT with outcome, analyses should be adjusted for such differences in baseline characteristics.

When comparing COVID-19 mortality rates in dialysis patients versus kidney transplant recipients, another complicating factor is the way how patients were diagnosed to have COVID-19. In hemodialysis units screening for COVID-19 may rely not only on symptoms but also as part of routine surveillance or screening after contact, whereas transplant patients are most often tested because they presented with symptoms.

Given these considerations we aimed in the present study to determine whether hemodialysis or kidney transplantation are associated with mortality in kidney failure patients with COVID-19 while accounting for comorbidities and the reason for COVID-19 testing.

MATERIALS AND METHODS

Study design and participants

For this study we used data from ERACODA.[10] This database was established in March 2020 and currently involves cooperation of approximately 200 physicians representing over 130 centers in 31 countries, mostly in Europe. Data was collected on adult (> 18 years) patients with kidney failure, either on hemodialysis or living with a functioning kidney allograft, who were diagnosed with COVID-19 based on a positive result on a real-time polymerase chain reaction assay of nasal and/or pharyngeal swab specimens, and/or compatible findings on CT scan or chest X-ray of the lungs. Data are voluntarily reported from outpatients and hospitalized patients by physicians responsible for the care of these patients.

The ERACODA database is hosted at the University Medical Center Groningen, the Netherlands. Data is recorded using REDCap software (Research Electronic Data Capture, Vanderbilt University Medical Center, Nashville, TN, USA) for data collection.[11] Patient information is stored pseudonymized. The study was approved by the Institutional Review Board of the University Medical Center Groningen (Netherlands) who deemed the collection and analysis of data exempt from ethics review regarding the Medical Research Involving Human Subjects Act (WMO).

Data collection

Detailed information was collected on patient (age, sex, ethnicity, frailty, comorbidities, hospitalization and medication use) and COVID-19 related characteristics (reason for COVID-19 screening, symptoms, vital signs and laboratory test results) at presentation. Frailty was assessed using the Clinical Frailty Score developed by Rockwood et al.[12] This score is widely used in non-COVID-19 epidemiological studies and ranges from 1, representing very fit, to a score of 9, representing terminally ill. Comorbidities were recorded from patient charts and obesity was defined as a Body Mass Index >30 kg/m^2. Kidney function was assessed by estimating glomerular filtration rate (eGFR) from serum creatinine at presentation using the CKD-EPI equation. Among dialysis patients, eGFR was assumed to be

0 for those with residual diuresis ≤200 ml/day, and 5 ml/min/1.73m^2 for those with residual diuresis >200 ml/day. The primary outcome was vital status at day 28 and the secondary outcomes were hospitalization, Intensive Care Unit (ICU) admission and in-hospital mortality within 28 days after presentation.

Statistical analysis

Baseline characteristics are presented for the total population, for transplant recipients and dialysis patients separately, and by reason for COVID-19 testing i.e. the presence of symptoms versus contact with a COVID-19 positive person/routine screening of patients who may have been asymptomatic. Continuous data are presented as mean ± standard deviation (SD) or as median and interquartile range in case of a non-normal distribution of data. Categorical data are presented as percentages. Characteristics were compared between groups using student's t-test for continuous variables (Mann-Whitney U-test for non-normally distributed data) and Pearson chi-2 statistics for categorical variables.

The associations of type of KRT (kidney transplantation vs. hemodialysis) with the primary and secondary outcomes were examined in the total population and by reason for COVID-19 testing. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional-hazards regression models. To account for the competing risk of mortality, cause-specific hazards were calculated for hospitalization and ICU admission.

Multiple models were constructed to account for potential confounders in a stepwise manner. Model 1 is a crude (unadjusted) model. In Model 2, we adjusted for age (continuous) and sex (male/female) and in model 3 we additionally adjusted for clinical frailty score. In model 4, we additionally adjusted for factors known to be associated with COVID-19 outcome, i.e. smoking (never, current, former), obesity (yes/no), hypertension (yes/no), diabetes (yes/no), heart failure (yes/no) and chronic lung disease (yes/no). In the final model (model 5), we further adjusted for time since the start of any KRT (continuous) and kidney function. The proportional-hazards assumption was investigated by testing interaction of log(time) with individual covariates.

All multivariable models were based on datasets constructed using multiple imputation to account for missing data. For 210 patients (13%) information was missing on clinical frailty score, for 235 on obesity (14%), for 249 (15%) on serum creatinine (required to calculate eGFR) and for 73 patients (4%) on duration of kidney failure. The proportion of missingness for clinical frailty score (13.1% vs. 11.3%, p=0.30) and obesity (13.0% vs. 16.5%, p=0.06) was similar for hemodialysis patients and kidney transplant recipients, while serum creatinine was missing more often in hemodialysis patients (16.5% vs. 11.1%, p=0.004) and duration of kidney disease was missing more often in transplant recipients (2.5% vs. 8.9%, p<0.001). To account for missing information, multiple imputation was performed with the chained equations method using all variables included in Model 4. Fully conditional specification was employed, meaning that data from available cases was used and that each variable with missing values was imputed using a regression model conditional on all of the other variables specified in the imputation model.[13,14] In total, 10 imputed datasets were created with 100 interactions. For the pooled coefficient and standard error Rubin´s Rules was used.[15]

To examine the robustness of our findings, we performed several sensitivity analyses, which are described in the supplementary material.

All analyses were performed using Stata version 14.0 (College Station, TX). A 2-sided - value less than 0.05 indicated statistical significance.

RESULTS

A total of 2,575 KRT patients who were diagnosed with COVID-19 between February 1st and December 1st, 2020 were included. After excluding patients on peritoneal dialysis due to their low number (n=99) and patients with missing information on the type of KRT (n=83), day 28 vital status (115 kidney transplant recipients and 221 dialysis patients) and/or the reason for COVID-19 screening (156 kidney transplant recipients and 433 dialysis patients), there were 1,670 patients left for the analyses. Of them, 496 were kidney transplant recipients and 1,174 hemodialysis patients (Figure S1).

Patient characteristics

The mean age of kidney transplant recipients was 56 years, which was 10 years younger than those on hemodialysis (Table 1). Overall, 62% were male and 85% were white/Caucasian, which was not different for the two groups. The prevalence of diabetes mellitus, coronary artery disease, heart failure, chronic lung disease and current or former smoking was higher in hemodialysis patients, who also had a higher clinical frailty score. Eighty-five percent of the kidney transplant recipients were diagnosed with COVID-19 after being tested because of symptoms, whereas this was the case in 61% of the hemodialysis patients. Hemodialysis patients were more frequently diagnosed with COVID-19 as a result of a routine screening or because of a COVID-19 contact while being asymptomatic. Consequently, more kidney transplant recipients than hemodialysis patients presented with symptoms like cough, shortness of breath, headache, nausea or vomiting, diarrhea, myalgia or arthralgia, and fever. Although their O_2 saturation at presentation was similar to those of hemodialysis patients, kidney transplant recipients had a higher temperature, respiration rate, pulse rate and C-reactive protein (CRP) levels. Kidney transplant recipients more often used RAAS inhibitors than hemodialysis patients and all of them were on immunosuppression (Table 1).

Among patients tested because of symptoms, transplant recipients generally had a higher prevalence of COVID-19-related symptoms compared with hemodialysis patients (Table 2). In comparison with those identified by routine screening, hemodialysis patients with COVID-19 identified by

testing because of symptoms were older and had more comorbidities, whereas symptomatic kidney transplant recipients had similar comorbidities. In both patient groups those with symptoms had higher CRP levels (Table S1).

Patient Survival

28-day probability of death in kidney transplant recipients was 16.9% (95% CI: 13.9-20.5%), which was lower than the 23.9% (95% CI: 21.6-26.5%) mortality in the hemodialysis patients. Figure S2 shows the survival for the overall group and for the subgroup of patients identified by screening because of symptoms.

Table 3 and the upper part of Figure 1 show that after adjustment for age and sex the risk for COVID-19 related mortality was higher in kidney transplant recipients when compared to dialysis patients. When additionally adjusting for differences in clinical frailty score, "classical" determinants for COVID-19 mortality (obesity, hypertension, diabetes, heart failure, chronic lung disease, smoking), and duration of kidney failure, mortality risk in kidney transplant recipients was significantly higher when compared to patients on hemodialysis (fully adjusted HR [aHR]: 1.78, 95% CI: 1.22-2.61). In the subgroup of patients that were diagnosed with COVID-19 because they were tested based on having symptoms the risk of death was similarly higher in kidney transplant recipients (aHR: 2.00, 95% CI: 1.31-3.06). Analysis of complete data without multiple imputation confirmed the main results (aHR: 2.42, 95% CI: 1.52-3.86) for transplant recipients compared with dialysis patients (Table S2).

Risk of hospitalization, ICU admission and in-hospital mortality

The risk of hospitalization was higher in kidney transplant recipients compared with hemodialysis patients in the total population (aHR: 1.20, 95% CI: 1.00-1.47) as well as in the subgroup of symptomatic patients (aHR: 1.28, 95% CI: 1.03-1.60) (Table S3). Similarly, the adjusted risk of ICU admission was higher in kidney transplant recipients compared with hemodialysis patients in the total population (aHR: 2.09, 95% CI: 1.33-3.29), and in symptomatic patients 2.10 (95% CI: 1.28-3.45) (Table S4). For the

association of kidney transplantation vs hemodialysis with in-hospital mortality, the aHR was 1.81 (95% CI: 1.19-2.75) in the total population and 2.16 (95% CI: 1.37-3.43) in symptomatic patients (Table S5). Only ~6% of the deaths (n=23) were reported not to be caused by COVID-19. An analysis restricted to COVID-19 related deaths showed results similar to the main results.

Sensitivity analyses

After excluding hemodialysis patients using immunosuppressive agents and/or who previously received a kidney transplant, the aHR for the association of being a kidney transplant recipient (vs. hemodialysis patient) with 28-day mortality was 1.62 (95% CI: 1.09-2.41) in the total population (n=1,541) and 1.68 (95% CI: 1.06-2.65) in the symptomatic group (n=1,051), (Table S6). In an analysis comparing kidney transplant recipients with hemodialysis patients on the kidney transplantation waiting list or in preparation to be listed, the aHR for kidney transplant recipients was 4.81 (95% CI: 2.25-10.29) in the total population (n=703) and 5.48 (95% CI: 2.26-13.27) in the symptomatic group (n=553, Table S7). Taking into account kidney recipients within their first post-transplant year the hazard ratio for 28-day mortality was 10.27 (95% CI: 2.40-43.94) compared to dialysis patients that were on the waiting list or in preparation for kidney transplantation (Table S8). The hazard ratio for kidney recipients in first year of transplantation was 2.17, (95% CI: 0.98-4.82) and was 1.72, (95% CI 1.17-2.53) after the first post-transplant year, compared with all hemodialysis patients (Table S9). Results were also similar to the overall results when analyzing hospitalized patients only (aHR: 1.82, 95% CI: 1.20-2.74 in the total population and 2.20, 95% CI: 1.39-3.47 in the symptomatic group) or when including those with missing information on reason for COVID-19 screening (aHR: 1.74, 95% CI: 1.26-2.42 in the total population and 1.89, 95% CI: 1.24-2.89 in the symptomatic group) (Table S11).

Overall crude mortality (i.e. mortality not limited to the 28 day window) was 19.9% and 27.7% in kidney transplant recipients and hemodialysis patients, respectively. For the risk of overall mortality in kidney transplant recipients (vs. hemodialysis patients), the aHR was 1.87 (95% CI: 1.31-2.67) in the total population and 2.04 (95% CI: 1.37-3.06) in the symptomatic group (Table S12). No significant

interactions in the risk associated with kidney transplantation compared to being on hemodialysis were found between subgroups except for subgroups defined by age (<65/≥65 years) (p=0.02) (Table S13).

DISCUSSION

Since the start of the COVID-19 outbreak, it has been a topic of discussion in the nephrology community whether hemodialysis or kidney transplant patients are more affected by COVID-19 related mortality. Here we present analyses derived from ERACODA, the largest database with comprehensive individual level data of patients on dialysis or living with a kidney transplant infected by SARS-CoV-2 in Europe. Our data indicate that 28-day mortality is higher for kidney transplant recipients compared to hemodialysis patients after adequate adjustment for age, sex, frailty and comorbidities. Stratified analyses limiting the dataset to patients tested because of symptoms, confirmed that kidney transplant recipients have a higher mortality risk. Finally, we show that only very few hemodialysis patients were admitted to the ICU, less than patients with a kidney transplant.

COVID-19 is particularly life threatening in patients on KRT, suggesting that kidney failure creates an environment for a more severe course of disease.[3] In our study, the unadjusted COVID-19 related 28-day mortality rate was 16.9% in transplant recipients and 23.9% in hemodialysis patients. These findings are in line with data from other regional and national registries.[6, 9, 16- 18] These studies also show lower, or a trend towards lower, mortality in kidney transplant patients in a crude analysis compared to hemodialysis patients. This finding is not unexpected because in our study hemodialysis patients were on average ten years older and had more comorbidities. In a region-wide registry study from the Flanders region of Belgium, cumulative mortality was 29.6% versus 14.0% among patients on hemodialysis and kidney transplant recipients, respectively. Adjustment for age alleviated cumulative mortality for dialysis patients (19.9%) and conversely higher mortality for transplant patients (23%).[19] This study demonstrates that adjustment for age is the first step towards obtaining a more reliable comparison of the mortality burden in patients on various modalities of kidney function replacement. In addition, it should be accounted for burden differences in comorbidities. Diabetes, obesity, respiratory and cardiovascular disease are all well identified predictors of COVID-19 related death in the general population [2,5] as well as in kidney failure patients [8, 16, 18], albeit to a lesser extent in these latter patient groups.[20] In a recent study,

Hilbrands et al. showed that clinical frailty score at presentation was the strongest predictor of COVID-19 related mortality in dialysis patients[7], an important patient characteristic that is unfortunately underreported in most studies.

Taking all these data into account, multivariable analysis for mortality was performed in our study with adjustment for age, sex, frailty and other classical determinants for COVID-19 mortality (diabetes, obesity, heart failure, COPD, smoking, hypertension, kidney function and duration of kidney disease). Doing so, we documented a significantly higher risk of mortality (HR 1.78 [1.22-2.61]) in kidney transplant recipients compared with hemodialysis patients. Several previous studies showed similar outcomes in transplant [21] or dialysis patients[22] compared with non-transplant/non-dialysis patients, but these were small studies. In the present study, the main finding was robust in the various sensitivity analyses that we performed. Analysis of overall instead of day 28 mortality showed similar results, as did exclusion of the very few dialysis patients using immunosuppressive treatments and/or had a kidney transplant previously. To account for potential selection bias, we provide an analysis of symptomatic and asymptomatic (contact or routine testing) patients separately; however, due to their small number, we were not confident that we could draw statistically well-founded conclusions for the latter.

We observed that the risk of death associated with being a transplant recipient was considerably higher in patients over 65 years. This may reflect longer kidney disease duration and longer chronic exposure to immunosuppressive agents. However, adjustment for duration of kidney failure did not materially affect our results. It may therefore well be that elderly subjects are more vulnerable to the risk enhancing effect of immunosuppressive agents, just as in the general population.

Under non-COVID-19 circumstances, kidney transplant recipients exhibit lower mortality rates than waitlisted dialysis patients after adjustment for age, sex, race, and cause of renal disease.[23] Similarly, a report of 56 waitlisted dialysis patients and 80 kidney transplant recipients in New York, found that waitlist status was independently associated with COVID-19 related mortality (Odds Ratio: 2.65, 95%CI: 1.18-5.96, p=0.02) and that waitlisted dialysis patients were more likely to require hospitalization (82% vs

65%) than kidney transplant recipients[8]. The French nationwide registry noticed similar findings.[24] The risk of contracting SARS-CoV-2 infection is higher in hemodialysis patients consistent with the difficulties to achieve social distancing while travelling to and from dialysis units. It should therefore be noted that overall risk of mortality could be the same or lower in kidney transplant recipients in case the risk of getting infected is lower in these patients. Previous studies have also reported that though the incidence of COVID-19 was higher in waitlisted dialysis patients as compared to kidney transplant recipients, the mortality rate remained lower.[24-26] This can be accounted for by the fact that many COVID-19 cases in dialysis patients are detected by a general screening policy, even in asymptomatic patients. In the present study, adequate adjusted analysis documents that kidney transplant recipients exhibit a higher mortality rate compared to waitlisted patients.

KRT patients have a frail immunological system. Chronic exposure to uremia alters the immune response in dialysis and kidney transplant recipients. In addition, a kidney transplant recipient requires lifelong immunosuppression, which affects both innate and adaptive immunity. Therefore, in kidney transplant recipients, viral infections are frequent[27] and lead to higher morbidity and mortality when compared to dialysis patients.[28] A role for immunosuppressive agents as the cause for the higher risk for COVID-19 mortality in kidney transplant recipients may be suspected. Indeed, when further examined in our data, patients during the first post-transplant year, i.e. when they are given the strongest immunosuppression, experience dramatically increased COVID-19 related mortality in comparison to waitlisted patients, a finding consistent with other studies [7, 29]. We also investigated the association of intensity and type of immunosuppressant use with mortality in kidney transplant recipients. Patients on dual therapy (vs. triple therapy) and immunosuppression excluding corticosteroids (vs. immunosuppression including corticosteroids) tended to have a lower risk of mortality, but these associations were not statistically significant (Table S14 and Table S15, respectively). Therefore, we are not able to confirm the role of immunosuppressant use in the observed excess risk of mortality in kidney

transplant recipients. However, future studies with larger sample sizes should examine the impact of immunosuppressive treatments on mortality in kidney transplant recipients."

Remarkably, the RECOVERY trial showed that corticosteroids would decrease COVID-19 mortality.[30] However, this concerns a relatively high dose to mitigate the cytokine storm related to a late stage of COVID-19 when ventilator support is needed,[30] whereas it has been shown that chronic low dose corticosteroid exposure is associated with higher influenza-related mortality in patients with various comorbidities,[31] but also with COVID-19-related mortality in patients with rheumatoid arthritis.[32-34]

Supportive care remains the mainstay of treatment for COVID-19. Despite hospitalization and ICU admission thresholds consistent across the centers, kidney transplant recipients were more often hospitalized and admitted to an ICU than hemodialysis patients. Hemodialysis allows facilities to monitor these patients three times a week and may delay or avoid hospitalization. Nevertheless, patients frequently develop symptoms that require admission and intensive care management. In our study, substantial mortality occurred in dialysis patients who were not offered ICU admission compared with kidney transplant recipients (71.1% vs 56.1%, p=0.01). This finding could be explained by advanced care being more frequently planned in hemodialysis patients, but speculatively could also be explained by an expected high risk of death in these patients leading to a restrictive policy for ICU admission. Such a policy of limiting care may have disserved the group of dialysis patients.

The strengths of this study are the completeness of data retrieved from the largest European database of KRT patients with COVID-19. This database encompasses detailed information on demographics, disease characteristics, hospital and ICU admission, and mortality. ERACODA also includes information on comorbidities, frailty, time from onset of kidney failure, reason for COVID-19 screening and mode of COVID-19 diagnosis, all factors important in determining whether a specific KRT impacts mortality risk in kidney failure patients with COVID-19.

Our study also has limitations. First, due to our study design we may not have captured enough asymptomatic cases of COVID-19, especially among kidney transplant recipients. Moreover, the database

might not include all patients in all participating centers. Testing policies may vary between centers and over time, but in general lead to reporting less cases in asymptomatic patients. Despite rapid implementation of telemedicine or scheduled calls in most centers during the pandemic, under-reporting of cases is still possible, particularly for transplant recipients. For these reasons, we also present the results of sensitivity analyses limited to the subset of transplant and hemodialysis patients that were identified in a similar manner (testing because of symptoms or hospitalization). We additionally accounted for any potential center effect. These analyses confirm our main findings. Second, ERACODA does not gather information on in-hospital patient management beyond 48 hours after admission. Change over time in recommendations for supportive care, immunosuppressive treatment and availability of specific therapies may have impacted outcome. Also, analysis taking into account a potential center effect did not show discordant results. Differences in in-hospital patient management between groups are therefore not likely to have had a major impact on our comparative results.

In conclusion, this large European study demonstrates that kidney transplantation dramatically impacts mortality in kidney failure patients with COVID-19. Thus, kidney transplant recipients with COVID-19 should be closely monitored and need intensification of infection mitigation strategies and prioritization of effective and safe COVID-19-vaccine distribution. In addition, these findings suggest that postponing transplantations may be justified, especially during highly active phase of the pandemic. Investigation of the potential effect of immunosuppression on outcome is also urgently needed. Finally, our data indicate that intensive care management should be considered for kidney failure patients based on demographics, comorbidities and disease characteristics, and that the mere fact of being a hemodialysis patient should not discourage physicians to admit such patients to an ICU.

AUTHORS' CONTRIBUTIONS

All authors contributed to data collection, study design, data analysis, interpretation, and drafting of this paper.

ACKNOWLEDGEMENTS

The ERACODA collaboration is an initiative to study prognosis and risk factors for mortality due to COVID-19 in patients with a kidney transplant or on dialysis that is endorsed by the ERA-EDTA. ERACODA is an acronym for European Renal Association COVID-19 Database. The organizational structure contains a Working Group assisted by a Management Team and Advisory Board.

The *ERACODA Working Group* members: Franssen CFM, Gansevoort RT (coordinator), Hemmelder MH, Hilbrands LB and Jager KJ.

The *ERACODA Management Team* members: Duivenvoorden R, Noordzij M, Vart P.

The *ERACODA Advisory Board* members: Abramowicz D, Basile C, Covic A, Crespo M, Massy ZA, Mitra S, Petridou E, Sanchez JE, White C.

Data Sharing Statement: Collaborators that entered data in ERACODA remain owner of these data. The database can therefore not be disclosed to any third party without the prior written consent of all data providers, but the database will be made available to the editorial offices of medical journals when requested. Research proposals can be submitted to the Working Group via COVID.19.KRT@umcg.nl. If deemed of interest and methodological sound by the Working Group and Advisory Board, the analyses needed for the proposal will be carried out by the Management Team.

We thank all people that entered information in the ERACODA database for their participation, and especially all healthcare workers that have taken care of the included COVID-19 patients.

CONFLICT OF INTEREST STATEMENT

Unrestricted research grants were obtained from the European Renal Association (ERA-EDTA), the Dutch Kidney Foundation, Baxter and Sandoz. Neither organization had any role in the design of the study, interpretation of results nor in writing of the manuscript.

FUNDING

ERACODA received unrestricted research grants from ERA-EDTA, the Dutch Kidney Foundation, Baxter and Sandoz.

SUPPLEMENTAL MATERIAL – TABLE OF CONTENTS

Table S1: Baseline characteristics of study population by type of kidney replacement therapy and reason for COVID-19 screening

Table S2: Association of kidney transplantation (KT) (vs. hemodialysis (HD)) with incidence of 28-day mortality, overall and by reason for COVID-19 screening without multiple imputation (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S3: Association of kidney transplantation (vs. hemodialysis) with incidence of hospitalization, overall and by reason for COVID-19 screening (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S4: Association of kidney transplantation (vs. hemodialysis) with incidence of ICU admission, overall and by reason for COVID-19 screening (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S5: Association of kidney transplantation (vs. hemodialysis) with incidence of in-hospital mortality, overall and by reason for COVID-19 screening (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S6: Association of kidney transplantation (vs. hemodialysis) with incidence of 28-day mortality, overall and by reason for COVID-19 screening (excluding hemodialysis patients that were using immunosuppressant and/or had kidney transplant previously) (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S7: Association of kidney transplantation (vs. hemodialysis) with incidence of 28-day mortality, overall and by reason for COVID-19 screening (among hemodialysis patients that were on waiting list or in preparation for kidney transplantation) (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S8: Association of kidney transplantation according to transplant duration (vs. hemodialysis) with incidence of 28-day mortality, overall and by reason for COVID-19 screening screening (among hemodialysis patients that were on waiting list or in preparation for kidney transplantation vs patients with kidney transplantation for ≤1year) (presented are hazard ratios (HR) with 95% confidence intervals (CI))

Table S9 Association of kidney transplantation according to transplant duration (vs. hemodialysis) with incidence of 28-day mortality, overall and by reason for COVID-19 screening (presented are hazard ratios (HR) with 95% confidence intervals (CI))

Table S10: Association of kidney transplantation (vs. hemodialysis) with incidence of 28-day mortality, overall and by reason for COVID-19 screening (among hospitalized patients only) (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S11: Association of kidney transplantation (vs. hemodialysis) with incidence of 28-day mortality, overall and by reason for COVID-19 screening (including those with missing information on reason for COVID-19 screening) (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S12: Association of kidney transplantation (vs. hemodialysis) with incidence of overall mortality (i.e. mortality not limited to the 28 day window), overall and by reason for COVD-19 screening (presented as hazard ratios (HR) with 95 % confidence intervals (CI))

Table S13: Association of kidney transplantation (vs. hemodialysis) with incidence of 28-day mortality across subgroups of age (<65/≥65 years), sex (female/male), duration of kidney disease (<5/≥5 years), diabetes (yes/no) and hypertension (yes/no)

Table S14: Association of amount of immunosuppressants with 3-months vital status among transplant patients in ERACODA (Presented are hazard ratio with 95% Confidence Interval)

Table S15: Association of type of immunosuppressants with 3-months mortality among transplant patients in ERACODA (Presented are hazard ratio with 95% Confidence Interval)

Figure S1: Flow chart of patient inclusion

Figure S2: Kaplan-Meier estimates of survival in hemodialysis patients and kidney transplant patients in the total population (panel A) and in the subset of patients that were screened for COVID-19 based on symptoms only (panel B)

REFERENCES

1) Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al.: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 28: 1054-1062, 2020. doi: 10.1016/S0140-6736(20)30566-3
2) Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al.: Factors associated with COVID-19-related death using OpenSAFELY. Nature 584: 430-436, 2020 doi: 10.1038/s41586-020-2521-4
3) Gansevoort RT, Hilbrands LB: CKD is a key risk factor for COVID-19 mortality. Nat Rev Nephrol 16:705-706, 2020. doi: 10.1038/s41581-020-00349-4
4) https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea Accessed on March 19, 2021
5) Wu Z, McGoogan JM: Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 323: 1239–1242, 2020. doi: 10.1001/jama.2020.2648
6) Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Álvarez JE, Garneata L, et al.: Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int 98: 1540-1548, 2020. doi: 10.1016/j.kint.2020.09.006
7) 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 35: 1973-1983, 2020. doi: 10.1093/ndt/gfaa261
8) Craig-Schapiro R, Salinas T, Lubetzky M, Abel BT, Sultan S, Lee JR, et al.: COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. Am J Transplant 21(4):1576-1585 2021. doi: 10.1111/ajt.16351
9) Sánchez-Álvarez JE, Pérez Fontán M, Jiménez Martín C, Blasco Pelícano M, Cabezas Reina CJ, Sevillano Prieto ÁM, et al.: SARS-CoV-2 infection in patients on renal replacement therapy. Report of the COVID-19 Registry of the Spanish Society of Nephrology (SEN). Nefrologia 40: 272-278, 2020. doi: 10.1016/j.nefro.2020.04.002
10) Noordzij M, Duivenvoorden R, Pena MJ, de Vries H, Kieneker LM, et al.: ERACODA: the European database collecting clinical information of patients on kidney replacement therapy with COVID-19. Nephrol Dial Transplant 35: 2023–2025, 2020. doi: 10.1093/ndt/gfaa179
11) Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al.: The REDCap consortium: Building an international community of software partners. J Biomed Inform 95: 103208, 2019. doi: 10.1016/j.jbi.2019.103208
12) Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CanMed Assoc: 173: 489–495. 2005. doi: 10.1503/cmaj.050051.
13) Liu Y, De A: Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. Int J Stat Med Res 4: 287-295, 2015. doi: 10.6000/1929-6029.2015.04.03.7.
14) Lee KJ, Carlin JB: Multiple Imputation for Missing Data: Fully Conditional Specification Versus Multivariate Normal Imputation. Am J Epidemiol 171: 624-632, 2010. doi: 10.1093/aje/kwp425
15) Little R, Rubin D. Statistical analysis with missing data. 1st ed. New York, NY: John Wiley; 1987.
16) Couchoud C, Bayer F, Ayav C, Béchade C, Brunet P, Chantrel F, et al.: Low incidence of SARS-CoV-2, risk factors of mortality and the course of illness in the French national cohort of dialysis patients. Kidney Int 98: 1519-1529, 2020. doi: 10.1016/j.kint.2020.07.042
17) 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 20: 3140-3148, 2020. doi: 10.1111/ajt.16185

18) Elias M, Pievani D, Randoux C, Louis K, Denis B, Delion A, et al.: COVID-19 infection in kidney transplant recipients: disease incidence and clinical outcomes. J Am Soc Nephrol 31: 2413-2423, 2020. doi: 10.1681/ASN.2020050639
19) De Meester J, De Bacquer D, Naesens M, Meijers B, Couttenye MM, De Vriese AS, et al.: Incidence, characteristics, and outcome of COVID-19 in adults on kidney replacement therapy: A regionwide registry study. J Am Soc Nephrol 32(2):385-396, 2021. doi: 10.1681/ASN.2020060875
20) ERA-EDTA Council, ERACODA Working Group: Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. Nephrol Dial Transplant 36: 87-94, 2021. doi: 10.1093/ndt/gfaa314
21) Sharma P, Chen V, Fung CM, Troost JP, Patel VN, Combs M, et al.: COVID-19 Outcomes Among Solid Organ Transplant Recipients: A Case-control Study. Transplantation. 105(1):128-137, 2021. doi: 10.1097/TP.0000000000003447
22) Chan L, Jaladanki SK, Somani S, Paranjpe I, Kumar A, Zhao S, et al.: Outcomes of Patients on Maintenance Dialysis Hospitalized with COVID-19. Clin J Am Soc Nephrol. 16(3):452-455, 2021. doi: 10.2215/CJN.12360720.
23) Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al.: Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant 11: 2093-2109, 2011. doi: 10.1111j.1600-6143.2011.03686.x
24) Thaunat O, Legeai C, Anglicheau D, Couzi L, Blancho G, Hazzan M, et al.: French nationwide Registry of Solid Organ Transplant Recipients with COVID-19. IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT). Kidney Int 98: 1568-1577, 2020. doi: 10.1016/j.kint.2020.10.008
25) Ravanan R, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, et al.: SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: A national cohort study. Am J Transplant 20: 3008-3018, 2020. doi: 10.1111/ajt.16247
26) Mohamed IH, Chowdary PB, Shetty S, Sammartino C, Sivaprakasam R, Lindsey B, et al.: Outcomes of renal transplant recipients with SARS-CoV-2 infection in the eye of the storm: A comparative study with waitlisted patients. Transplant 105: 115-120, 2021. doi : 10.1097/TP.0000000000003406
27) Fishman JA: Infection in organ transplantation. Am J Transplant 17: 856-879, 2017. doi: 10.1111/ajt.14208
28) Manuel O, López-Medrano F, Keiser L, Welte T, Carratalà J, Cordero E, et al.: Influenza and other respiratory virus infections in solid organ transplant recipients. Clin Microbiol Infect 20 Suppl 7: 102-108, 2014. doi: 10.1111/1469-0691.12595.
29) Clarke C, Lucisano G, Prendecki M, Gleeson S, Martin P, Ali M, McAdoo SP, et al.: Informing the risk of kidney transplantation versus remaining on the waitlist in the coronavirus disease 2019 era. Kidney Int Rep 6: 46-55, 2021. doi: 10.1016/j.ekir.2020.10.032
30) RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al.: Dexamethasone in hospitalized patients with Covid-19 - Preliminary report. N Engl J Med 25;384(8):693-704, 2021. doi: 10.1056/NEJMoa2021436.
31) Lee N, Leo YS, Cao B, Chan PK, Kyaw WM, Uyeki TM, et al.: Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients. Eur Respir J 45: 1642-1652, 2015. doi: 10.1183/09031936.00169714
32) Akiyama S, Hamdeh S, Micic D, Sakuraba A: Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Ann Rheum Dis Published online Oct 13, 2020 doi: 10.1136/annrheumdis-2020-218946
33) Gianfrancesco M, Hyrich KL, Al-Adely S, et al.: Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 79: 859-866, 2020. doi: 10.1136/annrheumdis-2020-217871.
34) Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, et al.: Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel

diseases: Results from an international registry. Gastroenterol 159: 481-491.e3, 2020. doi: 10.1053/j.gastro.2020.05.032

Table 1. Baseline characteristics of the study population by type of kidney replacement therapy

		Type of kidney replacement therapy		
	Overall (n=1,670)	Kidney transplant (n=496)	Hemodialysis (n=1,174)	p-value
Patient Characteristics				
Male sex, %	62	59	63	0.16
Age, year	63 ± 15	56 ± 14	66 ± 15	<0.001
BMI, kg/m²	26.6 ± 5.5	26.9 ± 5.0	26.6 ± 5.7	0.34
Race				0.24
Asian, %	3	3	3	
Black or African descent, %	6	7	5	
White or Caucasian, %	85	85	85	
Other or unknown, %	6	5	7	
Tobacco use				0.03
Current, %	7	5	8	
Prior, %	24	20	25	
Never, %	46	50	45	
Unknown, %	23	25	22	
Clinical frailty scale, AU	3.6 ± 1.8	2.9 ± 1.6	3.9 ± 1.7	<0.001
Comorbidities				
Obesity, %	22	23	22	0.69
Hypertension, %	84	86	83	0.14
Diabetes Mellitus, %	39	29	43	<0.001
Coronary artery disease, %	29	17	35	<0.001
Heart failure, %	21	8	26	<0.001
Chronic lung disease, %	13	9	15	0.003
Active malignancy, %	6	5	7	0.12
Auto-immune disease, %	4	5	4	0.73
Primary kidney disease				
Primary Glomerulonephritis., %	18	20	17	0.14
Pyelonephritis, %	2	4	1	0.003
Interstitial nephritis, %	3	4	3	0.37
Hereditary kidney disease, %	9	14	7	<0.001
Congenital diseases, %	2	4	2	0.002
Vascular diseases, %	12	8	14	0.001
Sec. glomerular disease, %	5	4	6	0.05
Diabetic kidney disease, %	21	9	26	<0.001
Other, %	17	16	17	0.70
Unknown, %	11	18	8	<0.001
Residual diuresis ≥200 ml/day	32	-	32	-
Transplant waiting list status				-
Active on waiting list, %	10	NA	10	
In preparation, %	10	NA	10	
Temporarily not on list, %	9	NA	9	
Not transplantable, %	67	NA	67	
Unknown, %	4	NA	4	
Time since transplantation				-
<1 year, %	6	6	NA	
1-5 years, %	31	31	NA	
>5 years, %	63	63	NA	
Medication				
Use of RAAS inhibition				
ACE-inhibitors, %	16	24	14	<0.001

ARB, %	15	20	12	<0.001
Use of immunosuppressive medication				
Prednisone, %	31	87	7	<0.001
Tacrolimus, %	24	79	1	<0.001
Cyclosporine, %	3	10	0.7	<0.001
Mycophenolate, %	21	70	0.5	<0.001
Azathioprine, %	2	6	0.3	<0.001
mTOR inhibitor, %	4	12	0.2	<0.001
Disease characteristics				
Reason for COVID-19 screening				<0.001
Symptoms	69	85	61	
Due to contact	23	12	28	
Routine	8	3	11	
Presenting symptoms				
Sore throat, %	13	16	12	0.02
Cough, %	52	63	47	<0.001
Shortness of breath, %	35	41	33	0.002
Fever, %	60	70	56	<0.001
Headache, %	12	19	9	<0.001
Nausea or vomiting, %	11	15	9	<0.001
Diarrhea, %	16	28	11	<0.001
Myalgia or arthralgia, %	24	34	20	<0.001
Vital signs				
Temperature, °C	37.5 ± 1.1	37.6 ± 1.1	37.4 ± 1.0	0.01
Respiration rate, /min	19 ± 6	21 ± 7	19 ± 5	<0.001
O2 saturation room air, %	94 ± 6	94 ± 7	94 ± 5	0.41
Systolic BP, mm Hg	135 ± 24	132 ± 22	136 ± 25	0.01
Diastolic BP, mm Hg	76 ± 15	78 ± 14	75 ± 15	<0.001
Pulse rate, BPM	83 ± 16	87 ± 17	82 ± 15	<0.001
Laboratory test results				
Creatinine increase (>25%)		26	-	
Lymphocytes, x1000/µL	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)	0.9 (0.6, 1.3)	0.52
CRP, mg/L	25 (6, 76)	40 (8, 88)	22 (6, 67)	0.001

Continuous variables are reported as mean ± SD or median (IQR). Kidney transplant/dialysis groups were compared using one way ANOVA, Kruskal Wallis test or Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. *Abbreviations are:* ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; °C, degree Celsius; CRP, C-reactive protein; BP, blood pressure; O2, oxygen; prim., primary;

Table 2. Baseline characteristics of study population by reason for COVID-19 screening and type of kidney replacement therapy, i.e. kidney transplantation (KT) or hemodialysis (HD)

	Symptoms (n=1,145)			Contact/Routine screening(n=525)		
%, n	KT 37 (n=424)	HD 63 (n=721)	p-value	KT 14 (n=72)	HD 86 (n=453)	p-value
Patient Characteristics						
Male sex, %	58	64	0.03	68	61	0.25
Age, year	57 ± 14	68 ± 15	<0.001	56 ± 15	64 ± 14	<0.001
BMI, kg/m^2	26.9 ± 4.9	26.9 ± 6.2	0.99	26.4 ± 5.6	26.0 ± 4.8	0.48
Race			0.31			0.76
Asian, %	3	3		1	2	
Black or African descent, %	7	6		7	5	
White or Caucasian, %	85	84		85	87	
Other or unknown, %	4	7		7	6	
Tobacco use			0.01			0.53
Current, %	5	7		6	10	
Prior, %	20	26		21	23	
Never, %	50	41		51	50	
Unknown, %	25	25		22	17	
Clinical frailty scale, AU	2.9 ± 1.5	4.1 ± 1.8	<0.001	3.0 ± 1.6	3.8 ± 1.7	0.001
Comorbidities						
Obesity, %	23	25	0.53	22	17	0.35
Hypertension, %	86	83	0.18	83	82	0.84
Diabetes Mellitus, %	28	47	<0.001	32	36	0.55
Coronary artery disease, %	17	39	<0.001	17	29	0.03
Heart failure, %	8	28	<0.001	10	22	0.02
Chronic lung disease, %	10	16	0.002	7	12	0.20
Active malignancy, %	4	8	0.02	8	5	0.26
Auto-immune disease, %	5	4	0.53	3	4	0.52
Primary kidney disease						
Primary Glomerulonephritis, %	20	9	<0.001	22	29	0.23

Pyelonephritis, %	4	2	0.06	3	1	0.04
Interstitial nephritis, %	4	3	0.58	3	2	0.78
Hereditary kidney disease, %	13	6	<0.001	18	7	0.003
Congenital diseases, %	4	1	0.001	4	2	0.33
Vascular diseases, %	8	15	<0.001	10	13	0.50
Sec. glomerular disease, %	3	6	0.05	6	6	0.88
Diabetic kidney disease, %	8	25	<0.001	15	28	0.03
Other, %	18	25	0.01	6	4	0.62
Unknown, %	18	7	<0.001	14	8	0.12
Residual diuresis ≥200 ml/day	NA	30		NA	35	
Transplant waiting list status						
Active on waiting list, %	NA	11		NA	9	
In preparation, %	NA	12		NA	9	
Temporarily not on list, %	NA	7		NA	11	
Not transplantable, %	NA	68		NA	65	
Unknown, %	NA	3		NA	6	
Time since transplantation						
<1 year, %	5	NA		14	NA	
1-5 years, %	32	NA		31	NA	
>5 years, %	64	NA		56	NA	
Medication use						
Use of RAAS inhibition						
ACE-inhibitors, %	24	12	<0.001	24	14	0.05
ARB, %	20	15	0.01	22	8	<0.001
Use of immunosuppressive medication						
Prednisone, %	88	9	<0.001	82	4	<0.001
Tacrolimus, %	78	2	<0.001	88	1	<0.001
Cyclosporine, %	11	1	<0.001	3	0	<0.001
Mycophenolate, %	70	1	<0.001	69	0.2	<0.001
Azathioprine, %	6	0.1	<0.001	3	1	0.09

mTOR inhibitor, %	13	0.1	<0.001	10	0.2	<0.001
Disease related characteristics						
Presenting symptoms						
Sore throat, %	17	16	0.70	15	6	0.01
Cough, %	68	61	0.03	36	25	0.07
Shortness of breath, %	44	41	0.23	19	20	0.80
Fever, %	74	69	0.09	48	36	0.06
Headache, %	20	9	<0.001	13	10	0.32
Nausea or vomiting, %	17	13	0.05	3	3	0.91
Diarrhea, %	29	14	<0.001	25	7	<0.001
Myalgia or arthralgia, %	36	23	<0.001	18	14	0.40
Vital signs						
Temperature, °C	37.6 ± 1.1	37.7 ± 1.0	0.20	37.2 ± 0.9	37.0 ± 1.0	0.17
Respiration rate, /min	21 ± 7	20 ± 5	<0.001	17 ± 4	18 ± 3	0.23
O2 saturation room air, %	94 ± 7	93 ± 6	0.02	96 ± 4	95 ± 4	0.37
Systolic BP, mm Hg	131 ± 21	136 ± 26	0.02	133 ± 23	136 ± 23	0.38
Diastolic BP, mm Hg	79 ± 14	73 ± 15	<0.001	76 ± 15	77 ± 14	0.59
Pulse rate, BPM	88 ± 17	83 ± 17	<0.001	82 ± 14	80 ± 12	0.37
Laboratory test results						
Creatinine increase (>25%)	27	-		15	-	
Lymphocytes, x1000/µL	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)	0.20	0.9 (0.6, 1.4)	1.0 (0.7, 1.4)	0.38
CRP, mg/L	45 (10, 91)	30 (10, 94)	0.35	10 (3, 39)	12 (3, 37)	0.83

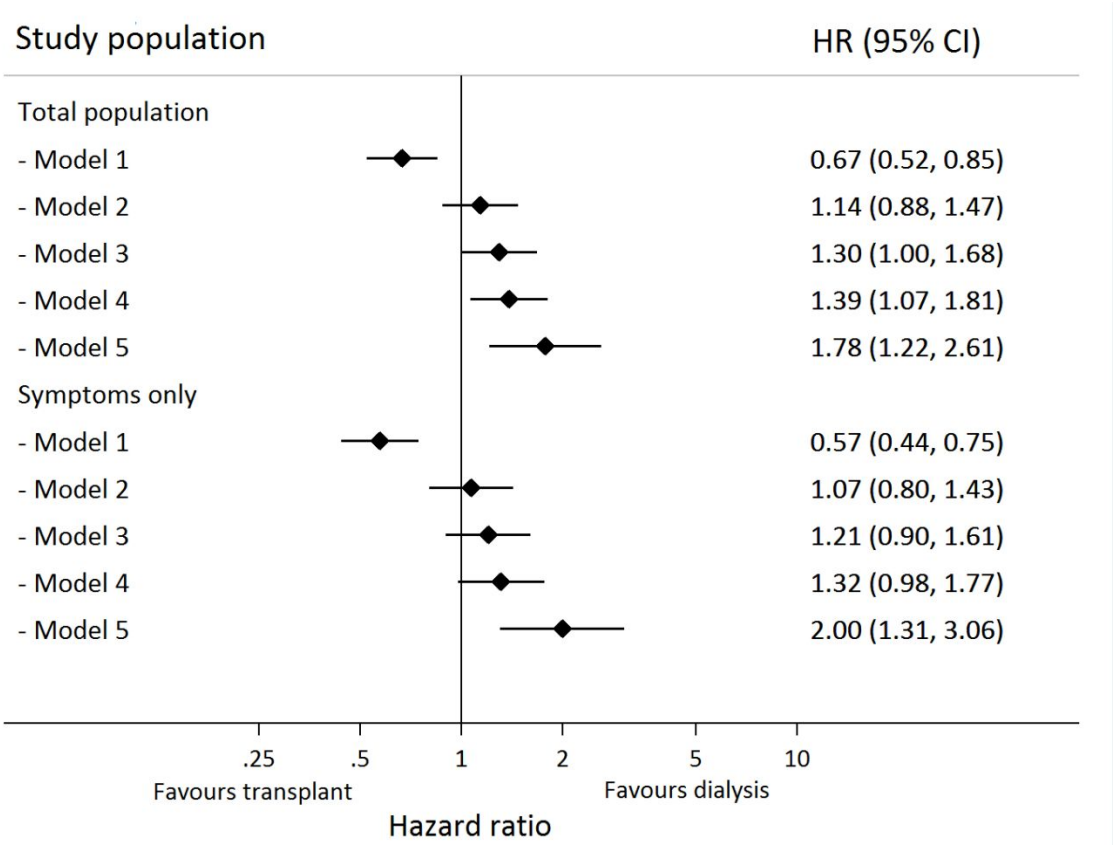
Continuous variables are reported as mean ± SD or median (IQR). Kidney transplant/dialysis groups were compared using one way ANOVA, Kruskal Wallis test or Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. *Abbreviations:KT, kidney transplant; HD, hemodialysis;* ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; °C, degree Celsius; CRP, C-reactive protein; BP, blood pressure; O2, oxygen; Sec., secondary.

Table 3. Association of type of kidney replacement therapy (kidney transplantation (KT) vs. hemodialysis (HD)) with incidence of 28-day COVID-19 related mortality, overall and by reason for COVID-19 screening Presented are hazard ratios (HR) with 95% confidence intervals (CI))

	Total			Symptoms			Contact/Routine		
Events (n)	HD 281(1,174)	KT 84(496)	p-value	HD 205 (721)	KT 75 (424)	p-value	HD 76 (453)	KT 9 (72)	p-value
Model 1	Ref.	0.67 (0.52, 0.85)	0.001	Ref.	0.57 (0.44, 0.75)	<0.001	Ref.	0.71 (0.36, 1.43)	0.34
Model 2	Ref.	1.14 (0.88, 1.47)	0.33	Ref.	1.07 (0.80, 1.43)	0.65	Ref.	0.99 (0.49, 1.99)	0.97
Model 3	Ref.	1.30 (1.00, 1.68)	0.05	Ref.	1.21 (0.90, 1.61)	0.21	Ref.	1.15 (0.57, 2.34)	0.69
Model 4	Ref.	1.39 (1.07, 1.81)	0.02	Ref.	1.32 (0.98, 1.77)	0.07	Ref.	1.19 (0.58, 2.46)	0.63
Model 5	Ref.	1.78 (1.22, 2.61)	0.003	Ref.	2.00 (1.31, 3.06)	0.001	Ref.	0.57 (0.17, 1.91)	0.36

Abbreviations: Hemodialysis (HD); Kidney transplant (KT),
Model 1 – crude
Model 2 – age, sex
Model 3 – Model 2 + frailty
Model 4 – Model 3 + obesity, hypertension, diabetes, heart failure, chronic lung disease, smoking
Model 5 – Model 4 + duration of kidney failure, kidney function

FIGURE LEGENDS



Model 1 – crude
Model 2 – age, sex
Model 3 – Model 2 + frailty
Model 4 – Model 3 + obesity, hypertension, diabetes, heart failure, chronic lung disease, smoking
Model 5 – Model 4 + duration of kidney failure, kidney function

FIGURE 1: Forest plot showing hazard ratios for association of type of kidney replacement therapy (kidney transplantation vs. hemodialysis) with 28-day mortality in the total study population and in the subgroup of those patients tested for COVID-19 based on symptoms only.

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