Collateral Effects and Mortality of Kidney Transplant Recipients during the COVID-19 Pandemic

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Key Points
- Despite significant collateral effects on kidney transplant recipients during the early COVID-19 pandemic, mortality remained unchanged.
- Considerable temporary reductions in admissions are safe, whereas reducing immunosuppression results in increased allograft rejection risk.

Abstract

Background Collateral effects and consequences of the coronavirus disease 19 (COVID-19) pandemic on kidney transplant recipients remain widely unknown.

Methods This retrospective cohort study examined changes in admission rates, incidences of diseases leading to hospitalization, in-patient procedures, and maintenance medication in long-term kidney transplant recipients with functioning graft during the early COVID-19 pandemic in Germany. Data were derived from a nationwide health insurance database. Analysis was performed from March 15 to September 30 and compared the years 2019 and 2020. Effects on mortality and adverse allograft events were compared with COVID-19-attributed effects.

Results A total of 7725 patients were included in the final analysis. Admissions declined in 2020 by 17%, with the main dip during a 3-month lockdown (~31%) but without a subsequent rebound. Incidences for hospitalization did not increase for any investigated disease entities, whereas decreasing trends were noted for non-COVID-19 pulmonary and urogenital infections (incidence rate ratio 0.8, 95% CI, 0.62 to 1.03, and 0.82, 95% CI, 0.65 to 1.04, respectively). Non-COVID-19 hospital stays were 0.6 days shorter (P=0.03) and not complicated by increased dialysis, ventilation, or intensive care treatment rates. In-hospital and 90-day mortality remained stable. Incidences of severe COVID-19 requiring hospitalization was 0.09 per 1000 patient-days, and in-hospital mortality was 9%. A third (31%) of patients with calcineurin-inhibitor medication and without being hospitalized for COVID-19 reduced doses by at least 25%, which was associated with an increased allograft rejection risk (adjusted hazard ratio 1.29, 95% CI, 1.02 to 1.63). COVID-19 caused 17% of all deaths but had no significant association with allograft rejections. All-cause mortality remained stable (incidence rate ratio 1.15, 95% CI, 0.91 to 1.46), also when restricting analysis to patients with no or outpatient-treated COVID-19 (0.97, 95% CI, 0.76 to 1.25).

Conclusion Despite significant collateral effects, mortality remained unchanged during the early COVID-19 pandemic. Considerable temporary reductions in admissions are safe, whereas reducing immunosuppression results in increased allograft rejection risk.

Introduction

Since emerging at the beginning of 2020, coronavirus disease 19 (COVID-19) has led to an ongoing pandemic that has dramatically affected medical care around the globe (1). Due to the contagious nature of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), millions of infections with many deaths have occurred. This has led to adaptations of the lives of both individuals and society to reduce viral transmission and to prevent severe disease courses (2,3). Both COVID-19 and these adaptations have dramatically influenced medical care. Studies on the general population have shown that hospital admissions for non-COVID-19 disease entities and the redemption of maintenance medication decreased considerably during the pandemic (4–7). Further, hospital admissions showed longer symptom-to-door time and reduced procedure rates (8). Data indicate an excess mortality rate at the...
population level during the pandemic, which is attributed not only to COVID-19 but also to non-COVID-19-related deaths, arguing for fatal collateral effects (9).

Kidney transplant recipients seem to be especially vulnerable, with an increased COVID-19-related mortality over the general population (10). Therefore, many transplant centers have developed protocols to protect kidney transplant recipients or candidates by pausing living transplantation programs, reducing medical contacts with infection risk, or postponing elective procedures (11,12). Additionally, ideas were raised to reduce immunosuppression in patients with COVID-19 risk or contact (13). Given the high burden of comorbidity in kidney transplant recipients, these ideas and adaptations might also cause harm. The drastic reduction of admissions for cardiovascular diseases as observed in the general population raises particular concern, considering the high cardiovascular risk of kidney transplant recipients (14,15). However, the collateral effects of the COVID-19 pandemic on kidney transplant recipients remain unknown. A comparison of collateral and COVID-19-related consequences is crucial to balance transmission protection and to maintain specific medical care. This applies both for future pandemics and for potential future COVID-19 waves. This study investigates the hypothesis of relevant collateral changes in the medical care of long-term kidney transplant recipients during the COVID-19 pandemic. The effect of these changes is compared with SARS-CoV-2-related effects.

Materials and Methods

Study Design and Data Collection

This retrospective cohort study is composed of anonymized nationwide administrative claim data of the German Local Health Care Funds (Allgemeine Ortskrankenkassen [AOK]). AOK is the largest sickness fund within Germany, providing insurance for 32% of the national population (16). Membership is open to the entire population without conditions of working status, income, age, or comorbidities (17). Although individuals insured with AOK constitute a significant proportion of the overall German population, they probably have a slightly lower general health status (18). As per the law, data on inpatient treatments, including dates, diagnoses, and procedures, must be disclosed to sickness funds. Outpatient treatments and prescriptions must be reported to apply for reimbursement. Beyond claims, core data consist of age, sex, insurance status, and day of death. Diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD-10) German Modification, and procedures are coded according to the International Classification of Procedures in Medicine, the “Operationen- und Prozedurenschlüssel” (OPS). Reimbursable outpatient treatments are defined by the “Einheitlicher Bewertungsmassstab” (EBM), and outpatient prescription by the World Health Organization ATC/DDD Index 2019/2020 (German modification). The local ethics committee of the Ärztekammer Hamburg approved this study (WF-022/21).

Study Population

The study population comprised adult long-term kidney transplant recipients with functioning graft. This population was chosen to investigate patients in a stable post-transplant situation without natural fluctuations in medical care. Thus, patients aged ≥18 years on January 1, 2017, who received kidney transplantation after 1998 and at least 1 year before the study period were included (OPS 5–555 and ICD 294:0 after January 1, 2017). Patients with graft loss and re-dialysis dependence defined as dialysis treatment within 6 months before the study period were excluded (OPS 8–853, 8–854, 8–855, 8–857, EBM 40823–40828 or surcharge 13602, 13610, 13611). To ensure adequate comparison and a stable post-transplant situation, these criteria were dynamically applied before the investigated periods in 2019 and 2020, respectively. Patients not continuously insured with the AOK since January 1, 2017, were excluded to assure data integrity.

Study Period and COVID-19 Incidences

The study period started on March 15, 2019 and terminated on September 30, 2020. The first SARS-CoV-2 infection in Germany was reported on February 27, 2020, followed by rapidly increasing COVID-19 incidences (19). In mid-March, the German Federal and State Governments released guidelines restricting social contacts, which led to a nationwide lockdown (20,21). Hospitals were urged to keep capacity for the care of COVID-19 patients, postponing elective procedures (21). Due to decreasing incidence, social and medical restrictions were gradually relaxed during June, followed by a period of low incidences until late September (19). Thus, we investigated the period from March 15, 2020, onward in comparison to the preceding year and further divided this period into two phases: the lockdown phase from March 15 to June 15 and the post-lockdown phase from June 16 to September 30.

Outcome Measures

For baseline description, we report age, sex, and comorbidities assessed by a combination of outpatient diagnoses and prescriptions in the preceding calendar year (22). Hospital stays were only counted if the admission and discharge dates were within the study period. As patients might have had several hospitals stays due to transfer between hospitals, we counted patients with adjacent completed hospital stays as one incidence. Incidences of selected diseases leading to hospitalization were assessed using ICD-10 principal diagnoses codes (Supplemental Table 1). For in-hospital treatments, we show length of hospital stay, procedures according to OPS codes (Supplemental Table 1), ventilation days, in-hospital mortality, and mortality within 90 days after admission. Changes in maintenance medication as assessed by ATC codes of redeemed prescriptions (Supplemental Table 1) were investigated by prescription rates and dose changes. Prescription was analyzed by comparing rates of patients with a corresponding redemption, and dose alterations were calculated by changes in defined daily doses (DDD) among patients with at least one prescription of the investigated drug. Further, we present all-cause mortality rates over the study period.

Statistical Analyses

Counts and percentages are reported for categorical variables and means and SD, and medians and interquartile
ranges (IQR) are reported for continuous variables. Hospital admissions were analyzed by total admissions per week. Further, we report rates for hospital admissions, redeemed outpatient medications, and all-cause mortality. Incidences of selected incident diseases entities leading to hospitalization and hospitalized COVID-19 are presented as incidence rate ratios (IRR). For the analysis of trends between 2019 and 2020, rate ratios with 95% confidence intervals (95% CI) of hospital admissions, redeemed outpatient medications, and all-cause mortality and IRR with 95% CI of the investigated disease entities leading to hospitalization were compared using Poisson regression models. Robust sandwich-variance estimator according to Huber and White was applied to account for potential overdispersion.

Characteristics of hospital stays between the investigated periods and characteristics of patients with or without COVID-19 were compared using a univariate chi-squared test for categorical variables and corrected using Fisher’s exact test for numbers less than five. The t test was used for normally distributed continuous variables, and the Mann–Whitney U test was used for non-normally distributed continuous variables. Cox regression models were used to calculate unadjusted and adjusted hazard ratios for allograft rejections of patients with a 25% reduction in steroids, calcineurin inhibitors (CNI), or both. Analyses were performed using Stata v16.0 (StataCorp, College Station, TX).

Results

Baseline Characteristics and Admission Rates

We identified 9739 patients who received a kidney transplantation at least 12 months before the study period. We excluded 1941 patients due to dialysis within the preceding 6 months, and 73 due to incomplete data (Supplemental Figure 1). A total of 7725 patients were investigated. The study population consisted of 38% women and had a mean age of 56.1 years (Table 1). Most frequent comorbidities were hypertension (85%), coronary artery disease (24%), diabetes (20%), and obesity (19%). Between the investigated periods of 2019 and 2020, 883 patients died or lost graft function, and 661 patients were additionally included because they received transplantation at least 12 months before.

From March 15 to September 30, 2020, there were 3063 admissions within 1,455,137 patient-days compared with 3800 admissions within 1,494,353 patient-days in the corresponding period in 2019 (rate ratio 0.89; Figure 1). Investigation of total weekly admissions showed that hospitalizations decreased during the first 12 weeks of observation and equalized over the remaining period. A general trend toward declining admissions in the summer months was also noted. The distribution corresponded well to the defined subphases and translated into a rate ratio for admissions of 0.69 (95% CI, 0.63 to 0.75) in the lockdown and 0.97 (95% CI, 0.90 to 1.05) in the post-lockdown phase compared with 2019 (Figure 1).

Characteristics of Hospitalizations

Characteristics of hospital stays were investigated for all non-COVID-19 admissions to analyze collateral effects (Table 2). Length of hospital stay was slightly shorter during the pandemic than it was in the preceding year (–0.6 days, P=0.03). There was no difference in dialysis (5.3% in 2019 versus 6.1% in 2020), ventilation (1.3% versus 1.3% for noninvasive and 1.8% versus 1.7% for invasive ventilation), or intensive care treatments (1.1% versus 0.9%). This equally applied for the lockdown and post-lockdown phases. In-hospital (2.2% versus 2.7%) and 90-day mortality (5.0% versus 5.6%) also remained unchanged during the pandemic.

Hospitalizations with COVID-19 had a mean length of 15.8 days. In-hospital rates of invasive ventilation and dialysis were each 11% (Supplemental Figure 2). In-hospital and 90-day mortality for admitted COVID-19 patients was 9% and 12%, respectively.

Incidences of Disease Entities Leading to Hospitalization

Hospitalizations for non-COVID-19 infectious diseases, such as pulmonary (IRR 0.8, 95% CI, 0.62 to 1.03) and urogenital infections (IRR 0.82, 95% CI, 0.65 to 1.04), showed a decreasing trend during the pandemic (Table 3). For cardiovascular diseases and allograft rejections, this trend was restricted to the lockdown phase, whereas overall incidence rates remained virtually constant (IRR 0.91, 95% CI, 0.75 to 1.12 for cardiovascular diseases: IRR 0.95, 95% CI, 0.82 to 1.10 for allograft rejections). None of the diseases showed an increase after the lockdown period. The IRR of hospitalized COVID-19 was 0.09 per 1000 patient-days over the total period (129 patients) and 0.12 in the lockdown phase (85 patients). In 16 patients, COVID-19 and allograft rejections occurred within the same hospital stay, but there was no patient where a hospitalized COVID-19 disease preceded an admission for an allograft rejection.

Changes in Maintenance Medication

For the evaluation of collateral effects on maintenance medication, drug analyses were restricted to patients without severe and hospitalized COVID-19. Rates of redeemed prescriptions did not decrease for any of the investigated cardiovascular or immunosuppressive drugs during the

| Table 1. Baseline characteristics of the study population |
|----------------------------------------------------------|
| Characteristics                                      | Study Population (N=7725) |
| Sex, n (%)                                           |
| Men                                                   | 4805 (62) |
| Women                                                 | 2920 (38) |
| Age, yr                                               |
| Mean (SD)                                            | 56.1 (13.5) |
| Median (IQR)                                         | 57.1 (48–66) |
| Comorbidities, n (%)                                  |
| Hypertension                                         | 6561 (85) |
| Coronary artery disease                               | 1846 (24) |
| Diabetes                                              | 1520 (20)  |
| Obesity                                               | 1448 (19)  |
| Congestive heart failure                              | 1283 (17)  |
| Chronic liver disease                                 | 1156 (15)  |
| Chronic obstructive pulmonary disease                 | 648 (8)    |
| Asthma                                                | 478 (6)    |
| Cancer                                                | 245 (3)    |
| Dementia                                              | 112 (1)    |

IQR, interquartile range.
The rate of patients with statin and belatacept therapy slightly increased in 2020 (IRR 1.05, 95% CI, 1.02 to 1.08 for statins; IRR 1.39, 95% CI, 1.07 to 1.81 for belatacept; Table 4). Analysis of drug dosing showed a prevailing reduction of immunosuppressive drugs, whereas doses of cardiovascular drugs remained stable (Table 4). Dose reduction was most distinctive for CNI and steroids. DDD of tacrolimus and cyclosporine were each reduced by 5% (–4.8 DDD, \( P < 0.001 \) and –3.9 DDD, \( P = 0.02 \), respectively) and DDD of steroids by 3% (–2.4 DDD, \( P < 0.001 \)). These declines were driven by a considerable proportion of patients reducing steroids (25% of patients with at least one prescription) or CNI (31%) by at least 25%. These patients had an increased allograft rejection risk compared with patients with \(<25\% \) dose reduction (hazard ratio [HR] 1.31, 95% CI, 1.02 to 1.67 for reduction of steroids; HR 1.37, 95% CI, 1.09 to 1.63 for CNI; and HR 1.40, 95% CI, 1.11 to 1.75 for both; Figure 2). Even after adjustment for age, time since transplantation, allograft rejection in the preceding year, and the not-investigated immunosuppressive, reductions of CNI (HR 1.29, 95% CI, 1.02 to 1.63) and steroids and CNI (HR 1.32, 95% CI, 1.05 to 1.66) were significantly associated with an increased allograft rejection risk. For steroids after adjustment, this association only showed a nonsignificant trend (HR 1.21, 95% CI, 0.94 to 1.55).

**Mortality and COVID-19 Infections**

In total, there were 132 deaths in 2019 and 142 in 2020. This translates into almost equal all-cause mortality rates for the total period (IRR 1.15, 95% CI, 0.91 to 1.46) and for the lockdown (IRR 1.11, 95% CI, 0.78 to 1.57) and post-lockdown phases (IRR 1.11, 95% CI, 0.80 to 1.53) compared with the previous year (Figure 3). When restricting analysis to patients with no or outpatient-treated mild SRAS-CoV-2 infections, mortality for all investigated periods showed a marginal decreasing trend but did not differ significantly from analysis including hospitalized COVID-19 patients or from the preceding year. Of the 142 deaths in 2020, 24 (17%) were accounted for by patients hospitalized with COVID-19. Patients with hospitalized SARS-CoV-2 infections were older and more likely to have diabetes, coronary artery disease, chronic liver disease, or chronic obstructive pulmonary disease (Supplemental Table 2). Steroid use in maintenance medication was also associated with being hospitalized with COVID-19, whereas mycophenolate therapy was less frequent among these patients (Supplemental Table 2).

**Discussion**

This study shows a 17% decline in hospital admissions without adverse consequences for long-term kidney transplant recipients having functioning grafts during the early COVID-19 pandemic in Germany. Significant changes in immunosuppressive medications were rare but were associated with an increased allograft rejection risk. All-cause mortality remained unchanged during the pandemic.

The observed decrease in admission rates corresponds to reported trends in the general population (5,6). This...
Table 2. Characteristics of hospital stays in 2019 and 2020 restricted non-COVID-19 admissions

| Characteristics               | 2019 (N=3800) | 2020 Non-COVID-19 (N=2922) | P Value | 2019 (N=1925) | 2020 Non-COVID-19 (N=1748) | P Value |
|-------------------------------|---------------|----------------------------|---------|---------------|---------------------------|---------|
| **Length of hospital stay, d** |               |                            |         |               |                           |         |
| Mean (SD)                     | 9.7 (12.4)    | 9.1 (10.8)                 | 0.03    | 10.5 (13.9)   | 10.1 (12.3)               | 0.39    |
| Median (IQR)                  | 6 (3–11)      | 6 (3–10)                   |         | 7 (3–11)      | 6 (3–11)                  |         |
| **Procedures, n (%)**         |               |                            |         |               |                           |         |
| Intensive care unit           | 42 (1)        | 25 (0.9)                   | 0.31    | 18 (1)        | 10 (0.9)                  | 0.76    |
| Dialysis                      | 201 (5)       | 179 (6)                    | 0.14    | 100 (5)       | 78 (7)                    | 0.13    |
| Invasive ventilation          | 69 (2)        | 51 (2)                     | 0.83    | 40 (2)        | 27 (2)                    | 0.76    |
| Noninvasive ventilation       | 51 (1)        | 37 (1)                     | 0.79    | 34 (2)        | 16 (1)                    | 0.34    |
| Tracheostomy                  | 12 (0.3)      | 7 (0.2)                    | 0.56    | 9 (0.5)       | 3 (0.3)                   | 0.39    |
| Extracorporal membrane oxygenation | 2 (0.1)  | 1 (0.0)                    | 1.00    | 1 (0.1)       | 1 (0.1)                   | 1.00    |
| **Ventilation, d**            |               |                            |         |               |                           |         |
| Mean (SD)                     | 1.5 (1.1)     | 1.4 (0.8)                  | 0.43    | 1.6 (1.3)     | 1.3 (0.5)                 | 0.21    |
| Median (IQR)                  | 1 (1–2)       | 1 (1–2)                    |         | 1 (1–2)       | 1 (1–1)                   |         |
| **Deaths, n (%)**             |               |                            |         |               |                           |         |
| In-hospital mortality         | 84 (2)        | 79 (3)                     | 0.19    | 44 (2)        | 36 (3)                    | 0.23    |
| 90-day mortality              | 183 (5)       | 164 (6)                    | 0.14    | 85 (5)        | 73 (6)                    | 0.04    |
| Total refers to the period from March 15 to September 30, whereas the lockdown phase is from March 15 to June 15 and the post-lockdown phase is from June 16 to September 30. IQR, interquartile range; COVID-19, coronavirus disease 2019.
Table 3. Incidence rates and incidence rate ratios of disease entities leading to hospitalization in 2019 and 2020

| Principal Diagnoses   | Total Incidence Rate 2019 | Incidence Rate Ratio (95% Confidence Interval) | P Value | Lockdown Incidence Rate 2019 | Incidence Rate Ratio (95% Confidence Interval) | P Value | Post-Lockdown Incidence Rate 2019 | Incidence Rate Ratio (95% Confidence Interval) | P Value |
|-----------------------|---------------------------|-----------------------------------------------|---------|-------------------------------|-----------------------------------------------|---------|----------------------------------|-----------------------------------------------|---------|
| Allograft rejections  | 0.25                      | 0.95 (0.82 to 1.10)                          | 0.51    | 0.29                          | 0.84 (0.69 to 1.04)                          | 0.11    | 0.28                            | 1.00 (0.83 to 1.21)                          | 0.97    |
| Cardiovascular diseases | 0.14                    | 0.91 (0.75 to 1.12)                          | 0.38    | 0.17                          | 0.89 (0.68 to 1.16)                          | 0.39    | 0.13                            | 0.97 (0.73 to 1.28)                          | 0.83    |
| Urogenital infections | 0.11                      | 0.82 (0.65 to 1.04)                          | 0.10    | 0.11                          | 0.78 (0.55 to 1.10)                          | 0.16    | 0.11                            | 0.92 (0.68 to 1.24)                          | 0.57    |
| Pulmonary infections  | 0.09                      | 0.80 (0.62 to 1.03)                          | 0.08    | 0.12                          | 0.83 (0.60 to 1.14)                          | 0.24    | 0.07                            | 0.74 (0.49 to 1.12)                          | 0.15    |
| Sepsis                | 0.07                      | 0.80 (0.62 to 1.03)                          | a       | 0.07                          | 0.83 (0.60 to 1.14)                          | a       | 0.07                            | 0.74 (0.49 to 1.12)                          | a       |

Incidence rates are given per 1000 patient-days. Total refers to the period from March 15 to September 30, whereas the lockdown phase is from March 15 to June 15 and the post-lockdown phase is from June 16 to September 30.

*aCriteria for sepsis coding changed between 2019 and 2020 impeding direct comparison.*
| Medication                  | 2019 Patients (N=7725), n (%) | 2020 Non-COVID-19 Patients (N=7383), n (%) | Rate Ratio (95% Confidence Interval) | P Value |
|-----------------------------|--------------------------------|--------------------------------------------|--------------------------------------|---------|
|                             | Rate per 1000 Patient-days    | Defined Daily Doses, Mean (SD)             | Rate per 1000 Patient-days           |         |
| Cardiovascular drugs        |                               |                                            |                                      |         |
| Statin                      | 3965 (51)                     | 4043 (54)                                  | 1.05 (1.02 to 1.08)                  | 0.003   |
| Calcium antagonist          | 3426 (44)                     | 3311 (44)                                  | 0.99 (0.96 to 1.03)                  | 0.3     |
| ACE-I                       | 2284 (30)                     | 2108 (28)                                  | 0.95 (0.90 to 1.00)                  | 0.29    |
| ARB                         | 2267 (29)                     | 2278 (30)                                  | 1.03 (0.99 to 1.09)                  | 0.18    |
| Antiplatelet agent          | 1747 (23)                     | 1689 (23)                                  | 0.99 (0.93 to 1.05)                  | 0.66    |
| Imunosuppressive drugs      |                               |                                            |                                      | 0.87    |
| Belatacept                  | 94 (1)                        | 127 (2)                                    | 1.36 (1.04 to 1.78)                  | 0.02    |
| Tacrolimus                  | 5271 (68)                     | 5147 (69)                                  | 1.00 (0.98 to 1.02)                  | 0.84    |
| Cyclosporine                | 1569 (20)                     | 1473 (20)                                  | 0.96 (0.90 to 1.02)                  | <0.001  |
| Mycophenolate               | 5713 (74)                     | 5480 (73)                                  | 0.99 (0.97 to 1.00)                  | 0.15    |
| Azathioprine                | 269 (4)                       | 249 (3)                                    | 0.95 (0.80 to 1.13)                  | 0.54    |
| Everolimus                  | 401 (5)                       | 426 (6)                                    | 1.09 (0.95 to 1.24)                  | 0.23    |
| Sirolimus                   | 269 (4)                       | 245 (3)                                    | 0.93 (0.79 to 1.11)                  | 0.43    |
| Steroids                    | 4797 (62)                     | 4585 (61)                                  | 0.98 (0.96 to 1.01)                  | 0.07    |

Percentages of total numbers refer to all patients without hospitalized COVID-19. Doses are presented in relation to patients with at least one prescription of the investigated drug. Data refers to the period from March 15 to September 30. ACE-I, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; COVID-19, coronavirus disease 2019.
decrease mainly affected non-COVID-19-related infectious diseases, which might be attributed to better hygiene, mask wearing, and social distancing (23). Admissions for cardiovascular diseases and allograft rejections remained rather stable, reflecting the high risk of these diseases for kidney transplant recipients. However, the absence of a rebound for any of the investigated disease entities after the lockdown suggests no adverse consequences of the decline in admissions. This is further underlined by stable in-hospital complications, even during the lockdown phase. Given that most acute or subacute graft failures and dialysis treatments for kidney transplant recipients are treated as inpatients in Germany, our findings indicate that graft loss rates also remained stable during the pandemic. Together, a temporary decrease in admissions appears safe. This could also have implications for the general care of long-term kidney transplant recipients because a relevant number of admitted patients might be treated as outpatients.

In contrast to distinct effects on admissions, there were only subtle changes in maintenance medication. Despite debates on its influence on COVID-19 (24), there was no decline in the redemption of angiotensin-converting-enzyme inhibitors. Statins were used more frequently in 2020, which is likely due to stricter guidelines on lipid-lowering therapy (25). Although dose reductions were overall minor, the prevailing reduction of immunosuppressives compared with cardiovascular drugs argues for specific effects. As our analysis was restricted to patients who were not hospitalized with COVID-19 and to outpatients, COVID-19 treatment was generally rare in transplant recipients (26). This finding is likely caused by collateral effects. Although our study cannot identify the exact collateral reason of this observation, general caution during the pandemic, former COVID-19 contacts, and more relaxed medical care with fewer CNI-level controls might have contributed. The preference for changes in CNI dosing could be explained by the convenient possibility of adjusting target trough levels, and steroid reduction could be explained by the association of long-term steroid use with worse COVID-19 outcomes (26,27). Minor total effects on these

### Figure 2

**HR for allograft rejections of patients with a 25% reduction in steroids, CNI, or both.** HR were calculated in comparison to patients with <25% dose reduction. Data refers to the period from March 15 to September 30. Adjustment was performed for age, time since transplantation, and rejection in the preceding 24 months. CNI, calcineurin inhibitor; HR, hazard ratio.

|                | Unadjusted | Adjusted |
|----------------|------------|----------|
| Steroid        | 1.31 (1.02–1.67) | 1.21 (0.94–1.55) |
| CNI            | 1.37 (1.09–1.63) | 1.29 (1.02–1.63) |
| Steroid & CNI  | 1.40 (1.11–1.75) | 1.32 (1.05–1.66) |

### Figure 3

**Rate ratios for total all-cause mortality in 2020 compared with 2019.** Total refers to the period from March 15 to September 30, whereas the lockdown phase is from March 15 to June 15 and the post-lockdown phase from June 16 to September 30. Analyses were performed to all patients and patients without hospitalized COVID-19 (non-COVID-19). COVID-19, coronavirus disease 2019; RR, rate ratio.

|                | All patients | Non-COVID-19 |
|----------------|--------------|--------------|
| Total          | 1.15 (0.91–1.46) | 0.97 (0.76–1.25) |
| Lockdown       | 1.11 (0.78–1.57) | 0.99 (0.69–1.42) |
| Post-lockdown  | 1.11 (0.80–1.53) | 0.89 (0.63–1.25) |
drugs were due to a quarter of patients reducing doses by at least 25%. For CNI, this reduction resulted in an increased allograft rejection risk, even after adjusting for known risk factors. This finding is in line with the literature because adequate CNI target levels are crucial to prevent allograft rejections (28). In accordance with data showing no or only slightly increased rejection rates after late steroid withdrawal, the association of steroid reduction with allograft rejections showed a non-significant trend and had no additional effect on CNI reduction (29).

Despite emerging data, it remains unclear whether kidney transplant recipients have an increased risk for COVID-19 infections and adverse disease courses (30–32). Data are still sparse, especially regarding incidence rates. During the study period, Germany reported a general COVID-19 incidence of 0.35% (19) with a 17% hospitalization rate (33). Compared with our collective, this translates into a 28-fold increase in kidney transplant recipients being hospitalized with COVID-19 compared with the general population. A recent study investigated hospitalized COVID-19 courses on the general population of the same insurance database in an overlapping period, allowing direct comparison (34). In-hospital mortality in this study was 22% and thus nearly doubled compared with our collective. In contrast, dialysis rates were only 6%, translating into a two-fold higher risk in kidney transplant recipients. The low coincidence of allograft rejection and COVID-19 observed in our study argues against an immunologic reason for higher dialysis rates in kidney transplant recipients. In fact, the higher risk for severe AKI is probably caused by a predisposition to the different mechanisms of COVID-19-related kidney injury such as direct or indirect tubular damage (35). A lower threshold for admissions in kidney transplant recipients, as shown in recent reports, could explain the differences in mortality (26). Known risk factors for COVID-19 such as age, diabetes, chronic obstructive pulmonary disease, dementia, and cardiac and liver diseases also applied to our collective (36). Further, maintenance medication with steroids was associated with the risk of being hospitalized with COVID-19. This supports findings correlating long-term steroid use to worse COVID-19 outcomes (26,27). Whereas some studies identified high doses of mycophenolate as a risk factor for COVID-19 in solid organ transplant recipients, most found no correlation (26,37–39). In contrast, our study argues for a negative association of mycophenolate with COVID-19. This protective effect is supported by in vitro data showing inhibition of coronaviruses by mycophenolate (40). Ultimately, it might be an effect of lower doses being protective and higher doses posing a risk for COVID-19.

Although COVID-19 had a high mortality rate and accounted for 17% of all observed deaths in our collective, all-cause mortality remained stable. This also applied to patients without severe COVID-19 courses, indicating no collateral effects on mortality.

To the best of our knowledge, this is the first study evaluating collateral effects of the COVID-19 pandemic in comparison to COVID-19-related consequences on kidney transplant recipients. The study population constitutes one of the largest transplant collectives investigated during the pandemic and comprises about 30% of the estimated total number of kidney transplant recipients with a functioning graft in Germany (41,42). Regarding most patient characteristics, our collective is highly similar to other studies on long-term kidney transplant recipients in Germany and other countries (43,44). Despite its strengths, our study has several limitations. Our study investigates patients in a long-term situation after kidney transplantation during the early COVID-19 pandemic in Germany. It remains to be investigated whether observed effects also apply to patients without stable graft function or other countries with different COVID-19 incidences. Further, information on outpatient treatments was restricted to redeemed medication. Effects of mild and outpatient-treated COVID-19 could thus not be investigated. However, this bias is probably minor because reports showed that <10% of SARS-CoV-2-positive kidney transplant recipients were treated as outpatients (26). Data on laboratory results were also not available in our database. We thus cannot clarify whether more relaxed control of laboratory data, including CNI levels, contributed to the observed changes. Stockpiling at the beginning of the pandemic also cannot be excluded. Future retrospective studies including laboratory and outpatient data will help in part to overcome these limitations. Further, prospective studies during future waves are needed to clarify the nature of changes during the pandemic.

In conclusion, despite considerable changes in admission rates, collateral effects during the early COVID-19 pandemic had no influence on mortality or graft loss rates. Thus, a temporary drastic reduction of hospital admissions appears safe. However, reducing immunosuppressive maintenance medication poses a relevant risk for allograft rejections and should be restricted to special situations. COVID-19 mortality is high but did not significantly influence all-cause mortality.

Disclosures
T.B. Huber has consultancy agreements with AstraZeneca, Boehringer-Ingelheim, DaVita, Deerfield, Fresenius Medical Care, GoldfinchBio, MantraBio, Novartis, and Retrophin, and received research funding from Amicus and Fresenius Medical Care. All remaining authors have nothing to disclose.

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Author Contributions
F. Grahammer, C. Günster, T. Huber, C. Schmidt-Lauber, and M. Spoden conceptualized the study and reviewed and edited the manuscript; F. Grahammer and C. Schmidt-Lauber were responsible for project administration; F. Grahammer and C. Günster supervised the study; F. Grahammer, C. Günster, and T. Huber were responsible for validation; C. Schmidt-Lauber and M. Spoden were responsible for data curation, formal analysis, and investigation; and C. Schmidt-Lauber was responsible for methodology, and wrote the original draft.
Data Sharing Statement

The data used in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to German data protection laws (Bundesdatenschutzgesetz). Therefore, they are stored on a secure drive in the Wissenschaftliches Institut der AOK to facilitate replication of the results. Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in German Social Law (SGB V §287). Requests for data access can be sent as a formal proposal specifying the recipient and purpose of the data transfer to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the AOK. For assistance in obtaining access to the data, please contact widio@widio-bv.aok.de.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl;doi:10.34067/KID.0006472021/-/DCSupplemental.

Supplemental Figure 1. Patient disposition.

Supplemental Figure 2. Characteristics of hospitalized COVID-19 patients.

Supplemental Table 1. Definition of procedures, diagnoses, and drugs.

Supplemental Table 2. Characteristics of patients with and without hospitalized COVID-19.

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