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LETTER TO THE EDITORS

Increased rejection rates in kidney transplantations during the COVID-19 pandemic

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Dear Editors,

The coronavirus disease-19 (COVID-19) pandemic constitutes a major challenge for transplantation medicine. Given the potential risk of severe acute respiratory syndrome coronavirus type 2 infection and adverse disease courses for recently transplanted recipients, many transplant centers have adapted kidney transplantation programs during the pandemic [1–3]. However, the severity of adaptions considerably differed between countries. Whereas numbers of kidney transplant procedures decreased substantially in the United States, Italy or France [1–3], partially accompanied by changes in early immunosuppressive regimens, countries of the Eurotransplant network virtually maintained transplant activity [4]. First reports indicate similar early outcomes of kidney transplantations in countries with extensive changes in transplantation activity and care [5], but modification and consequences in countries with a rather stable volume of kidney transplant procedures remain unclear. However, data on different strategies of handling kidney transplantations are important to navigate through the next phase of the pandemic and prepare for future pandemics.

This retrospective cohort study investigates the handling and early outcomes of kidney transplantations performed during the early COVID-19 pandemic in Germany using nationwide administrative claim data of the German Local Health Care Funds [Allgemeine Ortskrankenkassen (AOK)]. AOK constitutes a representative nationwide collective by providing insurance for 32% of the German population without preselection on age, working status, income, or comorbidities [6]. Patients with a minimum age of 18 years on 1 January 2017, who received kidney transplantation between 15 March and 30 September 2020 or in the corresponding period of 2019 were included. This study period was chosen as Germany experienced high COVID-19 incidences upon March 2020 [7]. Individuals not continuously insured with the AOK were excluded. Information on transplant hospital stays as well as subsequent hospital treatments within the study period were investigated by registered dates, procedures, and diagnoses. Further, analysis of outpatient prescriptions redeemed within 60 days after transplantation was performed. Data were compared between patients receiving transplantation in 2019 vs. 2020. The ethics committee of the Ärztekammer Hamburg approved this study (WF-022/21).

Three hundred and seventeen patients received kidney transplantation during the early COVID-19 pandemic compared to 355 patients in the corresponding period of 2019. This translates into a 10.7% decline in transplant activity. Distribution of transplantation types did not differ between years, with 18.9% living donor, 3.4% incompatible blood type and 2.5% multiorgan transplantations in 2020 (16.7%, $P = 0.949$; 3.5%, $P = 0.126$ and 2.5%, $P = 0.188$ in 2019, respectively; Table S1). Also, there was no change in age (50.8 vs. 51.2 years in 2019 and 2020, respectively; $P = 0.707$), sex (35.2% vs. 41.3% female; $P = 0.104$), and comorbidities of transplant recipients. Transplant hospital stays were 2.1 days shorter in 2020 (25.2 vs. 23.1 days, $P = 0.049$) but without increased rates of intensive care treatments or delayed graft function. Usage of rabbit antithymocyte globulin (rATG)-Thymoglobulin for immunosuppressive induction therapy did not vary between the COVID-19 pandemic and the previous year (6.5% vs. 8.2% in 2019 and 2020, respectively, $P = 0.391$). Regarding early maintenance immunosuppression, we found slight absolute reductions in patients taking cyclosporine (−6.2%, $P = 0.001$), mycophenolate (−5.3%, $P = 0.021$) and steroids (−7.4%, $P = 0.001$) (Table S2). Rates for other immunosuppressives or cardiovascular drugs did not change, and redeemed doses also remained almost constant.

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All-cause mortality was similar for patients transplanted during the COVID-19 pandemic or the corresponding period of 2019 (1.1% vs. 1.6% in 2019 and 2020, respectively; $P = 0.742$; Fig. 1). There was only one confirmed COVID-19 case in the study population. Re-admission rates were higher in 2020 compared to the previous year (55.8% vs. 65.6%, $P = 0.029$). Investigation of disease entities leading to re-admission showed a prevailing increase in allograft rejections (14.4% vs. 22.7%, $P = 0.035$). In contrast, re-admissions due to cardiovascular diseases and infections remained stable. Further, we observed a nonsignificant tendency towards increased re-dialysis rates after transplantation in 2020 (5.9 vs. 7.3%, $P = 0.483$).

This study shows that Germany virtually maintained its kidney transplantation programs during the COVID-19 pandemic. All types of transplantation, including living donor and complex transplantations were perpetuated and there was no pandemic-driven selection of transplant candidates. Together with the constant rATG-Thymoglobulin use, these findings indicate that selection, activity, and initial management of transplant procedures were handled independent of the COVID-19 pandemic in Germany. This approach is substantially different to those of other countries [1–3]. Still, we observe subtle changes in early transplant recipient care. These include shorter hospital stays, which might be explained by measures to save hospital capacities and avoid in-hospital COVID-19 transmissions [8]. Further, there were slight decreases in early immunosuppression maintenance therapy, whereas redemption of cardiovascular drugs remained unchanged. Declines in steroid therapy might reflect a tendency to avoid this drug

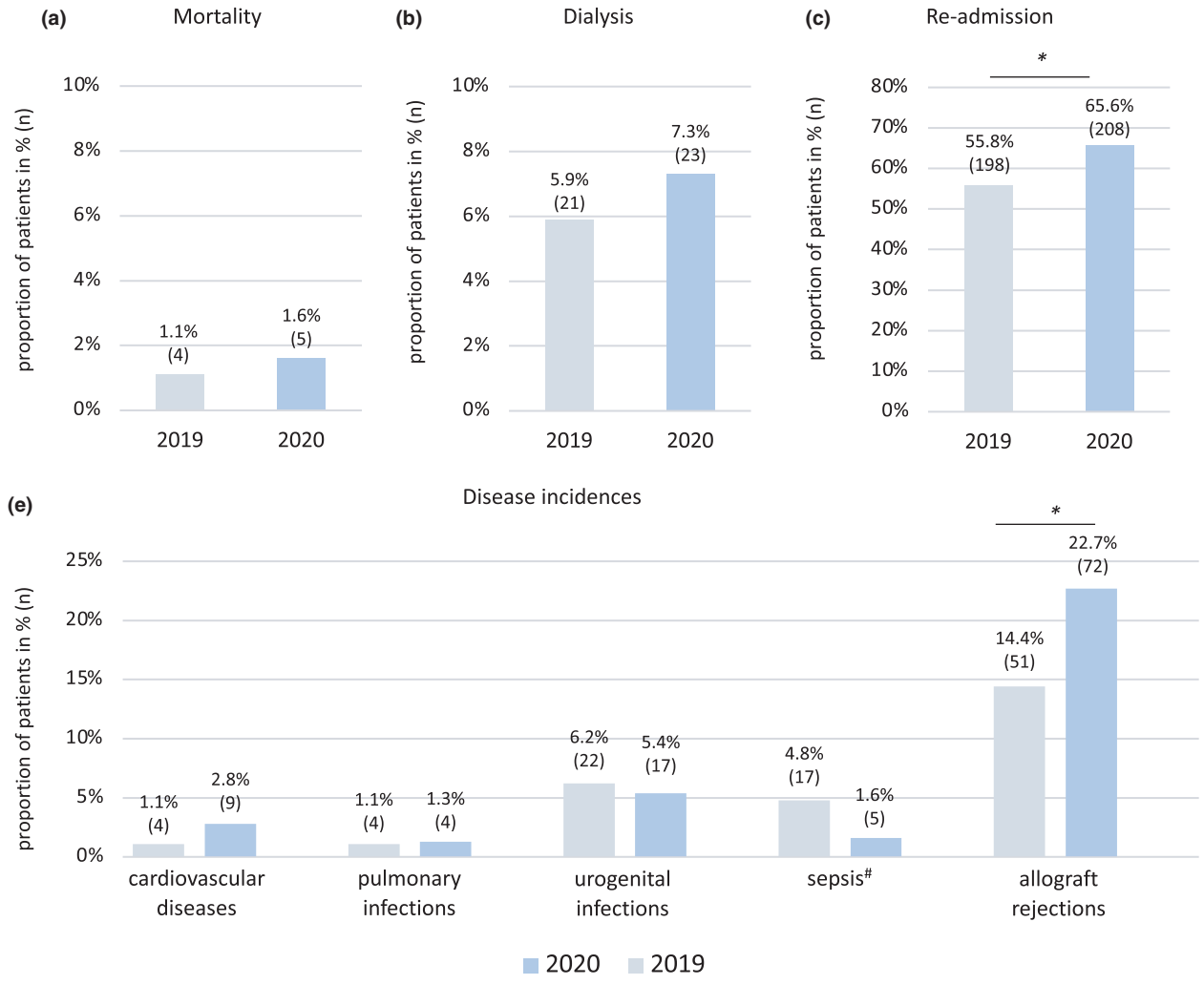

Figure 1 Outcomes and re-admissions of patients receiving kidney transplantation in 2019 and 2020. Rates of (a) all-cause mortality, (b) dialysis, (c) re-admission and (d) incidences of hospital admissions for selected disease entities after transplantation are presented. *P-value <0.05 tested with univariate χ^2-Test and corrected with Fisher's exact test for counts below five. #As criteria for sepsis coding changed between 2019 and 2020, a reliable statistical comparison is not possible.

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during the pandemic driven by studies associating long-term steroid use with adverse COVID-19 courses [9]. However, the cyclosporine decrease is probably rather due to a general renunciation [10].

Overall, perpetuation of transplant management was safe with constant rates of all-cause mortality, cardiovascular and infectious events. The finding of one COVID-19 case in our study further suggests no increased infection risk over the general population, whose incidence was 0.35% at that time [7], as nearly all transplant centers tested recipients before transplantation according to the Eurotransplant recommendations and a negative donor test was mandatory for transplantation. However, the observed increase in allograft rejections, which was associated with a tendency towards higher re-dialysis and re-admission rates, raise concern that medical care is not yet balanced between minimizing COVID-19 risk and maintaining graft care. Constant rates of delayed graft function indicate sufficient in-hospital care and observed minor changes in maintenance immunosuppression cannot fully explain the increased rejection rates. However, observed restrictions in in-hospital treatment could indicate a general looser medical care, which might have contributed to the finding in the out-patient setting. Unfortunately, out-patient data was not available when performing the study. Other limitations include missing information on other immunosuppressive induction agents such as basiliximab and on immunological details of the transplantations.

Conflicts of interest

All authors have no conflict of interest to declare.

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Data availability 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 wido@wido.bv.aok.de.

SUPPORTING INFORMATION

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

Table S1. Baseline characteristics, transplantation type and transplant hospital stay characteristics in 2019 and 2020.

Table S2. Early maintenance medication in 2019 and 2020.

REFERENCES

1. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, *et al*. Early impact of COVID-19 on transplant center practices and policies in the United States. *Am J Transplant* 2020; **20**: 1809.
2. Legeai C, Malaquin G, Lamotte C, *et al*. Impact of coronavirus disease 2019 on organ donation and transplantation in France. *Transpl Int* 2021; **34**: 204.
3. Vistoli F, Furian L, Maggiore U, *et al*. COVID-19 and kidney transplantation: an Italian survey and consensus. *J Nephrol* 2020; **33**: 667.
4. Eurotransplant. Preliminary Eurotransplant annual figures 2020 online. January 14, 2021. https://www.eurotransplant.org/2021/01/14/preliminary-eurotransplant-annual-figures-2020-online/ (accessed March 13th, 2020).
5. Bae S, McAdams-DeMarco MA, Massie AB, *et al*. Early changes in kidney transplant immunosuppression regimens during the COVID-19 pandemic. *Transplantation* 2020; **105**: 170.

6. Busse R, Blümel M, Knieps F, Bärnighausen T. Statutory health insurance in Germany: a health system shaped by 135 years of solidarity, self-governance, and competition. *Lancet* 2017; **390**: 882.
7. Robert Koch Institut. Täglicher Lagebericht des RKI zur Coronavirus-Krankheit-2019 (COVID-19). October 01, 2021. https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Okt_2020/2020-10-01-de.pdf?__blob=publicationFile (accessed June 22nd, 2021).
8. Kapsner LA, Kampf MO, Seuchter SA, *et al*. Reduced rate of inpatient hospital admissions in 18 German university hospitals during the COVID-19 lockdown. *Front Public Health* 2020; **8**: 594117.
9. Elias M, Pievani D, Randoux C, *et al*. COVID-19 infection in kidney transplant recipients: disease incidence and clinical outcomes. *J Am Soc Nephrol* 2020; **31**: 2413.
10. Webster A, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2005; (4): CD003961.