



**HAL**  
open science

## **Impact of the Kidney Transplantation Moratorium in France Because of the COVID-19 Pandemic: A Cohort-based Study**

Vincent Bonnemains, Florent Le Borgne, Emile Savoye, Camille Legeai, Myriam Pastural, Sahar Bayat, Rémi Lenain, Stéphanie Ragot, Karen Leffondré, Cécile Couchoud, et al.

► **To cite this version:**

Vincent Bonnemains, Florent Le Borgne, Emile Savoye, Camille Legeai, Myriam Pastural, et al.. Impact of the Kidney Transplantation Moratorium in France Because of the COVID-19 Pandemic: A Cohort-based Study. *Transplantation*, 2022, 106 (12), pp.2416-2425. 10.1097/tp.0000000000004369 . hal-03820511

**HAL Id: hal-03820511**

**<https://ehesp.hal.science/hal-03820511>**

Submitted on 8 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Impact of the kidney transplantation moratorium in France because of the COVID-19 pandemic: A cohort-based study.

Vincent Bonnemains<sup>1,#</sup>, MSc | Florent Le Borgne<sup>1,2,#</sup>, PhD | Emile Savoye<sup>3</sup>, MSc | Camille Legeai<sup>3</sup>, MD | Myriam Pastural<sup>3</sup>, MD | Sahar Bayat-Makoei<sup>4</sup>, PhD | Rémi Lenain<sup>1,5</sup>, MD | Stéphanie Ragot<sup>6</sup>, PhD | Karen Leffondré<sup>7</sup>, PhD | Cécile Couchoud<sup>3,8</sup>, MD, PhD | Yohann Foucher<sup>1,\*</sup>, PhD

1. INSERM UMR 1246 - SPHERE, Université de Nantes, Université de Tours, Nantes, France.
2. IDBC-A2COM, Nantes, France.
3. Agence de la biomédecine, Saint-Denis La Plaine, France.
4. Université de Rennes, EHESP, CNRS, INSERM, Arènes – UMR 6051, U1309, F-35000 Rennes, France.
5. Service de Néphrologie, Centre Hospitalier Universitaire de Lille, Lille, France.
6. INSERM, CIC-1402, Poitiers, France; Faculté de Médecine et de Pharmacie de Poitiers, Université de Poitiers, Poitiers, France.
7. Université de Bordeaux, INSERM, Bordeaux Population Health Research Center, UMR1219, Bordeaux, France.
8. Université de Lyon I, CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique Santé, Villeurbanne France.

#. Both authors equally contributed.

\*. Address for correspondence: INSERM UMR 1246 - SPHERE, 22 boulevard Benoni-Goullin, 44200 Nantes, France. Email: [yohann.foucher@univ-nantes.fr](mailto:yohann.foucher@univ-nantes.fr)

*Abstract:* 245 words.

*Body of manuscript:* 3988 words.

*Keywords:* Kidney transplantation, Moratorium, Simulations, Life expectancy, Cohort.

*Author contributions:* Y.F. supervised this work. F.L.B. and V.B. performed the simulations and other statistical analyses. C.C. performed the data extraction. All the authors participated in the design of the study and were engaged in the writing of the final proposal.

*Funding:* This work was supported by a public grant overseen by the French National Research Agency (ANR-20-COV8-0002-01). The funder had no role in the study design; the analysis, and interpretation of data; the writing of the report; or the decision to submit the report for publication.

*Conflict of interest:* The authors declared no conflict of interest for this study.

*Abbreviations:* ESRD - end-stage renal disease, KT - kidney transplantation, REIN - Renal Epidemiology and Information Network, BMI - body mass index, RMST - restricted mean survival time, RMWL - restricted mean survival time on the waiting list, ECD - expanded criteria donor, SCD - standard criteria donor, CI - 95% confidence interval.

*Posted history:* This manuscript was previously posted as a preprint: doi: <https://dx.doi.org/10.2139/ssrn.4052653>

## **Abstract**

*Background.* The COVID-19 pandemic has resulted in worldwide kidney transplantation (KT) moratoriums. The impacts of these moratoriums on the life expectancy of KT candidates remain unclear.

*Methods.* We simulated the evolution of several French candidate populations for KT using a multistate semi-Markovian approach and according to moratorium durations ranging from 0 to 24 months. The transition rates were modeled from the 63,927 French patients who began dialysis or were registered on the waiting list for KT between 2011 and 2019.

*Results.* Among the 8,350 patients active on the waiting list at the time of the French KT moratorium decided on March 16, 2020, for 2.5-month, we predicted 4.0 additional months [CI: 2.8, 5.0] on the waiting list and 42 additional deaths [CI: -70, 150] up to March 16, 2030 compared to the scenario without moratorium. In this population, we reported a significant impact for a 9-month moratorium duration: 135 attributable deaths [CI: 31, 257] up to March 16, 2030. Patients who became active on the list after March 2020 were less impacted: there was a significant impact for an 18-month moratorium (175 additional deaths [CI: 21, 359]) in the 10,862 prevalent ESRD patients on March 16, 2020 and for a 24-month moratorium (189 additional deaths [CI: 10, 367]) in the 16,355 incident ESRD patients after this date.

*Conclusion.* The temporary moratorium of KT during a COVID-19 peak represents a sustainable decision to free up hospitals' resources if the moratorium does not exceed a prolonged period.



## Introduction

As reported by the World Health Organization on February 17, 2022 <sup>1</sup>, 5,978,096 individuals died due to COVID-19. The risk factors for severe COVID-19 included old age and individuals with comorbidities, such as diabetes, obesity, hypertension, immunodeficiency, cardiovascular disease, or renal insufficiency <sup>2</sup>. The population with end-stage renal disease (ESRD) is therefore highly impacted.

At an individual level, the advantages of kidney transplantation (KT) were challenged due to the exposure of recipients to immunosuppressive drugs and their related over-mortality after SARS-CoV-2 infection <sup>3-5</sup>. At a population level, health care was reorganized to mobilize staff and equipment for patients with severe forms of COVID-19 to the detriment of transplantation activity. Altogether, a number of health decision-makers decided on regional or national KT moratoriums <sup>6</sup>. In France, this moratorium was decided on March 16, 2020, and KT activity officially stopped until May 2020 and remained limited until June 2020 <sup>7</sup>.

Recent literature has evaluated the impact of the moratorium and ways to improve pandemic preparedness. Thauvat et al. <sup>8</sup> described comparable 3-month COVID-19-related mortality between KT recipients and candidates in France, but they reported no long-term outcomes. Aubert et al. <sup>9</sup> extrapolated a worldwide loss of 37,664 patient life-years due to the decrease in the observed KT activity between 2019 and 2020 in 22 national cohorts. Vinson et al. <sup>10</sup> proposed extrapolations from a study entirely based on US-centered assumptions: KT was associated with a 5.8-year gain compared to dialysis in a 40-year-old candidate. Massie et al. <sup>11</sup> performed a simulation-based study from the data of the US scientific registry. They also concluded a benefit of no discontinuity in KT activity

compared to delaying KT after the pandemic, but with a magnitude lower than the previous listed studies. Considering a proportion of deaths lower than 50% among SARS-CoV-2-infected candidates on the waiting list and KT recipients, they predicted a life expectancy gained due to KT over the first 5 years of 2.9 months compared to delaying the transplantation up to 12 months.

Therefore, health decision-makers still face a complex situation. On the one hand, the results proposed by Aubert et al. <sup>9</sup> or Vinson et al. <sup>10</sup> call for the continuity of the transplantation activity, even if it means straining the resources of hospitals during pandemic peaks. However, the results reported by Massie et al. <sup>11</sup> support the strategy of temporarily stopping KT activity due to the limited impact on candidate mortality.

In this context, we aimed i) to describe the multistate evolution of ESRD patients before the COVID-19 pandemic using a multistate model, ii) to predict from this model the long-term impact of the observed KT moratorium in France, and iii) to predict the impact of alternative moratorium durations in cases of rebound, seasonality, or even other pandemics.

# Methods

## Study population

We conducted our study using the French Renal Epidemiology and Information Network (REIN) registry. We included children and adults at the time of their first dialysis or candidates for preemptive KT at the time of their registration on the waiting list (active or inactive). We did not include patients from overseas districts, and those without follow-up or registered for multiorgan transplantation. Details regarding this exhaustive registry have been described previously <sup>12</sup>. The age, sex, body mass index (BMI), diabetic status, history of cardiovascular comorbidities, region of residence, and calendar year were collected at the time of entry into the registry. For KT recipients, the donor age, blood type and donor type were also available. All dates related to registration or removal from waiting list, temporary inactive status, transplantation, dialysis and death were prospectively collected.

The training cohort, for estimating the predictive models, included all patients meeting the inclusion criteria defined above who entered the registry between September 1, 2011, and December 31, 2019, which was also the date of administrative censoring.

The prevalent cohort, for predicting the impact of the KT moratorium, included all the patients alive on March 16, 2020 (i.e., the first day of the French moratorium).

## Statistical analyses

*Estimation of the models before March 2020.* We estimated from the training cohort the natural history of the disease before the pandemic by using a semi-Markovian approach. The multistate structure is described in Figure 1. We estimated transition-specific multivariate proportional hazard models, and the baseline hazard functions were



obtained by using generalized Weibull distributions <sup>13</sup>. The goodness-of-fit was investigated by comparison with the Breslow estimator <sup>14</sup>. Piecewise exponential distributions were used when necessary. All the quantitative explanatory variables were categorized to avoid the log-linearity assumption. For each transition, patient age was categorized so that at least 20 events were observed in every category. The proportional hazards assumption was verified according to the Schoenfeld residuals and the plots of the log minus log survival. Because of their importance in predicting mortality, we considered patient age, BMI, diabetes status and the number of cardiovascular comorbidities. For the other covariates listed in the previous subsection, we performed a backward selection ( $p < 0.05$ , likelihood-ratio statistics). The resulting 17 models are presented in Supplementary Tables S1-6. In addition, we modeled the characteristics of the incident patients at the time of their entry into the registry (Supplementary Table S7). Finally, for each KT recipient, we modeled the donor characteristics according to the recipients' characteristics (Supplementary Table S8). We performed these estimations on complete cases without missing data.

*Simulation of the cohorts after March 2020.* In contrast with the training cohort, which was constituted by incident ESRD patients after 2011 in the registry, the cohort used to evaluate the impact of the KT moratorium was the patients alive on March 2020. Some of these patients were prevalent ESRD patients at the beginning of the registry in 2011. For these prevalent patients, we observed missing data at baseline. Therefore, we first imputed the missing data using multivariate imputation by chained equations <sup>15</sup>. Second, we simulated the monthly numbers of incident patients according to a Poisson distribution with expectancy equal to the observed number of incident patients in 2019. The inclusion days of these new patients were obtained by uniform distributions. Their characteristics were generated by using the previous embedded regressions (Table S7),

with 2019 as the calendar year. Third, we simulated the evolution of each individual by using the previous transition-specific models and the methodology described in Beyersmann <sup>16</sup> in the context of competing events. Left truncations of prevalent patients were considered. We tuned the baseline hazard functions of the models related to the transitions to the graft to ensure 3,600 KT's per year, as observed in 2019. For each simulated transition to the graft, the corresponding donor characteristics were simulated by using the regressions described in Table S8. We studied different scenarios according to the duration of the KT moratorium: 2.5 months, as observed in France and from 6 to 24 months.

*Estimations of the moratorium impact.* We studied three complementary populations: i) the patients active on the waiting list on March 16, 2020 (population A); ii) the patients inactive or not registered on the waiting list on March 16, 2020, but who will become active before March 16, 2025 (population B); and iii) the incident patients after March 16, 2020, who will become active candidates for KT before March 16, 2025 (population C). We considered two predictive windows of 5 and 10 years, from March 16, 2020 for patients active on the list at this time, or from the registration on the active list for the other two populations. The Covid-19-related mortality being correlated to age, we performed subgroup analyses to evaluate the KT moratorium's impacts in patients older or younger than 60 years. Patient survival was estimated by using the Kaplan-Meier estimator <sup>17</sup>, and the corresponding restricted mean survival time (RMST) was estimated by the area under the curve <sup>18</sup>. All deaths were considered regardless of the transplantation. The cumulative probabilities of transplantation or death on the waiting list were obtained by using the Aalen-Johannsen estimator <sup>19</sup>, and the restricted mean survival time on the waiting list (RMWL) by the area above the sum of the cumulative probability of transplantation and death before transplantation <sup>20</sup>. For each scenario, the

previous simulations were performed 1000 times to obtain the 95% confidence intervals (CIs). The statistical analyses were performed with R version 4.1.2.

## Results

### Description of the training cohort

The characteristics at the time of inclusion in the REIN registry of the training cohort are described in Table 1. Among the 76,980 incident ESRD patients between 2011 and 2019 with no missing data, 63,927 were included because of dialysis and 13,053 because of preemptive registration on the waiting list (4,441 active versus 8,612 inactive). The characteristics of the two cohorts were close (Supplementary Table S9). The mean recipient age was 67.2 years [ $\pm 16.3$ ] and 64.6% were male. The median follow-up time was 3.87 years. A total of 26,174 patients were registered on the waiting list after their entry into the REIN registry, 14,159 were transplanted, and 27,856 died (193 on the list for a preemptive transplantation, 834 with a functional graft and 26,829 in dialysis).

### Prognosis at 5 years of the patients active on the list on March 16, 2020 (population A)

The 8,350 patients are described at the time of their entry into the registry in Table 2. The mean age was 50.6 years [ $\pm 17.1$ ], 62.5% of patients were male, 23.9% had diabetes and 17.4% had cardiovascular comorbidities.

In the case of no KT moratorium, the outcomes are presented in Figure 2 and Table 3. We predicted a 5-year patient survival of 83.2% [CI: 82.5, 84.0], corresponding to 1,399 deaths [CI: 1,334, 1,463] and a mean life expectancy (RMST) equal to 4.62 years [CI: 4.60, 4.64] up to March 2025. The candidates had a 65.0% chance of being transplanted up to March 2025 [CI: 64.1, 66.0], corresponding to 5,430 transplantations [CI: 5,353, 5,511] and a mean survival time on the waiting list (RMWL) equal to 2.61 years [CI: 2.57, 2.64].

We then considered the observed 2.5-month moratorium in France. The impact on the mortality was negligible (the 5-year survival was 83.1% [CI: 82.4, 83.9] and the 5-year RMST was 4.62 years [CI: 4.60, 4.64]). The 5-year cumulative probability of KT equaled 61.3% [CI: 60.3, 62.3], corresponding to 312 KT losses [CI: 196, 424] and 2.9 supplementary months [CI: 2.2, 3.5] on the list.

We repeated the analyses for moratorium durations from 6 to 24 months (Supplementary Tables S10-11). Figures 2C and 2D present the results in terms of additional deaths and KT losses. The 5-year mortality remained comparable across all scenarios. The 5-year cumulative probability of KT decreased with moratorium duration and reached 33.0% [CI: 32.1, 34.0] for 24 months, corresponding to 2,672 KT losses [CI: 2,547, 2,785] and 18.0 additional months [CI: 17.5, 18.5] on the list up to March 2025.

**Prognosis at 5 years of patients who were inactive or not registered on the list on March 16, 2020 who will become active candidates before March 16, 2025 (population B)**

Population B counted an average of 10,862 patients (Table 2). The mean age of recipients was 50.2 years ( $\pm 17.3$ ), 62.7% of patients were male, 27.4% had diabetes, and 21.8% had cardiovascular comorbidities.

In the scenario without a KT moratorium, this population had a 78.5% estimated survival probability [CI: 77.8, 79.2] at 5 years post-registration on the active list (Figure 3A), corresponding to 2,338 deaths [CI: 2,242, 2,425] and a 5-year RMST equal to 4.49 years [CI: 4.46, 4.51]. These candidates had a 62.4% chance [CI: 61.6, 63.2] of being transplanted at 5 years after becoming active candidates, which corresponded to 6,869 transplantations [CI: 6,746, 6,996]. The 5-year RMWL was 2.51 years [CI: 2.48, 2.55].

For a 2.5-month moratorium, the impact on the mortality was negligible (the 5-year survival was 78.4% [CI: 77.7, 79.2] and the 5-year RMST was 4.49 years [CI: 4.46, 4.51]). The 5-year probability of being transplanted decreased to 60.9% [CI: 60.0, 61.8], which means 175 KT losses [CI: -1, 351]. The corresponding RMWL was 2.59 [CI: 2.56, 2.62]: 0.9 additional months [CI: 0.3, 1.5] on the list.

The impacts of longer moratoriums are illustrated in Figures 3C and 3D. The duration did not significantly impact the 5-year mortality of this population. For instance, the 5-year survival was 78.2% [CI: 77.4, 79.0] for a 24-month moratorium, which represents 28 additional deaths [CI: -107, 161] compared to the absence of a moratorium.

### **Prognosis at 5 years of incident ESRD patients after March 16, 2020 who will become active candidates before March 16, 2025 (population C)**

Population C included an average of 16,355 (28.8%) patients (Table 2). The mean recipient age was 52.4 years ( $\pm 18.0$ ), 63.8% of patients were male, 29.0% had diabetes, and 25.1% had cardiovascular comorbidities.

In this population, in the absence of a KT moratorium, the patient survival was estimated to be 86.0% [CI: 85.5, 86.5] at 5-year post-registration (Figure 4A). We estimated a 65.4% [CI: 64.6, 66.1] chance of being transplanted at 5 years (Figure 4B), corresponding to 10,774 transplantations [CI: 10,595, 10,960] and a 5-year RMWL equal to 2.63 years [CI: 2.60, 2.66].

For a 2.5-month moratorium, the 5-year post-registration patient survival remained at 86.0% [CI: 85.5, 86.5]. The 5-year cumulative probability of KT equaled 64.1% [CI: 63.4, 64.8], resulting in 209 KT losses [CI: -40, 481] and 0.7 additional months [CI: 0.2, 1.2] on the waiting list.

The impacts of alternative moratorium durations are illustrated in Figures 4C and 4D. The 5-year post-registration survival did not vary. For a 24-month moratorium, the 5-year post-registration cumulative probability of KT was 51.6% [CI: 50.8, 52.3].

### **Results for a predictive window at 10 years**

We performed the same analyses with predictions up to 10 years (Table 3, Supplementary Tables S10-11 and Figures S1-S3).

In the scenario without KT moratorium, the 8,350 patients of the population A had a 10-year survival of 64.6% [CI: 63.7, 65.5] and a 10-year cumulative probability of KT of 75.8% [CI: 75.0, 76.7]. For a 2.5-month moratorium, the survival decreased to 64.1% [CI: 63.2, 65.0] (42 additional deaths [CI: -70, 150]) and the cumulative probability of KT to 73.3% [CI: 72.4, 74.1] (213 KT losses [CI: 114, 323] and 4.0 additional months [CI: 2.8, 5.0] on the list). We estimated a significant over-mortality for a 9-month moratorium: the patient survival was 63.0% [CI: 62.1, 63.9], which represented 135 additional deaths [CI: 31, 257] up to March 16, 2030. However, we did not report a significant decrease in the 10-year RMST in any scenario. For instance, for a 24-month moratorium, the RMST decreased by 0.87 months [CI: -0.02, 1.77], corresponding to a total of 605 patient life-years lost [CI: -14, 1232].

In the 10,862 patients of the population B, we predicted a patient survival at 10 years post-registration equal to 58.7% [CI: 57.8, 59.6] and a cumulative probability of KT equal to 71.8% [CI: 71.0, 72.6] in case of no KT moratorium. We estimated a significant over-mortality for a 18-month moratorium, and the patient survival decreased to 57.1% [CI: 56.1, 58.0] (175 additional deaths [CI: 21, 359]). The 10-year RMST decreased by 0.58 months [CI: -0.40, 1.54], i.e., a total of 525 patient life-years lost [CI: -362, 1394].

In the 16,355 patients of the population C, we predicted a patient survival at 10 years post-registration equal to 68.2% [CI: 67.5, 68.9] and a cumulative probability of KT of 77.2% [CI: 76.5, 77.8]. For a 24-month moratorium, the patient survival was 67.1% [CI: 66.4, 67.7], resulting in 189 additional deaths [CI: 10, 367]. The 10-year RMST decreased by 0.10 months [CI: -0.54, 0.78], i.e., a total of 136 patient life-years lost [CI: -736, 1063].

### **Results according to patient's age**

Patients older than 60 were less impacted by KT moratoriums: they had a lower additional time on the waitlist and a lower overmortality than younger patients in each of the three populations.

In the population A, 4124 patients (49.4%) were older than 60. In case of a 9-month moratorium, we predicted 55 [CI: -27, 139] additional deaths at a 10-year horizon among these patients versus 80 [CI: 11, 150] among younger ones. Meanwhile, patients older than 60 spent 11.8 additional months on the waitlist [CI: 10.4, 13.4] whereas that time reached 14.4 months [CI: 12.8, 15.9] for younger patients.

In the population B, 5538 patients (51.0%) were older than 60 at that time. In case of an 18-month moratorium, we predicted 61 [CI: -67, 198] additional deaths at a 10-year horizon among these patients versus 113 [CI: 19, 207] among younger ones. Meanwhile, patients older than 60 spent 12.0 additional months on the waitlist [CI: 10.7, 13.4] whereas that time reached 15.5 months [CI: 14.2, 16.9] for younger patients.

In the population C, 6932 patients (42.4%) were older than 60 at that time. In case of a 24-month moratorium, we predicted 55 [CI: -98, 207] additional deaths at a 10-year horizon among these patients versus 134 [CI: 19, 246] among younger ones. Meanwhile, patients older than 60 spent 11.0 additional months on the waitlist [CI: 9.7, 12.2] whereas that time reached 14.1 months [CI: 12.9, 15.2] for younger patients.



Extensive results of this subgroup analysis can be found in Supplementary Tables S12-14.

## Discussion

Normally, the time to transplantation should be as short as possible <sup>21-23</sup>. However, the current COVID-19 pandemic questions temporally this certainty. Based on the French REIN registry, we extrapolated the impact of the French KT moratorium initiated on March 16, 2020 for three complementary populations: i) the patients active on the waiting list on March 16, 2020; ii) the patients inactive or not registered on the waiting list on March 16, 2020, but who will become active before March 16, 2025; iii) and the simulated incident patients after March 16, 2020, who will become active candidates for KT before March 16, 2025.

Overall, we reported nonsignificant impacts on 5-year patient survival. Our results illustrated that the impact of the moratorium should be observed over 10 years. For a 2.5-month moratorium, i.e., the interruption observed in France, the most impacted population was the 8,350 patients active on the waiting list on March 2020, for whom we predicted 42 attributable deaths [CI: -70, 150] up to March 2030 and 4.0 supplementary months [CI: 2.8, 5.0] on the waiting list. In this population, we reported a significant impact on the 10-year mortality for a 9-month moratorium duration: 135 attributable deaths [CI: 31, 257] up to March 16, 2030. For patients who would become active candidates after the KT moratorium, we reported no significant impact of a less than 18-month moratorium. In each population, patients younger than 60 were the most impacted, both in terms of mortality and time spent on the waitlist.

Our results did not confirm the important impact of the KT moratorium outlined by Aubert et al. <sup>9</sup> However, the authors extrapolated the mortality from a biased difference in life expectancy between KT recipients versus dialyzed patients <sup>24</sup>. They overestimated

the KT benefit by ignoring the immortal time bias <sup>25</sup> and time-dependent confounders <sup>26</sup>. Our results are more concordant with those proposed by Massie et al <sup>11</sup>, although they estimated a higher impact of a 12-month moratorium than we did.-This difference may be explained by them ignoring the informative censoring at KT and assuming the removals from the active list as deaths. Regardless of these differences, our results and those proposed by Massie et al. tend to validate the decision of temporary KT moratorium. Alternatively, our subgroup results (more or less than 60 years old) raise the question of age-driven moratorium strategies, given that older patients who have the highest Covid-19-related mortality are also the less impacted by the KT moratorium. Additional works on that matter with higher focus on Covid-19-related mortality would be useful to answer this question.

A strength of our study is that we performed individual simulations to reconstruct the prospective evolution of the French ESRD population, considering both the evolutions of the prevalent and the incident patients at the date of the KT moratorium. This method allowed us to estimate the long-term impact of the KT moratorium on the evolution of the waiting list and its consequences on the life expectancy of present and future generations. Another strength was the unselected nature of the study population, which was based on an exhaustive national registry.

However, our study must be understood in the context of its limitations. Extrapolating the evolution of populations is always associated with assumptions. First, we estimated our models based on incident patients in the REIN registry between 2011 and 2019. We selected this training cohort because of the lower frequency of missing data for incident ESRD patients who entered the registry after 2011. Our choice is open to criticisms, especially the possible bias of predictive models for extrapolations. For instance, future

downward variation in incidence trends may be expected, already observed in nondiabetic patients <sup>27</sup>. Second, we arbitrarily tuned the baseline hazard functions of transplantation so that the number of transplantations each year is realistic regarding the previous organ procurement. A possible improvement of our study would be to avoid such manual tuning by modeling the incidence of donations and the matching between grafts and candidates. It would then be relevant to allow a gradual reduction and then a gradual increase in the number of transplantations. We took as a reference a scenario with no moratorium corresponding to the transplant activity observed before the pandemic. An improvement of our study could be to consider a more realistic scenario where, despite the absence of a moratorium, transplantation activity would have been reduced (staff at hospitals and retrieval teams, limitation on the donor's pool, etc.). One can note that such analyses would have resulted in the estimation of smaller impacts of the KT moratoriums, which reinforce our conclusions. Third, we did not add an excess of mortality related to COVID-19 in our simulations. Even if the literature reported small differences <sup>28</sup> or even comparable <sup>8</sup> COVID-19-related mortality among KT infected candidates versus recipients, a perspective of our work for health crisis preparedness is to allow scenarios depending on the incidence of a novel pathogen or variants and the related mortality post-infection. Again, for the present study, one can note that if we had simulated an excess of posttransplant mortality, our results in favor of a temporary KT moratorium would have been reinforced. Fourth, we assumed that dialysis patients who have temporarily no access to kidney transplantation continue their dialysis treatment. However, the moratorium can lead to an increase in the number of dialysis patients potentially outnumbering the available capacity. Fifth, we presented results up to 5 and 10 years. These prognostic times influenced the results. This dependence must be considered by the readers. Moreover, the longest follow-up time in our training cohort was 8.3 years,

which calls for caution when interpreting 10-years outcomes. Sixth, we used the French national registry. Other countries have different waitlist managements. Especially, a practice in France is to firstly register KT candidates as inactive on the waiting list. These patients are mostly waiting for their pretransplant evaluation and/or searching for a potential living donor. The extrapolation of our results to different countries can be discussed. Lastly, we did not study the quality of life. A perspective of our work is to extend the results in terms of quality-adjusted life years, but additional assumptions are needed because information on the quality of life is not collected in the REIN registry. In particular, despite our model accounted for the duration since entry into the registry, we may consider finer modelling of the potential effect of extending pretransplant dialysis duration on quality of life, as well as on mortality after transplantation <sup>29</sup>.

In conclusion, our results offer arguments in support of the temporary KT moratorium during the first COVID-19 pandemic peaks. A temporary KT moratorium represents a sustainable decision to free up hospital resources if it does not exceed a prolonged period. By further predicting the impacts of several moratorium durations, we additionally believe that our results could help in future decision-making and improving pandemic preparedness.

## References

1. WHO Coronavirus (COVID-19) Dashboard. Accessed February 17, 2022. <https://covid19.who.int>
2. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020;46(5):846-848. doi:10.1007/s00134-020-05991-x
3. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int.* 2020;97(6):1083-1088. doi:10.1016/j.kint.2020.04.002
4. Hilbrands LB, Duivenvoorden R, Vart P, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant.* 2020;35(11):1973-1983. doi:10.1093/ndt/gfaa261
5. Jager KJ, Kramer A, Chesnaye NC, 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.* 2020;98(6):1540-1548. doi:10.1016/j.kint.2020.09.006
6. Early national and center-level changes to kidney transplantation in the United States during the COVID-19 epidemic - Boyarsky - 2020 - American Journal of Transplantation - Wiley Online Library. Accessed January 6, 2022. <https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.16167>
7. Agence de la Biomédecine. Mise à jour des recommandation concernant l'activité de prélèvement et de greffe d'organes et de tissus durant l'épidémie du coronavirus le SARS-CoV-2. Published May 12, 2020. Accessed June 2, 2020. <https://www.agence-biomedecine.fr/Recommandation-concernant-l-activite-de-prelevement-et-de-greffe-d-organes-et-1314>
8. Thaunat O, Legeai C, Anglicheau D, et al. IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT). *Kidney International.* 2020;98(6):1568-1577. doi:10.1016/j.kint.2020.10.008
9. Aubert O, Yoo D, Zielinski D, et al. COVID-19 pandemic and worldwide organ transplantation: a population-based study. *The Lancet Public Health.* 2021;6(10):e709-e719. doi:10.1016/S2468-2667(21)00200-0
10. Vinson AJ, Kiberd BA, Tennankore KK. Panic in the Pandemic: When Should Kidney Transplant Programs Close? *Kidney International Reports.* 2021;6(5):1232-1241. doi:10.1016/j.ekir.2021.02.017
11. Massie AB, Boyarsky BJ, Werbel WA, et al. Identifying scenarios of benefit or harm from kidney transplantation during the COVID-19 pandemic: A stochastic simulation

- and machine learning study. *American Journal of Transplantation*. 2020;20(11):2997-3007. doi:10.1111/ajt.16117
12. Couchoud C, Stengel B, Landais P, et al. The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. *Nephrol Dial Transplant*. 2006;21(2):411-418. doi:10.1093/ndt/gfi198
  13. Foucher Y, Mathieu E, Saint-Pierre P, Durand J, Daurès J. A semi-Markov model based on generalized Weibull distribution with an illustration for HIV disease. *Biom J*. 2005;47:825-833.
  14. N. E. Breslow. Discussion of Professor Cox's Paper. *Journal of the Royal Statistical Society*. 1972;34:216-217.
  15. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. 2011;45:1-67. doi:10.18637/jss.v045.i03
  16. Beyersmann J, Latouche A, Buchholz A, Schumacher M. Simulating competing risks data in survival analysis. *Stat Med*. 2009;28(6):956-971. doi:10.1002/sim.3516
  17. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*. 1958;53(282):457-481. doi:10.2307/2281868
  18. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. 2013;13(152):1-15. doi:10.1186/1471-2288-13-152
  19. Aalen OO, Johansen S. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. *Scandinavian Journal of Statistics*. 1978;5(3):141-150.
  20. Conner SC, Trinquart L. Estimation and modeling of the restricted mean time lost in the presence of competing risks. *Statistics in Medicine*. 2021;40(9):2177-2196. doi:10.1002/sim.8896
  21. Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. *Kidney Int*. 2000;58(3):1311-1317. doi:10.1046/j.1523-1755.2000.00287.x
  22. Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation*. 2002;74(10):1377-1381. doi:10.1097/01.TP.0000034632.77029.91
  23. Cosio FG, Alamir A, Yim S, et al. Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. *Kidney Int*. 1998;53(3):767-772. doi:10.1046/j.1523-1755.1998.00787.x

24. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. *JAMA Surg.* 2015;150(3):252-259. doi:10.1001/jamasurg.2014.2038
25. Foster MC, Varothai N, Weiner DE. Estimation of Life-Years Saved by Solid-Organ Transplant. *JAMA Surgery.* 2015;150(10):1015. doi:10.1001/jamasurg.2015.1936
26. Lenain R, Boucquemont J, Leffondré K, et al. Clinical trial emulation by matching time-dependent propensity scores: the example of estimating impact of kidney transplantation. *Epidemiology.* 2021;32(2):220-229. doi:10.1097/EDE.0000000000001308
27. R.E.I.N. (Réseau Epidémiologique et Information en (&hellip;)) - Agence de la biomédecine. Published June 8, 2020. Accessed June 9, 2020. <https://www.agence-biomedecine.fr/R-E-I-N-Reseau-Epidemiologique-et-Information-en-Nephrologie>
28. Mohan S, King KL, Husain SA, Schold JD. COVID-19–Associated Mortality among Kidney Transplant Recipients and Candidates in the United States. *CJASN.* 2021;16(11):1695-1703. doi:10.2215/CJN.02690221
29. Prezelin-Reydit M, Combe C, Harambat J, et al. Prolonged dialysis duration is associated with graft failure and mortality after kidney transplantation: results from the French transplant database. *Nephrol Dial Transplant.* 2019;34(3):538-545. doi:10.1093/ndt/gfy039

## **Ethics statement**

This study was performed in accordance with the Helsinki Declaration and approved by the scientific council of the REIN registry. The data collection was approved by the National Commission for Data Protection and Liberties (Comité National de l'Informatique et des Libertés, CNIL, No. 180092587).

## **Data sharing**

The dataset used in this study is not publicly available. The datasets from the REIN registry are available for research purposes, but an application must be submitted to, and



approved by, the executive committee. The process is explained at this address:

<https://www.agence-biomedecine.fr/Demande-d-acces-aux-donnees-individuelles-issues-des-prelevements-et-des>

## Tables

Mean ( $\pm$ standard deviation) Effective (%)	No dialysis and active on the list (N=4,441)	No dialysis and inactive on the list (N=8,612)	Dialysis (N=63,927)
Age in years	51.0 $\pm$ 16.7	54.1 $\pm$ 14.6	70.1 $\pm$ 14.9
Body mass index (kg/m <sup>2</sup> )			
$\leq$ 18	254 (5.7)	296 (3.8)	2,431 (3.8)
]18, 25]	1,975 (44.5)	3,497 (40.6)	25,651 (40.1)
]25, 30]	1,494 (33.6)	2,931 (34.0)	19,821 (31.0)
]30, 35]	599 (13.5)	1,404 (16.3)	9,988 (15.6)
>35	119 (2.7)	484 (5.6)	6,036 (9.4)
Male sex	2,786 (62.7)	5,323 (61.8)	41,613 (65.1)
Diabetes	794 (17.9)	2,056 (23.9)	30,007 (46.9)
Cardiovascular disease	679 (15.3)	1,794 (20.8)	38,875 (60.8)

**Table 1.** Description of the training cohort at the time of inclusion in the REIN registry according to the initial state (n=76,980).

Mean ( $\pm$ standard deviation) Effective (%)	Prevalent patients active on the list on March 2020 (N=8,350)	Prevalent patients not active on the list on March 2020 (N=10,862)	Incident patients in the registry after March 2020 (N=16,355)
Age in years	50.6 ( $\pm$ 17.1)	50.2 ( $\pm$ 17.3)	52.4 ( $\pm$ 18.0)
Body mass index (kg/m <sup>2</sup> )			
$\leq$ 18	241 (2.89)	399 (3.7)	633 (3.9)
]18, 25]	3,773 (45.2)	4,815 (44.3)	6,827 (41.7)
]25, 30]	2,684 (32.1)	3,140 (28.9)	5,625 (34.4)
]30, 35]	1,246 (14.9)	1,668 (15.4)	2,541 (15.5)
>35	406 (4.9)	839 (7.7)	730 (4.5)
Male sex	5,220 (62.5)	6,812 (62.7)	10,433 (63.8)
Diabetes	1,998 (23.9)	2,975 (27.4)	4,749 (29.0)
Cardiovascular disease	1,456 (17.4)	2,373 (21.8)	4,108 (25.1)

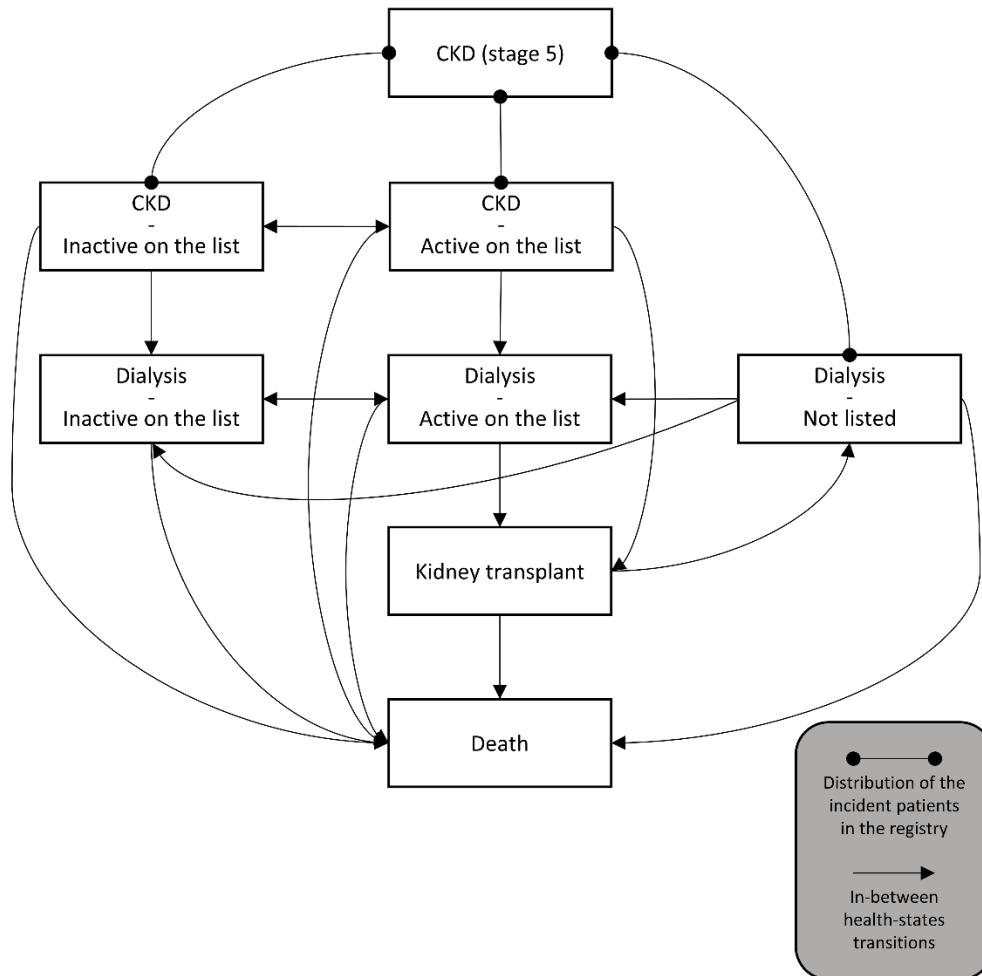
**Table 2.** Description of the three studied populations of candidates for KT transplantation: active on the waiting list on March 16, 2020; inactive or not registered on the waiting list on March 16, 2020, but who will become active before March 16, 2025; and incident patients after March 16, 2020, who will become active candidates for KT before March 16, 2025.

Outcome	Moratorium duration	Population	Prognostic time <sup>a</sup>	Patient survival	Number of deaths	Number of additional deaths	RMST (years)	Decrease in RMST (months)	Patient life-year lost
Mortality	0 month	Active (N=8,350)	5 years	83.2 [82.5, 84.0]	1,399 [1,334,1,463]	-	4.62 [4.60, 4.64]	-	-
			10 years	64.6 [63.7, 65.5]	2,955 [2,880, 3,032]	-	8.30 [8.25, 8.36]	-	-
		Not active (N=10,862)	5 years	78.5 [77.8, 79.2]	2,338 [2,242, 2,425]	-	4.49 [4.46, 4.51]	-	-
			10 years	58.7 [57.8, 59.6]	4,489 [4,361, 4,603]	-	7.89 [7.83, 7.95]	-	-
		Incidents (N=16,355)	5 years	86.0 [85.5, 86.5]	2,291 [2,202, 2,376]	-	4.69 [4.67, 4.70]	-	-
			10 years	68.2 [67.5, 68.9]	5,195 [5,055, 5,329]	-	8.53 [8.50, 8.57]	-	-
	2.5 months (observed in France)	Active (N=8,350)	5 years	83.1 [82.4, 83.9]	1,407 [1,345, 1,469]	8 [-79, 100]	4.62 [4.60, 4.64]	-0.03 [-0.37, 0.32]	-20.9 [-257.5, 222.7]
			10 years	64.1 [63.3, 65.0]	2,997 [2,919, 3,073]	42 [-70, 150]	8.29 [8.24, 8.34]	0.16 [-0.73, 1.05]	111.3 [-508.0, 730.6]
		Not active (N=10,862)	5 years	78.4 [77.7, 79.2]	2,341 [2,255, 2,432]	4 [-123, 139]	4.49 [4.46, 4.51]	0.00 [-0.36, 0.39]	-27.2 [-330.4, 354.8]
			10 years	58.5 [57.6, 59.3]	4,506 [4,398, 4,617]	17 [-145, 186]	7.88 [7.83, 7.94]	0.07 [-0.85, 1.06]	63.4 [-769.4, 959.5]
Incidents (N=16,355)	5 years	86.0 [85.5, 86.5]	2,291 [2,200, 2,377]	0 [-128, 121]	4.69 [4.67, 4.70]	-0.01 [-0.24, 0.22]	-13.6 [-327.1, 299.8]		
	10 years	68.1 [67.4, 68.8]	5,217 [5,080, 5,362]	22 [-161, 212]	8.53 [8.49, 8.57]	0.03 [-0.59, 0.69]	40.9 [-804.1, 940.4]		
Outcome	Moratorium duration	Population	Prognostic time <sup>a</sup>	Cumulative probability of KT	Number of KT's	Number of KT losses	RMWL (years)	Increase in RMWL (months)	Waitlist-year gain
KT activity	0 month	Active (N=8,350)	5 years	65.0 [64.1, 66.0]	5,430 [5,353, 5,511]	-	2.61 [2.57, 2.64]	-	-
			10 years	75.8 [75.0, 76.7]	6,333 [6,263, 6,407]	-	3.38 [3.31, 3.44]	-	-
		Not active (N=10,862)	5 years	62.4 [61.6, 63.2]	6,869 [6,746, 6,996]	-	2.51 [2.48, 2.55]	-	-
			10 years	71.8 [71.0, 72.6]	7,900 [7,774, 8,026]	-	3.30 [3.24, 3.35]	-	-
		Incidents (N=16,355)	5 years	65.4 [64.6, 66.1]	10,774 [10,595, 10,960]	-	2.63 [2.60, 2.66]	-	-
			10 years	77.2 [76.5, 77.8]	12,720 [12,536, 12,920]	-	3.45 [3.41, 3.50]	-	-
	2.5 months (observed in France)	Active (N=8,350)	5 years	61.3 [60.3, 62.3]	5,118 [5,033, 5,201]	312 [196, 424]	2.85 [2.81, 2.88]	2.85 [2.23, 3.46]	1,983.1 [1,551.7, 2,407.6]
			10 years	73.3 [72.4, 74.1]	6,120 [6,043, 6,189]	213 [114, 323]	3.71 [3.64, 3.77]	3.96 [2.83, 5.00]	2,755.5 [1,969.2, 3,479.2]
		Not active (N=10,862)	5 years	60.9 [60.0, 61.8]	6,695 [6,563, 6,828]	175 [-1, 351]	2.59 [2.56, 2.62]	0.92 [0.34, 1.49]	832.8 [307.8, 1,348.7]
			10 years	70.7 [69.9, 71.6]	7,771 [7,643, 7,907]	129 [-51, 307]	3.42 [3.36, 3.48]	1.41 [0.40, 2.40]	1,276.3 [362.1, 2,172.4]
Incidents (N=16,355)	5 years	64.1 [63.4, 64.8]	10,566 [10,385, 10,752]	209 [-40, 481]	2.69 [2.66, 2.72]	0.68 [0.18, 1.17]	926.8 [245.3, 1,598.6]		
	10 years	76.4 [75.7, 77.0]	12,582 [12,393, 12,787]	129 [-51, 307]	3.55 [3.50, 3.60]	1.11 [0.31, 1.94]	1,512.8 [422.5, 2,644.1]		

**Table 3.** Impact of the 2.5-months KT moratorium on the three studied populations of candidates for KT transplantation: active on the waiting list on March 16, 2020; inactive or not registered on the waiting list on March 16, 2020, but who will become active before March 16, 2025; and incident patients after March 16, 2020, who will become active candidates for KT before March 16, 2025. Abbreviations: KT = kidney transplantation, RMST = restricted mean survival time, RMWL = restricted mean survival time on the waiting list, [a, b] = 95% confidence interval from a to b. <sup>a</sup> Time from the beginning of the KT moratorium for patients active on the list at this time or from the registration on the active list for the other two populations (not active or incident patients).

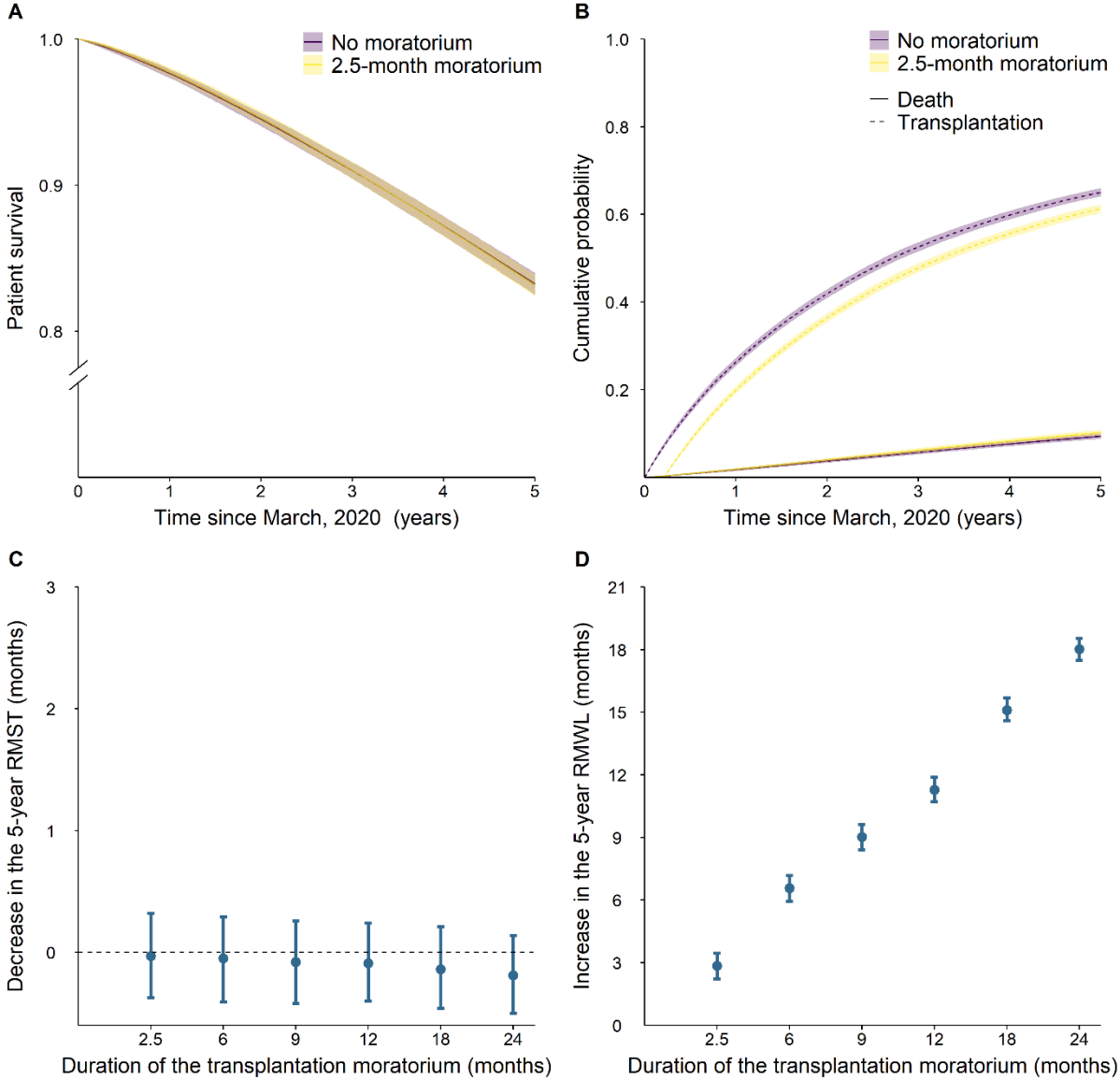
# Figures

**Figure 1.** Multistate natural history of end-stage renal disease from entry into the REIN registry (CKD, chronic kidney disease). Patients who started a dialysis while being registered on the waitlist at inclusion were considered beginning a dialysis first and being registered on the waitlist afterwards.



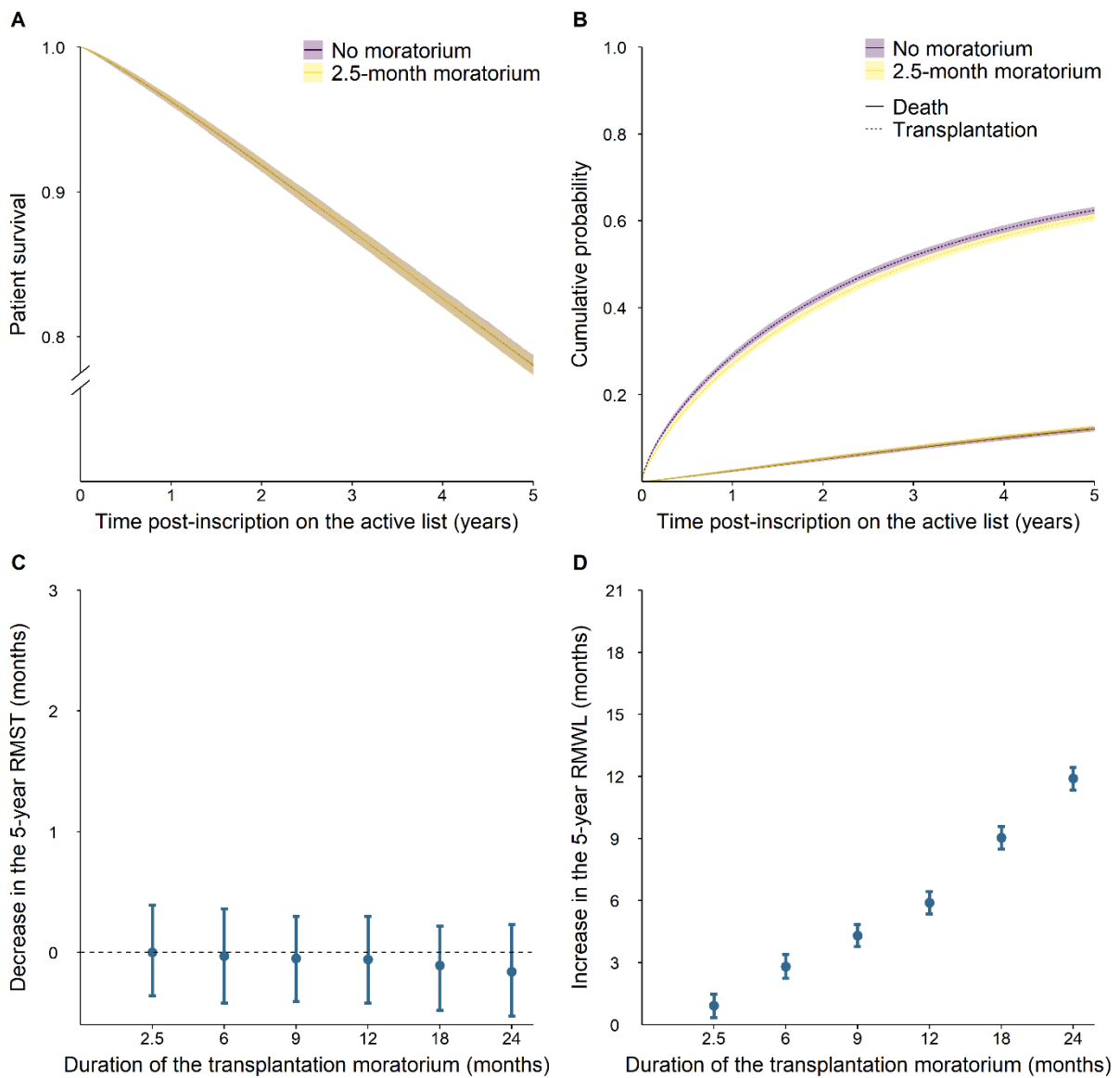
**Figure 1**

**Figure 2.** Impact of the KT moratorium on active patients on the waiting list on March 2020 (n=8,350). **A-** Overall patient survival. **B-** Cumulative probability of death and transplantation. **C-** Decrease in the 5-year life expectancy according to several moratorium durations compared to the scenario with no moratorium. **D-** Additional months on the waiting list up to 5 years according to several moratorium durations compared to the scenario with no moratorium.



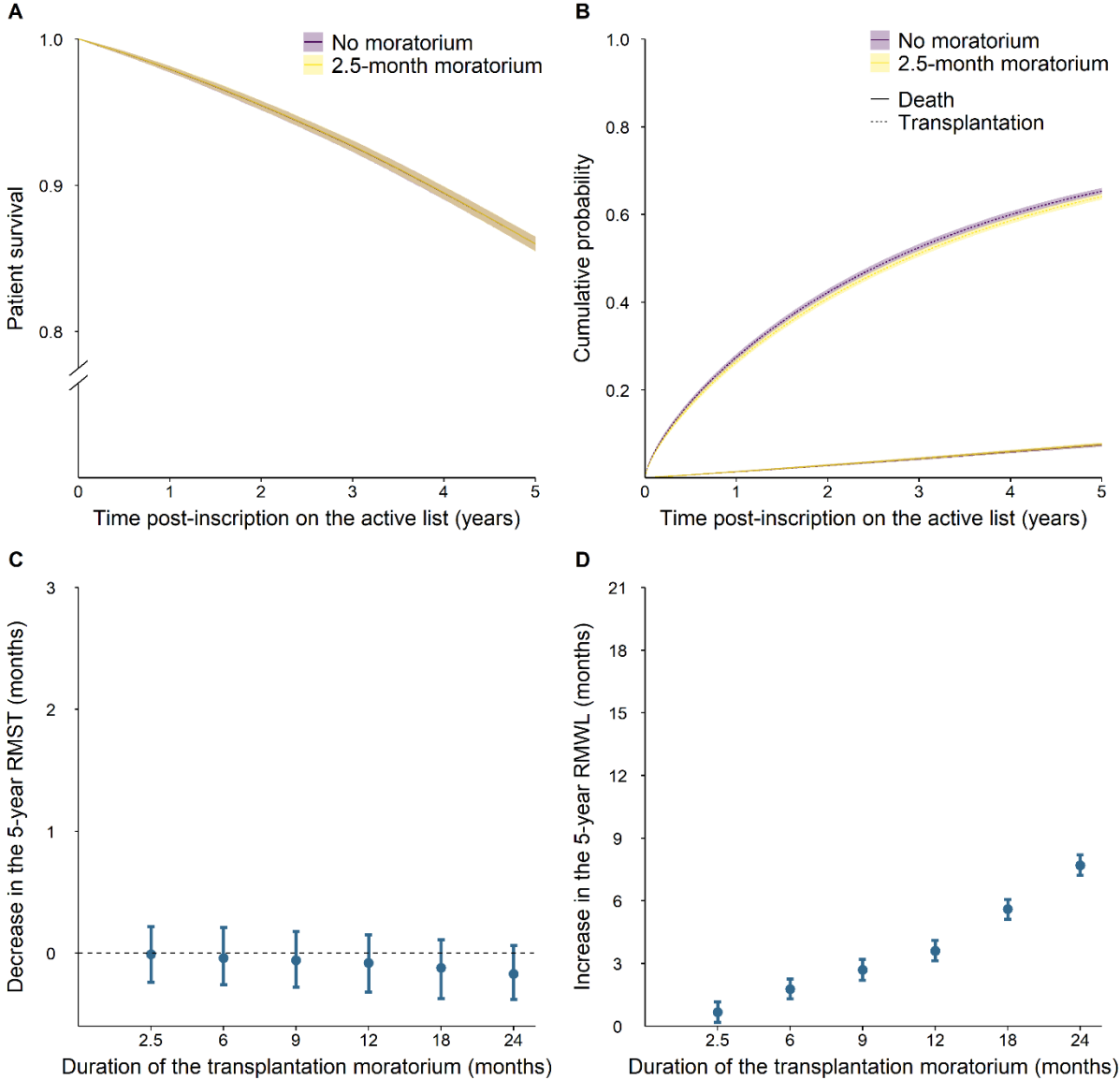
**Figure 2**

**Figure 3.** Impact of the KT moratorium on nonactive patients on the waiting list in March 2020 who will become active before March 2025 (n=10,862). **A-** Overall patient survival. **B-** Cumulative probability of death and transplantation. **C-** Decrease in the 5-year life expectancy according to several moratorium durations compared to the scenario with no moratorium. **D-** Additional months on the waiting list up to 5 years according to several moratorium durations compared to the scenario with no moratorium.



**Figure 3**

**Figure 4.** Impact of KT moratorium on incident patients in the REIN registry after March 2020 who will become active before March 2025 (n=16,355). **A-** Overall patient survival. **B-** Cumulative probability of death and transplantation. **C-** Decrease in the 5-year life expectancy according to several moratorium durations compared to the scenario with no moratorium. **D-** Additional months on the waiting list up to 5 years according to several moratorium durations compared to the scenario with no moratorium.



**Figure 4**