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*CORRESPONDENCE
Thomas Beaudrey,
thomas.beaudrey@chru-strasbourg.fr

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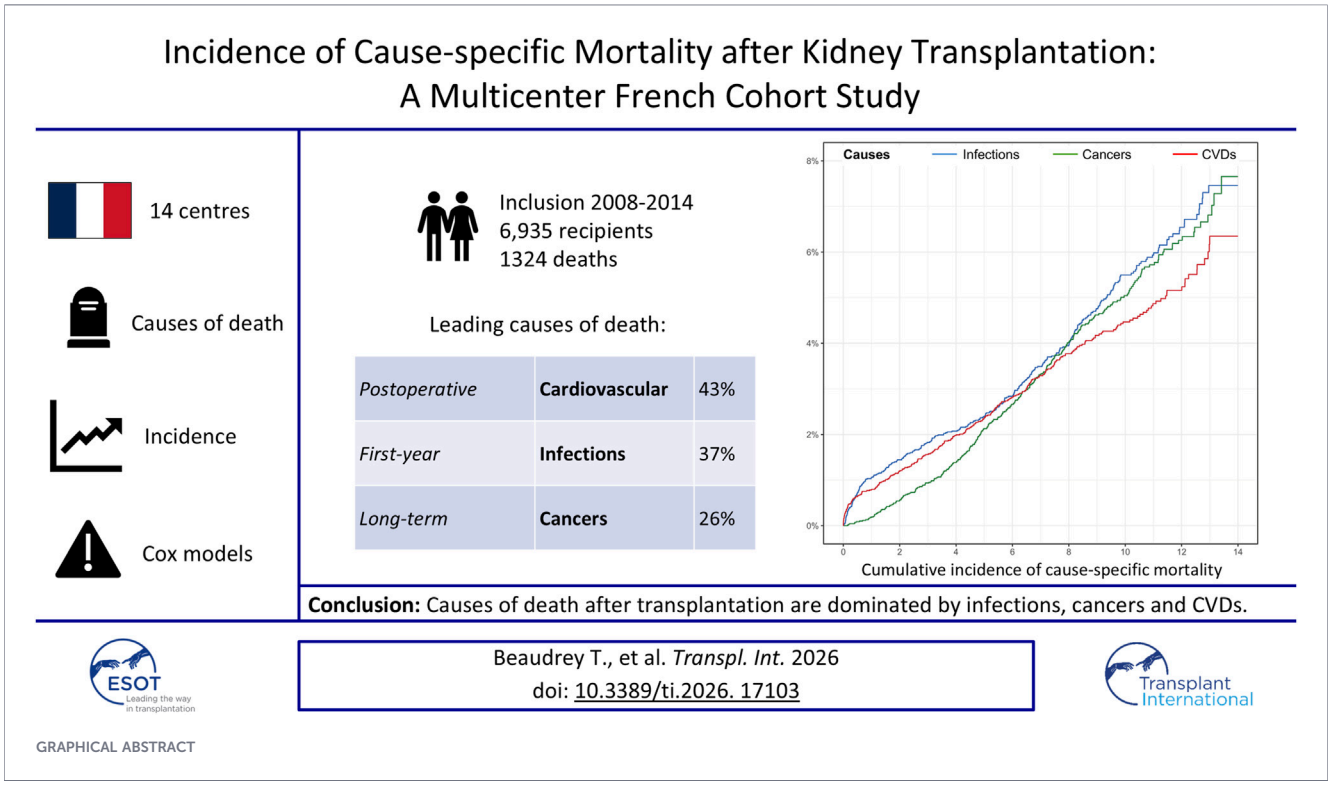
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Incidence of cause-specific mortality after kidney transplantation: a multicenter French cohort study

Thomas Beaudrey[1]*, François Séverac[2], Sébastien Loewert[1], Christophe Masset[3], Fanny Buron[4], Philippe Gatault[5], Marie-Pascale Morin[6], Coralie Poulain[7], Antoine Thierry[8], Dominique Bertrand[9], Valérie Chatelet[10], Yannick Le Meur[11], Anne-elisabeth Heng[12], Jean-Philippe Rerolle[13], Martin Planchais[14], Clément Gosset[15], Emmanuel Morelon[4], Antoine Sicard[15], Bruno Moulin[1], Magali Giral[3] and Sophie Caillard[1]

[1]Nephrology, Dialysis and Transplantation Department, Strasbourg University Hospitals, Strasbourg, France, [2]Public Health Department, Strasbourg University Hospitals, Strasbourg, France, [3]Institut de Transplantation-Urologie-Néphrologie (ITUN), Nantes University Hospital, Nantes, France, [4]Transplantation, Nephrology and Clinical Immunology Department, Edouard Herriot Hospital, Lyon University Hospitals, Lyon, France, [5]Nephrology, Dialysis and Transplantation Department, Tours University Hospital, Tours, France, [6]Nephrology Department, Rennes University Hospital, Rennes, France, [7]Nephrology, Dialysis and Transplantation Department, Amiens University Hospitals, Amiens, France, [8]Nephrology, Dialysis and Transplantation Department, Poitiers University Hospitals, Poitiers, France, [9]Nephrology, Dialysis and Transplantation Department, Rouen University Hospital, Rouen, France, [10]Nephrology, Dialysis and Transplantation Department, Caen Normandie University Hospital, Caen, France, [11]Nephrology, Dialysis and Transplantation Department, Brest University Hospital, Brest, France, [12]Nephrology, Dialysis Department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France, [13]Nephrology, Dialysis and Transplantation Department, Limoges University Hospital, Limoges, France, [14]Nephrology, Dialysis and Transplantation Department, Angers University Hospital, Angers, France, [15]Nephrology, Dialysis and Transplantation Department, Nice University Hospital, Nice, France

The incidence and temporal distribution of causes of death after kidney transplantation are insufficiently described in the literature, particularly in the first months after graft failure. We aimed to describe cause-specific mortality across the kidney transplant course in a French multicenter cohort. We included adult recipients of a kidney transplantation performed in 14 university hospitals between 2008 and 2014. We analyzed causes of death with graft function or occurring until 6 months after graft failure, classified as infection-related, cancer-related, cardiovascular disease-related, other causes, or unknown causes. Cause-specific hazard models were used to assess baseline factors associated with each cause. Among 6,935 recipients, 1,324 died during follow-up. The 10-year cumulative incidences of infection-related, cancer-related and cardiovascular disease-related death were respectively 5.5%, 5.0% and 4.5%. Cardiovascular deaths predominated in the earliest post-transplant period, infections during early follow-up, and cancers became increasingly prominent later. The early post-graft failure period was characterized by high mortality and predominance of infection-related deaths. Baseline factors associated with mortality varied across causes of death. Causes of death after transplantation are dominated



by three leading affections (infections, cancers and cardiovascular diseases), together accounting for nearly two-thirds of all deaths, with only modest differences in long-term incidence between them.

KEYWORDS

cancer, cardiovascular disease, causes of death, infectious disease, kidney transplantation

Introduction

Kidney transplantation remains the best treatment for end-stage kidney disease in eligible patients, offering better survival and quality of life than long-term dialysis [1–4]. Improvements in outcomes after transplantation have been driven in part by reductions in cardiovascular mortality over time, compared with patients who remain on dialysis [5–7]. However, a recent ERA registry study indicates that cardiovascular mortality rates are stable since 2010 [8]. At the same time, kidney transplant recipients remain exposed to specific long-term risks, including infections [9, 10], malignancies [11, 12], and cardiovascular disease [13–15] related to both pre-existing comorbidity and transplant-specific factors.

Several registry-based studies have described causes of death after kidney transplantation, but their conclusions are not fully consistent. In the United States, cardiovascular disease has long been reported as the leading cause of death, although missing cause-of-death data remain substantial in national registries [16–18]. In Australia and New Zealand, cancer-related mortality has become increasingly prominent over time [19]. In Europe, contemporary studies have yielded heterogeneous findings, with some reporting cancers or infections as the most frequent causes of death [20–22], whereas others still identify cardiovascular disease as the main contributor [23, 24]. These discrepancies likely reflect differences in population characteristics, calendar period, outcome definitions, and follow-up duration.

Interpretation has become even more complex in the contemporary era because the COVID-19 pandemic affected mortality patterns among kidney transplant recipients, particularly through infection-related deaths [25, 26]. In addition, many studies focus on death with a functioning graft or on overall patient death after transplantation, while deaths occurring shortly after graft failure are often analyzed separately or excluded. Yet this transition period may still be strongly influenced by transplantation-related factors, including persistent immunosuppression, recent hospitalization, and complications related to dialysis resumption.

A more precise description of cause-specific mortality across the transplant course is therefore needed. In particular, it is important to distinguish the relative contribution of infectious, oncologic, and cardiovascular causes according to time since transplantation and

Abbreviations: USRDS, United States Renal Data System; ANZDATA, Australian and New Zealand Dialysis and Transplant Registry; ASTRE, *ASsociation en Transplantation rénale pour la Recherche et l'Enseignement*; DIVAT, *Données Informatisées et VAlidées en Transplantation*; TRD, Transplantation-related death; CVD, Cardiovascular disease; IQR, Interquartile range; SPK, Simultaneous pancreas and kidney transplantation; BMI, Body mass index; PAOD, Peripheral arterial occlusive disease; COPD, Chronic obstructive pulmonary disease; PTLD, Post-transplantation lymphoproliferative disease; HR, Hazard ratio; CI, Confidence interval; HBV, Hepatitis B virus.

graft status. We conducted a large multicenter study using two French prospective transplant cohorts to describe the incidence and distribution of causes of transplantation-related death and to assess baseline factors associated with overall and cause-specific mortality. To better capture clinically relevant transplantation-related events, we included not only death with a functioning graft but also deaths occurring within 6 months after graft failure.

Patients and methods

Study design

A retrospective, multicenter cohort study was conducted across kidney transplantation departments at 14 university hospitals in France. The investigation included all single kidney or simultaneous pancreas-kidney transplant recipients aged 18 years or older who underwent transplantation between January 1, 2008, and December 31, 2014. This period was chosen to allow for sufficient follow-up time to enable the study of long-term mortality and its causes, distinguishing it from studies with shorter follow-up durations overestimating the weight of diseases associated with short-term mortality. Follow-up continued until December 31, 2021 and data were censored 6 months after resuming dialysis or at the date of the last medical consultation for patients lost to follow-up. The research protocol was approved by representatives from each participating center and the local ethics committees at Strasbourg University Hospitals (approval number: CE-2022-19) and was registered on *ClinicalTrials.gov* (identifier: NCT05529186). Data were sourced from two French multicenter, observational, prospective datasets. The first part of the cohort was drawn from the ASTRE database (approval number: DR-2012-518), which includes 11 centers within the Spiesser Network: Amiens, Angers, Brest, Caen, Clermont-Ferrand, Limoges, Poitiers, Rennes, Rouen, Strasbourg, and Tours university hospitals. The second portion was obtained from the DIVAT dataset (NCT02900040), encompassing three centers within the DIVAT Consortium: Lyon, Nantes, and Nice university hospitals. All participants gave their consent for the use of their anonymized personal data for research purposes. This clinical research was conducted in accordance with the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

Endpoints

The primary endpoint was transplantation-related death (TRD), defined as any death occurring after transplantation either with a functioning graft (Death With Graft Function) or within 6 months after graft failure. This definition was chosen to capture a clinically relevant period that remains closely linked to transplantation care, including the early phase after graft failure when patients may still be exposed to tapering immunosuppression, recent hospitalization, and complications related to dialysis resumption. In addition to overall TRD, we analyzed the three main cause-specific components of TRD: infection-related death, cancer-related death, and cardiovascular disease-related death.

For the primary analysis, follow-up extended from the date of transplantation to TRD. Follow-up was censored at pre-emptive retransplantation, at the end of follow-up, or 6 months after return to dialysis for patients who experienced graft failure and remained alive. This approach allowed us to examine mortality across the transplant course while specifically incorporating the early post-graft-failure period as part of transplantation-related mortality.

Causes of death

The underlying cause of death was defined according to the International Classification of Diseases, 11th Revision, as the disease or condition initiating the sequence of events leading directly to death. Causes of death were classified into five mutually exclusive categories: cardiovascular diseases, infections, cancers, other causes, and unknown causes. The three major categories of interest in this study were infection-related, cancer-related, and cardiovascular disease-related deaths. "Other causes" included deaths not belonging to these three categories (i.e., traumatisms, neurological disorders. . .), while "unknown causes" corresponded to deaths for which no reliable attribution could be established from the available data. For outpatients, undetermined causes of death and missing cause-of-death information could not always be distinguished and were therefore grouped together as unknown causes. Cause-of-death attribution was based on clinical determination within each participating center and adjudicated by a senior nephrologist serving as the local database reference. Detailed subcategories within each major cause-of-death group were analyzed descriptively.

Statistical analysis

The baseline characteristics of the patients were described using the median with interquartile range for continuous variables and numbers and proportions for categorical variables. The cumulative incidence of cause-specific transplantation-related deaths were estimated from baseline, as well as from graft failure in concerned patients, using the Kalbfleisch and Prentice method accounting for competing risks [27].

Sensitivity analyses regarding the distribution of causes of death were performed in various subgroups (database, type of death, age of recipient, sex, year of transplantation). It was also performed in a subcohort of patients who underwent their first single kidney transplantation, without prior solid organ transplantation. For this subcohort, death with graft function was used as the main outcome rather than transplantation-related death.

Cause-specific hazard regression models with a frailty term for transplant center were used to assess the factors associated with the main causes of transplantation-related death (infections, cancers and CVDs), including clinically relevant factors significantly associated with cause-specific TRD in univariable analysis. The time-to-event was calculated from the date of transplantation to the occurrence of TRD. Patients were censored 6 months after returning to dialysis, at new preemptive transplantation or at the end of the follow-up. The results are reported as hazard ratios (HR) with 95% confidence intervals (CIs). Fine-Gray subdistribution hazard models for competing risks with a robust variance estimator to account for within-center correlation were also fitted as a sensitivity analysis.

Missing data were handled using multiple imputation by chained equations [28, 29] with 50 imputed datasets. Estimates were computed for each imputed dataset and subsequently combined in accordance with Rubin's rules [30]. All analyses were conducted using R software, version 4.1.1 (R Core Team, 202 1; R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p values <0.05 were deemed to indicate statistical significance. Statistical analyses were conducted using R, version 4.1.1 (R Core Team; 2021) [31].

Results

Baseline characteristics

The study included 6,935 kidney transplantations performed between 2008 and 2014 in 14 French university hospitals. Median recipient age at transplantation was 53 years (IQR 42–63), and 62.5% of recipients were male. Median follow-up was 7.0 years (IQR 3.2–9.6). During follow-up, 1,324 recipients (19.1%) died according to the study definition of transplantation-related death, including 1,229 deaths with a functioning graft (Figure 1). In addition, 1,415 recipients (20.4%) experienced graft failure, and among them, 95 early deaths occurred within 6 months after graft failure. The ASTRE and DIVAT cohorts differed in several baseline characteristics (Table 1). Deceased recipients were older (63 [IQR 55–69] years old versus 51 [IQR 40–60], p < 0.001), more frequently exposed to expanded-criteria donors (N = 783, 59.1% vs. N = 1746, 31.1%, p < 0.001), had longer dialysis duration (2.3 [IQR 1.3–3.9] years vs. 2.0 [IQR 1.1–3.5], p < 0.001), and more often had diabetic or vascular nephropathy (N = 357, 27.0% vs. N = 956, 17.0%, p < 0.001), cardiovascular comorbidities (N = 553, 41.8% vs. N = 1,216, 21.7%, p < 0.001), smoking history (N = 640, 48.3% vs. N = 2,359, 42.0%, p < 0.001), delayed graft function (N = 335, 25.3% vs. N = 1,003, 17.9%, p < 0.001), cancer history (N = 170, 12.8% vs. N = 454, 8.1%, p < 0.001), and prior transfusions (N = 585, 44.2% vs. N = 1933, 34.5%, p < 0.001). Comparison of deceased and alive patients is presented in Supplementary Table S1. Missing data are summarized in Supplementary Table S2.

Cumulative incidence of cause-specific transplantation-related mortality

The cumulative incidence of cardiovascular disease-related death was the highest at 1 month (0.3% [0.2–0.5]), 0.2 points higher than infections (0.1% [0.0–0.2]). By 1 year, incidence of infection-related death (1.0% [0.8–1.3]), exceeded that of CVD (0.8% [0.6–1.0]) by 0.2 points. Cancer-related death remained marginal (0.2% [0.1–0.3]) at 1 year. At 5 years, infections and cardiovascular disease showed similar incidence (2.4% [2.1–2.8] and 2.4% [2.0–2.8], respectively), both approximately 0.3 points higher than cancers (2.1% [1.8–2.5]). At 10 years, infections remained the leading cause (5.5% [4.9–6.2]), 0.5 points higher than cancers (5.0% [4.5–5.7]) and 1.0 point higher than cardiovascular disease (4.5% [3.9–5.1]). Cumulative incidence curves are displayed in Figure 2.

Temporal distribution of causes of death

Among the 1,324 TRDs, infections were the first cause of death (N = 317 deaths, 23.9%), followed by cancers (N = 295, 22.3%) and cardiovascular diseases (N = 269, 20.3%), while 187 deaths (14.1%) were attributed to other causes and 256 (19.3%) remained of unknown cause. The leading cause of death differed according to the period after transplantation: cardiovascular disease was the leading cause within the first month (N = 18, 42.9%), infections predominated between 1 month and 1 year (N = 44, 37.3%), and cancers were the leading cause beyond 1 year (N = 277, 25.9%; Table 2). The three first single causes of death were pulmonary infections (N = 127, 9.6%), sudden death (N = 73, 5.5%) and lung cancer (N = 71, 5.4%, Figure 3). Detailed distributions of specific causes of death are presented in Supplementary Tables S3–S6.

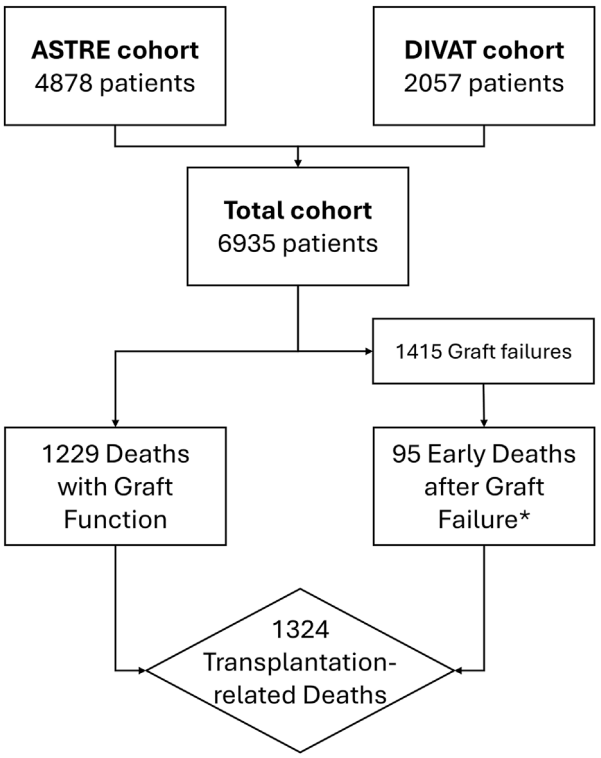


FIGURE 1
Flowchart of the multicenter cohort study. *Deaths that occurred within the first 6 months after graft failure.

Early deaths after graft failure

A total of 95 recipients died within 6 months after graft failure, representing 6.7% of patients who experienced graft failure. Among them, 44 deaths occurred during the first month. Mortality during this interval was markedly high, reaching a cumulative incidence of 6.8% (IQR 5.6–8.2) compared to only 2.0% (IQR 1.7–2.4) in the first 6 months post-transplantation. The incidence of infection-related and CVD-related deaths was respectively 2.8% (N = 39, 41.1%) and 1.1% (N = 16, 16.8%), whereas cancer-related deaths were uncommon, with an incidence of 0.4% (N = 6, 6.3%). Other causes included a substantial proportion of postoperative complications and hemorrhages (N = 12, 12.6%). Cumulative incidence of cause-specific early mortality after graft failure is presented in Figure 4.

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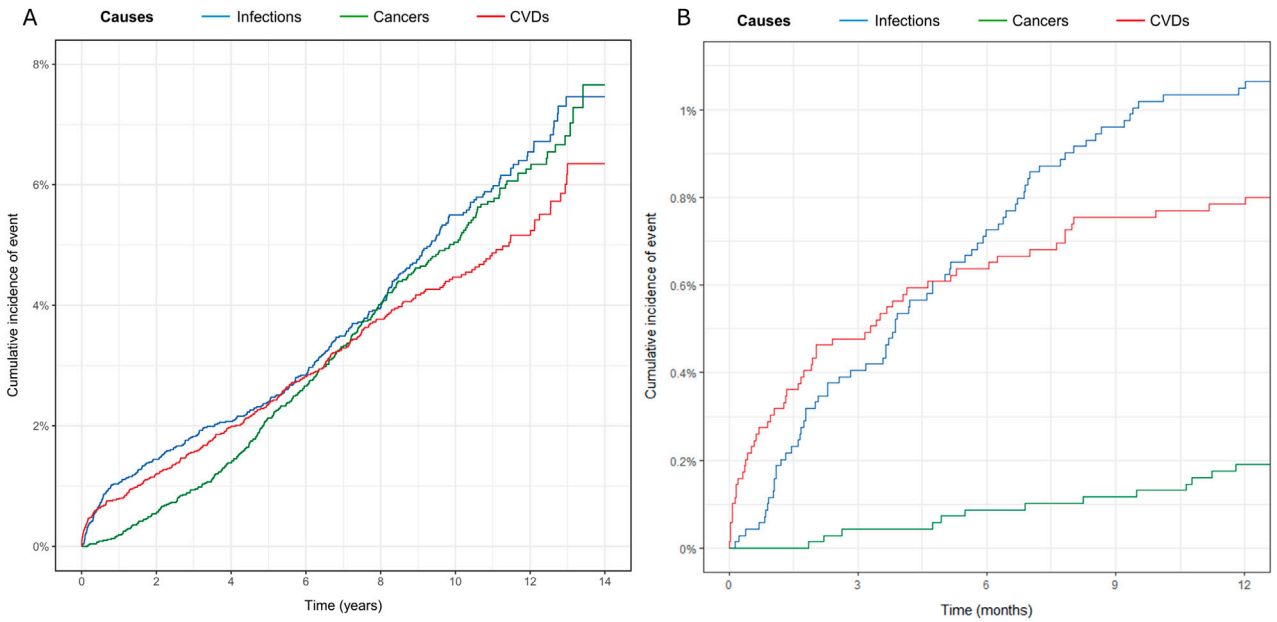
TABLE 1 Comparison of baseline characteristics between the Astre and Divat cohorts.

Variables	Total (n = 6,935)	ASTRE (n = 4,878)	DIVAT (n = 2,057)
Recipient baseline characteristics			
Male sex – N (%)	4,334 (62.5%)	3,063 (62.8%)	1,271 (61.8%)
Recipient age (years) – Med (IQR)	53 (42–63)	54 (43–63)	52 (40–63)
2008–2010 period – N (%)	2,774 (40.0%)	2032 (41.7%)	742 (36.1%)
Previous renal transplantation – N (%)	1,102 (15.9%)	699 (14.3%)	403 (19.6%)
Previous solid organ transplantation – N (%)	84 (1.2%)	60 (1.2%)	24 (1.2%)
SPK Transplantation – N (%)	295 (4.3%)	18 (0.4%)	277 (13.5%)
Diabetic nephropathy – N (%)	820 (11.8%)	356 (7.3%)	464 (22.6%)
Vascular nephropathy – N (%)	493 (7.1%)	279 (5.7%)	214 (10.4%)
Undetermined nephropathy – N (%)	1,038 (15.0%)	830 (17.1%)	208 (10.1%)
Preemptive transplantation – N (%)	1,089 (15.7%)	681 (14.0%)	408 (19.8%)
Dialysis duration (years) – Med (IQR)	2.1 (1.1–3.6)	2.0 (1.3–3.5)	2.15 (1.1–3.9)
EBV positive recipient – N (%)	6,627 (95.6%)	4,660 (96.6%)	1967 (97.0%)
HBV Seronegative – N (%)	2,187 (31.5%)	1,651 (33.8%)	536 (26.1%)
Transfusion history – N (%)	2,518 (36.3%)	1,677 (34.4%)	841 (40.9%)
Donor characteristics			
Living donor – N (%)	544 (7.8%)	329 (6.7%)	215 (10.5%)
Expanded criteria donor – N (%)	2,529 (36.5%)	1796 (36.8%)	733 (35.6%)
Recipient comorbidities			
Diabetes mellitus – N (%)	1,344 (19.4%)	769 (15.8%)	575 (28.0%)
Smoking history – N (%)	2,999 (43.2%)	2,235 (45.8%)	764 (37.1%)
Coronaropathy history – N (%)	762 (11.0%)	546 (11.2%)	216 (10.5%)
Arrhythmia history – N (%)	421 (6.1%)	272 (5.6%)	149 (7.2%)
Heart failure – N (%)	331 (8.8%)	251 (5.1%)	80 (3.9%)
PAOD – N (%)	610 (8.8%)	393 (8.1%)	217 (10.5%)
Stroke history – N (%)	291 (4.2%)	203 (4.2%)	88 (4.3%)
Cancer history – N (%)	624 (9.0%)	380 (7.8%)	244 (11.9%)
Perioperative factors			
Cold ischemia time (hours) – Med (IQR)	15.17 (12.0–19.2)	15.5 (12.3–19.4)	14.5 (11.5–18.5)
Delayed graft function – N (%)	1,338 (19.3%)	837 (17.2%)	501 (24.4%)
Depleting induction – N (%)	2,559 (36.9%)	1,289 (26.4%)	1,270 (61.7%)
Ciclosporin at baseline – N (%)	1865 (26.9%)	1709 (35.0%)	156 (7.6%)

Abbreviations: SPK, simultaneous pancreas-kidney transplantation; BMI, body mass index; PAOD, peripheral arterial occlusive disease; COPD, chronic obstructive pulmonary disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLA, human leucocyte antigen; mTOR, mechanistic target of rapamycin.

Sensitivity and stratified analyses

Sensitivity analyses showed some heterogeneity between subgroups (Supplementary Table S7): infections were the leading cause of death in the ASTRE cohort, whereas cancers and cardiovascular diseases were slightly more represented in DIVAT cohort. Infections predominated in recipients older than 55 years with a 10-year cumulative incidence of 9.2%, while cancers was the first cause of death among recipients younger than 55 years (10-year cumulative incidence: 2.8%). Regarding sex



Cumulative incidence of death by:	1 month	1 year	5 years	10 years
Infections	0.1 % [0.0 – 0.2]	1.0 % [0.8 – 1.3]	2.4 % [2.1 – 2.8]	5.5 % [4.9 – 6.2]
Cancers	0.0 % [0.0 – 0.0]	0.2 % [0.1 – 0.3]	2.1 % [1.8 – 2.5]	5.0 % [4.5 – 5.7]
Cardiovascular disease	0.3 % [0.2 – 0.5]	0.8 % [0.6 – 1.0]	2.4 % [2.0 – 2.8]	4.5 % [3.9 – 5.1]

FIGURE 2
Estimated cumulative incidence of the three main causes of death during total follow-up **(A)** and in the first year **(B)**. Abbreviation: CVD, cardiovascular disease.

TABLE 2 **Distribution of causes of death according to post-transplantation delay.**

Period	Delay	Total	Infection-related death	Cancer-related death	CVD-related death	Other causes	Unknown causes
TRD	Total follow-up	1,324	**317 (23.9%)**	295 (22.3%)	269 (20.3%)	187 (14.1%)	256 (19.3%)
Death with graft function	<1 month*	42	6 (14.3%)	0 (0.0%)	**18 (42.9%)**	14 (33.3%)	4 (9.5%)
	1 month–1 year*	118	**44 (37.3%)**	12 (10.2%)	31 (26.2%)	18 (15.3%)	13 (11.0%)
	>1 year*	1,069	228 (21.3%)	**277 (25.9%)**	204 (19.1%)	134 (12.5%)	226 (21.1%)
Death after graft failure	<6 months**	95	**39 (41.1%)**	6 (6.3%)	16 (16.8%)	21 (22.1%)	13 (13.7%)

*Post transplantation.
**Post graft failure. Bold values indicate the first cause of death for each period.

disparities, infections predominated in women (10-year cumulative incidence 5.7%) and cancers in men (10-year cumulative incidence 5.5%). Cumulative incidence curves for age and sex disparities are presented in Supplementary Figures S1-S4.

To allow better comparison with the existing literature, we performed a sensitivity analysis evaluating the incidence of death with graft function in a subcohort including only first single kidney transplant recipients without prior solid organ transplantation (N = 5,488). The distribution of causes of death differed slightly: Infections and cancers were equivalent (respectively N = 232, 23.5% and N = 229, 23.2%), followed by cardiovascular diseases (N = 196, 19.8%), unknown causes (N = 191, 19.3%) and other causes (N = 140, 14.2%). Cumulative incidences for this subcohort are presented in Supplementary Figure S5.

Because follow-up extended into the COVID-19 era, we performed a pre-pandemic sensitivity analysis censoring follow-up on December 31, 2019: The cause-specific mortality proportions remained of similar magnitude

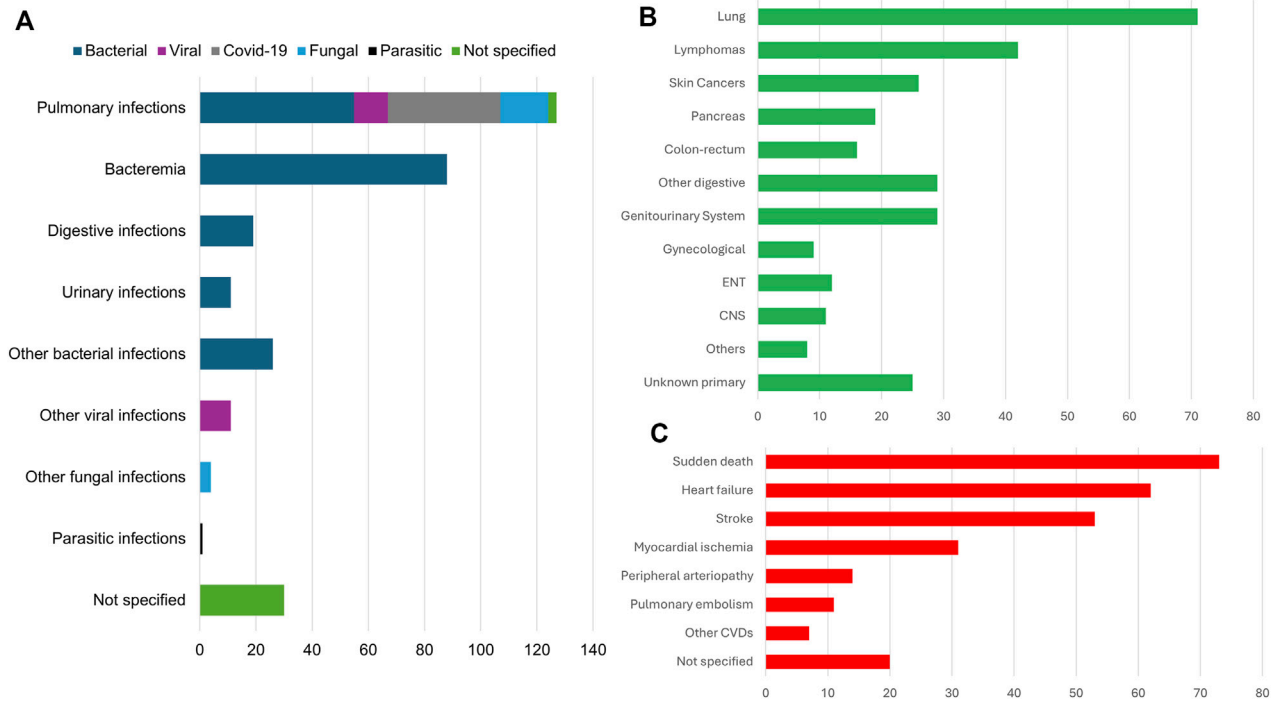


FIGURE 3
Absolute number of main causes of death in each etiologic category: infection-related causes of death **(A)**, cancer-related mortality **(B)** and cardiovascular disease-related mortality **(C)**. Abbreviations: ENT, ear, nose, throat; CNS, central nervous system; CVD, cardiovascular disease.

(infections, 23.4%; cancers, 21.8%; cardiovascular diseases, 22.3%).

Baseline factors associated with cause-specific mortality

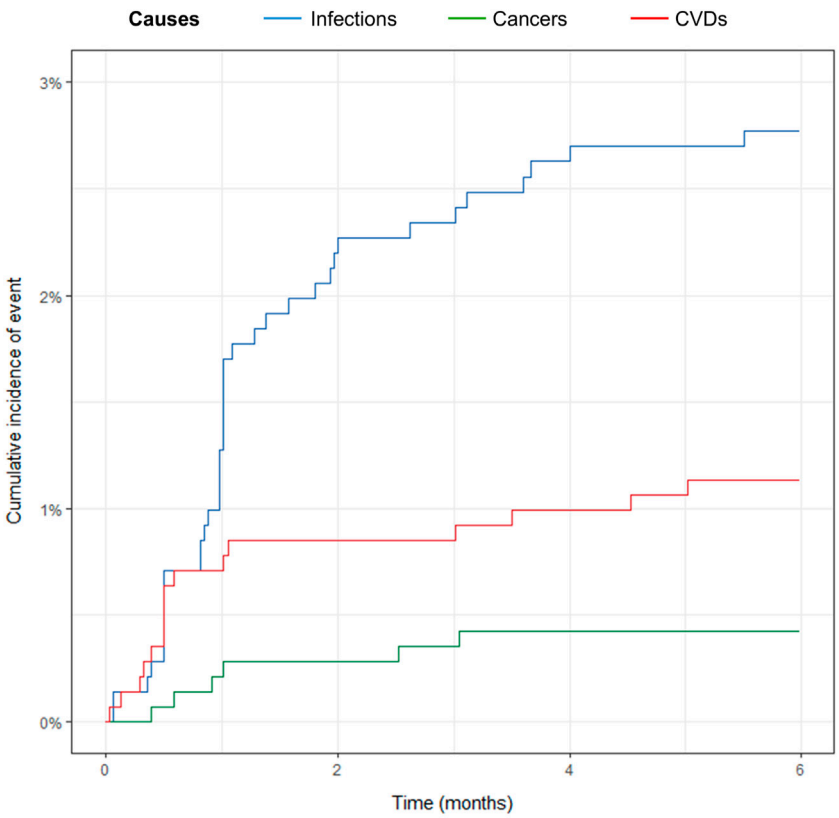
We used univariable and multivariable Cox models to determine baseline risk factors for cause-specific transplantation-related death (Figure 5). Age was independently associated with all causes of death. Infection-related deaths were influenced by ECDs, lack of HBV immunization, arrhythmia, cyclosporin induction, red blood cell transfusions, and a prior history of cancer. Cancer-related deaths were primarily associated with smoking, both active and former, and to a lesser extent with peripheral arterial disease and cancer history. CVD-related deaths were associated with ECDs, diabetic or vascular nephropathy, previous solid organ transplantation, established cardiovascular comorbidities (coronary artery disease, arrhythmia, peripheral arterial disease, stroke), and dialysis duration before transplantation. Supplementary Table S8 depicts the full multivariable model.

We also performed two additional models as a sensitivity analysis: A Fine and Gray competing-risk multivariable model assessing cause-specific TRD in the total cohort (Supplementary Table S9) and a Cox multivariable model assessing cause-specific Death With Graft Function in the subcohort of first single kidney transplant recipients (N = 5,488, Supplementary Table S10), with only marginal changes compared to the main multivariable Cox model.

Discussion

In this large multicenter French cohort, we provide a longitudinal description of transplantation-related mortality that accounts for both time since transplantation and the early period after graft failure. Cardiovascular disease and infections were the leading causes of death in the earliest post-transplant period, and cancer-related deaths became increasingly important later during follow-up. After graft failure, the first months were associated with a high proportion of infection-related deaths. Overall, these descriptive findings indicate that the differences in relative contribution between causes of death across periods remain moderate, and that infections, cancers, and cardiovascular diseases stand out as the three major causes burdening the prognosis of kidney transplant recipients throughout the transplant course, with similar 10-year cumulative incidences. By specifically including deaths occurring within 6 months after graft failure, we identify an underrecognized period of heightened vulnerability that remains closely linked to transplantation care. Our findings therefore extend contemporary European data by offering a more integrated view of mortality across the transplant course, with potential implications for how post-transplant surveillance and transitional care should be considered.

Contemporary studies suggest that post-transplant mortality cannot be captured by a single universal pattern, because the observed distribution of causes of death varies according not only to cohort characteristics and endpoint definition, but also to follow-up structure and duration, as the relative contribution of different causes changes over time after transplantation. Our study differed from previous reports in its inclusion criteria (recipients of simultaneous



Cumulative incidence of TRD by:	1 month	3 months	6 months
Infections	1.3 % [0.8 – 2.0]	2.3 % [1.6 – 3.2]	2.8 % [2.0 – 3.7]
Cancers	0.2 % [0.1 – 0.6]	0.4 % [0.1 – 0.8]	0.4 % [0.2 – 0.9]
Cardiovascular disease	0.7 % [0.4 – 1.3]	0.8 % [0.5 – 1.4]	1.1 % [0.7 – 1.8]

FIGURE 4
Estimated cumulative incidence of early deaths after graft failure, stratified by cause. CVDs, Cardiovascular diseases; TRD, Transplantation-related death.

kidney-pancreas transplantation or with a prior history of organ transplantation were included) and in its outcome definition (transplantation-related death, including deaths occurring within 6 months after graft failure). Nonetheless, results remained consistent in a sensitivity analysis restricted to a subcohort defined by more "traditional" inclusion criteria and outcome definitions, supporting the comparability of our findings with the existing literature. In the Belgian study of overall graft loss by Van Loon et al, malignancy, infection, and cardiovascular disease were all major contributors to recipient death [20]. The German studies by Abeling [21] and Mayrdorfer [23] were rather conflicting, the first depicting a majority of infection-related deaths and the second of cancer- and CVD-related deaths. Nationwide Finnish data, on the other hand, indicate that cardiovascular disease remains the leading cause of death, despite a decline in adjusted cardiovascular mortality over time [32]. In a small Italian cohort, infections and cancers were the prominent causes of death [33]. This heterogeneity was also observed within our own study: the ASTRE and DIVAT cohorts differed in baseline clinical characteristics, and the relative contribution of infection-, cancer-, and cardiovascular-related deaths was not identical between them, with infections predominating in ASTRE and cancers being slightly more represented in DIVAT. Additionally, as evidenced in our study, several factors may influence causes of mortality, such as sex and age. Indeed, cardiovascular risk and mortality is reported to be higher in men compared to women [34], and older age is related with an increased susceptibility to infections [35, 36]. Taken together, these studies illustrate the heterogeneity of contemporary post-transplant mortality and the importance of the analytical lens through which it is examined. In this context, our work contributes multicenter French data and broadens the existing literature by describing the incidence and distribution of cause-specific mortality across successive periods of the transplant course rather than on overall cause-of-death proportions alone, and by explicitly integrating deaths occurring shortly after graft failure, a critical period in the life of kidney transplant recipients. This approach provides additional insight into how the dominant threats to survival evolve according to time since transplantation and graft status, and our findings support a nuanced view in which infections, cancers, and cardiovascular diseases constitute an three-way burden, with their relative contribution potentially differing according to both patients characteristics and post-transplantation delay.

A distinctive feature of our study is the inclusion of deaths occurring within 6 months after graft failure. This period is often

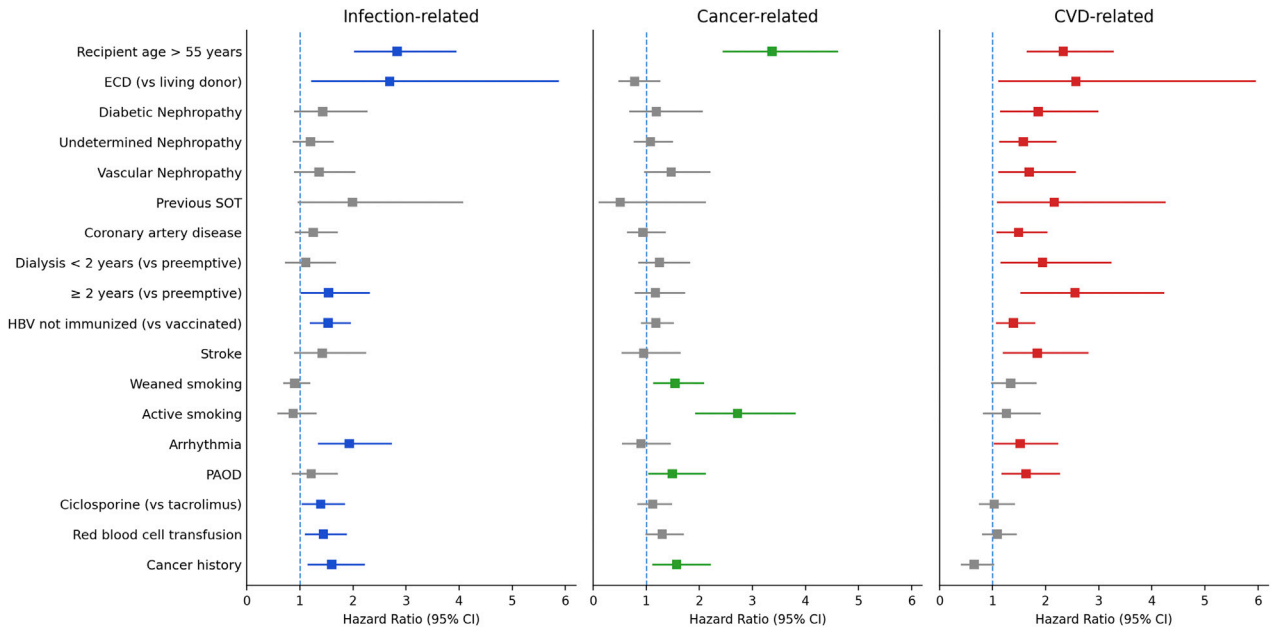


FIGURE 5
Hazard ratios of the Cox multivariable model for cause-specific transplantation-related death. Only the significant variables are displayed, the full model is available in Supplementary Table S8. Abbreviations: CVDs, Cardiovascular diseases; ECD, Expanded-criteria donor; SOT, solid organ transplantation; TRD, Transplantation-related death; VHB, Hepatitis B Virus; PAOD, Peripheral arteries obstructive disease.

overlooked in transplantation mortality studies, although it may still reflect transplantation-related vulnerability [37]. In our cohort, early death after graft failure was clinically important, with a markedly high mortality rate and a predominance of infection-related and postoperative deaths. This suggests that the transition from graft failure to dialysis resumption is a particularly fragile phase, likely reflecting the combined burden of recent allograft failure, ongoing or tapering immunosuppression, vascular access issues, and repeated healthcare exposure. By incorporating this interval into the definition of transplantation-related death, our study extends the conventional focus on death with a functioning graft and highlights an under-described phase of risk that deserves specific clinical attention.

The COVID-19 era should be taken into account when interpreting the contemporary distribution of causes of death in this cohort. SARS-CoV-2 contributed substantially to infection-related mortality during 2020–2021 [25, 26]. However, in the sensitivity analysis censoring follow-up before January 1, 2020, infections remained a major cause of death, suggesting that their contribution was not solely driven by the pandemic period. These findings should therefore be interpreted as reflecting a contemporary pattern of mortality in which infection remains a major component, while acknowledging that the pandemic likely amplified this burden and may have affected cause-of-death attribution in some cases.

The cause-specific analyses suggest a different pattern of baseline associations depending on the cause of death considered. Cardiovascular mortality showed the most consistent associations, spanning traditional cardiovascular risk factors (coronary artery disease, arrhythmia, stroke), nephropathies, and dialysis duration [38], in line with the recognized link between pretransplant cardiovascular burden and post-transplant cardiovascular events [15, 39, 40]. Other factors could contribute to cardiovascular mortality, such as delayed graft function [41], as evidenced in our previous study. Infection-related mortality was associated with a more heterogeneous set of factors, which appeared to fall into two broad categories: markers of clinical frailty (arrhythmia [42], expanded-criteria donor, [43], dialysis duration, [38], red blood cell transfusion) and markers of pre-existing immune vulnerability (cancer history, absence of HBV immunization, ciclosporine use). This may suggest that infection risk relates to an accumulation of frailty- and immunosuppression-related vulnerability already present at transplantation, although this interpretation remains speculative. Fewer baseline factors were associated with cancer-related mortality, limited essentially to age, smoking [44], and cancer history. This is broadly consistent with the contribution of lung cancer to cancer-related mortality in this cohort, but contrasts with the near-absence of associations for lymphoma, skin cancers, and other malignancies, for which relevant risk factors (such as cumulative immunosuppression exposure, viral events, or sun exposure) were likely not captured by the baseline variables considered here [45]. Associations involving HBV immunization status and transfusion history [46] should in any case be interpreted cautiously, as prognostic markers rather than causal determinants. Taken together, these findings suggest that the baseline clinical profile relates more consistently to cardiovascular death than to infection- or cancer-related death, for which unmeasured post-transplant factors may play a more important role.

These descriptive findings raise several hypotheses that may warrant further investigation. The observed distribution of causes of death across infectious, oncologic, and cardiovascular categories suggests that surveillance strategies focused on a single category alone may not capture the full burden of post-transplant mortality. The high proportion of infection-related and CVD-related deaths observed early after transplantation, together with the later contribution of cancer-related deaths, could be worth exploring in studies specifically

designed to evaluate the timing of post-transplant complications. The mortality observed in the months following graft failure also suggests that this period deserves further attention in future research, including in relation to care organization during this transition.

This study has several limitations. Cause-of-death classification relied on clinical adjudication in multicenter databases and may have been affected by misclassification, especially for sudden out-of-hospital deaths and during the COVID-19 period. A substantial proportion of deaths remained of unknown cause, although this proportion was markedly lower than that reported in US registry data [18]. The retrospective design limited the analysis to baseline predictors and did not allow assessment of important time-dependent factors such as rejection episodes, changes in immunosuppression, post-transplant diabetes, or post-transplant infections. Finally, as with any observational survival analysis, residual confounding bias cannot be excluded, and our findings should be regarded as hypothesis-generating rather than as a basis for firm clinical recommendations or causal conclusions.

In conclusion, this multicenter French study describes the temporal distribution of causes of death after kidney transplantation: cardiovascular causes dominated very early, infections during early follow-up, and cancers became more frequent later, although these differences across periods remained moderate and they consistently stood out as the three leading affections impacting the prognosis of kidney transplant recipients. By extending ascertainment to the first 6 months after graft failure, the study also draws attention to a period associated with elevated mortality that remains insufficiently characterized in the transplantation literature.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Strasbourg University Hospitals IRB, Number CE-2022-19. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

TB monitored data collection, collected, cleaned, and analyzed the data, and drafted the paper. FS wrote the statistical analysis plan, performed the statistical analyses, and drafted and revised the paper. SL and BM conceived the original idea, collected and analyzed the data, and revised the draft paper. CM, FB, PG, M-PM, CP, AT, DB, VC, YM, A-eH, J-PR, MP, CG, EM, and AS collected the data and revised the draft paper. MG contributed to the collaborative project, monitored data collection, and revised the draft paper. SC initiated the collaborative project, monitored data collection, analyzed the data, and drafted and revised the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/. The authors declare that they received no support from any organization for the submitted work. SC declares that she has financial relationship for congress travel and boards with the following companies: AstraZeneca, Alexion, Pierre Fabre, Chiesi, Pfizer, Samsung Bioepis.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.17103/full#supplementary-material

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