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How to cite

SCHREIBER, Peter W et al. Surgical site infections after kidney transplantation are independently associated with graft loss. In: American journal of transplantation, 2024, vol. 24, n° 5, p. 795–802. doi: 10.1016/j.ajt.2023.11.013

This publication URL: https://archive-ouverte.unige.ch/unige:185599

Publication DOI: 10.1016/j.ajt.2023.11.013

American Journal of Transplantation 24 (2024) 795–802

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Surgical site infections after kidney transplantation are independently associated with graft loss

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ARTICLE INFO

Keywords:
kidney transplantation
surgical site infection

ABSTRACT

Surgical site infections (SSIs) are common health care-associated infections. SSIs after kidney transplantation (K-Tx) can endanger patient and allograft survival. Multicenter studies on this early posttransplant complication are scarce. We analyzed consecutive adult

Abbreviations: ATG, antithymocyte globulin; BMI, body mass index; CNS, coagulase-negative staphylococci; HAI, health care-associated infection; HR, hazard ratio; K-Tx, kidney transplantation; OR, odds ratio; SOT, solid organ transplantation; SSI, surgical site infection; STCS, Swiss Transplant Cohort Study; Tx history, prior solid organ transplant.

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https://doi.org/10.1016/j.ajt.2023.11.013
Received 3 May 2023; Received in revised form 20 November 2023; Accepted 23 November 2023
Available online 30 November 2023

health care-associated infection
graft loss

K-Tx recipients enrolled in the Swiss Transplant Cohort Study who received a K-Tx between May 2008 and September 2020. All data were prospectively collected with the exception of the categorization of SSI which was performed retrospectively according to the Centers for Disease Control and Prevention criteria. A total of 58 out of 3059 (1.9%) K-Tx recipients were affected by SSIs. Deep incisional (15, 25.9%) and organ/space infections (34, 58.6%) predominated. In the majority of SSIs (52, 89.6%), bacteria were detected, most frequently *Escherichia coli* (15, 28.9%), *Enterococcus* spp. (14, 26.9%), and coagulase-negative staphylococci (13, 25.0%). A BMI $\geq$25 kg/m^2 (multivariable OR 2.16, 95% CI 1.07-4.34, $P = .023$) and delayed graft function (multivariable OR 2.88, 95% CI 1.56-5.34, $P = .001$) were independent risk factors for SSI. In Cox proportional hazard models, SSI was independently associated with graft loss (multivariable HR 3.75, 95% CI 1.35-10.38, $P = .011$). In conclusion, SSI was a rare complication after K-Tx. BMI $\geq$25 kg/m^2 and delayed graft function were independent risk factors. SSIs were independently associated with graft loss.

1. Introduction

Despite the progress in solid organ transplantation (SOT), infections remain one of the most common causes of death after kidney transplantation (K-Tx).[1] In Switzerland, kidneys are the most frequently transplanted organs, with more than 250 transplantations performed each year.[2] In the early posttransplant period, health care-associated infections (HAIs) represent a major burden of infectious diseases among SOT recipients.[3] Among HAIs, surgical site infections (SSIs) were found to have the highest prevalence in repeated point prevalence studies.[4,5] In general, SSIs contribute to relevant morbidity and mortality.[6,7] The postoperative length of stay has been reported to be longer among affected patients.[7] Deep incisional and organ/space infections have been associated with worse outcomes compared to superficial incisional infections.[6,7] After K-Tx, SSIs were associated with revision surgery and readmissions.[8,9] Data on SSIs after K-Tx derived from multicenter studies remain scarce. We addressed this infectious complication in the early posttransplant course within the Swiss Transplant Cohort Study (STCS).

2. Material and methods

2.1. Study design, population, and patient-related data

This study was part of a nested project on SSIs after SOT within the STCS (stcs.ch, ClinicalTrials.gov Identifier: NCT01204944). All Swiss transplant centers (Basel, Bern, Geneva, St. Gallen, Lausanne, and Zurich) contribute to the prospective data collection of the STCS. The ethics committees of all participating institutions gave their approval to the STCS and the responsible ethics committee (Kantonale Ethikkommission Zürich, Req. 2016-01532) approved this nested study. The STCS data set encompasses prospectively collected information on all SOTs performed after May 1, 2008. Dedicated research assistants record infections supervised by transplant infectious diseases physicians. The categorization of the extent of the SSI at diagnosis was retrospectively added by patient chart review, whereas all other data were retrieved from the STCS database. Out of a total of 3970 K-Tx recipients between May 2008 and September 2020, we were able to include 3059 (77.1%) K-Tx recipients in our analysis (Fig. 1). Chart review was limited to individuals with a documented SSI within 90 days after transplantation in the STCS database. SSIs were categorized into superficial incisional, deep incisional, and organ/space infections according to Centers for Disease Control and Prevention criteria.[10] If multiple pathogens were detected in a sample from a K-Tx recipient with SSI, all bacteria considered as clinically relevant, and as such prompting corresponding antibiotic treatment, were reported.

2.2. Statistical analyses

Baseline recipient and donor characteristics were descriptively reported, and the frequency of missing data was provided in footnotes. Incidence rates for transplant-related SSIs occurring within 90 days after K-Tx were calculated. Risk factors for SSIs were assessed with logistic regression; this analysis was limited to the complete data set. Variables addressed in the multivariable analysis were chosen based on a combination of clinical relevance and the results of univariable logistic regression (effect size, significance level $\leq$0.10) under consideration of the overall number of SSIs to prevent overadjustment. For the variable delayed graft function that was considered as an independent variable for SSI, we performed a sensitivity analysis with exclusion of 4 SSI cases with occurrence of SSI temporally before a potential diagnosis of delayed graft function. Transplant outcomes, encompassing death, and graft loss were extracted from the STCS data set and presented for a 1-year follow-up. Cumulative incidences of death and graft loss as competing risks were calculated. For visualization of the probabilities of death and graft loss in the first year after transplant, a 90-day landmark model considering the presence or absence of an SSI within 90 days after transplantation

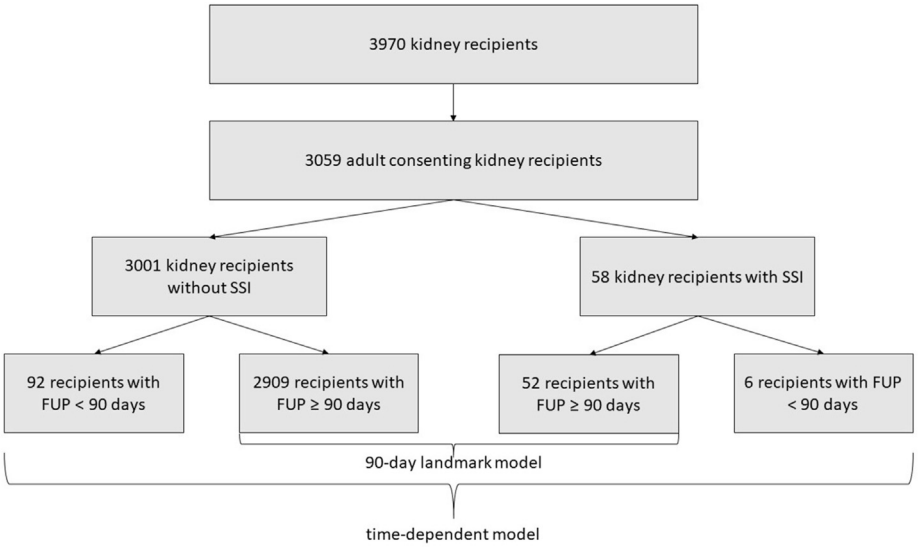

Figure 1. Flowchart of the study population selection. FUP, follow-up; SSI, surgical site infection.

was performed; for these analyses exclusively K-Tx recipients without graft loss or death within 90 days after K-Tx were considered (90-day landmark model, Fig. 1). Survival differences were investigated with the Gray test for the 90-day landmark model. To investigate short-term influences of SSIs on hazards for graft loss and death, we also considered cause-specific Cox proportional hazard models with SSI as a time-dependent variable including all kidney transplant recipients (time-dependent model, Fig. 1). To address an association between the occurrence of delayed graft function and graft loss in the first year posttransplant, we additionally performed cause-specific Cox proportional hazard models with inclusion of delayed graft function as an independent variable. As a sensitivity analysis, we also performed a cause-specific Cox proportional hazard model based on the population of the 90-day landmark model. In all Cox proportional hazard models, the exposure to SSIs was coded as permanent exposure. Cox proportional hazard models were fit for the endpoints of death or graft loss correcting for known predictors.[11,12] R version 4.2.1 was used for statistical analysis and visualization.[13]

3. Results

3.1. Study population

A total of 3059 K-Tx recipients with a median age of 55.4 years (interquartile range 44.6, 63.7) were included; 1959 (64%) were male (Table 1). The majority (2600, 85.0%) of K-Tx recipients were included after their first transplant. The most frequent causes leading to transplantation were glomerulonephritis (650, 21.2%), polycystic kidney disease (548, 17.9%), and nephrosclerosis (333, 10.9%). Approximately 60% of kidney grafts came from deceased donors, predominantly after brain death (1474, 51.3%). Induction immunosuppression consisted of basiliximab (2250, 73.6%) and antithymocyte globulin (764, 25.0%; in 118 [3.9%] patients combined with basiliximab). Maintenance immunosuppression contained tacrolimus in the majority of patients (2297, 75.1%). Routine perioperative antibiotic prophylaxis consisted of administration of amoxicillin/clavulanate (1 center), cefuroxime (3 centers), ceftriaxone (1 center), or piperacillin/tazobactam (1 center) within 30 to 60 minutes before incision. Routine antiinfective prophylactic strategies are described in the Supplementary Methods.

3.2. Incidence, categorization, and etiology of SSI

Of the overall 3059 K-Tx recipients, 58 (1.9%) individuals developed an SSI within 90 days after transplantation. Superficial incisional infections contributed to 9 (15.5%), deep incisional infections to 15 (25.9%), and organ/space infections to 34 (58.6%) SSIs. In 52 SSIs, bacteria were identified as causative pathogens. The most commonly detected bacteria were *Escherichia coli* (15/52, 28.9%), *Enterococcus* spp. (14/52, 26.9%), and coagulase-negative staphylococci (CNS; 13/52, 25.0%) (Fig. 2). In 1 (1.7%) SSI, *Candida albicans* was detected. Five (8.6%) SSIs were diagnosed exclusively based on clinical findings.

3.3. Risk factor analysis for SSI

In univariable analysis, higher age (odds ratio [OR] per 10-year increase 1.35, 95% CI 1.07-1.71, $P = .008$), BMI $\geq$ 25 kg/m^2 (OR 2.79, 95% CI 1.41-5.49, $P = .001$), longer cold ischemia time (OR per 10 minute increase 1.01, 95% CI 1.00-1.02, $P = .004$) and the occurrence of delayed graft function (OR 4.10, 95% CI 2.28-7.39, $P < .001$) were significantly associated with SSI (Table 2). Diabetes mellitus at transplantation tended to be associated with SSI (OR 1.91, 95% CI 1.00-3.66, $P = .062$). On the contrary, living kidney donation (OR 0.27, 95% CI 0.11-0.64, $P = .001$) was deemed protective against SSI.

In multivariable analysis, BMI $\geq$ 25 kg/m^2 (OR 2.16, 95% CI 1.07-4.34, $P = .023$) and occurrence of delayed graft function (OR 2.88, 95% CI 1.56-5.34, $P = .001$) were independent risk factors for SSI. A sensitivity analysis with exclusion of 4 SSI

Table 1
Baseline characteristics of 3059 kidney transplant recipients.

Variable	N = 3059
Recipient sex	
Female	1100 (36.0%)
Male	1959 (64.0%)
Median recipient age, y (IQR)	55.4 (44.6, 63.7)
Ethnicity[a]	
Caucasian	2757 (90.1%)
Asian	129 (4.2%)
African	103 (3.4%)
Other	53 (1.7%)
Recipient BMI[b]	
<25.0 kg/m^2	1376 (45.0%)
≥25.0 kg/m^2	1653 (54.0%)
Etiology	
Glomerulonephritis	650 (21.2%)
Polycystic kidney disease	548 (17.9%)
Nephrosclerosis	333 (10.9%)
Previous graft failure	226 (7.4%)
Diabetic nephropathy	222 (7.3%)
Reflux pyelonephritis	151 (4.9%)
Hereditary causes other than PCKD	117 (3.8%)
Interstitial nephritis	100 (3.3%)
Congenital	92 (3.0%)
HIV nephropathy	7 (0.2%)
Other	613 (20.0%)
Diabetes mellitus at transplantation	499 (16.3%)
Tx history	459 (15.0%)
Induction immunosuppression	
ATG[c]	764 (25.0%)
Basiliximab[c]	2250 (73.6%)
Other	163 (5.3%)
Maintenance immunosuppression[d]	
Tacrolimus-containing regimen	2297 (75.1%)
Cyclosporine A-containing regimen	480 (15.7%)
mTor inhibitor-containing regimen	45 (1.5%)
MMF or EC-MPS	2787 (91.1%)
Azathioprine	44 (1.4%)
Glucocorticoid	2777 (90.8%)
Donor sex (male)	1500 (49.1%)
Median donor age at donation in y (IQR)	55.0 (45.0, 64.0)
Type of donation	
DBD	1561 (51.0%)
DCD	272 (8.9%)
Living donation	1226 (40.1%)

ATG, antithymocyte globulin; BMI, body mass index; DBD, donation after brain death; DCD, donation after cardiocirculatory death; EC-MPS, enteric-coated mycophenolate sodium; IQR, interquartile range; MMF, mycophenolate mofetil; mTor, mammalian target of rapamycin; PCKD, polycystic kidney disease; Tx history, prior solid organ transplant.

[a] Data for 17 (0.6%) patients unknown.

[b] Data for 30 (1.0%) patients unknown.

[c] 118 (3.9%) of kidney transplant recipients received both ATG and Basiliximab.

[d] Maintenance immunosuppressive regimen started within the first 2 wk after transplantation, data for 178 (5.8%) patients unknown.

cases with occurrence of SSI temporally before a potential diagnosis of delayed graft function confirmed delayed graft function as an independent risk factor (OR 3.15, 95% CI 1.65-6.00, $P = .001$, Supplementary Table 4).

3.4. SSIs and posttransplant outcomes

In multivariable cause-specific Cox proportional hazard models coding SSI as a time-dependent variable, the presence of SSI (multivariable hazard ratio [mv HR] 2.71; 95% CI 0.84, 8.74; $P = .095$) tended to be associated with death (Table 3). Higher recipient age (mv HR per 10-year increase 1.05; 95% CI 1.02, 1.08; $P < .001$) was independently associated with death. On the contrary, higher donor age (mv HR per 10-year increase 0.99; 95% CI 0.99, 1.00, $P = .014$) and a living K-Tx were independently associated with improved survival (mv HR 0.44; 95% CI 0.22, 0.88; $P = .021$).

In multivariable cause-specific Cox proportional hazard models coding SSI as a time-dependent variable, the presence of SSI (mv HR 3.75; 95% CI 1.35, 10.38; $P = .011$) and higher donor age (mv HR per 10-year increase 1.01; 95% CI 1.00, 1.03, $P = .044$) were independently associated with graft loss. Living kidney donation was independently associated with reduced risk for graft loss (mv HR 0.36; 95% CI 0.22, 0.59; $P < .001$).

Cumulative incidences of death and graft loss based on the 90-day landmark model are visualized in Supplementary Figure A, B, respectively. Crude outcomes are summarized in Supplementary Table 1.

4. Discussion

In the present nationwide cohort study encompassing more than 12 years, SSIs occurred in less than 2% of K-Tx recipients. Among causative pathogens, *E. coli*, *Enterococcus* spp., and CNS were predominant. A BMI ≥ 25 kg/m^2 and occurrence of delayed graft function were independent risk factors for SSIs. SSIs were associated with graft loss in the first year after K-Tx.

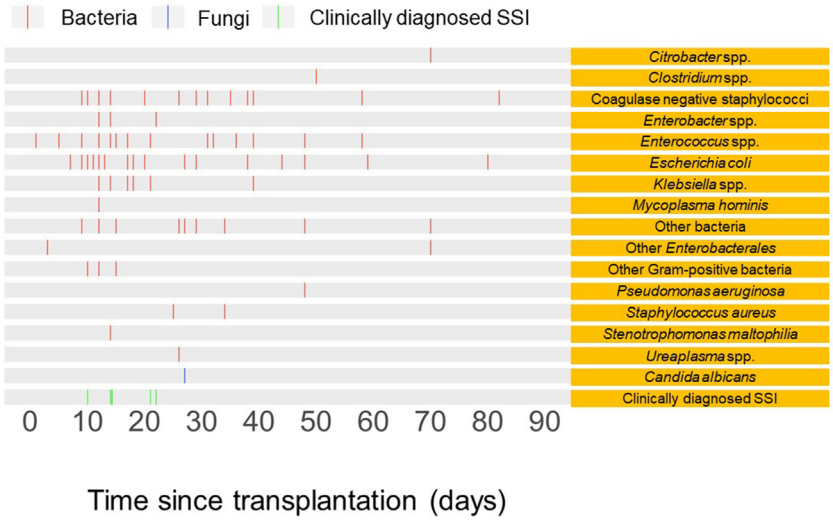

Figure 2. Temporal distribution of detected pathogens in surgical site infections after kidney transplantation. Two clinically diagnosed surgical site infections were reported 14 days after transplantation. SSI, surgical site infection.

The infection rate in our study was low compared to prior studies. A recent study from Ireland also reported comparable SSI rates,[14] whereas predominantly older studies found higher SSI rates.[15-19] It can be hypothesized that due to implementation of improved infection prevention and surgical practices in recent years, a longitudinal decrease in SSI rates could be observed. However, in a recent systematic review and meta-analysis on the preventable proportion of HAIs, the avoidable proportion of HAIs did not seem to decrease over time.[20] In our data set, we did not identify a temporal trend in SSI rates (data not shown).

Most SSIs were caused by *E. coli*, *Enterococcus* spp., and CNS. This finding is in line with prior studies. Harris et al[8] and Menezes et al[21] similarly reported a large proportion of SSIs caused by CNS, *Enterococcus* spp., and *E. coli*. Ostaszewska et al[9] also found a predominance of *Enterococcus* spp. among Gram-positive bacteria and of *E. coli* among Gram-negative pathogens. The origin of the pathogens causing SSI cannot be answered with our data. In infection prevention and control, most SSIs are considered to originate from the patient's endogenous flora.[22] In the present study, identical pathogens to those causing

Table 2
Risk factors for surgical site infections within 90 days after kidney transplantation.

	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Recipient sex (male)	1.66 (0.86, 3.22)	.117		
Recipient age (per 10-y increase)	1.35 (1.07, 1.71)	.008	1.20 (0.93, 1.55)	.151
Recipient BMI ($\geq$25 kg/m^2)	2.79 (1.41, 5.49)	.001	2.16 (1.07, 4.34)	.023
Tx history (yes)	1.00 (0.45, 2.26)	.992		
Diabetes mellitus at transplantation	1.91 (1.00, 3.66)	.062	1.28 (0.65, 2.51)	.487
Donor sex (male)	1.78 (0.98, 33.24)	.055		
Donor age (per 10-y increase)	0.91 (0.77, 1.07)	.258		
Type of donation (living)	0.27 (0.11, 0.64)	.001	0.57 (0.20, 1.63)	.276
Cold ischemia time (per 10-min increase)	1.01 (1.00, 1.02)	.004	1.01 (0.99, 1.02)	.361
ATG-containing induction immunosuppression	1.37 (0.75, 2.52)	.314		
Delayed graft function	4.10 (2.28, 7.39)	$<$.001	2.88 (1.56, 5.34)	.001
Maintenance regimen		.248		
Tacrolimus-containing	Reference			
Cyclosporine A-containing	1.54 (0.76, 3.13)			
Other regimen[a]	1.26 (0.30, 5.29)			

ATG, antithymocyte globulin; BMI, body mass index; CI, confidence interval; OR, odds ratio; Tx history, prior solid organ transplant.

[a] Either mammalian target of rapamycin (mTor) inhibitor-containing regimen or regimen containing neither cyclosporine A nor tacrolimus.

Table 3
Cause-specific Cox proportional hazard models for risk of death or graft loss in the first year after kidney transplantation treating surgical site infections (SSI) as time-dependent.

	Death				Graft loss			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
SSI	3.66 (1.14, 11.73)	.029	2.71 (0.84, 8.74)	.095	4.43 (1.61, 12.23)	.004	3.75 (1.35, 10.38)	.011
Recipient age (per 10-y increase)	1.05 (1.03, 1.08)	<.001	1.05 (1.02, 1.08)	<.001	1.02 (1.01, 1.04)	.007	1.01 (0.99, 1.03)	.284
Type of donation (living)	0.34 (0.17, 0.68)	.002	0.44 (0.22, 0.88)	.021	0.34 (0.21, 0.56)	<.001	0.36 (0.22, 0.59)	<.001
Donor age (per 10-y increase)	0.99 (0.99, 1.00)	.025	0.99 (0.99, 1.00)	.014	1.02 (1.00, 1.03)	.017	1.01 (1.00, 1.03)	.044

CI, confidence interval; HR, hazard ratio.

subsequently diagnosed SSIs were identified in urinary tract infections of 8 K-Tx recipients among 18 K-Tx recipients with corresponding data (data not shown). Future studies with per protocol sampling of donors and recipients combined with molecular typing methods are needed to address this research question.

In our multivariable analysis of risk factors for SSIs, we found BMI $>$ 25 kg/m^2 and occurrence of delayed graft function independently associated with SSIs. The association between higher BMI and SSIs after renal transplantation is supported by several prior studies.[8,9,15,16,18,23] Robot-assisted K-Tx could be a promising approach for SSI prevention, especially in obese patients, as recent reviews supported use of robot-assisted K-Tx in obese patients and reported lower SSI rates with robot-assisted K-Tx.[24,25] As delayed graft function might rather be a consequence than a cause of SSI, we reviewed the timeline of K-Tx recipients with SSI and delayed graft function and performed a sensitivity analysis with exclusion of 4 SSI cases with the occurrence of SSI temporally before a potential diagnosis of delayed graft function. This analysis confirmed the association of delayed graft function and subsequent SSI (Supplemental Table 4). In line with our findings, Wszola et al[15] and Menezes et al[16] reported delayed graft function as a risk factor for SSI. Freire et al[23] found use of ATG as a risk factor for SSIs in K-Tx recipients. We also addressed this variable in the risk factor analysis and did not detect an association with SSIs. The primary mechanism of ATG is depletion of T cells.[26] A review by Issa and Fishman from 2009 judged the impact of ATG on bacterial infections as unclear.[27] Future studies seem warranted to delineate the relevance of ATG use for induction therapy and the occurrence of SSIs.

In the present study, SSIs were associated with graft loss. This association remained significant in a sensitivity analysis including delayed graft function as an independent predictor of graft loss (Supplementary Table 3). Freire et al[23] also reported a significant association of SSIs after K-Tx and reduced graft survival. Similarly, Wong et al[18] found a significant association of surgical site complications and graft failure after K-Tx. In contrast, Menezes et al[21] did not detect an association of SSI and graft function. Ostaszewska et al[9] did not identify differences in delayed graft function, primary nonfunction, and serum creatinine levels between K-Tx recipients with SSI and those without SSI. Of note, in their study, more than 70% were superficial SSIs, suggesting a less severe subset of SSI likely to be associated with a lower impact on graft outcome. In line with prior studies, we also found an association of higher donor age and graft loss.[28,29] Resembling the findings from our study in simultaneous pancreas-kidney and pancreas transplant recipients, hospitalization was significantly longer in K-Tx recipients with SSI as compared to K-Tx recipients without SSI (Supplementary Table 5).[30]

The nationwide data collection with the contribution of all K-Tx centers and remarkable STCS participation of transplant patients[31] over more than 12 years are major strengths. The prospective collection of almost all analyzed variables contributed to data quality. We addressed associations between SSIs and transplant-related outcomes with 2 different populations in time-to-event analysis, ie, the 90-day landmark model and the time-dependent model. The time-dependent model enabled us to analyze data of K-Tx recipients with death or graft loss within the first 90 days after transplant and found a significant association of SSI and graft loss. The association of SSI with graft loss lost significance in the 90-day landmark model, but hazards for graft loss remained higher among K-Tx recipients with SSI supporting the findings of the time-dependent model (Supplementary Table 2).

Our study has several limitations that need to be considered. First, our data set did not include information on the administration of perioperative prophylaxis per individual. Second, we did not have data on body temperature during the transplant procedure. For SSI prevention, hypothermia should be avoided.[32,33] Thus, we were not able to address this variable in the risk factor analysis. Third, the categorization of SSIs was added retrospectively by chart review. Fourth, we did not have data on readmissions due to SSIs, hindering an analysis of this outcome. Fifth, the predominance of Caucasian ethnicity in the present study might limit the generalizability of the results. Sixth, we did not have data on the surgical practice and thus could not consider this variable for risk factor analysis.

To conclude, SSIs were an uncommon complication after K-Tx in our nationwide cohort but were independently associated with graft loss.

Funding

P.W.S. is supported by the academic career program "Filling the Gap" of the Medical Faculty of the University of Zurich. This study was performed in the framework of the Swiss Transplant Cohort Study, supported by the Swiss National Science Foundation (33CS30_201385), the Swiss University Hospitals (G15), and transplant centers.

Other: P.W.S. received travel grants from Pfizer and Gilead, honoraria as a speaker and advisory board member from Pfizer, and honoraria from Gilead as an advisory board member outside of the submitted work.

Declaration of competing interest

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. P.W.S. reports financial support was provided by University of Zurich. STCS reports financial support was provided by Swiss National Science Foundation. STCS reports financial support was provided by Swiss University Hospitals (G15) and transplant centers. P.W.S. received travel grants from Pfizer and Gilead, honoraria as a speaker and advisory board member from Pfizer, and honoraria from Gilead as an advisory board member outside of the submitted work. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Data can be requested for specified purposes after approval of a proposal by the Scientific Committee of the STCS and approval by the responsible ethics committees.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2023.11.013.

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