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# Surgical site infections after simultaneous pancreas kidney and pancreas transplantation in the Swiss Transplant Cohort Study

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## SUMMARY

**Background:** Among hospital-acquired infections, surgical site infections (SSIs) are frequent. SSI in the early post-transplant course poses a relevant threat to transplant recipients.

**Aim:** To determine incidence, risk factors for SSI and its association with post-transplant outcomes and pancreas transplant (P-Tx) recipients.

**Methods:** Adult simultaneous kidney–pancreas transplantation (SPK-T) and P-Tx recipients with a follow-up of at least 90 days were identified in the Swiss Transplant Cohort Study (STCS) dataset. Except for the categorization of SSIs according to Centers for Disease Control and Prevention (CDC) criteria, all other data were prospectively collected. Risk

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Surgical site infection  
Hospital-acquired infection



factors for SSI were investigated with logistic regression. A Weibull accelerated failure-time model was applied to address the impact of SSI on length of stay, correcting for transplant-related complications and delayed graft function.

**Findings:** Of 130 transplant recipients, 108 SPK-Tx and 22 P-Tx, 18 (14%) individuals developed SSI within the first 90 days after transplantation. Deep incisional (seven, 38.9%) and organ/space infections (eight, 44.4%) predominated. In the majority of SSIs (11, 61.1%; two SSIs with simultaneous identification of fungal pathogens) bacteria were detected with *Enterococcus* spp. being most frequent. The median duration of hospitalization after transplantation was significantly longer in recipients with SSI (median: 26 days; interquartile range (IQR): 19–44) than in patients without SSI (median: 17 days; IQR: 12–25;  $P = 0.002$ ). In multivariate analysis, SSI was significantly associated with increased length of stay and prolonged the duration of hospitalization by 36% (95% confidence interval: 4–79).

**Conclusion:** SSI after SPK-Tx and P-Tx occurred at a frequency of 14%. Among pathogens, *Enterococcus* spp. predominated. SSI was independently associated with a longer hospitalization after transplantation.

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## Introduction

Simultaneous kidney–pancreas (SPK-Tx) or pancreas transplantation (P-Tx) are common treatment strategies for individuals suffering from diabetes mellitus type 1. In 2019, the Organ Procurement and Transplantation Network registered 875 SPK-Tx and 125 P-Tx transplantations in the USA, whereas in Switzerland, a total of 340 kidney transplantations and a total of 25 pancreas or islet cell transplantations were performed [1,2].

Among healthcare-associated infections (HAIs), surgical site infections (SSIs) are highly prevalent. Swiss data gathered in a recent point-prevalence study reported SSI as the most frequently occurring HAI [3]. Similarly, in a US point-prevalence study from 2014, SSI and pneumonia, each detected at a frequency of 20.8%, were the most frequent HAIs [4]. SSI after SPK-Tx or P-Tx was associated with poorer graft survival and prolonged duration of hospital stay [5–7]. In addition, SSI often requires reoperation, contributing to transplant-related morbidity [6]. Data on SSI after SPK-Tx and P-Tx derived from multi-centre studies remain scarce. We sought to address this important infectious complication in the early post-transplant course within the Swiss Transplant Cohort Study (STCS).

## Patients and methods

### Study design, population, and patient-related data

This study was a nested project within the Swiss Transplant Cohort Study (STCS, [www.stcs.ch](http://www.stcs.ch), [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01204944) Identifier: NCT01204944). All Swiss transplant centres (Basel, Bern, Geneva, St Gallen, Lausanne, and Zurich) contribute to the prospective data collection of the STCS. The STCS contains data on all solid-organ transplants performed after May 1<sup>st</sup>, 2008. Each transplant recipient is requested to grant informed consent, prompting enrolment in the STCS and inclusion into research projects. More than 93% of all transplant recipients are enrolled in the STCS, allowing comprehensive prospective data

collection [8]. The STCS was approved by the Ethics Committees of all participating institutions. A separate approval was obtained for this nested study by the responsible Ethics Committee (Kantonale Ethikkommission Zürich, Req. 2016-01532). Among all individuals enrolled in the STCS between January 2008 and September 2021, adult patients with SPK-Tx or P-Tx and a follow-up of at least 90 days were selected (Figure 1). Individuals who received serial transplants (three SPK-Tx followed by a P-Tx, one P-Tx followed by another P-Tx) that were at least one year apart were treated as separate individuals in the analyses. In predefined time intervals, ranging from twice a week to every three months, transplant recipients are followed-up for occurrence of infections by dedicated research assistants. The research assistants are supervised by transplant infectious diseases physicians and predefined criteria for the diagnosis of infections are applied [9]. SSIs were defined according to Centers for Disease Control and Prevention (CDC) criteria [10]. The categorization of the extent of the SSI at diagnosis was retrospectively added by patient chart review, whereas all other data derived from the prospective data collection of the STCS. 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 CDC criteria [10]. The collection of these additional data included verification of SSIs reported in the STCS dataset by transplant infectious diseases physicians.

### Statistical analyses

Baseline recipient and donor characteristics were presented for SKP-Tx and P-Tx. Incidence rates were calculated for transplant-related SSIs occurring within 90 days after SKP-Tx or P-Tx. Risk factors for SSI were assessed with univariable and multivariable logistic regression. Based on findings from a previous study, cold ischaemia time and the transplant procedure (SPK-Tx vs P-Tx) were included in the multivariable model [5]. The duration of hospitalization in patients with and without SSI

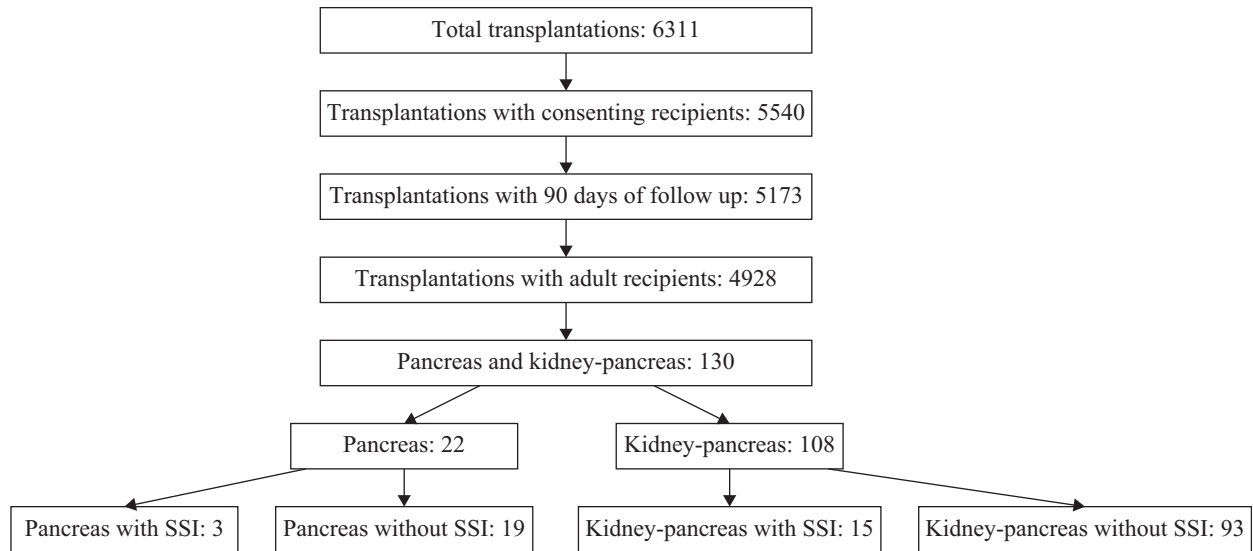


Figure 1. Flow chart of the study population selection. SSI, surgical site infection.

was compared using the Wilcoxon rank test. In order to adjust for other factors that might alter the length of stay, a Weibull accelerated failure-time model was fitted, including the variables SSI, delayed graft function, transplant-related complications, and age. The model enabled estimation of the event time ratio (ETR) for each of the covariates. Transplant-related complications that were considered likely to prolong hospitalization encompassed vascular complications affecting the graft and revision surgery or interventional drainage. Transplant outcomes, encompassing death, graft loss, need for insulin therapy, and a worsening of renal function to an estimated glomerular filtration rate  $<15\text{ mL/min}/1.73\text{ m}^2$  after SPK-Tx and death, graft loss, and need for insulin therapy after P-Tx were extracted from the STCS dataset and presented for the entire follow-up. R version 3.6.2 was used for statistical analysis and visualization [11].

## Results

### Study population

Overall, 108 SPK-Tx and 22 P-Tx recipients of median age 45 years (interquartile range (IQR): 37–51) and 43 years (IQR: 35–48), respectively, were included (Table I). Males contributed to 56% of SPK-Tx and to 59% of P-Tx recipients. All SPK-Tx and P-Tx were performed due to diabetes mellitus type 1. Among SPK-Tx recipients, five (5%) and among P-Tx recipients 15 (68%) individuals had had a previous transplantation. Among P-Tx recipients, 13 (59%) received the pancreas graft after previous kidney transplant. Among both SPK-Tx and P-Tx, Caucasian ethnicity was most frequent (SPK-Tx: 94, 88%; P-Tx: 21, 96%). Induction immunosuppression was administered in the vast majority of SPK-Tx and P-Tx recipients with thymoglobulin being most frequent (SPK-Tx: 85, 79%; P-Tx: 22, 100.0%). In the first week after transplantation, most SPK-Tx recipients (91, 84.3%) were started on a tacrolimus-based maintenance immunosuppressive regimen, whereas more than half of P-Tx recipients (12, 54.5%) received neither

tacrolimus, cyclosporine A nor a mammalian target of rapamycin inhibitor. Routine perioperative antibiotic prophylaxis for SSI prevention consisted of either amoxicillin/clavulanate or piperacillin/tazobactam.

### Incidence, categorization, and aetiology of surgical site infections

Among all 130 transplant recipients, 18 (13.8%) individuals (15 (13.9%) SPK-Tx recipients and three (13.6%) P-Tx recipients) developed SSI within the first 90 days after transplantation. Three (16.7%) SSIs were categorized as superficial incisional, seven (38.9%) as deep incisional SSIs, and eight (44.4%) as organ/space infections. There were nine (50%) bacterial SSIs (one with detection of multiple bacteria), five (27.8%) fungal SSIs (one with detection of multiple fungi), and two (11.1%) SSIs caused by fungi and bacteria. Two (11.1%) SSIs were diagnosed based on clinical findings. In the majority of SSIs after SPK-Tx, bacteria (9/15, 60%) were detected, most frequently enterococci (6/15, 40%) and coagulase-negative staphylococci (CoNS) (3/15, 20%) (Figure 2). In six SSIs at least one fungus was detected, including the species *Candida albicans* (4/15, 27%), *Candida non-albicans* (2/15, 13%), and *Aspergillus fumigatus* (1/15, 7%).

After P-Tx, in two SSIs bacteria were detected, the species being *Enterococcus* spp., *Streptococcus* spp., and other anaerobic bacteria. In one SSI, a fungus was identified (*Candida non-albicans*).

### Risk factor analysis for surgical site infections

Using logistic regression to identify possible risk factors for SSI, no significant association was detected with type of transplant procedure, recipient age, sex or body mass index, donor sex or age, cold ischaemia time, different induction therapies, routine perioperative antibiotic prophylaxis and the variable, if the current transplant was performed after a previous transplant (Table II). Similarly, no significant association

**Table I**  
Baseline characteristics of 108 simultaneous kidney–pancreas recipients and 22 pancreas recipients

Baseline characteristic	Kidney–pancreas (N = 108)	Pancreas (N = 22)	Total (N = 130)
Recipient sex			
Male	61 (56.0%)	13 (59.1%)	74 (56.5%)
Female	47 (43.5%)	9 (40.9%)	56 (43.5%)
Recipient age at transplantation, median (IQR)	44.7 (37.0–51.0)	42.6 (34.9–48.4)	44.4 (36.6–50.1)
Recipient ethnicity			
African	6 (5.6%)	1 (4.5%)	7 (5.4%)
Asian	1 (0.9%)	0	1 (0.8%)
Caucasian	94 (87.9%)	21 (95.5%)	115 (89.1%)
Other	6 (5.6%)	0	6 (4.7%)
Recipient BMI, median (IQR)	23.1 (21.1–25.3)	22.8 (20.5–25.0)	23.1 (21.1–25.3)
Tx history	5 (4.6%)	15 (68.2%)	20 (15.4%)
Induction immunosuppression			
None	3 (2.8%)	0	3 (2.3%)
Basiliximab	20 (18.5%)	0	20 (15.3%)
Thymoglobulin	83 (76.9%)	19 (86.4%)	102 (78.5%)
Basiliximab and thymoglobulin	2 (1.9%)	1 (4.5%)	3 (2.3%)
Rituximab and thymoglobulin	0	2 (9.1%)	2 (1.5%)
Maintenance immunosuppression <sup>a</sup>			
Tacrolimus-based regimen	91 (84.3%)	10 (45.5%)	101 (77.7%)
mTOR inhibitor-based regimen	1 (0.9%)	0	1 (0.8%)
Other	16 (14.8%)	12 (54.5%)	28 (21.5%)
CIT (h), median (IQR)			
Kidney	10.38 (8.92–11.66)		10.38 (8.92–11.66)
Pancreas	8.49 (7.18–9.57)	7.95 (6.77–9.43)	8.33 (7.08–9.55)
Donor sex			
Male	70 (64.8%)	15 (68.2%)	85 (65.4%)
Female	38 (35.2%)	7 (31.8%)	45 (34.6%)
Donor age, median (IQR)	33.0 (22.8–44.0)	30.5 (24.0–36.8)	33.0 (23.3–41.0)
Donor type			
DBD	108 (100.0%)	22 (100.0%)	130 (100.0%)

IQR, interquartile range; BMI, body mass index; mTOR inhibitor, mammalian target of rapamycin inhibitor; CIT, cold ischaemia time; Tx history, prior solid organ transplant; DBD, donation after brain death.

<sup>a</sup> Maintenance immunosuppressive regimen that was administered within the first week after transplantation. Other maintenance immunosuppression referred to a maintenance regimen that did not include cyclosporin A, tacrolimus, or a mammalian target of rapamycin inhibitor (mTOR inhibitor).

was detected in a multivariable analysis with adjustment for type of transplant procedure and cold ischaemia time.

### Association of surgical site infections with post-transplant outcomes

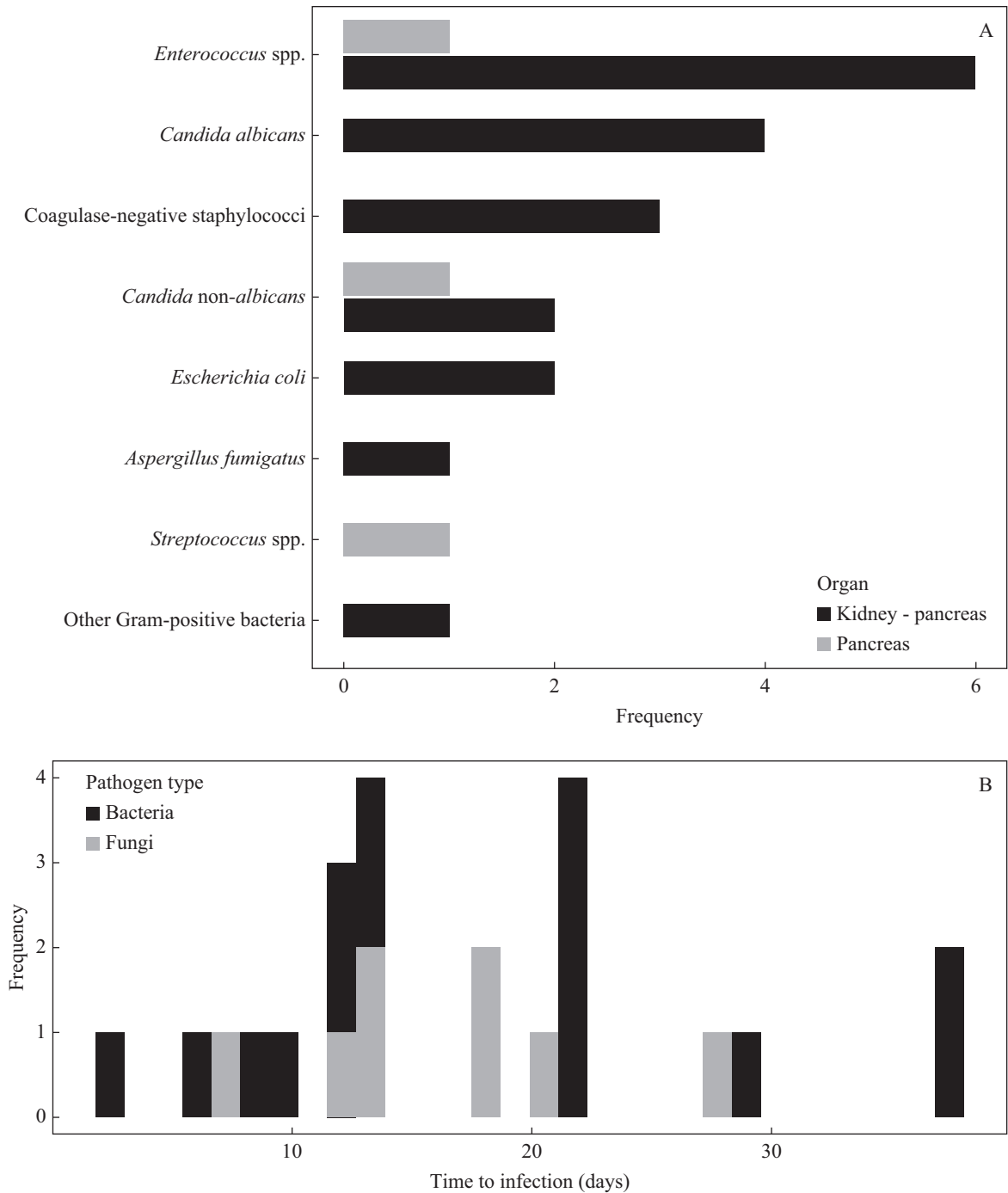
Post-transplant outcomes regarding death, graft loss, and need for insulin therapy (as well as a worsening of renal function to an estimated glomerular filtration rate <15 mL/min/1.73 m<sup>2</sup> after SPK-Tx) were similar among transplant recipients with SSI and without SSI (Supplementary Table S1). Overall, the median length of hospital stay after transplantation was longer in patients with SSI (median: 26 days; IQR: 19–44) than in patients without SSI (17; 12–25; *P* = 0.002). This observation was consistent, if we focused exclusively on SPK-Tx (SSI: 23; 18–49; no SSI: 17; 12–25; *P* = 0.009) or P-Tx (SSI: 28; 26–31; no SSI: 15; 13–19; *P* = 0.055) recipients. When correcting for other possible reasons for prolonged length of hospital stay, such as delayed graft function, age- or transplant-related complications, it was found that SSIs, delayed graft function, and transplant-related complications were significantly associated

with an increase in the length of stay (Table III). After adjustment for the covariates age, transplant-related complications, and occurrence of delayed graft function, patients with SSI were found to stay 36% (95% CI: 4–79) longer in the hospital than patients without SSI.

### Discussion

In the present cohort study on SSI after SPK-Tx or P-Tx, there was an incidence of 14% with a predominance of organ/space infections. The majority of SSIs were caused by bacteria, with *Enterococcus* spp. being most frequently identified. Individuals with SSI were significantly longer hospitalized after transplant compared to recipients without SSI.

The incidence of SSI was often higher in previous studies, ranging between 20% and 50% [5–7, 12]. One study reported SSI at a lower frequency with 14% for SPK-Tx and 9% for pancreas after kidney transplantation [13]. One explanation for these differences could be that most studies used older data compared to the present study. It may be speculated that, due to improved practices in infection prevention, a longitudinal



**Figure 2.** Frequency of detected pathogens in surgical site infections after simultaneous pancreas–kidney and pancreas transplantation (A) and time to occurrence of surgical site infection by pathogen (B). Multiple pathogens were detected in two surgical site infections after simultaneous pancreas–kidney transplantation and in one surgical site infection after pancreas transplantation.

decrease in SSI might be observed. Furthermore, the country in which the study was performed might be relevant for the incidence of SSI. The World Health Organization reported an increased burden of HAIs in low- and middle-income countries with SSIs being the most frequent HAI [14].

Among all SSIs, deep incisional and organ/space infections are the most relevant SSIs in terms of morbidity and mortality. Besides our study, few studies have addressed this categorization

[5,6]. Resembling the findings of Smets *et al.* and Natori *et al.*, organ/space infections predominated in the present study [5,6]. In contrast to Natori *et al.*, deep incisional SSIs were found more frequent than superficial incisional SSIs [5].

In line with previous studies, the vast majority of SSIs was caused by bacteria, with frequent detection of *Enterococcus* spp. and CoNS [5,6,12,15]. By contrast, Perdiz *et al.* reported a high proportion of Gram-negative pathogens causing SSIs



**Table II**

Univariate and multivariate logistic regression for identification of risk factors for surgical site infections 90 days post transplant

Risk factor	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Transplant procedure				
Kidney–pancreas	Reference		Reference	
Pancreas	0.98 (0.21, 3.34)	0.98	0.99 (0.26, 3.8)	0.99
Recipient sex				
Female	Reference			
Male	0.72 (0.26, 1.99)	0.52		
Recipient age (years)	0.96 (0.91, 1.02)	0.19		
Recipient BMI (kg/m <sup>2</sup> )	1.03 (0.89, 1.19)	0.68		
Tx history	1.12 (0.24, 3.86)	0.87		
CIT pancreas (min)	1.00 (0.99, 1.00)	0.70	1.00 (0.99, 1.00)	0.70
Induction immunosuppression with thymoglobulin	1.09 (0.32, 5.00)	0.90		
Routine perioperative antibiotic prophylaxis				
Piperacillin/tazobactam	Reference			
Amoxicillin/clavulanate	1.50 (0.52, 4.95)	0.47		
Donor sex				
Female	Reference			
Male	0.62 (0.22, 1.74)	0.35		
Donor age (years)	1.02 (0.97, 1.06)	0.51		

OR, odds ratio; CI, confidence interval; BMI, body mass index; Tx history, prior solid organ transplant; CIT, cold ischaemia time.

[7]. Fungal SSIs were predominantly due to *Candida* spp., resembling the findings from Natori *et al.* and Kawecki *et al.* [5,15].

A recent mono-centric study from Canada with inclusion of 445 patients aimed at identification of risk factors for SSI after SPK-Tx and pancreas after kidney transplantation [5]. The authors found an increased SSI risk for SPK-Tx recipients and longer cold ischaemia time. Perdiz *et al.* identified acute tubular necrosis, post-transplant fistulas, and an episode of rejection as independent risk factors, whereas Smets *et al.* identified cefamandole prophylaxis as independent risk factor [6,7]. Among the variables addressed, we identified no significant risk factor for SSI. However, our analysis might be hampered by the low frequency of SSI in our cohort and the overall limited number of SPK-Tx and P-Tx recipients. Our cohort did not include data on the individually administered perioperative antibiotic prophylaxis, but if we considered the different routinely administered perioperative prophylaxis, no significant association with SSI was found.

Data on transplant outcomes due to SSI among SPK-Tx and P-Tx patients are still scarce. In a Canadian cohort of SPK and pancreas after kidney recipients, a longer hospital stay and 16-fold odds for graft loss within three months post transplant was

reported [5]. Smets *et al.* observed two graft losses in direct relation to SSI among 20 patients with SSI and a significant longer hospital stay in recipients with SSI [6]. In line with prior studies, we confirmed a prolonged duration of hospitalization for transplant recipients with SSIs [5–7]. The application of a Weibull accelerated failure-time model enabled a more accurate estimate of the association between the investigated variables and prolongation of hospital stay. These findings might be helpful for identification of individuals with likely prolonged hospital stay and the expected extent of prolongation by the occurrence of associated variables. A better understanding of these associations could be crucial for optimized allocation of resources in healthcare. The current study identified no significant differences among the further assessed outcome variables.

Strengths of this study include the multi-centric design with almost exclusive use of prospectively collected data. The STCS dataset is highly representative for transplantations performed in Switzerland given an enrolment of more than 90% of all solid organ transplantations performed in Switzerland [8]. The use of widely established CDC definitions for SSIs enables insights into severity of SSIs and will allow comparisons with future studies.

The present study also has some limitations. The categorization of SSIs was assessed retrospectively. The overall low number of SSIs limited statistical power and thus hindered more detailed statistical analyses. No information was collected on the administration of perioperative prophylaxis per individual patient. Data on routinely used perioperative antibiotic prophylaxis were gathered, but there might have been adaptations due to pre-transplant colonization of transplant recipients.

To conclude, SSIs were detected at a similar frequency after SPK-Tx and P-Tx. SSI was associated with significantly longer hospitalization after transplant procedure.

**Table III**

Multivariate accelerated failure-time model predicting time to discharge

Variable	ETR (95% CI)	P-value
Surgical site infection	1.36 (1.04–1.79)	0.025
Transplant-related complication	1.68 (1.37–2.07)	<0.001
Delayed graft function	1.40 (1.04–1.97)	0.029
Age (years)	1.00 (0.9–1.01)	0.767

ETR, event time ratio.

**Conflict of interest statement**

P.W.S. received travel grants from Pfizer and Gilead, speaker's honorary from Pfizer, and fees for advisory board activity from Pfizer and Gilead outside of the submitted work. All other authors declared no conflicts of interest.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2022.07.009>.

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