First day plasma amylase detects patients at risk for complications after simultaneous pancreas-kidney transplantation

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<p>Tiivistelmä – Referat – Abstract</p> <p>Tutkimuksen tarkoitus: Samanaikainen haima- ja munuaissiirto on ainoa parantava hoito tyyppin 1 diabetekseen, mutta siihen liittyy huomattava leikkauksen jälkeisten komplikaatioiden riski. Tietoa näiden komplikaatioiden ennustetekijöistä on vähän. Tämän tutkimuksen tarkoituksena on selvittää erilaisten laboratoriotutkimusten kykyä ennustaa siirron jälkeisiä komplikaatioita.</p> <p>Aineisto ja menetelmät: Kaikki Suomessa ennen helmikuuta 2020 toteutetut samanaikaiset haima- ja munuaissiirrot analysoitiin retrospektiivisesti. Ensimmäisten kolmen leikkauksen jälkeisen päivän plasman amylaasin, dreeniamylaasin, C-reaktiivisen proteiinin, c-peptidin, plasman trypsinogeenin ja leukosyyttien tasot kerättiin, ja niiden kykyä ennustaa leikkauksen jälkeistä sairastuvuutta (mitattiin Comprehensive Complication Indexillä, CCI) ja komplikaatioita 90 päivän sisällä tarkasteltiin ROC-analyysillä.</p> <p>Tulokset: Tutkimukseen sisällytettiin 164 potilasta ja näistä potilaista relaparotomiaa vaativia komplikaatioita oli kolmellakymmenelläyhdeksällä. Korkeimman AUC-arvon perusteella ensimmäisen leikkauksen jälkeisen päivän plasman amylaasi ennusti parhaiten 90 päivän sairastuvuutta ja Youden-indexin avulla optimaaliseksi raja-arvoksi määrittyi 6 kertaa ylempi normaali viiteraja. Negatiivinen ja positiivinen ennustearvo tälle raja-arvolle oli 0.81 ja 0.71 sille, että potilas joutui relaparotomiaan. Vastaavasti arvot olivat 0.91 ja 0.71 sille, että potilaan CCI ylitti 47.7 (vastaa kahden reoperaation sairastuvuutta).</p> <p>Johtopäätökset: Ensimmäisen leikkauksen jälkeisen päivän plasman amylaasitason perusteella voidaan ennustaa haima- ja munuaissiirrepotilaan riski leikkauksen jälkeisiin komplikaatioihin. (176 sanaa)</p>			
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First day plasma amylase detects patients at risk for complications after simultaneous pancreas-kidney transplantation

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Abbreviations

AUC, area under curve

BMI, body-mass-index

CCI, the Comprehensive Complication Index

CD, Clavien-Dindo

CIT, cold ischemia time

CRP, C-reactive protein

IQR, interquartile range

NPV, negative predictive value

PAK, pancreas-after-kidney transplantation

PPV, positive predictive value

PTA, pancreas-transplantation alone

ROC, receiver operating characteristics

SPK, simultaneous pancreas-kidney transplantation

VAC, vacuum assisted closure

WBC, white blood cell count

Abstract

Simultaneous pancreas-kidney transplantation (SPK) carries a high risk of major postoperative complications, but knowledge on early warning signs and surrogate markers for postoperative complications is scarce. Our aim was to analyze the complication-predictive value of different laboratory tests in pancreas transplantation. All SPKs in Finland between January 2010 and February 2020 were retrospectively analyzed. Levels of first three day plasma amylase, drain fluid amylase, C-reactive protein, c-peptide, plasma trypsinogen and white blood cell count were assessed for their performance predicting cumulative postoperative complications (assessed using Comprehensive Complication Index, CCI) within 90 days from transplantation by using ROC-analyses. Of the 164 SPK patients included, 39 suffered at least one complication requiring laparotomy. First day plasma amylase had the best value in predicting complications based on its high AUC-value and easy clinical applicability, with an optimum cut-off of 6 times the upper normal limit. Negative predictive values (NPV) and positive predictive values (PPV) of this cutoff were 0.81 and 0.71 for any relaparotomy, and 0.91 and 0.71 for Comprehensive Complication Index > 47.7 (which equals the morbidity of two relaparotomies), respectively. In conclusion, first day plasma amylase could be able to detect patients at risk for complications after SPK.

Keywords: simultaneous pancreas-kidney transplantation, pancreas transplantation outcomes, postoperative complications

Introduction

Simultaneous pancreas-kidney transplantation (SPK) has established its importance as endocrine replacement therapy for patients with type 1 diabetes and end-stage kidney disease ^{1,2}. However, severe postoperative complications still negatively affect both short- and long-term outcomes ^{3–5}. Majority of the complications are related to the pancreas allograft and include hemorrhage, vascular thrombosis, graft pancreatitis, intra-abdominal infections, pancreatic fistula, peripancreatic fluid collections, and anastomotic leakage ⁶. Early relaparotomy rates reported in previous studies range from 23% to 44%, and first month pancreas graft loss-rates range from 3.1% to 18% ^{4,6–10}.

Most previous studies have focused on examining the incidence of early complications, or the effect of early complications on the long-term patient and graft survival ^{4,6,11}. However, the knowledge on early warning signs and surrogate markers for postoperative complications is still scarce. Risk factors established for increased rate of postoperative complications include high donor BMI, non-traumatic donor death, donor age, long pancreas cold ischemia time, and long duration of recipient dialysis treatment ^{4,6,12,13}. An association has previously been suggested between high recipient peak C-reactive protein (CRP) and increased need for relaparotomy, and between peak serum amylase and the incidence of intra-abdominal infections ^{14,15}. More information, however, is needed on the role of laboratory tests in predicting the short-term outcomes and the total initial morbidity of pancreas transplant patients. The Comprehensive Complications Index (CCI), which is a novel continuous scale for integrating the total burden of postoperative complications, can be used as an end-point to assess that morbidity ¹⁶.

The aim of this retrospective study was to investigate the role of laboratory tests as possible surrogate markers for postoperative complications. In addition, our aim was to characterize the burden of postoperative complications after SPK using the CCI-score as an end-point.

Patients and Methods

Patients

A retrospective study was performed to investigate the value of plasma amylase, drain fluid amylase, C-reactive protein (CRP), C-peptide, plasma trypsinogen and white blood cell count (WBC) in predicting postoperative complications after SPK. SPKs were started in March 2010 in our institution,

which serves as the only transplant center for the whole country of Finland. All the transplantations performed before 1st of February 2020 were included in the study. All transplants were from donors after brain death (DBD). None of the transplants were from donors after circulatory death (DCD) as there was no active DCD program in Finland during the study period.

The pancreas was procured en-bloc with donor spleen, and Y-graft derived from donor iliac artery was used for the construction of arterial anastomosis. Pancreas implantation was done intra-abdominally anastomosing the Y-graft to the recipient's common iliac artery and the pancreas portal vein to recipient inferior vena cava. All transplantations were performed using enteric proximal jejunal exocrine drainage. Two percutaneous drains are left in the vicinity of pancreas graft. All transplantations were ABO-compatible and cytotoxic crossmatch negative. University of Wisconsin solution (UW) was used for cold preservation. All patients received induction with a single dose of anti-thymocyte globulin (ATG-Fresenius/Grafalon 8mg/kg) before transplantation ¹⁷. Immunosuppression was a combination of tacrolimus and mycophenolate for maintenance, and steroids for the first 3 to 6 months. Thrombosis prophylaxis comprised of low molecular weight heparin (LMWH)-drugs (2500 IU/ml dalteparin, 20 – 40mg enoxaparin, or 2500 – 3500 IU/ml tinzaparin twice daily), for 14 to 28 days postoperatively. Antimicrobial prophylaxis comprised of piperacillin/tazobactam, ciprofloxacin, and fluconazole or anidulafungin for four postoperative days, trimethoprim-sulfamethoxazole for six months, and valganciclovir for three months for cytomegalovirus (CMV) seropositive patients, and six months for CMV seronegative recipients of grafts from CMV seropositive donors. No routine surveillance or screening imaging are performed postoperatively at our center. Indications for re-operation at our center include conservatively, radiologically or endoscopically untreatable hemorrhage or infection. This study had the approval of the the institutional review board of Helsinki University Hospital Abdominal Center (HUS/115/2020).

Data

Morning plasma amylase, drain fluid amylase, CRP, c-peptide, plasma trypsinogen and WBC values were recorded for the first three postoperative days. Peak values were defined as the highest value within these days. Values are reported relative to the upper normal limit for the sake of comparability between different assays and institutions.

All postoperative complications during the first 90 postoperative days were recorded from electronic patient records and graded according to the Clavien-Dindo-classification (CD) ¹⁸. Pancreas graft-

related complications were defined as intra-luminal hemorrhage from enteroanastomosis, intra-abdominal hemorrhage from pancreas, pancreatitis, intra-abdominal infection, pancreatic fistula, peripancreatic fluid collection, ileus, duodenojejunal anastomotic leak, or graft loss. Kidney graft-related complications include ureteral anastomotic stricture, fluid collections around kidney graft, pyelonephritis and hematuria needing treatment.

The total burden of postoperative complications during the first 90 postoperative days was calculated for each patient using the Comprehensive Complication Index (CCI) ¹⁶. Briefly, CCI is calculated first as a raw score, where each complication receives a score according to CD-classification. The true CCI-score is then acquired by scaling the raw score between 0 and 100 (0 means no complications and death equals 100). A CCI-score value of 47.7 was chosen for a cut off-value to divide between patients with high and low morbidity, because it equals the postoperative morbidity of two relaparotomies. Clavien-Dindo-classification is based on the invasiveness of the treatment, and in the case of overlapping treatment methods for a single complication, only the treatment method that entitled to the highest CD-classification was recorded. For example, in the case of a patient suffering from sudden loss of blood, receiving a blood-transfusion (grade 2) and requiring surgical revision for hemorrhage (grade 3b), only the latter was recorded.

Statistics

Continuous data are expressed as median and interquartile range (IQR), as none of the variables were normally distributed. Categorical data are summarized as proportions and percentages. Differences between two groups in continuous variables were compared with the Mann-Whitney U test and in categorical variables with the Chi-squared test. The predictive values of different laboratory tests were compared with AUC values that were calculated using ROC-curve with four different state variables: the need for relaparotomy, having a pancreas graft-related complication, the need for relaparotomy with pancreas graft-related complications (other than hemorrhage), and CCI-score equal to or more than 47.70 (equivalent to two or more relaparotomies). Youden-index was used to determine an optimal laboratory test cutoff-value for distinguishing the cohort between a possible high and low complication group. Survival probabilities were estimated using the Kaplan-Meier method. Regarding patient survival, death was the event and patients were censored at last follow-up. Regarding pancreas graft survival, pancreatectomy was the event and patients were censored at last follow-up or if death occurred. Logrank test was used to compare the survival distributions. A two-sided P value of <0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics (version 25, IBM Corporation, Somers, NY).

Results

Patients

Between March 14th 2010 and February 1st 2020, 165 simultaneous pancreas-kidney transplantations were performed. One patient was excluded from the cohort due to a hyperacute rejection leading to necrosis of the pancreas graft and pancreatectomy during the initial operation. All patients had type 1 diabetes. The demographic data of patients are presented in Table 1.

Laboratory tests

The results of the ROC-curve analyses for different laboratory tests predicting relaparotomy, pancreas graft related relaparotomy (with and without hemorrhage), and CCI > 47.7 are presented in Table 2. Peak plasma amylase and first day plasma amylase had the highest AUC-values and as only minor differences were observed between these two, further analyses were continued with first day plasma amylase, since the clinical applicability of first day value was considered higher than peak value during the first three days.

Youden-index was used to determine a cutoff-value of 6.0 times the upper normal limit (Youden-index 0.575) for first day plasma amylase. The cohort was divided by this cutoff to assess for differences between the groups. The differences in recipient age, initial length of recipients hospital stay and donor BMI were statistically significant between the groups (Table 1).

Complications and survival

During the first 90 postoperative days, 47 relaparotomies were performed on 39 (24%) patients. The indications for every relaparotomy are presented in Table 3. Out of these 39 patients, 10 (26%) required intra-abdominal vacuum assisted closure-therapy (VAC) and the number of VAC-dressing changes performed in operating room ranged from one to five in these patients. Twenty-eight patients (17%) had at least one relaparotomy due to pancreas graft-related complication and thirteen of them (46%) suffered from pancreas graft-related complication other than hemorrhage. Nine patients (5.4%) suffered from severe postoperative graft pancreatitis. Postoperative pancreatitis was diagnosed on average at 19th postoperative day, ranging from 8 to 44 days. Median first day plasma amylase was significantly higher in patients needing relaparotomy compared to patients without relaparotomy, and when pancreas graft-related complications requiring laparotomy were observed, the difference was more pronounced (Table 4). There was no significant difference in median first day plasma amylase

among patients with rejection or patients with kidney graft associated complications compared to patients without (Table 4).

One patient (0.6%) died with functioning pancreas graft during the 90 days due to cardiac complications after an operation to repair a dissection of left common iliac artery. Twelve-month patient and pancreas graft survival data are shown in Figure 1. Five pancreas grafts (3.0%) were lost during the first 12 months. Four of these were lost during the 90 postoperative day follow-up period due to persistent intra-abdominal fungal infections. There was a significant difference in pancreas graft survival between the two groups divided by first day plasma amylase over 6 times the upper normal limit (logrank test, p -value < 0.001). All kidney grafts were functioning at the end of follow-up. Only one patient was diagnosed with a postoperative partial venous thrombosis of the pancreas graft and was successfully treated conservatively with tinzaparin.

Comprehensive Complication Index

The median CCI was 29.6 (IQR: 20.9 – 40.2) and the general distribution of CCI-score is illustrated in Figure 2. Out of 164 patients, 91 patients (55.5%) with complications had no complications over CD-IIIa and out of these, 62 patients (37.8%) had a CD-II complication at most. Twenty-seven patients (16.5%) had no complications at all. The difference in distribution of CCI-score in the groups divided by first day plasma amylase over 6 times upper normal limit was statistically significant (median 70.5 (IQR: 44.9 – 92.7) vs. median 29.6 (IQR: 20.9 – 39.5), $p < 0.001$) (Figure 3).

Twenty-three patients (13.8%) had a CCI-score of more than or equal to 47.7 which is equivalent to two or more relaparotomies and 10 out of these 23 (43%) had first day plasma amylase over 6 times the upper normal limit. Two patients (1.2%) had a CCI-score of 100: one died during the first 90 postoperative days and the other had 13 severe complications during the first 90 postoperative days.

Clinical applicability of first day plasma amylase

The cutoff of 6 times the upper normal limit for plasma amylase distinguishes the difference in the distribution of complications and overall morbidity (expressed as CCI-score) as expressed in Table 5.

In order to further assess the potential clinical applicability of this cutoff-value, a binary classification test was performed using three different outcomes: [1] need for relaparotomy ($n=39$), [2] having a pancreas graft-related complication ($n=44$) and [3] having a CCI-score of 47.7 or more ($n=23$). For

all relaparotomies, sensitivity and specificity were 0.26 and 0.97, negative predictive value (NPV) and positive predictive value (PPV) were 0.81 and 0.71, respectively. For pancreas graft-related complications sensitivity and specificity were 0.23 and 0.97, NPV and PPV were 0.77 and 0.71, respectively. And for CCI-score of 47.7 or more, sensitivity and specificity were 0.43 and 0.97, NPV and PPV were 0.91 and 0.71, respectively.

Discussion

SPK is associated with a risk of very high morbidity as previous studies have shown and our assessment of total initial morbidity with CCI-score underscores this. Studies examining possible surrogate-markers for postoperative complications in pancreas transplantation are scarce and most of them performed nearly 20 years ago, not necessarily reflecting the current protocols and outcomes of SPK ^{14,15}. Our study brings new insight on the role of plasma amylase as a prognostic marker for complications within 90 days. We believe that elevated plasma amylase is a result of different pancreas graft tissue damaging factors such as long cold-ischaemia time and related reperfusion injury as well as mechanical irritation during the surgery. As such, it could be speculated that a more damaged pancreas graft could leak more exocrine fluid to abdominal cavity where its absorption to circulation could elevate the plasma amylase, thus establishing a link between the condition of the graft and plasma amylase. Cutoff-value of 6 times the upper normal limit for first day plasma amylase seems to distinguish well between high and low complication risk groups, and especially complications related to the pancreas graft seem to be highly associated with elevated plasma amylase. The NPV and PPV of this cutoff-value as a test for high morbidity (CCI > 47.7) were relatively high, 0.91 and 0.71 respectively. These findings suggest that first day plasma amylase could be used to identify patients at risk for severe postoperative complications. We believe that patients with low first day plasma amylase could have their treatment regimen lightened, for example drains could be taken out, antibiotics could be reduced or the patient could be mobilized earlier. On the contrary, patients with plasma amylase over 6 times the upper normal limit should be closely monitored, maybe even CT-scanned for the exclusion of hemorrhage or intra-abdominal fluid collections.

Our literature search found only few previous studies assessing the role of laboratory tests as surrogate-markers for complications in SPK. Peak plasma amylase has been previously suggested by Knight et al. to correlate with an increased risk of intra-abdominal infections, especially pancreatic abscess, after pancreas transplantation, but the peak plasma amylase used in their study was defined

by first week maximum instead of first day maximum ¹⁵. The problem with this approach is that possible graft pancreatitis or intra-abdominal infection would also elevate plasma amylase levels, thus diminishing the clinical relevance of elevated plasma amylase in predicting complications ¹⁹. A study performed by Wullstein et al. showed a correlation between elevated peak CRP (defined in their study as first three-day maximum) and the need for a relaparotomy in SPK patients ¹⁴. CRP, however, is a relatively nonspecific parameter for inflammation and while severe infections rarely occur during the first three days after SPK, we believe that elevated first day plasma amylase may be more accurate and specific in predicting graft pancreas related complications. When comparing CRP and plasma amylase in our cohort, the latter was significantly better in predicting complications. While drain fluid amylase is routinely used as a diagnostic marker for pancreas related complications after general pancreatic surgery, no relevant studies investigating its role in pancreas transplantation could be found ²⁰. Our results show that drain fluid amylase could be nearly as good as plasma amylase in predicting severe pancreas graft-related complications, but plasma amylase showed more significant AUC-values and was more precise in dividing patients between high and low morbidity groups, and for this reason, was chosen as the primary variable. The other laboratory parameters (C-peptide, CRP and trypsinogen) investigated in this study showed a positive but less significant correlation with postoperative morbidity and complications. Peak white blood cell count showed no significant association with postoperative complications.

These previous studies focusing on the role of laboratory test parameters in predicting complications have not assessed the total initial morbidity, rather the end-point used has been the incidence of first severe complication. Using CCI-score as a continuous end-point, we have shown that elevated plasma amylase does not only correlate positively with the incidence of severe pancreas graft-related complications but also with total morbidity during the first 90 postoperative days. The most significant advantage of CCI is that it accounts for the severity of total cumulative complications. The CCI has been used to assess morbidity and outcomes in only few studies concerning transplantation, predominantly liver transplantation. One study reported a median CCI-score of 47.6 during 6 months postoperatively in 441 liver transplant patients ²¹. No studies with similar study design to ours could be found, but a study investigating the outcomes of pancreatoduodenectomy in high-risk patients reported a mean CCI-scores ranging from 23.9 to 30.1 during 30 postoperative days ²². Our 90-day median was 29.6, ranging from 0 to 100, expressing the high diversity in total morbidity associated with SPK.

Our study has some limitations of note. Due to our aggressive thromboprophylaxis the prevalence of severe postoperative complications in our cohort does not necessarily reflect what has been reported by previous studies. No grafts were lost due to graft thrombosis, which according to literature is the most prevalent reason for pancreas graft loss in SPK. However as a tradeoff, the susceptibility for hemorrhage increased, contributing to our high relaparotomy-rate for hemorrhage. Our overall relaparotomy rate (24%) however is at the lower end compared to reported cohorts, and our graft-loss-rate is very low (3.0% during the first 12 months) ^{4,6-10}.

It might be argued that using plasma amylase to predict pancreatitis or pancreas graft-related complications is biased because pancreatitis elevates plasma amylase levels ¹⁹. However, in our cohort, clinically overt graft pancreatitis requiring relaparotomy was observed at 8th postoperative day the earliest and on average at 19th postoperative day, and thus we believe that first day plasma amylase is a relatively specific marker for pancreatic tissue injury manifesting later as pancreatitis. In addition, there may be other laboratory tests that were not measured in this study, such as plasma lipase, which is used in some centers in diagnosis of acute pancreatitis ²³. Lipase is not in routine use in Finland and has not been measured after SPK in our center. Consequently, we are unfortunately not able to assess its predictive value, but it is likely to behave similarly to amylase. There was no active DCD program in our country during the study period and we are not able to assess our findings in the context of DCD. Our cohort sample size was small (n=164) and single-center derived, needing external validation. This study was retrospective and as such prone to recall and misclassification biases, and causality can not be concluded.

Conclusion

Elevated plasma amylase after SPK correlated significantly with the incidence of pancreas graft-related complications and total initial morbidity, expressed by CCI-score. We suggest that a cutoff-value of 6 times the upper normal institutional limit for plasma amylase during the first postoperative day could be used to better characterize the patients with high and low risk of severe postoperative complications, especially pancreas graft-related ones, during the first 90 postoperative days. We also suggest that plasma amylase could be used as a helpful surrogate-marker for postoperative complications in future clinical trials.

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Table 1. Recipient and donor characteristics of 164 simultaneous pancreas-kidney transplant patients, divided into two groups according to first day plasma amylase (cutoff: 6 times the normal upper limit for plasma amylase)

Recipient characteristics	All patients (n=164), n (%) or median (IQR)	Amylase below 6 times the upper limit (n=150), n (%) or median (IQR)	Amylase over 6 times the upper limit (n=14), n (%) or median (IQR)	p-value
Age, years	43 (36 – 49)	42 (36 – 49)	49 (40 – 51)	0.035
Men, n (%)	110 (67%)	101 (67%)	9 (64%)	0.78
BMI	24.1 (21.6 – 27)	24.1 (21.9 – 27)	22.5 (20.6 – 27.2)	0.36
Duration of diabetes, years	34 (27 – 40)	34 (27 – 39)	38 (34 – 41)	0.12
Duration of dialysis treatment, months	13 (9 – 18)	13 (9 – 18)	10 (7 – 18)	0.41
First day drain fluid amylase (U/l)	2040 (780 – 4400)	1920 (710 – 3600)	12 200 (7300 – 19 900)	<0.001
Length of hospital stay, days	17 (13 – 25)	16 (13 – 23)	30 (17-39)	0.003
Time from the end of operation to first laboratory test measurement, hours	22 (14 – 26)	22 (14 – 26)	18 (13 – 26)	0.41
Donor characteristics				
Age, years	41 (29 - 49)	41 (27 – 49)	49 (38 – 54)	0.06
Men n, (%)	85 (52%)	79 (53%)	6 (43%)	0.58
BMI	23.5 (21.7 – 25.5)	23.4 (21.6 – 25)	25.3 (23.9 – 27.3)	0.014
Nontraumatic cause of death n, (%)	127 (77%)	114 (76%)	13 (93%)	0.15

Graft characteristics and intraoperative factors				
Pancreas cold ischemia time, (h)	7.9 (6.6 – 9.0)	7.9 (6.3 – 9.0)	8.1 (7.5 – 9.2)	0.22
Kidney cold ischemia time, (h)	9.8 (7.6 – 10.9)	9.8 (7.7 – 10.9)	10.0 (7.4 – 10.8)	0.96
Estimated blood loss (ml)	500 (300 – 700)	500 (300 – 700)	500 (500 – 800)	0.52
Operating room- time (h)	4.5 (4.2 – 5.1)	4.5 (4.3 – 5.1)	5.0 (4.2 – 5.3)	0.54
HLA-mismatch:				
A and B	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.88
DR	2 (1 – 2)	2 (1 – 2)	1 (1 – 2)	0.39

Abbreviations: BMI – body mass index, HLA – human leukocyte antigen,

Table 2. AUC-values for different laboratory tests, results of ROC-curve analysis

State variable	First day plasma amylase	First day drain fluid amylase	Peak plasma amylase	Peak drain fluid amylase	Peak plasma trypsinog en	Peak c- peptide	Peak WBC	Peak CRP
Relaparotomy (n=39)	0.66	0.59	0.68	0.60	0.62	0.67	0.54	0.65
Pancreas graft related complications, all (n=44)	0.72	0.67	0.70	0.68	0.65	0.61	0.51	0.63
Pancreas graft related relaparotomy, bleedings excluded (n=13)	0.83	0.81	0.83	0.82	0.68	0.69	0.36	0.67
CCI-score > 47.70 (n=23)	0.71	0.67	0.73	0.68	0.58	0.68	0.45	0.68

Abbreviations: AUC – area under curve, CCI – Comprehensive Complications Index, CRP – C-reactive protein, ROC – receiver operating characteristic, WBC – white blood cell count

Table 3. Indications for all relaparotomies during 90 days in 39/164 SPK-patients, excluding changes of vacuum assisted closure (VAC)-dressings in surgical theatre. Note that a patient could have undergone more than one relaparotomy (47 relaparotomies in 39 patients).

Indications for relaparotomy	n
Graft pancreatitis or peritonitis	10
Graft pancreatitis and fungal infection, leading to graft loss	4
Hemorrhage, intra-abdominal, kidney region	6
Hemorrhage, intra-abdominal, pancreas region	7
Hemorrhage, intra-luminal, enteroanastomosis	8
Hemorrhage, no focus	1
Ileus	2
Pancreatic fistula	2
Duodenal perforation	1
Ureteral anastomotic stricture	4
Intra-abdominal fluid collection	1
Rupture of abdominal fascia	1
Total	47

Table 4. Median first day plasma amylase ratio to upper normal limit in view of complications after 164 simultaneous pancreas-kidney transplants

	Without		With		p-value
	N	First day plasma amylase ratio, Median (IQR)	N	First day plasma amylase ratio, Median (IQR)	
Relaparotomy	125	1.1 (0.4 – 2.3)	39	2.4 (0.7 – 6.0)	0.002
Pancreas graft related relaparotomy, bleedings excluded	151	1.1 (0.4 – 2.4)	13	6.8 (2.6 – 7.7)	<0.001
Pancreas graft related relaparotomy, all	136	1.0 (0.4 – 2.3)	28	2.7 (0.9 – 6.6)	0.001
Pancreas graft loss	160	1.1 (0.5 – 2.6)	4	7.8 (4.5 – 10.0)	0.007
Pancreas graft-related complications, all	120	0.9 (0.4 – 1.9)	44	2.5 (0.9 – 5.4)	<0.001
Peripancreatic fluid collection	158	1.1 (0.4 – 2.5)	9	4.0 (1.8 – 6.4)	0.006
Rejection of pancreas graft ¹	134	1.2 (0.4 – 2.9)	30	1.1 (0.7 – 2.1)	0.89
Rejection of kidney graft ¹	131	1.1 (0.5 – 2.4)	33	1.4 (0.4 – 4.8)	0.48
Kidney graft related complications	127	1.1 (0.5 – 2.7)	37	1.2 (0.5 – 2.6)	0.74

¹ Rejection was recorded if diagnosed with biopsy or when pharmacologically treated

Table 5. Morbidity and complications after 164 simultaneous pancreas-kidney transplantations in view of first day plasma amylase (cutoff: 6 times the upper normal limit for plasma amylase)

	Amylase under 6 times the upper normal limit (n=150)	Amylase over 6 times the upper normal limit (n=14)	p-value
CCI-score over 47.7* (n=23)	13 (8.7%)	10 (71.4%)	<0.001
Relaparotomy, any (n=39)	29 (19.3%)	10 (71.4%)	<0.001
Pancreatic complications, all (n=44)	34 (22.7%)	10 (71.4%)	<0.001
Pancreas graft-related relaparotomy, bleedings excluded (n=13)	5 (3.3%)	8 (57.1%)	<0.001
Pancreas graft-related relaparotomy, all (n=28)	20 (13.3%)	8 (57.1%)	<0.001
Pancreas graft loss (n=4)	1 (0.7%)	3 (21.4%)	<0.001
Kidney graft-related complications (n=38)	31 (20.7%)	6 (42.9%)	0.057

*Value of 47.7 is equal to two relaparotomies or equivalent postoperative morbidity

Abbreviations: CCI – Comprehensive Complication Index.

Figures

Figure 1. a Patient (event: death, censored at follow-up) and **b** pancreas graft survival (event: pancreatectomy, censored at follow-up or if death occurred) of 164 simultaneous pancreas-kidney transplant patients, divided by first day plasma amylase, cutoff: 6 times upper normal institutional limit. **a** $p = 0.23$ **b** $p < 0.001$ (log rank).

Patients at risk

Amylase < 6 times upper limit	150	150	144	131	125
Amylase > 6 times upper limit	14	13	12	12	12

a Patient survival, event: death, censored at follow-up

Patients at risk

Amylase < 6 times upper limit	150	149	145	131	126
Amylase > 6 times upper limit	14	11	10	10	10

b Pancreas graft survival, event: pancreatectomy, censored at follow-up or if death occurred

Figure 2. The distribution of Comprehensive Complication Index- score in 164 simultaneous pancreas-kidney transplant patients.

Figure 2. The distribution of Comprehensive Complication Index- score (CCI) in 164 simultaneous pancreas-kidney transplant patients

Figure 3. The distribution of Comprehensive Complication Index- score in 164 simultaneous pancreas-kidney transplant patients in view of first day plasma amylase (cutoff: 6 times the upper normal limit for plasma amylase).

Figure 3. The distribution of Comprehensive Complication Index- score (CCI) in 164 simultaneous pancreas-kidney transplant patients in view of first day plasma amylase (cutoff: 6 times the upper normal limit for plasma amylase)