transplantology

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The Role of Late-Onset Inflammatory Markers in the Prediction of Complications and Graft Survival after Pancreas Transplantation

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Abstract: Background: Despite great progress in graft survival and complication rates, pronounced inflammatory responses are common after pancreas transplantation (PT). Subsequent to the first postoperative increase in inflammatory markers, we have frequently observed a second peak of C-reactive protein (CRP) and white blood cells (WBCs) following PT. This analysis is to assess the incidence and clinical relevance of late-onset increases in inflammatory markers following PT. Materials and methods: We analyzed all consecutive PTs over a 20-year period. The second peak of CRP (SCP) and WBCs (SWP) was defined as an increase >3 days after PT subsequent to a relevant initial decrease. Results: Of 116 patients, 60 (51.7%) developed SCP. SCP was not associated with pancreas graft loss or with thrombosis at discharge or at 90 days after PT (6.7% vs. 0.0%, $p = 0.1$; 8.3% vs. 1.8%, $p = 0.2$; and 15.0% vs. 3.6%, $p = 0.06$, respectively). Patients with SCP had more complications overall at discharge and at 90 days (85.0% vs. 50.0%, $p < 0.001$ and 93.3% vs. 76.8%, $p = 0.02$). In multivariable analysis, SCP was significantly associated with pre-transplant HbA1c (OR 2.1 (95% CI: 1.3–3.8); $p = 0.005$) and female gender (OR 0.03 (95% CI: 0.004–0.14); $p \leq 0.001$). No significant association was found between SCP and pancreas cold ischemia time (OR 1.0 (95% CI: 1.0–1.0); $p = 0.1$), donor age (OR 1.01 (95% CI: 0.96–1.06); $p = 0.7$), recipient age (OR 0.9 (95% CI: 0.9–1.0); $p = 0.1$), or recipient BMI (OR 0.9 (95% CI: 0.9–1.4); $p = 0.3$). SWP did not differ in patients with or without SCP ($p = 0.07$) and there was no correlation with pancreas graft loss or relaparotomy ($p = 0.3$ and $p = 0.6$, respectively). Insulin-free graft survival after 1, 5, and 10 years did not differ between patients with SCP and those without SCP (95.0%, 90.2%, 90.2% vs. 96.1%, 91.2%, 88.7%, respectively; $p = 0.964$). Conclusion: Late-onset inflammatory reactions are frequently seen in PT and are correlated with higher overall complication rates. They are not correlated, however, with graft-specific complications or insulin-free graft survival.

Keywords: pancreas transplantation; C-reactive protein peak; insulin-free graft survival

Citation: Hügli, S.; Müller, P.C.; Pfister, M.; Rössler, F. The Role of Late-Onset Inflammatory Markers in the Prediction of Complications and Graft Survival after Pancreas Transplantation. *Transplantology* **2023**, *4*, 90–101. https://doi.org/10.3390/transplantology4020010

Academic Editor: Naoaki Sakata

Received: 17 February 2023
Revised: 24 April 2023
Accepted: 2 June 2023
Published: 6 June 2023

1. Introduction

Pancreas transplantation (PT) is mainly performed in the context of simultaneous pancreas and kidney transplantation (SPK) [1], which represents a treatment for patients with insulin-dependent diabetes mellitus and end-stage kidney disease [1,2]. With excellent long-term patient and graft survival and high rates of insulin independence, SPK provides a survival benefit compared with deceased donor kidney transplantation alone [3,4]. Despite criticisms regarding high rates of morbidity and graft loss, notable progress has been achieved, with decreasing complication rates and better long-term outcome over recent decades [5–8]. Novel surgical techniques along with effective immunosuppression and improved postoperative management have contributed to this success [1,9,10]. However, PT is still associated with significant morbidity and surgical complications [11,12] related to the complex surgery and organ procurement [13,14], together with risks from recipients' diabetes-related comorbidities. In addition, pronounced inflammatory responses are common after PT, mainly due to severe ischemia–reperfusion injury, causing microvascular damage leading to graft thrombosis, pancreatitis, and graft loss [15,16]. This is enhanced

by the generally exacerbated inflammatory phenotype of type I diabetes patients with chronic kidney disease [17] due to their glycemic and uremic status. Other factors known to promote the inflammatory response in PT are reperfusion of two grafts in the setting of SPK, long-lasting pancreas procurement and implantation with prolonged ischemia, and pancreatic exocrine function. The C-reactive protein (CRP) level and white blood cell (WBC) count are important non-specific inflammatory markers of clinical deterioration at an early stage [18,19]. In the regular postoperative course, CRP and WBC values increase up to day 3 and represent a normal physiologic response to surgery [20,21]. High CRP concentrations after day 3 have been shown to negatively predict postoperative infectious complications after abdominal surgery [18]. In PT, early high postoperative CRP levels have been associated with pancreas graft-related complications [20], leading to graft pancreatectomy [22]. While most severe complications after PT occur in the early postoperative period [23,24], little is known about the later pattern of complications and the clinical impact of CRP and WBC levels during the later course. We have regularly observed such a later second rise of CRP in patients who have undergone PT. On the one hand, serious complications such as graft thrombosis and infection have to be ruled out in such patients. On the other hand, costly, unguided work-up may be carried out unnecessarily in search of a non-existent infection. In PT, this dilemma is aggravated by high-dose immunosuppression, so clinical assessment is hampered by patients not exhibiting the typical clinical signs and symptoms of infection. Consequently, these patients generally undergo extended diagnostic work-up, including CT, followed by frequent reoperations and antibiotic treatment. The aim of the present study was to analyze the incidence and clinical implications of a second CRP peak (SCP) and WBC peak (SWP) after PT.

2. Materials and Methods

2.1. Patients

Based on our prospective database, we performed a retrospective review of patients who underwent PT at the University Hospital of Zürich over a 20-year period from 2001 to the end of 2020. No patient was excluded from initial analysis. For final analysis of secondary peaks, patients with CRP increases within 3 days after early relaparotomies were excluded. The local ethics committee reviewed and approved the study protocol (project number 2016-01710).

2.2. Surgical Details

All organs were from donors after brain death and transport was by static cold storage. The backtable was prepared carefully to exclude vascular and capsular lesions, and the spleen was removed. Arterial reconstruction of the pancreas was performed at the backtable using an arterial Y-graft with anastomoses from the donor external iliac artery to the superior mesenteric artery and from the donor internal iliac artery to the splenic artery. The portal vein was dissected to a length of approximately one centimeter. After median laparotomy, pancreas grafts were always implanted first and as whole organ with duodenum. Arterial anastomosis was via Y-graft to the right common iliac artery. Venous drainage was mostly via the portal vein to the inferior vena cava. The duodenal segment was anastomosed to the second jejunal loop. Only a small number of PTs featured venous portal or mesenteric drainage and duodeno–duodenostomy. No bladder drainage was used. Pancreas reperfusion was performed directly after the completion of pancreatic vascular anastomoses. Enteric drainage was performed after the safe completion of reperfusion and hemorrhage control. Bowel anastomosis was carried out through the hand-sewn two-layer technique between the donor duodenum and the recipient jejunum, approximately 50 cm distal to the Treitz ligament. The Roux-en-Y loop was not used. The kidney was subsequently grafted to the left and anastomosed to the external iliac vessels. The kidneys were placed extraperitoneally, through retroperitoneal dissection on the left side via the median laparotomy, without the need for a new incision. Ureteral anastomosis was performed

according to the extra-vesical Lich–Gregoir technique and splinted with a double-J stent for 3–4 weeks after transplantation.

2.3. Perioperative Regimen

Induction therapy comprised steroids and basiliximab until the end of 2010, and thenceforth antithymocyte globulin. Maintenance therapy consisted of tacrolimus in combination with mycophenolic acid and rapid 5-day steroid taper. Up to the end of 2017, single-shot antibiosis with amoxicillin and clavulanic acid (Augmentin©) was given intravenously around 30 min prior to surgery. The postoperative antibiotic treatment was decided case by case. From 2018 to the end of 2020, routine antibiotic therapy with piperacillin/tazobactam (Tazobac©) was given for at least 1 week, starting immediately after surgery.

2.4. Outcome Assessment

Complications up to 90 days after transplantation were assessed according to the validated and severity-oriented Clavien–Dindo classification [25,26]. Minor complications were defined as $\leq$grade IIIa, major complications as $\geq$grade IIIb. The Comprehensive Complication Index (CCI), a continuous metric model, was used to measure the postoperative morbidity on a scale from 0.0 (uneventful) to 100.0 (death) [27,28].

2.5. C-Reactive Protein

CRP concentrations were assessed for the first 20 days after PT. Normal CRP was defined as <5 mg/L, according to our laboratory standard. The primary CRP peak (PCP) was defined as the highest CRP level within 3 days after PT. SCP was defined as a rebound with a ratio of 1.5 > 3 days after PT, subsequent to a relevant initial decrease. A CRP increase of at least 61 mg/dL was needed for SCP to be deemed to have occurred. This CRP threshold of 61 mg/dL was derived from analysis of the receiver operator characteristic (ROC) curve, determining the point on the curve with the shortest distance to specificity and sensitivity of 100%.

2.6. White Blood Cells

WBC counts were assessed for the first 20 days after PT. The normal WBC level was defined as <9.6 G/L, according to our laboratory standard. WBCs were assessed in patients with and without SCP. A second WBC peak (SWP) was calculated according to the above-mentioned criteria for SCP: occurring >3 days after PT, subsequent to a relevant initial drop, and rebound with a ratio of 1.5.

2.7. Graft Function

Insulin-free survival was deemed present when there was no need for insulin treatment after transplantation and hemoglobin A1C (HbA1c) values were in the range 4.4–5.9%, corresponding to a functioning pancreas graft. Kidney function was assessed via calculation of the glomerular filtration rate (GFR) according to the Chronic Kidney Disease Epidemiology Collaboration equation [29,30].

2.8. Statistical Analysis

Patient characteristics and postoperative data were summarized with descriptive statistics. Nominal and ordinal data are presented as absolute and relative numbers (n, %). Interval and continuous data are expressed as mean $\pm$ standard deviation (SD) if normally distributed or as median and range if not normally distributed. To test continuous data for normal distribution, the Shapiro–Wilk test was used. For comparison of the subgroups of patients with or without SCP and SWP to nominal data, the χ^2 test or, in the case of low frequencies, Fisher's exact test was used. For continuous and ordinal scaled data such as CRP and WBC values, CCI, and Clavien–Dindo classification between subgroups with or without SCP, Student's t-test was used for normally distributed data and the Wilcoxon–

Mann–Whitney test for non-normally distributed data. Statistical analyses were conducted using *R* version 4.0.4 [31]. The level of statistical significance was set at a *p*-value of 0.05.

3. Results

3.1. Donor and Recipient Characteristics

Patient characteristics and surgical details are summarized in Table 1. Within the study period, we performed a total of 139 PTs. Of these, 116 were included for the final analysis of SCP and SWP calculations. The remaining cases had to be excluded due to CRP increases within 3 days after early relaparotomies, because this would have biased the results for secondary peak analysis according to our definition. In total, 116 PTs were included in the analysis, whereof 112 (96.5%) were primary SPK and 4 (3.5%) were pancreas after kidney (PAK) transplantations. No patient underwent PT before or without kidney transplantation.

Table 1. Patients' characteristics and surgical details.

	SCP ***n* = 60**	**No SCP** ***n* = 56**	***p*-Value**
Male, *n* (%)	30 (50.0)	20 (35.7)	0.2
Age [years]	43.4 (±8.6)	42.5 (±7.1)	0.5
Recipient BMI (kg/m^2)	24.2 (±3.7)	23.0 (±2.7)	0.05
Time of diabetes [years]	31.2 ± 8.9	29.6 ± 9.9	0.4
Time on transplant waitlist [months]	12.3 ± 10.0	16.0 ± 10.3	0.05
Chronic dialysis, n (%)	39 (65.0)	42 (75.0)	0.3
Donor age [years]	33.7 ± 11.5	31.5 ± 11.9	0.4
Donor BMI (kg/m^2)	23.1 ± 2.7	22.1 ± 3.4	0.1
Duration of surgery [min]	345.5 ± 99.1	333.0 ± 86.0	0.5
CIT pancreas [min]	549.6 ± 172.4	535.1 ± 165.6	0.6
Rewarming time pancreas [min]	39.4 ± 10.0	31.4 ± 5.5	0.07
CIT kidney [min]	655.6 ± 183.0	654.2 ± 191.1	1.0
Rewarming time kidney [min]	47.2 ± 17.2	42.7 ± 9.9	0.5

Values are presented as mean ± standard deviation. Percentages may not add up to 100% due to rounding. SCP, second C-reactive protein peak; BMI, body mass index; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; CIT, cold ischemia time; SD, standard deviation.

3.2. CRP Course and Complications

The postoperative CRP course of patients with and without SCP is shown in Figure 1A. Sixty patients (51.7%) developed SCP (median 9 days after SPK, range 5–20 days). The average duration of follow-up for patients with and without SCP was 85.2 and 104.2 months, respectively ($p = 0.1$). The mean overall CRP peak values in patients with SCP and without SCP were 161.2 mg/dL and 33.6 mg/dL, respectively ($p < 0.001$). The mean PCP did not differ significantly between patients with major and minor complications (139.1 mg/dL vs. 100.1 mg/dL, $p = 0.06$) or between those with and without pancreas graft loss (125.3 mg/dL vs. 106.9 mg/dL, $p = 0.7$).

The complications are summarized in Table 2. The overall complication rate at discharge and up to 90 days after PT was 68.1% and 85.3%, respectively. Both at discharge and after 90 days, patients with SCP had developed more overall complications than those without SCP (85.0% vs. 50.0%, $p < 0.001$ and 93.3% vs. 76.8%, $p = 0.02$, respectively). The same applied for major complications (26.7% vs. 1.8%, $p < 0.001$). Both at discharge and at 90 days after operation, patients with SCP had a higher CCI than patients without SCP (33.6 vs. 4.35, $p < 0.001$ and 39.7 vs. 20.9, $p < 0.001$, respectively). SCP was not significantly associated with graft-related complications, such as pancreas graft loss (6.7% vs. 0.0%;

$p = 0.1$), kidney graft loss (1.7% vs. 0.0%; $p = 1.0$), and pancreas graft thrombosis, at discharge or after 90 days (8.3% vs. 1.8%, $p = 0.2$ and 15.0% vs. 3.6%, $p = 0.06$, respectively). The specific causes of SCP are listed in Table 3. In 33 out of 60 cases (55%), the cause could not be clearly identified or only non-specific peri-pancreatic fluid was found, and these patients were treated with antibiotics only. Less common causes for SCP were urinary tract infection ($n = 10$, 16%), wound infection ($n = 4$, 7%), percutaneous drainage of peri-pancreatic fluid collections ($n = 4$, 7%), and rejection ($n = 1$, 2%). Only eight patients (13%) had a major complication and underwent relaparotomy subsequent to SCP. The causes were bleeding ($n = 2$), intraabdominal abscess ($n = 2$), ileus ($n = 1$), and kidney graft thrombosis ($n = 1$); in the remaining two cases, there were no conclusive intraoperative findings. In patients with SCP, postoperative computed tomography (CT) or magnetic resonance imaging (MRI) was performed more frequently (61.7% vs. 25.0%, $p < 0.001$) and antibiotic therapy was started more often in the postoperative course (80.0% vs. 19.6%, $p < 0.001$). The CRP levels in SCP were not associated with evidence of infection nor the severity of complications.

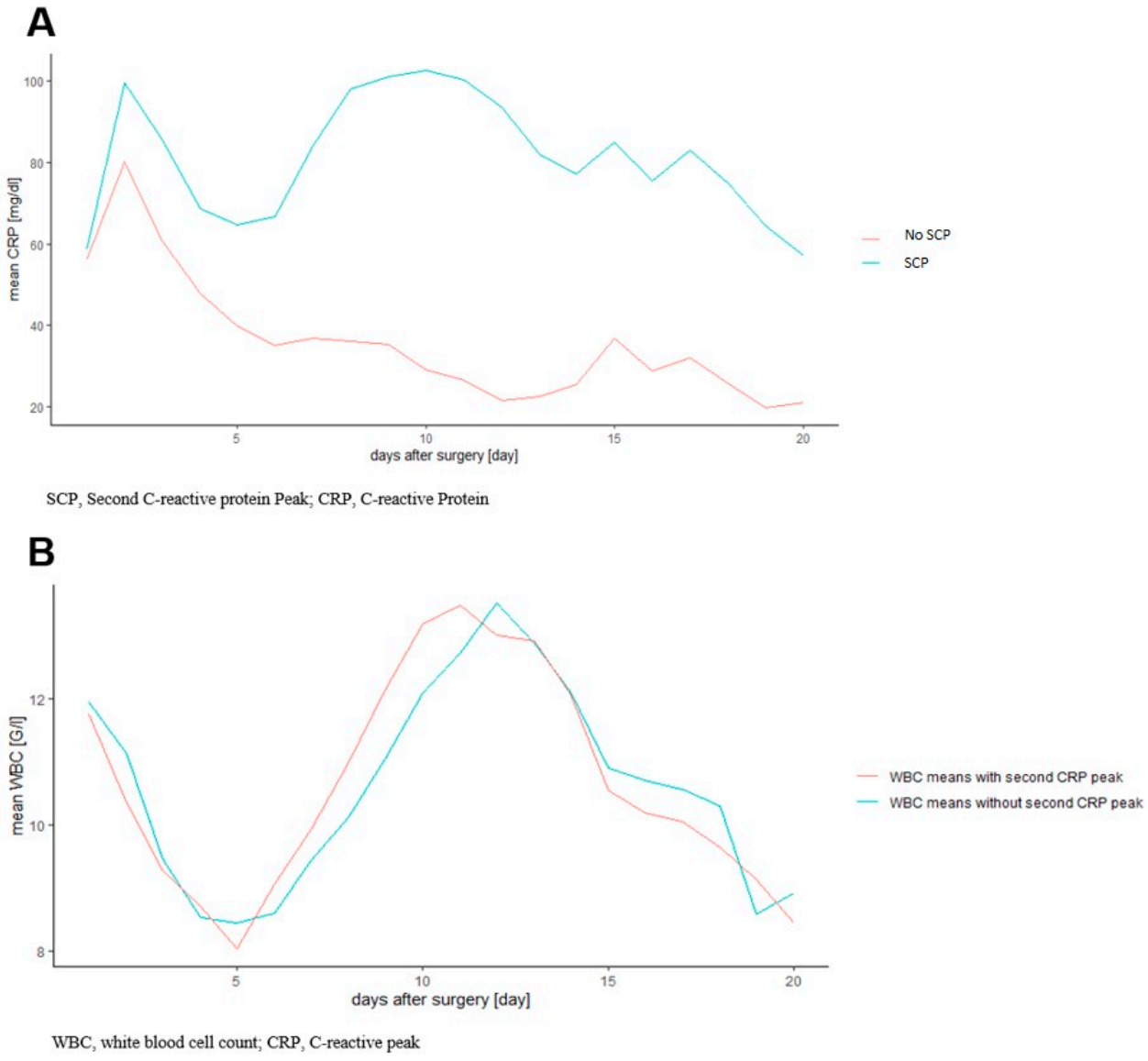

Figure 1. (**A**) Mean CRP course over the 20-day postoperative interval, plotted for patients with and without the occurrence of a second CRP peak. (**B**) Mean WBC course over the 20-day postoperative interval, plotted for patients with and without the occurrence of a second CRP peak.

Table 2. Outcome in patients with or without a second CRP peak.

	SCP ***n* = 60**	**No SCP** ***n* = 56**	***p*-Value**
Any complications until discharge, *n* (%)	51 (85.0)	28 (50.0)	<0.001
Any complications until 90 days, *n* (%)	56 (93.3)	43 (76.8)	0.02
CCI at discharge, median (range)	33.6 (0.0–63.9)	4.35 (0.0–47.4)	<0.001
90-day CCI, median (range)	39.7 (0.0–71.9)	20.9 (0.0–49.5)	<0.001
Highest Clavien–Dindo complication, *n* (%)			<0.001
I	1 (1.7)	7 (12.5)	
II	16 (26.7)	17 (30.6)	
IIIa	14 (23.3)	2 (3.6)	
IIIb	20 (33.3)	2 (3.6)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Routine antibiotics, *n* (%)	10 (16.7)	8 (14.3)	0.8
Postoperative antibiotics, *n* (%)	48 (80.0)	11 (19.6)	<0.001
Postoperative imaging (CT or MRI), *n* (%)	37 (61.7)	14 (25.0)	<0.001
Graft thrombosis, *n* (%) • at discharge • within 90 days	 5 (8.3%) 9 (15%)	 1 (1.8%) 2 (3.6%)	 0.2 0.06
Graft loss, *n* (%)	4 (6.7%)	0 (0%)	0.1

Percentages may not add up to 100% due to rounding. SCP, second C-reactive protein peak; CCI, Comprehensive Complication Index; CT, computed tomography; MRI, magnetic resonance imaging.

Table 3. Causes of a second CRP peak.

Causes of SCP ***n* = 60**	**Treatment**
33 (55%) non-specific (no clear diagnosis)	Antibiotics only
10 (16%) UTI	Antibiotics only
4 (7%) wound infection	Local wound treatment
4 (7%) peri-pancreatic fluid collection	Percutaneous drainage
2 (3%) bleeding	Relaparotomy
2 (3%) intraabdominal abscess	Relaparotomy
2 (3%) no relevant finding	Relaparotomy
1 (2%) rejection	Steroids
1 (2%) ileus	Conservative
1 (2%) kidney graft removal for thrombosis	Relaparotomy

Percentages may not add up to 100% due to rounding. SCP, second C-reactive protein peak; UTI, urinary tract infection.

The analysis of factors associated with the incidence of SCP is listed in Table 4. In multivariable analysis, SCP was significantly associated with pre-transplant HbA1c (OR 2.1 (95% CI: 1.3–3.8); $p = 0.005$) and female gender (OR 0.03 (95% CI: 0.004–0.14); $p \leq 0.001$). SCP was not associated with pancreas cold ischemia time (OR 1.0 (95% CI: 1.0–1.0); $p = 0.1$), donor age (OR 1.01 (95% CI: 0.96–1.06); $p = 0.7$), recipient age (OR 0.9 (95% CI: 0.9–1.0); $p = 0.1$), or recipient BMI (OR 0.9 (95% CI: 0.9–1.4); $p = 0.3$).

Table 4. Uni- and multivariable analysis of factors associated with a second CRP peak.

	Univariable			Multivariable		
	OR	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
Donor age	1.0	0.97–1.04	0.8	1.01	0.96–1.06	0.7
Recipient age	1.0	0.95–1.05	1.0	0.9	0.9–1.0	0.1
Recipient BMI	1.07	0.95–1.2	0.3	0.9	0.9–1.4	0.3
CIT pancreas	1.0	1.0–1.0	0.9	1.0	1.0–1.0	0.1
Female gender	1.1	0.54–2.27	0.9	0.03	0.004–0.14	<0.001
HbA1c pre TPL	1.3	0.98–1.9	0.08	2.1	1.3–3.8	0.005

CIT, cold ischemia time; BMI, body mass index; TPL, transplantation; HbA1c, hemoglobin A1c.

3.3. Outcome According to Antibiotic Regimen

Routine postoperative antibiotic therapy was administered to 15.5% of all patients. The rate of SCP (55.6% vs. 51.0%, $p = 0.8$), the rates of minor and major complications (77.8% vs. 81.6%, $p = 0.7$ and 18.4% vs. 22.2%, $p = 0.7$, respectively), and the median CCI at discharge and at 90 days (0 vs. 20.9, $p = 0.1$ and 26.1 vs. 31.4, $p = 0.8$, respectively) did not differ between patients with and those without routine antibiotic therapy.

3.4. WBC and Second CRP Peak

The WBC count did not differ significantly between patients with and without SCP ($p = 0.07$), although it was somewhat higher with SCP (16.6 G/L vs. 14.4 G/L) (Figure 1B). Eighty-seven patients (75%) developed an SWP, with a mean count of 15.3 G/L. The presence of an SWP was associated with overall complications both before discharge and up to 90 days after PT, and also with the administration of antibiotics ($p = 0.01$, $p = 0.03$, and $p = 0.02$, respectively). SWP was not associated with graft-related complications, e.g., pancreas graft loss, kidney graft loss, and relaparotomy ($p = 0.3$, $p = 1.0$, and $p = 0.6$, respectively).

3.5. Patient and Graft Survival

Survival curves are shown in Figure 2. After 1, 5, and 10 years, patients with SCP and those without SCP did not differ in overall survival (100%, 95.6%, 84.2% vs. 100%, 100%, 94.5%; $p = 0.4$) or in insulin-free survival (95.0%, 90.2%, 90.2% vs. 96.1%, 91.2%, 88.7%; $p = 0.9$). The mean HbA1c did not differ between patients with and without SCP preoperatively (7.8 ± 1.2 vs. 7.4 ± 1.3, $p = 0.09$), after 6 months (5.6 ± 0.8 vs. 5.4 ± 0.7, $p = 0.4$), or within 1 year after transplantation (5.6 ± 0.8 vs. 5.7 ± 0.8, $p = 0.7$). After 1, 3, and 5 years, the mean glomerular filtration rate did not differ between patients with SCP and those without SCP (71.4 ± 18.5 vs. 70.5 ± 16.3, $p = 0.8$; 67.6 ± 20.3 vs. 72.1 ± 19.6, $p = 0.3$; 63.8 ± 23.9 vs. 69.7 ± 19.5, $p = 0.2$, respectively).

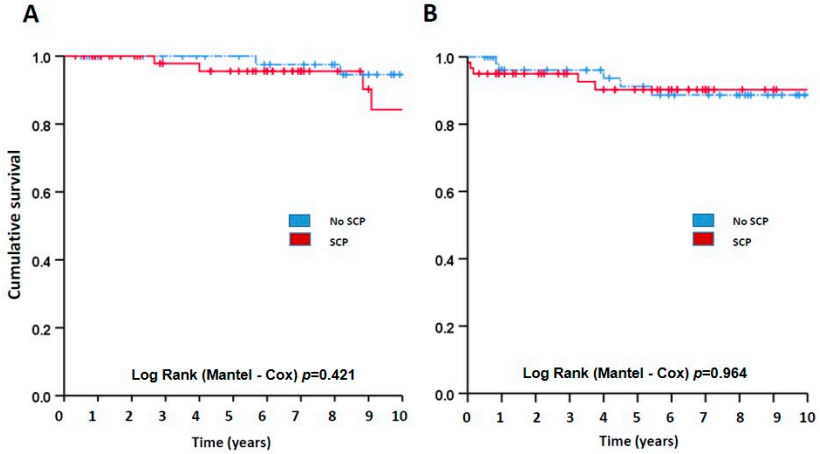

Figure 2. Overall and insulin-free survival. (**A**) Overall survival. (**B**) Insulin-free survival. SCP, second C-reactive protein peak.

4. Discussion

To the best of our knowledge, this is the first study to identify the occurrence of a secondary inflammatory peak following PT and evaluate the clinical implications. SCP and SWP occurred in more than half of the patients in the postoperative course after PT, underlining the high clinical relevance of this finding. Analysis of postoperative inflammatory markers, such as CRP or WBC, is important for the early detection of surgical complications. However, the interpretation of the results together with the clinical findings can be difficult, especially in immunosuppressed patients. Early postoperative CRP elevations in PT have been related to impairment of the microcirculation, which may lead to pancreatitis [15]. Wullstein et al. found a correlation between PCP and graft-specific morbidity after SPK [22]. Severe morbidity such as graft thrombosis most often occurs in the early postoperative period, within the first 2–4 days [23,24]. However, a later CRP increase from day 3 after surgery can no longer be attributed to the regular surgical trauma and is usually an expression of surgical or infectious complications [32–34]. Such a secondary inflammatory reaction, with a corresponding second CRP elevation, has previously been described after long-course hyperthermic intraperitoneal chemotherapy (HIPEC) [35], though without any relevant impact on postoperative complications. The same applies to WBC counts, where values from day 4 after surgery have been associated with surgical complications such as pancreatic fistulas after pancreatic resections [36,37]. Our clinical observations over the years showed that a second peak of inflammatory markers after PT was common, occurring in more than half of our cohort. Patients with SCP developed more complications, underwent diagnostic work-up more frequently, and were more likely to receive antibiotics in the postoperative period. The same applies to WBC counts, where a second peak was also related to complications. However, both SCP and SWP were not associated with graft-specific complications, such as thrombosis and graft loss, nor with differences in overall and insulin-free survival. This finding was presumably influenced by the fact that most graft thromboses and losses occurred early after transplantation. For this reason, some were, by definition, not included in the analysis of SCP. Moreover, in more than half of the patients, the cause of the SCP was not identified. The incidence of SCP was significantly associated with pre-transplant levels of HbA1c. This could most likely be related to the negative effects of poorly controlled diabetes mellitus on the progression of vascular disease and wound healing. On the other hand, female gender was protective for the incidence of SCP. This is interesting, as previous data failed to show a relevant impact of recipient gender on outcome after SPK [38,39]. Importantly, we found no association between SCP and donor age, recipient age, or the duration of cold ischemia in this cohort. While these factors had previously been negatively associated with the occurrence of complications after SPK [40–42], their impact on such a specific event as the SCP has not been analyzed to date.

The overall rates of complication and relaparotomy were in accordance with the literature, where relaparotomy rates of up to 32% have been reported [11,23,43]. Most complications were minor; the major complications were relaparotomies for bleeding, hematoma, and peri-pancreatic fluid collections. The rate of graft thrombosis was 6% within the first month after PT. While Troppmann et al. reported a higher incidence of pancreatic graft thrombosis (27%) [11], Ollinger et al. found lower rates, ranging between 5.1% and 13.3% in different postoperative periods [6]. Interestingly, SCP did not correlate with graft thrombosis or graft loss. Even though patients with SCP developed more graft losses in absolute, this was not statistically significant. We found that complications and even pancreas graft loss did not negatively affect patients' survival or long-term kidney function. The incidence of other complications, especially intestinal ones, was low. In addition, no mortality was observed for graft pancreatectomy or for relaparotomies. The generally low threshold for reoperation after PT may be explained by the frequency of unclear findings on CT and MRI, together with unspecific clinical symptoms under immunosuppression. In this cohort, in more than half of patients with SCP, postoperative CT revealed a non-specific reaction around the pancreas graft, with either diffuse fluid collec-

tion, stranding, or edema as the only finding. These findings are common after PT [44], detected in up to 40% of postoperative CT scans [45]. In other cases, focal edematous swelling of the attached residual portion of the mesentery was found. However, in the majority of cases, there was no clear abscess or hematoma to drain. In these unspecific cases, further diagnostic work-up and the selection of subsequent therapy are complicated by unclear clinical symptoms due to immunosuppression and long-term diabetes, often without clear signs of clinical deterioration. In most cases, the laboratory findings regarding inflammation did not correspond with the clinical appearance. Importantly, these non-specific findings were not associated with worsening pancreas and kidney graft survival and had no negative impact on kidney graft function. This is in contrast to previous literature on peripancreatic fluid collections, where a significant negative impact on pancreas allograft survival has been described [46]. In contrast to our results, Singh et al. only analyzed clinically significant fluid collections and most of them were either caused by pancreatic graft fistulas or duodenal stump leaks [46]. However, the pathophysiology of non-specific peripancreatic fluid collection and its effect on pancreas graft function is poorly understood. It could be associated with an inflammatory response to the surgical intervention, resulting from the exocrine secretions of the organ, and reflected by a late increase in inflammation levels. To date, however, there are few and mostly old data on this topic, and further in-depth analyses are needed. In the context of the early postoperative period in these highly immunosuppressed patients, our treatment consisted of empiric antibiotics in most cases. This is consistent with previous reports, where antibiotics were given without clear infectious foci [45]. Furthermore, the significance and consequences of SCP for the further course of events often remained unclear. Only a minority of patients underwent relaparotomy following SCP (11%), in two cases even with negative intraoperative findings. Interestingly, the routine administration of antibiotics did not prevent SCP or complications, including relaparotomy. This is in contrast to previous reports, where infectious complications were the main cause of morbidity and mortality after PT and the administration of broad-spectrum prophylactic antibiotics, antifungal, and antiviral agents was recommended [47,48]. These recommendations, however, are based on smaller studies with mainly bladder-drained PT, which involves a higher risk of recurrent infections and urologic complications [7,49]. In our cohort, all PTs were performed with enteric drainage, as enteric complications are rare overall [12,50] and the need for later conversion from bladder to intestinal exocrine drainage is avoided [7].

In summary, our recommendations for everyday clinical practice are as follows. In patients with SCP, we suggest the selective performance of further imaging procedures in the event of high suspicion of intra-abdominal pathologies or in the presence of a concomitant sudden increase in blood sugar levels. If CT reveals only non-specific peripancreatic alterations in an otherwise stable and normoglycemic patient, watchful waiting is recommended. The indications for antibiotic therapy should always be carefully evaluated and antibiotics administered only to patients who have a clear infectious focus. Furthermore, our results imply that routine broad-spectrum antibiotic therapy does not reduce post-transplant complications and should, therefore, not be administered.

The present study has limitations. As this is a retrospective analysis, there may be problems with bias and missing data. Moreover, recipient and donor selection criteria evolved and immunosuppressive regimens changed during the study period. Finally, we did not include measurements of procalcitonin, as these were not routinely obtained at our center.

5. Conclusions

Late-onset increases in inflammatory markers are frequent after PT and associated with higher complication rates, although not with graft-related complications such as thrombosis. SCP and SWP do not affect insulin-free or overall survival. In more than half of the patients, the causes remain unspecific and should be interpreted carefully together with the clinical course of the patient and radiological findings. Routine postoperative

administration of broad-spectrum antibiotics did not prevent SCP. Our findings highlight the complexity of the perioperative course of PT and emphasize the need for a specialized and dedicated multidisciplinary team.

Author Contributions: S.H.: analysis and interpretation of data. Drafting the article and revising it critically. Final approval of the version to be published. P.C.M.: conception and design, drafting the article and revising it critically. Final approval of the version to be published. M.P.: analysis and interpretation of data. Revising the article critically. Final approval of the version to be published. F.R.: conception and design, analysis and interpretation of data. Drafting the article and revising it critically. Final approval of the version to be published. All authors have read and agreed to the published version of the manuscript.

Funding: No funding or financial support was provided for the study.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee Zürich on 10 September in 2021 (project number 2016-01710) for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets presented in this article are not readily available because of local restrictions. Requests to access the datasets should be directed to the corresponding author F.R. According to local policies, data must remain under controlled access due to patient protection and ethical laws in Switzerland.

Conflicts of Interest: All authors of this manuscript declare no conflict of interest.

Abbreviations

CT	computed tomography
CRP	C-reactive protein
GFR	glomerular filtration rate
HbA1c	hemoglobin A1c
MRI	magnetic resonance imaging
SCP	second C-reactive protein peak
SD	standard deviation
SPK	simultaneous pancreas and kidney transplantation
PCP	primary C-reactive protein peak
PT	pancreas transplantation
WBC	white blood cells

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