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GRAFT DYSFUNCTION IN SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION (SPK): RESULTS OF CONCURRENT KIDNEY AND PANCREAS ALLOGRAFT BIOPSIES

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ABBREVIATIONS

AMR: Antibody-mediated rejection

ATN: Acute tubular necrosis

SPK: simultaneous pancreas kidney

PAK: Pancreas after kidney

PASPK: Pancreas after simultaneous pancreas kidney

TCMR: T-cell mediated rejection

Abstract

Simultaneous pancreas and kidney transplants offer significant therapeutic advantages but present a diagnostic approach dilemma in the diagnosis of rejection. Since both organs are from the same donor the kidney has been traditionally treated as the "sentinel" organ to biopsy, presumably representing the status of both allografts. Truly concurrent biopsy studies, however are needed to confirm this hypothesis. We examined 101 concurrent biopsies from 70 patients with dysfunction in either or both organs. Results showed concurrent rejection in 23/57 (40%) of cases with rejection. 19/57 (33.5%) and 15/57 (26.5%) showed kidney or pancreas only rejection, respectively. The degree and type of rejection differed in the majority (13/23, 56.5%) of cases with concurrent rejection, with the pancreas more often showing higher rejection grade. Taking into account pancreas dysfunction a positive kidney biopsy should correctly predict pancreas rejection in 86% of the instances. However, the lack of complete concordance between the two organs, the discrepancies in grade and type of rejection, and the tendency for higher rejection grades in concurrent or pancreas only rejections, all support the rationale for pancreas biopsies. The latter provide additional data on the overall status of the organ, as well as information on non-rejection related pathologies.

MAIN BODY TEXT

INTRODUCTION

Results in simultaneous pancreas kidney transplantation (SPK) continue to improve in regards to both patient and allograft survival rates, due to lower incidence of technical failure as well as improved immunosuppression protocols (1). However, rejection remains a challenge, and its occurrence in either organ leads to significantly higher likelihood to shortened graft survival to less than 5 years after transplantation (2). Since both organs are from the same donor, it is generally expected that rejection would affect both organs either simultaneously or sequentially (3-8), but this has been shown not to be always the case (9-11). Because timing of the diagnosis of acute rejection is of crucial importance, the establishment of a protocol that maximizes diagnostic accuracy and efficacy is important. In the setting of SPK, this is also essential because the laboratory markers for suspected kidney rejection (increase in serum creatinine) are overall considered more reliable than the ones for pancreas rejection (increase in lipase and amylase) (8). Also added to these concerns is the perceived simplicity and safety of kidney allograft biopsy, as contrasted to the hazards attributed to the pancreas allograft biopsy. The kidney has therefore, been used by most transplant teams as a mirror/sentinel of the pancreas assessment for monitoring acute rejection in both organs (8, 12-15).

Animal studies have strengthened this approach by showing significant concurrence of rejection in both organs, and also by challenging the idea that the pancreas is more prone to rejection than the kidney (3,7). On the other hand, large clinical studies of truly concurrent biopsies of both organs are lacking. The current study addresses this question in a set of biopsies that were collected simultaneously in a prospective manner, when one or both organs showed dysfunction. The clinical findings were correlated with the presence, type and degree of acute rejection, in addition to chronic rejection and other non-rejection related pathologies

in either organ, in order to determine the potential usefulness of each organ to be a potential surrogate for rejection in the other.

MATERIALS AND METHODS

A total of 322 pancreas transplants were performed at our center from October 2006 to date (193 SPK transplants, 14 pancreas after kidney transplants and 15 pancreas transplants alone). Standard immunosuppression includes induction with steroids and Thymoglobulin (7.5mg/kg) and maintenance therapy with tacrolimus, sodium mycophenolate and steroids. Regarding operative technique, both organs were placed intraperitoneally, using the the right iliac vessels for the pancreas and left iliac vessels for the kidney. Most of the times the pancreas was placed with the head down, and only in a few cases the pancreas was placed with the head up. We routinely used systemic endocrine drainage in all cases. For exocrine drainage we used bladder drainage at the beginning of the series and shifted gradually to enteric drainage, which represented more than 70% of the cases.

After obtaining IRB approval, a retrospective review of a prospectively collected database was performed. Between November 2011 and July 2017, 70 patients required biopsy evaluation for graft dysfunction. Per our protocol, both the pancreas and the kidney were biopsied if abnormal function developed in either or both organs. Kidney dysfunction was defined as an unexplained raise in serum creatinine (≥20% above baseline), and/ or the presence of significant proteinuria (≥1g/24hrs) in enteric drained pancreas transplants. Pancreas dysfunction was defined as hyperglycemia (fasting hyperglycemia or impaired OGTT) and/or elevated pancreatic enzymes (≥100% above baseline).

Simultaneous biopsies of both organs were obtained preferentially by laparoscopy as previously described (16). In a minority of cases (7.2%) the biopsies were obtained at the time of a laparotomy.

Out of 106 biopsy attempts, adequate samples for both pancreas and kidney were obtained in 101 instances. We excluded from this study cases with inadequate biopsies for one or both organs, cases of surveillance/protocol biopsies (normal graft function in both organs) biopsies performed in PTA, PAK or PASPK (pancreas transplant alone, pancreas after kidney or pancreas after simultaneous pancreas kidney) transplants. Tissue adequacy was judged according to previously published Banff guidelines and the same guidelines were used for histological evaluation and diagnosis of rejection, including routine performance of C4d stain (immunohistochemistry on paraffin embedded sections) (17-21).

Determination of agreement (concordance) for acute rejection included assessment of degree of severity according to the kidney and pancreas Banff grading schemas (19).

Although the kidney and pancreas acute T-cell mediated acute rejection (TCMR) Banff grading schemas are not identical, an equivalence was made based on the most important organ specific lesions defining rejection. Equivalence for kidney and pancreas rejection grades was defined as follows: Kidney borderline = pancreas indeterminate, kidney Type 1A = pancreas Grade I; kidney Types 1B and 2 = pancreas Grade II; kidney Type 3 = pancreas Grade III (severe rejection, necrotizing arteritis). Diagnosis of acute antibody mediated allograft rejection (AMR) was considered generally equivalent in kidney and pancreas. When the TCMR rejection grade was equivalent in the two organs but AMR was additionally present in one of them, the overall degree of rejection was considered higher in the organ with AMR.

Based on these criteria the cases with rejection in both organs were further divided regarding the severity of rejection (grade) in the following groups: a) equivalent rejection grade, b) higher rejection grade in the kidney, c) higher grade of rejection in the pancreas.

For statistical analysis, the data was analyzed with the Fisher´s exact probability test (two by two contingency tables, 2 tailed). In addition standard studies for diagnostic tests were done to calculate sensitivity, specificity as well as positive and negative predictive values.

RESULTS

Patient population

The 101 kidney/pancreas biopsy sets corresponded to 70 patients (40 males, 30 females) with a mean age of 41 (range 25-61). There were 22 patients with bladder drainage and 48 patients with enteric drainage. Most patients (48, 68.6%) had a single biopsy set, whereas 15 patients (21.4%) had two, 5 (7.24 %) had three and 2 (2.8%) patients had four biopsy sets. The 101 biopsy sets were done at a mean post-transplant time of 39 months (range 0.2-105). They were performed during the first year post-transplant in 30 cases, during the second and third post-transplant year in 17 cases, during the fourth and fifth post-transplant year in 26 cases and beyond the fifth post-transplant year in 28 cases.

Biopsies were performed due to dysfunction of the kidney graft in 47 cases, dysfunction of the pancreas graft in 31 cases and dysfunction of both grafts in 23 cases. (Table 1)

Kidney dysfunction group

Among the 47 patients with kidney dysfunction 21 patients had kidney rejection (45%). According to Banff classification there were 2 borderline rejections, 10 T-cell mediated rejections (TCMR) grade 1A, 3 TCMR grade 1B, 3 antibody mediated rejections (AMR) and 3 mixed (TCMR/AMR) rejections. Among these 21 patients with kidney rejection, concomitant pancreas rejection was found in 5 patients. Pancreas rejections were classified as indeterminate rejection in 1 case, TCMR grade 1 in 3 cases and AMR in the other case. There were 26 patients without kidney rejection in this group of kidney dysfunction. Diagnosis in this

subgroup was a normal kidney in 10 cases, drug toxicity in 6 cases, acute tubular necrosis (ATN) in 4 cases, chronic changes in 4 cases, and BKV nephropathy in 1 case. Interestingly, there were 2 pancreas rejections (TCMR grade 1 in both cases) among the cases without kidney rejection (8%).

Pancreas dysfunction group

Biopsies for pancreas only dysfunction was performed in 31 cases. Kidney rejection was found in 11 cases (35%). According to Banff classification there were 5 borderline rejections, 5 TCMR grade 1A and 1 TCMR grade 1B. Among these 11 patients concomitant pancreas rejection was found in 9 patients. Pancreas rejections were classified as indeterminate rejection in 1 case, TCMR grade 1 in 5 cases and TCMR grade 2 in 3 cases. On the other hand there were 20 patients without kidney rejection in the biopsy. Diagnosis in this group was a normal kidney in 15 cases, ATN in 3 cases, drug toxicity in 1 case and chronic changes in 1 case. In this subgroup of patients without kidney rejection, pancreas rejection was found in 8 cases (40%). Pancreas rejections were classified as indeterminate rejection in 1 case, TCMR grade 1 in 5 cases, TCMR grade 2 in 1 case and AMR in 1 case. Of note, in one case of kidney borderline rejection the pancreas was normal on appearance and the diagnosis was of suspected autoimmune recurrence of diabetes, in accordance with the clinical presentation and laboratory findings.

Dysfunction of both grafts group

We have performed simultaneous biopsies in 23 cases with dysfunction of both grafts. Kidney rejection was found in 10 cases (43%). According to Banff classification there were 8 TCMR grade 1A, 1 TCMR grade 1B and 1 mixed rejection. Among these 10 patients concomitant pancreas rejection was found in 9 patients. Pancreas rejections were classified as indeterminate rejection in 1 case, TCMR grade 1 in 7 cases and TCMR grade 2 in the other case. On the other hand there were 13 patients without kidney rejection in their biopsy. Diagnosis in this group was a normal kidney in 7 cases, drug toxicity in 1 case, acute tubular

necrosis (ATN) in 1 case, chronic changes in 2 cases and BKV nephropathy in 2 cases. In this group of patients without kidney rejection, pancreas rejection was found in 5 cases (38%). Pancreas rejections were classified as TCMR grade 1 in 3 cases, TCMR grade 2 in 1 case and AMR in 1 case.

Incidence of rejection and analysis of sensitivity and specificity of dysfunction variables

Overall there were 57 cases with rejection among the 101 biopsies (56.5%).

Kidney dysfunction (with or without pancreas dysfunction) was present in 70 cases because of a rise in creatinine (65) or proteinuria over 1g/L in enteric drained patients (9). When kidney dysfunction was present kidney rejection was found in 44% of the cases with a sensitivity of 74% and a specificity of 34%. In addition, in this setting pancreas rejection was found in 30% of the cases with a sensitivity of 55% and a specificity of 22% (Table 2).

Pancreas dysfunction (with or without kidney dysfunction) was present in 54 cases because of elevated pancreatic enzymes (31) or hyperglycemia (27). When pancreas dysfunction was present kidney rejection was found in 39% of the cases with a sensitivity of 50% and a specificity of 44%. In addition, in this setting pancreas rejection was found in 57% of the cases with a sensitivity of 82% and a specificity of 63% (Table 2). For pancreas dysfunction, there was no difference in the incidence of pancreas rejection when the reason for biopsy was hyperglycemia (63%) vs elevated enzymes (55%) (p=NS).

Combined kidney and pancreas dysfunction was present in 23 cases. Kidney rejection was found in 43% of them with a sensitivity of 24% and a specificity of 78%, and pancreas rejection was found in 61% of them with a sensitivity of 37% and a specificity of 86% (Table 2).

Analysis of concordance of rejection and types of rejection

Overall there were 80 graft rejections in 57 patients. There were 19 patients with kidney only rejection, 15 patients with pancreas only rejection and 23 patients with rejection of both grafts. (Table 1) As there were 34 patients with rejection of one graft only and 23 patients with rejection of both grafts, concordant rejection was found in only 40% of the cases with rejection findings (Figure 1).

The concordance rate varied widely among groups, as well as which was the rejected organ, when only one organ was rejected. In the "kidney only" dysfunction group concordance of rejection was observed in only 22% of sets, with discordant rejections predominantly consisting of kidney only rejection (70%) with rare pancreas only rejection (8%).

In the "pancreas only" dysfunction group, concordance of rejection was observed in 47% of sets. The discordant rejections consisted mostly of pancreas only rejection (42%) with a minority being kidney only rejection (11%). In the group with dysfunction in both organs, concordance of rejection was found in 60% of sets. The discordant rejections included more pancreas only rejections (33%) than kidney only rejections (7%) (Figure 2).

Acute rejection was present in both organs in 23 biopsy sets of which 10 had the same degree of severity in both organs and 13 had different degrees of severity of rejection among the two organs. In 7 cases, rejection was more severe in the pancreas whereas in 6 cases it was more severe in the kidney (3 TCMR only and 3 combined TCMR and AMR). (Figure 1).

Analysis of rejection type (i.e. TCMR vs. AMR) and grade (i.e. mild TCMR vs. moderate-severe TCMR) in the kidney only, kidney and pancreas, and pancreas only rejection groups showed that the incidence of AMR was more or less equally distributed among these groups (16%,17.5% and 13.5%, respectively) (Figure 3). In contrast, the highest grades of TCMR (moderate-severe) were observed only in the pancreas grafts in the setting of either

concordant kidney and pancreas rejection (17.5%) or in pancreas only rejection (13.5%) (Figure 3). This finding could indicate that either the cases of concordant rejection are more severe and thus more extensive in their tissue distribution and/or the pancreas may be more "rejection prone". Two cases of discordant rejection findings are illustrated in Figure 4.

Correlation of kidney rejection with pancreas rejection

The sensitivity, specificity, positive and negative predictive values of the kidney biopsy results for the corresponding pancreas biopsy varied significantly depending on the presence or absence of pancreas dysfunction (Table 3).

Based on these results, an algorithm was devised for predicting pancreas rejection using the kidney biopsy and pancreas dysfunction data (Figure 5). Accordingly a positive kidney biopsy would correctly predict pancreas rejection in 86% of the cases if there is concurrent pancreas dysfunction, but only in 24% of the cases in its absence.

A kidney biopsy negative for rejection would correctly predict absence of rejection in the pancreas in 92% of the cases when there was no evidence of pancreas dysfunction, but only in 61% of cases if there is concurrent pancreas dysfunction.

DISCUSSION

In pancreas transplantation there is no reliable non-invasive laboratory test or imaging study for detection of graft rejection. Elevation of pancreatic enzymes (amylase and lipase) are widely used for monitoring the pancreas graft despite their low sensitivity and specificity for rejection. In addition, in simultaneous pancreas and kidney transplantation kidney function

tests are also used as a surrogate marker for pancreas monitoring as concordant rejection is often assumed. Hence when kidney dysfunction is detected most of the programs would initially biopsy only the kidney and treat accordingly. Pancreas biopsies are therefore usually limited for patients with normal kidney function tests and/or negative kidney biopsy results along with pancreatic enzyme elevations or hyperglycemia. However, the concordance of rejection among grafts has been challenged in several studies (11,13,15). Anatomically different tissues that originate from the same donor may present in practice with different immunogenic challenges (22). With respect to SPK, lack of concordance may represent a true biological difference or simply a sampling variation. The question has not been conclusively answered, neither has been previously explored in concurrent biopsies in consecutive clinical cases.

This study is the first to report the results of simultaneous kidney and pancreas biopsies done per protocol in the setting of any organ dysfunction. These set of biopsies can therefore show the incidence of rejection and concordance among grafts in different dysfunction settings. This material allowed us to calculate the sensitivity and specificity of kidney and of pancreas dysfunction for rejection. Not surprisingly, kidney dysfunction has good sensitivity for kidney rejection (74%) and low sensitivity for pancreas rejection (55%). In contrast, pancreas dysfunction has low sensitivity for kidney rejection (50%) and high sensitivity for pancreas rejection (82%). However, specificity of neither of them has been sufficiently high to justify avoiding a biopsy for diagnosis.

Regarding the analysis of concordance we decided to only include the cases with rejection as they reflect the true incidence of concordant and discordant rejection. When no rejection cases are counted as concordant findings, concordance is therefore dependent on the incidence of rejection. In our series, we found that concordant rejection was present in 40% of the cases and discordant rejection in 60%. Concordant rejection was more frequent when both

organs had dysfunction (60%) in comparison with when only the pancreas (47%) or only the kidney had dysfunction (22%).

In addition, even in the cases where concordant rejection was found, there was a discordant type or discordant degree of rejection in 56.5% of the cases. Among these patients pancreas rejection was more severe in 54%, therefore treatment according to kidney rejection only findings would have been incomplete for the pancreas in these cases.

This prospective series of patients provides new and interesting data to help answer the question of which organ to biopsy when the patient presents with either kidney or pancreas dysfunction, or both.

One approach would have been to biopsy only the kidney. Our data shows that with this approach we would have missed 40% of the pancreas rejections. In more detail, we would have missed 2 out of 7 pancreas rejections (29%) in the kidney dysfunction group, 8 out of 17 pancreas rejections (47%) in the pancreas dysfunction group and 5 out of 14 pancreas rejections (36%) in the both organs dysfunction group. Another approach would have been to biopsy the kidney first, and then biopsy the pancreas in all patients with pancreas dysfunction and a negative kidney biopsy. With this approach we would have missed relatively few pancreas rejections (only 8% of the cases with a negative kidney biopsy without pancreas dysfunction) (Figure 5), however we would have treated patients according to the type and degree of rejection found in the kidney. As previously discussed, this treatment would have been incomplete for almost 20% of patients with pancreas rejection. This finding is similar to the discordant types and degrees of rejection found by Parajuli et al. from the University of Wisconsin. (11)

Aside from obtaining a precise diagnosis in terms of type and degree of pancreas rejection, pancreas biopsies provide information of great value about the graft. Assessing the degree of chronic damage on the graft could impact the decision on the treatment as well. For instance, a patient with hyperglycemia was found to have a TCMR grade 1A on the kidney with severe chronic damage on the pancreas. After treatment for kidney rejection, the persistence of hyperglycemia was then characterized as a pancreas failure and no further treatment was added. On another case, a "normal" pancreas on appearance (no chronic damage nor acute inflammation) on a patient with sudden onset of diabetes symptoms 6 years after transplant was then diagnosed as recurrence of autoimmune diabetes.

Our results indicate further a potentially true biological difference in the way kidney and pancreas are rejected. The fact that higher degrees of TCMR were observed only in the pancreas, in cases of concordant or pancreas only rejection, as well as the overall rejection grade of discrepancies being more often in disfavor of the pancreas, point to a liability of the pancreas if the kidney with its particular histology and biology is used as mirror/sentinel for the significantly different pancreas having potentially higher propensity for immunological injury.

Pancreas tissue for diagnosis can be obtained transcystoscopically (23), enteroscopically (transduodenal) (24), percutaneously (25), laparoscopically or by open laparotomy (26). The larger series reported of pancreas biopsies are with the percutaneous technique (27-29), showing a tissue yield from 88 to 96% with very low morbidity (0.6 – 2.6%) and only one graft loss reported in more than 1000 cases. Our group has recently reported the technique, yield and safety of the laparoscopic approach with results comparable to these percutaneous series (16).

In conclusion, pancreas biopsies in experienced hands have been proved to be safe and reliable with different techniques. Simultaneous pancreas kidney transplant patients with graft

dysfunction benefit from simultaneous pancreas and kidney biopsies as discordant rejection is found in up to 60% of the patients with rejection. In addition, in patients with concordant rejection, discordant types and degree of rejection are found in half of these patients. Pancreas tissue when available, also provides important information regarding the chronicity of the graft and the presence of other entities.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

FIGURE LEYENDS:

Figure 1:

Title: Kidney-pancreas acute rejection incidence, concordance and severity.

In most instances (n=44) neither organ showed rejection. Isolated kidney or pancreas rejection occurred in 19 and 15 cases, respectively. The 23 cases with simultaneous kidney and pancreas rejection displayed higher degree of rejection in the pancreas or in the kidney in 7 and 6 instances, respectively. Ten biopsy sets showed the same degree of rejection. Cases with more severe rejection in the kidney than in the pancreas corresponded to either higher degree of TCMR (50%) or to the occurrence of concurrent AMR (50%).

Kid - Pan - = Absence of rejection in both organs. Kid + Pan - = Kidney only rejection. Kid – Pan + = Pancreas only rejection. Kid + Pan + = Rejection of both organs. P>K = Pancreas rejection more severe than kidney rejection. K>P = Kidney rejection more severe than pancreas rejection. K=P = Kidney and pancreas rejection with equivalent severity.

Figure 2:

Title: Correlation between organ dysfunction and concordance of organ rejection

Concordance of rejection varied widely among the three organ dysfunction settings.

Figure 3:

Title: Correlation between concordance of organ rejection and severity/type of rejection.

Whereas the incidence of AMR is relatively evenly distributed among the groups, the moderate/severe grades of TCMR are observed exclusively in the combined kidney and pancreas and pancreas only rejection groups. AMR = Antibody Mediated Rejection. Mod = Moderate. Sev = Severe. TCMR = T-cell Mediated Rejection

Figure 4:

Title: Histology of two cases with discordant rejection findings.

Legend: A,B,C and D: Diagnostic discordance in simultaneous pancreas and kidney allograft biopsies.

A and B: Pancreatic and renal biopsies in a patient biopsied for dysfunction of both organs. The pancreas biopsy showed mixed T-cell mediated and acute antibody mediated rejection, defined by prominent septal infiltrates with ductitis (arrows) and acinar, interacinar infiltrates with acinar cell damage (upper right corner), respectively. C4d stain in the pancreas (not shown) highlighted interacinar capillaries. In contrast the kidney biopsy was free of any inflammation and was negative for the C4d stain (not shown). Some tubular cell injury was noted.

C and D: Pancreas and kidney biopsies in a patient presenting with kidney dysfunction. The pancreas biopsy (C) had normal architecture and was free of inflammation (i.e. no rejection). In contrast the kidney biopsy showed mixed acute rejection (T-cell mediated and antibody mediated) with arteritis and extensive tubulointerstitial infiltrates.

Figure 5:

Title: Algorithm for predicting pancreas rejection using the kidney biopsy results and pancreas dysfunction data.

Kidney biopsy findings in correlation with pancreas dysfunction data, can help predict pancreas rejection or its absence. When kidney rejection was present, concurrent pancreas rejection occurred in 86% of the cases with pancreas dysfunction but only in 24% of the cases without pancreas dysfunction. When kidney rejection was absent, pancreas rejection occurred in 39% of the cases with pancreas dysfunction but only in 8% of the cases without pancreas dysfunction.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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Table 1

Presence of Acute Rejection in Pancreas and Kidney in Relationship to Graft Dysfunction

Dysfunction	Rejection	Pancreas +	Pancreas -
Kidney (47)	Kidney + (21)	5	16
	Kidney - (26)	2	24
Both (23)	Kidney + (10)	9	1
	Kidney - (13)	5	8
Pancreas (31)	Kidney + (11)	9	2
	Kidney - (20)	8	12

Footnotes:

(+) = presence of rejection. (-) = absence of rejection

Table 2: Correlation Between Organ Dysfunction and Rejection

	Kidney Rejection	**Pancreas Rejection**	
	73.8%	55.26%	*Sensitivity*
Kidney	33.9%**^	22.2%*	*Specificity*
Dysfunction	44.3%	30 %	*Pos. PV*
	64.52%***	45.16%	*Neg. PV*
Both Kidney	23.8%	36.8%	*Sensitivity*
& Pancreas	78% (p<.0001)^	85.7% (p=.007)[#]	*Specificity*
Dysfunction	43.5%	60.9%	*Pos. PV*
	59%	69.2%	*Neg. PV*
Pancreas	50%	**81.58%**	*Sensitivity*
Dysfunction	44% (p=.01)*	63.49% (p=.001)**[#]	*Specificity*
	38.9%	57.4%	*Pos. PV*
	55.3%	85% (p=.05)***	*Neg. PV*

Footnotes:

*Comparison of the correlation between kidney dysfunction and pancreas rejection vs. pancreas dysfunction and kidney rejection. Pancreas dysfunction is more specific for kidney rejection than the reverse.

** and *** Comparison of the correlation between kidney dysfunction and kidney rejection vs. pancreas dysfunction and pancreas rejection. Pancreas dysfunction is more specific for pancreas rejection than kidney dysfunction for kidney rejection and also has better negative predictive value for pancreas rejection than kidney dysfunction for kidney rejection.

^ Comparison of the correlation between kidney dysfunction and kidney rejection vs. kidney & pancreas dysfunction and kidney rejection. Combined pancreas and kidney dysfunction is more specific for kidney rejection than kidney dysfunction only.

[#] Comparison of the correlation between pancreas dysfunction and pancreas rejection vs. kidney and pancreas dysfunction and pancreas rejection. Combined pancreas and kidney dysfunction is more specific for pancreas rejection than only pancreas dysfunction.

Table 3: Correlation between Kidney Rejection ± Pancreas Dysfunction and Pancreas Rejection

	Kidney Rejection Overall^ (p=.0035)	Kidney rejection with Pancreas dysfunction	Kidney rejection without Pancreas dysfunction	
Pancreas Rejection	60.53%	58.06%	71.43%	*Sensitivity*
	69.84%	86.9% (p=.04*)	60.0%*	*Specificity*
	54.76%**	85.7% (p=.0001*,p=.02**)	23.81%*	*Pos. PV*
	74.58%	60.6% (p=.007*)	92.31%*	*Neg. PV*

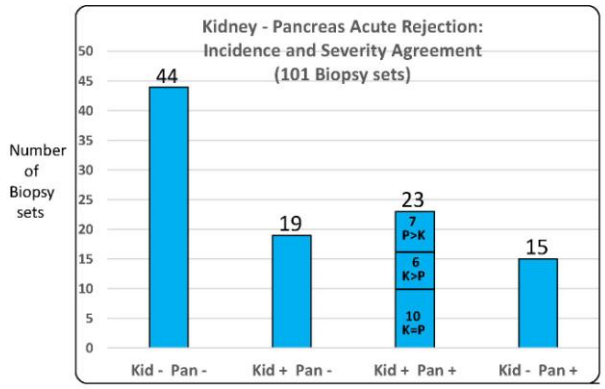
Footnotes:

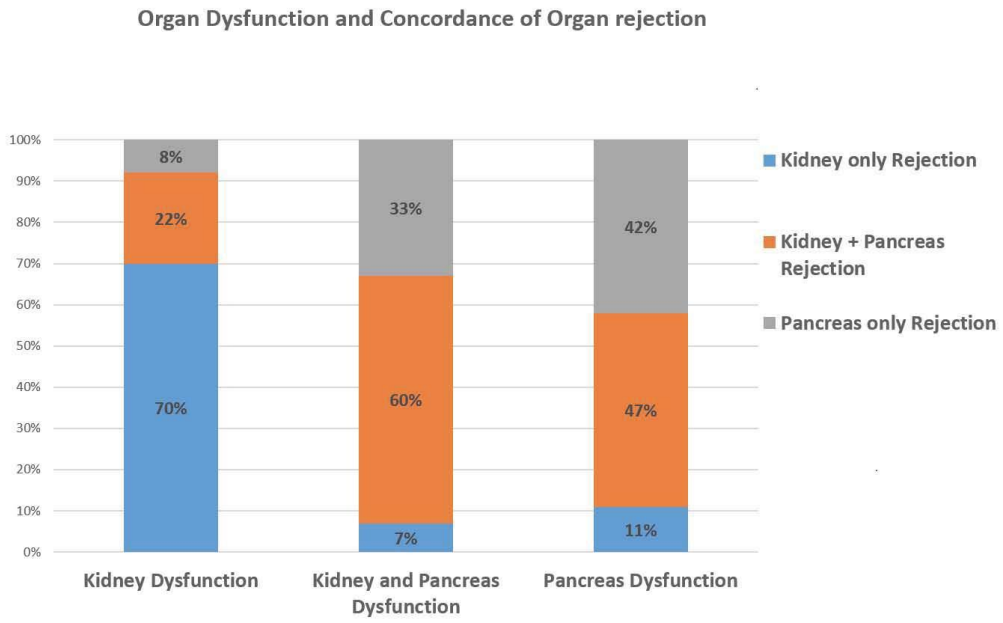
^ Overall correlation between Kidney rejection and Pancreas rejection.

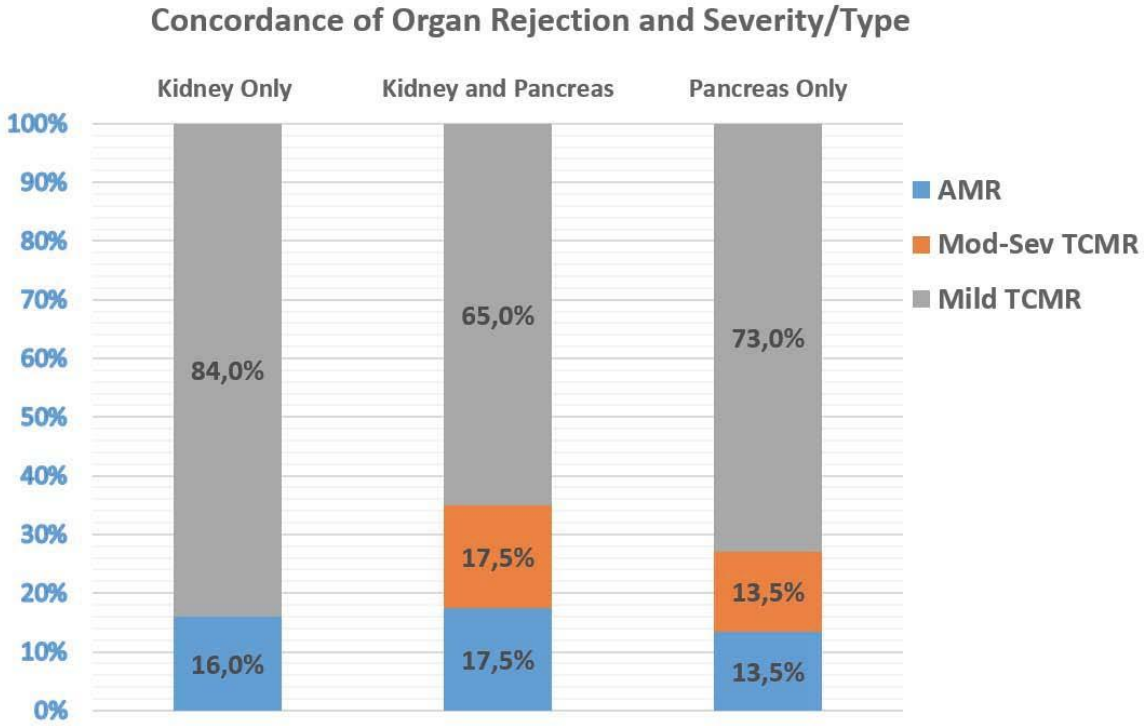
*Correlation between Kidney rejection and pancreas rejection with and without associated pancreas dysfunction.

**Correlation of kidney rejection with pancreas dysfunction vs. kidney rejection overall and pancreas rejection.

Figure 1







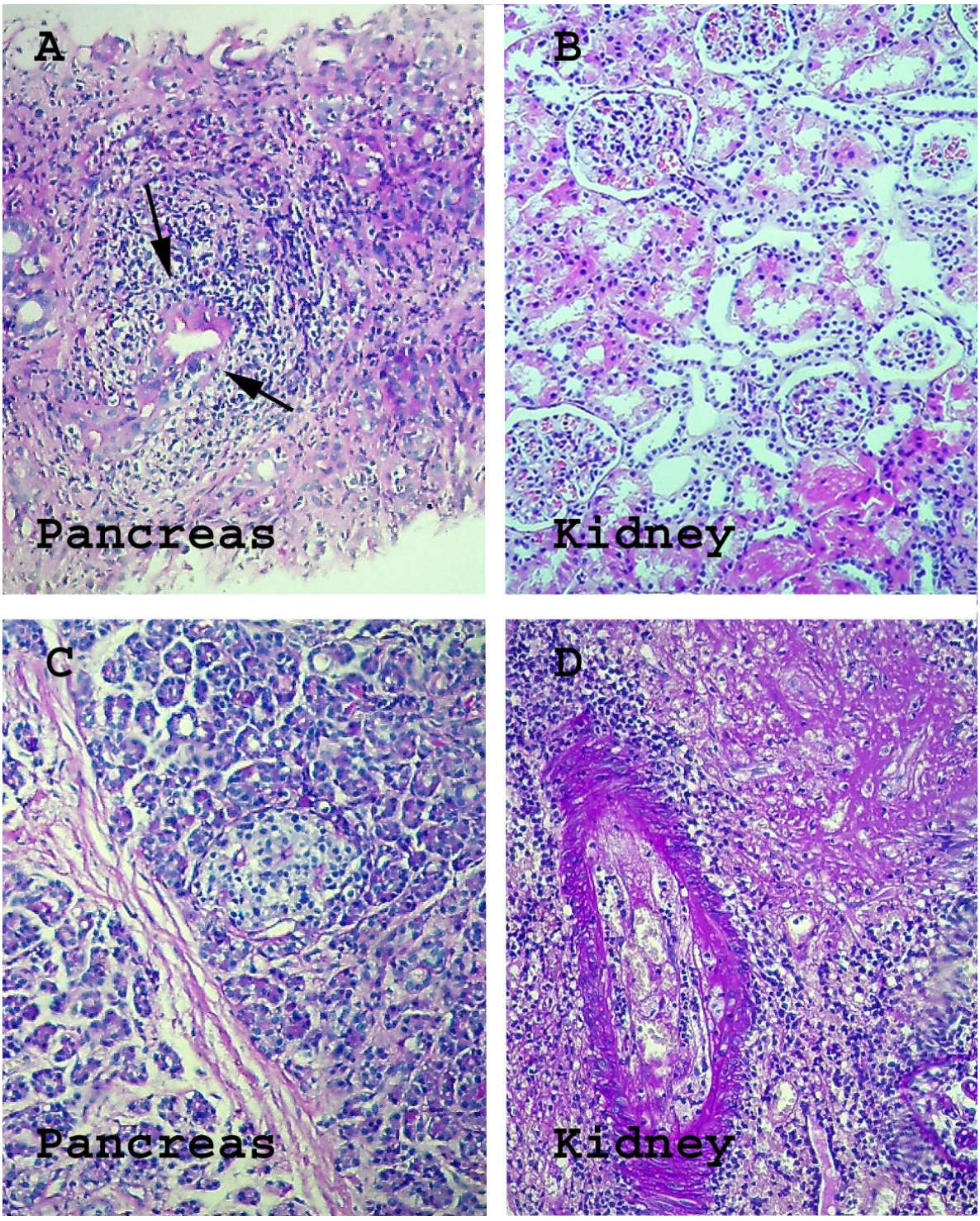


Figure 5