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Sex matching does not impact the outcome after simultaneous pancreas-kidney transplantation

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Abstract

Background: Several studies in solid organ transplantation have shown a correlation between donor and recipient sex mismatch and risk of graft loss. In this study, we aimed to analyze the impact of donor and recipient sex matching on patient and pancreas graft survival in a large single-center cohort.

Methods: We retrospectively analyzed all first simultaneous pancreas-kidney transplants performed between 1979 and 2017 at the Medical University of Innsbruck.

Results: Of 452 patients, 54.6% (247) received a sex-matched transplant. Patient survival (P = .86), death-censored pancreas graft survival (dcPGS, P = .26), and death-censored kidney graft survival (dcKGS, P = .24) were similar between the sex-matched and sex-mismatched groups. Patient survival and dcPGS at 1, 5, and 15 years were 95.9%, 90.0%, and 62.1% and 86.1%, 77.1%, and 56.7% in the sex-matched group and 93.6%, 86.2%, and 62.4% and 83.1%, 73.3%, and 54.3% in the sex-mismatched group. Sex matching led to a lower odds of severe postoperative complications (41.2% vs 49.0%; OR 0.57, 95%CI 0.33-0.97; P = .038); however, no increased odds of other adverse postoperative outcomes was detected.

Conclusion: Our study demonstrates that sex matching reduced the odds of postoperative complications but did not impact other early and late outcome parameters in our cohort.

1 | INTRODUCTION

Simultaneous pancreas-kidney transplantation (SPK) is the gold standard in treatment of end-stage renal disease in patients with type 1 diabetes mellitus (T1DM). It restores physiologic blood glucose control and leads to a better kidney graft and patient survival compared with kidney transplantation alone.[1] However, Eurotransplant data show that there are far more pancreas grafts available than used for

transplantation.[2] As well, SPK is known to have the highest complication rate of any abdominal organ transplantation.[3] Thus, it is extremely important that we understand which pancreata should and should not be transplanted to obtain the best possible outcomes.

Differing donor and recipient sex combinations have been described to have an impact on graft survival in solid organ transplantation. Various studies in stem cell,[4-6] kidney,[7-11] liver,[12-14] lung,[15,16] and heart transplantations[17-19] indicate the importance of gender

matching in this field. Differences in outcomes after kidney transplantation related to donor-recipient sex concordance have been attributed to mismatches in graft size, nephron mass or vessel diameter, or small-for-size in liver transplantation.[6,20,21] It has also been postulated that estrogen and testosterone levels and their impact on ischemia/reperfusion injury[22] as well as immunologic factors such as the H-Y antigen may play a role in this context.[6,23,24] The importance of sex matching has been investigated in the setting of pancreas transplantation; however, only few reports address the impact of recipient and donor sex as well as sex matching on the outcome after pancreas transplantation.[25-28] A large US registry study recently reported that sex matching significantly decreased the risk for pancreas graft failure.[25] As a substantial impact of sex matching on postoperative outcome could potentially impact organ allocation and postoperative monitoring, we herein investigate the effect of donor-recipient sex concordance on short- and long-term outcomes after pancreas transplantation in a single-center cohort of one of the highest-volume pancreatic transplant centers in the Eurotransplant region.

2 | MATERIALS AND METHODS

2.1 | Study population

The study was approved by the ethics board of the Medical University of Innsbruck (No. 1249/2017). All consecutive, first-time simultaneous pancreas-kidney transplants performed between December 1979 and December 2017 were recorded in a database in a retrospective fashion. Donor characteristics (age, sex, blood type, donor height, body mass index [BMI], cause of death, pancreas donor risk index [PDRI], HLA phenotype, date of transplantation), operative data (cold ischemic time [CIT], warm ischemic time [WIT], type of venous drainage, exocrine pancreatic drainage), recipient characteristics (age, sex, blood group, wait list time, BMI, HLA phenotype, panel reactive antibodies [PRA] at the time of transplantation), and postoperative details (last follow-up, cause of death, surgical complications according to Clavien-Dindo classification, postoperative graft function, need for exogenous insulin after discharge, early immunologic complications, and cause of graft loss) were recorded. Patients alive but without data records for 4 years were defined as lost to follow-up. After exclusion of patients lost to follow-up (n = 39; 8.6%), 452 patients were included in this study.

2.2 | Surgical procedure

Standard exocrine drainage consisted of a duodenojejunostomy in the proximal jejunum (approximately 40 cm distal to the ligament of Treitz; performed routinely after 1997). For reconstruction of the mesenteric and splenic arteries, the donor iliac bifurcation (Y graft) was used. Venous drainage was established via the donor portal vein anastomosed either to the vena cava (systemic endocrine drainage) or to the superior mesenteric vein (portal endocrine drainage). In cases of segmental pancreas transplantation,

TABLE 1 Recipient and donor characteristics of sex-matched and sex-mismatched simultaneous pancreas-kidney transplantations from January 1979 to December 2017

	Sex Match	Sex Mismatch	P
Number	247	205	
Recipient sex female (%)	22.3	51.7	<.01
Recipient age (years) mean (SD)	42.7 (9.4)	40.8 (9.3)	.05
Recipient BMI (kg/m^2) mean (SD)	23.5 (3.0)	23.4 (3.0)	.9
Recipient T1DM (%)	95.1	95.5	.8
Donor sex female (%)	22.3	48.3	<.01
Donor age (years) mean (SD)	28.9 (10.4)	31.5 (11.7)	.01
Donor BMI (kg/m^2) mean (SD)	23.5 (2.3)	22.8 (2.4)	<.01
Donor height (cm) mean (SD)	176.4 (9.2)	172.0 (9.7)	<.01
Donor death cause CVA (%)	20.2	31.7	<.01
Transplant < 1997 (%)	21.1	25.4	.3
HLA mismatch (>3/6) (%)	83.3	78.0	.09
PRA > 20% (%)	10.5	10.7	.4
Exocrine drainage (%)			
Bladder drainage	18.6	19.2	.8
Enteric drainage	79.8	78.3	
Other	1.6	2.5	
Endocrine drainage (%)			
Systemic	92.7	95.6	.2
Portal	7.3	4.4	
Pancreas CIT (hours) mean (SD)	12.7 (3.3)	12.3 (3.2)	.2
Pancreas WIT (minutes) mean (SD)	32.8 (8.7)	32.2 (7.9)	.5
Follow-up (years) mean (SD)	10.8 (7.2)	10.7 (7.4)	.8
C-Peptide (ng/mL)	5.7 (2.1)	6.0 (2.9)	>.9
Creatinine (mg/dL)	1.2 (0.4)	1.3 (1.0)	.8
Waiting time (months) mean (SD)	7.4 (8.6)	5.8 (5.8)	.04
PDRI mean (SD)	1.11 (0.3)	1.23 (0.4)	<.01

Abbreviations: BMI, body mass index; CIT, cold ischemic time; CVA, cardiovascular accident; HLA, human leukocyte antigen; PDRI, pancreas donor risk index; PRA, panel reactive antibody; SD, standard deviation; T1DM, type 1 diabetes mellitus; WIT, warm ischemic time.

occlusion of the pancreatic duct with Ethibloc (Ethicon), reconstruction with a Roux-en-Y loop of jejunum, delayed duct occlusion with extra-peritonealization of the cut surface of the pancreas, or bladder drainage was performed (standard techniques for exocrine drainage before 1997).[29]

TABLE 2 Recipient and donor characteristics of donor-recipient sex constellations after simultaneous pancreas-kidney transplantations from January 1979 to December 2017

	MM	MF	FM	FF	P
Number	192	99	106	55	
Recipient age (years) mean (SD)	43.3 (9.5)	42.9 (8.4)	38.8 (9.7)	40.8 (9.5)	.001
Recipient BMI (kg/m^2) mean (SD)	23.7 (2.9)	23.8 (2.8)	23.0 (3.2)	22.7 (3.0)	.044
Recipient T1DM (%)	94.8	92.9	98.1	96.4	.3
Donor age (years) mean (SD)	27.9 (9.7)	35.2 (11.5)	28.1 (10.9)	32.4 (11.7)	<.001
Donor BMI (kg/m^2) mean (SD)	23.8 (2.1)	22.5 (2.5)	23.1 (2.3)	22.3 (2.5)	<.001
Donor height (cm) mean (SD)	179.6 (7.0)	166.2 (5.6)	177.6 (9.5)	165.8 (7.4)	<.001
Donor death cause CVA (%)	15.1	37.4	26.4	38.2	<.001
Transplant < 1997 (%)	21.9	19.2	31.1	18.2	.1
HLA mismatch (>3/6) (%)	95.2	96.1	91.3	90.0	.3
PRA > 20% (%)	4.2	4.2	3.9	10.3	.8
Exocrine drainage (%)					
Bladder drainage	79.3	82.3	74.5	81.5	.3
Enteric drainage	19.1	17.7	20.6	16.7	
Other	1.6	0	4.9	1.9	
Endocrine drainage (%)					
Systemic	92.1	93.9	97.1	94.5	.4
Portal	7.9	6.1	2.9	5.5	
Pancreas CIT (hours) mean (SD)	12.4 (3.3)	12.1 (3.2)	12.6 (3.3)	13.5 (3.3)	.10
Pancreas WIT (minutes) mean (SD)	33.0 (8.7)	32.3 (8.6)	32.1 (7.2)	32.2 (8.8)	.8
Follow-up (years) mean (SD)	10.8 (7.1)	9.8 (6.8)	11.4 (7.9)	10.8 (7.7)	.6
C-Peptide (ng/mL)	5.7 (2.1)	5.5 (2.9)	6.6 (2.8)	5.7 (2.0)	.2
Creatinine (mg/dL)	1.2 (0.4)	1.6 (1.3)	1.0 (0.3)	1.2 (0.5)	<.001
Waiting time (months) mean (SD)	6.9 (7.7)	5.2 (5.4)	6.4 (6.1)	9.1 (11.0)	.050
PDRI mean (SD)	1.08 (0.32)	1.27 (0.40)	1.25 (0.36)	1.17 (0.37)	<.001

Abbreviations: BMI, body mass index; CIT, cold ischemic time; CVA, cardiovascular accident; HLA, human leukocyte antigen; PDRI, pancreas donor risk index; PRA, panel reactive antibody; SD, standard deviation; T1DM, type 1 diabetes mellitus; WIT, warm ischemic time.

2.3 | Immunosuppressive regimens

In transplants performed before 1997, only two patients (1.9%) received therapy with a non-steroidal induction agent (anti-thymocyte globulin, ATG). Most patients received maintenance immunosuppression consisting of either cyclosporine A (98.1%) combined with azathioprine (82.7%) or mycophenolic acid (MMF) (3.8%). All patients received steroids for inductions and as maintenance therapy. After 1997, most patients received induction therapy consisting either of ATG 81.6% or Alemtuzumab 6.9%. All patients received steroids for induction (500 mg intra-operatively) and maintenance immunosuppression (post-transplant steroid taper; 5 mg/d prednisolone as maintenance). In the majority of cases, tacrolimus (initial 12-14 ng/mL, gradually decreased to 8 ng/mL at 9 months, to 4-6 ng/mL after 12 months) (93.4%) and MMF (2000 mg/d) (91.4%) was given postoperatively. Some patients received cyclosporine A (initial trough Levels 180-200 ng/mL, stepwise decreased to 100-130 ng/mL at 9 months, to 80 to 100 ng/mL at 12 months, and to 60 to 80 ng/mL afterward) (6.6%), sirolimus (initially about 8 ng/mL, decreased to 5-6 ng/mL at 9 months, 3-5 ng/mL at 12 months, and 3 ng/mL afterward) (4.6%), or azathioprine (1.0-1.5 mg/kg body weight) (0.3%) as maintenance immunosuppression.
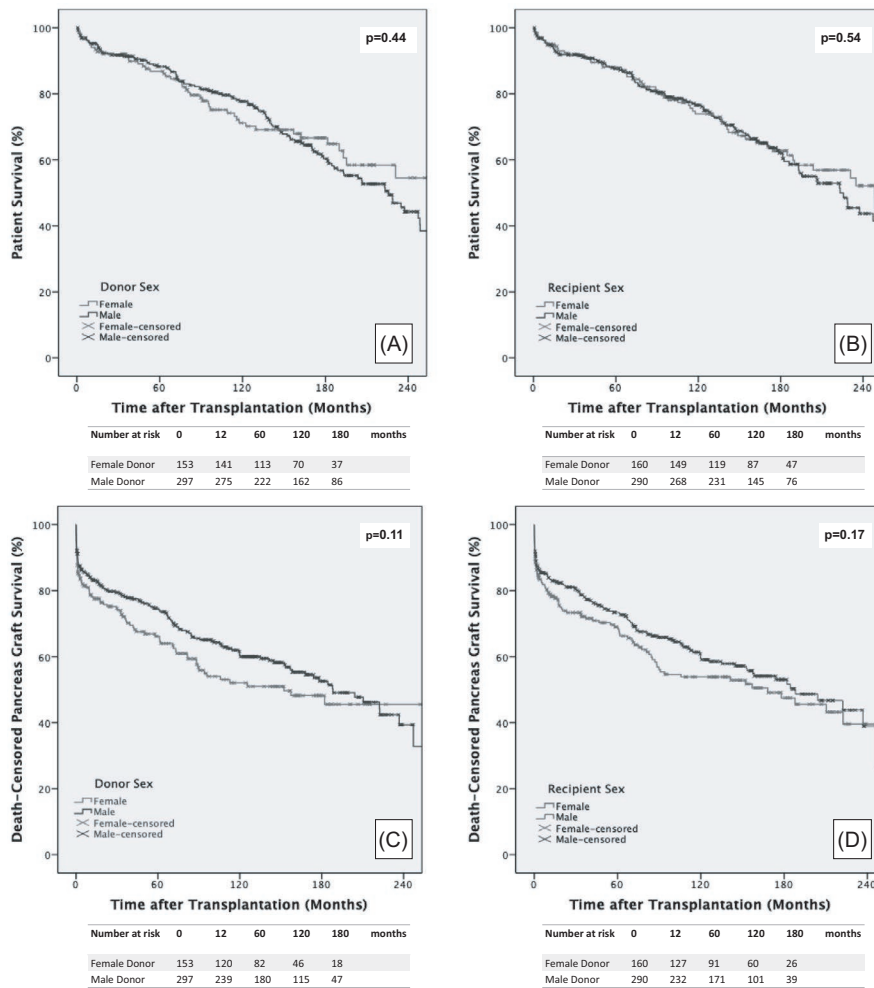
FIGURE 1 Patient survival and death-censored pancreas graft survival (dcPGS) according to donor sex (A, C) and recipient sex (B, D). For patient survival, survival curves for both, donor (A) and recipient (B) sex, are similar (log-rank *P* = .44 and *P* = .54). The same is seen for dcPGS of donors (C) and recipients (D) (log-rank *P* = .11 and *P* = .17, respectively)

2.4 | Definitions

"Sex match" was defined as transplantation from a male donor to a male recipient (M → M) or female donor to a female recipient (F → F). "Sex mismatch" was defined as transplantation from a male donor to female recipient (M → F) or female donor to male recipient (F → M). Death-censored pancreatic graft survival (dcPGS) was defined as functioning graft without the need for exogenous insulin excluding graft loss as a result of patient death. Cause of graft loss was categorized as thrombosis, acute rejection, chronic rejection, infection of the graft, bleeding complication, and unknown causes. Pancreas delayed graft function (PDGF) was defined as need for exogenous insulin during the initial postoperative phase with subsequent wean. The pancreas donor risk index (PDRI) was calculated according to the publication by Axelrod et al[30] Follow-up time was calculated from date of transplantation until date of last known clinical status or death. Immunologic complications were clinically or histologically suspected/proven and treated rejection of the kidney or pancreas graft.

2.5 | Outcome parameters

Primary outcome parameters were patient survival and death-censored pancreas graft survival (dcPGS). Secondary outcome parameters

were odds of PDGF, independence of insulin upon hospital discharge, severe postoperative complications (Clavien-Dindo Grade ≥ 3b), immunologic complications, and a length of hospital stay >25 days, as this represents the median length of hospital stay in our cohort.

2.6 | Statistical analysis

Results are expressed as mean ± standard deviation (SD) for continuous variables and counts and percentages for categorical variables. For continuous variables, Student's *t* test was applied for normal distribution, and Mann-Whitney *U* test and Kruskal-Wallis test were applied for variables with non-normal distribution. For categorical variables, chi-square test was used. Patient survival and graft survival were estimated using the Kaplan-Meier method, and the log-rank test was used to compare unadjusted survival curves. Cox proportional hazards models for patient survival and graft survival were used to adjust for donor and recipient factors. Proportional hazards were visually inspected with complementary log-log plots. Odds of PDGF, independence of insulin upon hospital discharge, severe postoperative complications, and length of stay >25 days were estimated using univariable logistic regression. Significance was classified as *P* ≤ .05 (two-sided). Confidence intervals (CI) are presented on a 95% level. Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation).

3 | RESULTS

3.1 | Study population

A total of 452 patients undergoing first simultaneous pancreas-kidney (SPK) transplantation from 1979 to 2017 were included in the analysis with a mean follow-up of 10.7 ± 7.3 years. About 54.6% (n = 247) of the SPK transplant were sex-matched. Compared with sex-mismatched transplants, sex-matched transplants displayed significantly higher recipient age (42.7 vs 40.8 years; *P* = .05), lower donor age (28.9 vs 31.5 years; *P* = .01), higher donor BMI (23.5 vs 22.8; *P* < .01), lower donor height (176.4 vs 172 cm; *P* < .01), lower rate of CVA as cause of donor death (20.2% vs 31.7%; *P* < .01), and a lower PDRI (1.11 vs 1.23; *P* < .01). Significantly fewer female recipients received a sex-matched transplant (22.3% vs 51.7%; *P* < .01). There were no differences in recipient BMI, type of diabetes mellitus, HLA matching, PRA > 20%, surgical technique, or transplantation date before 1997 (Table 1).
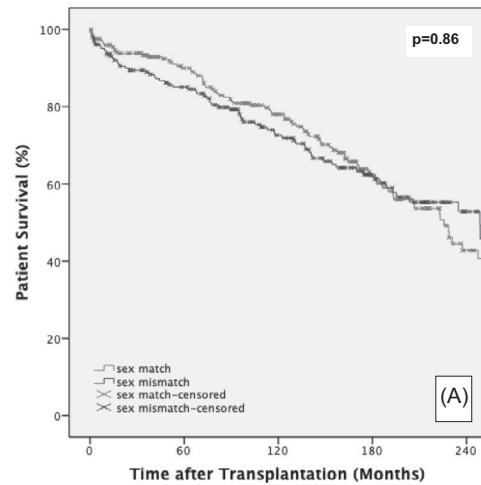
In 192 cases (42.5%), male donor organs were transplanted into male recipients (M → M), 99 were cases M → F (21.9%), in 106 F → M (23.5%), and in 55 F → F (12.2%). Between the different donor-recipient sex constellations, significant differences were observed in terms of recipient age, recipient BMI, donor age, donor BMI, donor height, frequency of CVA as donor cause of death, creatinine level, and mean PDRI. A detailed summary can be found in Table 2.

3.2 | Impact of donor and recipient sex on patient survival and pancreas graft survival

Patient survival was similar between recipients of female and male donor organs (log-rank *P* = .44; Figure 1A) and between female and male recipient sex (log-rank *P* = .54; Figure 1B). As well, dcPGS showed no statistically significant difference regarding donor (log-rank *P* = .11; Figure 1C) or recipient (log-rank *P* = .17; Figure 1D) sex. Though not statistically significant, recipients of male donor organs and male recipients receiving organs from either sex had a trend toward superior dcPGS.

3.3 | Impact of donor and recipient sex match on patient survival and pancreas graft survival

Patient survival, dcPGS, and dcKGS were similar between sex-matched and sex-mismatched transplants (Figure 2A, log-rank *P* = .86; Figure 2B, log-rank *P* = .26, Figure 3A, log-rank *P* = .24). Patient survival at 1, 5, 10, and 15 years was 95.9%, 90.0%, 78.0%, and 62.1% in the sex-matched and 93.6%, 86.2%, 72.6%, and 62.4% in the sex-mismatched groups. DcPGS at 1, 5, 10, and 15 years was 86.1%, 77.1%,

FIGURE 2 Patient survival (A), death-censored pancreas graft survival (dcPGS) (B), and death-censored kidney graft survival (dcKGS) (C) of sex-matched and sex-mismatched SPK transplantations performed from 1979 to 2017. No statistically significant difference was seen between the cohorts (log-rank *P* = .86, log-rank *P* = .26, and log-rank *P* = .24)
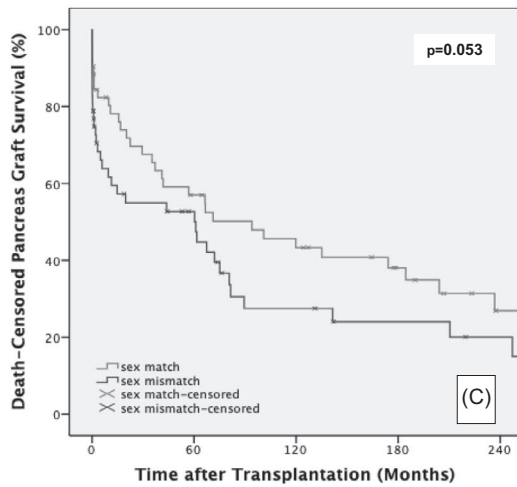

Number at risk	0	12	60	120	180	months
Sex Match	246	230	183	129	65	
Sex Mismatch	204	186	152	129	65	
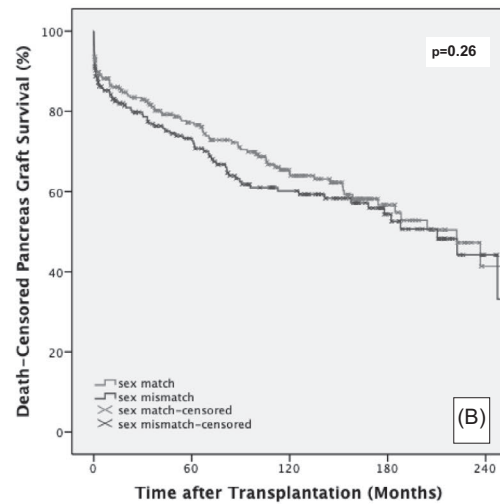
Number at risk	0	12	60	120	180	months
Sex Match	246	202	147	89	33	
Sex Mismatch	204	157	115	72	32	
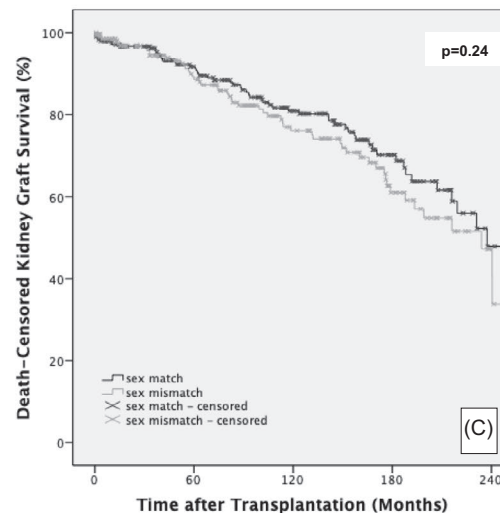
Number at risk	0	12	60	120	180	months
Sex Match	246	222	172	113	49	
Sex Mismatch	204	182	135	82	37	
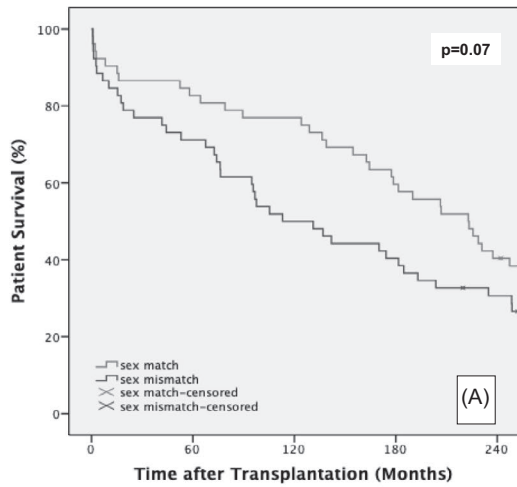
Number at risk

	0	12	60	120	180	months
Sex Match	51	46	43	40	31	
Sex Mismatch	51	44	37	26	21	
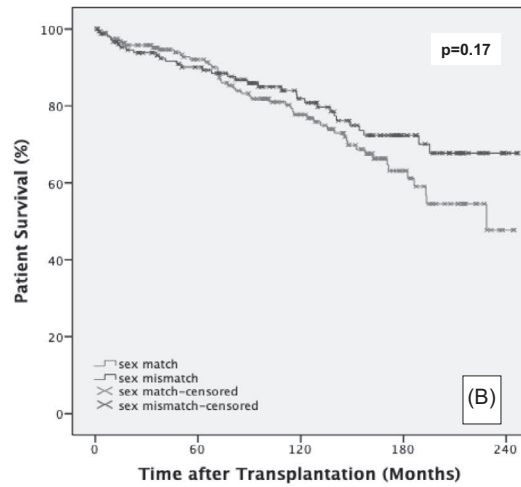
Number at risk

	0	12	60	120	180	months
Sex Match	194	183	140	89	34	
Sex Mismatch	152	142	115	77	37	

Number at risk

	0	12	60	120	180	months
Sex Match	51	37	26	19	12	
Sex Mismatch	51	27	20	9	6	
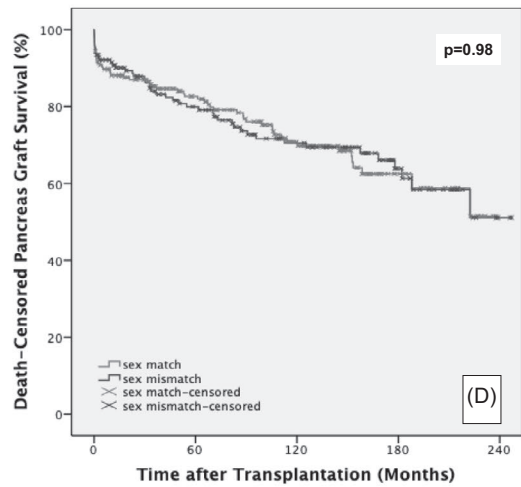
Number at risk

	0	12	60	120	180	months
Sex Match	194	165	121	70	21	
Sex Mismatch	152	130	95	63	26	
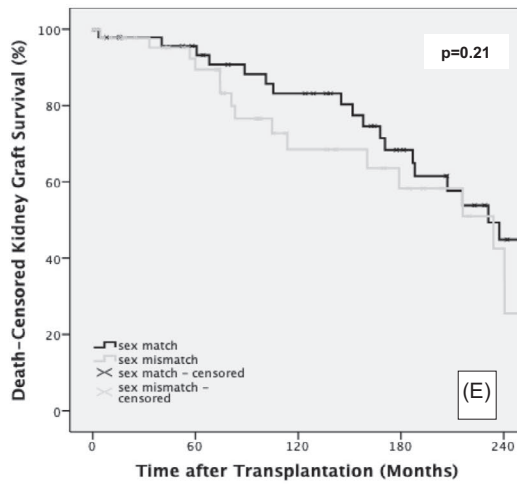
Number at risk

	0	12	60	120	180	months
Sex Match	51	45	40	33	21	
Sex Mismatch	51	42	32	16	11	
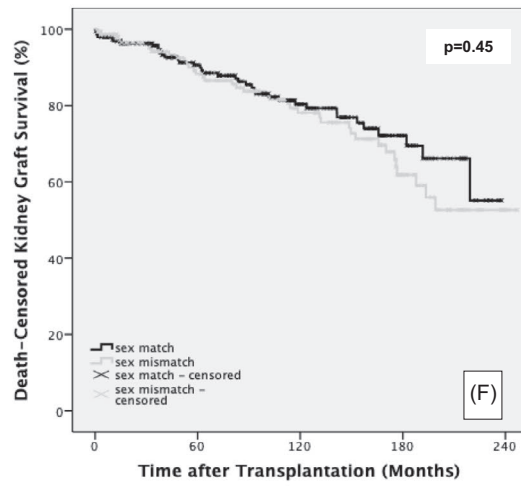
Number at risk

	0	12	60	120	180	months
Sex Match	194	180	132	80	28	
Sex Mismatch	153	140	104	66	26	

FIGURE 3 Patient survival, death-censored pancreas graft survival (dcPGS), and death-censored kidney graft survival (dcKGS) for sex-matched and sex-mismatched pancreas transplants from 1979 to 1996 (A, C, and D) and 1997 to 2017 (B, D, and E). In both eras, sex matching did neither influence patient survival (A, log-rank P = .07; B, log-rank P = .17), dcPGS (C, log-rank P = .053; D, log-rank P = .98), nor dcKGS (E, log-rank P = .21; F, log-rank P = .45)

64.7%, and 56.7% in the sex-matched group compared with 83.1%, 73.3%, 60.1%, and 54.3% in the sex-mismatched group with a mean-estimated pancreas graft survival of 17.6 years (95%CI 15.0-20.3) and 14.0 years (95%CI 12.2-15.8), respectively. Causes of pancreas graft loss were similar between sex-matched and sex-mismatched transplants. In both cohorts, grafts loss was most frequently due to rejection (24.3% vs 30.2%, P = .15) followed by patient death (19.0% vs 14.6%, P = .2) and graft thrombosis (6.5% vs 4.9%, P = .5) (Table 3). DcKGS was 97.1%, 81.7%, 81.0%, and 70.2% in the sex-matched and 98.5%, 88.6%, 76.15%, and 61.0% in the sex-mismatched group at 1, 5, 10, and 15 years after transplantation, respectively (Figure 2). Sex-matched grafts showed a similar risk of PGF to sex-mismatched grafts (HR 1.19, 95% CI 0.88-1.61, P = .26; Table 4). Factors with a significant impact on PGS in our single-center cohort were PDRI (HR 2.13, 95%CI 1.40-3.26, P < .01), donor age (HR 1.02, 95%CI 1.00-1.03, P = .04), donor height (HR 0.98, 95%CI 0.96-0.99, P = .01), Clavien-Dindo Grade ≥3b (HR 2.96, 95%CI 1.95-4.50, P < .01), year of transplantation (HR 0.952, 95%CI 0.93-0.97; P < .01), and transplantations performed before 1997 (HR 2.73, 95%CI 1.99-3.73; P < .01) (Table 4). When adjusting for PDRI, donor age, donor height, Clavien-Dindo Grade ≥ 3b, and year of transplantation on multivariable analysis, no significant difference in dcPGS was seen between sex-matched and sex-mismatched groups (aHR 0.78, 95%CI 0.51-1.18; P = .2; Table 5).

3.4 | Impact of donor and recipient sex match on secondary outcome parameters

Pancreas delayed graft function occurred in 53.9% of recipients of a gender-matched and in 57.0% of gender-mismatched transplant with 86.0% and 89.1% of patients being independent of insulin at hospital discharge. Mean length of hospital stay was 29.2 ± 15 and 30.9 ± 18.2 days in sex-matched and sex-mismatched groups,

respectively. Clavien-Dindo ≥3b complications occurred in 41.2% of sex-matched and 49.0% of sex-mismatched transplants. In 20.1% of sex-matched and 25.2% of sex-mismatched cases, immunologic problems were seen. Sex-matched recipients had 43% decreased odds of severe postoperative complications (OR, 0.57; 95%CI 0.33 to 0.97; P = .038) (Table 6); however, comparing individual postoperative complications including immunologic complications, pancreas graft rejection, abscess, graft pancreatitis, bleeding, relaparotomy, and intra-abdominal infection, only relaparotomy rates (27.5% vs 38.2%, P = .035) were significantly less frequent in sex-matched recipients (Table 7). Similar odds of PDGF (OR 0.74; 95% CI 0.45 to 1.21; P = .2), need for exogenous insulin at hospital discharge (OR 0.49; 95% CI 0.22 to 1.10; P = .08), immunologic complications (OR 0.65; 95% CI 0.36 to 1.18; P = .16), and length of hospital stay >25 days (OR 1.69; 95% CI 0.99 to 2.90; P = .055) compared with sex-mismatched recipients were observed (Table 6).

3.5 | Impact of donor and recipient sex match on patient survival and pancreas graft survival by era of transplantation

Of the entire cohort, 104 (23.0%) SPK transplants were performed before and 348 (77%) after 1997. In the earlier era, sex-matched pancreas transplants were associated with a trend toward better patient survival (Figure 3A, log-rank P = .07) as well as dcPGS (Figure 3C, log-rank P = .053) without reaching statistical significance; dcKGS was similar in both groups (Figure 3E, log-rank P = .2). One-, 5-, 10-, and 15-year patient survival for SPK transplants performed before 1997 were 90.4%, 82.7%, 76.9%, and 59.6% for sex-matched group and 84.6%, 71.2%, 50.0%, and 40.4% for sex-mismatched group with corresponding dcPGS of 78.1%, 67,6%, 43.3%, and 38.1% for sex-matched and 61.7%, 52.7%, 27.5%, and 24.1%. DcKGS at 1, 5, 10,

TABLE 3 Frequencies of causes of pancreas graft loss after simultaneous pancreas-kidney transplantation in sex-matched recipients compared to sex-mismatched recipients

Cause of pancreas graft loss	Overall n = 452			1979 - 1996 n = 104			1997 −2017 n = 348		
	Sex match (%)	Sex mismatch (%)	P	Sex match (%)	Sex mismatch (%)	P	Sex match (%)	Sex mismatch (%)	P
Thrombosis	6.5	4.9	0.5	9.6	11.5	0.8	5.6	2.6	.2
Rejection	24.3	30.2	0.15	48.1	55.8	0.4	17.9	21.6	.4
Infection	3.2	2.9	0.9	3.8	1.9	0.6	3.1	3.3	>.9
Hemorrhage	0.8	1.5	0.5	0	0	n.a.	1.0	2.0	.5
Patient death	19.0	14.6	0.2	28.8	25.0	0.7	16.4	11.1	.2
Other	0.8	0.5	0.7	1.9	1.9	>0.9	0.5	0.0	.4

TABLE 4 Unadjusted hazard ratios of donor, recipient, and perioperative factors for death-censored pancreas graft failure

Variable	HR (95% CI)	P
Sex Match	1.19 (0.88-1.61)	.3
Female recipient	0.94 (0.68-1.28)	.7
Female donor	0.81 (0.59-1.11)	.2
PDRI	2.13 (1.40-3.26)	<.01
Donor age, per year	1.02 (1.00-1.03)	.04
Donor BMI	0.96 (0.89-1.03)	.3
Donor height, per cm	0.98 (0.96-0.99)	.01
Recipient age, per year	0.99 (0.97-1.00)	.11
Recipient BMI	1.02 (0.96-1.09)	.6
Pancreas CIT, per hour	1.01 (0.96-1.06)	.8
Pancreas WIT, per minute	1.00 (0.98-1.02)	.8
PDGF	1.57 (0.98-2.50)	.06
Clavien-Dindo ≥ 3b	2.96 (1.95-4.50)	<.01
Year of Transplantation, per year	0.95 (0.93-0.97)	<.01
Transplant before 1997	2.73 (1.99-3.73)	<.01

Abbreviations: BMI, body mass index; CI, confidence interval; CIT, cold ischemic time; HR, hazard ratio; PDGF, pancreas delayed graft function; PDRI, pancreas donor risk index; WIT, warm ischemic time.

and 15 years were 97.9%, 95.6%, 83.2%, and 74.6% for sex-matched

TABLE 5 Multivariable Cox regression analysis for death-censored pancreas graft failure for 341 SPK recipients from 1979 to 2017

Variable	HR (95% CI)	P
Sex Match	0.78 (0.51-1.18)	.2
Donor age, per year	1.01 (0.98-1.06)	.4
PDRI	1.26 (0.42-3.72)	.7
Donor height, per cm	0.98 (0.95-0.99)	.02
Clavien-Dindo Grade ≥ 3b	3.18 (2.07-4.90)	<.01
Year of transplantation, per year	1.02 (0.98-1.07)	.3

Abbreviations: HR, hazard ratio; PDRI, pancreas donor risk index.

TABLE 6 Odds of postoperative complications after simultaneous pancreas and kidney transplantation in sex-matched recipients compared to sex-mismatched recipients (n = 306)

	OR (95% CI)	P
PDGF	0.74 (0.45-1.21)	.2
Independence of insulin at discharge	0.49 (0.22-1.10)	.08
Immunologic complication	0.65 (0.36-1.18)	.2
Clavien-Dindo ≥ 3b	0.57 (0.33-0.97)	.038
Length of hospital stay > 25 d	1.69 (0.99-2.90)	.055

Abbreviations: CI, confidence interval; OR, odds ratio; PDGF, pancreas delayed graft function.

TABLE 7 Comparison of occurrence of postoperative complications after simultaneous pancreas-kidney transplantation in sex-matched recipients compared to sex-mismatched recipients after 1997

Postoperative complications	Sex matched (%)	Sex mis-matched (%)	P
Immunologic complications	19.7	25.2	.2
Rejection pancreas graft			
Clinically suspected and treated	7.3	11.4	.6
Biopsy-proven rejection	5.8	3.4	
Abscess	8.8	11.9	.3
Graft pancreatitis	6.7	9.9	.3
Bleeding	16.6	22.5	.2
Relaparotomy	27.5	38.2	.035
Intra-abdominal infection	23.4	25.2	.7

and 97.8%, 89.4%, 68.5%, and 58.3% for sex-mismatched transplants. In transplantations after 1997, however, sex matching influenced neither patient survival (Figure 3B, log-rank P = .17), dcPGS (Figure 3D, log-rank P = .98), nor dcKGS (Figure 3F, log-rank P = .5). In this era, 1-, 5-, 10-, and 15-year patient survival in the sex-matched cohort was 97.4%, 92.0%, 77.7%, and 63.1% and 96.6%, 90.1%, 81.9%, and 74.9% in the sex-mismatched cohort. DcPGS for transplants performed after 1997 was 88.1%, 82.6%, 70.8%, and 62.5% in the sex-matched group and 90.8%, 79.9%, 70.5%, and 63.9% in the sex-mismatched group at 1, 5, 10, and 15 years after SPK transplantation, respectively. DcKGS was 96.9%, 90.6%, 80.4%, and 72.1% in the sex-matched cohort and 98.7%, 88.3%, 78.1%, and 61.9% in the sex-mismatched cohort at 1, 5, 10, and 15 years after transplantation.

3.6 | Impact of donor-recipient sex constellations on patient survival and graft survival and secondary outcome parameters

Patient survival as well as dcPGS was similar between the different donor-recipient sex combinations (Figure 4A, P = .37; Figure 4D, P = .34) with a mean-estimated patient survival of 18.6 years (M → M, 95%CI 16.5-20.7), 18.6 years (M → F, 95%CI 15.8-21.4), 19.5 years (F → M, 95%CI 16.4-22.6), and 21.7 years (F → F, 95%CI 17.8-25.7) and a mean-estimated dcPGS of 17.8 years (M → M, 95%CI 14.9-20.6), 13.7 years (M → F, 95%CI 11.4-16.0), 14.22 years (F → M, 95%CI 11.7-16.7), and 14.8 years (F → F, 95%CI 11.7-18.2). After splitting the cohort into transplants performed before and after 1997, no significant differences in patient survival or dcPGS were seen (Figure 4B,C, P = .13 and P = .51; Figure 4E,F, P = .37 and 0.37). DcKGS differed significantly between the four possible sex combinations (Figure 3C, P = .015). The M → M group displayed superior dcKGS with a mean-estimated survival of
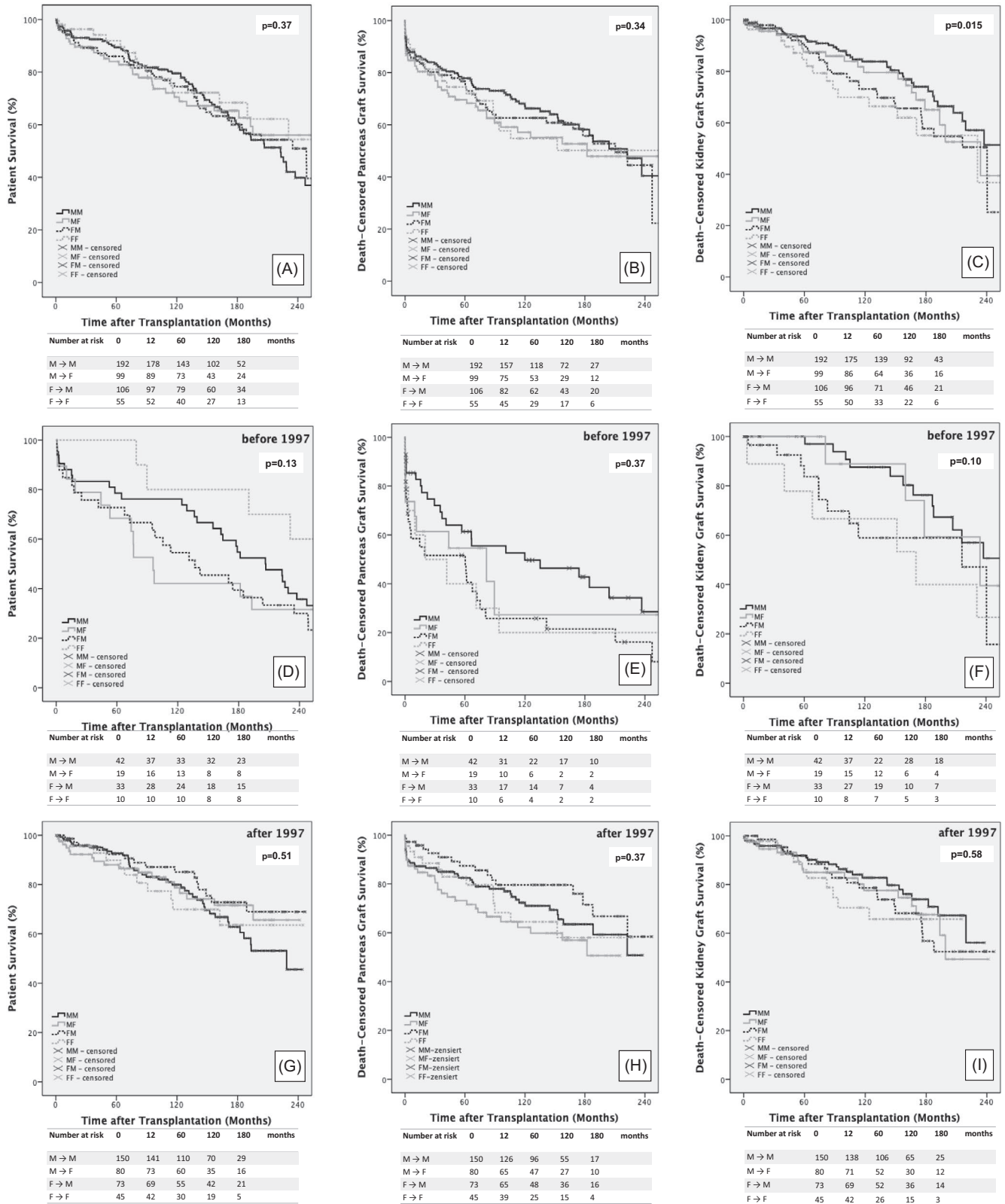
FIGURE 4 Patient survival, death-censored pancreas graft survival (dcPGS), and death-censored kidney graft survival (dcKGS) for donor-recipient combinations (M → M, M → F, F → M, and F → F) in pancreas transplants from 1979 to 2017 (A, B, and C), from 1970 to 1996 (D, E, and F), and from 1997 to 2017 (G, H, and I). Patient survival and dcPGS were similar in the cohort transplanted before (D, log-rank *P* = .13; E, log-rank *P* = .37) and after 1997 (G, log-rank *P* = .51; H, log-rank *P* = .37). From 1979-2017, significant differences were found in dcKGS (C, log-rank *P* = .015). However, after splitting the cohort in an era before (F, log-rank *P* = .1) and after 1997 (I, log-rank *P* = .58), dcKGS was similar between the four possible sex combinations

Postoperative complications	MM (%)	MF (%)	FM (%)	FF (%)	P
Immunologic complications	20.9	28.2	21.9	15.6	.4
Rejection pancreas graft					
Clinically suspected and treated	5.5	13.0	9.7	13.3	.9
Biopsy-proven rejection	6.8	3.9	2.8	2.2	
Abscess	10.1	11.5	12.3	4.4	.5
Graft pancreatitis	8.8	12.8	6.8	0	.09
Bleeding	15.5	21.8	23.3	20.0	.5
Relaparotomy	29.7	40.5	35.6	20.0	.051
Intra-abdominal infection	25.2	24.4	26.0	17.8	.8

TABLE 8 Comparison of occurrence of postoperative complications after simultaneous pancreas-kidney transplantation in different donor-recipient sex constellations after 1997

22.8 years (95%CI 20.1-25.4) compared with 16.4 years (95%CI 12.9-20.0) in the F → F group (P = .036). After splitting the cohort into groups transplanted before and after 1997, this difference was no longer observed (Figure 3B, P = .1; Figure 3D, P = .58). In addition, no differences were observed in frequency of postoperative complications, though a tendency was seen toward higher relaparotomy rates in M → F (40.5%) and F → M (35.6%) (Table 8; M → M 29.7%, F → F 20.0%; P = .051).

4 | DISCUSSION

The present study investigates the impact of donor-recipient sex matching on short- and long-term outcomes after pancreas transplantation in a high-volume single-center cohort. Our data show that sex matching does not influence patient survival, dcPGS, and dcKGS in our cohort even after adjustment for other significant donor- and recipient-related factors. Sex matching does reduce the risk of severe postoperative complications; however, after comparing the rates of different postoperative complications, only a higher incidence of re-laparotomy rates, 27.5% in sex-matched vs 38.2% in sex-mismatched transplants (P = .035), was observed. No influence was observed on other postoperative outcome parameters such as PDGF, insulin independency, length of hospital stay >25 days, and immunologic complications. After dividing the cohort in the four possible donor-recipient sex combinations (M → M, M → F, F → M, and F → F), similar patient survival and dcPGS were seen and only dcKGS showed a significant difference between the groups (log-rank P = .015); the M → M group displayed a significantly higher dcKGS than the F → F group. However, after further splitting this cohort into transplants before (log-rank P = .1) and after 1997 (log-rank P = 58), the difference in dcKGS was no longer seen. Though a trend toward higher relaparotomy rates in sex-mismatched recipients was seen (M → F 40.5%, F → M 35.6% vs M → M 29.7%, F → F 20.0%; P = .051), this did not reach statistical significance after further division in donor-recipient sex combinations. Other postoperative complications were similar between the four possible groups. Our data reveal that only donor age, donor height, postoperative complications, year

of transplantation, and transplants performed before 1997 have a statistically significant impact on dcPGS. Sex matching—though not statistically significant—seemed to influence patient survival, dcPGS, and dcKGS more in transplants performed before 1997.

As described previously by our center[29] and others,[31,32] transplants performed in earlier years show significantly inferior graft survival. Öllinger et al[29] described that pancreas transplants performed before 1997 displayed a significantly inferior graft survival when compared to transplants performed after 1997. Thus, we decided to use this same cutoff point for this analysis. This inferior outcome has largely been attributed to inferior surgical expertise/routine, lack of modern induction—only two out of 104 patients received ATG in this cohort—and immunosuppressive therapy (mostly cyclosporine A and azathioprine based) with subsequent higher rates of immunologic complications and acute rejections.[29,32]

Also, in sex-mismatched transplants, inferior outcomes and increased rates of graft rejection have been reported.[6,7,19,23,33,34] Along with hormonal and size-related factors, the H-Y antigens have been hypothesized to account for this observation. These are minor histocompatibility antigens encoded on the Y chromosome containing regions of high immunogenicity.[24,35] Their role has been highlighted in hematopoietic cell transplantation, where grafts from female donors to male recipients lead to an increased risk of graft-versus-host disease but a decrease in non-relapse mortality and, in some studies, a lower relapse rate.[23,36,37]

Unfortunately, the importance of sex mismatch in solid organ transplantation is less clear. H-Y antibodies have been investigated in kidney transplantation. Tan et al[7] tested serum samples from 118 consecutive kidney transplant recipients with kidney biopsies for the presence of H-Y antigens using ELISA and Western blot. Female recipients of male kidney grafts developed H-Y antibodies more frequently than all other combinations. The authors further confirm an association between the presence of H-Y antibodies and acute rejection with plasma cell infiltrates in biopsied kidneys. Some studies in kidney,[6,7,24,35] liver,[34,38] and heart transplantations[19,33] show this sex-related risk of rejection while others do not.[25,38-40] Our data do not support the theory of H-Y antibodies, as sex matching influences neither patient survival nor graft survival.

To date, few studies exist focusing on the impact of sex on the outcome after pancreas transplantation. Li et al examined the influence of donor-recipient sex mismatch on the long-term survival of pancreatic grafts in a large registry study (n = 24,195) using the Scientific Registry of Transplant Recipients (SRTR).[25] As described in our population, they found that recipient and donor sex individually had no impact on PGS. In contrast to our findings, however, they reported that sex-matched donor-recipient pancreas transplant pairings resulted in a significant reduction in PGF. In a single-center study (n = 163), Colling et al[26] compared pancreas graft survival between male and female pancreas transplant recipients. While overall PGS was similar between the two groups, early PGF was significantly higher in women than men. Schäffer et al (n = 218) reported that recipients of female donor organs developed more frequently and earlier episodes of acute rejection after SPK.[27] In addition, the male donor to female recipient pairing had the best long-term kidney and pancreatic graft function. Hilling et al[28] focused on the contribution of donor and recipient characteristics to outcomes after pancreas transplantation in a retrospective single-center analysis (n = 170); factors significantly influencing PGS were female recipient sex and enteric graft drainage as well as donor-recipient match on BMI.

There were several limitations to this study. First, we analyzed results over a period of thirty-eight years. Over time, surgical techniques, immunosuppressive protocols, organ acceptance and utilization criteria, and recipient selection have changed profoundly and outcomes are, as shown in our analysis, not similar across the study period. In addition, details about the postoperative hospital stay as well as some important donor and recipient factors including donor age, donor BMI, donor height, donor cause of death, and PDRI were missing for recipients prior to 1997. Therefore, these patients were not included in the multivariable models. Based on the split demographics, several confounding variables including donor age, donor height, donor cause of death, creatinine levels at discharge, and PDRI were identified which may have disadvantaged mismatched groups and potentially bias reported long-term outcomes. As well, though this study, to our knowledge, represents one of the largest single-center studies on this topic with the longest follow-up thus far, it might be underpowered to detect differences in outcomes between the two groups and especially in the stratified donor-recipient sex combinations.

In summary, our data show no influence of sex matching on early postoperative outcome, patient survival, dcPGS, or dcKGS in transplants performed either before or after 1997. Factors associated with PGF were a high PDRI, donor age and BMI, postoperative complications, year of transplantation, and transplants performed before 1997. Thus, it can be concluded that in the modern era with current techniques and immunosuppression, transplanting sex-mismatched organs is a safe practice that we should continue to perform to offset organ shortage.

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CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

FM participated in research design, data collection and statistical analysis, data interpretation, and writing of manuscript. JWE, RO, MM, BC, TS, SS, and SS performed data interpretation and critical revision of article. CEH, MR, and HH performed statistical analysis and critical revision of article. CB performed data collection/interpretation. RM and DÖ performed critical revision of article. CM participated in data interpretation, drafting article, and critical revision of article.

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