

## *A Comprehensive Case Series: Outcomes and Insights from the First Three Simultaneous Pancreas Kidney Transplants at Ramathibodi Hospital*

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**Abstract**

**Background:** Pancreas transplantation, particularly in the context of Type 1 diabetes mellitus (T1DM) with end-stage renal disease (ESRD), has emerged as a pivotal therapeutic intervention, substantially ameliorating both the clinical and quality-of-life outcomes for affected individuals. While previous research has underscored its efficacy in enhancing longevity, mitigating cardiovascular risks, and improving overall well-being, its widespread adoption, particularly the simultaneous pancreas-kidney transplantation (SPK) approach, remains constrained by various factors, notably donor availability and the requisite multidisciplinary care infrastructure.

**Methods:** This study presents the treatment outcomes of the initial three cases of SPK performed at Ramathibodi Hospital in Thailand. The operative techniques employed adhered to established protocols, including intraoperative porto-enteric drainage for endocrine function and enteric drainage for exocrine function. Noteworthy intraoperative considerations encompassed meticulous vascular reconstruction, heparinization protocols, and vigilant monitoring of hematological parameters to forestall potential complications.

**Results:** Each case presented unique clinical profiles and postoperative trajectories. Complications, such as postoperative hematoma and declining hematocrit levels, were managed judiciously, with successful resolution and favorable graft outcomes observed during subsequent follow-up periods. Importantly, all patients demonstrated prompt postoperative glycemic control and satisfactory renal function, obviating the need for further dialysis or medical intervention.

**Conclusion:** SPK emerges as a highly efficacious therapeutic avenue for individuals afflicted with T1DM and ESRD, offering tangible improvements in health outcomes and the prospect of restored quality of life. As evidenced by the outcomes of the initial cases presented herein, SPK holds promise as a viable treatment modality warranting further exploration and dissemination within the clinical landscape.

**Keywords:** Simultaneous pancreas-kidney transplantation, Type 1 diabetes mellitus, End-stage renal disease, Kidney transplantation

**INTRODUCTION**

In type I diabetes mellitus (T1DM), pancreas transplantation is the most effective treatment option for improving quality of life,<sup>1,2</sup> prolonging life,<sup>3</sup> and decreasing the risk of atherosclerotic disease and cardiovascular events,<sup>4,5</sup> cerebrovascular events, cardiovascular disease, and kidney disease. In the case of type I diabetes mellitus that turns into end-stage renal disease (ESRD), simultaneous pancreas-kidney transplantation (SPK) is still a treatment of choice to correct both T1DM and ESRD at the same time.<sup>3,6</sup> For the patient who underwent a simultaneous pancreas-kidney transplant in 2018-2019 in the USA, the one-year mortality rate remained low at 2.6%; the 5-year survival rate was 92.7%,<sup>7</sup> and the glycemic control and diabetes-related complications were significantly better after the transplantation.<sup>8-11</sup>

Anyway, in Thailand, the SPK is not a widespread operation that can be performed in many hospitals due to the lack of quality donors, the complexity of the operation, and post-operative care that requires multidisciplinary team care after the surgery.

In Ramathibodi Hospital, the first 3-cases of SPK was performed from 2022-2023. This report objects to presenting the treatment outcome of the first 3 cases in our hospital.

**OPERATIVE DETAILS****Bench Surgery**

After the kidney graft's dissection and vascular reconstruction were done, the kidney graft was then perfused with HTK solution until clear. For the pancreas, the dorsal end of SMA and splenic artery were side-to-end anastomosed using Prolene 8-0 and the ventral end of SMA was sutured with Prolene 6-0 continuously. The duodenal C-loop was flushed with 100 ml of Nystatin solution.

**Operation**

The operation was done by intraperitoneal approach with a midline incision. The kidney was first placed at the right iliac fossa after the ascending colon was mobilized along the white line of Toldt. The arterial inflow came from the external iliac artery, and venous outflow came via an external iliac vein. A urologist performed the ureteroneocystostomy using the Lich-Gregoir technique.

The pancreas was then placed intraabdominal at the root of the mesentery, the arterial inflow came from the donor's iliac vein graft that extended from an external iliac artery, and the pancreas's portal vein to the recipient's SMV was anastomosed with Prolene 6-0. The side-to-side jejunojejunostomy was performed with Maxon 3-0.

After the bleeding was carefully controlled and stopped, the Jackson-Pratt drain was placed just below the pancreas.

### Post-operative care

After surgery, the patient was admitted to the ICU. The patient's vital signs and fasting blood sugar were monitored hourly for the first 8-24 hours. Systemic heparinization and insulin were administered intravenously to keep PTT level 40-50 seconds and fasting blood sugar 100-150 mg/dl. The goal of urine output was 1.5-2 ml/

kg/hour. The patient's hematocrit test was done every 6 hours to monitor the bleeding complication.

After 24 hours post-operation, if the patient was extubated, vital signs and laboratory tests showed no active problem, the patient was moved to the inpatient unit. At the ward, blood tests were done daily, including CBC, serum creatinine, fasting blood sugar, serum amylase, and FK506 level. After five days of operation, intravenous heparin was off, and 75 mg of clopidogrel was started instead. The parameters are shown in Figures 1-4.

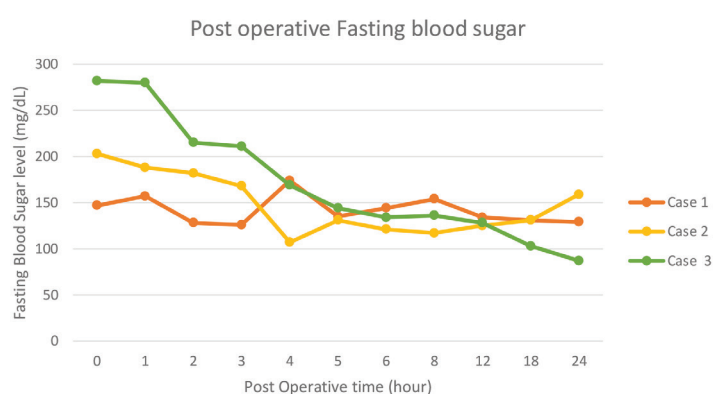


Figure 1

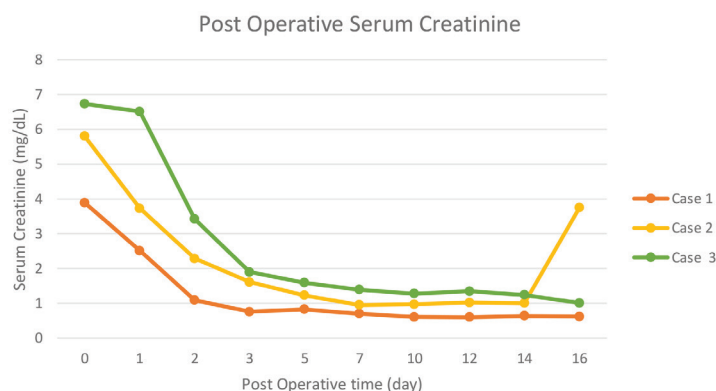


Figure 2

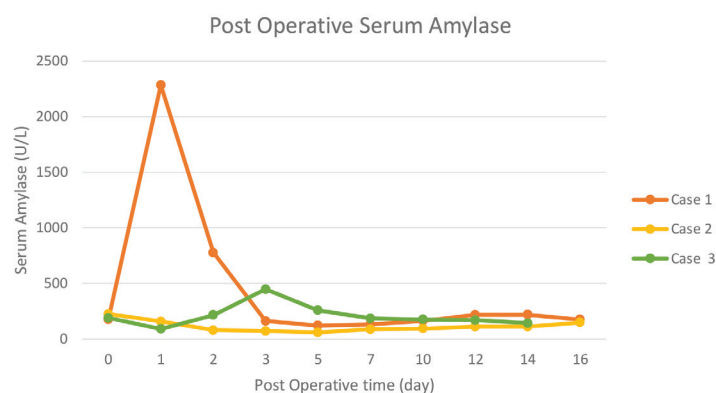


Figure 3

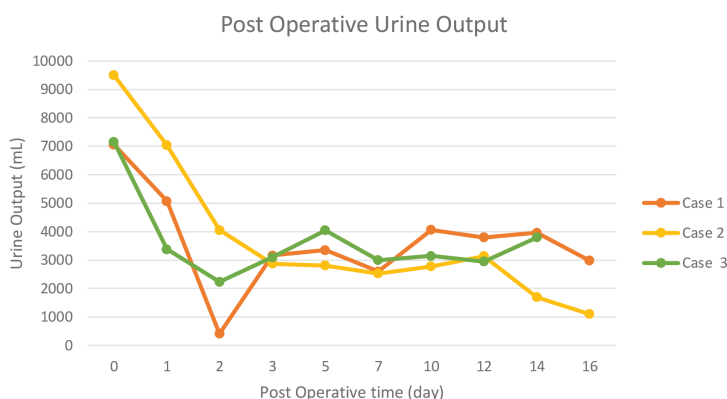


Figure 4

## CASE 1

### Recipient profile

A 36-year-old Thai female was diagnosed with T1DM at ten years of age and turned to ESRD at nine years before transplantation. She needed to be hemodialyzed three times/week via the left arteriovenous fistula at the left forearm and control her blood sugar by using 12 units of long-acting insulin (Lantus) once daily and four units of short active insulin (Novorapid) premeal subcutaneously. Her baseline HbA1C was 6.9. She also had diabetic retinopathy in both eyes, a history of right 5<sup>th</sup> toe amputation from an infected diabetic foot ulcer many years ago, which was healed at the time of the surgery, pulmonary tuberculosis, which was completely treated in 2015 with 1TRZE + 1IRZ + 7IR regimen. She was given 75mg of clopidogrel daily from her central vein stenosis. Her physical examination was unremarkable, with no old abdominal surgical scar. Her body weight was 45.9 kg, and her height was 156 cm.

### Donor profile

A 20-year-old Myanmar male with subarachnoid hemorrhage from head trauma. He didn't have a known underlying disease. His body weight was 55 kg, his height was 170 cm, and his BMI was 25.9 kg/m<sup>2</sup>. No history of cardiac arrest nor CPR was noted, and his blood pressure was controlled by inotropic drugs. His initial creatinine was 0.66 mg/dL, peak creatinine was 0.91 mg/dL, and terminal creatinine was 0.89 mg/dL; his urine output was 1,260 ml in the last 8 hours.

Both are blood group B and Rh positive. Their HLA mismatch was 4/6 (HLA-A 0/2, HLA-B 2/2, HLA-DR 2/2), and their panel reactive antibodies were 0%. The serum crossmatch showed negative T and B cells. The induction regimen was anti-thymocyte globulin (ATG), followed by a maintenance regimen of tacrolimus (Prograf), MMF (Cellcept), and prednisolone.

The kidney's cold ischemic time was 7 hours 35 minutes, and the kidney's relative warm ischemic time was 35 minutes. The pancreas's cold ischemic time was 9 hours 34 minutes, and the pancreas's relative warm ischemic time was 12 minutes. Intraoperative blood loss was 2,000 ml.

### Post-operative monitoring

In the first 24 hours, the patient had hypovolemic hypotension and required large-volume resuscitation and vasopressor. The urine output was 250-300 ml/hour in the first 24 hours.

Because of the raising of the serum amylase, to rule out vascular complication or collection, a CT scan of the whole abdomen was performed on postoperative day 9. The findings were: patent all vascular anastomosis, focal enlargement of pancreatic parenchyma, no collection, no active contrast extravasation.

After adjusting the immunosuppressive level, the patient was discharged on postoperative day 17 with a serum creatinine of 0.62 mg/dL, and none of the glycemic control medication was needed. At 1-year follow-up, serum creatinine was 0.82 mg/dL, and fasting blood glucose was 90 mg/dL.

## CASE 2

### Recipient profile

A 32-year-old Thai female was diagnosed with T1DM at 19 years of age and turned to ESRD three years prior to transplantation; she needed to be hemodialyzed two times/week and control her blood sugar by using eight units of insulin on non-hemodialysis days. Her baseline HbA1C was 6.46. Her physical examination was unremarkable, with no old abdominal surgical scar. Her body weight was 50.15 kg, and her height was 156 cm.

### Donor profile

A 33-year-old Thai male with subarachnoid hemorrhage and intraventricular hemorrhage from head trauma. He didn't have a known underlying disease. His body weight was 62 kg, his height was 155 cm, and his BMI was 25.8 kg/m<sup>2</sup>. No history of cardiac arrest nor CPR was noted, and his blood pressure was controlled by inotropic drugs. His initial creatinine was 0.66 mg/dL, peak creatinine was 0.91 mg/dL, and terminal creatinine was 0.89 mg/dL; his urine output was 940 ml in the last 8 hours, and no proteinuria.

Both are blood group O, Rh positive, their HLA mismatch was 4/6 (HLA-A 1/2, HLA-B 2/2, HLA-DR 1/2), panel reactive antibodies 0%, the serum cross matches showed negative both T and B cells, the induction regimen was anti-thymocyte globulin (ATG) and followed by maintenance regimen of tacrolimus (prograf), MMF (cellcept) and prednisolone.

The kidney's cold ischemic time was 6 hours 17 minutes, and the kidney's relative warm ischemic time was 23 minutes. The pancreas's cold ischemic time was 8 hours 21 minutes, and the pancreas's relative warm ischemic time was 21 minutes. Intraoperative blood loss was 1,500 ml.

### Post-operative monitoring

In the first 24 hours, the urine output was 250-300 ml/hour in the first 24 hours. Plasma glucose and PTT levels were closely monitored by adjusting the insulin and heparin levels, with the goal of FBS being 100-150 mg/dL and PTT 40-50 seconds.

After following up on the hemoglobin level at postoperative days 0-3, the hemoglobin level declined from 14.6 to 4.5 g/dL, without any hemodynamic instability nor shortage of urine noted. To rule out intraabdominal

hemorrhage/hematoma, the CT whole abdomen study was performed, with the finding of a 6-cm acute hematoma at the posterior aspect of the transplanted pancreas (Figure 5).

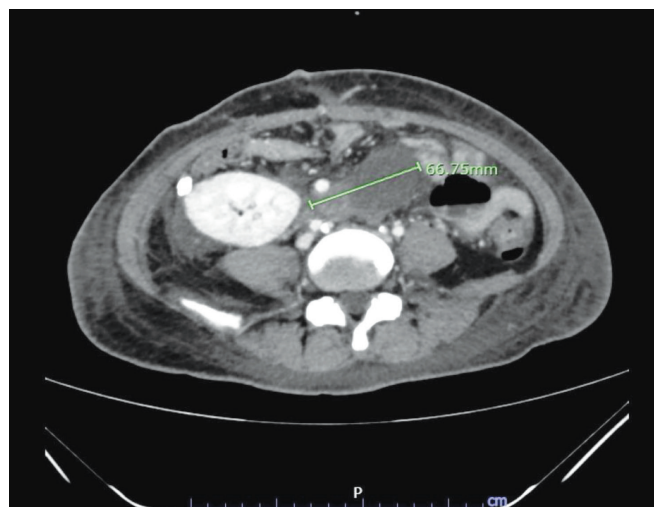


Figure 5 Hematoma at pancreas

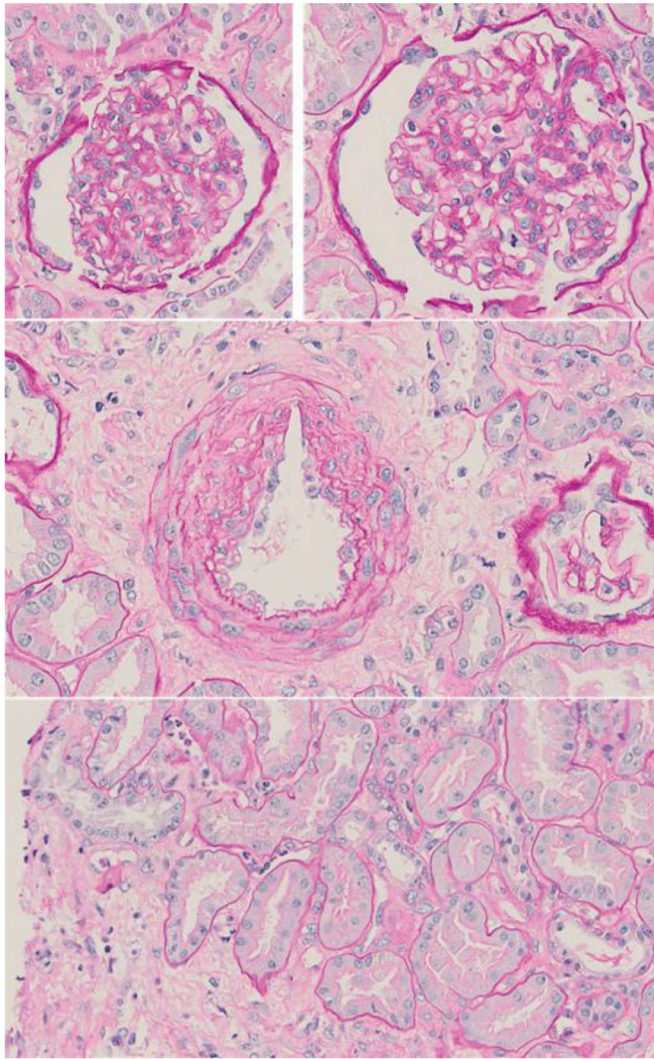
The patient underwent re-operation due to intraabdominal hematoma with suspected active intraabdominal bleeding. However, the intraoperative finding was only an old blood clot at the Cul de sac, with no active bleeding from vascular anastomosis or pancreas graft. After the reoperation, the hemoglobin has become stable.

On postoperative day 9, the serum creatinine rose from 2.9 to 4.7 and up to 5.6 on postoperative day 13. A kidney biopsy was performed to rule out graft rejection (Figure 6).

The pathological report was shown transplant glomerulitis with peritubular capillaritis. (Figure 6) Negative for C4d staining, no evidence of BKVAN (SV40 negative), Banff schema: i0, t0, g2, v1, ptc2, ci0, ct1, cv0, mm0, ah0, c4d0, ti0, i-IFTA0, t-IFTA0 and DSA was negative. Laboratory screening: HLA Ab screening negative, Lipase 429 U/L (23-300), Amylase 148 U/L (30-110), urine protein 3+, UPCR 2.48

This finding made the active antibody-mediated rejection suspicious. Methylprednisolone 500 mg daily, ATG 1.5 mg/kg/day for three days, IVIG 2 g/kg, and plasmapheresis once a couple of days were done for three sessions, and the serum creatinine and amylase were declined.





**Figure 6** Kidney biopsy

She was discharged at postoperative day 39 with a serum creatinine of 1.29 mg/dl, and non-glycemic control was needed.

After following up at eight months post-operative, the patient did well with a serum creatinine of 0.81 mg/dl, fasting plasma glucose of 78 mg/dl, HbA1C of 5.45%, and C-peptide of 2.32 ng/ml.

### CASE 3

#### *Recipient profile*

A 31-year-old Thai male was diagnosed with T1DM at 15 years of age and turned to ESRD at 2.5 years before transplantation; he needed to be hemodialyzed three times/week and control his blood sugar by using eight units of Lantus subcutaneously, and 8 unit of Novorapid

premeal. His baseline of HbA1C was 9.26. His physical examination was unremarkable, with no old abdominal surgical scar. His body weight was 69 kg, her height was 172 cm.

#### *Donor profile*

A 23-year-old Thai male with subdural hemorrhage from head trauma. He didn't have a known underlying disease. His body weight was 60 kg, his height was 180 cm, and his BMI was 18.51 kg/m<sup>2</sup>. No history of cardiac arrest nor CPR was noted, and his blood pressure was controlled by inotropic drugs. His initial creatinine was 0.5 mg/dl, peak creatinine was 0.8 mg/dL, and terminal creatinine was 0.8 mg/dl; his urine output was 1040 ml in the last 8 hours and no proteinuria.

Both are blood group O, Rh positive. Their HLA mismatch was 4/6 (HLA-A 1/2, HLA-B 2/2, HLA-DR 1/2), and their panel reactive antibodies were 0%. The serum cross-matches showed negative T and B cells. The induction regimen was anti-thymocyte globulin (ATG), followed by a maintenance regimen of tacrolimus (Prograf), MMF (Cellcept), and prednisolone.

The kidney's cold ischemic time was 4 hours 2 minutes, and the kidney's relative warm ischemic time was 28 minutes. The pancreas's cold ischemic time was 5 hours 28 minutes, and the pancreas's relative warm ischemic time was 20 minutes. Intraoperative blood loss was 700 ml.

#### *Post-operative monitoring*

In the first 24 hours, the urine output was 250-300ml/hour in the first 24 hours. Plasma glucose and PTT levels were closely monitored by adjusting the insulin and heparin levels, with the goal of FBS being 100-150mg/dl and PTT 40-50 seconds.

The patient's hematocrit dropped from 29.9% to 19.9% without hemodynamic change, no inotropic drug requirement, and no decrease in the urine output. Ultrasound bedside was performed, and it found that the vascular anastomosis of the transplant kidney and pancreas were intact with a good flow. So, conservative management with close monitoring was done. After a serial blood transfusion, the patient's hematocrit was stable at 24%. On postoperative day 5, after the drainage fluid test for pancreatic leakage was negative, the Jackson drain was pulled off.

On postoperative day 11, the patient developed a fever with a body temperature of 38-38.5 °C. the empirical antibiotic was prescribed. After the septic workup was done and negative for all tests. The patient's fever was resolved on 3rd day of antibiotics, and the course of antibiotics was seven days.

After the immunosuppressive drugs were carefully adjusted, the patient was discharged from the hospital with a length of stay of 22 days with serum creatinine of 1.17 mg/dl and fasting plasma glucose of 95-140 mg/dl without glycemic control.

At four months follow-up after the surgery, the patient was doing well with a serum creatinine of 1.15 mg/dl and fasting plasma glucose of 113 mg/dl.

### DISCUSSION

Following the first pancreas transplantation at the University of Minnesota in 1966,<sup>12</sup> the outcomes of this procedure underscored the efficacy of Simultaneous Pancreas Kidney Transplantation (SPK) as a preeminent therapeutic intervention capable of enhancing patients' quality of life while concurrently mitigating morbidity and mortality.<sup>1</sup> The evolution of the operative technique for SPK has transpired progressively, encompassing diverse approaches such as intra-/retro-peritoneal methodology, along with porto-enteric/systemic-enteric drainage for endocrine function and bladder/enteric drainage for exocrine function. Numerous studies have documented surgical complications, prominently featuring vascular graft thrombosis or bleeding as the most prevalent, in addition to intraabdominal infection, pancreatitis, and enteric anastomosis/duodenal stump leakage, along with small bowel obstruction.<sup>13,14</sup>

In all instances, our operative approach adhered to intraoperative Porto-enteric drainage for endocrine function and enteric drainage for exocrine function. Given the proclivity for vascular complications, encompassing both thrombosis and bleeding, a systematic heparinization protocol was implemented, accompanied by vigilant monitoring of Partial Thromboplastin Time (PTT) levels, drain output, and hematocrit levels.

In a singular case, a patient necessitated re-laparotomy due to a declining hematocrit level associated with a hematoma observed on a computed tomography (CT) scan despite elevated serum amylase and lipase levels. However, no pathological findings were discerned. Another case exhibited a postoperative hematoma and

diminished hematocrit levels, successfully managed through conservative measures.

All cases demonstrated the ability to transition off intravenous insulin within 24 hours postoperatively, with a concurrent urine output ranging between 250-300 ml/hour during the initial 24 hours. In the 6 to 12-month postoperative follow-up, all patients exhibited commendable graft function, obviating the need for hemodialysis or medical glycemic control.

Finally, pancreas transplantation is an effective treatment for patients with type 1 Diabetes Mellitus, particularly simultaneous pancreas-kidney transplantation, which improves patients' quality of life and reduces morbidity and mortality rates. However, in Thailand, the scarcity of suitable donors and the limited dissemination of surgical techniques pose challenges, restricting data collection for research and hindering the development of systems and surgical techniques to maximize patient benefits in the future.

### CONCLUSION

Simultaneous pancreas-kidney transplantation represents a highly effective treatment modality for individuals with Type 1 diabetes mellitus (DM) and end-stage renal disease (ESRD). This approach offers significant advantages in reducing cardiovascular risks and enhancing long-term quality of life, enabling patients to regain a semblance of normalcy.

### AUTHORSHIP CONTRIBUTION STATEMENT

N.K. participated in research design, the writing of the paper, data collection, critical revision, and approval of the final version of the article. R.K. participated in data collection and the writing of the paper. N.A. participated in writing the paper, as well as in interpretation and critical revision. G.G., B.S., S.K., C.N., S.W., J.B., and S.L. participated in the data collection and critical revision and approved the article

### ETHICAL APPROVAL

The Ramathibodi Hospital Institutional Review Board reviewed and approved this study (Approval No. MURA2024/247).

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

# ABBREVIATIONS

T1DM – Type 1 diabetes Mellitus

ESRD – End-stage renal disease

SPK – Simultaneous Pancreas Kidney Transplantation

HTK solution – Histidine-Tryptophan-Ketoglutarate solution

SMA – Superior Mesenteric artery

SMV – Superior Mesenteric vein

HLA – Human Leukocyte Antigen

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