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Ewaluacja protokołu i wyników przeszczepienia trzustki i trzustki z nerką w Klinice Chirurgii Ogólnej i Transplantacyjnej, Szpitala Klinicznego Dzieciątka Jezus UCK WUM.

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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Wykaz stosowanych skrótów:

BMI – z ang. *body mass index* – wskaźnik masy ciała

CF – z ang. *cystic fibrosis* - mukowiscydoza

CFLD – z ang. *cystic fibrosis liver disease* - Choroba wątroby związana z mukowiscydozą

CFTR – z ang. *cystic fibrosis transmembrane conductance regulator* - błonowy regulator przewodnictwa związany z mukowiscydozą

CIT – z ang. *cold ischemic time* - Czas zimnego niedokrwienia

CMV – z ang. *cytomegalovirus* - cytomegalowirus

CT – z ang. *computed tomography* – tomografia komputerowa

EPI – z ang. *exocrine pancreatic insufficiency* - niewydolność zewnątrzwydzielnicza trzustki

Ig – z ang. *immunoglobulin* - immunoglobulina

IVC – z ang. *inferior vena cava* – żyła główna dolna

NAFLD – z ang. *nonalcoholic fatty liver disease* - Niealkoholowa stłuszczeniowa choroba wątroby

OPTN – z ang. *Organ Procurement and Transplantation Network* - sieć pozyskiwania i przeszczepiania narządów

PAK – z ang. *pancreas after kidney (transplantation)* – przeszczepienie trzustki po nerce

PDRI - z ang. *pancreas donor risk index* - wskaźnik ryzyka dawcy trzustki

P-PASS – z ang. *pre-procurement pancreas allocation suitability score* – ocena użyteczności alokowanej trzustki przed przeszczepieniem

PTA – z ang. *pancreas transplantation alone* – przeszczepienie samej trzustki

SPK/SPKTx – z ang. *simultaneous pancreas and kidney transplantation* - jednoczasowe przeszczepienie trzustki i nerki

SPLTx – z ang. *simultaneous pancreas and liver transplantation* - jednoczasowe przeszczepienie trzustki i nerki

TyG index – z ang. *triglyceride-glucose index* - indeks trójglicerydowo-glukozowy

Streszczenie:

Przeszczepienie trzustki jest jedną z najbardziej złożonych procedur transplantacyjnych, stanowiąc wyzwanie chirurgiczne, internistyczne i organizacyjne. Wymaga starannej kwalifikacji biorców, precyzyjnego przygotowania dawców oraz sprawnej koordynacji pobrania i przeszczepienia narządów. Operacja wiąże się z dużym ryzykiem i wymaga od zespołu chirurgicznego najwyższych kompetencji. Mimo postępu w technikach chirurgicznych i leczeniu immunosupresyjnym, wyniki przeszczepień trzustki przez wiele lat pozostawały niezadowalające – zarówno w Polsce, jak i na świecie.

Celem rozprawy doktorskiej była ocena wyników przeszczepiania trzustki w Polsce, walidacja skal predykcyjnych P-PASS i PDRI w polskiej populacji dawców oraz analiza wpływu nowego protokołu postępowania wdrożonego w Klinice Chirurgii Ogólnej i Transplantacyjnej Szpitala Klinicznego Dzieciątka Jezus UCK WUM. Dodatkowo, badania obejmowały ocenę długoterminowych efektów przeszczepienia trzustki, w tym wpływu na ryzyko epizodów kardiologicznych.

Pierwszym etapem badań była retrospektywna analiza wszystkich przeszczepień trzustki wykonanych w Polsce w latach 1998–2015. W ramach projektu „Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study" zebrano największą w Polsce bazę danych dawców i biorców, obejmującą 407 przypadków. Analiza wykazała, że skale P-PASS i PDRI – szeroko stosowane w Eurotransplancie i OPTN – nie mają wystarczającej wartości predykcyjnej w polskiej populacji. Ich skuteczność w przewidywaniu wyników przeszczepień była zbliżona do losowej. Jednocześnie potwierdzono kluczowe znaczenie wieku i wskaźnika masy ciała (BMI) dawcy dla powodzenia przeszczepienia.

W drugiej publikacji, „Retrospective Analysis of Pancreas Transplants in Poland in Years 1998–2015", wykazano brak istotnej poprawy wyników przeszczepiania trzustki w Polsce przez niemal dwie dekady. Po roku od operacji mniej niż 70% przeszczepionych trzustek zachowywało prawidłową funkcję. Dalsza analiza pozwoliła określić optymalne grupy dawców i biorców – najlepsze wyniki uzyskiwano, gdy dawcy byli młodsi niż 30 lat i mieli BMI poniżej 25, a biorcy byli w wieku 21–30 lat.

Na podstawie wniosków z badań oraz doświadczeń zespołu Kliniki opracowano w 2016 roku nowy standard postępowania obejmujący selekcję biorców, technikę pobrania, opracowanie narządu i sposób leczenia pooperacyjnego. W efekcie wdrożenia tego protokołu uzyskano

znaczącą poprawę wyników – odsetek czynnych przeszczepów po roku wzrósł do 93%, co zbliża Klinikę do najlepszych ośrodków europejskich i światowych.

Trzecia publikacja – „Combined Liver-Pancreas Transplantation as Novel Treatment for Patient with Cystic Fibrosis: A Case Report" – opisuje pionierską w Polsce operację jednoczasowego przeszczepienia wątroby i trzustki u pacjentki z trzewną postacią mukowiscydozy. Przypadek ten potwierdził wysoki poziom organizacyjny i techniczny zespołu chirurgicznego.

Ostatnia część badań („Substantial Reduction of Cardiovascular Risk in Pancreatic Transplant Recipients") dotyczyła długoterminowej oceny korzyści metabolicznych po przeszczepieniu trzustki. Do walidacji ryzyka epizodów sercowo-naczyniowych wykorzystano wskaźnik TyG index (Triglyceride-Glucose Index), który jest uznanym markerem insulinooporności i predyktorem chorób układu krążenia. Wyniki wykazały istotną redukcję wartości TyG index już po 3 miesiącach od przeszczepienia, wynikającą ze spadku stężenia glukozy i trójglicerydów. Oznacza to znaczące zmniejszenie ryzyka epizodów kardiologicznych potwierdza długofalowe korzyści metaboliczne wynikające z przeszczepienia trzustki.

Podsumowując, przedstawiona praca dokumentuje rozwój i efekty pracy zespołu pod kierunkiem prof. Wojciecha Lisika w Klinice Chirurgii Ogólnej i Transplantacyjnej UCK WUM. Wdrożenie nowego protokołu przeszczepiania trzustki przyniosło znaczącą poprawę wyników klinicznych i potwierdziło skuteczność tej metody w leczeniu zaawansowanej cukrzycy typu I. Przeprowadzone analizy potwierdzają, że przeszczepienie trzustki nie tylko przywraca normoglikemię, ale również istotnie redukuje ryzyko sercowo-naczyniowe, stanowiąc skuteczną terapię przyczynową u odpowiednio dobranych pacjentów.

Streszczenie w języku angielskim:

Title: Evaluation of the protocol and outcomes of pancreas and simultaneous pancreas-kidney transplantation at the Department of General and Transplant Surgery, Infant Jesus Clinical Hospital, University Clinical Center of the Medical University of Warsaw.

Pancreas transplantation represents a major surgical, medical, and organizational challenge. It requires meticulous recipient selection, careful donor evaluation, and precise coordination of organ procurement and transplantation. The procedure is technically demanding, carries substantial perioperative risk, and calls for the highest level of surgical expertise. Despite advances in surgical techniques and immunosuppressive therapy, the outcomes of pancreas transplantation have long remained suboptimal both in Poland and internationally.

The aim of this doctoral dissertation was to evaluate pancreas transplantation outcomes in Poland, to validate the predictive donor-assessment scales P-PASS and PDRI in the Polish population, and to analyze the effects of a new procedural protocol implemented at the Department of General and Transplant Surgery, Infant Jesus Clinical Hospital, Medical University of Warsaw. Additionally, the research included long-term follow-up focused on the metabolic and cardiovascular benefits of pancreas transplantation.

The first stage of the study comprised a nationwide retrospective analysis of all pancreas transplants performed in Poland between 1998 and 2015. Within the project *"Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study"*, the largest national database of donors and recipients was created, encompassing 407 cases. The analysis demonstrated that both the P-PASS and PDRI scales—widely used within Eurotransplant and OPTN—showed limited predictive value under Polish conditions, with accuracy comparable to random selection. However, donor age and body mass index (BMI) were confirmed as key predictors of transplant outcomes.

The second publication, *"Retrospective Analysis of Pancreas Transplants in Poland in Years 1998–2015,"* revealed no significant improvement in long-term results over nearly two decades. One year after surgery, fewer than 70% of grafts retained satisfactory function. The analysis further identified optimal donor and recipient profiles—favorable outcomes were observed for donors younger than 30 years with a BMI below 25, and for recipients aged 21–30 years.

Based on these findings, and on the clinical experience of the surgical team, a new standardized protocol for donor selection, organ procurement, graft preparation, and postoperative management was implemented in 2016. This comprehensive approach resulted in a marked improvement in clinical outcomes: graft survival at one year increased to 93%, aligning the center's results with the best European and international standards.

The third study, *"Combined Liver-Pancreas Transplantation as Novel Treatment for a Patient with Cystic Fibrosis: A Case Report,"* documented a pioneering combined liver and pancreas transplantation in Poland, demonstrating the team's advanced technical and organizational capabilities.

The final investigation, *"Substantial Reduction of Cardiovascular Risk in Pancreatic Transplant Recipients,"* evaluated long-term metabolic and cardiovascular benefits following pancreas transplantation. Cardiovascular risk was assessed using the TyG index (Triglyceride-Glucose Index), a validated surrogate marker of insulin resistance and predictor of atherosclerotic and metabolic diseases. A significant reduction in TyG index values was observed as early as three months post-transplantation, driven by decreased serum glucose and triglyceride levels. These findings confirm the long-term cardiovascular benefits of successful pancreas transplantation beyond glycemic control and insulin independence.

In summary, this dissertation documents the progress and outcomes achieved by pancreas transplantation team led by Professor Wojciech Lisik in the Medical University of Warsaw. Implementation of a new, rigorously standardized protocol has led to a substantial improvement in graft survival and patient outcomes. The results confirm that pancreas transplantation not only restores normoglycemia but also significantly reduces long-term cardiovascular risk, representing an effective causal therapy for selected patients with advanced type 1 diabetes.

Wstęp:

Przeszczepienie trzustki stanowi wyzwanie chirurgiczne, internistyczne oraz organizacyjne. Wykonanie tej procedury wymaga dużego zaangażowania zespołów lekarskich na etapie selekcji i przygotowania kandydatów na długo zanim zostaną wpisani na Krajową Listę Oczekujących. Przygotowanie dawcy, wykonanie i weryfikacja niezbędnych badań oraz wykonanie próby krzyżowej i w końcu procedowanie pobrania narządów stanowi wyzwanie logistyczne oraz organizacyjne. Zwieńczeniem tego wysiłku jest operacja przeszczepienia trzustki – procedura wymagająca od chirurga wysokich umiejętności, cierpliwości oraz śródoperacyjnej elastyczności. Przebieg przeszczepienia narządu miąższowego jest znacznie bardziej skomplikowany niż najczęściej wykonywane operacje chirurgiczne. Są to dłuższe operacje, wykonywane u pacjentów z licznymi problemami towarzyszącymi wynikającymi z choroby zasadniczej (przede wszystkim cukrzycy typu I). Mierzenie się z takim wyzwaniem motywuje do zagłębienia się w najdrobniejsze szczegóły w poszukiwaniu najlepszego możliwego do osiągnięcia protokołu leczenia.

Tematem pracy doktorskiej jest próba podsumowania wyników przeszczepiania trzustki w Polsce oraz ewaluacja protokołu i wyników przeszczepiania trzustki zgodnie ze szczegółowym protokołem stosowanym w Klinice Chirurgii Ogólnej i Transplantacyjnej, Szpitala Klinicznego dzieciątka Jezus UCK WUM.

Autor rozprawy doktorskiej już w trakcie studiów lekarskich poświęcał swój czas i uwagę przeszczepieniom trzustki. Był obserwatorem i aktywnym uczestnikiem wielu takich operacji. Po rozpoczęciu szkolenia specjalizacyjnego w Klinice Chirurgii Ogólnej i Transplantacyjnej Warszawskiego Uniwersytetu Medycznego kontynuował swoje zainteresowanie i zaangażowanie w temacie przeszczepiania trzustek uczestnicząc we wszystkich opisanych etapach leczenia. W trakcie szkolenia specjalizacyjnego w Klinice Chirurgii Ogólnej i Transplantacyjnej oraz w trakcie zbierania materiałów do rozprawy doktorskiej autor przeszedł drogę od obserwatora do autora pobrań wielonarządowych i autora przeszczepień trzustek. Rozprawa doktorska jest zatem podsumowaniem pracy zespołu transplantacji trzustki Pana Profesora Wojciecha Lisika – promotora rozprawy, ale również pracy własnej autora.

Wielokrotnie udowodniono, że przeszczepienie trzustki od samego początku przysparzało wielu problemów i w dalszym ciągu stanowi duże wyzwanie transplantologiczne. Leczenie immunosupresyjne biorcy, sama metoda chirurgiczna i skrupulatność poszczególnych etapów procedury zmieniały się, stopniowo przyczyniając się do poprawy wyników przeszczepiania

trzustki na Świecie. W latach 80', 90' XX wieku i pierwszej dekadzie XXI wieku wyniki przeszczepiania trzustki z nerką były stosunkowo niezadowalające, ale stopniowo poprawiały się dając znaczny odsetek dobrze funkcjonujących narządów. W tym samym okresie przeszczepienie samej trzustki było rzadsze, ale i obarczone bardzo dużym odsetkiem niepowodzenia, inaczej niż w przypadku przeszczepienie jednoczasowego trzustki z nerką. W Polsce do roku 2015, jak wykazała analiza wieloośrodkowa, wyniki przeszczepienia trzustki w każdym schemacie pozwalały na oczekiwanie dobrej czynności narządu u mniej niż ok 65% biorców po roku od przeszczepienia.

Ażeby poprawić wyniki, przede wszystkim należało zidentyfikować problem. Narzędziem do tego była analiza restrospektywna wszystkich przeszczepień trzustki oraz jednoczasowo trzustki z nerką wykonanych w Polsce, dla których możliwe było uzyskanie dokumentacji medycznej. Na potrzeby pracy naukowej zatytułowanej: „Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study", zebrano największą w Polsce zbiorczą bazę danych zawierającą informację na temat dawców, biorców oraz przeszczepionych narządów. Baza danych znacznie wykraczała poza zakres danych będących w posiadaniu agendy rządowej do spraw transplantacji - Poltransplantu.

Celem tej pracy i pierwszym elementem analizy retrospektywnej było porównanie dwóch skal służących do określenia jakości dawcy na potrzeby pobrania i przeszczepienia trzustki. W Polsce i w większości krajów Europy do oceny trzustki pobieranej od dawcy używa się opracowanej w ramach Eurotransplantu skali P-PASS (Pre-Procurement Pancreas Allocation Suitability Score). Drugą skalą jest opracowana w USA, na podstawie danych z UNOS, skala PDRI (Pancreas Donor Risk Index). Obie te skale od wielu lat uznawane są za wiarygodne i dobrze spełniające swoje zadanie na etapie organizacji szczegółów pobrania narządów. W zależności od lokalizacji Poltransplant w Polsce, Eurotransplant w takich krajach jak Belgia, Holandia czy Niemcy oraz OPTN (Organ Procurement and Transplantation Network) w Stanach Zjednoczonych opierają koordynację pobrania trzustki na tych dwóch skalach. Mimo to, w literaturze przedmiotu znaleźć można badania podważające wiarygodność tych narzędzi. W Polsce nie przeprowadzono wcześniej takiego badania, mimo wdrożenia skali P-PASS do użycia.

Drugi manuskrypt zatytułowany: „Retrospective Analysis of Pancreas Transplants in Poland in Years 1998-2015" przygotowany na podstawie danych zebranych w archiwach wszystkich oddziałów zajmujących się przeszczepianiem trzustek oraz pracujących przy nich poradniach

transplantacyjnych to retrospektywna analiza wyników przeszczepień trzustki w Polsce w latach 1998-2015 r. Zebrane dane na temat dawców, operacji przeszczepienia, biorców, czasu dobrej czynności przeszczepionych narządów oraz długości życia biorców były podstawą do głębokiej i szeroko zakrojonej analizy.

Na podstawie uzyskanych danych oceniono czas życia biorców po przeszczepieniu trzustki lub po jednoczasowym przeszczepieniu trzustki z nerką. Określono również czas dobrej funkcji trzustki przeszczepionej. Za moment utraty czynności trzustki przeszczepionej przyjęto moment powrotu do stosowania insuliny egzogennej lub moment usunięcia trzustki przeszczepionej z powodu powikłań. Obliczone wyniki podzielono na 2 przedziały czasu zgodnie z analogicznym podziałem zaproponowanym w Biuletynie Poltransplantu. Wyniki przeżycia biorców trzustki i czas dobrej czynności trzustki przeszczepionej porównano odpowiednio dla obu tych przedziałów czasowych tj. od stycznia 1998 roku do grudnia 2006 roku oraz od stycznia 2007 roku do listopada 2015 roku. W kolejnych etapach wykonano szczegółową analizę statystyczną danych dawców trzustek przeszczepionych, następnie wykonano korelację czasu dobrej czynności trzustki przeszczepionej w zależności od wieku dawcy, wskaźnika BMI dawcy oraz wieku biorcy. W trakcie analizy statystycznej zebranych danych wykazano istotny wpływ tych parametrów na wynik przeszczepienia trzustki. Z tego powodu podjęto próbę identyfikacji optymalnych dawców i preferowanych grup biorców w zależności od tych parametrów.

Wnioski z tych dwóch prac oraz obserwacje własne członków zespołu chirurgicznego były przyczyną i sugestią do poszukiwania skutecznej metody poprawy wyników przyczynowej metody leczenia cukrzycy typu I oraz jej postępujących powikłań.

Zespół chirurgów kierowany przez Pana Profesora Wojciecha Lisika opracował i wdrożył od 2016 roku nowy standard selekcji biorców, wykonywania pobrań, opracowania trzustek na stoliku bocznym, techniki wykonywania przeszczepienia oraz schematu leczenia biorców przeszczepienia trzustki. Liczne małe zmiany, precyzja i powtarzalność każdego elementu tego procesu oraz olbrzymie zaangażowanie członków zespołu zajmującego się przeszczepieniami trzustek skutkował znaczącą i szybką poprawą osiąganych wyników. Od stycznia 2016 roku do końca września 2025 roku wykonaliśmy 90 przeszczepień trzustki (samej trzustki lub jednoczasowo z przeszczepieniem nerki). W grupie biorców trzustki, aż 93% zachowało dobrą czynność narządu przeszczepionego po roku od przeszczepienia. W stosunku do wcześniej rejestrowanych wyników, tj. poniżej 70% rocznego przeżycia narządów, świadczy to o olbrzymim postępie. Opisane wyniki pozwalają równać się z najlepszymi ośrodkami w Europie

i na Świecie względem jakości wykonywanych przeszczepień. Ponadto, takie rezultaty pozwalają proponować kolejnym pacjentom skuteczną terapię leczenia cukrzycy typu I jakim jest przeszczepienie trzustki.

Kolejnym etapem rozwoju możliwości terapeutycznych było zakwalifikowanie do pionierskiej operacji jednoczasowego przeszczepienia wątroby i trzustki pacjentki z trzewną postacią mukowiscydozy. To medyczne wyzwanie, którego warunkiem była wysoka sprawność i przygotowanie zespołu chirurgicznego pozwoliło młodej pacjentce zyskać nową perspektywę na życie. A dla zespołu chirurgów Kliniki Chirurgii Ogólnej i Transplantacyjnej było świadectwem wysokich umiejętności i kunsztu. Z uwagi na unikalny charakter tej procedury zdecydowano się opisać i z sukcesem opublikować manuskrypt traktujący o tym przypadku, sposobie wykonania procedury przeszczepienia i wczesnych wyzwaniach w okresie po przeszczepieniu. Z tego samego powodu autor zdecydował się dołączyć do rozprawy doktorskiej artykuł zatytułowany: „Combined Liver-Pancreas Transplantation as Novel Treatment for Patient With Cystic Fibrosis: A Case Report".

Pojedyncze, wyjątkowe przypadki medyczne nie stanowią o skuteczności terapii względem szerszej populacji pacjentów. Dlatego w Klinice Chirurgii Ogólnej i Transplantacyjnej Szpitala Klinicznego Dzieciątka Jezus przeprowadzono badanie oceniające wpływ przeszczepienia trzustki na zmianę ryzyka wystąpienia epizodów kardiologicznych – „Substantial reduction of cardiovascular risk in pancreatic transplant recipients". Do walidacji ryzyka posłużono się uznanym w środowisku kardiologicznym wskaźnikiem TyG idnex (wyliczanym na podstawie stężenia glukozy i trójglicerydów w surowicy krwi). TyG index jest parametrem pierwotnie zwalidowanym do oceny insulinooporności oraz ryzyka rozwinięcia zespołu metabolicznego u pacjenta. W kolejnych badaniach określono, że TyG index jest również predyktorem wystąpienia choroby niedokrwiennej serca i niealkoholowego stłuszczenia wątroby (NAFLD). Założeniem badania było wykorzystanie potwierdzonej, pozytywnej korelacji TyG index do oceny ryzyka epizodów kardiologicznych przed przeszczepieniem oraz w różnych punktach czasowych po przeszczepieniu trzustki. Fakt utrzymywania się długookresowej niezależności od insuliny egzogennej tj. dobrej czynności trzustki przeszczepionej jest często niewystarczający by przekonać sceptyków do tej formy leczenia ciężkich form cukrzycy. Założeniem badania było wykorzystanie uznanego przez środowisko medyczne parametru do wykazania wieloletniej korzyści wynikającej z wykonania przeszczepienia trzustki i dobrej czynności trzustki przeszczepionej. Badanie to miało za zadanie zweryfikować również

skuteczność protokołu przeszczepienia trzustki wdrożonego w Klinice Chirurgii Ogólnej i Transplantacyjnej.

Celem prezentowanej pracy jest:

1. Walidacja skali P-PASS i PDRI służących do określania jakości dawców na potrzeby pobrania trzustki w populacji ;
2. Retrospektywna analiza wyników przeszczepienia trzustki oraz znalezienie optymalnych grup dawców i biorców
3. Prezentacja trudnego przypadku, dla którego przeszczepienie trzustki okazało się być skuteczną terapią
4. Prezentacja wyników przeszczepiania trzustki według aktualnego protokołu
5. Określenie korzyści w perspektywie wieloletniej obserwacji dla grupy pacjentów po przeszczepieniu trzustki.

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1.

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Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study

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Statistical Analysis C
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Background: Pre-procurement pancreas suitability score (P-PASS) and pancreas donor risk (PDRI) index are scoring systems believed to predict suitability of pancreatic grafts. Most European countries and the United States apply PDRI, while Poltransplant keeps using P-PASS: more than 16 points raises a red flag for graft use. Recent data discourage use of PDRI to predict pancreas graft survival. The aim of the present study was to assess PDRI and P-PASS as predictors of transplanted pancreas survival in a Polish population.

Material/Methods: From February 1998 to September 2015, 407 pancreas transplantations were performed in Poland: 370 (90.9%) simultaneous pancreas-kidney transplantation and 37 (9.1%) pancreas transplantation alone or pancreas after kidney. The endpoint was death-uncensored 12-month graft survival with satisfactory glycemic control without insulin.

Results: Average P-PASS was 15.9±2.66 and PDRI was 0.96±0.37. Recipients who survived 12 months with good graft function had an average P-PASS score of 15.7 and PDRI of 0.95. Recipients with death-uncensored graft loss had a mean P-PASS of 16.4 and PDRI of 0.99. Univariate analysis revealed donor age, body mass index (BMI), and P-PASS to be significant risk factors for 1-year pancreas graft survival.

Conclusions: P-PASS, but not PDRI, is a reliable tool to predict pancreas graft survival in the Polish population.

MeSH Keywords: Donor Selection • Pancreas Transplantation • Tissue and Organ Procurement

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Background

Transplantation of suboptimal pancreatic grafts often result in severe transplant pancreatitis and thrombosis, which are life-threatening complications that affect both graft and recipient survival. Hence, reliable assessment of a donor and quality of the harvested pancreas is of utmost importance. Histopathology of the graft seems an obvious solution, but steatosis and fibrosis do not correlate with donor age or BMI. Fibrosis is frequent in donors <40 years old [1]. Measurement of tissue adenosine triphosphate metabolites with magnetic resonance spectroscopy prior to transplantation is reliable but too cumbersome to be applied in clinical practice [2]. Recently, measurement of donor hemoglobin A1c levels has been used as a prognostic factor of pancreatic graft survival, but it was not added to the standard criteria [3].

To minimize the risk of complications, in 2008, Eurotransplant introduced use of the pre-procurement pancreas allocation suitability score (P-PASS) as a reliable indicator of graft quality. The model was constructed from donor age and BMI, length of ICU stay, duration of cardiac arrest, serum sodium and amylase concentrations, and catecholamine requirement. P-PASS scores over 16 are considered high risk [4]. However, subsequent studies showed an increased early complication rate but no difference in graft survival with higher P-PASS [5,6]. To overcome the problem of subjective criteria of pancreas donor assessment, in 2010 UNOS introduced a pancreas donor risk index (PDRI), calculated from a huge database of 9400 transplants [7]. The index was constructed from donor sex, age, BMI, cause of death, serum creatinine, donation after cardiac death status, and cold ischemia time. A Dutch study validated both indices in a population of 350 pancreas transplant recipients. P-PASS had no predictive value, while a PDRI over 1.24 was associated with reduced graft survival both in univariate and multivariate analysis [8]. A large UK retrospective analysis showed PDRI to be a relevant predictor for simultaneous pancreas-kidney transplantation (SPKTx) but not for pancreas transplantation alone (PTA) or pancreas after kidney (PAK) transplantation modality [9]. However, a Brazilian study [10] and a Spanish study [11] failed to confirm the usefulness of PDRI. This raises the question of reliability and repeatability of these results in other populations. To validate both indices for the Polish population, we analyzed available data of pancreata transplanted in all 4 centers across the country since 1998.

Material and Methods

Although the first successful simultaneous pancreas-kidney transplantation (SPKTx) in Poland was performed in 1988, systematic accumulation of deceased donor data allowing calculation of PDRI and P-PASS in a national registry of Poltransplant was started in 1998. By the end of 2015, 407 utilized pancreas donors have been recorded: 370 SPKTx and 37 pancreas transplant alone (PTA) or pancreas after kidney (PAK) transplants. All data from the registry were retrieved and missing data, whenever available, were sought in one of 4 active pancreas transplant centers. Donor data are shown in Table 1.

Table 1. Deceased donor characteristics of utilized pancreas grafts.

	Mean ±SD (or%)	Data completeness
Age (years)	29.2±9.6	100.0%
BMI (kg/m²)	24.1±3.2	99.3%
Male sex (%)	68.8	100.0%
CVA as cause of death (%)	34.7	100.0%
ICU stay (days)	4.6±3.7	99.3%
Donor cardiac arrest* (%)	15.5	100.0%
Dopamine dose (ug/kg/min)	2.8±3.4	72.0%
Norepinephrine dose (ug/kg/min)	0.02±0.03	72.0%
Serum creatinine (mg/dL)	1.11±0.65	99.5%
Serum sodium (mmol/L)	151.9±13.9	100.0%
Serum amylase (IU/L)	159±156	91.6%
Cold ischemia time (hours)	9.43±0.11	78.6%
P-PASS	15.9±2.6	87.2%
PDRI	0.957±0.376	78.1%

* Cardiac arrest prior to or during intensive care, donation after cardiac definition of death was never a source of pancreas graft.

P-PASS and PDRI were calculated according to original formulas described by Vinkers [4] and Axelrod [7]. Both indices were calculated for 294 donors. Follow-up data were not available for 1 patient. Twelve-month pancreas graft survival was defined as recipient and graft survival with fasting C peptide levels exceeding 0.5 ng/ml and satisfactory glycemia control without regular insulin administration.

Statistical analysis

Patient and graft survival were calculated according to Kaplan-Meier method (Statistica 12). To identify risk factors for pancreas graft loss within 12 months after transplantation, Cox regression analysis was performed and hazard ratios were calculated. Nonlinear regression models were constructed, probability of 12-month survival was calculated, and receiver operating characteristic (ROC) curves were drawn.

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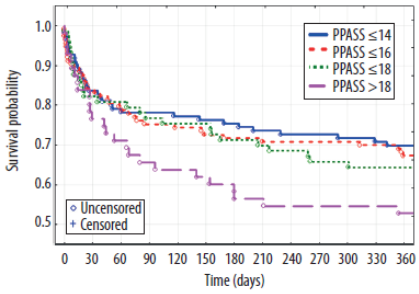

Figure 1. Twelve-month pancreas graft survival according to P-PASS quartile.

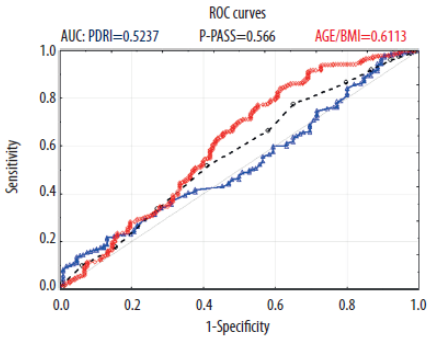

Figure 2. ROC curves and C-statistic of 3 models of prediction of 12-month death-uncensored pancreas graft survival.

Results

Death-uncensored pancreas graft survival was 66%, 55.6% and 44.4%, at 1, 5, and 10 years, respectively. The lowest 12-month graft survival (54%) was observed in the PAK/PTA group. During the first month, 16.9% of pancreatic grafts are lost due to early complications, including early patient mortality (2.5%). Pancreas transplants that survived over 12 months came from younger donors (27.7 *vs.* 32 years, p<0.001), with lower BMI (23.8 *vs.* 24.5 kg/m^2, p<0.04) and with lower P-PASS (15.7 *vs.* 16.4 points, p<0.03). PDRI was also lower in this group (0.944 *vs.* 0.992 points), but the difference was not significant (p=0.3). Cox hazard ratios were 1.039 (CI: 1.022–1.056) for donor age, 1.057 (CI: 1.005–1.111) for donor BMI, and 1.082 (CI: 1.015–1.154) for P-PASS. The confidence interval for PDRI hazard ratio was 0.798–2.158, and thus was not reliable as a prognostic factor of pancreatic graft survival. Pancreas 1-year graft survival according to P-PASS group is shown in Figure 1. Neither of the other donor-dependent factors succeeded in differentiating between surviving and non-surviving grafts.

When logistic regression models were used to calculate survival probability and ROC curves were drawn, the area under the curve (AUC) was 0.566 when P-PASS was used in estimation and 0.524 when PDRI was used. However, a simple model constructed from donor age and BMI resulted in an AUC of 0.611. Probability of death-uncensored 12-month graft survival could be calculated with Z=2.6302–0.0449×[DONOR AGE] – 0.0292×[DONOR BMI]. Graft survival estimation ROC curves of P-PASS, donor age/BMI, and PDRI prediction models are shown in Figure 2.

Discussion

Studies appraising PDRI admit its C-statistic hardly exceeds 0.5, and thus is useless in predicting graft function. It should be noted that donor age and BMI are redundant in the original PDRI equation [7], and BMI coefficient has a negative value while BMI ≥25 kg/m^2 coefficient is positive, which is inconsistent. In our study, the ROC AUC for PDRI was insignificant and almost equal to 0.5. A study by Amaral et al. did not confirm correlation of PDRI with pancreas graft survival, but the quality of the study was questionable because the percentage of incomplete records that were excluded from analysis was 73% [10]. Our data is far more complete, with nearly 100% of 1-year follow-up and 27.8% of missing records. An earlier study from the Amaral group identified independent risk factors for pancreatic graft loss: recipient BMI, induction therapy, donor age, iliac venous drainage, and transplantation of the pancreas as the first graft. A risk stratification model was constructed and ROC curves were calculated, yet the model included few donor-dependent and non-modifiable variables; therefore, its applicability was limited [12]. We did not analyze recipient-dependent factors and tailored our study to allow deciding whether to accept a potential pancreas donor. A study by Blok showed PDRI over 1.24 to be a significant risk factor for graft loss [8]. We had only 74 cases of transplantation with such high PDRIs, but 12-month survival in this group was 67.6% (not significantly different from the low-PDRI group). Although PAK and PTA transplants were not analyzed separately, PDRI index in our study proved unreliable. Instead, we confirmed the usefulness of P-PASS in predicting graft survival; when interquartile differences were analyzed, a P-PASS over 18 points predicted significantly inferior outcomes. This substantially extends the previous limit of 16 points [4]. The most efficient model of prediction we built consisted of only 2 variables – donor age and BMI – and its ROC AUC was superior to P-PASS and PDRI. Although P-PASS and donor age/BMI models proved significant, C-statistics of 0.566 and 0.611 are not impressive and only slightly superior to a 50%/50% chance. Their clinical applicability should be very limited. In our national study, grafts from the worst prognosis quartiles still have

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over 50% chance of surviving beyond 1 year. Hence, the field of pancreases suitable for transplantation is most likely bigger than we use today, although caution and reasonable clinical judgement in accepting grafts at risk is needed.

Conclusions

Recipient- and surgeon-dependent factors were not analyzed in our study. Of course, quality of the recipient contributes to pancreatic graft survival. However, there are no risk prediction systems that specifically address this issue. Some general surgery risk prediction models can be applied with variable effectiveness [13].

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2.

Retrospective Analysis of Pancreas Transplants in Poland in Years 1998-2015

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ABSTRACT

Transplantation of the pancreas is an established method for the treatment of complicated diabetes mellitus. As the numbers of diabetic patients increase so does the need for efficient treatment methods. Despite significant perioperative risk and complications related to immunosuppression, pancreas transplant remains the best therapeutic option for selected patients.

Methods. The analysis was based on the comparison of characteristics of all organ donors and recipients in years 1998 to 2015. The collected data were divided into 2 periods to facilitate identification of populational changes.

Results. The total number of pancreas transplants in Poland was 139 in years 1998 to 2006 and 268 in years 2007 to 2015. The largest differences revealed by the comparison of donor-related variables in both periods were those related to the doses of pressor amines, duration of circulatory arrest, and duration of stay at the intensive care unit. The critical finding consisted in the improvement of short-term survival of recipients and organs being observed in contrast to the surprising lack of improvement in long-term survival. Reduced likelihood of transplantation success was observed already in overweight patients (body mass index 25-29.99 kg/m^2).

Conclusions. No significant changes were observed with regard to pancreas transplant outcomes over the period of many years. Transplantation success is determined by 1-year survival of the organ, and the therapeutic success is measured by long-term disease-free survival of the patient. In the era of rapid advances in numerous areas of medicine, the lack of significant extension of patient survival times warrants a closer look of our knowledge on pancreas transplants.

THE history of pancreas transplantations in Poland started in 1987, when Professor Stanisław Zieliński from Szczecin performed a simultaneous transplantation of kidney and pancreatic fragments. Unfortunately, the surgery was unsuccessful. One year later, on February 4, 1988, a team led by Professor Jacek Szmidt performed the first successful pancreas and kidney transplant. The second successful pancreas and kidney transplant was carried out in the same year, on April 29, by Professor Wojciech Rowiński and Professor Janusz Wałaszewski.

Much progress has been made in transplantology since these first successful pancreas transplants with regard to both the surgical technique and the post-transplant care. This progress facilitated a significant improvement in distant outcomes. Despite this progress, however, the early post-operative complication rate after pancreas transplants remain high. As can be easily guessed, this argument is frequently used by the opponents of these procedures. Instead, however, it should be considered a trigger for thorough analysis of organ transplantation outcomes and search for novel solutions to save health and lives of patients with severe diabetes. Pancreas transplants are dedicated to

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patients treated for complicated type 1 or type 2 diabetes [1,2]. Depending on clinical setting and concomitance of renal insufficiency, pancreas may be transplanted either simultaneously with the kidney (simultaneous pancreas-kidney, SPK) or after the kidney transplant (pancreas-after-kidney, PAK). Pancreas transplant alone (PTA) may be performed to treat labile diabetes without KDIGO/WHO class IV or V nephropathy. Numerous studies have demonstrated significantly longer survival of patients having undergone SPK as compared with diabetic patients undergoing hemodialysis [3,4].

The objective of our study was to carry out a multifactorial analysis of the outcomes of pancreas transplant procedures carried out in Poland over a period of 18 years, and to identify factors of importance for the success of pancreas transplant.

METHODS

A total number of 407 pancreas transplants were performed in Poland between January 1998 and the end of November 2015. Of these, 370 organs were transplanted in the SPK setting, 34 organs were transplanted in the PTA setting, and the remaining 3 transplants followed the PAK scheme.

Data on the post-transplantation period were collected for 406 recipients, accounting for database completeness of 99.75%. As part of the methodology, data were divided into 2 subperiods, January 1998 to December 2006 and January 2007 to November 2015, to reflect the change in the methodology of statistical data being presented in POLTRANSPLANT bulletins. The analysis of donor and recipient data collected over 18 years was used to identify nationwide populational trends in both groups.

The retrospective analysis included primarily the parameters taken into consideration in 2 scales used to assess the collected organs—P-PASS and PDRI—as well as the recipient's age and sex. These parameters are based on 1-year graft survival as the criterion for transplantation success [5–7]. This was also the criterion used in our study. Follow-up data were also available for time points of 3 months, as well as 3, 5, and 10 years after the transplant.

There are 4 centers providing pancreas transplant services in Poland, including the Central Teaching Clinical Hospital of the Medical University of Warsaw, the Infant Jesus Clinical Hospital in Warsaw, the Independent Public Clinical Hospital in Katowice, and the Central Clinical Hospital of the Ministry of the Interior in Warsaw. Two transplants had been performed at a currently inoperative facility of the Pomeranian Medical University in Szczecin. Data used in this study were obtained from POLTRANSPLANT and the aforementioned treatment centers.

The study was conducted in compliance with the Helsinki Congress (as revised in 2013) and the Istanbul Declaration.

STATISTICAL ANALYSIS

The potential for graft and recipient survival was assessed using the Kaplan-Meier method (Statistica 13, StatSoft, Tulsa, Okla, United States). Actual survivals were determined by calculating the ratio of living recipients/grafts to the number of all records after elimination of records for which the required follow-up time had not yet been reached (Tables 4-6). Table 1 lists all available donor data including information on data completeness. Mean, median, standard deviation, maximum, and minimum values were calculated along with statistical significance determined using the Fisher exact test. Table 2 lists the calculated mean, median,

Table 1. Summary of Donor Data, 1998-2015

Parameter	Number of Records Collected	Mean	Median	Minimum	Maximum	Standard Deviation		*P*
Age	407	29.192	27	12	59	9.593		<.00001
Male	407						280 yes 127 no	<.00001
Body weight (kg)	406	74.480	75	45	120	13.103		=.00001
Height (m)	404	1.754	1.75	1.55	2.00	0.088		=.00003
BMI	403	24.103	24.05	16.3265	37.182	3.169		<.00001
Cerebrovascular cause of death	407						174 yes 233 no	<.00001
Time in the ICU (d)	403	4.623	4	1	36	3.734		<.00001
Circulatory arrest	407						63 yes 344 no	<.00001
Circulatory arrest duration (min)	48	19.250	15	1	120	19.838		<.00001
Dopamine/dobutamine	293	2.738	1.9	0	20.0	3.364		<.00001
Levonor	293	0.027	0.015	0	0.33	0.035		<.00001
Creatinine (mg/dL)	404	1.112	0.98	0.22	6.50	0.649		<.00001
Serum sodium	406	151.932	151	122	200	13.868		<.00001
Serum amylase	373	158.974	112		1054	156.644		<.00001
Serum lipase	133	91.292	41	1	912	135.300		<.00001
Cold preservation time (h)	320	8.209	8.050	1.333	19.25	2.744		=.0245
P-PASS	355	15.946	16	10.0000	25.000	2.656		<.00001
PDRI	318	0.957	0.885	0.2900	2.150	0.382		<.00001

Abbreviations: ICU, intensive care unit.

Table 2. Summary of Donor Data in 1998-2006 vs 2007-2015

	1998-2006				2007-2015			
Parameter	Mean	Median	Standard Deviation		Mean	Median	Standard Deviation	
Age	29.17	26	9.898		29.21	27	9.449	
Male				101 yes 38 no (27.3%)				179 yes 89 no (33.2%)
Body weight (kg)	73.62	75	11.85		74.92	75	13.7	
Height (m)	1.756	1.75	0.0766		1.753	1.75	0.0941	
BMI	23.81	23.88	2.806		24.25	24.15	3.334	
Cerebrovascular cause of death				55 yes (39.6%) 84 no			44.4% yes	119 yes (44.4%) 149 no
Time in the ICU (d)	3.8	3	3.405		5.041	4	3.829	
Circulatory arrest				15 yes (10.8%) 124 no				48 yes (17.9%) 220 no
Circulatory arrest duration (min)	11.40	5	11.50		20.16	15	20.48	
Dopamine/dobutamine	4.227	4	3.299		2.066	0	3.179	
Levonor	0.0126	0	0.0240		0.0337	0.0235	0.0373	
Creatinine (mg/dL)	0.989	0.91	0.387		1.175	1	0.742	
Serum sodium	154	152	13.79		151	150	13.86	
Serum amylase	137	99	144		169	127	161	
Serum lipase	87.91	42	150		93.99	38	124	
Cold preservation time (h)	8.457	8.708	2.760		8.126	7.917	2.740	
P-PASS	15.21	15	2.552		16.26	16	2.643	
PDRI	0.981	0.88	0.115		0.949	0.89	0.377	

Abbreviations: BMI, body mass index; ICU, intensive care unit.

and standard deviation values for all donor parameters in both subperiods. Table 3 presents the analysis of respective recipient data.

RESULTS

The total number of pancreas transplants in Poland was 139 in years 1998 to 2006 (3 PTA and 136 SPK transplants) and 268 in years 2007 to 2015 (33 PTA, 3 PAK, and 232 SPK transplants). All 3 implantations carried out according to the PAK protocol were performed in patients who had lost their pancreas following a previous SPK transplant. Table 1 lists the donor parameters taken into consideration in the aforementioned prediction models together with cold ischemia time, as included in one of these models. Each parameter was subject to normal distribution and was therefore useful for significance analysis. One hundred percent completeness of data was achieved for donor age, sex, cause of death, and potential temporary circulatory arrest. Lower completeness was achieved for donor serum lipase level data. None of the organs was collected from donors in whom permanent circulatory arrest was the cause of death. P-PASS and PDRI outcomes are also included in Table 1. One of the parameters in the following table, namely the CIT (cold ischemic time) parameter, is not directly related to the graft donor. However, it was included in the analysis due to being a component of the PDRI scale.

The greatest discrepancies, in the comparison of parameters in subperiods as presented data in POLTRANSPLANT bulletins, were observed for the mean doses of pressor amines (ie, dopamine/dobutamine [reduction by 51.1%] and noradrenaline [increase by 167.5%]). Significant changes in mean values were observed for duration of circulatory arrest (increase by 65.7%), duration of intensive care unit stay (increase by 32.7%), percentage of female donors (increase by 21.6%), cerebrovascular causes of donor death (increase by 12.1%), percentage of donors with a history of temporary circulatory arrest (increase by 8.6%), and cold ischemia time (reduction by 4%). For the remaining parameters, changes in mean values were insignificant (<2%). Those trends are shown in the Table 2. Slight variability trends were observed following the analysis

Table 3. Variability in Recipient-related Parameters in Years 1998-2006 and 2007-2015

	1998-2006				2007-2015			
Recipient-related Parameter	Mean	Median	Standard Deviation		Mean	Median	Standard Deviation	
Age	38.2	38	7.429		38.36	37	8.02	
Male				67 yes 60 no 12 unknown				144 yes 124 no

Table 4. Survival of Graft Recipients

Survival of Graft Recipients		
	1998-2006	2007-2015
3 months	87%	94.40%
1 year	79.90%	91.80%
3 years	79.10%	80.00%
5 years	77.70%	76.50%
10 years	65.50%	-

of transplant in both subperiods with regard to the prediction scales P-PASS (mean value increased by 6.3%) and PDRI (mean value reduced by 3.3%). For mean serum amylase and lipase levels, standard deviation values were larger than the mean values themselves, reflecting an exceptionally broad range of results. For this reason, these parameters were considered unreliable.

In addition, the collected data provided information on 2 recipient parameters, namely recipient's age and sex. Although none of the prediction models made use of recipient parameters, statistical analysis revealed a significant correlation between the recipient's age and transplantation success. Data were analyzed in 2 subperiods defined as before to compare variability trends (Table 3).

No significant change was observed with regard to the recipient's age in both subperiods. Slight prevalence of male recipients was observed in both subperiods. No correlations were observed between the recipient's sex and transplantation outcome or graft survival.

In a manner analogous to that used in the analysis of donor-related parameters, recipient survival and graft survival times (separately for pancreatic and renal transplants) were compared in 2 groups of patients. Recipient survival times were characterized by significant improvement in short-term follow-up (7.4 percentage points after 3 months and 11.9 percentage points after 1 year). After 3 years of follow-up, the differences in recipient survival fall below the significance level (Table 4).

Pancreatic graft survival times are suggestive of an improvement in short-term transplant outcomes. A decrease in 3-year survival rates was observed compared to the 1998 to 2006 period (Table 5).

Improvement in the survival of renal grafts was observed at 3 months and 1 year after the transplant. A clear reduction in the percentage of surviving renal grafts was observed after 3 years (Table 6).

Table 5. Survival of Pancreatic Grafts

Survival of Pancreatic Grafts		
	1998-2006	2007-2015
3 months	71.20%	76.40%
1 year	61.20%	68.20%
3 years	59.70%	54.20%
5 years	56.80%	37.50%
10 years	40.30%	-

Table 6. Survival of Renal Grafts

Survival of Renal Grafts		
	1998-2006	2007-2015
3 months	83.7%	89.4%
1 year	77.00%	83.8%
3 years	73.30%	66.9%
5 years	67.40%	51.3%
10 years	48.80%	-

DISCUSSION

This study is the first and largest summary of data on pancreas transplants in Poland, as it provides details of 407 transplant procedures performed over a period of nearly 18 years. The fact that the pancreas and kidney transplant is the best method for the treatment of patients with type 1 diabetes complicated with end-stage renal disease was the reason for thorough, multifactorial analysis of transplantations carried out to date [3]. An additional motivation for the study consisted in that this treatment modality is also efficient in patients with type 2 diabetes [8,9]. Multicenter character and long observation time contribute to the high scientific value of this study.

The analysis of a possibly broadest set of data on each transplantation procedure combined with the follow-up of graft recipients facilitate identification of trends and variability in donor-related study parameters and determination of their impact on transplantation outcomes. In line with global findings, most transplantations performed in Poland are simultaneous pancreas and kidney transplantations, which ensure the longest graft survival times and the highest quality of life for the patients [10].

Prediction scales are used to ensure the possibly best outcomes. Organ suitability is determined by POLTRANSPLANT using the P-PASS scale, whereas the PDRI scale is in use in the United States. In the P-PASS scale, the cut-off level is set at 17 points; according to numerous authors, grafts with scores above this value are characterized by worse survival outcomes [11].

In our analysis, the comparison of both periods revealed an increase in mean P-PASS scores; however, the threshold of 17 points was not exceeded. Despite the fact that the mean P-PASS score rose to the value of 16.26 (ie, close to the aforementioned threshold of 17 points), an increase was observed in short-term graft survival rates.

Despite the problems with the collection of data on cold preservation times as described by the developers of the PDRI scale [4], as many as 320 relevant records could be found in our study material. Thus, no limitation was set on our study with regard to this parameter.

The time point of 3 months was considered the first time point of significance for this study since it was critical for the success of transplantation due to the early complications following the procedure. Some authors exclude from their analyses all grafts lost in the first 90 days after the procedure and relevant data are not included in the statistics [12]. In

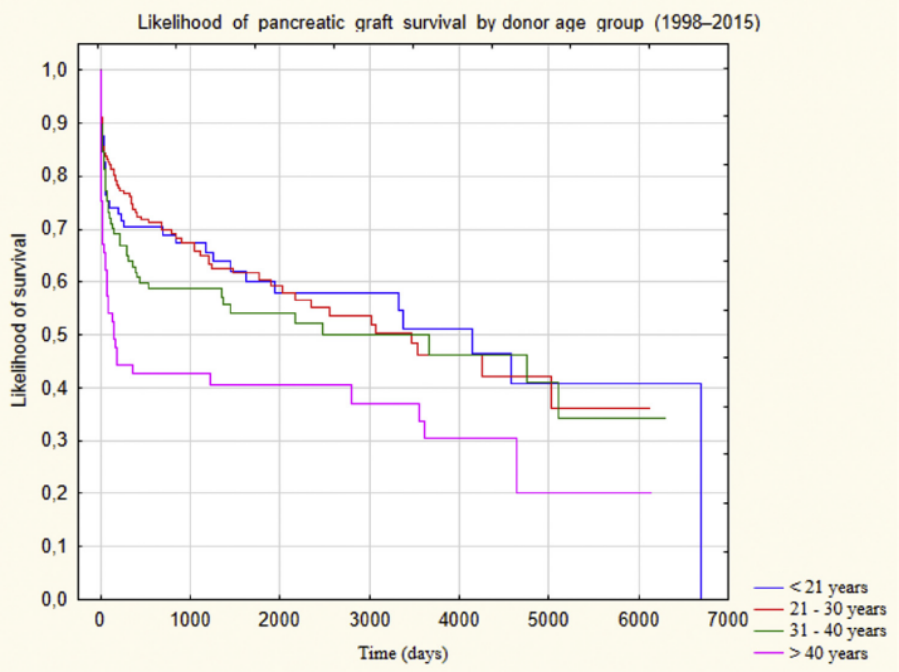

Fig 1. Likelihood of pancreatic graft survival by age group (1998-2015).

an obvious manner, this translates to markedly better transplantation outcomes and makes comparison of results unreliable. One-year survival rates were included in the analysis since numerous studies [5,6,13] considered this time point to be the final endpoint and thus the determinant of transplant success or failure. Time points of 3, 5, and 10

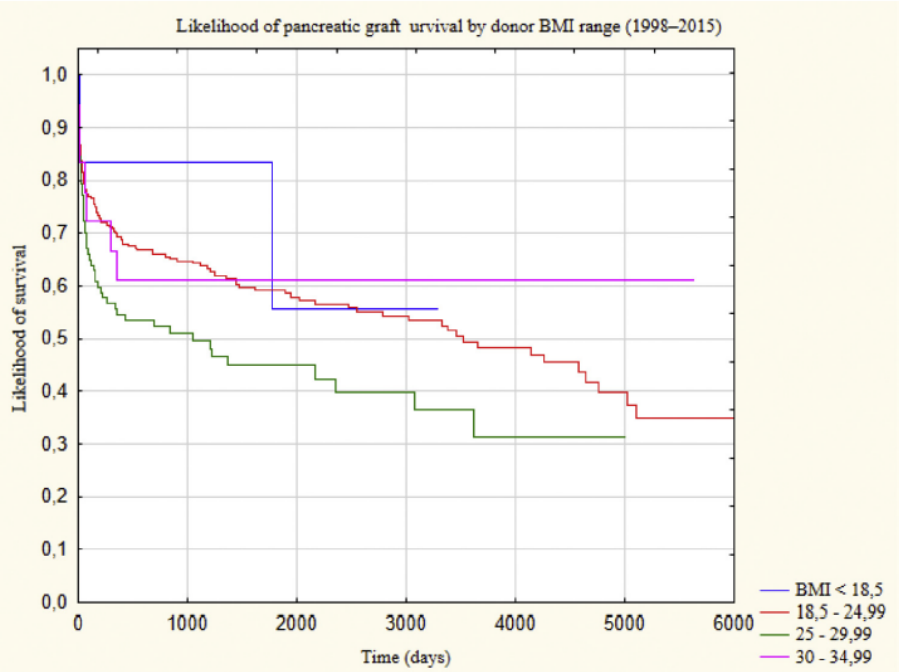

Fig 2. Likelihood of pancreatic graft survival by BMI range (1998-2015).

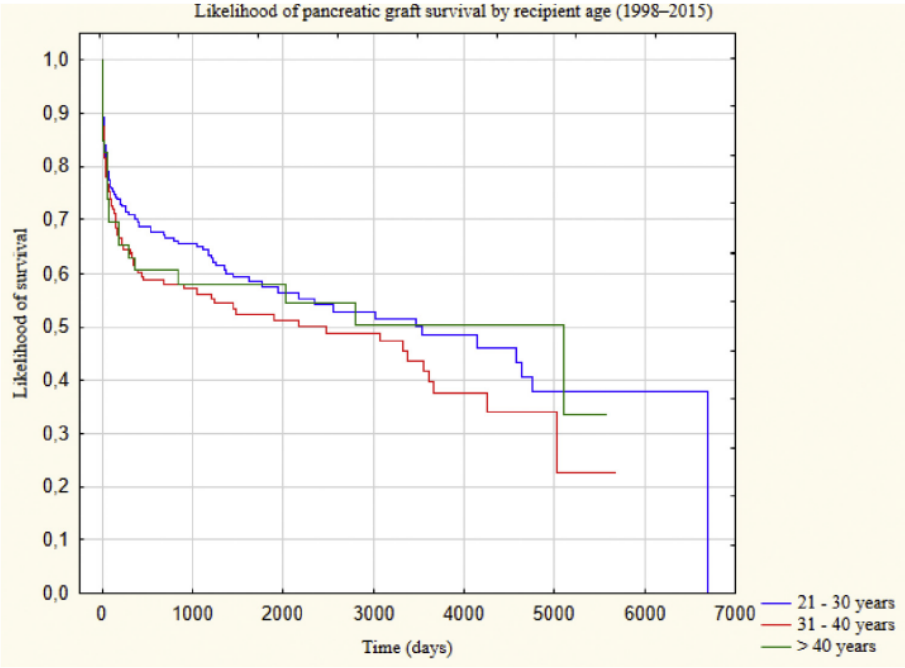

Fig 3. Likelihood of pancreatic graft survival by recipient age (1998-2015).

years were used in long-term follow-up. As shown by our analysis, only the short-term survival rates for pancreatic and renal grafts were longer in the second study subperiod, whereas the 3-, 5-, and 10-year survival rates were reduced. This may be due to the significant increase in the incidence of risk factors as reported hereinabove. In this context, it must be noted that the overall recipient survival times were not reduced, and even increased instead in short-term analyses.

Kaplan-Meier analysis was used to study the relationship between the survival of pancreatic grafts and donor's age; the latter variable was categorized into 4 groups. The analysis was performed for transplants performed in the entire study period. A marked decrease in graft survival as the function of time after the procedure was observed for donors older than 40 years, as compared with younger donors. The 3 remaining groups of donors were characterized by relatively similar pancreatic graft survival times (Fig 1).

In contrast to publications highlighting the markedly worse survival times for grafts obtained from donors with body mass index (BMI) above 30.00 [9], a marked reduction in the likelihood of graft survival was also observed for organs collected from donors with lower BMI values (25-29.99) [14]. Too few organs had been collected from donors with a BMI of 30 or more to ensure reliable comparison of relevant data with other donor groups.

Using recipient age groups analogous to these used in the donor population, a small difference in graft survival was observed for individual groups (Fig 2). The highest survival rates were observed in recipients aged 21 to 30 years (Fig 3).

CONCLUSIONS

The above analysis revealed no significant changes in pancreas transplant outcomes over a period of 18 years. Interestingly, only the short-term survival of transplant recipients was extended significantly in the second study subperiod, and no change was observed with regard to long-term survival rates. It is quite disturbing that despite the growing experience in transplantology, the survival times of pancreatic and renal grafts were markedly reduced. As the numbers of pancreas transplant procedures are dropping worldwide while the number of diabetic patients is increasing at a rapid pace, the lack of promising results may be of crucial importance. Taking this into account and considering the widespread unwillingness as well as, in many cases, the lack of appropriate knowledge of the procedure among health care professionals, one should expect that the number of diabetic patients who would not receive proper treatment will be increasing. The lack of inter-facility cooperation, maintenance of detailed databases, and analyses of transplantation failures leads to an inability to draw objective conclusions relevant for the entire population of transplant recipients. Sharing of the results and findings is required for all pancreas transplanting facilities as is the identification of factors crucial for the improvement in long-

term survival of grafts and reduction of early post-transplantation complications.

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3.

Combined Liver–Pancreas Transplantation as Novel Treatment for Patient With Cystic Fibrosis: A Case Report

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ABSTRACT

Background. A 21-year-old woman diagnosed with cystic fibrosis developed cirrhosis, exocrine pancreatic insufficiency, and insulin-dependent diabetes mellitus. The patient qualified for double organ liver–pancreas transplantation beyond typical indications. The respiratory symptoms of cystic fibrosis were moderate and well-treated. The patient was endangered mainly by liver insufficiency and recurrent hypoglycemia, which was due to the treatment of diabetes with high doses of insulin. Computed tomography showed mild bronchiectasis, cirrhotic liver, splenomegaly, and atrophy of the pancreas. *Pseudomonas aeruginosa* colonized the upper respiratory tract. Gastrointestinal complications were sufficient for the patient to be qualified for combined liver–pancreas transplantation.

Methods. First, a standard hepatectomy was performed. The liver was transplanted orthotopically. Subsequently, the team performed pancreas transplantation through a separate incision. The donor's duodenum was anastomosed to the recipient's jejunum, close to the ligament of Treitz.

Results. No serious complications were noted during the postoperative period. Transplanted organs started functioning without delay. The patient was discharged after 6 weeks in general good condition. Twenty months later, the patient felt well, and the grafts kept functioning properly.

Conclusion. Combined liver–pancreas transplantation in patients with CF restores exocrine and endocrine pancreatic function and minimizes the risk of life-threatening complications associated with liver insufficiency. Improvement of life quality coincides with the possibility of discontinuing insulin and pancreatic enzyme supplementation. The combination of liver and pancreas transplantation may prevent advanced pulmonary complications, extend the prognosis of survival, and improve the long-term life quality.

CYSTIC fibrosis (CF) is the most common lethal genetic disease in White populations [1]. In 2022, it was estimated that >162,400 people were living with CF across 94 countries, of which around 105,000 were diagnosed [2]. The disease is inherited in an autosomal recessive manner and is caused by a defect in the *CFTR* gene, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is an ABC transporter-class ion channel for chloride and bicarbonate ions in secretory epithelia. Its function maintains the correct ion gradient that causes osmosis to draw water out of the cells [3].

As CFTR is required for proper secretion in various organs, its dysfunction or absence results in a multisystem disease primarily involving the respiratory, gastrointestinal, genitourinary, and endocrine systems and sweat glands. Lung disease is

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present in all individuals with CF and is the major cause of their mortality. The upper respiratory tract is also frequently involved, causing chronic sinus disease in 38% of those with CF [4]; about 82% of CF patients require pancreatic enzyme replacement therapy due to exocrine pancreatic insufficiency (EPI). The endocrine function of the pancreas is also widely impaired. Almost every fifth patient develops CF-related diabetes (CFRD), which differs from type 1 diabetes mellitus, as it is not only due to lack of insulin and glucagon but also fluctuating resistance to insulin caused by inflammation and other reasons [5,6], Hepatobiliary complications are less common, although worth noting, as 3% of all individuals with CF develop liver disease and cirrhosis. Liver failure is responsible for >4% of deaths among those with CF; the Cystic Fibrosis Foundation reported 10 cases in 2022 [5]. Mental health problems such as anxiety and depression are increasingly also recognized as major complications of CF [4].

The life expectancy of individuals with CF has increased significantly over the past years due to improvements in care. As the CF population ages, new complications emerge, and the prevalence of CF-associated liver disease (CFLD) and CFRD increases. [3] An already well-established therapy for liver cirrhosis is the transplantation of this organ. In the case of complete pancreatic insufficiency coexisting with liver disease, transplantation of both organs appears to be a possible therapeutic approach.

We report here a case of a woman with CF who underwent successfully combined transplantation of liver and pancreas, conducted by one surgical team, being the first surgery of the kind ever performed in Poland.

CASE REPORT

A 19-year-old woman with CF developed cirrhosis, EPI, and CFRD. She was diagnosed at 3 years of age. In her case, the disease was caused by the homozygous F5*08del* variant of the *CFTR* gene, which is the most common and severe [5].

Her respiratory tract symptoms were moderate, thanks to effective care since early childhood. She was treated with mucolytics: domase alfa and ambroxol in daily nebulization and acetylcysteine in tablets. She had chronic respiratory tract infections mainly due to colonization by *Pseudomonas aeruginosa,* which was treated with colistin nebulization daily. A computed tomography (CT) scan and ultrasound (US) of her thorax revealed mild bronchiectasis and sparse atelectasis but no other focal lesions (Fig 1). The lungs were also aerated well, and the patient got normal spirometry and plethysmography results. She did not have asthma. During the cardiologic assessment, no abnormalities were found. The cardiac stress tests revealed correct physical efficiency and effort tolerance. The patient's subjective exertion during physical activity was assessed to be absent using the Borg CR10 scale. In the past, she underwent fronto-spheno-ethmoidectomy and septoplasty as a treatment for chronic sinusitis.

The patient developed complete pancreatic insufficiency. She required pancreatic enzyme supplementation and took 7 capsules of pancreatin daily, 300 mg each, which gives 175,000 PhEur units of lipase in total. Nevertheless, she continued to have recurrent abdominal pain, bloating, and other dyspeptic symptoms. A contributing factor to those symptoms was ineffective bile secretion due to liver insufficiency. She needed external intake of bile acids in tablets for compensation.

The woman was diagnosed with CFRD when she was 12 years old. She was treated with an insulin pump. However, her diabetes management was poor. Despite continuous monitoring of her blood glucose levels, the patient experienced episodes of hypo- and hyperglycemia. Findings in the abdominal CT scan corresponded with clinical presentation, showing complete fatty atrophy of the pancreas.

She was diagnosed with CFLD, followed by cirrhosis and portal hypertension. In the past, she underwent banding of the esophageal varices twice. CT showed fibrosis and macronodular regenerative hyperplasia of the liver. Her left lobe, caudate, and quadrate lobes were significantly enlarged. The spleen was significantly enlarged to 200 mm. Numerous blood vessels of collateral circulation were visible in the US (Fig 2).

Initially, the patient was to be qualified for liver transplantation alone. However, the experts in the field of transplantology conducted a unique treatment of combined liver−pancreas transplantation. In September 2020, she was added to the transplant waiting list. In the month of transplantation, she scored 11 points on the Model for End-Stage Liver Disease and was assigned to the A6 class in the Child-Pugh classification. The patient weighed 57 kg at a height of 167 cm. Her blood type was O-negative, and her panel-reactive antibody score was 0%, 3% maximum. Before the surgery, the patient was in general good condition and stayed home.

The donor of both organs was a 23-year-old deceased woman who had stayed in the intensive care unit for 6 days. Her body weight was around 11 kg less than the recipient's. Her blood type was O-positive. She tested positive for cytomegalovirus (CMV) immunoglobulin (Ig)G; the recipient was CMV IgG-negative. Cross-match was negative.

The transplantation was performed by one experienced team on September 30, 2021. The hepatectomy was performed first. The donor's liver was implanted orthotopically using the piggyback technique by a transverse incision in the upper abdomen. A stent was inserted in the biliary anastomosis. Subsequently, the pancreas was transplanted into the right iliac fossa by separate longitudinal incision. Pancreas arterial anastomosis to the right common iliac artery and venous anastomosis to the inferior vena cava (IVC) were performed. The donor's duodenum was anastomosed to the recipient's jejunum ~ 20 cm from the ligament of Treitz. The entire surgery took 9 hours and was uneventful. Cold ischemia time (CIT) of the liver was 7 hours 20 minutes. CIT of pancreas was 11 hours 20 minutes. Total blood loss volume was around 1800 mL.

After the surgery, the immediate function of both organs was observed. The US showed satisfactory flow in the accessible blood vessels of the grafts. The patient had normal blood glucose levels the day after the transplantation without external insulin dosage. On November 3, the biliary stent was removed during endoscopic retrograde cholangiopancreatography, which required incising the ampulla of Vater.

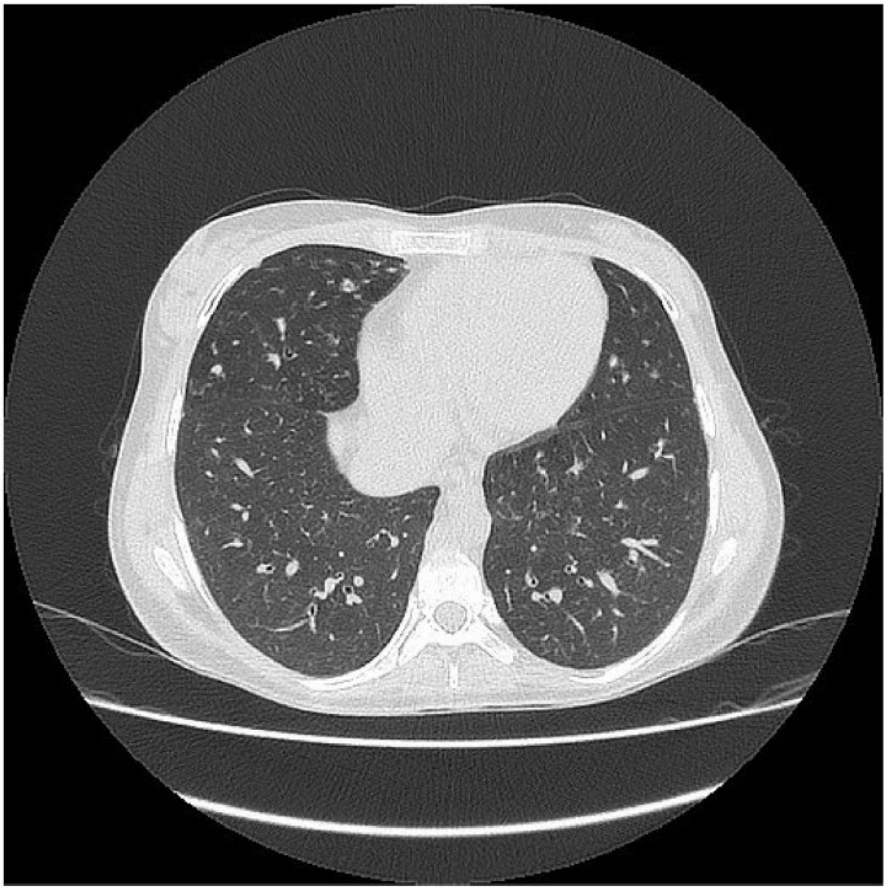

Fig 1. Computed tomography of thorax cavity Signet ring sign typical for bronchiectasis is visible mainly dorsally in both lungs.

An immunosuppressive therapy standard for pancreas transplantation was administered: mycophenolate mofetil, tacrolimus, and prednisone, with thymoglobulin induction. Apart from nystatin and cotrimoxazole, additional prophylaxis with valganciclovir was required due to the donor's CMV IgG-positivity. Pancreatin supplementation was no longer necessary.

After 26 months, the patient felt well, and both transplanted organs continued functioning properly.

DISCUSSION

Reports of simultaneous liver and pancreas transplantation in patients with CF remain uncommon but have increased in recent years. Pancreas–liver–kidney transplantation was described in a CF patient in 1994. The patient was a 21-year-old man with pancreatic insufficiency requiring pancreatic enzymes and insulin, as well as liver cirrhosis and renal failure [7]. In one study of 9 pediatric patients with CF, the 3 combined liver–pancreas transplanted patients benefited from the pancreas transplant, as they were significantly less likely to require pancreatic enzymes or insulin after transplantation than the liver-only transplanted group, with no increase in complications or a decrease in survival rates. This advantage not only minimizes long-term diabetes complications and improves quality of life, but it may also prevent pulmonary decline and reduce mortality [8].

A recent United Network for Organ Sharing study found CFRD in 18% of adolescents and 55% of adults undergoing liver transplantation for CFLD [9]. Importantly, developing diabetes in CF is a major independent risk factor for death, despite insulin treatment, and is associated with a 30% to 55% increase in mortality [10,11]. New-onset diabetes post-liver transplant in children with CF occurs in ~60% of patients in the first years after transplant [12,13], likely related to the use of immunosuppression. The role of simultaneous liver–pancreas transplantation in patients with CF pancreatic insufficiency who do not have CFRD requires careful examination of risks and benefits.

Isolated pancreas transplantation in patients with type 1 or 2 diabetes can result in euglycemia, normal glycosylated hemoglobin levels, and insulin independence. Furthermore, 5-year graft survival after a single pancreas transplant is around 85% [14]. It is reasonable to assume that simultaneous liver

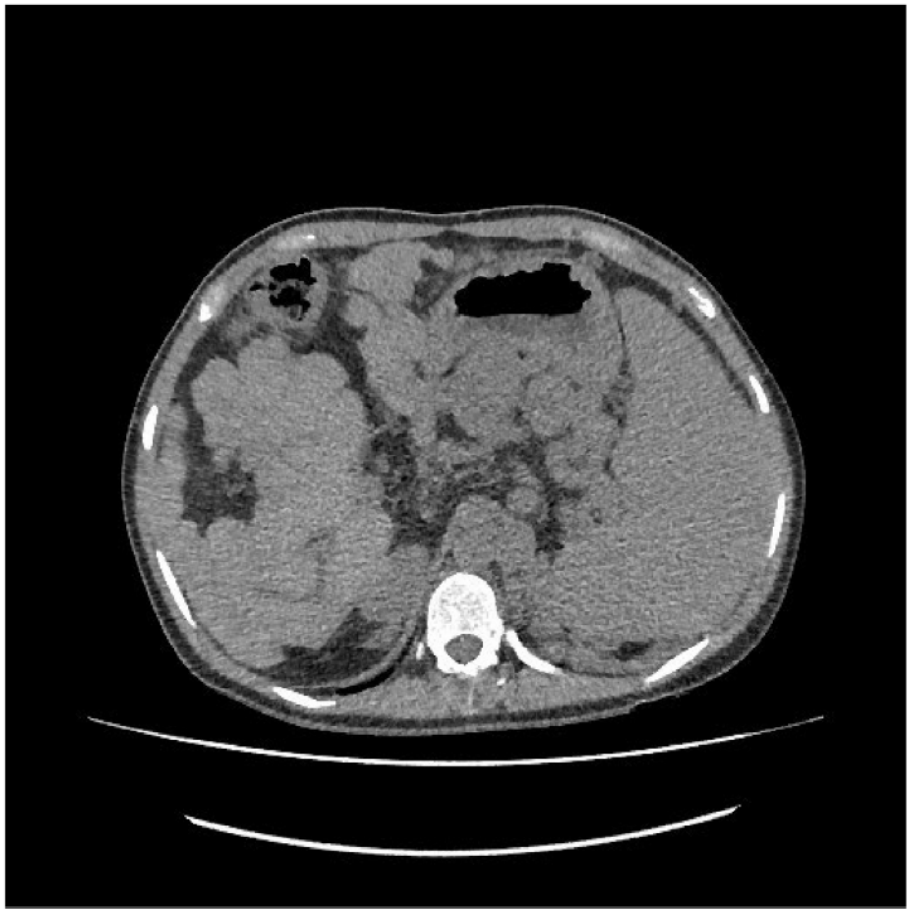

Fig 2. Computed tomography scan of the abdominal cavity computed tomography scan of the abdomen showed a cirrhotic liver and significantly enlarged spleen.

−pancreas transplantation has better long-term pancreatic graft survival than isolated pancreas transplantation [15].

Diabetes has been shown to have negative effects on the already reduced pulmonary function seen in patients with CF. When compared with patients with CF without diabetes, the forced expiratory volume in those with diabetes is significantly lower in all age groups. The increased death rate in patients with CF and diabetes appears to be attributed in part to the faster onset of pulmonary deterioration [16].

The liver is transplanted orthotopically before implanting a pancreas to prevent insufficient blood flow in IVC. The pancreas is typically transplanted heterotopically. The donor's common iliac artery is anastomosed to the recipient's external iliac artery. Blood drainage from the pancreas occurs through the portal vein anastomosed to the IVC or the iliac vein for systemic circulation. In our patient, an anastomosis with the IVC was employed. Portal-to-portal anastomosis results in a higher incidence of thrombosis and does not provide a metabolic advantage over portal-systemic anastomosis [17,18]. Because of the stable synthetic activity of the liver, Enoxaparin was applied before pancreas transplantation to protect the pancreas from thrombosis, which is described as the most common surgical complication after this procedure [19,20]. The role of anticoagulant therapy for nonocclusive thrombosis has not been defined; however, in the setting of pancreas transplantation, this approach is well-accepted and efficacious [21].

Pancreatic juice is drained through the donor's duodenum anastomosis, usually with the recipient's small intestine. In our patient, an anastomosis with the jejunum was performed directly after the ligament of Treitz, preserving the physiologic flow of pancreatic juice. Regarding surgical technique, experts acknowledged that enteric drainage should be favored over bladder drainage in terms of infectious, metabolic, and urinary tract problems. However, overall outcomes are similar regardless of exocrine drainage location. Despite increased bleeding rates, duodenoduodenostomy did not increase the frequency of surgical complications compared with duodenojejunostomy. It was unrelated to superior immunologic results, which might be attributed to easier access to endoscopic biopsies [22].

Due to the higher immunogenicity of the pancreas in simultaneous liver and pancreas transplantation, immunosuppression appropriate for the pancreas is employed. The standard immunosuppressive treatment currently includes induction with thymoglobulin, tacrolimus, mycophenolate mofetil, and glucocorticoids. Alemtuzumab or basiliximab can also be used instead of thymoglobulin for induction [23,24]. Thymoglobulin induction was conducted in our patient. When compared with basiliximab, the use of thymoglobulin reduces the chance of pancreatic rejection, which is highly warranted given the difficulties in identifying the rejection of this organ [24].

CONCLUSION

Simultaneous organ transplantation in CF is feasible and successful. Because most patients with CF have EPI and are likely to develop diabetes mellitus as they age, a combination of liver and pancreas transplants should be investigated.

DECLARATION OF COMPETING INTEREST

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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4.

New York, January 29, 2026

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Department of General, Gastroenterology and Oncologic Surgery
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Warsaw,Poland

Dear Dr Śmigielska

We are pleased to inform you that your manuscript:

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Authors: Paweł Skrzypek, Małgorzata Buksińska-Lisik, Paweł Ziemiański, Antonina Respondek, Kaja Śmigielska, Karol A Sadowski, Justyna Domienik-Karłowicz, Maciej Kosieradzki, Wojciech Lisik
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Title: Substantial reduction of cardiovascular risk in pancreatic transplant recipients

Abstract

Pancreatic transplant is the best causal treatment for type I diabetes. The TyG index is a reliable predictor of the long-term risk of cardiovascular episodes. The purpose of this study is to demonstrate a reduction in the risk of cardiovascular episodes resulting from the use of the TyG index in pancreatic transplant patients.

The analysis was carried out on data obtained from 86 patients undergoing pancreatic transplantation at the Department of General and Transplantation Surgery, Warsaw. Serum triglyceride and glucose levels were recorded at the stage of qualification for transplantation and at 1, 3, 6, and 12 months after transplantation.

The repeated measures ANOVA model was applied to the group of patients with complete data (n = 14), showing a statistically significant effect of time. The difference between "Before" and "After 12 months" proved statistically significant. The mixed model confirmed the significant effect of time on the TyG index value. The mean TyG index value decreased significantly 1 month after transplantation and remained stable.

The trend analysis was performed for the TyG index values at three time points: pre-transplant, early follow-up, and late follow-up. The mean TyG index decreased significantly as early as at 1–3 months.

On the basis of a detailed analysis in a group of pancreas transplant a strong and positive correlation between transplantation and the reduction of TyG index was proved indicating a reduction in the long-term risk of cardiovascular episodes in this group of patients.

Introduction:

Pancreatic transplant is the best causal treatment for type I diabetes. It may also be a therapeutic option in patients with refractory type II diabetes mellitus. Diabetes mellitus is a systemic disease that, in the long term, may lead to severe disability and even death [1]. Despite the perfectly established indications, pancreatic transplants are performed much less frequently than renal or liver transplants [2]. This is surprising, since the number of individuals with diabetes in Poland exceeds 2.5 million, about 10% of whom are diagnosed with type I diabetes

[3]. It is estimated that about 10% of diabetic patients may benefit from pancreatic or simultaneous pancreas-kidney transplants.

Pancreatic transplantation surgery is a complex and difficult surgical procedure, with surgical as well as medical complications not being uncommon in the early postoperative period. They are the consequences of complicated surgery, long hospital stay, and immunosuppressive therapy. The awareness of the risks and the low level of knowledge about the long-term benefits of pancreatic transplants among physicians and patients determine the limitation in the number of pancreatic transplants performed.

Pancreatic transplants were repeatedly proven to provide long-term independence from exogenous insulin or, less frequently, to stabilize glycemic levels with a significant reduction in insulin requirements [4]. Correlating the results of pancreatic transplant with a recognized prognostic parameter should effectively verify the validity of this method of diabetes treatment.

The TyG index (a parameter calculated from blood glucose and triglyceride levels) is a well-established tool for determining insulin resistance, as well as the risk of non-alcoholic fatty liver disease or arterial stenosis in diabetic patients [5–7]. The TyG index value has been proven to be a reliable predictor of the long-term risk of cardiovascular episodes.

The purpose of this study is to demonstrate a reduction in the risk of cardiovascular episodes resulting from the use of the TyG index in pancreatic transplant patients.

Methods:

The analysis was carried out on data obtained from 86 patients undergoing pancreatic transplantation at the Department of General and Transplantation Surgery of the Infant Jesus Clinical Hospital, University Clinical Center of the Medical University of Warsaw. The surgeries were performed from January 2016 to May 2025. All patients had been qualified for surgery according to the same standards. Patients were subjected to transplantation surgery according to a standardized surgical procedure as developed by a team from the Department of General and Transplantation Surgery at the Medical University of Warsaw. A four-drug immunosuppression regimen including tacrolimus, mycophenolate mofetil, glucocorticosteroids, and induction of immunosuppressive treatment with rabbit anti-human thymocyte immunoglobulin (thymoglobulin) was used.

Of the 86 patients, 22 were subjected to pancreas transplant alone (PTA). One patient was subjected to pancreas transplant after a prior kidney transplant (pancreas after kidney, PAK). 49 recipients received a simultaneous pancreas-kidney transplant (SPKTx). One patient received a simultaneous pancreas-liver transplant (SPLTx).

Serum triglyceride and glucose levels as recorded in milligrams per deciliter (mg/dL) at the stage of qualification for transplantation and at 1, 3, 6, and 12 months after transplantation were retrospectively analyzed within the described group of transplant recipients. For each of the points on the timeline, the TyG index was calculated according to the appropriate formula, i.e., as the natural logarithm of the product of the triglyceride level and one half of the serum glucose concentration.

Complete data were obtained for 14 patients (out of 81 analyzable, i.e., 17.3%). No data from before and from at least one post-transplant measurement point could be found in only 5 patients, facilitating a trend analysis in 76 pancreas recipients, i.e., 93.8%. The deficiencies in the database were due to the individualized approach to each patient. Follow-up visits are managed according to the patients' needs rather than according to a uniform, rigid pattern.

Two mathematical models were used. A repeated measures ANOVA model was used for the group of 14 patients with complete data. For the 76 patients with pre-transplant results and at least one post-transplant result, a repeated measures analysis was performed with the measurement points at 1 and/or 3 months and the measurement points at 6 and/or 12 months being taken into account collectively. Next, the trends for the changes in glucose and triglyceride levels, as well as in the TyG index, were analyzed along the timeline for the entire study group.

Results:

Two organ recipients who died within 2 weeks of transplantation were excluded from the analysis. In addition, loss of function was observed for 3 transplanted organs within 12 months of transplantation. The above figures translate to a one-year survival rate of 97.7%. In the group of pancreas recipients operated on by the team of the Department of General and Transplantation Surgery, good organ function was maintained after one year by 96.43% of recipients.

Trend analysis of TyG index values at consecutive time points: before transplantation and at 1, 3, 6, and 12 months after transplantation:

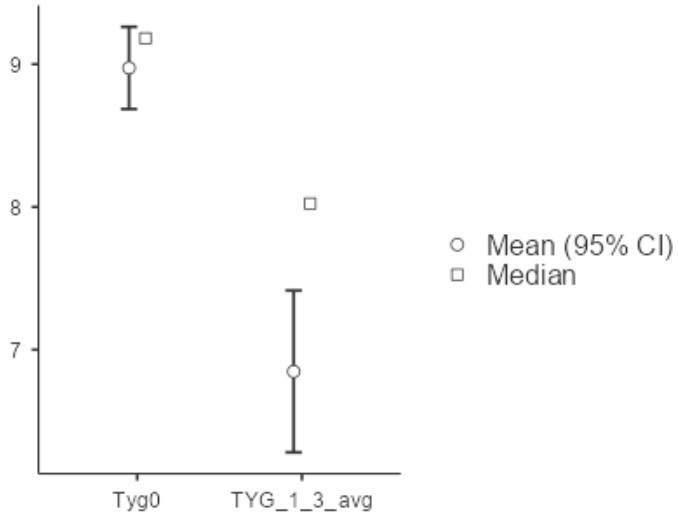
In the first step, the repeated measures ANOVA model was applied to the group of patients for whom complete data were available (n = 14), showing a statistically significant effect of time ($p < 0.001$). However, in pairwise comparisons, only the difference between "Before" and "After 12 months" time points proved statistically significant, which limits the interpretation of the conclusions of this analysis. Due to the incompleteness of data in a wider group of patients, the main analysis was performed using a linear mixed model to account for missing observations.

The mixed model confirmed the significant effect of time on the TyG index value [$F(4, \sim65) = 21.0$, $p < 0.001$]. The mean TyG index value decreased significantly as early as 1 month after transplantation and remained at a reduced level in subsequent months ($p < 0.001$ for all comparisons relative to baseline). The greatest decrease was observed between the pre-transplant period and one month after the procedure, the differences between individual post-transplant periods being insignificant, suggesting a rapid therapeutic effect and stabilization.

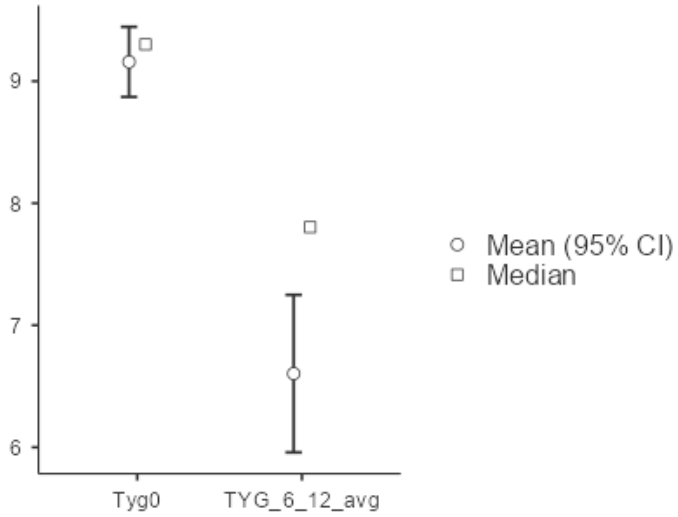
Analysis of trends at months 1 and 3 collectively, and months 6 and 12 collectively:

The trend analysis was performed for the TyG index values at three time points: pre-transplant (TyG0), early follow-up (TyG_1_3_avg), and late follow-up (TyG_6_12_avg). The mean TyG index decreased significantly as early as at 1–3 months ($M = 6.85$ vs. 8.97; $p < 0.001$; $d = 0.91$), the decrease also persisting after 6–12 months ($M = 6.60$ vs. 9.16; $p < 0.001$; $d = 1.25$). The difference between the early and late follow-up time points was smaller but remained significant ($p = 0.024$; $d = 0.41$). Due to the non-normality of distribution (Shapiro-Wilk's $p < 0.001$), a Wilcoxon test was also performed, which confirmed the significance of all comparisons ($p < 0.01$).

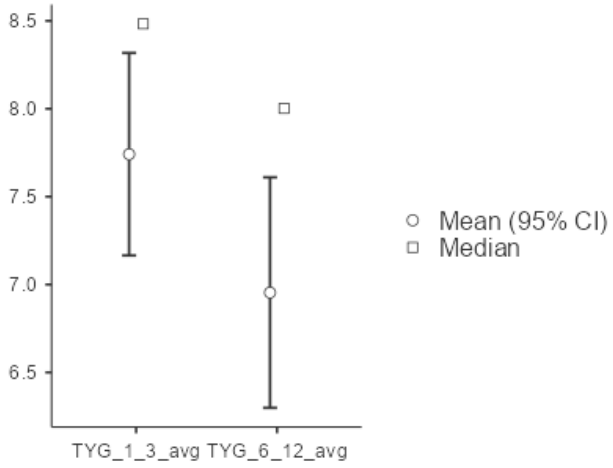
TyG 0 vs. TyG at 1 and 3 months



TyG 0 vs. TyG at 6 and 12 months

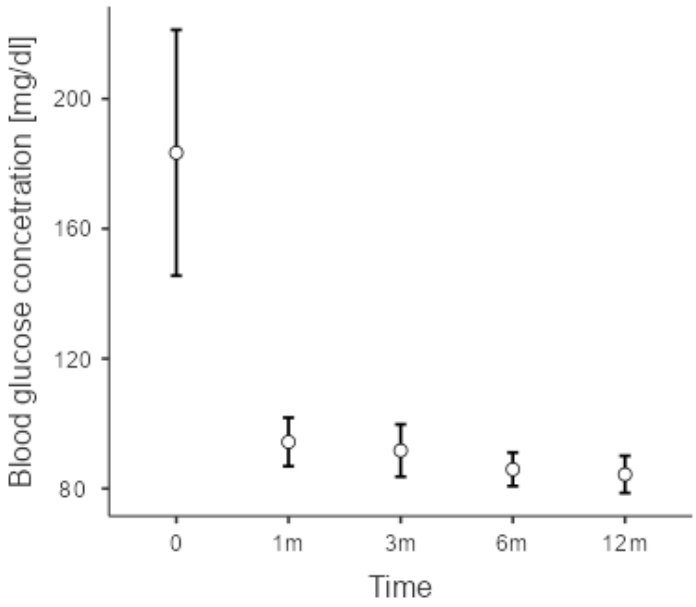


TyG at 1 and 3 months vs. TyG at 6 and 12 months



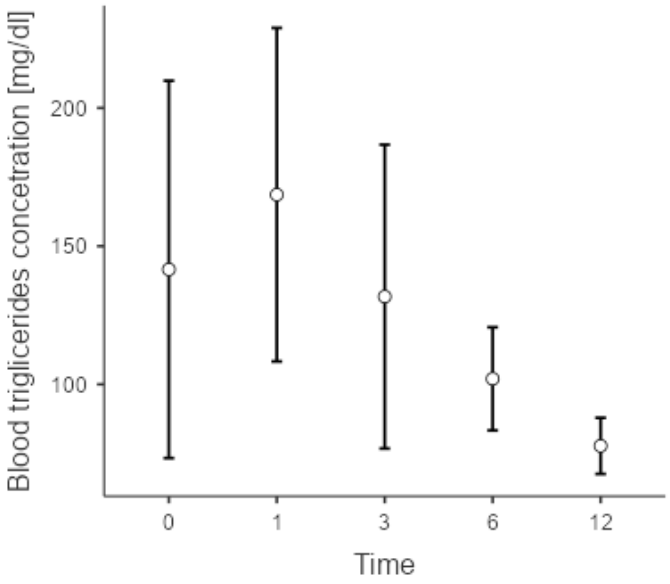
Glucose levels

A significant decrease in glucose levels was observed over time ($F(4, 52) = 29.2$; $p < 0.001$), mainly between baseline and month 1. At subsequent time points, the values remained stable, indicating a sustained improvement in glycemic control after transplantation.



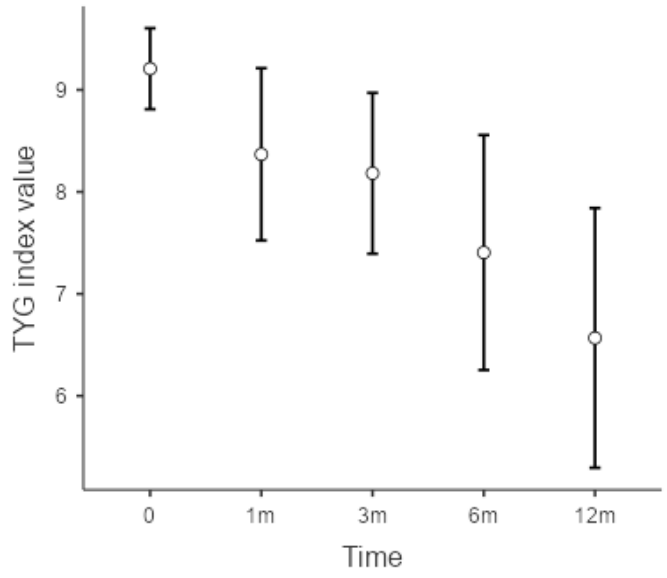
Triglycerides

Triglyceride concentration changed significantly over time ($F[4, 28] = 5.98$; $p = 0.001$). After an increase at months 1–3, a gradual decline was observed with the lowest level at 12 months.



Average TyG index over time

A repeated measures ANOVA model was used to assess changes in TyG index values over time, encompassing the total of five time points (0, 1, 3, 6, and 12 months after transplantation). A significant effect of time was observed ($F[4, 52] = 6.27$; $p < 0.001$). The value of the TyG index declined steadily, the highest and the lowest levels being observed before transplantation and after 12 months, respectively. The observed trend suggests a gradual and sustained improvement in metabolic parameters.



Discussion

Pancreatic transplant has been a modality of diabetes treatment for more than 50 years. Over this time, the treatment method was undergoing numerous modifications, finally being refined to achieve satisfactory treatment results, i.e., 12-month transplant survival rates of ca. 90% [8]. At the authors' center, the function of the transplanted pancreas is maintained after one year in 96.43% of recipients, with nearly 98% of organ recipients surviving at least one year after the procedure. Such achievements warrant our research and observation results being considered on an equal footing with those of the world’s leading centers.

Our study unequivocally proved that the risk of cardiovascular complications, i.e., the most common cause of death worldwide, is long-term reduced at several months of follow-up after pancreas transplantation [9]. The effect of pancreatic transplant on the glycemic and body fat metabolism is so great that high statistical significance was achieved even in a relatively small

population of patients. This was confirmed by two different statistical models as used by the authors.

A limitation of the presented study is the lack of a control group, which would allow for a more objective comparison of the results. The authors considered it unethical to seek patients with diabetes who met the indications for pancreatic transplantation and then deliberately observe them without attempting to implement the best available treatment - pancreatic transplantation. The authors noted that the biochemical parameters recorded at the beginning of each patient's follow-up already reflected many years of advanced diabetes along with associated comorbidities. For this reason, it is reasonable to compare these baseline results with those observed after pancreatic transplantation.

As has been repeatedly pointed out, early surgical complications are the weak point in pancreas transplantations. Worldwide, the most common complication consists in early organ thrombosis, which occurs in 3.7% and 5.9% of recipients of simultaneous pancreas-kidney transplant and pancreas transplant alone, respectively [10]. One case of transplant thrombosis in a PTA recipient occurred at the authors' center. This translates to the overall rate of 1.2% of pancreatic thrombosis cases in the entire study group; with regard to SPKTx recipients, the rate was 0% in the total of 49 cases. The second frequently reported complication, requiring prompt surgical or medical interventions, is pancreatitis [11]. The authors repeatedly observed postoperative inflammation of the transplanted pancreas, diagnosed on the basis of imaging studies and elevation of serum amylase and lipase levels. However, careful observation of the aforementioned results and swift responses to the alarming changes make it possible to avoid aggravating symptoms that would require reoperation in the vast majority of cases. One case of organ loss was recorded in the study group due to increased inflammatory changes in the early postoperative period. The third case of organ loss within the study group was due to a leaking duodeno-intestinal anastomosis (1.2% for the study group). In the literature, this complication accounts for approximately 2.5–2.9% of pancreas transplants [12, 13].

The authors note that pancreas alone and pancreas-kidney transplants are pursued only in patients with severe diabetes and coexisting severe or rapidly progressive complications, e.g., KDIGO grade V renal failure [14]. This group of patients, as has been repeatedly proven, benefits tremendously from pancreas transplantation even despite the risk of complications amounting to several percent. Moreover, it has been proven that simultaneous pancreas and kidney transplants are more beneficial for patients with diabetes and end-stage renal failure than

kidney transplants from a living donor, followed by diabetes being treated with exogenous insulin [15].

The TyG index was originally developed as a surrogate parameter for the determination of tissue insulin resistance [16]. Over several years, it has been validated and adapted as a reliable parameter determining the risk of cardiovascular complications [17, 18]. The TyG index has already been used multiple times in transplant patients. The benefits of kidney transplantation for cardiovascular risk have been demonstrated with the TyG index. [19]. The utility of the TyG index as a predictor of cardiovascular risk and a predictor of overall mortality was demonstrated in a group of nearly 1,000 patients undergoing liver transplantation [19]. In addition, it was demonstrated that the TyG index can be successfully used as a marker of increased risk of diabetes after transplantation in heart transplant patients. The TyG index has been studied as a risk factor for developing a severe form of pancreatitis in patients treated for native pancreatitis [20].

So far, the effect of pancreatic transplants on the decrease in the risk of cardiovascular episodes has not been described in terms of the TyG index. The authors are aware of the limitations of the small size of the study group. All patients who underwent pancreatic transplantation were included in the analysis. An additional limitation was the fact that only a proportion of patients attended follow-up visits at the scheduled time points and completed the recommended examinations. In many cases, good graft function of the transplanted pancreas resulted in progressively poorer adherence to follow-up visits.

An unquestionable advantage of the presented analysis consists in the achievement of high statistical significance. Thus, pancreatic transplant should be considered an effective way to reduce the distant risk of cardiovascular episodes in patients with type I diabetes, while this observation should be confirmed in a larger group of patients.

Conclusions

On the basis of a detailed analysis in a group of transplant recipients (PTA, SPK, or, in one case, SPL) receiving the treatment at a single center and according to a uniform scheme, a strong and positive correlation between transplantation and the reduction of TyG index was proved. In addition, as demonstrated using two statistical models, the TyG index values gradually decrease over the first 12 months after transplantation, indicating a sustained and initially progressive

reduction in the long-term risk of cardiovascular episodes in this group of patients. Substantial reduction of cardiovascular risk in pancreatic transplant recipients was statistically proven.

Authors declare no conflicts of interest.

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Figures:

1. TyG 0 vs. TyG at 1 and 3 months - TyG index before transplantation accordin to 1 and 3 months after transplantation
2. TyG 0 vs. TyG at 6 and 12 months - TyG index before transplantation accordin to 6 and 12 months after transplantation
3. TyG at 1 and 3 months vs. TyG at 6 and 12 months - TyG index 1 and 3 months after transplantation accordin to 6 and 12 months after transplantation
4. Blood glucose levels according to time
5. Blood Triglycerides levels according to time
6. Blood TyG concentrations according to time

Podsumowanie i wnioski:

Analiza skali P-PASS oraz skali PDRI w ramach pracy naukowej zatytułowanej: „Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study", w korelacji z wynikami wykonanych w Polsce przeszczepień wykazała, że zarówno P-PASS, jak i skala PDRI nie mają wystarczającego potwierdzenia w wynikach by opierać na nich sedno doboru dawców trzustki. Obie skale posiadają mierną wartość przy typowaniu najlepszych dawców trzustki – porównywalną statystycznie do rzutu monetą. Efektem pobocznym tej analizy było zidentyfikowanie dwóch czynników mających istotne statystycznie znaczenie przy doborze dawców trzustki tj. wiek i parametr BMI dawcy (wyliczany na podstawie wagi i wzrostu). Zarówno skala PDRI, jak i P-PASS zawierają w swoim modelu matematycznym oba te parametry.

Powyższy manuskrypt nie stał się podstawą do zmiany zasad doboru dawców trzustek w Polsce. Jest to procedura w znacznym stopniu regulowana przez agendę rządową tj. Poltransplant (który schemat działania opiera na Ustawie z dnia 1 lipca 2005 r. o pobieraniu, przechowywaniu i przeszczepianiu komórek, tkanek i narządów, zwanej Ustawą Transplantacyjną). Jednak wyniki pracy stały się istotną wskazówką dla zespołu Kliniki Chirurgii Ogólnej i Transplantacyjnej przy ostatecznym doborze dawców i dążeniu do jak osiągania jak najlepszych wyników przeszczepiania trzustek.

Publikacja zatytułowana: Retrospective Analysis of Pancreas Transplants in Poland in Years 1998-2015 wykazała, że w trakcie 18 lat wykonywania przeszczepień trzustki w 4 ośrodkach nie dokonano żadnej istotnej zmiany skutkującej poprawą odsetka trzustek utrzymujących dobrą funkcję w obserwacji długookresowej. Mimo rosnącego doświadczenia, stopniowego zwiększania liczby wykonywanych przeszczepień oraz coraz lepszej dostępności sprzętu i materiałów przez niemalże 2 dekady wyniki pozostawały na podobnym, niesatysfakcjonującym poziomie. Autorzy wykazali, że po roku od przeszczepienia znacząco poniżej 70% przeszczepionych trzustek utrzymuje satysfakcjonującą czynność. W obserwacji długookresowej uzyskano jedynie niewielką poprawę przeszczepionych narządów po 3 miesiącach i po roku od przeszczepienia. Jednocześnie obserwowano istotny spadek odsetka biorców z dobrą czynnością przeszczepionych narządów już po 3 latach.

W ramach drugiej części tej analizy wykonano podział liczbowych czynników charakteryzujących dawców i biorców mogących mieć wpływ na wyniki przeszczepień. Na tej podstawie określono również przedziały wieku i wskaźnika masy ciała (BMI), w przypadku

których wyniki przeszczepienia narządów były statystycznie najlepsze. Biorąc pod uwagę, że do analizy włączono 407 przeszczepień (w skali Polski zebrano maksymalną osiągalną w tamtym czasie bazę danych) pozwoliło to wyciągnąć wiarygodne wnioski. Ustalono że częstsze przeszczepianie trzustek pochodzących od dawców w wieku do 30 lat rokuje na lepsze efekty po przeszczepieniu. Ponadto dawcy o wskaźniku masy ciała BMI przekraczającym 25 w Polskiej populacji determinują gorsze spodziewane wyniki przeszczepień trzustki określane długością czasu dobrej funkcji narządu przeszczepionego. Wnioskiem ważniejszym z punktu widzenia lekarzy rodzinnych, internistów i innych rozważających skierowanie pacjentów do ośrodka transplantacyjnego jest fakt, że zauważalnie lepsze wyniki przeszczepienia trzustki już na wczesnym okresie obserwacji zanotowano u pacjentów w wieku od 21do 30 lat. Pacjenci kwalifikowani do przeszczepienia trzustki w późniejszym okresie mają często bardziej zaawansowane powikłania cukrzycy. Ale przede wszystkim mają istotnie mniejsze szanse na skuteczne leczenie choroby zasadniczej – cukrzycy.

Trzeci manuskrypt pod tytułem: „Combined Liver-Pancreas Transplantation as Novel Treatment for Patient With Cystic Fibrosis: A Case Report" jest prezentacją możliwości organizacyjnych i technicznych zespołu Kliniki Chirurgii Ogólnej i Transplantacyjnej w zakresie nietypowych i trudnych pacjentów wymagających przeszczepienia trzustki.

Badanie ostatnie, wieńczące cykl artykułów rozprawy doktorskiej nosi tytuł: „Substantial reduction of cardiovascular risk in pancreatic transplant recipients". W manuskrypcie jednoznacznie dowiedziono, że już we wczesnym okresie po przeszczepieniu trzustki (tzn. po 3 miesiącach od operacji) w badaniach zauważalne są zmiany świadczące o mniejszym ryzyku wystąpienia epizodów kardiologicznych. Oczywistym wydaje się, że po skutecznym przeszczepieniu trzustki redukcji ulega średnia wartość stężenia glukozy w surowicy krwi – świadcząc o poprawie kontroli cukrzycy. W większości przypadków jest to wyleczenie cukrzycy, o czym świadczy brak potrzeby stosowania insuliny egzogennej. Jednak badanie wykazało również szybko postępujące obniżenie stężenia trójglicerydów w surowicy krwi. Te dwa parametry, będąc składowymi TyG index, wspólnie przyczyniają się do istotnej redukcji wartości TyG index. Wyniki takie świadczą jednoznacznie o pozytywnym wpływie przeszczepienia trzustki na wieloletnie rokowanie pacjenta poprzez redukcję ryzyka epizodów kardiologicznych. Po poprawie kontroli glikemii oraz zatrzymaniu progresji powikłań cukrzycy jest to kolejny ważny argument promujący przeszczepienie trzustki jako skuteczną metodę leczenia w wybranych przypadkach cukrzycy.

Wyniki zaprezentowanych analiz były podstawą i narzędziem pomocnym we wdrożenia nowego, restrykcyjnego protokołu przeszczepienia trzustki. Poprawa wyników wykonywanych przeszczepień w stosunku do ogólnopolskich wyników osiąganych przez wiele lat jest najlepszym podsumowaniem wysiłków zespołu Kliniki Chirurgii Ogólnej i Transplantacyjnej. Wyniki ostatniej część rozprawy doktorskiej są potwierdzeniem zasadności stosowanej terapii i skuteczności protokołu przeszczepiania opracowanego przez zespół Pana Profesora Wojciecha Lisika.

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Warszawa, dnia 08.12.2025

AKBE/ 370 / 2025

Lek. Paweł Skrzypek
Katedra i Klinika Chirurgii Ogólnej
i Transplantacyjnej WUM

OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 08 grudnia 2025 r. przyjęła do wiadomości informację na temat badania pt. " Radykalna redukcja ryzyka sercowi- naczyniowego u biorców przeszczepu trzustki."
Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U.z 2018r poz.617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Warszawa, 23.02.2026 r.

Name And Surname: Kaja Śmigielska

STATEMENT

I declare that in the study entitled *"Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study"* Śmigielska K, Skrzypek P, Czerwiński J, Michalak G, Durlik M, Grochowiecki T, Nazarewski S, Szmidt J, Ziaja J, Król R, Cierpka L, Lisik W, Kosieradzki M. my scientific input was 10%.

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Kaja Śmigielska-Skrzypek

Warszawa, 24.02.2026 r.

Name And Surname: Jarosław Czerwiński

STATEMENT

I declare that in the study entitled *"Usefulness of Pancreas Donor Risk Index and Pre-Procurement Pancreas Allocation Suitability Score: Results of the Polish National Study"* Śmigielska K, Skrzypek P, Czerwiński J, Michalak G, Durlik M, Grochowiecki T, Nazarewski S, Szmidt J, Ziaja J, Król R, Cierpka L, Lisik W, Kosieradzki M. my scientific input was 2%.

Jarosław Czerwiński

Elektronicznie podpisany przez Jarosław Czerwiński
Data: 2026.03.03 17:37:56 +01'00'

Warszawa, 24.02.2026 r.

Name And Surname: Grzegorz Michalak

STATEMENT

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Warszawa, 29.10.2025 r.

Name And Surname: Marek Durlik

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Warszawa, 28.10.2025 r.

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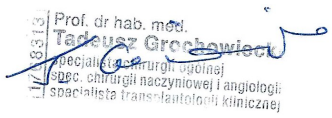

Warszawa, 28.10.2025 r.

Name And Surname: Sławomir Nazarewski

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Sławomir Nazarewski

Warszawa, 23.02.2026 r.

Name And Surname: Jacek Szmidt

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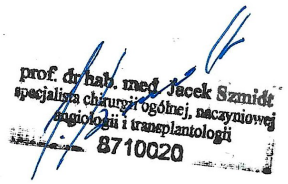

Warszawa, 28.10.2025 r.

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prof. dr hab. n. med. i n. o zdrowiu Robert Król

Katowice, 28.10.2025 r.

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Warszawa, 23.02.2026 r.

Name And Surname: Kaja Śmigielska

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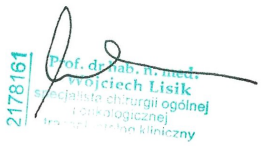

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Name And Surname: Damian Zienkiewicz

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I declare that in the study entitled *"Combined Liver-Pancreas Transplantation as Novel Treatment for Patient With Cystic Fibrosis: A Case Report"* Zienkiewicz D, Kalman P, Skrzypek P, Ziemiański P, Pacholczyk M, Kosieradzki M, Lisik W. my scientific input was 30%.

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Name And Surname: Paulina Kalman

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Paulina Kalman

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Name And Surname: Marek Pacholczyk

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STATEMENT

I declare that in the study entitled *"Substantial reduction of cardiovascular risk in pancreatic transplant recipients"* Skrzypek P, Buksińska-Lisik M, Ziemiański P, Respondek A, Śmigielska K, Sadowski K, Domienik-Karłowicz J, Kosieradzki M, Kosieradzki M, Lisik W. my scientific input was 10%.

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Warszawa, 23.02.2026 r.

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Name And Surname: Justyna Domienik-Karłowicz

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Name And Surname: Maciej Kosieradzki

STATEMENT

I declare that in the study entitled *"Substantial reduction of cardiovascular risk in pancreatic transplant recipients"* Skrzypek P, Buksińska-Lisik M, Ziemiański P, Respondek A, Śmigielska K, Sadowski K, Domienik-Karłowicz J, Kosieradzki M, Lisik W. my scientific input was 2%.

M. Kosieradzki

Warszawa, 23.02.2026 r.

Name And Surname: Wojciech Lisik

STATEMENT

I declare that in the study entitled *"Substantial reduction of cardiovascular risk in pancreatic transplant recipients"* Skrzypek P, Buksińska-Lisik M, Ziemiański P, Respondek A, Śmigielska K, Sadowski K, Domienik-Karłowicz J, Kosieradzki M, Lisik W. my scientific input was 10%.