

Evaluation of the impact of intraoperative mean arterial pressure on the long-term results of simultaneous pancreas and kidney transplantation

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Abstract

Introduction. *Simultaneous pancreas and kidney transplantation (SPKT) is an effective method of surgical treatment for patients suffering from type 1 diabetes mellitus (DM 1) in combination with end-stage renal disease as a result of diabetic nephropathy. Mean arterial pressure (MAP) of at least 90 mmHg improves hospital survival of grafts and recipients after SPKT. This paper presents the study investigating the effect of intraoperative MAP on long-term outcomes after SPKT.*

Objective. *The study objective was to evaluate the impact of the factor MAP at reperfusion in patients undergoing SPKT on the 15-year survival of kidney grafts, pancreas grafts and recipients.*

Material and methods. *A retrospective study of the effect of the MAP value at the stage of transplant reperfusion on the long-term treatment*

outcomes of 86 patients who underwent SPKT from 01.01.2007 to 12.31.2024 at the Kidney and Pancreas Transplantation Department of N.V. Sklifosovsky Research Institute for Emergency Medicine. There were 52 men (60%) and 34 women (40%), with a median age of 35 (31;39) years. Initially, the ROC analysis divided the patients into two groups: group I consisted of patients with MAP of <90 mmHg ($n=23$); group II consisted of patients with an average MAP of ≥ 90 mmHg ($n=63$). The primary point was to study the effect of a combination of factors, including the MAP value on reperfusion, on the 15-year survival rate of kidney grafts, pancreas grafts and recipients after SPKT. The end point was to analyze the 15-year survival rate of kidney grafts, pancreas grafts and recipients depending on the level of MAP during reperfusion.

Results. There was a statistically significant increase in the risk of a fatal outcome in recipients over the next 15 years after surgery, with a 5.66-fold increase in the duration of renal replacement therapy for each year ($p=0.018$), a 1.067-fold increase in BMI per 1 kg/m^2 ($p=0.036$), and a 1.782-fold decrease in the mean arterial pressure during reperfusion below 90 mmHg ($p=0.021$). The influence of the other factors was statistically insignificant. There was a statistically significant dependence of the risk of 15-year loss of a kidney graft ($p=0.017$), a pancreatic graft ($p=0.042$) and the lethality of recipients ($p=0.005$) on the level of mean arterial pressure during reperfusion. The 15-year survival rate of renal allografts was 42.3% in the group with $\text{MAP} \geq 90$ mmHg, and 38.2% in the group with $\text{MAP} < 90$ mmHg; the survival rate of pancreatic allografts was 60.8% and 48.9%, respectively; and the survival rate of recipients was 78.8% and 57.4%, respectively.

Conclusion. The MAP value of ≥ 90 mmHg during the reperfusion is a statistically significant factor of the increase in the 15-year survival rates

of a kidney graft ($p=0.017$), pancreas graft ($p=0.042$), and recipients ($p=0.005$) after SPKT.

Keywords: simultaneous pancreas and kidney transplantation, mean arterial pressure, 15-year graft survival, 15-year recipient survival

Conflict of interests Authors declare no conflict of interest

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BMI, body mass index

DM 1, diabetes mellitus, type 1

MAP, mean arterial pressure

OR, odds ratio

PG, pancreas graft

RAG, renal allograft

ROC analysis, receiver operating characteristic analysis

RRT, renal replacement therapy

SPKT, simultaneous pancreas and kidney transplantation

Introduction

Simultaneous pancreas and kidney transplantation (SPKT) is an effective method of surgical treatment of patients with type 1 diabetes mellitus (DM1) combined with end-stage renal disease due to diabetic nephropathy [1–3]. The improvement of surgical techniques [4, 5] and immunosuppressive therapy protocols, the use of new surgical techniques, and the optimization of donor conditioning seen over the past two decades have contributed to a significant improvement in outcomes after SPKT and an increase in graft and recipient survival [6–8].

It is known that stable intraoperative hemodynamic parameters have a positive effect on early outcomes [9–11]. In particular, a mean arterial pressure (MAP) of at least 90 mmHg has a positive effect on early outcomes and hospital survival of kidney and pancreas grafts and recipients. This value is of particular importance during renal allograft reperfusion (RAR), as a number of studies have shown [2, 10]. However, the influence of this parameter on long-term outcomes in SPKT has not been sufficiently studied.

This article has analyzed the long-term SPKT outcomes for 15-years.

Objective. To evaluate the impact of mean arterial pressure at the time of reperfusion on the 15-year survival of kidney and pancreas grafts and recipients after simultaneous pancreas and kidney transplantation.

Material and methods

A retrospective analysis of the impact of mean arterial pressure variable at the stage of transplant reperfusion on the long-term treatment outcomes was performed in 86 patients who underwent SPKT in the period from 01.01.2007 to 31.12.2024 in the Kidney and Pancreas Transplantation Department of the N.V. Sklifosovsky Research Institute for Emergency Medicine.

Inclusion criteria for the study were the following:

- technically successful SPKT;
- recipients must be 18 years of age or older;
- obtained consent from patients to participate in the study.

Non-inclusion criteria for the study:

- isolated kidney transplant;
- isolated pancreas transplant;
- combined KT with other organs (heart, liver).

Exclusion criteria:

- patients with insufficient or missing data on intraoperative hemodynamic parameters and outcomes.

Initially ROC analysis was performed to evaluate the prognostic accuracy and determine the optimal MAP values at the time of reperfusion, allowing the classification of recipients into two groups depending on the primary graft function. Based on the results, recipients were divided into two groups: Group I included the recipients with MAP <90 mmHg at the time of reperfusion, Group II included the recipients with MAP \geq 90 mmHg at the time of reperfusion.

The primary point of the study was to identify modifiable factors that influenced 15-year survival of recipients after SPKT. The search was based on data from literature sources, as well as previously conducted foreign studies, according to which factors influenced early and late outcomes after SPKT [13–17].

The endpoint of the study was an analysis of 15-year survival of kidney and pancreas grafts and recipients in relationship of the MAP level at reperfusion.

Loss of pancreas graft (PG) function was defined as either of the following the resumption of insulin therapy, PG removal, retransplantation, or patient death. Loss of renal allograft (RAG) function was defined as a return to dialysis, renal graft removal, retransplantation, or patient death. Graft survival was assessed from the time of transplantation to the time of functional loss, with data censored for deaths in patients with functioning grafts at the time of analysis.

Demographic and clinicopathological characteristics of donors included age, gender, cause of death, creatinine and urea levels, total amylase level, and length of stay in the intensive care unit.

The demographic and clinicopathological characteristics of the recipients included the data of gender, body mass index (BMI), type and length of renal replacement therapy (RRT), history of diabetes, and the presence of comorbid cardiac pathology.

Quantitative variables were assessed for compliance with normal distribution using the Shapiro–Wilk test. Quantitative variables with normal distribution were described using arithmetic means and standard deviations. In the absence of normal distribution, quantitative data were described using the median and the lower and upper quartiles (Me (Q₁;Q₃)). Categorical data were described using absolute values and percentages. Comparison of two groups for a quantitative variable with normal distribution, provided the variances were equal, was performed using Student's t-test. Comparison of two groups for a quantitative indicator with a non-normal distribution was performed using the Mann–Whitney U-test. Comparison of percentages in the analysis of four-field contingency tables was performed using Fisher's exact test (for values of the expected phenomenon less than 10). To calculate patient and graft survival rates in relationship to MAP levels, a Kaplan–Meier plot with the Mantel–Cox log-rank test was used. Cox's multiple regression method was used to calculate the risk coefficients for the factors and assess the significance of the odds ratios within the 95% confidence interval.

Differences were considered statistically significant at $p < 0.05$. Microsoft Office graphic editors v. 16.16.27, SPSS v. 27.0 and StatTech v. 2.8.8 were used to create diagrams and graphs.

Results

The initial ROC analysis demonstrated a relationship between primary kidney graft function and MAP values at reperfusion. The resulting ROC curve is shown in Fig. 1.

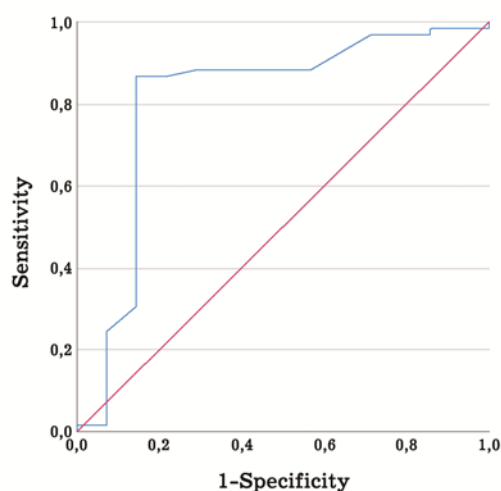


Fig. 1. ROC-curve characterizing the relationship of the primary graft function from the MAP values

The resulting ROC curve was characterized by an AUC of 0.81 ± 0.08 ; 95% CI (confidence interval) [0.66–0.96]. The model was statistically significant ($p < 0.001$).

MAP value at the cut-off point was 90 mmHg: at MAP values under 90 mmHg at reperfusion, a higher risk of developing delayed kidney graft function was noted, whereas at MAP values of 90 mmHg and above, the risk of developing a delayed kidney graft function was considered low. The sensitivity and specificity of the model at the selected MAP threshold were 85.5% and 85.7%, respectively.

Since in our study, a 100% primary PG function was achieved in all recipients, only the MAP values at renal graft reperfusion were used for the ROC curve construction model.

Thus, the recipients were distributed into two groups with respect to the mean arterial pressure values at renal graft reperfusion: group I included the recipients with $MAP < 90$ mmHg and group II included those with $MAP \geq 90$ mmHg.

The main demographic, clinical and pathological characteristics of the two groups were compared and presented in Table 1.

Table 1. Baseline original demographic, clinical and pathological characteristics of donors and recipients, factors of transplantation in the studied groups

Parameter	Group I (n=23)	Group II (n=63)	p
Donors:			
Age, years, M±SD	29.2±7.66	28.1±5.97	p=0.462*
Gender, male/female, n (%)	20 (85.7%)/3 (14.3%)	52 (83.9%)/11 (16.1%)	p=0.958**
Traumatic brain injury, males/females, n (%)	16 (71.4 %)/ 7 (28.6%)	39 (62.9%)/24 (37.1%)	p=0.600**
Acute cerebrovascular accident, men/women, n (%)	7 (28.6%)/16 (71.4%)	24 (37.1%)/39 (62.9%)	p=0.600**
Blood creatinine, µmol/L, Me (Q ₁ ;Q ₃)	94 (74;104)	91.1 (73;108)	p=0.822***
Blood urea, mmol/L, Me (Q ₁ ;Q ₃)	5.5 (4.2;7.4)	4.7 (3.9;6.3)	p=0.214***
Total blood amylase, U/L, Me (Q ₁ ;Q ₃)	73 (62;156.2)	60.5 (47.3;161)	p=0.599***
Donor's hospital stay, days, Me (Q ₁ ;Q ₃)	2 (2;3)	2 (1;2.5)	p=0.235***
Recipients:			
Age years M±SD	35.57±5.9	34.84±5.52	p=0.607*
Gender, male/female, n (%)	11 (47.6%)/12 (52.4%)	22 (35.5%)/41 (64.5%)	p=0.437**
BMI, kg/m ² , Me (Q ₁ ;Q ₃)	21.4 (20.1;22.7)	20.7 (19.3; 22.2)	p=0.164***
History of diabetes, years, Me (Q ₁ ;Q ₃)	28 (23;31)	24 (20;28)	p=0.129***
RRT duration, years, Me (Q ₁ ;Q ₃)	4 (1;6)	2 (1;4)	p=0.241***
Concomitant cardiac pathology:			
Hypertension, n (%)	8 (38%)	17 (27.4%)	p=0.566**
Ischemic heart disease, n (%)	2 (9.5%)	12 (19.3%)	p=0.311**
Transplantation factors:			
The number of incompatible antigens in the HLA system, Me (Q ₁ ;Q ₃)	5 (4;6)	5 (4;6)	0,794***
– cold ischemia time, hours:	7 (5;9)	7.5 (6;10)	0.334***
– RAG, Me (Q ₁ ;Q ₃)	8.5 (7;9)	9 (8;10.5)	0.081***
– PAG, Me (Q ₁ ;Q ₃)			
– surgical technique for pancreatic juice drainage of:			
<i>making duodenoduodenoanastomosis,</i> n (%)	12 (57.1%)	38 (61.3%)	0.799**
<i>making duodenojejunostomy,</i> n (%)	6 (28.6%)	17 (27.4%)	1.000**
<i>Positive bacteriology examination of perfusate,</i> n (%)	4 (19%)	5 (8.1%)	0.221**

Notes: Differences in parameters are statistically significant at p<0.05; * Student's t -test; ** Fisher's exact test; *** Mann-Whitney U-test

Cox regression was used to assess the complex impact of factors on 15-year recipient survival. The results are presented in Table 2.

Table 2. Analysis of the impact of predictors on the 15-year survival rate of recipients after simultaneous pancreas and kidney transplantation

Risk factor	Risks in the presence of the factor		p
	Risk ratio	95% [CI]	
DONOR-ASSOCIATED FACTORS			
Donor age, years	0.953	[0.65–1.14]	0.509
Donor gender, male/female	1.62	[0.75–4.85]	0.875
Body mass index, kg/m ²	0.45	[0.11–1.85]	0.923
Blood creatinine, µmol/L	0.95	[0.43–2.05]	0.901
Donor length of hospital stay, days	1.03	[0.19–5.89]	0.665
RECIPIENT-ASSOCIATED FACTORS			
Recipient age, years	1.107	[0.148–3.089]	0.181
Recipient gender, male/female	0.171	[0.020–1.450]	0.105
Duration of renal replacement therapy, years	5.66	[1.34–24.3]	0.018*
History of diabetes mellitus, years	1.13	[0.88–2.95]	0.512
Body mass index, kg/m ²	1,067	[1.009–1.885]	0.036*
Hypertension	0.640	[0.134–3.052]	0.576
Ischemic heart disease	0.298	[0.029–3.022]	0.306
TRANSPLANTATION FACTORS			
Surgery duration, min	0.999	[0.988–1.009]	0.783
RAG cold ischemia time, hours	0.900	[0.615–1.917]	0.589
PAG cold ischemia time, hours	0.898	[0.412–1.960]	0.788
Volume of intraoperative infusion, mL	1.001	[0.965–1.007]	0.190
MAP < 90 mmHg	1.782	[1,336–6,437]	0.021*
Volume of intraoperative blood loss, mL	0.950	[0.31–1.94]	0.884
Intraoperative use of catecholamines	0.71	[0.22–1.99]	0.485
Early extubation in the operating room	3,006	[0.533–16.958]	0.212
The number of incompatible antigens in the HLA system	1.021	[0.82–1.23]	0.951

Notes: * – the impact of the factor is statistically significant (p<0.05)

According to the analysis results, the risk of developing a fatal outcome in recipients over the next 15 years statistically significantly increased by 5.66 times (p=0.018) with every 1-year increase in the length of RRT; by 1.07 times (p=0.04) with an increase in BMI by 1 kg/m²; and by 1.78 times (p=0.021) with a decrease in the mean arterial pressure during reperfusion to lower than 90 mmHg. The impact of other factors was statistically insignificant.

Fig. 2 shows the RAG survival graphs in groups I and II over 15 years.

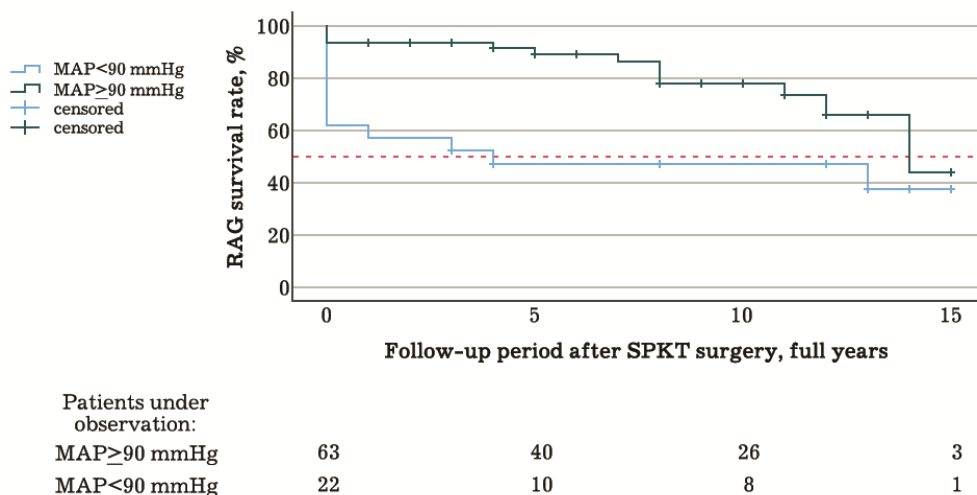


Fig. 2. Comparison of 15-year renal allograft survival rates in the study groups

The relationship of the risk of the RAG function loss from the MAP values at reperfusion was statistically significant ($p=0.017$). The median period of the RAG function loss in patients of group II was 14 years, while in group I it was only 4 years. The mean period of the RAG function loss was 12.2 ± 0.7 years with $\text{MAP} > 90$ mmHg, and 7.3 ± 1.5 years with $\text{MAP} < 90$ mmHg. The 15-year RAG survival rate was 42.3% in group II, and 38.2% in group I, respectively.

Fig. 3 shows the graphs of 15-year survival of PG in the studied groups of recipients.

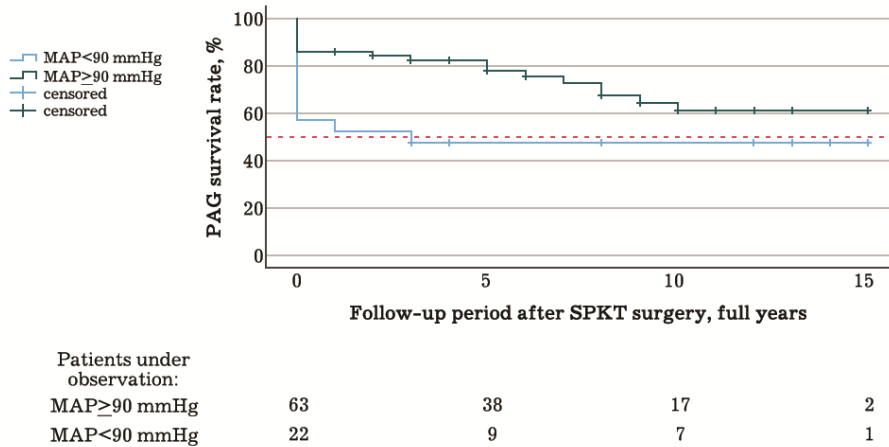


Fig. 3. Comparison of 15-year pancreas allograft survival rates in the study groups

The relationship of the PG function loss from the MAP values at reperfusion was statistically significant ($p=0.042$). The mean period of PG loss was 10.8 ± 0.8 years in patients in group II, while in patients in group I it was 7.3 ± 1.6 years, respectively. The 15-year survival rate of PG in group II was 60.8%, while in group I it was 48.9%.

Fig. 4 shows graphs of 15-year recipient survival rates in two groups after SPKT.

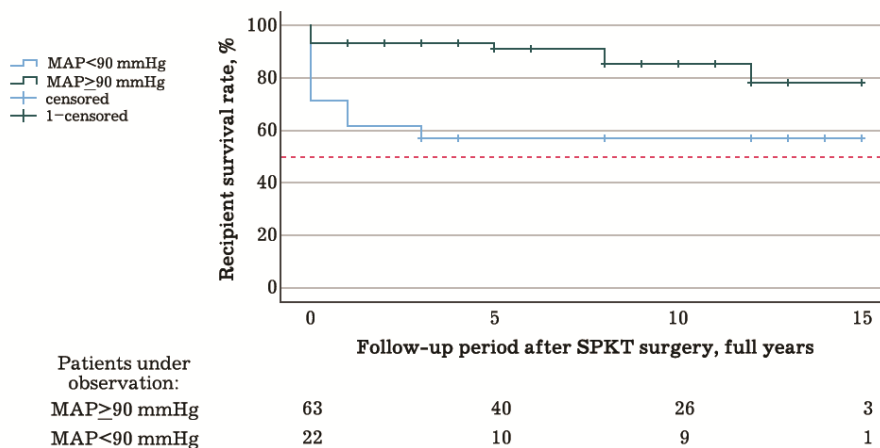


Fig. 4. Comparison of 15-year recipient survival rates in the study groups

The relationship of the risk of death in recipients after SPKT from the mean arterial pressure (MAP) values at reperfusion was statistically significant ($p=0.005$). The median time points for the occurrence of fatal outcomes within a given time period were not reached in either group. The mean time to death in group II was 13.2 ± 0.6 years, while in group I it was 8.8 ± 1.6 years. A 15-year survival rate of recipients in group II was 78.8%, while in group I it was 57.4%, respectively.

Обсуждение

Discussion

Successful outcomes in SPKT depend on a combination of factors. Proper patient management in the intraoperative period plays a significant role in this process. Studies have shown that stable intraoperative hemodynamic parameters at reperfusion stages of the grafts have a positive effect on early postoperative outcomes [2, 10, 12]. Adequate intraoperative graft perfusion and normovolemic status of recipients are key factors in preventing reperfusion injury that, according to some authors, is the main cause of early graft dysfunction [2, 11, 18]. Other studies emphasize the importance of factors such as the surgery duration, cold ischemia time for grafts, as well as the stability of hemodynamic parameters at reperfusion stages, which can also have a significant impact on both short-term and long-term results and the function of transplanted organs [10, 11, 19].

With regard to isolated kidney transplantation, a number of series have shown that MAP below 70 mmHg, as well as a decrease in intraoperative central venous pressure below 8 mmHg during renal graft reperfusion were associated with an increased incidence of early RAG dysfunction [10, 20]. On the other hand, MAP above 95 mmHg in combination with a central venous pressure above 12 mmHg was

associated with an increased incidence of immediate primary RAG function, as well as with better long-term outcomes [21, 22]. In their study, R. Sucher et al. demonstrated that a mean arterial pressure (MAP) exceeding 91 mmHg during graft reperfusion resulted in better early and late results; this work was performed in relation to SPKT [10]. Our study assessing the impact of hemodynamic parameters such as the primary initial graft function and the in-hospital graft and recipient survival rates on the early results in SPKT indicated a favorable effect of MAP exceeding 90 mmHg of [2]. However, prior to this study, no studies had been conducted on the MAP on long-term results after SPKT.

Among the general factors that significantly influence the early and late outcomes in SPKT, three groups can be distinguished [13, 14]. It is customary to distinguish between a donor-dependent group, a recipient-dependent group, and a group of transplantation factors. Among the donor-associated factors, the most significant are considered to be gender, age, donor BMI, and the length of donor stay in hospital [23, 24]. Recipient-dependent factors include age, gender, BMI, the type and length of diabetes, the RRT type and period, and the presence of comorbid pathology [15-17]. Among the transplantation factors, the most significant are the surgery duration, the graft preservation period, the intraoperative infusion therapy volume and blood loss, MAP at reperfusion lower than 90 mmHg, the rate of early extubations in the operating room, and immunological HLA incompatibilities in the donor-recipient pair [25–27]. The design of our study included the investigation of the impact of all three groups of factors on the 15-year survival of recipients, with the subsequent isolation of a separate MAP parameter in the event of its statistically significant impact on the long-term graft and recipient survival rates. The results obtained in this study when examining the effect of MAP values on the long-term survival are

consistent with those from a similar study conducted by our foreign colleagues [10].

One more fact should be separately noted. In our previous study, we noted that all patients who underwent SPKT achieved primary initial PG function regardless of the MAP level at the time of PG reperfusion. This can be easily explained by the initially low blood flow velocity in the pancreas; therefore, the MAP value during PG reperfusion is not as crucial as during RAG reperfusion. However, in this study, we analyzed the MAP data during PG reperfusion and the impact of these values on the 15-year survival. The relationship of the risk of PG function loss from MAP values at reperfusion assessed using the Mantel-Cox log-rank test, was statistically significant ($p=0.042$). The 15-year PG survival amounted to 60.8% in the group with $\text{MAP} \geq 90$ mmHg, and only to 48.9% in the group with mean arterial pressure < 90 mm Hg, respectively.

In this study, donor-associated and recipient-dependent factors were also studied as predictors of 15-year graft and recipient survival. Among these, the length of recipient RRT ($p=0.018$) and the increase in recipient BMI ($p=0.036$) showed a statistically significant increase in the risk of death over the next 15 years. This is confirmed by a number of foreign studies, in particular, C. J. Webb et al. found that transplantation in the pre-dialysis stage of end-stage renal failure pose a statistically significant effect on the reduction in the number of complications and reduces the time of hospitalization [28]. In addition, L. S. Martins et al. revealed a 5.5-fold increase in the risk of adverse outcomes for recipients when RRT was administered at the time of surgery [17].

In recipients with a $\text{BMI} \geq 30$ kg/m², an increase in post-transplant complications was observed, including delayed RAG function and PG acute rejection and thrombosis, according to the study by M. S. Sampaio et al. [29].

Finally, the limitations of this study should be discussed. Our study design relied solely on MAP without directly assessing blood-flow-related variables such as stroke volume or cardiac output. Using data obtained through advanced hemodynamic monitoring methods might further deepen and more specifically examine their impact on graft reperfusion and postoperative outcomes.

It is worth noting that at the moment there is an insufficient number of studies aimed at investigating the impact of intraoperative factors on the outcomes in SPKT, which may be the grounds for investigating this issue by continuing the studies with a prospective design in the future.

Conclusions

1.The risk of developing a fatal outcome in recipients over the next 15 years statistically significantly increased by 5.66 times ($p=0.02$ with every 1-year increase in the length of RRT; by 1.07 times ($p=0.04$) with an increase in BMI by 1 kg/m^2 ; and by 1.78 times ($p=0.02$) with a decrease in the mean arterial pressure during reperfusion to lower than 90 mmHg.

2.Mean arterial pressure ≥ 90 mmHg during the reperfusion stages is a factor associated with increased 15-year survival of kidney grafts ($p=0.02$), pancreas grafts ($p=0.04$), and recipients ($p=0.005$).

3.Maintaining an optimal level of intraoperative blood pressure is essential for the successful functioning of kidney and pancreas transplants in the late postoperative period.

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