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Impact of long-distance (up to 3.500 km) deceased donor liver transportation on cold ischemia time, initial graft function and transplant outcomes

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Abstract

Rationale. *Currently, a long-distance transportation of the deceased donor livers is not a routine practice for Russian transplantation centers; therefore, a research-based analysis of even relatively small single-center experience seems to be a topical task.*

The study purpose *was to evaluate the impact of long-distance donor liver transportation on the cold ischemia time, the initial graft function as well as on immediate and long-term transplant outcomes.*

Material and methods. *The retrospective single-center study included the data on specific features and results of 72 consecutive deceased donor liver transplantations. The cases were allocated into two groups depending on cold ischemia time: for less than 9 hours (group 1; n = 41) and for 9 hours or longer (group 2; n = 31). The parameters of donor*

organ transportation, characteristics of donors and recipients, specific features of surgery and the early postoperative period, immediate and long-term outcomes were compared between the groups. For the entire sample size, the relationship between the distance from the donor hospital to the transplant center, the transportation type and time, and the cold ischemia time were assessed.

Results. *Donor livers were delivered from hospitals 40-3500 km away from the transplant center, including by using regular air flights in 67% of cases. Transportation time varied from 1 to 8 h (median 3.5 h), which made 41% (interquartile range: 35-54%) of cold ischemia time.*

No statistically significant differences between the groups were seen in the donor, recipient and surgery characteristics. The median distance was 509 km in group 1 (interquartile range 130-1321 km), and 1321 in group 2 (interquartile range 897-3441 km), p<0.001; transportation time was 3.5 h (interquartile range : 2.5–4.7 h) and 3.5 h (interquartile range: 3.3–7.0 h), p = 0.022, the cold ischemia time was 8 h (interquartile range: 7–9.5 h) and 10 hours (interquartile range: 9-10.5 h), p <0.001, in group 1 and group 2, respectively, the difference being statistically significant for all parameters.

Despite the tendency to increases in the incidence of the early allograft dysfunction (6/41 in group 1, 9/31 in group 2; p = 0.155), primary graft non-function (1/41 in group 1, 3/31 in group 2; p = 0.308), and the graft loss incidence during the first 6 weeks (4/41 in group 1; 7/31 in group 2; p = 0.189), these differences did not reach the statistical significance.

Conclusion. *The results of this retrospective study have confirmed the feasibility and clinical efficacy of donor liver transplantation after long-distance transportation. However, cold ischemia time exceeding 9 hours is the risk factor for poor initial graft function.*

Keywords: organ donation, liver transplantation, transportation

Conflict of interests Authors declare no conflict of interest
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CVA, cerebrovascular accident
ALT, alanine aminotransferase
AST, aspartate aminotransferase
BMI, body mass index
BP, blood pressure
CI, confidence interval
CIT, cold ischemia time
EAD, early allograft dysfunction
FFP, fresh frozen plasma
HAT, hepatic artery thrombosis
HCC, hepatocellular carcinoma
IQR, interquartile range
LC, liver cirrhosis
LT, liver transplantation
MLV, mechanical lung ventilation
MOFS, multiple organ failure syndrome
PNF, primary non-function

Introduction

Transportation of a donor organ is an integral part of its transplantation process, and its duration largely determines the cold

ischemia time (CIT) [1-3]. The results of the studies to search for the factors affecting the initial function of transplanted organs and the surgery outcomes indisputably prove that an increase in CIT is significantly associated with an increasing risk of an early graft dysfunction or primary graft non-function [4-6]. Expanding the criteria for the donor organ suitability for transplantation is a necessary measure in the context of the growing need for operations; and CIT minimizing in most cases seems to be the only real way to achieve acceptable results of organ transplantation.

Though coordinating the work of donor services and transporting donor organs over long distances are none of new issues in the world practice, their relevance for the Russian program of organ transplantation, including liver transplant, has become apparent only in recent years. This is mainly due to the development of regional donor and transplantation programs. Over the recent decade, the number of deceased donor liver transplantations (LT), and centers where this intervention is performed has increased 3-fold; there were 121 transplants performed in 10 centers in 2010, and 341 transplants in 28 centers in 2019 [7, 8].

In 2009, the first report of the Russian Transplantation Society noted according to its Register "*at the time of reporting, in contrast to the practice of developed countries in Europe and the United States, Russia does not have a national system for organizing organ donation. The task of ensuring the work of transplant centers is being solved by them individually, and only in Moscow, St. Petersburg and Yekaterinburg - by independent centers for coordinating organ donation*" [9]. Despite an increased number of effective deceased donors and organs removed for transplantation in the latest years, there were no systemic changes in the organization of the donor process: as a rule, organs were sent from donor hospitals to the nearest transplant centers. With such an approach, the

time required for transportation and the transportation distance were minimal, which, however, was not consistent with the minimum cold ischemia time.

In the long run, when local donor programs are combined into a coordinated national system and organ allocation is implemented on the basis of a central single waiting list, the need for transporting donor organs, including over long distances, will increase many times. Therefore, it is already now relevant to investigate the impact that long-time transportation has on the transplantation outcomes.

A distinctive feature of the deceased donor liver transplantation program which has been operating in the *State Research Center – Burnasyan Federal Medical Biophysical Center* since 2012, is in using a high rate of grafts obtained at a significant distance from the Center. In this regard, the data accumulated for years may be retrospectively analyzed in order to assess the impact of donor liver transportation on the CIT, the initial graft function, and immediate and long-term results of operations.

Material and methods

The analysis included data of 72 liver transplantations from postmortem donors performed consecutively at the *State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency of Russia* in the period from May 2012 to September 2018. The organs were obtained from 71 donors; in one case, a split transplant was performed. The commonly accepted parameters pertinent to donors, recipients, grafts, and surgical interventions were investigated. The graft dysfunction in the early postoperative period (early allograft dysfunction or EAD) was defined according to K. Olthoff's criteria, 2010 [10]; a primary graft non-function (PNF) was defined according to UNOS

criteria, 2014 [11]. All cases were divided into two groups depending on the graft cold ischemia time (CIT): "Group 1" implied CIT up to 9 hours, and "Group 2" implied CIT of 9 hours or more.

The choice of the cutting point equal to 9 hours was determined primarily by the ideas developed in native practice about the acceptable liver graft CIT. For example, Ya.G. Moisyuk et al. [12] analyzing a series of 220 consecutive operations found that CIT of over 8 hours was an independent risk factor for poor initial graft function and increased the risk of EGD by 2.5 times; and CIT of less than 6 hours was the criterion mandatory for a "standard liver donor". O.O. Rummo et al. [13] having analyzed a 7-year liver transplantation experience (317 operations) in the Republic of Belarus showed that the total graft ischemia time in no single case exceeded 9 hours. Meanwhile, the distance to the most remote donor base did not exceed 350 km, and a well-developed road network made it possible to transport the organ in up to 4 hours.

Statistical data processing

To describe the quantitative variables, the median and the interquartile range (IQR) were calculated, as well as their minimum and maximum values. For qualitative parameters, the absolute frequencies were presented; where appropriate, relative frequencies expressed as a percentage were given. The nonparametric Mann–Whitney two–sided test was used to determine differences in quantitative variables between two independent groups, and the exact two-sided Fisher test was used for qualitative variables. To assess the relationship between two quantitative abnormally distributed variables, Spearman's rank correlation coefficient (R) was calculated, and its statistical significance was checked using Student's t-test.

The graft and recipient survival rates were calculated by the Kaplan-Meier method with a 95% confidence interval (95% CI). When calculating the relative risk of an event occurrence, 95% CI was also given. Calculations were performed using Statistica 12 software package (Stat Soft Inc., USA).

Results

Distance, transportation time, and graft cold ischemia time

In 4 cases (6%), procurements were performed in the clinic of the Center andno organ transportation was required. In other cases, the organs were retrieved in donor hospitals located in 18 cities of the Russian Federation at a distance of 40-3500 km. The transportation time ranged from 1 to 8 hours (median 4 hours, IQR: 3-5 h) and was determined not only by distance, but also by the kind of transportation used: the ground vehicles were used for transportation over the distance from the donor base less than 400 km (n = 19; 27%), and regular air flights were used for transportation over a greater distance (n = 48; 67%) (Fig. 1).

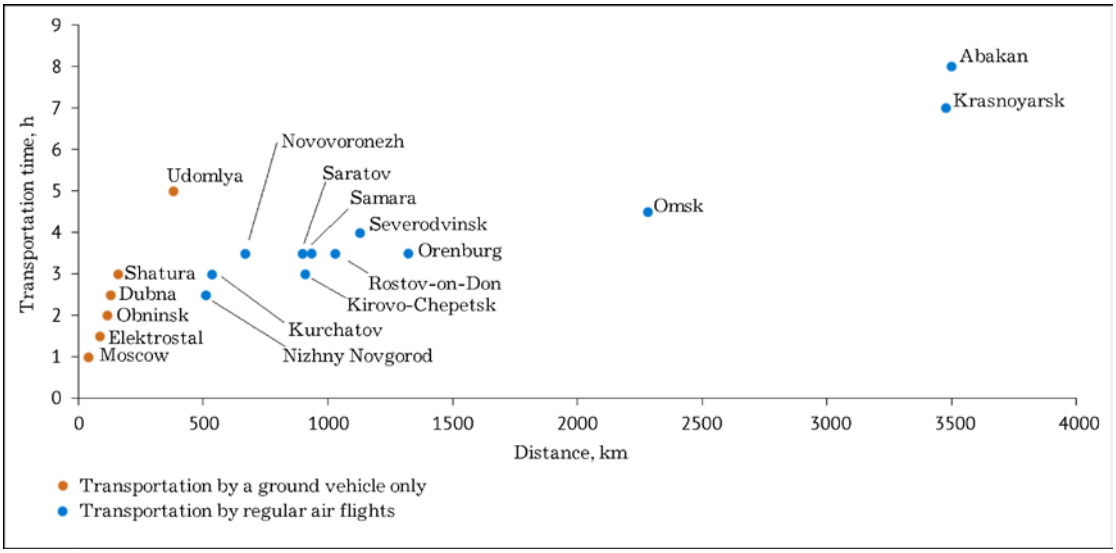

Fig. 1. Median transportation time depending on the distance from the donor hospital

Transportation time was a significant part (median 44%, IQR: 36-56 %) in CIT. Despite the obvious trend of increasing CIT time with increasing distance from the donor base (Fig. 2A) and transportation time (Fig. 2B), a statistically significant relationship between these parameters was obtained only in the cases when an air transportation was used; the R coefficient values were 0.31 ($p < 0.050$) and 0.34 ($p < 0.050$).

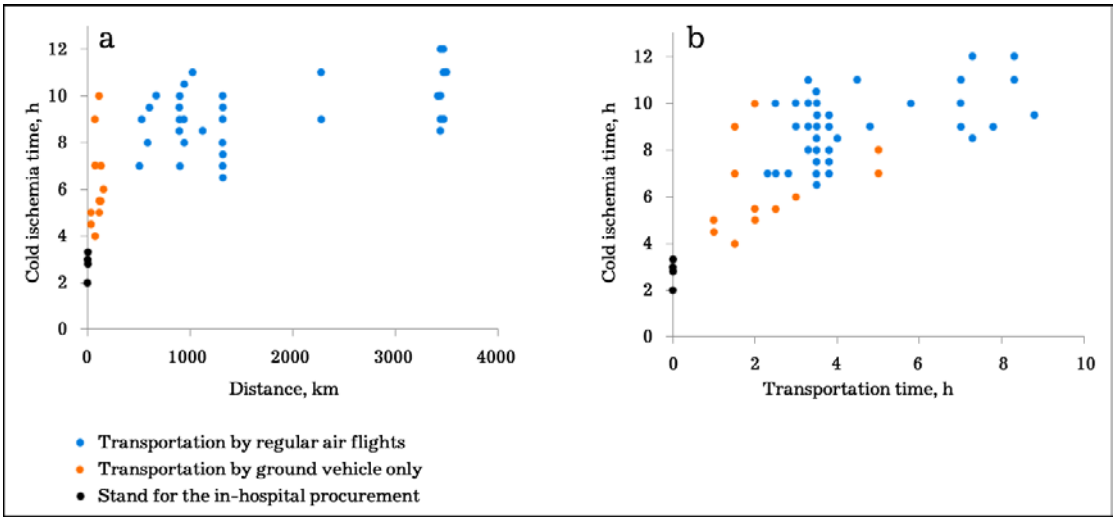

Fig. 2. Relationship between the graft cold ischemia time and the distance to the donor base (A), the transportation time (B)

The median graft CIT *without taking into account the transportation* time per se in the entire study group was 4.3 hours (IQR 3.0-5.5 hours): 3.8 hours (IQR 2.8-4.5) when using only motor vehicle transport, 4.7 hours (IQR 3.9–5.8 hours) when using air transport, $p = 0.015$, statistically significant. The increase in this CIT component when using regular air flights is likely due to pre-flight procedures and the time required to leave the aircraft.

Characteristics of donors and recipients

A comparative analysis in the characteristics of effective donors and obtained grafts revealed no clinically or statistically significant differences in any of the parameters, except for the CIT, which value was used to form the groups (Table 1). The decision on the organ suitability for transplantation was made on the basis of a combined assessment of clinical and laboratory donor data, the visual assessment of the liver before and after the perfusion with preservative solution, which was immediately reported to the transplant center. An urgent histological examination was not performed; in retrospective morphological control, the degree of macrovesicular steatosis in none of the cases was higher than the assessment made by the donor service surgeon.

Table 1. Characteristics of donors and grafts. Quantitative parameters are presented as Median [25–75%] (minimum - maximum)

	All cases	**Group 1** **CIT < 9 h**	**Group 2** **CIT ≥9 h**	***p***
N	**71** (100%)	**41** (58%)	**30** (42%)	
CIT, h	**8** [7–9,5], (2–12)	**7** [6–8], (2–8,5)	**10** [9–10,5], (9–12)	**<0.001**
Age, years	**46** [34–57], (20–63)	**48** [35–57], (20–63)	**45** [34–56], (20–63)	0.635
Male, n (%)	**46** (65%)	**27** (66%)	**19** (63%)	1.000
Cause of brain death, n (%) Trauma CVA	 **16** (23%) **55** (77%)	 **8** (20%) **33** (80%)	 **8** (27%) **22** (73%)	 0.569

MLV duration, days	**2** [1–2], (1–7)	**2** [1–2], (1–7)	**2** [2–2], (1–7)	0.290
AST, U/L	**30** [19–42], (10–160)	**30** [20–35], (10–160)	**30** [19–44], (10–84)	0.888
ALT, U/L	**24** [17–36], (7–92)	**24** [17–40], (8–92)	**24** [16–35], (7–73)	0.472
Blood bilirubin, mcmol/L	**9** [6–12], (2–23)	**9** [6–12], (3–23)	**9** [6–11], (2–17)	0.592
Blood creatinine, mmol/L	**102** [76–140], (33–525)	**109** [75–134], (33–525)	**97** [76–143], (59–247)	0.788
Na, mmol/L	**149** [142–156], (124–178)	**150** [143–158], (124–178)	**145** [140–154], (129–177)	0.382
BP support, n (%): No support Dopamine Norepinephrine Dopamine + Norepinephrine	 **13** (18%) **14** (20%) **40** (56%) **4** (6%)	 **9** (22%) **8** (20%) **22** (53%) **2** (5%)	 **4** (13%) **6** (20%) **18** (60%) **2** (7%)	0.819
Dopamine dose, mcg/kg/min	**5** [4–7], (2–15)	**6** [5–7], (4–15)	**5** [3.5–6.5], (2–9)	0.203
Dose of norepinephrine, ng/kg/min	**265** [170–450], (50–1300)	**265** [185–450], (80–800)	**270** [125–450], (50–1300)	0.935
Steatosis by				

visual assessment, n (%) 0% ≤ 30% 31–50%	 **27** (38%) **43** (60%) **1** (2%)	 **17** (41%) **23** (56%) **1** (3%)	 **10** (33%) **20** (77%) **0** (0%)	 0.509
Donor Risk Index [14]	**1.58** [1.39–1.94]. (1.11–2.32)	**1.58** [1.28–1.94]. (1.11–2.26)	**1.64** [1.46–1.96]. (1.25–2.32)	0.317

Notes: BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MLV, mechanical lung ventilation; CVA, cerebrovascular accident

The selection of patients for transplantation was made according to commonly accepted criteria, taking into account the donor-recipient blood group compatibility, the severity of liver transplant candidate condition, the anthropometric ratio of the donor and recipient characteristics and was not dependent on the distance between the donor base and anticipated CIT. Exceptions were the individual cases when the candidate for transplantation had a pronounced adhesive process in the abdominal cavity after previous surgical interventions or a widespread parasitic lesion, and the expected long-term hepatectomy could lead to an increase in the graft CIT to 14 hours or more. In all operations, we tried to minimize the warm ischemia time – in no case did it exceed 50 minutes. There were no statistically significant differences between the groups in the preoperative patient characteristics and the main parameters of operations (Table 2).

Table 2. Characteristics of patients and surgery. Quantitative parameters are presented as Median [25–75%] (minimum - maximum)

	All cases	**Group 1** **CIT < 9 h**	**Group 2** **CIT ≥9 h**	***p***
N	**72** (100%)	**41** (57%)	**31** (43%)	
Age, years	**46** [40–54], (24–67)	**47** [40–54], (25–67)	**44** [39–56], (24–66)	0.676
Male, n (%)	**42** (62%)	**26** (70%)	**16** (52%)	0.344
BMI, kg/m^2	**25** [22–28], (15–38)	**26** [23–28], (18–38)	**23** [21–28], (15–33)	0.183
MELD	**16** [12–21], (8–37)	**15** [12–21], (8–35)	**17** [12–20], (8–37)	0.560
MELD-Na	**17** [12–24], (8–37)	**17** [12–21], (8–35)	**19** [12–25], (8–37)	0.690
Indications to primary LT, n (%)				
Viral LC	**26** (42%)	**18** (53%)	**8** (29%)	
HCC	**13** (21%)	**7** (20%)	**6** (21%)	
LC of unknown etiology	**9** (14%)	**4** (12%)	**5** (18%)	>0.050
Cholestatic LC	**8** (13%)	**3** (9%)	**5** (18%)	
Autoimmune LC	**3** (5%)	**0** (0%)	**3** (10%)	
Others	**3** (5%)	**2** (6%)	**1** (4%)	
Retransplantation, n (%)	**10** (14%)	**7** (17%)	**3** (10%)	0.499

Urgent LT, n (%)	**3** (4%)	**2** (5%)	**1** (3%)	1.000
Surgery duration, h	**7** [6–8], (3–15)	**7** [6–8], (3–9)	**7,5** [6,5–8], (4–15)	0.192
Transfusion of blood components:				
FFP, ml	**2400** [1850–3000], (1000–6100)	**2200** [1700–3000], (1150–4450)	**2450** [1900–2900], (1000–6100)	0.656
Packed RBCs, ml	**600** [0–1200], (0–2700)	**570** [0–1200], (0–2500)	**650** [300–1100], (0–2700)	0.263
Blood reinfusion, ml	**700** [0–1200], (0–5700)	**750** [0–1000], (0–3000)	**600** [0–1200], (0–5700)	0.690

Notes: HCC, hepatocellular carcinoma; BMI, body mass index; FFP, fresh frozen plasma; LT, liver transplantation, LC, liver cirrhosis

Thus, the two compared groups differed in the graft CIT and transportation parameters (Table 3). Remaining characteristics were comparable, which made it possible to correctly analyze the transplantation results and assess the impact of prolonged donor organ preservation on the initial graft function and surgery outcomes.

Table 3. Parameters of donor organ transportations. Quantitative parameters are presented as Median [25–75%] (minimum - maximum)

	All cases	**Group 1** **CIT < 9 h**	**Group 2** **CIT ≥9 h**	***p***
N	**72** (100%)	**41** (57%)	**31** (43%)	
Transportation time, h	**3.5** [2.5–4.7], (0–	**3.5** [2.3–3.8], (0–	**3.5** [3.3–7], (1.5–	**0.022**

	8.8)	7.3)	8.8)	
Distance, km	**907** [382–1321], (0–3498)	**509** [130–1321], (0–3445)	**1321** [897–3441], (75–3498)	**<0.001**
Transportation method, n (%)				**0.005**
Without transportation	**4** (6%)	**4** (10%)	**0** (0%)	
Road transport	**20** (28%)	**16** (39%)	**4** (13%)	
Air transport	**48** (66%)	**21** (51%)	**27** (87%)	
The transportation time share in the total duration of cold ischemia time, %	**41** [35–54], (0–92)	**44** [36–50], (0–85)	**39** [33–64], (17–92)	0.760

Initial graft function and transplant outcomes (Table 4)

The relative incidence rates of reversible EAD and PNF in the group of patients who received a graft with CIT of 9 hours or more were 2 and 5 times higher, respectively, than in the group with CIT of less than 9 hours, but these differences were not statistically significant. The relative risk of poor initial graft function (all cases of EAD and PNF) for Group 2 was 2.27 (95% CI: 1.01-5.08). The tendency to a higher peak level of cytolytic enzymes, reflecting the severity of ischemic and reperfusion injury, in patients of Group 2 did not show statistical significance. Moreover, the cumulative analysis of all cases did not reveal a statistically significant relationship between the graft CIT and the maximum AST or ALT levels in the postoperative period; the R coefficient was 0.17 ($p > 0.05$).

The relative risk of death in the early postoperative period due to poor initial graft function at CIT of at least 9 hours was 6.61, which, however, was not statistically significant; 95% CI 0.81-53.78.

Table 4. Initial graft function and transplant outcomes

	All cases	**Group 1** **CIT < 9 h**	**Group 2** **CIT ≥9 h**	***p***
N	**72** (100%)	**41** (57%)	**31** (43%)	
EAD, n (%)	**15** (21%)	**6** (15%)	**9** (29%)	0.155
PNF, n (%)	**4** (6%)	**1** (2%)	**3** (10%)	0.308
Peak AST/ALT, U/L	**648** [413–1433], (85–8039)	**554** [334–962], (85–8039)	**748** [482–3880], (109–6573)	0.072
MLV for over 24 h, n (%)	**18** (25%)	**8** (21%)	**10** (32%)	0.275
Graft losses and fatal outcomes within 6 weeks after LT, n (%)	**11** (15%)	**4** (10%)	**7** (23%)	0.189
Causes of the graft losses, n: PNF HAT Rejection Recipient's death	 **4** **1** **1** **5**	 **1** **0** **0** **3**	 **3** **1** **1** **2**	0.463
Causes of death, n: Absent/poor initial graft function MOFS Sepsis	 **6** **3** **2**	 **1** **2** **1**	 **5** **1** **1**	0.308
6-month graft and recipient survival	**79%** (68–89%)	**84%** (73–96%)	**71%** (46–85%)	> 0.050

Notes: HAT, hepatic artery thrombosis*;* MOFS, multiple organ failure syndrome

Discussion

In this case series, with comparable characteristics of donors, initial patient conditions and surgical interventions, no statistically significant differences were found in terms of the initial graft function and the immediate transplant outcomes, which claims in favor of reasoning and clinical feasibility of using grafts with CIT time of 9-12 hours. On the other hand, the current tendency to an increased incidence of poor initial graft function with increasing CIT time is consistent with the results of previous studies and current ideas that one of the key points in organizing and coordinating the transplant process is to minimize the preservation period.

This analysis has some limitations that should be taken into account in the critical review of the results obtained. First, a relatively small number of cases did not allow us to reach the desired statistical power, which could have potentially resulted in underestimating the significance of some relationships. Second, organs for transplantation were obtained mainly from donors who met the standard criteria, so it would be imprudent to extrapolate the findings to the situations where the liver from expanded criteria donors or marginal donors was used for transplantation.

In all cases, active conditioning of a deceased donor was performed throughout the entire period of time from the diagnosis of death to the start of cold perfusion. The target values of the donor's physiological parameters during this period are shown in Table 5.

Table 5. Target values of basic physiological parameters during deceased donors-conditioning

Parameter	Target values
Heart rate	60-120 beats/min
Blood pressure	Systolic BP: over 100 mmHg Mean arterial pressure: no lower than 70 mm Hg
Central venous pressure	6-10 mm Hg (8-15 cm H_2O)
Diuresis rate	0.5-3 ml•kg/h
Blood plasma electrolytes	Na^+: 130-150 mmol/L K^+, Ca^+, Mg^+, P^+: within the normal range Blood glucose: 4-8 mmol/L
Arterial blood gases	pH: 7.35-7.45 $PaCO_2$: 35–45 mm Hg PaO_2: at least 80 mm Hg SpO_2: no less than 95%

Special attention was paid to maintaining adequate hemodynamic parameters by controlling the circulating blood volume and cardiac output, using dopamine and/or norepinephrine if necessary, while considering the optimal doses not exceeding 10 μg/kg min and 500 ng/kg/min, as well as vasopressin infusion at a dose of no more than 2 U/h and/or intravenous boluses of desmopressin at a dose of 1-4 mg every 6 hours to correct the manifestations of diabetes insipidus under the control of the diuresis rate.

In current clinical practice, when a histidine-tryptophan-ketoglutarate solution is used for preservation, and the donor organ is transported in a customary isothermal container without the possibility of temperature monitoring and control, the threshold value of the safe CIT for a graft from a standard criteria donor should be considered 12 hours.

Liver from an expanded criteria donor can also be transported over long distances, but in this case the CIT should not exceed 9 hours. The choice of these time limits is based on the acquired experience and does not mean that their excess excludes the possibility of successful transplantation. If the specified time limits are exceeded, additional objective data are needed to assess the risk of a primary graft non-function, and therefore the feasibility of performing transplantation; such data could have been obtained during normothermic perfusion of the donor organ after its delivery to the transplantation center. However, such technologies are not yet available in Russia.

Conclusion

Even taking into account the large area of the country and the long distances between donor hospitals and transplantation centers, a currently available capability to transport donor liver over distances of up to 3,500 km with predicted satisfactory results of its transplantation allows for active interregional cooperation. The increase in the acceptable distance of donor organ transportation may be achieved by:

1) optimizing the logistics of the process and increasing the share of transportation time in the structure of cold ischemia without its prolongation over 12 hours;

2) modifying the current practice of the static cold storage through the use of more efficient preservation solutions (for example, the University of Wisconsin solution);

3) using specially designed transportation containers ensuring an active maintenance of the required temperature, which could safely increase the cold ischemia time;

4) implementing new technologies to assess the viability and functional full-value of the donor organ immediately before its transplantation.

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*The Editorial Board of "Transplantologiya" journal considered it possible to publish a brief discussion that arose between the reviewer and the authors of the "*Impact of long-distance (up to 3.500 km) deceased donor liver transportation on cold ischemia time, initial graft function and transplant outcomes":

The presented study undoubtedly deserves attention and discussion, since the number of research devoted to the organ transportations is small. In the context of involving an increasing number of medical organizations in organ donation and transplantation activities in different subjects of the Russian Federation, the study of the specific features of donor organ transportations over different distances, including considerable distance, is undoubtedly relevant.

The study presents a unique experience for Russia in organizing the organ donation process, when the donation coordination center and donor hospitals are at a considerable distance from each other, up to 3,500 km, and, in my opinion, the experience in the donor process logistics in such conditions deserves a specific description.

It should be noted that among the results obtained, the share of the liver transportation time in CIT duration is comparable and does not differ statistically significantly between the groups, despite the statistically significant differences in transportation time, distance, and mode of transportation, which suggests that there are some additional factors that pose detrimental impact on the donor organ during transportation, especially by air (Y. Huang et al., 2016) [2]. The authors revealed a tendency towards an increase in the incidence of an early liver graft dysfunction, a primary graft non-function, and an early graft loss in

[2] Huang Y, MacQuillan G, Adams LA, Garas G, Collins M, Nwaba A, et al. Effect of airplane transport of donor livers on post-liver transplantation survival. *World J Gastroenterol*. 2016;22(41):9154–9161. PMID: 27895402 https://doi.org/10.3748/wjg.v22.i41.9154

the group with CIT of over 9 hours, however, no statistical significance was obtained. Similar trends were obtained by E. Totsuka et al. (2002) [3], but the authors revealed the statistical significance of the results obtained, and it is worth noting that they used the UW preservative solution, which made it possible to lengthen CIT to 12 or more hours.

It is well known that CIT of the donor liver exceeding the standard time frame is a significant risk factor in reducing the graft and recipient survival. Therefore, based on the cumulative data presented in the study and available in the experience of foreign colleagues, we can talk about a today possibility of transplanting the donor liver after its transportation over long distances, with a mandatory consideration of other donor risk factors, guiding either by their absence or their minimum. In other words, the necessity and feasibility of transporting the liver from an expanded criteria donor over long distances must be carefully weighed against the risks to liver transplant recipients.

Yours respectfully,
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The key parameters that must be taken into account when planning and implementing a liver transplantation in terms of a considerable

[3] Totsuka E, Fung JJ, Lee MC, Ishii T, Umehara M, Makino Y, et al. Influence of cold ischemia time and graft transport distance on postoperative outcome in human liver transplantation. *Surg Today*. 2002;32(9):792–799 PMID: 12203057 https://doi.org/10.1007/s005950200152

distance of the donor hospital from the transplant center include: the departure time of the aircraft which is to transport the donor organ, the duration of the air flight, the required time to travel to the departure airport and then from the arrival airport to the transplantation center. Taking into account the experience gained to date, the predicted duration of cold ischemia time for the donor organ at the moment of its delivery to the operating room of the transplantation center differs from the actual time by no more than 10-15 minutes.

The risks of a possible increase in transportation time associated with an unpredictable delay or cancellation of departure due to bad weather conditions, as well as for other reasons beyond the control of the donor team, cannot be neglected. To prevent these circumstances from affecting the recipient safety, it is fundamentally important to determine the time of the transplantation start, and, if necessary, to adjust it. In case of an extreme prolongation of cold ischemia time, the transplantation should be canceled, and the donor organ should be disposed of according the established procedure.

The second aspect that can significantly affect the graft cold ischemia time is technically difficult hepatectomy (retransplantation at a later date, extensive surgical interventions on abdominal organs in previous history). For such patients, the use of a donor organ with an estimated CIT exceeding 10 hours at the time of delivery to the operating room seems to be an extremely risky situation that should be avoided at the stage of choosing a candidate for transplantation. In standard cases, the time from the removal of the donor organ out of a transport container to its placement into the patient's abdominal cavity does not exceed 30–35 minutes.

The issue of the feasibility to transport donor organs over long distances is still debated throughout the world. The most striking example

is the evolution of the policy of liver and kidney allocation in the United States where those principles have been repeatedly revised over a relatively short period of time. However, the approach assuming that each potential donor should be considered as a multi-organ one remains indisputable. The approval of such a concept by the Russian professional community and the results of its practical implementation over the past decade have been illustrated by the data of the Russian Transplant Society Register.

One should take into account that the full-value use of the donor resource is currently possible only in certain regions of the Russian Federation, where the leading centers for kidney, liver and heart transplantation are concentrated. In other territories, there arise situations when any of the donor organs (for example, the liver) is not in demand for transplantation within the region due to the lack of its own transplant program. In such situations, from ethical and clinical points of view, the only correct solution seems to be the transfer of such an organ to a center where it can be transplanted. Of course, given an inevitable prolongation of cold ischemia time, organs from expanded criteria donors should not be transported over long distances due to an unreasonably high risk of primary graft non-function after transplantation.

In case of urgent transplantation, when, due to the patient's condition severity, the operation is always associated with a high risk of a severe early graft dysfunction, it is optimal to use the organ with the shortest possible time of cold ischemia. In no opportunity to obtain such an organ within the next 24–48 hours (when it is still possible to maintain a relatively stable condition of the patient due to intensive care measures), we consider it justified to use an organ removed from the donor located at a considerable distance from the transplantation center.

We should emphasize that the practical work associated with a long-distance transportation and the performance of donor liver transplants with extended periods of cold ischemia imply a regular analysis of the patient clinical outcomes, and also determine the relevance of fundamental and applied scientific research in this area. So, in 2017–2018, with the support of the Russian Science Foundation (RSF Grant No. 17-75-10010), for the first time in the native practice, we used the method of interstitial microdialysis for the early diagnosis of liver transplant dysfunction. The data obtained convincingly indicate that the glucose metabolism parameters in the graft are closely interrelated with the nature of its function recovery in the early postoperative period.

Since 2019, within the framework of the next project (RSF Grant No. 19-75-10040), the interval for obtaining interstitial fluid samples has been expanded due to making the test during the explantation of the donor's liver and its transportation. To date, we have 10 observed cases when the interstitial concentrations of glucose and its metabolites were determined from the moment of organ removal (the first test was made before the start of cold perfusion) to the seventh post-transplant day. Despite a relatively small number of cases, we can state that under conditions of static cold preservation with the histidine-tryptophan-ketoglutarate solution, the metabolic activity in the donor liver decreases, but does not stop completely. In all cases, we recorded two parallel processes: glycogenolysis and anaerobic glycolysis. The changes in interstitial glucose and lactate concentrations over the time of preservation and their values at the end of cold ischemia, apparently, can be used to predict the viability and initial function of the donor liver.

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