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Preoperative recipient data and immunosuppression levels are predictive of early patient survival after liver transplantation

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Abstract The role of donor, preoperative, intraoperative, and postoperative factors in predicting patient survival after liver transplantation was evaluated by the Bio Medicus data package on a database containing 162 variables filled with records from 100 consecutive first-liver transplant cases. Donor data did not predict outcome. Recipient preoperative data (Child status, HCV status) were predictive using life table and Cox regression methods. Recipient intraoperative data (by-pass time, warm ischemia time, delay in arterial revascularization, and packed red blood cell requirements) were predictive of outcome using life table analysis. Recipient postoperative data (rejection, sepsis, primary dysfunction, and hepatic artery thrombosis) were predictive of outcome.

Key words Liver transplantation outcome · Prognostic

Introduction

Outcome of liver transplantation has been correlated with several factors [1–7]. These can be classified into four well defined categories: donor factors, preoperative factors, intraoperative factors, and postoperative factors. The large number of components involved explains the difficulty in predicting patient survival.

The aims of this study are the identification of factors, the quantification of the relative role of each one separately and a multidisciplinary analysis of results.

Patients and methods

Donor population

One hundred consecutive multi-organ donors were referred and considered suitable for harvesting and liver transplantation. Perfusion was carried out by UW solution. Donor age range was from 7 to 59 years. The most common causes of death were head trauma and cerebral vascular accident.

Recipient population

One hundred consecutive orthotopic liver transplants were performed at the Transplantation Service of the Catholic University of Rome, Italy from April 1987 to July 1997. All cases considered in the study were first transplants. There were 90 adults and 10 children. Indications for transplantation were post-hepatitis B cirrhosis (HBV; 20.6%), post-hepatitis C cirrhosis (HCV; 30.4%), post-hepatitis B–C (HBC) cirrhosis (6.9%), alcoholic cirrhosis (12.7%), cryptogenetic cirrhosis (6.0%), acute liver failure (5.9%), primary biliary cirrhosis (2.8%), congenital hepato-biliary disease (9.8%), or miscellaneous (4.9%).

Statistics

All data were collected from donor and recipient charts and a 162-variable database was filled. Data were evaluated by the Bio Medicus Data Package using life table and Cox regression analysis. To avoid additional effects of late events on patient survival, a 6-month end-point was chosen.

Table 1 Life table analysis of donor data (*3mGS* 3 months graft survival, *6mGS* 6 months graft survival, *NS* not significant, *ICU* intensive care unit, *AST* aspartate transaminase)

	Range or %	Mean ± SD	*n*	3mGS	6mGS	*P* value
Age (years)						
< 30	7–30	18.9 ± 7.0	64	86	81	NS
> 31	31–59	40.7 ± 7.2	27	70	60	
Weight (kg)						
< 70	38–70	56.2 ± 15.5	62	79	73	NS
> 71	72–100	79.6 ± 7.9	27	85	81	
Cause of death						
Trauma	63%		61	80	76	NS
Hemorrhage	28%		27	70	66	
ICU stay (days)						
< 4	1–4	2.1 ± 0.9	72	80	77	NS
> 5	5–15	6.8 ± 2.4	24	70	60	
PO_2 (mm Hg)						
< 125	44–124	92 ± 23	32	78	78	NS
> 126	130–530	205 ± 92	53	83	75	
Systolic blood pressure (mm Hg)						
< 80	70–80	78.6 ± 3.5	8	50	50	0.0535
> 81	90–160	113 ± 16	83	79	75	
Central venous pressure (cmH_2O)						
< 8	3–8	5.3 ± 2.3	40	83	77	NS
> 9	9–19	12 ± 3	23	70	65	
Dopamine (mcg/kg per min)						
< 9	1–9	5.8 ± 1.9	61	78	76	NS
> 10	10–20	12.3 ± 3.0	15	93	86	
AST (IU/l)						
< 89	8–87	38.9 ± 17.6	78	82	76	NS
> 90	92–438	154.9 ± 91.0	21	67	67	
Donor Na (mEq/l)						
< 154	126–154	143 ± 7	68	84	82	0.0534
> 155	156–180	165 ± 6	28	73	61	
Prothrombin time (%)						
< 60	31–60	51.3 ± 7.2	34	88	79	NS
> 61	61–103	74.7 ± 10.6	55	74	72	
Fibrinogen (mg%)						
< 300	91–290	213.3 ± 60.3	36	83	80	NS
> 301	302–1250	469.1 ± 169.1	40	80	74	

Results

Life table analysis

The life table analysis, which shows the results in terms of patient survival from 1 to 6 months, is summarized here.

Donor data

Statistically significant differences were found between patients with systolic blood pressure higher than 80 mmHg and patients with systolic blood pressure lower than 81 mmHg (see Table 1 for details).

Recipient preoperative data

Statistically significant differences were found between patients in Child C status and patients in Child status A and B, between HCV cirrhosis and HBC cirrhosis, and between HCV cirrhosis and alcoholic cirrhosis (see Table 2 for details).

Recipient intraoperative data

Statistically significant differences were found between patients with warm ischemia time less than 60 or more than 61 min, between patients who required less than 20 or more than 21 packed red blood cell units, and between patients in which the arterial revascularization was completed less than 50 or more than 51 min after

Table 2 Life table analysis of recipient preoperative data (*3mGS* 3 months graft survival, *6mGS* 6 months graft survival, *NS* not significant, *D* donor, *R* recipient, *GI* gastrointestinal tract, *HCV* post-hepatitis C cirrhosis, *ALCOHOL* alcoholic cirrhosis, *HBV* post-hepatitis B cirrhosis)

	Range or %	Mean ± SD	*n*	3mGS	6mGS	*P* value
Age (years)						
< 49	16–49	37 ± 9	58	79	75	NS
> 50	50–62	55 ± 4	33	85	77	
Gender						
Female	40%		41	80	75	NS
Male	60%		60	78	74	
Gender match/mismatch (D → R)						
Female → female	19.4%		19	89	83	NS
Male → female	21.4%		21	71	66	
Female → male	19.4%		19	72	74	
Male → male	39.8		39	79	74	
Previous upper GI bleeding						
No	68.9%		62	79	75	NS
Yes	59.8%		28	79	71	
Child status						
A + B	69%		69	87	82	0.0058
C	27%		27	59	55	
Indication						
HCV	30.4%		31	96	96	*
ALCOHOL	12.7%		13	76	65	*, **
HBV	20.6%		21	64	58	**

* $P < 0.05$; ** $P < 0.01$

Table 3 Life table analysis of recipient intraoperative data (*3mGS* 3 months graft survival, *6mGS* 6 months graft survival, *NS* not significant, *PRBC* packed red blood cells)

	Range	Mean ± SD	*n*	3mGS	6mGS	*P* value
Cardiac index (Vmin per m^2)						
< 4.0	1.3–4.0	3.3 ± 0.7	33	86	84	NS
> 4.1	4.1–5.2	4.7 ± 0.8	61	83	78	
VO_2 (ml/min per m^2)						
> 121	123–192	148 ± 18	56	85	82	NS
< 120	56–119	87 ± 23	39	81	77	
Lactate (mM/l)						
< 9.9	3.6–9.3	7.0 ± 1.5	16	94	87	NS
> 10.0	10.0–16.5	12.4 ± 1.8	19	84	84	NS
Warm ischemia time (min)						
< 60	40–60	52.1 ± 5.0	54	89	81	0.0301
> 61	61–110	70.0 ± 9.6	32	63	63	
By-pass time (min)						
< 150	60–150	108.1 ± 20.7	52	87	81	0.0047
> 151	151–346	202.5 ± 48.3	23	65	60	
Delay in arterial revascularization (min)						
< 50	12–50	36.4 ± 8.3	39	95	89	0.0048
> 51	53–225	97.8 ± 41.6	27	67	63	
PRBC (units)						
< 20	8–20	14.8 ± 3.6	56	86	82	0.0488
> 21	22–67	36.4 ± 12.7	31	71	64	

the venous revascularization (delay in arterial revascularization) (see Table 3 for details).

Recipient postoperative data

Statistically significant differences were found between patients with or without primary dysfunction (transaminases peak higher than 3500 IU/l during the first 96 h), between patients with or without arterial thrombosis, between patients with or without rejection, and between patients with or without sepsis (see Table 4 for details).

Cox regression analysis

All variables were matched against the 6-month graft survival (see Table 5 for details).

Table 4 Life table analysis of recipient postoperative data (*3mGS* 3 months graft survival, *6mGS* 6 months graft survival, *NS* not significant, *AST* aspartate transaminase)

	Range or %	Mean ± SD	*n*	3mGS	6mGS	*P* value
Biliary complication						
No	83.8%		82	80	76	NS
Yes	16.2%		16	88	81	
Hemoperitoneum (surgery)						
No	94.8%		91	82	78	0.056
Yes	5.2%		5	60	40	
Second surgery (complications)						
No	85.6%		82	84	80	0.052
Yes	14.4%		14	64	56	
Cerebral bleeding						
No	90%		88	84	79	NS
Yes	10%		10	60	60	
Primary dysfunction (AST IU/l)						
< 3500	48–3486	920 ± 824	78	90	84	0.0001
> 3501	3520–11650	5781 ± 2584	19	47	47	
Thrombosis						
No	94%		92	85	80	0.0000
Yes	6%		6	22	22	
Rejection						
No	33%		31	77	64	0.0067
Yes	67%		63	91	90	
Sepsis						
No	53%		49	91	89	0.0060
Yes	47%		44	73	64	

Table 5 Cox regression analysis (*HCV* post-hepatitis C cirrhosis)

	n	r^2	*P* value
Simple			
Child	94	6%	0.0132
HCV	96	11%	0.0005
Delay in arterial revascularization	65	10%	0.0083
Primary dysfunction	92	10%	0.0012
Thrombosis	93	7%	0.0065
Rejection	89	7%	0.0119
Sepsis	88	8%	0.0066
Multivariate			
HCV + rejection	89	14%	0.0011
Child + rejection	87	10%	0.0103
HCV + sepsis	88	14%	0.0007
Child + sepsis	86	11%	0.0058
HCV + rejection + sepsis	86	19%	0.0003
HCV + rejection + primary dysfunction	89	20%	0.0001
HCV + sepsis + primary dysfunction	88	22%	0.0000

Donor data

None of the donor parameters correlates with graft survival.

Recipient preoperative data

Child class C status and HCV status significantly correlate with graft survival.

Recipient intraoperative data

Only delay in arterial revascularization significantly correlates with graft survival.

Recipient postoperative data

Primary dysfunction, arterial thrombosis, rejection, and sepsis significantly correlate with graft survival (Figs. 1, 2).

Cox regression (multivariate) analysis

The associations between HCV status and rejection, between Child C status and rejection, between HCV status and sepsis, and between Child status and sepsis improved the links. The multiple associations between HCV status, rejection, and sepsis; between HCV status, rejection, and primary dysfunction; and between HCV status, sepsis, and primary dysfunction achieved the highest level of correlation ($r^2 = 22\%$, $P < 0.00001$).

Discussion

Prediction of outcome is today a common field of interest in the medical literature. Several models have been

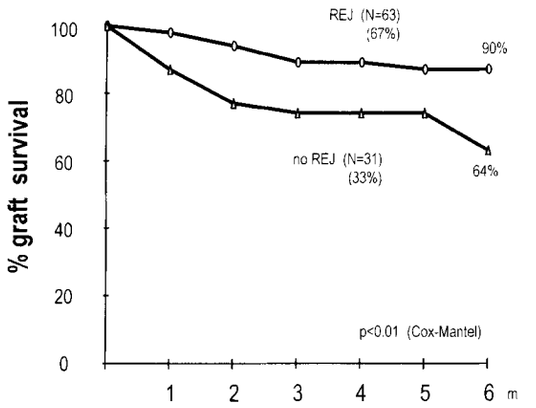

Fig. 1 Actuarial graft survival of patients with episodes of rejection (*REJ*) versus patients with no episodes of rejection (*no REJ*). The rates at 6 months were 90% and 64%, respectively ($P < 0.01$, Cox-Mantel)

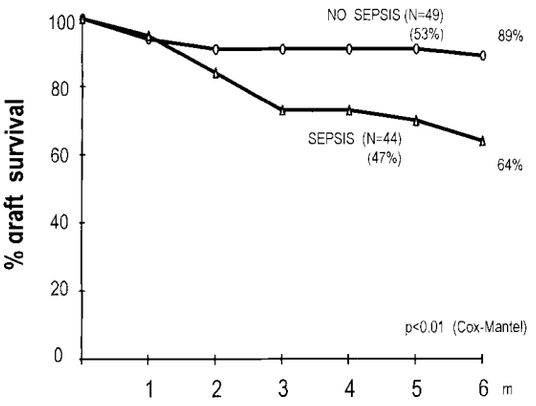

Fig. 2 Actuarial graft survival of patients with no episodes of sepsis versus patients with episodes of sepsis. The rates at 6 months were 89% and 64%, respectively ($P < 0.01$, Cox-Mantel)

proposed and some of them are currently used in clinical practice. Transplantation of organs, and of the liver particularly, poses a different issue. The number of determinants is larger and so many additional factors may be involved. The complexity of the system can be visualized as multiple cogs, some small and some large, which, although running at different speeds and in different directions, are responsible for the overall success. It is easy to imagine the difference of power in each factor but it is very difficult to identify and to quantify the relative role of each one separately.

Four main categories of factors have been suggested to predict the outcome after liver transplantation: donor factors, preoperative factors, intraoperative factors, and postoperative factors. Each category of factors is generally studied by four well-defined groups of physycians, not always sharing the same point of view and the same methods of analysis. Thus donor data are examined by intensive care unit (ICU) specialists, recipient preoperative data are analyzed by hepatologists, intraoperative data are evaluated by anesthesiologists, and postoperative data are studied by transplant surgeons. Very few interdisciplinary reports in which all data are simultaneously matched have been published up to date. Indeed, each study often considers only one or two categories. This limits the analysis without taking into account factors from other categories.

The dichotomy in predicting transplant outcome stems from the donor–recipient dualism. Which are more important, donor or recipient factors? For a long time, donor factors were considered strong predictors of graft survival [2, 3]. The indications for liver harvesting were extremely selective: age was confined to 45 years and no donors with alterations in liver function tests were accepted. To date, several reports have been published on liver transplantation from elderly donors [8, 9] and there are papers which report acceptable results even with so-called marginal donors [10]. Even if we report a better outcome with younger donors, the difference does not reach statistical significance. It should be noted that there were no donors over 60 years in our analysis. Donor weight was correlated with transplant outcome. In particular, overweight donors often present a fatty liver [11]. Overweight donors were not accepted in our series. Increased knowledge and the improvement in the care of the critical patients probably justifies the lack of correlation between graft survival and the length of donor stay in ICU. Today donors also present a better respiratory and cardiovascular support, as documented by the appropriate PO_2, the records of hemodynamic data, and the results of ematochemical samples. Regarding systemic blood pressure, we would like to note that, using the 80-mmHg cut-off, the difference in transplant outcome presents a P value of 0.051, which is very close to the statistical significance level. Donors with blood pressure lower than 80 mmHg (70–80 mmHg) presented a worse outcome; there were only eight cases in this group, however, and four are still alive.

Our group reported in 1991 the prognostic value of donor serum sodium levels on transplant outcome of a limited set of cases [12]. Three years later, other authors with a wider experience agreed on the prognostic value of donor natriemia [13] and, more recently, a multi-center study confirmed this in more than 600 cases [14]. Results of life table analysis regarding donor sodium showed no significant difference (even if the P value of 0.053 is very close to the significance level). No correlation was found between donor sodium and graft survival using the Cox regression method. We explain this finding as due to the present policy of not accepting donors with high sodium levels.

Recipient factors are commonly considered stronger than donor factors [5–7]. Recipient factors can be classi-

fied into three categories: preoperative, intraoperative, and postoperative.

An elderly recipient was considered as a negative factor but in our experience, recipients older than 50 years did not present a worse outcome than younger ones [15]. It should be noted that we did not transplant patients older than 60 years. Gender was reported as one parameter able to predict outcome [3]. In particular, the donor female to recipient male transplant was described as a less favorable match. We have not observed this effect as it is not large enough in terms of patient survival, probably because of the size of subsets in this series. Indication for liver transplantation also correlates with patient survival [5, 6]. The statistically significant difference in graft survival as predicted by Child status does not represent a new observation in this field. Authors in the United States have reported similar data with different outcome for patients with scores of UNOS-4 and UNOS-3 [5]. The etiology of liver disease has also been correlated with patient survival [16, 17]. The negative effects of the HBsAg positivity and more strongly of the HBV DNA positivity have been reported elsewhere [18, 20]. In our experience, HCV patients show a better patient survival than both HBV and post-alcoholic patients.

Several efforts have been made to correlate intraoperative data with outcome. Even if in the literature there are reports that indicate that an increase in oxygen consumption during the postanhepatic phase and the persistence of high levels of lactate at the end of surgery are prognostic factors, no extensive study has been published as yet [21, 22]. We have failed to confirm this. The negative effect of large transfusion requirements has been reported elsewhere and was verified by our experience [23]. In our experience, the by-pass time, the warm ischemia time, and the delay in arterial revascularization predict graft survival by life table methods. Probably these parameters represent a clustering of different problems which may occur during surgery. Reasons which may prolong the length of veno–venous bypass are several: here the degree of portal hypertension, the length of warm ischemia time, technical problems, and the surgeon's skill are underlined.

The last category of factors comprises the recipient postoperative data. Until the 1980s survival depended on technical complications and on the degree of recovery after transplantation. Hemoperitoneum, vascular complications (portal vein, hepatic artery), biliary complications (biliary leak, kinking of biliary anasthomosis), and cerebral complications (bleeding, abscess) were more relevant than immunosuppression-related complications.

In the past we have published a wide spectrum of postoperative recovery, ranging from normal function to impaired function, primary dysfunction, and primary non-function [24]. As a result, patients with high levels of transaminases and a poor hepatic function were enlisted for retransplantation at an early stage. Today management of posttransplant recovery has improved remarkably due to the progress achieved in critical care (e.g., prostaglandin treatment, total parenteral nutrition with branched-chain amino acids, perioperative ultrafiltration/dialysis [25]. For these reasons, retransplantation has been reserved for more selected cases [26, 27]. We did not find any correlation between graft survival and biliary complications and cerebral bleeding. We also observed by life table analysis a relevant but not significant difference for patients who underwent surgical treatment for hemoperitoneum and for other complications.

Primary dysfuntion and hepatic artery thrombosis remain negative prognostic indexes, even if their relative roles in postoperative death have been reduced [28–32]. However, the differences in graft survival, as evidenced by life table analysis of primary dysfunction and arterial thrombosis, probably call for further evidence in this field. Life table analysis shows that patients with rejection episodes presented a 1- to 6-month survival better than patients who did not experience rejection ($P < 0.01$) and patients with sepsis presented a worse outcome than patients without sepsis ($P < 0.01$).

Besides primary dysfunction and hepatic artery thrombosis, immunosuppression-related events remain the strongest predictors of outcome. The protective role of rejection is not new in organ transplantation [33]. On the other hand, sepsis is associated with a poor survival. Our opinion is that death is often due to excessive immunosuppression, which means reduced recovery and increased susceptibility to bacterial, viral, protozoal, and mycotic infections. It is possible that patients experiencing rejection episodes are more responsive to infections.

In conclusion, we identified and quantified the factors predictive of outcome: (1) Child status and HCV status for recipient preoperative data; (2) warm ischemia time, by-pass time, delay in arterial reperfusion for the intraoperative data; and (3) immunosuppression data – rejection and sepsis – as well as primary dysfunction and arterial thrombosis for the postoperative data.

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References

1. Mimeault R, Grant D, Ghent C (1989) Analysis of donor and recipient variables and early graft function after orthotopic liver transplantation. Transplant Proc 21: 2355–2382
2. Pruim J, Woerden WF van, Knol E (1989) Donor data in liver grafts with primary non-function – a preliminary analysis by the European Liver Registry. Transplant Proc 21: 2383–2399
3. Kahn D, Galaver JS, Makowka L, et al (1993) Gender of donor influences outcome after orthotopic liver transplantation in adults. Dig Dis Sc 38: 1485–1488
4. Makowka L., Gordon R. D., Todo S. (1987) Analysis of donor criteria for the prediction of the outcome in clinical liver transplantation. Transplant Proc 19: 2378–2399
5. Baliga P, Merion RM, Turcott JG (1992) Preoperative risk factor assessment in liver transplantation. Surgery 112: 704–711
6. Cuervas-Mons V, Millan I, Gavaler JS (1987) Prognostic value of preoperatively obtained clinical and laboratory data in predicting survival following orthotopic liver transplantation. Hepatology 6: 922–927
7. Clavien PA, Argemiro de Camargo C Jr, Croxford R (1994) Definition and classification of negative outcomes in organ transplantation. Ann Surg 220: 109–120
8. Wall WJ, Mimeault R, Grant DR (1990) The use of older donor livers for hepatic transplantation. Transplantation 49: 377
9. Emre S, Schwartz ME, Altaca G (1997) Safe use of hepatic allografts from donors older than 70 years. Transplantation 62: 62–69
10. Mor E., Klintmalm GB., Gonwa TA (1992) The use of marginal donors for liver transplantation. Transplantation 53: 383–386
11. Todo S, Makowka L (1989) Primary non-function of hepatic allografts with preexisting fatty infiltration. Transplantation 47: 903–999
12. Avolio AW, Agnes S, Magalini SC (1991) Importance of donor blood chemistry data (AST, serum sodium) in predicting liver transplant outcome. Transplant Proc 23: 2451–2499
13. Xavier Gonzales F, Rimola A, Grande L (1994) Predictive factors of early postoperative graft function in human liver transplantation. Hepatology 20: 565–573
14. Figuras T, Busquets T, Grande L (1996) The deleterious effect of donor high plasma sodium on extended preservation in liver transplantation. Transplantation 61: 410–619
15. Pirsch JD, Kalayoglu M, D'Alessandro AM et al (1991) Orthotopic liver transplantation in patients 60 years of age and older. Transplantation 51: 431–499
16. Rakela J (1992) Hepatitis C viral infection in liver transplant patients: how good is it really? (editorial) Gastroenterology 103: 338–339
17. Rizzetto M, Macagno S, Chiaberge E (1987) Liver transplantation in hepatitis delta virus disease. Lancet ii:469–499
18. Lauchart W, Muller R, Pichlmayr R (1987) Long term immunoprophylaxis of hepatitis B virus reinfection of human liver allografts. Transplant Proc 19: 4051–4099
19. Agnes S, Avolio AW, Magalini SC (1989) Results of liver transplantation for hepatitis delta disease without employment of immunoprophylaxis. Transplant Proc 21: 2426–2429
20. Samuel D, Bismuth A, Mathieu D (1991) Passive immunoprophylaxis after liver transplantation in HBsAg positive patients. Lancet ii:813–899
21. Avolio AW, Agnes S, Pelosi G (1991) Intraoperative trends of oxygen consumption and blood lactate as predictors of primary dysfunction in liver transplantation. Transplant Proc 23: 2263–2299
22. Avolio AW, Agnes S, Pelosi G (1991) Determinants of hemodynamic compensation during veno–venous bypass in liver transplantation. Transplant Proc 22: 1535–1536
23. Shaw BW, Wood RP, Gordon RD (1985) Influence of selected patients' variables and operative blood loss on six months survival following liver transplantation. Semin Liver Dis 5: 385–389
24. Avolio AW, Agnes S, Magalini SC (1992) "Recovery index" a useful tool for quantification of liver injury after liver transplantation and predict one-year survival. Transplant Proc 24: 2707–2708
25. Greig PD, Woolf GM, Sinclair SB (1989) Treatment of primary liver graft nonfunction with prostaglandin E1. Transplantation 48: 447–499
26. Mora NP, Klintmalm GB, Cofer JB (1990) Results after liver retransplantation (RETx): a comparative study between "elective" vs "nonelective" RETx. Transplant Proc 22: 1509–1599
27. Kamath GS, Plevak DJ, Wiesner RH (1991) Primary nonfunction of the liver graft: when should we retransplant? Transplant Proc 23: 1954–1999
28. Agnes S, Avolio AW, Magalini SC (1991) Is primary non-function still a suitable indication to liver retransplantation? Transplant Proc 23: 2261–2262
29. Ploeg RJ, D'Alessandro AM, Knechtle SJ, et al (1993) Risk factors for primary dysfunction after liver transplantation: a multivariate analysis. Transplantation 55: 807–813
30. Clavien PA, Harvey PRC, Strasberg SM (1992) Preservation and reperfusion injury in liver allografts: an overview and synthesis of current studies. Transplantation 53: 957–969
31. Hidalgo EG, Abad J, Cantarero JM (1989) High-dose intra-arterial urokinase for the treatment of hepatic artery thrombosis in liver transplantation. Hepatogastroenterology 36: 529–532
32. Marujo WC, Langnas AN, Wood RP (1991) Vascular complications following orthotopic liver transplantation: outcome and role of urgent revascularization. Transplant Proc 23: 1484–1486
33. Calne RY, Rolles K, White DK (1979) Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidney, 2 pancreases, and 2 livers. Lancet ii:1033–1039