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ORIGINAL ARTICLE

Older liver graft transplantation, cholestasis and synthetic graft function

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Summary

Older liver grafts are often discarded because of conservative selection criteria. We report on our clinical experience with graft-age related outcome. Patients transplanted with livers older than 70 years (70.2–80.2 years, $n = 38$) were compared with controls transplanted with livers younger than 70 years. Pairs were matched for age, gender, indication and cold ischemic time. Mean donor age was 73.4 ± 2 vs. 39 ± 16 years. Patient and graft survival did not differ between both groups after 1-year follow-up ($P = 0.19$ and $P = 0.24$ respectively). Retransplantation rate was 10.5% vs. 5.3% ($P = 0.40$). Initial poor function occurred in two patients in the study group versus four patients in the control group ($P = 0.69$). The incidence of rejection episodes was comparable. Parameters of cholestasis and protein synthesis showed no difference 1-year post-transplant. Mean age of donor organs in matched pairs group B was near by half of that in the older donor group A (39.0 vs. 73.4 years). Post-transplant outcome as indicated by patient and graft survival was comparable between both groups. Donor organ age had no impact on postoperative organ function. We recommend to accept liver grafts from organ donors older than 70 years to expand the donor pool.

Introduction

Reports about older liver donors have been published since the late 1980s [1]. Still today, it is discussed which age comprises older donors. Is an old donor older than 50, 60, 70 or even 80 years? The same is true for the recipient [2,3].

The growing body of evidence about transplantation using organs from older donors shows that age *per se* is not a valuable argument excluding these grafts that are urgently needed. The development in using older donor organs is in accordance to the medical success in civilized countries. This means more ageing societies and the evolving awareness about the biological age of the whole body in contrast to the biological age of single organs [4].

As the report of the European liver transplant registry shows, a growing number of liver grafts is coming from donors older than 60 years [5]. Indeed, almost 20% of livers in 2001 came from donors older than 60 years. Moreover, reports of liver transplantation from donors older than 80 years have recently been published [6]. Even in fulminant liver failure octogenarian grafts have successfully been used [7].

As more positive results emerge with organs from older donors, the 'brain barrier' of old age will move to more principal questions of actively supporting cadaveric organ donation or not by donor hosting hospitals, their medical staff and the relatives confronted with this question. Hence, it is still necessary to prove the value of older organ donation. We therefore retrospectively analysed the outcomes of grafts and recipients of organs older than 70 years at our department.

Patients and methods

Patients

Between January 1995 and October 2003, 41 livers from donors older than 70 years were transplanted in 41 recipients. The recipients of older liver organs were compared with matched controls. Patients transplanted with livers older than 70 years were compared with con-

trols transplanted with livers younger than 70 years. Pairs were matched for age, gender, diagnosis and cold ischemic time (CIT). The matching procedure was performed by searching for controls of 1500 liver-transplanted patients in the liver transplant registry of our department. Main diagnosis and gender were crucial in this matching. Age and CIT were adjusted as exactly as possible. Donor age of controls was a random result of the matching procedure in a range from 15.0 to 69.9 years. The maximal range of age and CIT allowed in the definite pairs were ±9 years and ±90 min of CIT. Three of 41 patients were excluded from the analysis because it was not possible to find an adequate matched control. Thus, 38 patients with older liver grafts (group A) were compared with 38 patients with younger liver grafts (group B).

Data

Data sampled for organ donors included cause of death, ICU stay, macroscopically visible steatosis, pressor use and dose, blood pressure, serum osmolality, serum sodium, liver function tests and CIT. Data sampled for older liver recipients and controls were patient and organ survival, retransplantion rate, surgical complications, reason for graft loss, initial nonfunction (INF), initial poor function (IPF), preservation injury, intra- and postoperative organ function as determined by immediate intraoperative and 24-h bile production, liver function tests, need for haemodialysis, microbiology proofed infection episodes and prolonged mechanical intubation. We also recorded initial immunosuppression regimen, number of rejection episodes, and need for steroid and OKT3 rejection therapy. Liver function tests and retention parameters were followed up for 1 year.

Liver transplantation

Orthotopic liver transplantation (OLT) was performed using standard surgical techniques including veno-venous bypass [8]. During surgery, aprotinin was administered as a bolus of 500 000 U and subsequently as continuous infusion at 100 000 U/h to avoid reperfusion fibrinolysis [9]. After surgery, patients were allowed to breath spontaneously, and no anaesthetic drugs were administered so as to achieve extubation as soon as possible [10].

All the 76 patients received primary OLT and University of Wisconsin solution was used for donor organ preservation in all cases. In each case, individual decision for accepting the cadaveric organ donation based on clinical and biochemical parameters of the organ donor was carried out by the responsible explanting surgeon. Moreover, the organ was reevaluated by the transplanting surgeon prior to the transplantation procedure.

Postoperative management

In case of postoperative mechanical ventilation, positional manoeuvres including lateral position were performed routinely. Mobilization and physiotherapy were started at day 1 after surgery [10].

Initial poor function (IPF) and preservation injury was defined according to postoperative aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) serum levels. IPF was diagnosed if serum AST and/or ALT levels exceeded 1500 U/l on two consecutive measurements within the first 48 h after OLT [11]. Preservation injury was classified according to AST serum levels during the first 72-h post-transplant as minor (peak AST <500 U/l), moderate (peak AST 500–1000 U/l) or severe (peak AST >1000 U/l) injury [12].

All patients received either cyclosporine-based or tacrolimus-based immunosuppressive therapy as rejection prophylaxis. The diagnosis of graft rejection was based on clinical, laboratory and histologic findings. In case of rejection, high-dose methylprednisolone was given as a bolus of 3×500 mg. In case of steroid-resistant rejection, OKT3, a murine monoclonal antibody against T cells (5 mg daily for 5–7 days), was administered. In patients receiving cyclosporine-based induction therapy, we switched to tacrolimus-rescue therapy [10].

Systemic infectious and antiviral prophylaxis was administered perioperatively. Laboratory diagnosis of infection was obtained by appropriate collections of blood, sputum, and urine, as well as oral, rectal and genital swabs for microbiological testing. Based on the test results, the initial antibiotic therapy was modified according to resistance testing [10].

Statistical analysis

The follow-up ranged between 1 and 7 years. Data were expressed as mean ± SEM. Graft and patient survival rates were analysed using the Kaplan–Meier method and compared with the log-rank test. To compare both groups on their demographic and postoperative characteristics, paired *t*-test, unpaired *t*-test and chi-squared test were used, as indicated (GraphPad Prism version 3.00 for Windows, GraphPad Software (http://www.graphpad.com). *P*-values of <0.05 were considered statistically significant.

Results

Patients (donor and recipient data)

Matched pairs did not differ in mean age (50.6 vs. 50.9 years, $P = 0.66$). The matching for age was

significantly effective ($r = 0.88$, $P < 0.0001$). Matched pairs did also not differ in mean CIT (531 vs. 532.5 min, $P = 0.87$). The matching for CIT was significantly effective ($r = 0.94$, $P < 0.0001$), too. Most patients received primary OLT for alcohol cirrhosis ($n = 15$), hepatitis B or hepatitis C-related cirrhosis ($n = 10$) or hepatocellular carcinoma ($n = 6$). The whole group studied existed of 23 male and 15 female pairs. Detailed recipient demographics are given in Table 1.

Table 1. Recipient demographics.

Parameter	Group A old grafts	Group B young grafts
Number of patients	38	38
Sex (male/female)	23/15	23/15
Age at OLT (mean ± SD)*	50.9 ± 9.3	50.6 ± 9.9
Range*	25.4–66.9	19.1–64.3
Indication for OLT		
ETHO	15	15
Hepatitis C	1	1
Hepatitis C and ETHO	2	2
Hepatitis B	2	2
Hepatitis B and haemochromatosis	1	1
Hepatitis B and ETHO	1	1
Autoimmune	2	2
Cryptogenic	4	4
HCC and ETHO	3	3
HCC and hepatitis C	2	2
HCC and hepatitis B	1	1
PBC	1	1
PSC	2	2
M. Wilson	1	1

ETHO, alcoholic cirrhosis; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.
*$P = 0.66$.

Mean donor age was 73.4 ± 2.3 vs. 39 ± 16.2 years. In group B, 23 (60.5%) liver grafts were from donors younger than 40 years. In group A, 21 liver grafts were harvested by the local explantation team, while 22 liver grafts in group B were local offers, too. Table 2 gives a summary of the donor demographics. Mean follow up for older liver recipients (group A) was 903 ± 118 days and for controls (group B) 2240 ± 216 days respectively.

Outcome (patient and graft survival, retransplantation rate)

Patient and graft survival were similar between both groups according to the Kaplan–Meier estimates (Figs 1 and 2). Causes for death of six patients in group A up to date were cardiovascular disease, intracranial bleeding, sepsis, multiorgan failure, de novo cancer and hepatic failure because of hepatic artery thrombosis. In group B one of five patients died of cardiac arrest, one of intracranial bleeding, one of HCC reoccurrence, one patient had de novo cancer and one hepatic failure because of reoccurrence of alcohol disease.

Table 2. Donor demographics.

Parameter	Group A old grafts	Group B young grafts	*P*-value
Age (years)	73.4 ± 2.3	39.0 ± 16.2	
Range	70.2–80.2	15.0–69.3	
Sex (male/female)	17/21	25/13	
CIT (min)	532 ± 163	532.5 ± 162	0.87
Range	272–966	241–999	
Cause of death			
Intracerebral bleed	32	22	0.01
Anoxic brain damage	3	5	0.46
Head injury	2	11	0.006
Unknown	1	0	0.32
Catecholamines (N)	33	35	0.66
Dopamine (mg/kg × min)	5.6 ± 6.3	5.3 ± 5.6	0.88
Noradrenaline (mg/kg × min)	0.16 ± 0.16	0.15 ± 0.18	0.84
Diastolic blood pressure (mmHg)	67 ± 14	75 ± 19	0.06
Sodium (mmol/l)	146 ± 18	146 ± 8	0.93
ALT (U/l)	23 ± 17	52 ± 86	0.04
AST (U/l)	39 ± 57	49 ± 53	0.46
γ-GT (U/l)	40 ± 61	78 ± 174	0.23
ICU stay (days)	2.5 ± 2.6	5.1 ± 11.6	0.18
Range	0–13	0–60	
Macroscopic steatosis	4	8	0.21

CIT, cold ischemic time; γ-GT, gamma-glutamyl transpeptidase, ICU, intensive care unit; N, numbers.

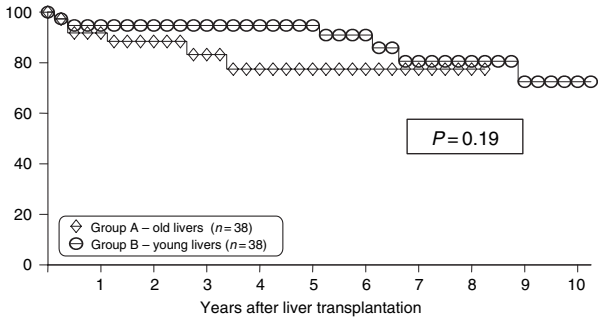

Figure 1 Patient survival (%).

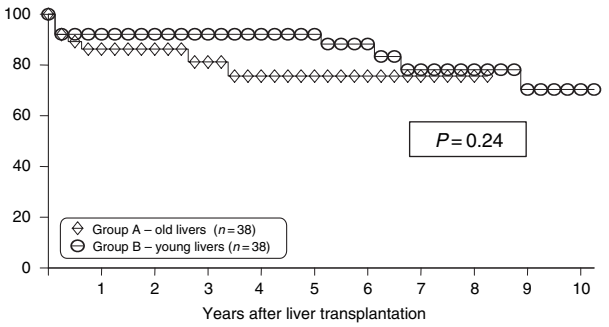

Figure 2 Graft survival (%).

Moreover, retransplantation rate was also comparable, reaching 10.5% vs. 5.3% after 7-years follow-up ($P = 0.40$). In group A, four patients required retransplantation while only two patients in group B were affected. One of the patients in group A was retransplanted because of initial non-function (INF), while two retransplantations were related to rejection. The fourth retransplantation in this group was required because of liver failure for fulminant HCV reinfection. The two retransplantations in group B were because of hepatic artery thrombosis (in combination with fulminant hepatitis C virus reinfection) and vena cava stenosis.

Postoperative liver graft quality and function (preservation injury, bile flow, INF, IPF)

With respect to preservation injury, patients in group A showed more moderate preservation injury compared with group B, however, no significant differences for minor, moderate or severe preservation injury between both groups were observed (Table 3). In addition, intraoperative bile flow was noted in 28 liver grafts in group A and in 36 in group B ($P = 0.03$). After 24 h, mean bile flow in the older donor recipients was 120 ± 21 ml and in the recipients of younger livers 223 ± 29 ml, reaching statistically significant difference ($P = 0.01$).

Table 3. Postoperative results.

Parameter	Group A old grafts	Group B young grafts	*P*-value
Retransplantation rate (%)	10.5	5.3	0.40
INF	1/38	0/38	0.32
IPF	2/38	4/38	0.16
Preservation injury			
Severe	5	8	0.37
Moderate	7	2	0.08
Low	26	28	0.62
Prolonged mechanical ventilation	3/38	1/38	0.16
Haemodialysis	11	6	0.17
Rejection (episodes)	11	19	0.06
Steroid bolus	6	12	0.11
OKT3	5	4	0.72
Others	0	3	0.08
Infection (episodes)	9	13	0.31

INF, initial nonfunction; IPF, initial poor function.

INF was observed in only one patient (group A), while IPF occurred in two recipients in group A and in four recipients in group B. All patients with IPF developed normal liver function within 3 months following OLT. None of these was retransplanted after 7-years follow-up. The differences between groups A and B were not statistically significant for INF ($P = 0.32$) or IPF ($P = 0.16$) respectively.

Postoperative course

A total of 34 of the liver recipients in group A and 26 in group B received tacrolimus-based induction therapy. The remaining patients were treated with cyclosporine A-based therapy for rejection prophylaxis. The incidence of rejection episodes in group A was 11 (28.9%) compared with 19 (50%) rejection episodes in group B ($P = 0.06$). Rejection treatment consisted of steroid bolus in six (15.7%) cases and of OKT3 in five (13.2%) cases in group A. In group B, rejection was treated with steroid bolus in 12 (31.6%) cases, with OKT3 in four (10.5%) cases, and with increasing primary immunosuppression or switch to tacrolimus in three (7.9%) cases (Table 3).

In group A, three patients had prolonged ventilation times of 24 h, 3 and 9 days, respectively, while only one patient in group B had a prolonged ventilatory support of 51 days ($P = 0.16$). In addition, haemodialysis was required by 11 (28.9%) patients in group A and by six (15.8%) patients in group B ($P = 0.17$). Infections recorded during primary hospitalization following OLT occurred in nine (23.7%) patients in group A as well as in 13 (34.2%) patients in group B ($P = 0.31$).

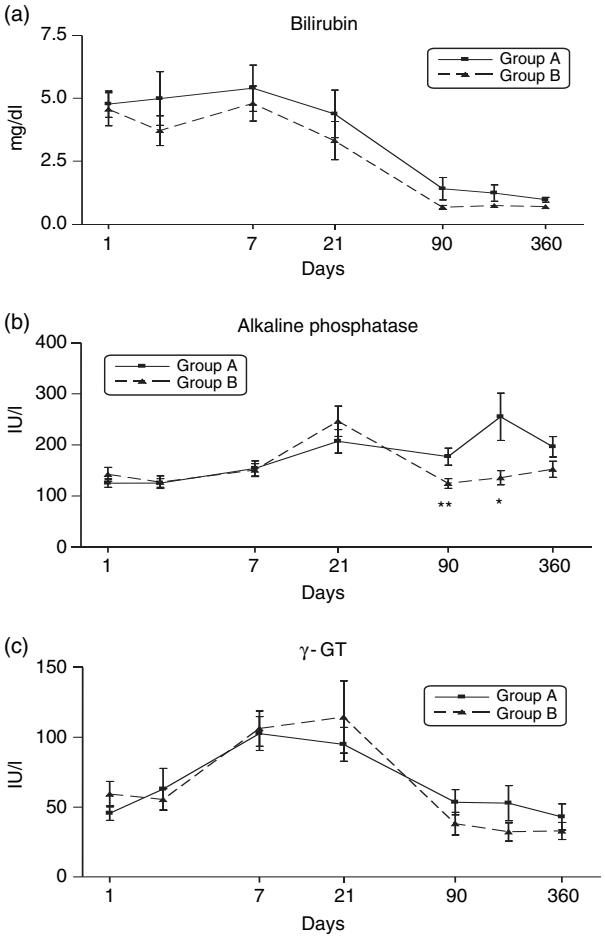

Figure 3 Biochemical parameters for measurement of cholestatic injury post-transplant; (a) bilirubin levels (0.1–1.2 mg/dl), (b) alkaline phosphatase (40–300 U/l) and (c) gamma-glutamyl transpeptidase (<55 U/l). Significant differences $*P < 0.05$ and $**P < 0.01$.

Laboratory parameters (cholestatic parameters, protein synthesis)

To clarify whether older livers are more cholestatic [13,14], we analysed postoperative development of bilirubin, alkaline phosphatase and gamma-glutamyl transpeptidase (γ-GT), as shown in Fig. 3a–c. No differences were seen in the post-transplant serum bilirubin levels, and the slope of bilirubin clearance was similar in both groups 7-days post-transplant (Fig. 3a). There were significant differences in the levels of the alkaline phosphatase after 3 and 6 months, however, these were within the range of the normal references (alkaline phosphatase <300 U/l, Fig. 3b). Alkaline phosphatase is a weak parameter to distinguish cholestatic liver disease and also varies significantly with age [15]. The most sensitive parameter for cholestatic injury, the γ-GT, showed no significant differences between both the groups (Fig. 3c)

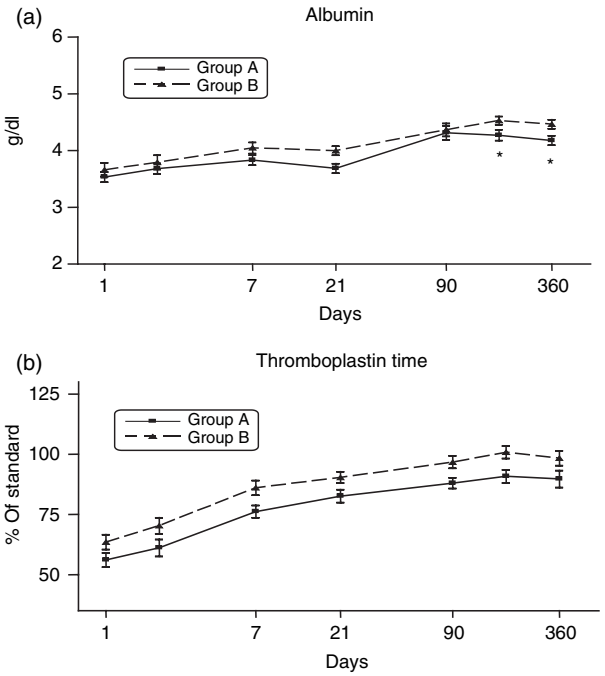

Figure 4 Biochemical parameters for measurement of protein synthesis post-transplant; (a) serum albumin (3.6–5.0 g/dl) and (b) and thromboplastin time (70–130%). Significant differences $*P < 0.05$.

[16]. Bile tree epithelium lesion as indicated by γ-GT was increasing in both groups until day 7 post-transplant and plateaued up to day 21 followed by a steep decrease to normal values.

As it was reported that older livers experience lower protein synthesis [14,17–20], we further analysed postoperative development of serum albumin and prothrombin time, as measured by the method of Quick (thromboplastin time given as per cent of local laboratory standard). Serum albumin levels and thromboplastin time were continually lower in recipients from older liver graft, however, both parameters were within normal reference range beyond postoperative day 7 (Fig. 4a,b).

Discussion

Today several strategies to expand the donor organ pool have been investigated. Like in microvesicular and macrovesicular steatosis the value and safety of aged organs have been questioned [21–23]. Case reports of successfully transplanted steatotic organs as well as transplantation of organs older than 80 years have challenged traditional views on so called 'marginal organs' [24]. The same is true for growing experience with nonheart-beating donors.

As research on steatotic livers, nonheart-beating donors and older organs shows, it is not the old or steatotic organ being a limiting factor to transplantation, instead it is many

other factors contributing to successful organ transplantation. However, despite several encouraging case reports on successful liver transplantation using aged donor liver grafts [25], we believe that it is still necessary to prove the value of organ donation from aged donors. Using a matched-pairs analysis we retrospectively analysed the outcomes of grafts and recipients after liver transplantation with organs donated from brain death donors older than 70 years.

According to our results patient and graft survival were comparable between both study groups after 1-year follow-up. As older liver donors are used increasingly success in patient and graft survival will need to be reviewed with long-term follow-up. Moreover, no differences were observed regarding the post-transplant liver graft quality or the postoperative course. Overall, organ donation from older donors (where donor age is >70 years) is not a limit for use of donor organs as shown in this study.

However, if donor age of >65 years is combined with macrovesicular steatosis of >15%, an increased risk of graft and patient loss may be associated, as Salizzoni *et al.* reported [22]. Another combination potentially leading to poor outcome postliver-transplantation is the combination of older liver grafts with cold ischemia over 12 h, as shown by Washburn *et al.* (liver grafts older than 60 years) and Emre *et al.* (liver grafts older than 70 years) [13,25]. Even so, it was found that older livers can be safely used within a CIT of 9 h [13,25], which is in accordance to our results. Thus, combination of several factors with increased donor age would lead to a higher risk background rather than donor age as an individual factor having profound influence on outcome in liver transplantation. Therefore, individual allocation of aged livers should be recommended.

Viral disease is discussed as a risk factor for the use of older liver grafts in liver transplantation. Twenty patients in this matched pairs study were transplanted for cirrhosis related to viral disease or other diagnosis in association with viral disease. Even though these patients comprised a major group in this matched pairs analysis, the outcome was not negatively influenced so far.

Problems associated with older liver grafts such as reduced capacity in protein synthesis [17,19], reduced capacity in liver regeneration [18,20], prolonged intractable cholestasis after liver transplantation [13,14,26], increased preservation injury [27,28] or increased incidence of primary nonfunction [29] were not a matter of concern in our study population.

In the available literature for older liver grafts it is repeatedly stated that older liver grafts are more cholestatic [13,14]. This should implicate more postoperative complications and a decrease in organ and patient survival. The most sensitive parameter for cholestatic injury, the γ-GT, showed no significant differences between both study groups, as did serum bilirubin levels and alkaline phosphatase. Clinically the older liver grafts had lower bile fluid production after transplantation as mentioned above, but this did not affect the overall bilirubin clearance.

Moreover, the protein synthesis is decreasing in older liver grafts according to experimental research in animals and clinical studies in liver transplant patients [18]. Thus, lower protein and coagulation factor synthesis in recipients of older liver grafts can be judged as inferior graft function compared with younger liver grafts. However, although our data support the existing experimental and clinical data on lower protein synthesis by older livers, the differences found were always within the normal range of standard laboratory references. An observation, which is in accordance with other studies [6,13]. Similar, no increase of postoperative preservation injury occurred, as was the incidence of INF or IPF. Moreover, the postoperative course was not negatively affected in the group of patients who received an 'old' liver.

With respect to data on reduced liver regeneration in older liver grafts, these data originate from animal models of liver resection or living-related liver transplantation. In consequence, these data cannot be applied for whole liver transplantation. Therefore, the regenerative capacity may be reduced in older liver grafts but this is not of proven significance for whole liver transplantation.

To conclude, several studies supporting our view that donor age *per se* is not a valuable parameter to exclude organs from the donor pool. Moreover, the resistant opinion about older liver grafts, cholestasis, regenerative capacity and protein synthesis are not a matter of concern according to our data. Therefore, even liver grafts from donors older than 70 years may be accepted for ALT without increasing the risk for recipient's postoperative complications. Nevertheless, among the factors contributing to the organ shortage are cultural and psychological barriers to donation and missed opportunities to request donation, as Alexander and Zola stated in 1996 [30]. Of the most basic categories for expanding the donor pool are incentives for individuals and families, changing regulations surrounding consent, educating the public and professionals, and redefining the pool of acceptable organs. Especially the latter one is probably the one, which could be most influenced by the transplant community. Interestingly already Makowka *et al.* [26] found in 1987 that '56% of the donors considered poor by conservative selection criteria produced livers with good early post-transplant function'.

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