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ORIGINAL ARTICLE

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Putative survival predictors in right-graft (adult) recipients after in situ split-liver transplantation: a retrospective single-center analysis

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Abstract In situ split-liver transplantation (isSLT) is an innovative surgical technique that is effective in expanding the cadaveric organ pool. Through isSLT, the bipartition of a single liver provides a right graft for an adult recipient (75% of the total liver volume, comparable to a normal whole liver of smaller size) and a left lateral graft for a pediatric recipient. In the present study we investigated the potential predictive value of donor and patient characteristics for 1-year survival, early postoperative graft function markers, and hemostatic parameters in 24 adult recipients that underwent isSLT, and we compared this cohort with a group of 29 whole-liver recipients. An overall coagulation abnormality score (CAS) that we derived by assigning one point for each abnormality in the hemostatic tests was also calculated. Through univariate comparison, the age of donor and patient was significantly associated with poor survival after isSLT, though not in the case of whole-liver transplantation. In a multivariate logistic regression model that we fitted for 1-year survival of right-graft recipients by entering donor and patient age, only the latter showed statistical significance ($P=0.04$). Among early postoperative graft function markers and hemostatic parameters, a platelet count of $\leq 50\times10^9$/l and a CAS of >2 on day 8 after isSLT indicated a reduced survival rate after isSLT. A CAS of >2 on day 8 was predictive for 1-year survival in whole-liver recipients as well. Multivariate Cox regression analysis identified the CAS as an independent predictor of survival ($P=0.0214$) in right-graft recipients. This study suggests that early postoperative CAS calculation may be a putative survival predictor in right-graft recipients after isSLT.

Keywords Split-liver transplantation · Adult recipients · Survival predictors · Whole-liver transplantation · Coagulation abnormality score

Introduction

During the past decade the number of patients awaiting liver transplantation has increased dramatically [9]. However, the discrepancy between available cadaveric donors and demand has resulted in a growing death rate for potential recipients [9]. This problem is particularly important in the European countries in which the number of liver donations is lower than the continental organ procurement average [4]. Thus, the shortage of cadaveric donors has necessitated a search for more effective strategies to maximize the liver graft pool [16]. In situ split-liver transplantation (isSLT) is an innovative surgical technique through which bipartition of a single liver, performed in the heart-beating cadaveric donor before preservation of the organ, provides a right

graft (segments I, IV, and V—VIII) for an adult recipient and a left lateral graft (segments II and III) for a child recipient [6, 14]. The right graft comprises approximately 75% of the total liver volume, which is anatomically and functionally comparable to a normal whole liver of smaller size [14]. The variables likely able to affect outcome of isSLT are similar to those involved in full-size liver transplantation, namely donor-related characteristics, early postoperative graft function markers (GFMs), and hemostatic parameters (HPs) [8]. However, previous reports of liver-splitting series failed to stress the impact of early postoperative GFMs and HPs on right-graft recipient survival [8, 13, 14]. On the other hand, a deeper knowledge of the factors affecting isSLT outcome, including donor-related factors, is crucial if this technique is to be expanded further and the cadaveric donor pool enlarged [8]. In the present study, we investigated the predictive value of donor and recipient characteristics for 1-year survival as well as early postoperative GFMs and HPs in 24 consecutive right-graft recipients after isSLT, and then we compared this group with a control group of patients who received a whole-liver (WL) transplant within the same period.

Patients and methods

Right-graft donor characteristics

This study comprised 24 consecutive split cadaveric livers (right grafts) that were transplanted in adult recipients from July 1997 to May 1999 at the Department of Transplantation in Genoa. One procedure was carried out in 1997, whereas 16 and seven procedures were performed in 1998 and 1999, respectively. Cadaveric donors were signalized by the Nord Italia Transplant (NITp) organization (Milan) and by the Regional Coordination Office (Genoa). In 14 cases, donors were signalized out of our regional district. In all cases, in situ liver splitting was performed on heart-beating cadaveric donors (HBCDs) by the surgical team of our department. For logistic reasons, all right grafts were transplanted into adult recipients in Genoa, whereas the left lateral grafts were transplanted into pediatric recipients in Bergamo (Liver Pediatric Transplant Center), Milan (Policlinico Hospital), Rome (Gemelli Hospital), London (King's College Hospital), Birmingham, and Hamburg.

The inclusion criteria for donor selection were: donor-recipient age difference < 30 years, intensive care unit (ICU) recovery ≤ 5 days, total bilirubin ≤ 2.5 mg/dl, alanine aminotransferase (ALT) ≤ 300 U/l, γ-glutamyl transpeptidase (γ-GT) ≤ 150 U/l, hemoglobin (HB) ≤ 10 g/dl, sodium level < 160 mmol/l (with the exception of two cases), hemodynamic stability within the last 24 h, normal portal blood flow evaluated by Doppler ultrasonography, and no evidence of macroscopic and histological liver damage [1]. Donors with a history of cardiac arrest were not considered for isSLT. The donor work-up protocol did not require special invasive examination.

The donor parameters that were considered in this study were: donor age, ALT, aspartate aminotransferase (AST), γ-GT, alkaline phosphatase (ALKP), white blood cells (WBCs), platelet (PLT) count, prothrombin time (PT), activated partial thromboplastin time (aPTT), creatinine, blood urea nitrogen (BUN), Na^+, and K^+

Table 1 Right-graft recipient diagnosis (*PNC* post-necrotic cirrhosis, *PHC* post-hepatitis cirrhosis, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *HDV* hepatitis delta virus, *HCC* hepatocellular carcinoma)

Diagnosis	Male	Female	No. of transplants
PNC (HCV)	5	4	9
PHC	1	2	3
PNC (HBV)	1	1	2
PNC (HBV–HDV)	–	2	2
Cryptogenic cirrhosis	1	–	1
Oxaluria	–	1	1
Budd–Chiari syndrome	–	1	1
α_1-antitrypsindeficit	–	1	1
Hemangioendothelioma	–	1	1
Primary sclerosing cholangitis	1	–	1
Adenomatosis	1	–	1
HCC	1	–	1

Right-graft recipient characteristics

The diagnostic categories for right-graft recipients ($n = 24$) are given in Table 1. Priority for transplantation was set according to the United Network of Organ Sharing (UNOS) scoring system [20]. Of the 24 right-graft recipients followed by our team, two had UNOS status 1, 15 UNOS status 2B, and seven UNOS status 3. All adult recipients were informed about the details of the procedure and they consented to undergo isSLT at the time of acceptance, while they were on the waiting list. They repeated their consent when called for transplantation.

The pre-operative patient characteristics considered in this study were: recipient age, diagnostic category, UNOS status, and waiting time for transplantation. These parameters were included in univariate analyses, as were donor–recipient age ratio and cold ischemia time (CIT).

In situ liver splitting

We performed liver splitting on HBCDs before organ preservation using the technique described for procurement of the left lateral lobe (segments II and III) in a living donor [14]. The left hepatic artery and left portal vein were isolated, whereas the right portion of the hepatoduodenal ligament was untouched [1]. Attention was given to the saving of the arterial branch to segment IV. Separation of the biliary duct was carried out via an intra-parenchymal approach, after partial parenchymal resection by either electrocoagulation or 4/0 and 5/0 Prolene for vessel suture ligation to divide the parenchymal bridge between the left lateral lobe and the left median segment in continuity with the remaining right liver [1, 14]. After the dissection had been completed, the two liver sections were separated, each with its own vascular pedicles and biliary drainage. University of Wisconsin (UW) solution was used as rinse, and sequential re-vascularization (portal and arterial) was performed, after which the perfusion of segment IV was monitored carefully. There was usually only a slight cyanotic appearance around the anterior part of this segment, without the necessity of further surgery. The right graft was composed of segments I, IV, and V–VIII. If the technique of splitting that is described above is used, the right graft will contain approximately 75% of the total liver volume, which is anatomically and functionally comparable to a normal whole liver of smaller size [14]. Peri-operative prophylaxis was carried out as previously described [5].

Intra-operative transfusions of packed red cells (PRCs), fresh frozen plasma (FFP), and PLTs were supplied. The criteria for blood component support were: major surgical blood loss,

pre-operative and/or intra-operative coagulopathy, fibrinolysis, hypothermia, and hypocalcemia. We managed the PRC transfusions to keep HB concentrations at 8–10 g/dl during the intra-operative period, taking care to avoid HB levels of over 10 mg/dl postoperatively to reduce the risk of hepatic artery thrombosis due to high blood viscosity.

Early postoperative parameters

GFMs and HPs were measured daily in each liver recipient for the first 8 days after transplantation. All assays were performed at the Clinical Chemistry Laboratory of S. Martino University Hospital, where a Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) automated analyzer was used for biochemical assays and a Stago (Boehringer Mannheim) automated analyzer was used for hemostatic markers. GFMs included AST (laboratory range 7–30 U/l), ALT (1–21 U/l), γ-GT (8–78 U/l), ALKP (20–40 U/l), and total bilirubin (TB; 1.1 mg/dl). HPs included PLTs (laboratory range 100–400×10^9/l), PT (range 80–110%, expressed as each patient-plasma clotting time as a percentage of that of a reference plasma pooled from normal subjects), aPTT (ratio 0.88–1.22, expressed as the ratio of each patient-plasma clotting time to plasma pooled from normal subjects), and fibrinogen (150–300 mg/dl). Moreover, we derived a coagulation abnormality score (CAS) by assigning one point for each abnormality in the hemostatic tests independently of the degree of abnormality, in agreement with Bontempo et al. [3]. The CAS ranged from 0 to 4, depending on the number of abnormal tests for each patient.

Whole-liver transplantation

A group of patients ($n=29$) who received a WL transplant during the same period as right-graft recipients was used for comparison. The enrollment criteria for WL transplants were: no missing data with regard to donor characteristics, a post-transplantation survival ≥8 days, and no censoring after admission. The patients were associated with the following diagnostic categories: post-necrotic cirrhosis was established in 18 (14 men and four women), chronic cirrhosis in four (two men and two women), primary biliary cirrhosis in two (two women), hepatocellular carcinoma in two (one man and one woman), and miscellaneous in four (two men and two women). Four recipients had UNOS status 1, 22 UNOS status 2B, and three UNOS status 3. The age of WL recipients was 49.53 ± 10.1 years.

The organ procurement criteria for cadaveric donors for WL transplantation included sub-optimal donors (age > 60 years) and/or grafts (macro-steatosis ≤ 30% in pre-perfusion frozen-section biopsy). The age of cadaveric WL donors was 51 ± 14.29 years. We carried out WL transplantation using the piggyback technique [18]. The criteria for intra-operative transfusions were the same as those that were adopted for isSLT.

Follow-up

The mean follow-up for right-graft recipients was 2.16 ± 1.32 years (median: 3 years, range: 0.08–3 years). Overall 1-year survival was 70.83%. The mean follow-up for WL control recipients was 2.00 ± 1.43 years (median: 3 years, range: 0.08–3 years), with a 1-year survival of 75.86%.

Statistical analysis

The univariate association of cadaveric liver donor and pre-operative recipient characteristics with survival was tested by a series of simple logistic regression models. We fitted a multiple logistic regression model for survival by using donor and recipient factors that were found to be significant in the univariate analysis. Correlation between early postoperative values and CIT was calculated via Spearman's ranked test. The significance of differences in early graft function values (expressed as means ± SEM) between recipients who died and those who were alive at the time of follow-up was calculated for each postoperative day via the Mann–Whitney U test. CAS values were estimated by unpaired t-test with Welch's correction. Early postoperative parameters that differed significantly after undergoing Mann–Whitney and unpaired t-tests were dichotomized at their median value and evaluated with the Kaplan–Meier product-limit estimator. We used the log-rank test to compare survival curves. The odds ratio was calculated via Fisher's exact test. Early postoperative parameters that were significantly associated with survival were introduced into multivariate regression analysis (Cox proportional hazard survival regression). Only statistical analyses with a power ≥0.8 for the goodness of sample size were performed. The difference between patients was assumed to be significant at $P<0.05$ with a two-tailed null hypothesis. No adjustment was fixed to the nominal P value that resulted from the analyses in view of the descriptive nature of this study. We performed the statistical analyses and graphic representations using the software packages STATISTICA 6.0 with Power Analysis Model (StatSoft, Tulsa, Okla.,USA), Prism 3.02 (GraphPad Software, San Diego, Calif., USA), and a logistic regression calculator (http://members.aol.com/johnp71/javastat.html).

Results

A series of simple logistic regression models was used for the testing of the univariate association of characteristics of the cadaveric liver donors (Table 2) and pre-operative right-graft recipients (Table 3) with 1-year survival. Only donor age ($P=0.04$) and recipient age ($P=0.0034$) were significantly associated with survival. Using the same analysis technique in the WL group, we observed no statistical significance (data not shown). In particular, neither donor age ($P=0.262$) nor recipient age ($P=0.991$) showed a significant univariate association with survival. The age of cadaveric donors selected for isSLT (34 ± 15 years) differed significantly from that of cadaveric donors for WL transplantation (51 ± 14 years) ($P=0.0001$), whereas no difference was determined for recipient age (48 ± 12 vs 49 ± 10 years, respectively; $P=0.739$). In the multiple logistic regression model fitted by our entering donor and right-graft recipient characteristics found to be significant in the univariate analysis (Table 4), only recipient age was predictive for 1-year survival ($P=0.04$).

In right-graft recipients, the ALT value on day 0 post-isSLT was the unique GFM to be related to CIT ($r=0.48$, $P=0.01$). On the other hand, no relationship between CIT and right-graft recipient 1-year survival was determined (Table 3). The mean value of CIT during isSLT was 474 ± 78 min (range: 353–630 min, median: 480 min) while CIT in WL transplantation was 475 ± 93 min (range: 295–633 min, median: 480 min), without significant differences between these procedures ($P=0.967$). Absence of significant correlation between each GFM and

Table 2 Univariate association between liver donor characteristics and 1-year survival in right-graft recipients (*OR* odds ratio, *CI* confidence interval)

Characteristic	Range	Median	χ^2	OR	95% CI	*P*
Donor age (years)	10–66	31	4.18	1.07	0.99–1.15	0.04
ALT (U/l)	14–272	36.5	0.0746	0.99	0.98–1.01	0.784
AST (U/l)	6–125	27.5	0.297	0.99	0.96–1.02	0.585
γ-GT (U/l)	6–107	21.5	1.32	0.97	0.94–1.01	0.249
ALKP (U/l)	14–229	116	0.14	0.99	0.96–1.02	0.707
WBCs ($\times 10^9$/l)	4.3–81	12	1.47	1.00	0.99–1.00	0.224
PLT count ($\times 10^9$/l)	41–418	143	1.36	1.00	1.00–1.01	0.242
PT (%)	11–106	33	0.021	1.01	0.79–1.3	0.886
aPTT (s)	0.4–1.22	0.9	0.2	0.98	0.93–1.04	0.648
Creatinine (mg/dl)	0.43–2.8	1.0	1.41	0.33	0.05–2.08	0.234
BUN (mg/dl)	6–104	28	1.42	0.97	0.93–1.01	0.232
Na (mmol/l)	129–189	151	0.08	1.01	0.93–1.09	0.775
K (mmol/l)	2.4–8.7	4.1	2.17	0.22	0.02–1.93	0.14

Table 3 Univariate association between preoperative right-graft recipient characteristics and 1-year survival (*OR* odds ratio, *CI* confidence interval)

Characteristic	Range	Median	χ^2	OR	95% CI	*P*
Recipient age (years)	13–61	48.2	8.55	0.8	0.65–0.98	0.0034
Donor–recipient age ratio	0.2–3.69	0.69	0.12	0.78	0.2–2.94	0.72
Diagnosis	–	–	0.014	1.01	0.77–1.24	0.903
UNOS status	–	–	0.31	0.99	0.97–1.01	0.57
Waiting time (months)	0.2–27	8	1.53	1.08	0.81–1.05	0.214
CIT (min)	353–630	480	1.09	1.00	0.99–1.01	0.34

Table 4 Multivariate logistic regression model fitted for 1-year survival in right-graft recipients by inclusion of donor and patient characteristics found to be significant in the univariate analysis of Table 2 and Table 3. Overall model: $\chi^2 = 9.528$; −2 log likelihood: 28.97 (null model) −19.44 (converged); $P = 0.0085$ (*OR* odds ratio, *CI* confidence interval)

Characteristic	OR	95% CI	*P*
Donor age	0.96	0.89–1.03	0.33
Recipient age	0.81	0.66–0.99	0.04

CIT was noted after WL transplantation (data not shown).

The mean values of GFMs were measured for the first 8 days post-isSLT in right-graft recipients and grouped in relation to 1-year survival (Fig. 1). Of these parameters, only ALT on day 8 post-isSLT showed a significant increase in short-term survivors ($P < 0.01$), although the log-rank test demonstrated no significant difference in the Kaplan–Meier survival curves when the patients were stratified according to the ALT median value on that day ($P = 0.061$). If the same approach was followed, a statistical significance of early GFMs in WL recipients grouped in relation to 1-year survival was noted only for ALT increase on day 1 ($P = 0.031$) and on days 2 and 3 ($P = 0.049$) in short-term survivors (Fig. 1). According to ALT median values on days 1–3, no significant differences in survival curves were found by log-rank test ($P > 0.05$). The comparison of postoperative ALKP values in WL recipients, even if without statistical significance, did not reach a power ≥0.8, failing analysis enrollment criteria of this study (data not shown).

During the intra-operative period, transfusions performed on right-graft recipients, which supplied PRCs, FFP, and PLTs, showed no significant differences between patients grouped for 1-year survival (Table 5). The same finding was noted in WL recipients (Table 5). An overall comparison between right-graft and WL recipients showed that a significantly higher number of FFP units were transfused during isSLT (20.25 ± 3.11 vs 12.60 ± 2.22, respectively; $P = 0.017$).

Early HPs were measured in each right-graft recipient on the same days post-isSLT, as for GFMs. PT and fibrinogen showed an increasing trend, both in patients who survived for at least 1 year and in those who died within 1 year, without statistical significance on any day post-isSLT (Fig. 2). PT increased progressively in the short-term survival group, reaching the same PT values as for survivors on day 11 post-isSLT (data not shown). Moreover, no significant difference in aPTT ratio was determined (Fig. 2). In WL recipients, no statistical significance for early PT, aPTT ratio, and fibrinogen was noted between short-term and long-term survivors (Fig. 2).

In right-graft recipients, the PLT count showed higher mean values on all early postoperative days in 1-year survivors (Fig. 3). The PLT count increased significantly in the group of survivors starting on day 7 post-isSLT ($P < 0.05$), reaching a major significance on day 8 ($P < 0.005$) (Fig. 3). The Kaplan–Meier survival

Table 5 Intra-operative blood products usage in right-graft and whole-liver recipients grouped for 1-year survival. Blood products are expressed as number of units

Blood product	Right-graft recipients			Whole-liver recipients		
	Survivors	Non-survivors	*P*	Survivors	Non-survivors	*P*
PRCs	8.2 ± 1.30	9.8 ± 2.61	0.458	8.18 ± 1.81	9 ± 3.20	0.943
FFP	18.53 ± 3.24	25.4 ± 8.51	0.406	13.22 ± 2.91	10.87 ± 2.51	0.622
PLTs	1.26 ± 0.28	2.2 ± 0.73	0.238	1 ± 0.26	0.62 ± 0.32	0.526

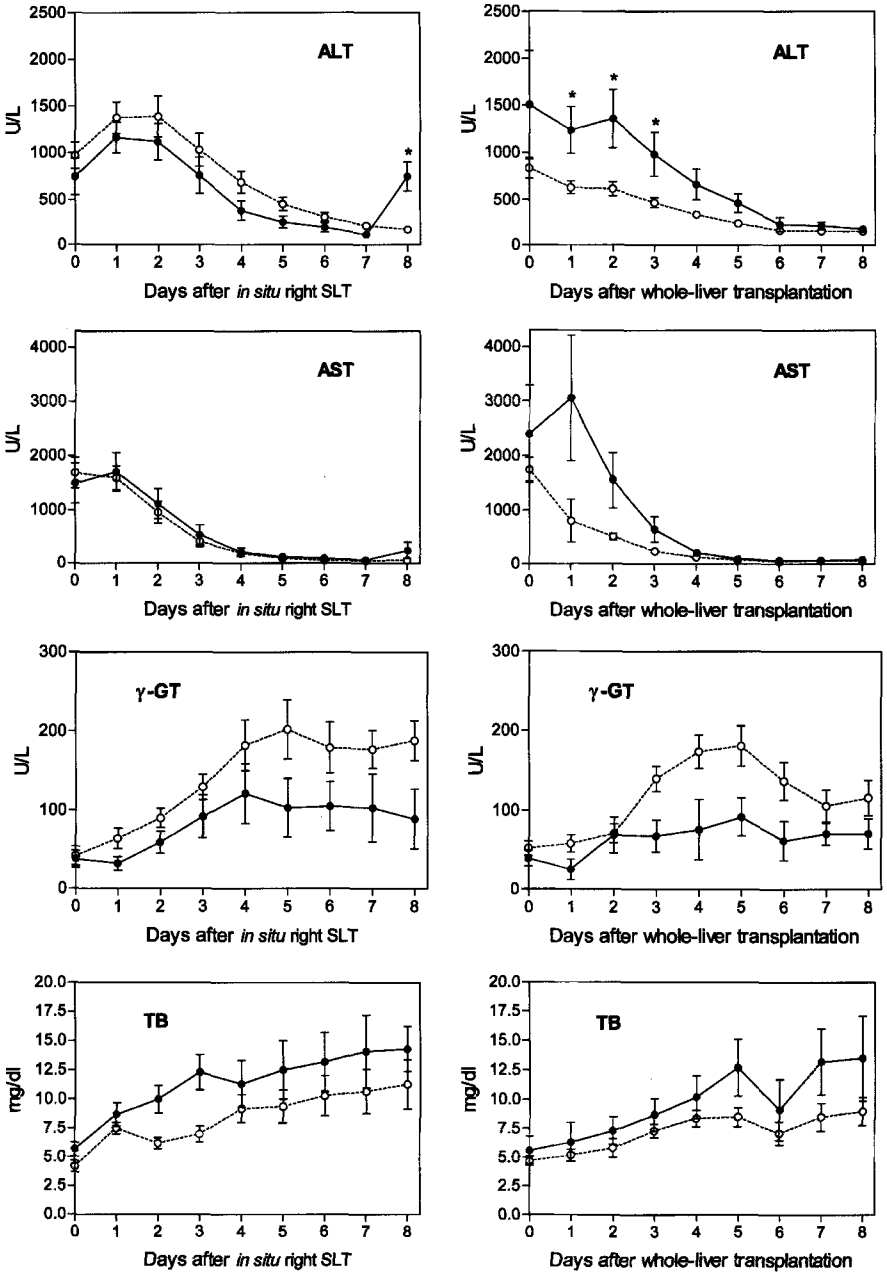

Fig. 1 Early postoperative (means ± SEM) ALT, AST, γ-GT, and TB in patients who survived for less than 1 year (*solid circles*) and who survived for at least 1 year (*open circles*) after in situ right split-liver transplantation (*SLT*) (*left*; $*P < 0.01$) and whole-liver transplantation (*right*; $*P < 0.05$)

curves revealed better survival for right-graft recipients who had PLT counts $>50\times10^9$/l on day 8 post-isSLT than for those with PLT counts $\leq 50\times10^9$/l (88 vs 28%) (Fig. 3). The log-rank test showed a significant difference between survival curves for PLT values measured on day 8 post-isSLT ($\chi^2 = 9.61$, $P = 0.0019$), with the chance of survival for at least 1 year being significantly higher in right-graft recipients with PLT counts $>50\times10^9$/l (odds ratio = 18.75, $P = 0.0086$). In WL recipients, the PLT count showed higher mean values in

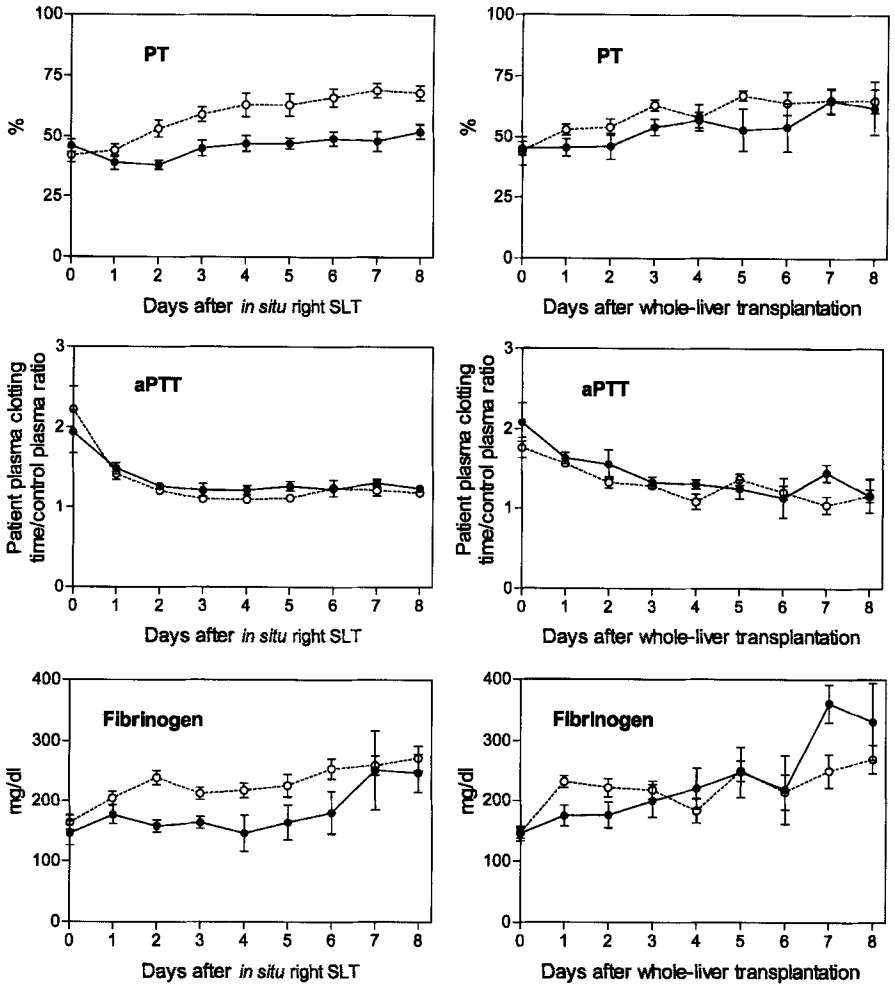

Fig. 2 Early postoperative (means ± SEM) PT, aPTT, and plasma fibrinogen in patients who survived for less than 1 year (*solid circles*) and who survived for at least 1 year (*open circles*) after in situ right split-liver transplantation (*SLT*) (*left*) and whole-liver transplantation (*right*)

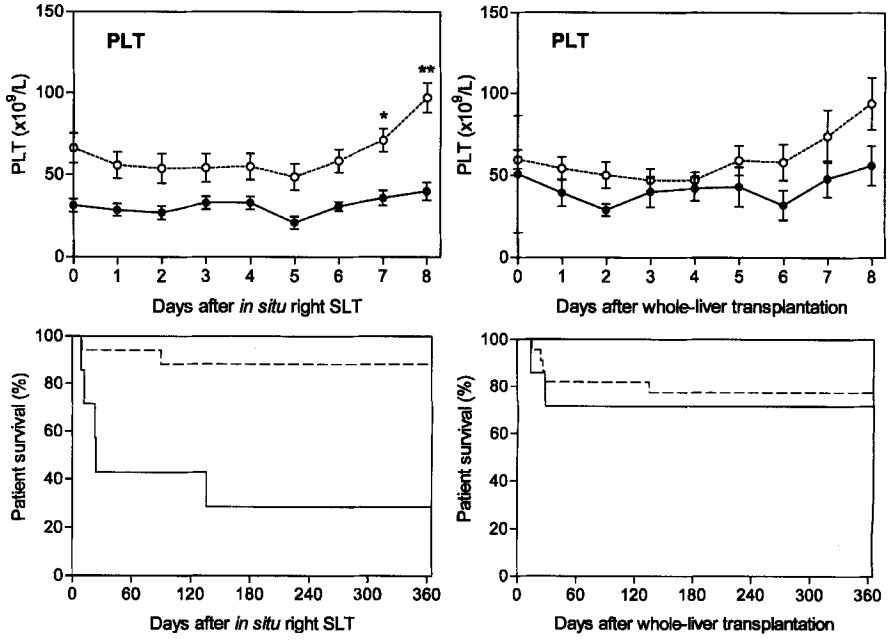

Fig. 3 Early postoperative (means ± SEM) PLT count in patients who survived for less than 1 year (*solid circles*) and who survived for at least 1 year (*open circles*) after in situ right split-liver transplantation (*SLT*) (*upper left*; $*P < 0.05$, $**P < 0.005$) and whole-liver transplantation (*upper right*), with comparison of the Kaplan–Meier 1-year survival curves for right-graft recipients (*bottom left*; $P = 0.0019$) and whole-liver recipients (*bottom right*; $P = 0.721$) stratified into two groups according to the median postoperative PLT value on day 8 (*broken line* PLT count $> 50 \times 10^9$/l, *solid line* PLT count $\leq 50 \times 10^9$/l)

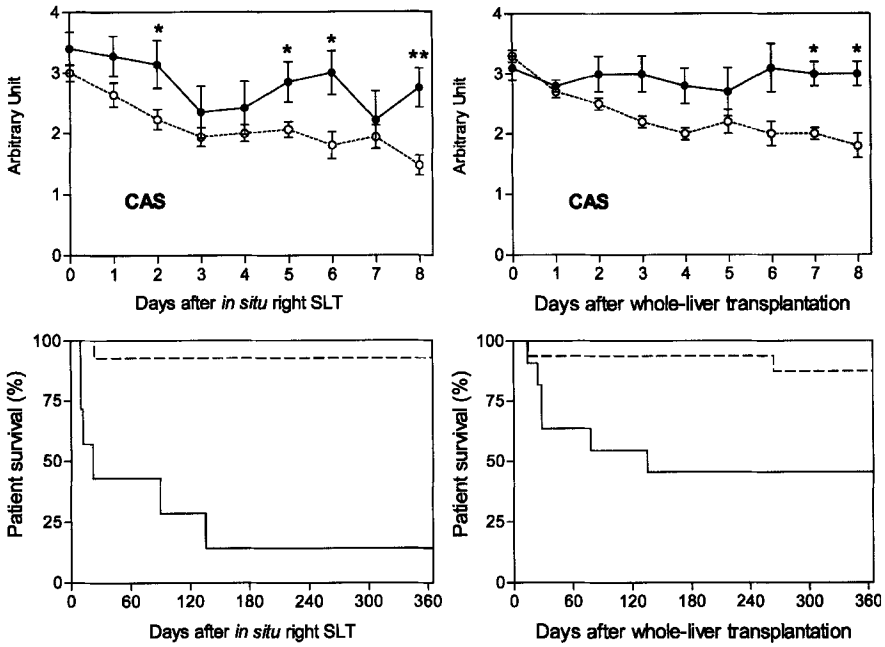

Fig. 4 Early postoperative (means ± SEM) CAS in patients who survived for less than 1 year (*solid circles*) and who survived for at least 1 year (*open circles*) after in situ right split-liver transplantation (*SLT*) (*upper left*; $*P < 0.01$, $**P < 0.0005$) and whole-liver transplantation (*upper right*; $*P = 0.005$), with comparison of the Kaplan–Meier 1-year survival curves for right-graft recipients (*bottom left*; $P < 0.0001$) and whole-liver recipients (*bottom right*; $P = 0.0162$) stratified into two groups according to the median postoperative CAS value on day 8 (*broken line* CAS ≤ 2, *solid line* CAS > 2)

the group of 1-year survivors than in short-term survivors, with an increasing trend in both groups of patients that started on day 6 after surgery (Fig. 3). Although a marginally significant increase in PLT value was noted on day 8 in the group of WL recipients who survived for at least 1 year ($P = 0.053$), no significance was found after survival-curve comparison ($P = 0.721$) (Fig. 3).

An overall score assessed for CAS showed, in right-graft recipients, higher postoperative values on days 2, 5, 6 ($P < 0.01$), and 8 ($P < 0.0005$) in the non-survivor group (Fig. 4). The Kaplan–Meier curves revealed better survival for patients with a CAS of ≤ 2 than for patients with a score of > 2 on day 8 post–isSLT (94 vs 14%), with a significant difference on log-rank test ($\chi^2 = 15.85$, $P < 0.0001$; Fig. 4). In right-graft recipients with a CAS of ≤ 2 on day 8 post-isSLT, the chance of survival at 1 year was higher than in the patients with a CAS of > 2 (odds ratio = 84, $P = 0.0006$). In WL recipients, an improving CAS trend was determined in 1-year survivors until it reached a major significance on day 8 post-transplantation ($P = 0.005$). The Kaplan–Meier curves revealed a better survival for WL recipients with a CAS of ≤ 2 than for patients with a CAS of > 2 on postoperative day 8 (94 vs 45%), as sustained by log-rank test ($\chi^2 = 5.784$, $P = 0.0162$). The chance of 1-year survival was significantly higher in WL recipients with a CAS of ≤ 2 on day 8 post-transplantation (odds ratio = 7.8, $P = 0.0384$).

All postoperative variables that affected right-graft recipient survival were further analyzed for their potential independent significance by Cox proportional hazard survival regression (overall model fitted with $\chi^2 = 18.16$ and $P = 0.00041$). Only the CAS showed a statistical significance as independent predictor for survival ($P = 0.0214$).

Discussion

Differently from previous analyses performed on isSLT [8, 10, 13, 14], this study focused mainly on the potential predictive significance of early postoperative factors for survival. With this aim, GFMs and HPs were evaluated for survival at 1 year in 24 consecutive patients who received a right graft (75% of the whole liver volume) by isSLT. In agreement with previous studies [8], several donor characteristics were also analyzed for recipient survival. Moreover, considering the critical role of cold ischemia during procurement of the right graft [14, 15], we evaluated GFMs and HPs for their correlation with CIT. For better comparison with previously published series focusing on survival predictors in liver transplantation [2, 8, 12], we also investigated donor and recipient characteristics, as well as early postoperative factors, in a control group of patients who underwent WL transplantation within the same period as for isSLT, following statistical analyses equal to that series.

In view of the lack of a common Italian priority score for liver transplantation [4], in our department as well as in the majority of Italian transplantation centers, priority is assigned according to the UNOS scoring system [20]. However, medical urgency status for liver registrants was revised on an interim basis by UNOS during 1997 and redefined permanently in 1998 [20]. In this study, priority for transplantation was assigned retrospectively according to the most recent UNOS scoring

system, although some of the candidates for liver transplantation were originally introduced onto the waiting list and received transplants in accordance with the former UNOS criteria. Thus, at the time of transplantation, of the 24 right-graft patients that were surveyed by our team, two had UNOS status 1 (8.3%), 15 UNOS status 2B (62.5%), and seven UNOS status 3 (29.1%). In the present study, 17 of 24 recipients (70.8%) were alive after both 1-year and 3-year follow-up; six of seven deaths (85.7%) occurred within the first 100 days after transplantation, in agreement with other series [8]. The cause of death was multi-organ failure in five cases, heart failure in one case, and sepsis in one case. Five deaths were observed in patients with UNOS status 2B, whereas the other two deaths occurred in those with UNOS status 1. Although univariate analysis showed no statistical significance between UNOS status and 1-year survival, our overall patient survival rate is lower than previous isSLT reports [8, 10, 13, 14]. On the other hand, in some of those series the percentage of non-urgent recipients out of hospital at the time of transplantation (patients at home, originally listed as UNOS status 4 and absent in our series) was over 60% [14]. In addition, other series failed to specify the exact number of patients with status 2B and 3 [8]. Our department gives priority to patients that present the worst clinical condition, and at the time of transplantation two recipients were high-risk, whereas 15 recipients were in critical and potentially high-risk condition, notwithstanding that life expectancy without transplantation for patients with status 2B was more than seven days. In recipients undergoing urgent isSLT, survival was reported to be less than 70% at 1 year (67%) and 3 years (65%) [8]. In the WL transplantation group, a better overall 1-year survival than in right-graft recipients was noted (75.86%). In the WL group, patients with UNOS status 2B were in the majority (75.8%), although some of them were on the borderline for being shifted towards status 2A. Considering these problems, UNOS has recently proposed to change the current statuses 2A, 2B, and 3 to a continuous numerical scale based on a patient's risk of 3-month mortality on the waiting list for liver transplantation (UNOS-modified MELD model), which would provide an increased number of medically urgent categories by which potential liver recipients might be differentiated [19]. The changes in UNOS statuses are actually under study by the National Transplantation Center and Italian macro-regional organ-procurement organizations for possible adoption with regard to the policy of liver allocation. In any case, our results, as well as those provided by other large isSLT series, suggest caution in the use of split liver grafts in urgent or high-risk recipients.

In the largest series to date of cadaveric liver donors ($n=55$) that were analyzed for recipient survival after undergoing isSLT, only a donor hospital stay of more than 5 days was considered to be a donor-related independent survival predictor in a multivariate logistic regression analysis, although this variable approached (but did not reach) statistical significance ($P=0.063$) [8]. At our department, donor hospital recovery of more than 5 days is an exclusion criterion for isSLT [1], which makes the comparison of our data with previous series unreliable with respect to this variable. Differently from Ghobrial et al., where donor age was not related to recipient survival ($P=0.955$) [8], this variable was the only donor characteristic in our study to be significantly associated with right-graft recipient survival by univariate comparison. Interestingly, in the study by Ghobrial et al. the median donor age was 20 years, whereas in our series the median age of liver donors was 31 years. Other than in WL transplantation, where donor age is progressively increased without affecting post-transplant outcome [11], the results of this series seem to suggest caution regarding donor age and isSLT outcome. Moreover, a significant relationship between increasing age of recipients and poor survival was found, and in a multivariate logistic regression model that we fitted by entering donor and recipient age, the latter resulted as independent predictor of survival. These findings indicate that increasing age of both donor and patient may impact on right-graft isSLT recipient survival, which suggests caution, especially with regard to recipient age. The strategy of exclusion of in situ split-liver cadaveric donors that are older than a cut-off value (e.g., 40 or 50 years) as well as right-graft recipients of increasing age may be more effective than the donor–recipient age ratio simply being used [1].

None of the early postoperative GFMs had a significant impact on survival in either right-graft recipients or in the WL control group. The ALT value on day 0 post-isSLT was the unique marker to be related to CIT, whereas no relationship between CIT and survival was determined. It is likely that the lack of impact of CIT on post-transplant survival in our series may be due to the containment of CIT (mean value: 7.89 h) to slightly below the average CIT for liver transplantation (8.8 h) fitted in the U.S. Scientific Registry of Transplant Recipients analytic model [21].

The liver plays a key role in the regulation of hemostasis, and postoperative measurement of HPs is useful for the monitoring of patients who have undergone WL transplantation [12, 17]. Differently from previous studies performed on WL recipients [12, 17], neither early aPTT ratio nor PT revealed a predictive value for survival in either right-graft or WL recipients in this analysis. Conversely, the PLT count increased significantly, starting on day 7 post-isSLT in 1-year survivors. Recipients with PLT counts $>50\times10^9$/l on day 8 post-isSLT had significantly better prognoses than recipients with PLT counts $\leq 50\times10^9$/l. Odds ratio calculation confirmed the major chance of survival for

patients with PLTs $>50\times10^9$/l on day 8 post-isSLT. However, these data should be considered with caution in the case of the lower PLT count observed in short-term survivors starting on day 0 post-isSLT. Nevertheless, the PLT count in both donors and right-graft recipients before transplantation did not present any significant difference (data not shown). Interestingly, no significant difference in postoperative PLT count was noted in WL recipients when they were stratified for 1-year survival. Thrombocytopenia is an early post-transplant complication that occurs uniquely in liver transplant recipients [5]. It is noteworthy that activated PLTs participate in monocyte and neutrophil recruitment, which suggests possible PLT antimicrobial activity by enhancing cell-mediated antimicrobial action [7, 22]. Although a possible role of thrombocytopenia in post-transplant infections has been suggested [5], in this isSLT series only one patient died of sepsis.

In agreement with Bontempo et al. [3], by assigning an overall score for each abnormality in postoperative HPs, apart from the degree of abnormality (CAS), we determined a better 1-year survival for patients with a CAS of ≤ 2 on day 8 than for patients with a CAS of >2 in both right-graft and WL recipients. The lower CAS noted on day 8 post-transplantation in 1-year survivors cannot be attributed to the corrective effect of transfusion with blood derivatives, since no statistical difference was determined in the intra-operative supply of PRCs, FFP, and PLTs between survivors and non-survivors, in accordance with previous findings with regard to WL transplantation [3, 12]. The CAS on day 8 post-isSLT was identified as an independent predictor for 1-year survival, when Cox proportional hazard survival regression was used. Although the predictive survival value of the CAS may be extended at 3 years after isSLT, this would sound like a forced interpretation when one considers the absence of late graft and/or patient loss in our series. In fact, in the WL transplantation group, two incidences of graft loss and two of patient death were observed within 3 years, which failed to confirm the predictive survival value of the CAS in the long term.

A diffusion of the isSLT technique is hoped for into the countries in which the shortage of liver donors makes it impossible for all patients with end-stage liver disease to receive a transplant [4, 8]. On the other hand, isSLT requires experienced liver surgeons and the necessary logistic conditions by the surgical teams, as well as the donor and recipient hospitals [14]. Because isSLT has been adopted only within the past few years, there are relatively few published series regarding this procedure. Although previous studies that focused on potential predictors for survival after isSLT were not completely homogeneous with regard to donors, patients, and methods of analysis and results, the search for potential "universal predictors" of survival for patients who are to undergo isSLT remains the Holy Grail for many liver surgeons. In this study, in univariate analysis, increased age of donors and right-graft recipients was predictive for poor survival. Moreover, a low PLT count and high CAS on day 8 post-isSLT were related to short-term survival. Finally, in a multivariate analysis the CAS was the unique independent predictor for 1-year survival in adult recipients. To our knowledge, this is the first isSLT series in which the CAS has been investigated retrospectively. Further series of isSLT should be analyzed so that the prognostic significance of the CAS in right-graft recipients can be confirmed.

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