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ORIGINAL ARTICLE

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Pretransplantation risk factors for graft loss after liver transplantation in cirrhotic patients; effect of cytomegalovirus serologic status

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Abstract This study analyzes the effect of the preoperative variables of donors and recipients on graft survival after liver transplantation (LT). Preoperative data from a cohort of 122 cirrhotic patients who underwent primary LT were evaluated prospectively. The influence of these variables as risk factors for graft loss was assessed. During follow-up (median: 33 (19–59) months) there were 38 (31.1%) graft losses (22 deaths and 16 retransplantations). Variables that showed statistical association with graft loss on univariate analysis ($P < 0.150$) were: positivity of the CMV serologic status of the donor ($P = 0.028$), the UNOS score of recipient ($P = 0.048$) and advanced donor age ($P = 0.124$). When these variables were introduced into the multivariate study, the CMV serologic status of the donor was the only variable that was independently associated with graft loss (relative risk = 2.97, 95% confidence interval = 1.05–8.39; $P = 0.039$). Donor CMV-seropositivity is a significant pretransplantation determinant for graft loss in liver transplant recipients.

Keywords Prognosis · Liver transplantation · Cytomegalovirus

Introduction

Liver transplantation (LT) is the treatment chosen for selected patients with advanced liver disease. The improvements in surgical and anesthetic techniques, the introduction of new immunosuppressive agents, the accumulated experience in postoperative management, and an improved selection of donor and recipient have led to an increase in survival. However, 1 and 5 year recipient death rates of approximately 15% and 22% and graft failure rates of 30% and 40% respectively, continue to be reported from most centers [1].

The criteria for recipient and donor selection are crucial, as the demand for LT has risen faster than the availability of donor livers. It is essential to identify the preoperative risk factors associated with outcome in order to make this selection and to choose the optimal time for LT.

Almost all previous studies of predictors of outcome in LT have included patients presenting a wide range of etiologies of liver disease, sometimes including patients with acute and chronic liver disease, and have analyzed retrospectively a limited number of variables. In some cases donor variables have been excluded and distinct end-points have been analyzed, thereby hindering the interpretation of results [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

Cytomegalovirus (CMV) causes illness in liver transplant recipients, and there is evidence that CMV infection is associated with decreased graft and patient survival among kidney [13], heart [14], lung [15], intestine [16] and liver recipients [17]. In addition to directly infectious syndromes, CMV, by its immunomodulatory effect, enhances susceptibility to opportunistic infections [18] and probably to chronic allograft dysfunction [19]. It has also been related to post transplantation hepatitis C evolution [20]. The aim of this study is to assess the influence of preoperative recipient and donor variables, including CMV serologic status, on graft survival after LT in a cohort of cirrhotic patients.

Table 1 Variables with and without prognostic significance in univariate analysis ($n = 122$)

Variables	Mean ± SD (range) or N	*P* value
Recipient variables		
Sex (male/female)	72/50	0.306
Age (years)	54.2 ± 9.8 (23–71)	0.192
Etiology (viral/non-viral)	67/55	0.153
HCC (yes/no)	28/94	0.953
Creatinine (mg/dl)	0.9 ± 0.3 (0.4–1.7)	0.884
Albumin (g/dl)	30.9 ± 5.7 (17–47)	0.943
Bilirubin (mg/dl)	2.96 ± 3.45 (0.6–32)	0.972
Prothrombin time (%)	68.3 ± 15.3 (31–105)	0.813
Previous ascites (yes/no)	101/21	0.604
Previous hepatic encephalopathy (yes/no)	42/80	0.682
Previous variceal bleeding (yes/no)	39/83	0.620
Child–Pugh score (A/B/C)	24/61/37	0.602
CMV serologic status (positive/negative)	116 / 6	0.461
UNOS score (1/2–3/4)	67/55/0	0.048
Triceps skin fold (% EV[a])	127.2 ± 80 (22–465)	0.752
Midarm muscle circumference (% EV[a])	98.1 ± 13.5 (68.6–136.9)	0.311
MEGX test (ng/ml)	25.9 ± 19.3 (3.3–84.8)	0.823
Aminopyrine breath test (%)	1.56 ± 1.41 (0.008–6.07)	0.264
Donor variables		
Sex (male/female)	80 / 42	0.302
Age (years)	46.7 ± 19.2 (14–87)	0.124
Sodium (mEq/l)	148 ± 10.9 (123–166)	0.553
CMV serologic status (positive/negative)	94/28	0.028
Dopamine infusion > 10 μg/Kg per min (yes/no)	47/75	0.342
Intensive care unit stay (h)	72.2 ± 59 (12–312)	0.550
Sex-match (MM/MF/FF/FM)[b]	47/34/15/26	0.552

[a] *EV* expected value in the age- and sex-matched healthy population of the area served by the hospital [21]

[b] *MM* donor and recipient male, *MF* donor male and recipient female, *FF* donor and recipient female, *FM* donor female and recipient male

Patients and methods

We prospectively analyzed data collected from a cohort of 122 consecutive patients who underwent primary LT for liver cirrhosis from February 1994 to June 1997 at our center. Patients were followed-up from transplantation to graft loss, which was defined as either patient death or retransplantation.

Cirrhotic patients with moderate or severe renal failure who underwent combined liver-kidney transplantation, patients with fulminant hepatic failure and patients with non-hepatocellular carcinoma (HCC) cancer were excluded from the study.

The recipient and donor variables studied are listed in Table 1. Medical status of the recipient was rated by UNOS (United Network for Organ Sharing) score as follows: UNOS 1: patient stable at home; UNOS 2: waiting for transplant at home, but requiring medical support; UNOS 3: unstable, in need of continuous hospitalization; UNOS 4: requiring a life supporting system (intensive care unit) [7]. For the analysis we grouped UNOS in two strata: UNOS 1: patients with good quality of life and UNOS 2 plus 3: patients with frequent or continuous hospitalization (only 10 patients were classified as UNOS 3). No patients with status 4 were included in our study because recipients requiring life support tend to have acute hepatic failure and were thus excluded from the study. Triceps skin fold and midarm muscle circumference were expressed as percentage of the expected value of the age- and sex-matched healthy population of the area served by the hospital, according to an epidemiologic study of anthropometric evaluation of the Catalonian population. [21] Aminopyrine breath test and monoethylglycinexylidide (MEGX) test were performed as previously described. [22, 23]

The etiology of hepatic cirrhosis was: alcoholic in 43 patients (35.2%), post-hepatitic in 46 (35.2%) (42 hepatitis C and 4 hepatitis B), mixed (alcohol and virus) in 21 (17.2%), cholestatic in 9 (7.4%),

autoimmune in 1 (0.8%) and cryptogenic in 2 (1.6%). Hepatic cirrhosis was diagnosed by hepatic needle biopsy or by clinical criteria when biopsy was not possible. HCC was suspected from imaging techniques and confirmed by needle-biopsy and/or by increased α-fetoprotein levels. Tumor stage was established by ultrasonography, angiography with lipiodol when not contraindicated, and lipiodol-computed tomography. Extra-abdominal metastases were ruled out by chest and brain computed tomography and bone scintigraphy.

Indications for transplantation in patients with non-cholestatic cirrhosis were: ascites and Child-Pugh classification grade C, refractory ascites, spontaneous bacterial peritonitis, encephalopathy, and recurrent variceal hemorrhage in patients with severe deterioration of hepatic function (Child-Pugh classification B—C). Transplantation was indicated in patients with primary biliary cirrhosis and sclerosing cholangitis, when predicted survival calculated by disease-specific models [24, 25] was worse than the expected survival after LT in our Unit. Only patients with HCC under 5 cm, with fewer than 3 hepatic nodules and without macroscopic vascular invasion were accepted for LT.

LT was performed following standard surgical techniques, and the vena cava was preserved in all but 5 patients (95.9%). The immunosuppressive regimen included sequential therapy starting with thymoglobulin and methylprednisolone, followed by cyclosporine or tacrolimus, prednisone, and azathioprine. Prednisone was withdrawn after 3 months whenever possible. Rejection episodes were treated with methylprednisolone, and steroid-resistant rejection was treated with OKT3 monoclonal antibody or tacrolimus.

In the postoperative period, hepatitis B immunoglobulin was administered to patients with hepatitis B surface antigen positivity. No anti-CMV prophylaxis was administrated. Our strategy for CMV was that of deferred therapy, which involves waiting for the onset of symptoms in patients before treatment, with special attention to patients at high risk, like seronegative recipients who received a seropositive liver, or patients receiving OKT3.

Statistical analysis

Preoperative recipient and donor variables were analyzed for their association with graft survival. Continuous variables are presented as the mean ± standard deviation (SD). In the univariate analysis, we used a log-rank test from Kaplan Meier survival analysis for categorical variables and a univariate Cox proportional hazards survival analysis for continuous variables. Variables with $P < 0.150$ on univariate analysis were included as candidate variables in a multivariate Cox proportional hazards regression analysis to identify those with independent prognostic value. This was performed using a forward stepwise method for covariate selection. The analyses were performed for the full observation period (59 months) and for the first 18 months by censoring at this time all observation times greater than 18 months. The latter was done because pretransplant variables can only be expected to predict prognosis for a limited period after transplantation. Since results for both analyses were similar, only those from the total observation period are presented.

To fully explore the effect of variables with prognostic significance on graft survival rates, we studied the correlation between these variables and post-transplantation complications that can induce graft loss.

Comparison between baseline recipient and donor characteristics and the correlation between postoperative complications were analyzed by T-test for continuous variables and by Chi-square test for categorical variables.

All statistical calculations were performed using the SPSS 8.0 program for windows (SPSS Inc., Chicago. Illinois).

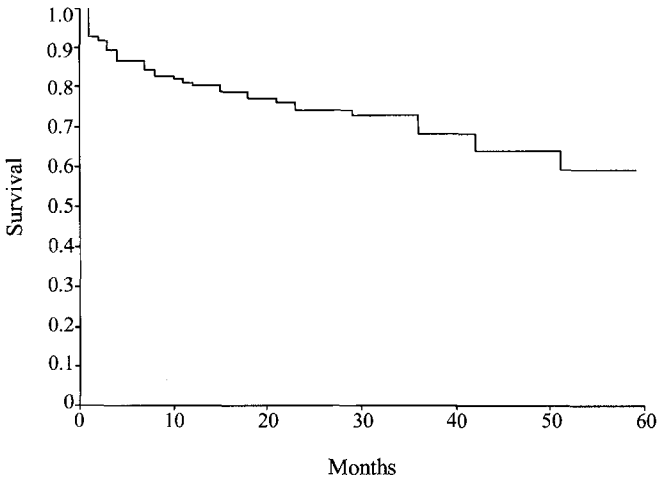

Fig. 1 Cumulative graft survival probabilities. Kaplan–Meier survival curve after LT for 122 cirrhotic patients

Table 2 Causes of graft loss during follow-up ($n = 38$)

Causes	*n*
Retransplantation	16 (42.1%)
Rejection	5
Primary non-function	3
Hepatic arterial thrombosis	3
Recurrent virus C cirrhosis	2
Ischemic type biliary complications	2
Portal thrombosis	1
Patient death	22 (57.9%)
Infection	7
Recurrent virus C cirrhosis	4
Rejection	2
Recurrent hepatocellular carcinoma	1
Other cancer	4
Cerebral vascular accident	2
Sudden death	1
Cerebral anoxia	1
Total	38 (100%)

Results

Median follow-up was 33 (19–59) months. One patient committed suicide and was censored at 33 months. Graft survival probability at 18 and 59 months was 77% and 59.4% respectively (Fig. 1). Patient survival probability for the same periods of time was 85.2% and 71.8% respectively. Among the 122 transplantations, there were 38 (31.1%) graft losses, 22 deaths, and 16 retransplantations. The causes of graft loss are listed in Table 2.

Variables with $P < 0.150$ on univariate analysis (Table 1) were: positivity of the CMV serologic status of the donor ($P = 0.028$), recipient UNOS status score 2 or 3 ($P = 0.048$), and advanced donor age ($P = 0.124$). Graft

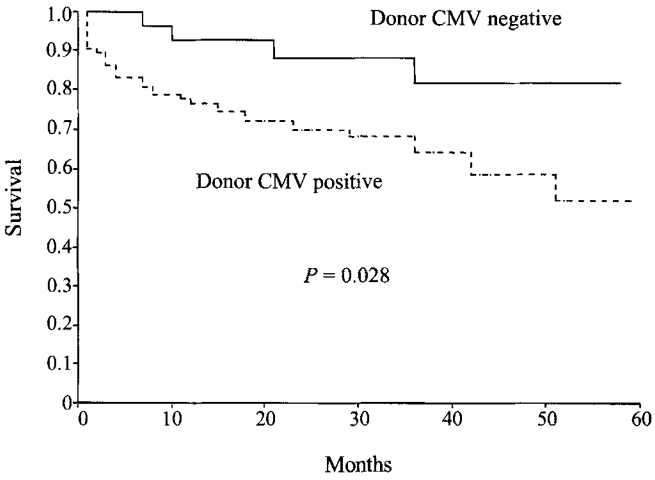

Fig. 2 Cumulative graft survival probabilities for patients stratified

Table 3 Probability of graft loss at 59 months by donor and recipient CMV-matching according to Kaplan–Meier curves

Donor CMV serologic status	Recipient CMV serologic status	*n* (%)	Probability of graft loss
Negative	Negative	2 (1.6)	0
Negative	Positive	26 (21.3)	19.3
Positive	Negative	4 (3.3)	25
Positive	Positive	90 (73.8)	50.6

loss probabilities were: 18.1% and 47.9% for CMV-negative and CMV-positive donors respectively and 36% and 45.9% for recipients classified as UNOS 1 and UNOS 2–3 respectively. Mean donor age was 45.1 ± 19.6 years for grafts that survived and 50.2 ± 19.6 years for grafts that did not.

When these variables were introduced into the multivariate analysis, donor CMV serologic status was the only variable that was independently associated with graft survival (Coefficient $\beta = 1.09$, Standard error = 0.53, Wald $X^2 = 4.24$, Risk ratio = 2.97, 95% Confidence interval = 1.05–8.38; $P = 0.039$). Graft survival curves according to donor CMV serologic status are shown in Fig. 2, and detailed graft survival probabilities according to donor and recipient CMV matching are shown in Table 3.

Analysis of baseline donor and recipient characteristics of CMV-positive and CMV-negative donors is shown in Table 4. Donor age was significantly lower in CMV-negative donors ($P = 0.025$).

No statistically significant correlation was found between the donor CMV serologic status and the post-transplantation complications (Table 5). Twenty-three patients (18.8%) had post-transplantation symptomatic CMV disease: 18 patients had viral syndrome and 5 had focal diseases (3 hepatitis, 1 enteritis and 1 pneumonitis). All were treated with intravenous ganciclovir. No graft losses were directly related to CMV disease (all infectious deaths were from bacterial or protozoal infections).

Thirty-four patients (27.9%) had one or more acute rejection episodes, all were treated with methylprednisolone boluses, 7 patients received tacrolimus, and two of them OKT3 monoclonal antibody. Six patients (4.9%) suffered chronic rejection, all were treated with methylprednisolone, two received OKT3 and 1patient received tacrolimus for steroid-resistant rejection. Patients who suffered at least one episode of rejection tended to have a greater risk of CMV symptomatic disease (viral syndrome or focal disease) (32.4%) than patients who had no rejection episodes (17%) but it was not statistically significant ($P = 0.064$).

When recipients with hepatitis C were analyzed separately ($n = 63$), a tendency towards a worse prognosis was found in recipients of CMV-positive livers but it was not statistically significant: probability of graft loss was 31.4% when donor was CMV-positive and 6.5% when it was CMV-negative ($P = 0.062$). In this group there was no correlation between post-transplantation CMV disease and recurrence of hepatitis C ($P = 0.271$) nor graft loss ($P = 0.544$)

Discussion

In a prospectively followed cohort of 122 cirrhotic recipients of liver transplants, transplantation of a liver from a serologically CMV-positive donor was associated with an almost threefold increase of the relative risk for graft loss. After 59 months of follow-up, the probability of graft loss was 47.9% and 18.1% for positive and negative donor CMV respectively. These results generally match those reported by other authors [17].

Falagas et al. [17], found a difference in the survival rates among the four CMV serologic strata of donors and recipients; the highest risk occurred among CMV-seronegative patients who received a transplant from a CMV-seropositive donor. We did not detect differences in survival between recipients with distinct CMV serologic status since only six out of the 122 patients were seronegative.

Results from other studies are not so conclusive, but a tendency to worse prognosis among recipients of CMV-positive livers is shown. Stratta et al. [26], found no correlation between CMV serologic status and patient survival; however, the presence of donor CMV seropositivity, irrespective of recipient serologic status, was an independent predictor for the subsequent development of CMV disease, and there was a trend for decreased survival in patients who developed CMV disease

Table 4 Baseline donor and recipient characteristics according to donor CMV serologic status ($n = 122$)

Variables	Donor CMV (+) n or mean ± SD ($n = 94$)	Donor CMV (-) n or mean ± SD ($n = 28$)	P Value
Recipient variables			
Sex (male/female)	58/36	14/14	0.271
Age (years)	54.4 ± 9.3	53.4 ± 11.4	0.703
Etiology (viral/non-viral)	51/43	16/12	0.792
HCC (yes/no)	21/73	7/21	0.772
Creatinine (mg/dl)	0.89 ± 0.34	0.86 ± 0.23	0.545
Albumin (g/dl)	30.9 ± 6.0	30.6 ± 4.6	0.710
Bilirubin (mg/dl)	2.65 ± 2.13	4 ± 6	0.253
Prothrombin time (%)	68.2 ± 15.4	68.6 ± 15.2	0.922
Previous ascites (yes/no)	79/15	22/6	0.578
Previous hepatic encephalopathy (yes/no)	35/59	7/21	0.233
Previous variceal bleeding (yes/no)	30/64	9/19	0.984
Child–Pugh score	8.31 ± 2.0	8.14 ± 1.98	0.702
CMV serologic status (positive/negative)	90/4	26/2	0.625
UNOS 1/2–3/4	51/43/0	16/12/0	0.796
Triceps skin fold (% EV[a])	125.7 ± 78.9	131.9 ± 86.1	0.794
Midarm muscle circumference (% EV[a])	98.3 ± 13.9	97.6 ± 12.1	0.852
MEGX test (ng/ml)	26.8 ± 20.8	22.9 ± 13.2	0.361
Aminopyrine breath test (%)	1.39 ± 1.30	2.01 ± 1.62	0.165
Donor variables			
Sex (male/female)	60/34	20 / 8	0.464
Age (years)	48.9 ± 18.8	39.2 ± 18.9	0.025
Sodium (mEq/l)	148 ± 11	147 ± 9	0.702
Dopamine infusion > 10 µg/kg per min (yes/no)	37/57	10/18	0.735
Intensive care unit stay (h)	73.9 ± 58.7	66.4 ± 60.5	0.576
Sex-match (MM/MF/FF/FM)[b]	38/23/12/21	9/11/3/5	0.504

[a] *EV* expected value in the age- and sex-matched healthy population of the area served by the hospital. [21]
[b] *MM*: donor and recipient male, *MF* donor male and recipient female, *FF* donor and recipient female, *FM* donor female and recipient male

Table 5 Probability of postoperative complications at 59 months by donor CMV serologic status according to Kaplan–Meier curves ($n = 122$)

Complications	n (%)	Probability if donor CMV positive (%)	Probability if donor CMV negative (%)	P Value
Infection[a]	58 (47.5)	80.4	55.6	0.382
Bacterial infection[b]	48 (39.3)	61	31.8	0.131
CMV-disease[c]	23 (18.8)	27	21.8	0.322
Invasive fungal infection	7 (5.7)	8.2	0	0.127
Acute rejection	34 (27.8)	29.6	32.5	0.901
Chronic rejection	6 (4.9)	17.2	0	0.152
Graft disfunction[d]	20 (16.4)	16.1	17.8	0.833
Hepatic arterial thrombosis	12 (9.8)	12.4	7.8	0.502
Biliary complications[e]	24 (19.7)	23.1	17.8	0.705
HCV recurrence	23 (18.8)	32.6	19.2	0.511

[a]Probability of major infection: including bacterial, CMV-disease, invasive fungal infection and protozoal infection (only 1 case)
[b]Not including urinary and catheter infections
[c]Including systemic or focal infection, no asymptomatic viremia
[d]Including initial poor function and primary nonfunction (17 and 3 cases respectively)
[e]Including biliary fistulas, estenosis, obstruction and cholangitis

compared with those who did not. This trend, however, did not reach statistical significance. Likewise, data from Gayowski et al. [27], whose study comprised 130 patients, were not statistically significant. However, there was a trend for a difference in mortality rates among donor and recipient CMV serologic groups, especially if the group of CMV-seronegative donors and recipients was compared with the other groups.

The influence of immunosuppression in these results is controversial. These studies differ in the use of ta-

crolimus, an immunosuppressive agent associated with a slight increase in survival rates in LT recipients and a lower incidence of CMV infection after transplantation [28]. The study by Stratta et al. [26], was conducted before the introduction of tacrolimus as immunosuppressor, Falagas et al. [17], like us, administered tacrolimus only to a few patients (6 and 7 patients respectively), and Gayowski et al. [27] included patients who underwent LT under tacrolimus-based primary immunosuppression.

It is difficult to determine whether death is directly attributable to CMV in patients with multifactorial causes of death. A relationship between CMV infection and chronic allograft rejection has been described [19], but the complex interactions between CMV and other risk factors for chronic liver allograft dysfunction have yet to be completely elucidated. The relationship between CMV infection and acute rejection is a consequence of changes in the immunosuppressive treatment. Treatment of acute rejection episodes with antilimphocytic drugs like OKT3 has been associated with an unusually high incidence of CMV disease [26], and the decrease of immunosuppression when an active CMV infection is detected, increases the risk of acute rejection. We found no correlation between rejection and postoperative CMV disease.

CMV viremia has also been described as a risk factor for allograft cirrhosis after LT for hepatitis C [20]. In our patients with pretransplantation hepatitis C, a trend towards a worse prognosis was found when the donor was CMV-positive, but in this group, no correlation was found between postoperative CMV disease and hepatitis C recurrence or graft survival.

Pre-transplantation CMV serologic status is associated with post-transplantation CMV disease [17, 26] invasive fungal disease [17] and bacteremia [17, 18] which may be facilitated by the immunosuppressive properties of the virus. We found no correlation between donor CMV serology and cause of graft loss, because there were only four grafts lost in CMV-negative donors. We point out that all grafts lost due to infection or rejection occurred in recipients of a CMV-positive liver, but none were directly related to CMV disease. In our patients there was no significant correlation between the donor CMV serologic status and post-transplantation complications, but CMV disease, bacterial infection (excluding bound, urinary and catheter infections), invasive fungal disease, chronic rejection and HCV recurrence were more frequently in recipients of a CMV-positive liver.

Our approach to CMV disease prevention, based on deferred therapy, did not influence our results. The incidence of post transplantation CMV symptomatic disease is similar to that of other groups with the same CMV strategy and higher than that of others who applied preemptive CMV treatment [29], but ganciclovir treatment was curative in all cases and no death related to CMV occurred.

Pre-transplantation medical status of the recipient was significant in the univariate but not the multivariate analysis. UNOS status has been reported to be associated with prognosis, [2, 7] but patients with bad prognosis are always those hospitalized in the ICU (status 4), and no patients with this status were included in our study because recipients usually classified as UNOS 4 are those with fulminant hepatic failure, who were excluded from the study.

Advanced donor age has been extensively related with prognosis [7, 10, 30]. In our patients, donor age was significantly higher in CMV-positive donors, and for this reason, donor age could be a confounding factor on the effect of CMV on survival. However, in the multivariate analysis only donor CMV serology was significant. Perhaps, as Hoofnagle et al. found [30], the association with poor graft survival is related to the quality of the graft as judged by the harvesting surgeon, and not exclusively to donor age. However, macroscopic graft quality was not assessed in our study.

Cholestatic liver disease has been associated with favorable prognosis [31]. We did not analyze this variable because we included only nine patients with cholestatic cirrhosis. Etiology classified as viral and non-viral did not show prognostic value.

In almost all the previous studies on prognostic factors in LT, parameters of preoperative kidney function were found to strongly correlate with survival after transplantation [3, 6] for this reason, our study included only patients with normal renal function or mild renal impairment (the maximal value of preoperative serum creatinine was 1.8 mg/dl) because in those with poorer function, a combined liver-kidney transplantation was routinely performed.

As in our study, other authors suggest that other risk factors do not show prognostic value. Advanced recipient age [2] has been reported not to be associated with decreased survival of patient or graft. The analysis of pre-transplantation nutritional status is controversial and difficult to interpret because this parameter has been measured in very different ways in previous studies [6, 10, 11, 12]. Variables of hepatic function such as the Child-Pugh classification or MEGX test have not shown significant prognostic value in some studies [4, 8]. As in our study, no differences in survival have been observed between well-selected patients with an HCC and those without cancer [5]. Other non-preoperative variables, such as the presence of steatosis in donor liver biopsy, total ischemia time, number of intraoperative packed red blood cells transfused, or cytotoxic crossmatch, were not included (when included in the analysis they were not statistically significant, data not shown).

In conclusion, cirrhotic patients who received an organ from a CMV seropositive donor had an increased

risk of graft loss. This observation suggests the need to intensify preemptive measures against postoperative complications in recipients who receive an organ from a CMV seropositive donor.

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