

# Prognostic Model for Early Acute Rejection After Liver Transplantation

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Hepatic graft rejection is a common complication after liver transplantation (LT), with a maximum incidence within the first weeks. The identification of high-risk patients for early acute rejection (EAR) might be useful for clinicians. A series of 133 liver graft recipients treated with calcineurin inhibitors was retrospectively assessed to identify predisposing factors for EAR and develop a mathematical model to predict the individual risk of each patient. The incidence of EAR ( $\leq 45$  days after LT) was 35.3%. Multivariate analysis showed that recipient age, underlying liver disease, and Child's class before LT were independently associated with the development of EAR. Combining these 3 variables, the following risk score for the development of EAR was obtained: EAR score  $[F(x)] = 2.44 + (1.14 \times \text{hepatitis C virus cirrhosis}) + (2.78 \times \text{immunologic cirrhosis}) + (2.51 \times \text{metabolic cirrhosis}) - (0.08 \times \text{recipient age in years}) + (1.65 \times \text{Child's class})$ . Risk for rejection  $= e^{F(x)}/1 + e^{F(x)}$ . The combination of age, cause of liver disease, and Child's class may allow us to predict the risk for EAR. (*Liver Transpl* 2001;7: 246-254.)

Acute rejection is a common complication after liver transplantation (LT), especially within the first weeks after the procedure. Its incidence is variable, ranging between 40% and 80% in different series.<sup>1-9</sup> However, despite this greater incidence within the first weeks after LT, acute rejection may appear several months or even years after the procedure. Contrary to early rejection episodes, these late episodes are considered to be the consequence of a lower degree of immunosuppression.<sup>10</sup>

Different studies have aimed to identify patients with a greater risk for developing acute rejection,<sup>2,3,11-17</sup> but with some exceptions, they have been limited to a

small number of patients and focused on a limited number of risk factors, and results are frequently controversial. For this reason, there is no consensus about the majority of factors predisposing to the appearance of acute rejection after LT.

We studied a large number of potential parameters predisposing to early acute rejection (EAR) after LT and constructed a simple predicting rule that is easy to apply to allow simple and rapid identification of these high-risk patients.

## Patients and Methods

### Cohort Study

Patients undergoing LT at the Clinica Universitaria de Navarra (Pamplona, Spain) between April 1990 and April 1999 were retrospectively evaluated and selected for this study if they fulfilled the following criteria: (1) adult (age  $> 18$  years), (2) primary LT, (3) immunosuppressive regimen based on cyclosporine (CsA) or tacrolimus as the major immunosuppressant immediately after LT, and (4) patient or graft survival of 45 days or more after LT, or less in the case of an episode of acute rejection within that time.

During this period, 15 patients were excluded from the study for the following reasons: age younger than 18 years (1 patient), patient or graft survival less than 7 days without developing acute rejection (5 patients), and immunosuppression other than CsA or tacrolimus in the immediate postoperative period (9 patients). The final study group included 133 patients undergoing primary LT.

### Immunosuppressive Treatment

All patients included on the study were treated with calcineurin inhibitors; 83 patients, conventional CsA (Sandimmun; Novartis Pharma, Basilea, Switzerland); 32 patients, CsA microemulsion (Neoral; Novartis Pharma); and 17 patients, tacrolimus (Prograf; Fujisawa Ireland Ltd, Killorglin, Ireland) as the main immunosuppressant.

*CsA group.* The first 83 patients were administered intravenous CsA, which was subsequently switched to the oral route. Intravenous CsA was administered as an intravenous infusion at a dose of 2 mg/kg over 6 hours every 12 hours, starting postoperative day 1. CsA levels were measured daily by radioimmunoassay, and doses were adjusted to maintain whole-blood concentrations between 250 and 300 ng/mL

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before the next CsA dose within the first 3 months after LT. An intravenous bolus of 1,000 mg of methylprednisolone was administered in the anhepatic phase of surgery. In the postoperative period, steroid doses were tapered from 200 mg of methylprednisolone day 1 to 20 mg of prednisone by day 6, 15 mg by day 180, 10 mg by day 365, 5 mg by the end of the second year, and lower doses subsequently. Azathioprine was administered at a dose of 1 to 2 mg/kg/d orally, starting when the platelet count was less than 50,000/ $\mu$ L.

**CsA microemulsion group.** An initial dose of 5 mg/kg every 12 hours was administered as an oral solution through a nasogastric tube within the first 6 hours after LT. Blood levels were measured to achieve the same therapeutic levels described for conventional CsA. Steroid doses during surgery and within the first 30 days were the same described for CsA and were tapered to 15 mg by day 30, 10 mg by day 90, 5 mg by day 180, and finally discontinued at the end of the first year. Azathioprine was administered with the same schedule as that described for patients receiving conventional CsA.

**Tacrolimus group.** Tacrolimus was administered orally at a dose of 0.05 mg/kg every 12 hours, starting within the first 6 hours after LT. Blood levels were measured by radioimmunoassay, and doses were adjusted to maintain levels of 10 to 12 ng/mL in the first 2 weeks, 9 to 11 ng/mL in weeks 3 and 4, and 7 to 9 ng/mL in weeks 5 to 12. An initial dose of 5 mg/kg of intravenous methylprednisolone was administered in the intraoperative period and in the first postoperative day, followed by a daily dose of 20 mg of prednisone orally within the first month. Doses were subsequently tapered to 15 mg by day 30, 10 mg by day 90, 5 mg by day 120, and discontinued at the end of the first year. Eleven patients also were administered azathioprine, with the same schedule as that described for patients administered conventional CsA.

### Assessment of Acute Rejection

Diagnosis of acute rejection was based on clinical, biochemical, and histological criteria. In patients with clinical and biochemical suspicion of acute rejection, a liver biopsy was performed (unless contraindicated because of severe coagulopathy) to obtain histological confirmation of rejection. Liver biopsy was not performed in 2 episodes. In these 2 patients, the diagnosis of rejection was established because of the presence of impaired liver function test results, with eosinophilia and leukocytosis when other potential causes of graft dysfunction had been ruled out. The diagnosis of rejection was retrospectively confirmed when liver function test results and all other biochemical abnormal results returned to normal values after treatment for acute rejection was initiated.

Histological criteria for acute rejection included the presence of: (1) mixed inflammatory but predominantly mononuclear infiltrate in portal triads, with activated lymphocytes, neutrophils, and frequently eosinophils; (2) subendothelial inflammation of portal and/or terminal hepatic veins; and (3) inflammation and/or damage of biliary epithelium. At least 2 of these 3 characteristics had to be present in the liver biopsy specimen to establish the diagnosis of acute rejection.<sup>18</sup> The

rejection activity index was obtained according to the recommendations of the Third Banff Conference on Allograft Pathology.<sup>19</sup>

### Definition of EAR

As stated before, acute rejection is especially frequent within the first weeks after LT, decreasing thereafter. Several investigators have established different definitions for EAR and late acute rejection, and the limit between the 2 events has been placed at 30 days,<sup>2,10</sup> 45 days,<sup>3</sup> and 3<sup>11</sup> or 6 months<sup>20</sup> after LT. In our series, more than 90% of the episodes of acute rejection developed within 45 days after transplantation; for this reason, the barrier between early and late rejection was defined as 45 days. We defined the day of appearance of EAR as the post-LT day in which the impairment of liver function test results that led to performing the diagnostic liver biopsy was first detected.

### Treatment of Acute Rejection

Acute rejection episodes were generally treated with the administration of 1,000 mg of methylprednisolone daily for 3 consecutive days, followed by an oral recycle of prednisone. Steroid-resistant acute rejection was treated with OKT3 (Orthoclone; Ortho-Biotech, Raritan, NJ). Some patients with mild acute rejection episodes were treated with an increased dosage of anticalcineurin drugs.

### Statistical Analysis

Results are expressed as mean  $\pm$  SD and median and interquartile range in the case of parametric or nonparametric variables, respectively. Actuarial incidence of early graft rejection was estimated with the Kaplan-Meier<sup>21</sup> method.

A stepwise logistic regression analysis was performed to identify the group of variables independently associated with the development of acute rejection within 45 days after LT. Seventy-three preoperative, intraoperative, and postoperative potential variables were considered to enter the model. Those variables significant at *P* less than .2 in the univariate analysis were subsequently included in the multivariate analysis, and a stepwise selection model was used to identify the variables independently associated with the appearance of EAR.

The potential variables introduced in the logistic regression analysis are listed next.

**Preoperative factors.** Recipient factors are age; sex; blood group type A, type B, type O (ABO) and Rh; cause of liver disease; Child's class; liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase,  $\gamma$ -glutamyl transpeptidase, total bilirubin) immediately before LT; serum creatinine level immediately before LT; gammaglobulin levels; immunoglobulin A, immunoglobulin G, and immunoglobulin M levels; presence or absence of antinuclear antibodies, antimitochondrial antibodies, smooth muscle antibodies, or antibodies to liver/kidney microsome; history of blood transfusions before LT; cytomegalovirus and Epstein-Barr virus serological status, panel reactive antigen status; presence of

hepatocellular carcinoma; presence of autoimmune disease before LT; positivity for the most frequent HLAs; days of permanence in the waiting list; and in women, antecedent of pregnancy or abortion before LT.

Donor factors include age, sex, cause of death, ABO blood group and Rh, Epstein-Barr virus and cytomegalovirus serological status, hours in the intensive care unit, and presence or absence of the more prevalent HLA antigens.

Donor-recipient interaction factors are sex match, ABO group match, Rh match, cross-match, and HLA-I, HLA-II, HLA-A, and HLA-B mismatches.

**Intraoperative factors.** These are arterial and portal ischemic times; number of units of red blood cells, fresh frozen plasma, cryoprecipitate, and platelets administered during the transplantation surgery; and intraoperative administration of aprotinin and prostaglandin E<sub>1</sub>.

**Postoperative factors.** These are immunosuppressive regimen, moderate to severe preservation injury (defined as aspartate transaminase level >600 U/L within the first 72 hours after LT),<sup>22</sup> and abdominal bleeding requiring a new laparotomy within 48 hours after LT.

To identify the individual risk for EAR for a given patient, an equation was developed with those variables independently associated with EAR, as follows:

$$F(x) = \beta_0 + \beta_1x_1 + \beta_2x_2 + \dots + \beta_ix_i$$

where  $x_1, x_2, \dots, x_i$  are the significant prognostic factors and  $\beta_1, \beta_2, \dots, \beta_i$  are the regression coefficients. Each regression coefficient means that the effect of every prognostic factor is multiplied by the value of the regression coefficient. The greater the risk scores, the greater the probability of developing the event under study, in this case, the appearance of EAR.

After obtaining the equation formula, the predicted individual risk could be calculated with the transformation:

$$R \text{ (predicted probability of EAR)} = \frac{e^{F(x)}}{1 + e^{F(x)}}$$

Fit of the logistic model was assessed by the Hosmer-Lemeshow goodness-of-fit test.<sup>23</sup>

The sensitivity and specificity of our predictive model was estimated by means of a receiver operating characteristic (ROC) curve.<sup>24</sup> Statistical analysis was performed using the Statistical Package for Social Sciences, version 9.0.1, (SPSS Inc, Chicago, IL, 1999).

*P* less than .05 indicates statistical significance in all analyses.

## Results

Baseline characteristics of the cohort study population are listed in Table 1.

### Incidence of Acute Rejection

Among the 133 patients included on the study, 47 patients (35.3%) developed at least 1 episode of acute rejection within 2 to 2,380 days after LT. Forty-three

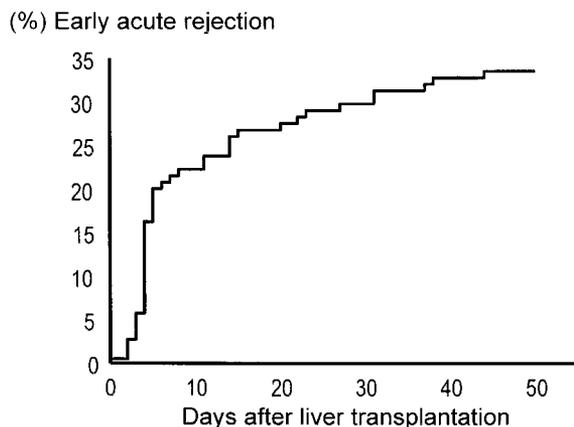
**Table 1.** Characteristics of the 133 Patients Included on the Study

	No.	%
Age (yr)*	55.28 ± 9.76	
Sex		
Men	98	73.7
Women	35	26.3
Liver cirrhosis		
No†	3	2.3
Yes	130	97.7
Indication for LT		
Alcoholic cirrhosis	48	36.1
HCV cirrhosis	46	33.8
HBV cirrhosis	8	6
PBC, autoimmune CAH, adult idiopathic ductopenia	9	8.8
Metabolic cirrhosis‡	13	9.8
Miscellaneous§	10	7.5
Hepatocellular carcinoma		
No	91	68.4
Yes	42	31.6
Child's class (n = 130)		
A	16	12.3
B	63	48.5
C	51	39.2
Recipient blood group		
Group A	65	48.9
Group B	7	5.3
Group O	61	45.8
Recipient Rh		
Negative	28	21.1
Positive	105	78.9
Days on the waiting list	82 (25-173)	
Immunosuppressive regimen		
CsA	83	62.4
CsA microemulsion	32	24.1
Tacrolimus	18	13.5

\*Mean ± SD.  
†Familial amyloid polyneuropathy, 1 patient; polycystic liver disease, 1 patient; epitheloid hemangioendothelioma, 1 patient.  
‡Hemochromatosis, 8 patients;  $\alpha_1$ -antitrypsin deficiency, 3 patients; Wilson's disease, 2 patients.  
§Cryptogenic cirrhosis, 5 patients; Budd-Chiari syndrome, 2 patients; no cirrhosis, 3 patients.  
||Median (interquartile range).

patients (32.3%) developed 1 episode of acute rejection, and 4 patients (3%) developed a second episode. Cumulative incidences of acute rejection at the end of 1, 3, and 5 years after LT were 33.9%, 33.9%, and 36.6%, respectively.

Forty-four of the 47 first episodes of acute rejection (93.62%) were EAR (shown in Figure 1). The median time of appearance of EAR after LT was 5 days (interquartile range, 4 to 13 days). Rejection activity indices



**Figure 1.** Actuarial incidence of rejection within the first 45 days after LT (n = 133).

of the EAR episodes were 2 (6 cases), 3 (8 cases), 4 (9 cases), 5 (11 cases), 6 (4 cases), 7 (2 cases), and 8 (1 case). In 3 cases, the rejection activity index was not obtained because liver biopsy was not performed (2 cases) or it was performed after the initiation of treatment for rejection (1 case).

Only those patients with episodes of EAR were included in the statistical analysis of predisposing factors.

#### Factors Associated With the Appearance of EAR: Univariate Analysis

Only 7 variables showed an association with EAR with a significance level less than .20 in univariate analysis. They were cause of liver disease, recipient age, Child's class, number of cryoprecipitate units administered during LT surgery, presence of preservation injury, and route of administration of immunosuppressive treatment in the immediate postoperative period (intravenous CsA *v* CsA microemulsion or tacrolimus). Results of univariate analysis are listed in Table 2.

#### Factors Independently Associated With EAR: Multivariate Analysis

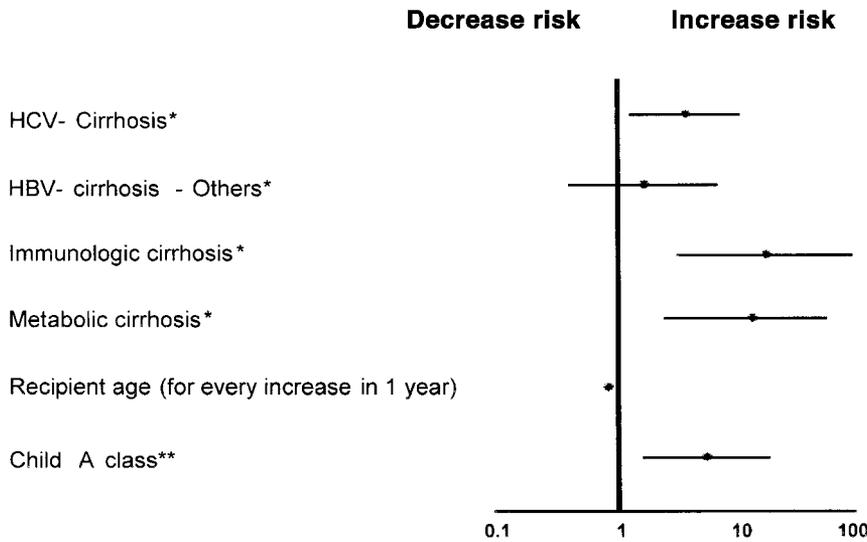
Three variables were independently associated with the development of EAR in the multivariate logistic regression model: cause of liver disease, recipient age, and Child's class. The results of multivariate analysis are shown in Figure 2 and Table 3.

The strongest association with the appearance of

**Table 2.** Parameters Potentially Associated With the Development of EAR by Univariate Analysis

Variable	Incidence of EAR (%)	Unadjusted OR (96% CI)	P*
Cause of liver disease			
Alcoholic cirrhosis	18.8	1	
HCV cirrhosis	35.6	2.39 (0.93-6.17)	.0714
HBV cirrhosis—others†	22.2	1.24 (0.33-4.66)	.7524
Immune cirrhosis‡	66.7	8.67 (1.81-41.41)	.0068
Metabolic cirrhosis§	69.2	9.75 (2.45-38.87)	.0012
Recipient age (for every 1-year increase)		0.96 (0.92-0.94)	.0247
Child's class			
B and C	30.7	1	
A	56.3	2.90 (1.00-8.42)	.0499
Cryoprecipitate (U administered during LT)		1.07 (1.00-1.14)	.0312
AST immediately before LT (for every 1-U/L increase)		1.009 (0.99-1.02)	.0859
Preservation injury			
No or mild	28.4	1	
Moderate to severe	48.4	2.36 (1.03-5.39)	.0415
Route of immunosuppression			
Oral (tacrolimus and CsA microemulsion)	26	1	
Intravenous (CsA)	37.3	1.69 (0.78-3.67)	.1799

Abbreviations: OR, odds ratio; CI, confidence interval; AST, aspartate aminotransferase.  
\*Wald test.  
†Familial amyloid polyneuropathy, 1 patient; polycystic liver disease, 1 patient; epitheloid hemangioendothelioma, 1 patient; Budd-Chiari syndrome, 2 patients; cryptogenic cirrhosis, 5 patients.  
‡Autoimmune CAH, 2 patients; PBC, 6 patients; idiopathic adult ductopenia, 1 patient.  
§Hemochromatosis, 8 patients;  $\alpha_1$ -antitrypsin deficiency, 3 patients; Wilson's disease, 2 patients.



**Figure 2.** Factors independently associated with the development of EAR after LT by multivariate logistic regression analysis. \*Reference stratum, alcoholic cirrhosis. \*\*Reference stratum, Child's classes B and C.

EAR was an immunologically mediated underlying liver disease.

In comparison with alcoholic liver cirrhosis (reference stratum), patients undergoing LT for metabolic liver disease (hemochromatosis, Wilson's disease, and alpha<sub>1</sub>-antitrypsin deficiency) and hepatitis C virus (HCV) cirrhosis had a significantly greater risk for EAR.

Recipient age was also independently associated with EAR: younger recipients were at greater risk. For every 1-year increase in recipient age at the time of LT, the risk for EAR decreased by 8%.

Finally, the functional reserve of liver transplant recipients before LT was also independently associated with EAR. Those patients in Child's class A at the time of LT had a risk for developing EAR 5 times greater than those in Child's classes B and C.

### Calculation of the EAR Risk Score

After multivariate analysis, the regression coefficients listed in Table 3 and the risk factors independently associated with the presence of EAR were used to generate the following equation:

$$\begin{aligned} \text{EAR score} = & 2.44 + (1.14 \times \text{HCV-cirrhosis}) \\ & + (2.78 \times \text{PBC/autoimmune CAH} \\ & \quad / \text{idiopathic adulthood ductopenia}) \\ & + (2.51 \times \text{metabolic cirrhosis}) \\ & - (0.08 \times \text{recipient age in years}) \\ & + (1.65 \times \text{Child's class}), \end{aligned}$$

where PBC is primary biliary cirrhosis and CAH is

**Table 3.** Variables Independently Associated With the Development of EAR by Multivariate Logistic Regression Analysis

	Regression Coefficient ( $\beta$ )	SE ( $\beta$ )	Adjusted OR	95% CI	<i>P</i> *
Cause of liver disease					
HCV cirrhosis	1.14	0.55	3.13	(1.07-9.15)	.038
HBV cirrhosis—others	0.47	0.73	1.62	(0.38-6.78)	.513
PBC, autoimmune CAH, idiopathic adult ductopenia	2.78	0.86	16.07	(2.96-87.12)	.001
Metabolic cirrhosis	2.51	0.77	12.34	(2.70-56.37)	.001
Recipient age	-0.08	0.03	0.92	(0.88-0.97)	.003
Child's class A	1.65	0.63	5.22	(1.51-18.03)	.009
Constant	1.65	1.37			

\*Wald test.  
Abbreviations: OR, odds ratio; CI, confidence interval.

chronic active hepatitis. The different variables are coded as follows: HCV cirrhosis (0 = no, 1 = yes), PBC/autoimmune CAH/adult idiopathic ductopenia (0 = no, 1 = yes), metabolic cirrhosis (0 = no, 1 = yes), and Child's class (0 = Child's class B or C, 1 = Child's class A).

For example, for a hypothetical patient aged 26 years who underwent LT for autoimmune CAH and with good hepatocellular function (Child's class A), the score for acute rejection would be:

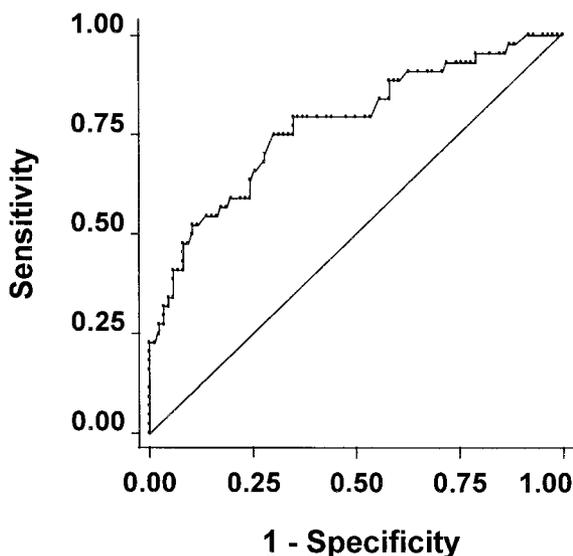
$$\begin{aligned} \text{EAR} &= 2.44 + (1.14 \times 0) + (2.78 \times 1) \\ &+ (2.51 \times 0) - (0.08 \times 26) + (1.65 \times 1) \\ &= 4.79 \end{aligned}$$

The predicted risk for EAR for this patient would be:

$$\text{EAR risk} = e^{4.79} / (1 + e^{4.79}) = 0.827$$

which means this patient has a probability of 82.7% of developing an episode of acute rejection within 45 days after LT.

The Hosmer-Lemeshow goodness-of-fit test (Chi-squared = 5.27;  $df = 8$ ;  $P = .728$ ) showed that the constructed multivariate model supported the data well. Finally, the regression model was completed, with the construction of an ROC curve (Fig. 3). The calculation of the area under the curve (0.77) indicated an



**Figure 3.** ROC curve for the logistic regression model using recipient age, cause of liver disease, and Child's class as independent predictors of EAR. Sensibility (true-positive fraction) and 1-specificity (false-positive fraction) are computed for each possible value of the predicted model. The area under the ROC curve is 0.77.

acceptable discriminative ability of our model. With the combination of these prognostic factors, our model was able to classify correctly 77% of patients who will experience EAR after LT.

## Discussion

Acute rejection is a frequent complication after LT, with an incidence ranging between 40% and 80% in different series.<sup>1-9</sup> In most series, such as ours, most episodes of graft rejection developed in the first weeks after LT, leading to a distinction between early and late graft rejection. Late graft rejection is frequently the consequence of a reduction in immunosuppressive therapy,<sup>10</sup> its response to immunosuppression is worse,<sup>2</sup> and it poses a greater risk for progression to chronic rejection.<sup>10</sup>

Conversely, EAR develops in a certain population of patients despite adequate immunosuppression, and in most cases, it responds to treatment.<sup>2</sup> However, this must not lead to an underestimation of its importance because treatment of the rejection is associated with a number of side effects, such as an increased risk for infections,<sup>25</sup> recurrence of hepatitis C in patients who underwent transplantation for HCV cirrhosis,<sup>26</sup> and such metabolic complications as diabetes mellitus, hyperlipidemia, or hypertension.<sup>27</sup>

In our series, EAR appeared in 35.3% of the transplant recipients, with a median time of 5 days. This incidence is similar to that of some series<sup>6,12,28,29</sup> and clearly less than that of others.<sup>2,11,30</sup> These different incidences may be caused mainly by the diagnostic criteria of acute rejection. As an example, those centers that perform protocol biopsies at the end of the first week after LT reported a greater incidence of acute rejection than centers performing liver biopsy only when clinically indicated.<sup>31</sup>

Because acute rejection does not uniformly develop in all patients after LT, one could speculate that identification of these patients with a greater risk for rejection could be useful to modify the immunosuppressive regimen. In this report, we propose an easy way to identify these high-risk patients, using a score that may predict the individual risk of a given patient.

The only 3 factors independently associated with EAR in our series were recipient age, Child's class immediately before LT, and cause of the indication for LT. Therefore, younger patients, those with better hepatocellular liver function (Child's class A), and those who underwent transplantation for liver diseases other than alcoholic cirrhosis had a greater risk for EAR.

Several<sup>3,11</sup> but not all studies<sup>12,13</sup> have shown an

inverse association between recipient age and incidence of acute rejection. This association has also been described for kidney transplant recipients.<sup>32</sup> This link may reflect the immunologic changes that appear with aging; namely, the reduction in total lymphocyte count; change in lymphocyte subsets, with a switch from T helper subtype 1 to T helper subtype 2 predominance; and a decreased response to antigenic stimuli.<sup>33,34</sup> All these changes lead to a decrease in both interleukin-2 and interferon- $\gamma$  synthesis.<sup>35,36</sup> The final result is a debilitated response of the immune system.

The risk for EAR was also different depending on the cause of liver disease in the recipient. Overall, patients with a lower risk for EAR were those who underwent transplantation for hepatitis B virus (HBV) cirrhosis and alcoholic cirrhosis.

In comparison to patients with alcoholic cirrhosis, those who underwent transplantation for HCV cirrhosis, metabolic cirrhosis, and immunologically mediated cirrhosis had risks 3, 12, and 16 times greater for developing EAR, respectively.

The lower incidence of EAR in patients with alcoholic cirrhosis added to a greater prevalence of bacterial infection after LT in some series<sup>12</sup> suggests an immunologic disturbance responsible for these 2 abnormalities. The immunosuppressive effects derived from alcohol consumption persist for several weeks or even months after alcohol withdrawal,<sup>37,38</sup> which might explain the reduced incidence of EAR in patients with alcoholic cirrhosis and the lack of difference in the incidence of chronic rejection compared with other causes.<sup>12</sup> However, the potential effect of alcohol consumption in our patients should be negligible because most of our transplant recipients had not consumed alcohol in the 6 months immediately before LT and remained abstinent in the postoperative period.

The greater incidence of EAR in patients who underwent transplantation for HCV cirrhosis compared with patients with alcoholic cirrhosis might be explained by the misdiagnosis of EAR instead of hepatitis C. Both entities may have common histopathologic features.<sup>39</sup> In our series, the differential diagnosis between both entities was not only based on histopathologic features (including rereview of liver biopsy specimens), but also on evolution after treatment and time of appearance. In this series, two thirds of the EAR episodes developed in the first 2 weeks after LT, a period in which hepatitis C recurrence is very uncommon.

One important aspect to consider is that none of the patients with HBV cirrhosis developed EAR during follow-up. This finding has been previously described by others<sup>12,14,15</sup> and may be a reflection of the deranged

immune system in patients chronically infected by HBV. Additionally, hyperimmune immunoglobulin prophylactically administered to these patients to avoid graft reinfection also could have contributed to the decreased incidence of EAR because of its immunosuppressive properties.<sup>12</sup>

However, although they had the lowest incidence of EAR, the absence of events (EAR) in this reduced number of patients who underwent LT for HBV cirrhosis (8 patients) did not allow its independent introduction in the multivariate analysis as a potential predictive value. For this reason, this group of patients was combined with a group of patients undergoing LT for different reasons (2 patients, Budd-Chiari syndrome; 5 patients, cryptogenic cirrhosis; and 3 patients, diseases other than hepatic cirrhosis).

The strongest association with EAR in our series was immunologically mediated liver disease as the indication for LT. Compared with the patients who underwent LT for alcoholic cirrhosis, those who underwent LT for PBC, autoimmune CAH, or adulthood idiopathic ductopenia had a risk 16 times greater for EAR. This increased incidence of acute rejection had been previously described<sup>13,16</sup> and may reflect the persistence of a hyperactive immune system in these patients, prone to react with self and nonself antigens.

Those patients undergoing LT for metabolic cirrhosis also showed an increased risk for EAR. Compared with patients with alcoholic cirrhosis, those who underwent LT for metabolic cirrhosis showed a 12-fold increased risk for EAR. This greater incidence of EAR in these patients has not been described before. Conversely, in other series, patients who underwent LT for metabolic cirrhosis had an intermediate risk for acute rejection compared with other causes.<sup>3</sup> There is no clear explanation for this finding. Considering the heterogeneity of this group of patients, it is possible there is an unidentified underlying factor shared by these 3 causes and responsible for this greater incidence of rejection. In any case, additional prospective analysis of 3 causes separately would help clarify this finding.

Finally, the third factor independently associated with EAR was hepatocellular function of the liver transplant recipients. Those patients with good liver function, namely, patients in Child's class A, had a risk for EAR 5 times greater than those in Child's class B or C.

The influence of functional hepatic reserve on the development of EAR has not been previously reported as an independent risk factor. The link between hepatic function and acute rejection may be related to the immunologic disturbances described in patients with liver cirrhosis. An additional immunosuppressive factor may

be the coexistence of malnutrition in advanced cirrhosis. Protein-calorie malnutrition is a common finding in patients with cirrhosis, related more to the severity than to the cause of liver disease.<sup>40</sup> Because malnutrition is considered the most prevalent acquired immunodeficiency,<sup>41</sup> it is reasonable to think that those patients with worse hepatocellular function would be more severely malnourished, and subsequently more immunosuppressed, explaining the reduced incidence of EAR when liver function fails. In accordance with this idea, a recent report showed a reduced incidence of acute rejection in malnourished patients compared with patients with a better nutritional state.<sup>17</sup>

In summary, acute rejection is a common complication within the first 45 days after LT. However, the risk for EAR appears to be different among transplant recipients. Younger patients, those who undergo LT for liver diseases other than alcoholic cirrhosis, and those with better hepatocellular function are at greater risk. We propose a mathematical model to help clinicians identify those patients at high risk by combining 3 simple parameters related to patient characteristics.

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## Erratum

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In the article by Gómez-Manero et al entitled "Prognostic Model for Early Acute Rejection After Liver Transplantation," which appeared in the March 2001 issue (Vol 7, No 3, pp 246-254), the following corrections should be noted. On page 246, the sentence beginning on line 13 of the abstract should read as follows: "Combining these 3 variables, the following risk score for the development of EAR was obtained: EAR score [F(x)] = 2.44 + (1.14 × hepatitis C virus cirrhosis) + (2.78 × immunologic cirrhosis) + (2.51 × metabolic cirrhosis) - (0.08 × recipient age in years) + (1.65 × Child's class A)." On page 250, in Table 3, the value for the Constant Regression Coefficient ( $\beta$ ) should be listed as 2.44. On page 251, the sentence beginning on line 14 of the first column should read as follows: "The predicted risk for EAR for this patient would be:

$$\text{EAR risk} = e^{4.79}/1 + e^{4.79} = 0.99$$

which means this patient has a probability of 99% of developing an episode of acute rejection within 45 days after LT."